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Blood Pressure Monitoring in Clinical Practice

Improved Oscillometry by Signal Fusion

VOLUME 1

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Blood Pressure Monitoring in Clinical Practice: Improved Oscillometry by Signal Fusion

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Abstract

The accurate measurement of blood pressure (BP) is essential for the diagnosis and management of medical conditions. Intermittent non-invasive blood pressure (NIBP) is regularly used in different care units, as it is a readily available method to ascertain BP. This study aims to identify and interpret the current gaps and needs in clinical practice regarding NIBP monitoring.

First, based on a review of the literature on current BP monitoring protocols, a set of questions were prepared, and 12 interviews were conducted with health professionals. The interviews were followed by shadowing work in the hospital. The results indicate that there are some problems associated with NIBP that can have both ethical and financial negative consequences. It was found that the difficulty in establishing thresholds for defining clinically relevant changes in BP dynamics and the unreliability of NIBP readings in several clinical contexts, namely hypotension, are the most considerable problems in need of intervention. From this investigation, a list of suggestions to future research is summarized, among which stand out the improvement of NIBP accuracy and NIBP adaptive sampling frequency.

In the second part of this thesis, four NIBP algorithms were implemented and a comparative analysis of their performance in presented. Three oscillometric methods and two variations of a palpation method were tested to estimate blood pressure, against invasive reference. Results show that patients' tension profile can have an impact on all methods' performance. It is evident that it is challenging to make an algorithm perform as expected when applied to different types of patients.

In clinical practice, the goal is to have BP continuously monitored in a non-invasive way. Furthermore, the current global health reality heads towards a system of telemonitoring solutions. In the future, research on developing cuffless monitoring technologies should be continued and improved.

Resumo

A medição precisa da pressão arterial é essencial para o diagnóstico e tratamento de diversas condições médicas. A monitorização intermitente e não-invasiva é usada regularmente em diferentes unidades clínicas, uma vez que é um método de fácil aplicação. Este estudo tem como objetivo identificar e interpretar as principais lacunas e necessidades atuais da prática clínica em relação à monitorização não-invasiva da pressão arterial.

Com base na revisão da literatura sobre os protocolos atuais de monitorização, elaborou-se um conjunto de perguntas e foram realizadas 12 entrevistas a profissionais de saúde, seguidas de um acompanhamento do seu trabalho. Os resultados indicam que existem alguns problemas associados à monitorização não-invasiva que podem ter consequências negativas, tanto humanas como financeiras. A dificuldade em estabelecer limiares para definir alterações clinicamente relevantes na dinâmica da pressão arterial e a fiabilidade reduzida das leituras em vários contextos clínicos, nomeadamente hipotensão, destacam-se como os problemas mais consideráveis a necessitar de intervenção. A partir desta investigação, é resumida uma lista de sugestões para futuras pesquisas, entre as quais se destacam a melhoria da precisão da medição não invasiva e o desenvolvimento de uma frequência de amostragem adaptativa.

Na segunda parte desta tese, foram implementados quatro algoritmos de medição não-invasiva e é apresentada uma análise comparativa do seu desempenho. Foram testados três métodos oscilométricos e duas variações de um método palpatório, usando a monitorização invasiva como referência. Os resultados mostram que o perfil tensional dos pacientes pode ter um impacto no desempenho de todos os métodos. A dificuldade em fazer um algoritmo funcionar conforme o esperado quando aplicado a diferentes tipos de pacientes é evidente.

Na prática clínica, um dos objetivos é ter a pressão arterial monitorizada continuamente, de forma não-invasiva. Além disso, a realidade atual da saúde a nível global caminha para um sistema de soluções de telemonitorização. Nesse sentido, o trabalho futuro deve apontar para o desenvolvimento de tecnologias de monitorização sem braçadeira.

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Acronyms

AAMI Association for the Advancement of Medical Instrumentation.
ABP Arterial Blood Pressure.
AHA American Heart Association.
AHFTU Advanced Heart Failure Treatment Unit of Cardiology B.
ANSI American National Standards Institute.

BP Blood Pressure.

CC Correlation Coefficient.
CDV Cardiovascular disease.
CO Cardiac Output.
CVP Central Venous Pressure.

DBP Diastolic Blood Pressure.

EDPVR End-Diastolic Pressure–Volume Relationship.
ESC European Society of Cardiology.
ESH European Society of Hypertension.
ESPVR End-Systolic Pressure–Volume Relationship.

GWA General Ward of Cardiology A.
GWB General Ward of Cardiology B.

HR Heart Rate.

ICU Intensive Care Unit.
IEC International Electrotechnical Commission.
IFMBE International Federation for Medical and Biological Engineering.
IOS International Organization for Standardization.

LAA Linear Approximation Algorithm.
LVEDP Left-Ventricle Ejection End-Diastolic Pressure.

MAA Maximum Amplitude Algorithm.
MAE Mean Absolute Error.

MAP Mean Arterial Pressure.

NCD Noncommunicable diseases.

OMW Oscillometric Waveform.
OR Operation Room.
OWE Oscillometric Amplitude Envelope.

PPG Photoplethysmogram.
PPW Pulse Pressure Wave.
PV Pressure-Volume.

QQ Quantile-Quantile.

RMSE Root-Mean-Square Deviation.

SBP Systolic Blood Pressure.
STD Standard Deviation.
SVA Slope Variation Algorithm.
SVR Systemic Vascular Resistance.

WHO World Health Organization.

1

Introduction

This thesis addresses the problem of blood pressure monitoring in current clinical practice. A clinical investigation was conducted to assess what are the main problems and opportunities of intervention in this scope. Also, a comparative analysis was made to non-invasive blood pressure estimation algorithms, aiming at evaluation of their performance in different clinical contexts.
In this chapter we present the thesis motivation (section 1.1), followed by section 1.2 that describes the main contributions and their relevance and section 1.3, where thesis organization is presented.

1.1 Context and Motivation

"Cardiovascular diseases (CDV) are the number 1 cause of death globally, taking an estimated 17.9 million lives each year.", according to World Health Organization, in 2020. A CVD is defined as a group of disorders of the heart and blood vessels, including hypertension, heart failure, coronary heart disease, and several other conditions. WHO predicts that CVDs are still going to be the leading causes of death in the future, and estimate that, by 2030, an increase on deaths up to 23-24 million people [8]. In 2013, WHO and 194 countries agreed on a list of global mechanisms to reduce the number of premature deaths from noncommunicable diseases (NCDs), also known as chronic diseases, by 25% by 2025. The focus of this agreement comprises four principal NDCs - cardiovascular diseases, cancer, chronic respiratory diseases and diabetes. The sixth target in the Global NCD action plan calls for 25% reduction in the global prevalence of raised blood pressure [9].
Blood pressure (BP) is an essential parameter in the assessment of a patient's cardiovascular status. In clinical practice there are two principal measurement technologies available with inherent limitations and boundary conditions. Invasively measured BP, artery catheter, here forward referenced as Arterial Blood Pressure (ABP), is considered the gold standard technique, offering reliable BP monitoring with a high resolution in time and pressure. Systolic, mean and diastolic BP are provided on a beat-by-beat basis. Arterial catheterization is mainly restricted to acute patients and special hospital settings (Operation Room and Intensive Care Unit). Given the invasiveness of ABP, it needs trained personnel and it is associated with infections and other complications. Therefore,

its use tends to be minimized. As an alternative to ABP there is the non-invasive blood pressure (NIBP) measurement technology, based on oscillometry using cuffs, and it is typically applied at lower risk patients. This technique allows intermittent BP measurements currently at fixed intervals, which can lead to missed critical phases of hypotension or hypertension. Another drawback is its lower accuracy. Given these limitations observed in NIBP, research in continuous NIBP measurements and alternative technologies has been ongoing for decades [10].
Intermittent NIBP is an often-used measurement technique that can be described from an engineering perspective as a sampling problem of a signal – here the patient's blood pressure - with varying unknown frequency content. There is an obvious interest in having non-invasive intermittent measurements with an accuracy closer to the invasive measurement performance and adaptive measurement intervals. Clinical drivers comprise e.g., early detection of critical states to trigger interventions on time, improved tracking and documentation of medication therapy, reduction of infections as well as improved patient sleep and comfort.

1.2 Contributions and Relevance

In this thesis we investigate and interpret the current intermittent NIBP monitoring, aiming to improve both diagnosis and treatment of CVDs.
We conducted several interviews in a cardiology department, followed by shadowing work of health professionals. From this investigation resulted a detailed report on current clinical practice regarding blood pressure monitoring in different acuity settings and clinical contexts. Furthermore, a list of current gaps and opportunities of intervention was presented. This work was submitted for the 8th European Medical and Biological Engineering Conference and accepted for presentation and publication in International Federation for Medical and Biological Engineering (IFMBE) proceedings.
In a second part of this thesis, we analyse four algorithms that estimate BP non-invasively, three using oscillometry and one using palpation method. The comparative analysis here described has the purpose of highlight the principal features that affect algorithm's performance, and not to elect the best algorithm.

1.3 Thesis Organization

This thesis is outlined as follows:
Chapter 2 – Physiological Background
This chapter describes the physiological context that underlies this thesis. Concepts addressed are cardiovascular system, cardiac function, vascular function and cardiovascular pathophysiology.
Chapter 3 – Literature Review
In this chapter the state-of-the-art of the current assessment of blood pressure is described,

both invasive and non-invasive. Also introduces how photoplethysmogram is being investigated as an innovative contribution to assess blood pressure non-invasively.

Chapter 4 - Intermittent Non-Invasive Blood Pressure Measurement: Gaps and Clinical Needs

In this chapter we report the investigation conducted in a cardiology department to assess the current gaps and needs in clinical practice. It describes how the interviews were designed and performed, and the results and conclusions of the investigation are presented.

Chapter 5 – Methods

This chapter initiates the second part of this thesis, where NIBP estimation algorithms are comparatively analysed. It is described how pre-processing and segmentation of signals were performed. Also, the feature extraction process for invasive and non-invasive signals is presented. Finally, the algorithms are detailed and a new approach to palpation algorithm is described.

Chapter 6 – Results

This is the chapter where results from NIBP estimation algorithms implementation are presented, and a comparative analysis is performed. It is also discussed how patients' tension profile can impact the algorithms performance.

Chapter 7 – Conclusions and Future Work

This chapter summarizes the main findings and outlines further research directions.

2

Physiological Background

2.1 Cardiovascular System

For a living cell to perform its activities it is required the supply of metabolic substrates – such as glucose, oxygen or amino acids – and the elimination of the products of its metabolism – carbon dioxide, lactic acid or heat, for instance. In small organisms, this transfer occurs directly, since all cells are relatively exposed to the external environment. On the opposite, large organisms need complex systems that facilitate the circulation of gases, fluid, electrolytes large molecules and heat between cells and the outside environment, as is the case of human beings [3].

This exchange is assured by the cardiovascular system, that is composed by the heart, the blood vessels and the lymphatic system.

The right and left sides of the heart are separated by the pulmonary and systemic circulations, and therefore the blood follows an in-series circuit. The pulmonary circulation is the blood flow within the lungs that is involved in the exchange of gases between the blood and alveoli. The systemic circulation is comprised of all the blood vessels within and outside of organs excluding the lungs [3].

This in-series relationship implies that the volume of blood ejected from each side of the heart per time – defined as cardiac output – closely matches the volume of blood ejected from the other side, in order to avoid major shifts of blood between pulmonary and systemic circulations. On the other side, the circulations of most major organ systems are arranged in parallel, as the blood flows to the body from aorta (arterial system) and returns to the heart by the superior and inferior vena cava (venous system). This parallel arrangement is designed to prevent that blood flow changes in one organ significantly affect blood flow in other organs [3].

As blood flows through organs, some of the fluid is filtrated by the lymphatic system. The lymphatic vessels collect the excess fluid from within the tissue interstitium, that is then filtered in the lymph nodes and returned to the venous circulation. This process has the purpose to produce and supply different types of the white blood cells for immune function, remove excess fluids from body tissues and to absorb fatty acids [3].

The maintenance of the hemodynamic balance depends on several well-designed parts of

a complex system, described in detail in the next sections.

2.2 Cardiac Function

2.2.1 Functional Anatomy of the Heart

The heart is composed by four chambers: right atrium, right ventricle, left atrium and left ventricle. The atria receive blood returning to the heart and pump it to the ventricles, which consequently pump the blood into the systemic and pulmonary circulation. Valves located at the entrance and exit of both ventricles conduct the blood circulation within the heart – the atrioventricular valves, mitral and tricuspid, and the semilunar valves, aortic and pulmonary [1].

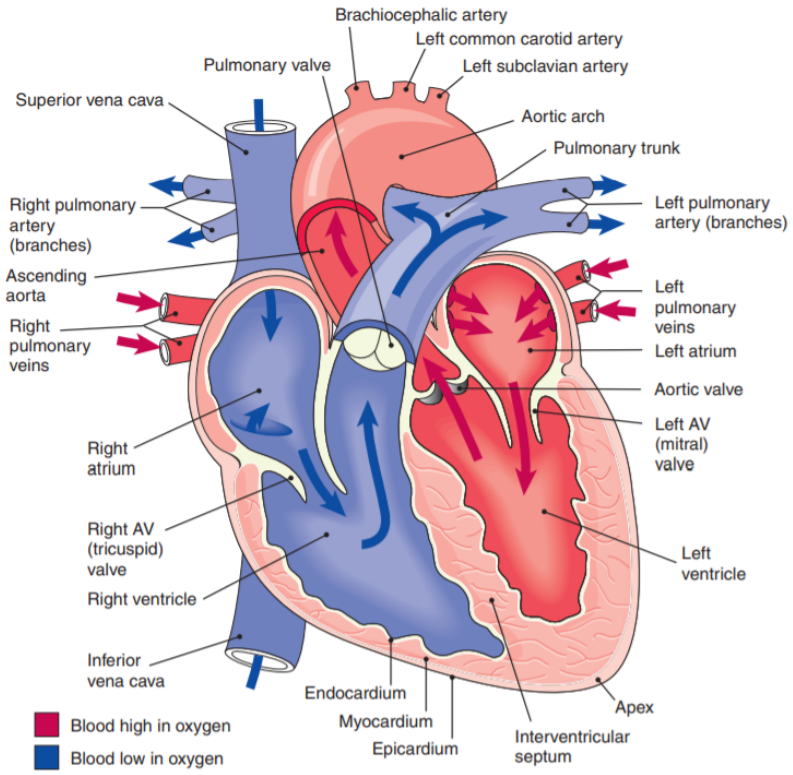


Figure 2.1: Heart chambers, valves, and direction of circulatory flow. Adapted from [1].

Arterial blood, so-called after receiving oxygen in the lungs, enters the left atrium by way of the pulmonary veins. Blood flows from the left atrium, across the mitral valve, and into the left ventricle. The left ventricle has a thick muscular wall that allows it to generate high pressures during contraction. It ejects blood across the aortic valve and into the aorta, from where it is pumped to all cells, via the arterial system (arteries, arterioles and capillaries). In capillaries, blood transfers the needed metabolic substrates to cells and receives the respective metabolic products, and it is now called venous blood. Venous blood returns to the heart by the venous system (capillaries, venules and veins), entering

in the right atrium via large systemic veins (the superior and inferior vena cava). The right atrium is a highly distensible chamber that can easily expand to accommodate the venous return at a low pressure. Blood flows from the right atrium, across the tricuspid valve, and into the right ventricle, from where it circulates across pulmonary valve into the lungs, via pulmonary arteries, where it receives oxygen and repeats the cycle [3].
The tricuspid and the mitral valves have fibrous strands (chordae tendineae) attached to papillary muscles, located in the ventricular walls. These muscles contract simultaneously with ventricles, generating tension that prevents the valves to open and blood to return to atria, consequently. This is fundamental to maintain a unidirectional blood flow in the heart [11].

2.2.2 The Cardiac Mechanical System

The pumping action of the heart is divided into two phases: systole, when the ventricles contract and eject blood from the heart, and diastole, when the ventricles are relaxed and the heart is filled with blood [12].
Pressure and volume fluctuations inside the heart are well known and can be described by the Pressure-Volume (PV) loop diagram (presented in Figure 2.2). The following description applies to the left side of the heart, but the right side presents similar behaviour [12].

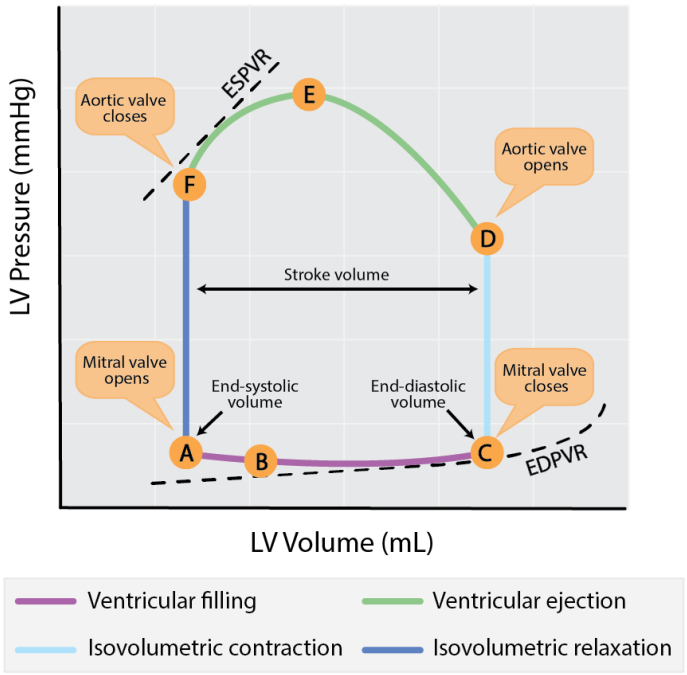


Figure 2.2: Work diagram (pressure-volume loop) of the left ventricle. Adapted from [2].

A single PV loop is the summation of the pressure and volume behaviour that occurs within a single ventricle during a cardiac cycle. Point C represents the end of diastole.

The ventricle is as its maximum full, and systole is about to begin. When the ventricle starts to contract, the mitral valve closes, and we move in the diagram to point D. The transition between points C and D represent an iso-volumetric contraction, since there is a change in pressure with constant volume. When the pressure in the ventricle exceeds the pressure in aorta, the aortic valve opens, entering the ejection phase, represented between points D and F. From point D, the pressure is still being generated through the ejection phase until it peaks the systolic pressure, in point E. As the ventricle exhausts its capacity to contract and begins to relax, the pressure within the chamber drops until is lower than the pressure in the aorta, that is when aortic valve closes. Systole has now ended, and diastole is starting, so this moment is defined as the end-systolic pressure volume point. As the ventricle relaxes but all valves are closed, pressure within the ventricle drops at a constant volume, so this moment is defined as iso-volumetric relaxation. The pressure drops until it gets lower than the atrial pressure, at which point the mitral valve is going to open. The ventricle fills through diastole and a single heartbeat is completed [2].
The maximal pressure that can be developed by the ventricle at any given left ventricular volume is described by the end-systolic pressure–volume relationship (ESPVR). The slope of the end-diastolic pressure–volume relationship (EDPVR) at any point along the curve is the reciprocal of ventricular compliance [2].

2.3 Vascular Function

2.3.1 Blood Vessels

Left ventricle pumps blood across the aortic valve into the aorta, from where it is distributed to all cells of the body. The aorta branches into large and small arteries, that are responsible for the regulation of the blood pressure. Autonomic nerves determine these vessels constriction and dilation, establishing the amount of blood that reaches specific organs. Small arteries branch into arterioles, and those into capillaries. Capillaries are responsible for slowing down the blood velocity and enabling the exchange of substances between blood and body tissues. They converge into successively large vessels, the veins, that conduce the blood back to the heart, via vena cava [3].
The different types of vessels can be grouped by their primary function: distribution/ resistance (aorta, large and small distributing arteries), exchange (capillaries, small venules), and capacitance (large venules, veins, vena cava), described in Figure 2.3.

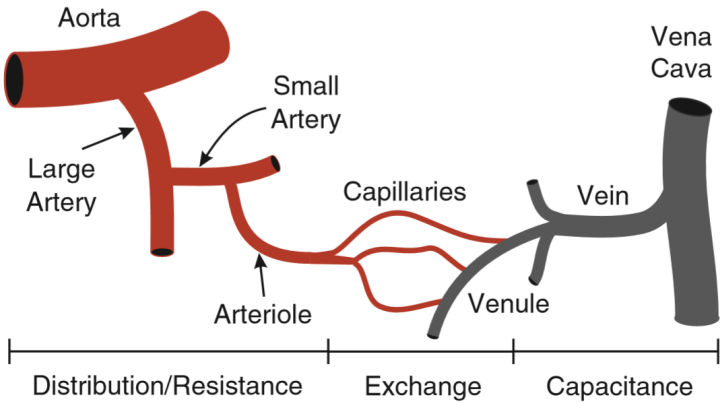


Figure 2.3: Types of blood vessels found in circulation. Adapted from [3].

2.3.2 Arterial Blood Pressure Waveform

When blood is ejected into the aorta from left ventricle, the aortic pressure rises. The maximal aortic pressure following ejection is defined as systolic blood pressure (SBP). As the ventricle is refilling with oxygenated blood from left atrium, the aortic pressure drops. The lowest pressure in the aorta, just before the left ventricle new ejection, is defined as diastolic blood pressure (DBP). The difference between the systolic and diastolic pressures is the aortic pulse pressure [12].
The average pressure during the aortic pulse cycle is defined as mean arterial (or aortic) pressure (MAP), which reflects the blood perfusion into all body tissues. MAP is determined by the cardiac output (CO), systemic vascular resistance (SVR), and central venous pressure (CVP). This relationship is expressed in equation 2.1 [3].

$$MAP = (CO \cdot SVR) + CVP \tag{2.1}$$

These values contribute to a pulse pressure wave (PPW), that reflects the pressure exerted by the blood in the arterial wall. The PPW is transmitted from aorta into arterial network. The main pressure wave (P1 illustrated in Figure 2.4) travels in aorta and it reaches two reflection sites – the first site is the juncture between thoracic and abdominal aorta, that leads to appearance of the first reflection wave (P2 illustrated in Figure 2.4); the second site is between the abdominal aorta and common iliac arteries, and causes the reflection of the main wave again, that appears as a second reflection wave (P3 illustrated in Figure 2.4) [13].
The summation of the main wave and its two reflections results in the PPW, from which SBP, DBP and MAP can be estimated. Figure 2.4 illustrates the PPW recorded at the radial artery [4].

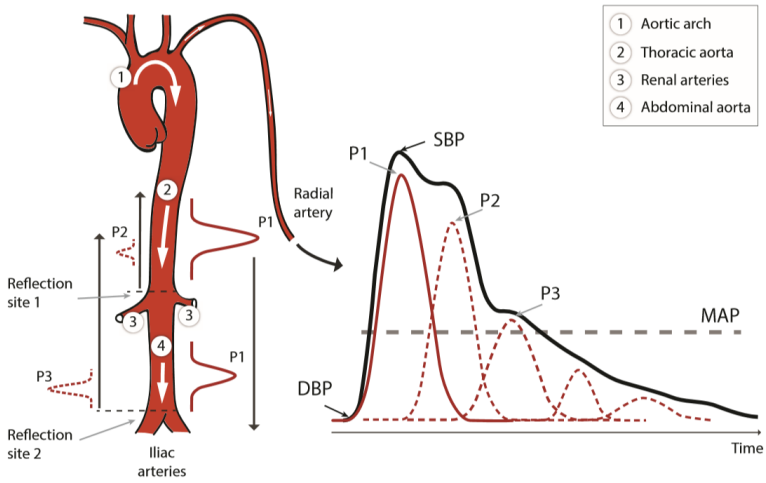


Figure 2.4: Morphology of the pulse pressure wave at the radial artery. On the left, a sketch of the arterial system from the aorta/arm to the iliac arteries. On the right, a pulse pressure wave decomposed in the corresponding forward pulse (P1) and pulses reflect at the first (P2) and second (P3) reflection sites. Adapted from [4].

2.4 Cardiovascular Pathophysiology

2.4.1 Hypotension

Hypotension is often defined clinically as a systolic arterial pressure <90 mmHg, or a diastolic pressure <60 mmHg. As MAP is influenced by both cardiac output and systemic vascular resistance, a decrease in either will reduce arterial pressure [3].
Cardiac output is the product of heart rate and stroke volume. Hypovolemia, arrythmias, heart failure and cardiogenic shock are some examples of conditions that affect heart rate and stroke volume. Circulatory shock and autonomic disfunction are causes to low systemic vascular resistance. Hereupon, hypotension is a relevant clinical sign that can be used to diagnose several pathologies of the cardiovascular system [3].
When hypotension occurs, the body attempts to restore arterial pressure by activating neurohumoral compensatory mechanisms, aiming to constrict systemic vascular beds and stimulate the heart. These mechanisms can make the diagnosis of the hypotension state difficult, since they can mask the low values for a significant period, leading to its late detection and possibly the need for more aggressive interventions [3].

2.4.2 Hypertension

Hypertension is defined as elevations either in diastolic or systolic pressures above normal values. Normal arterial pressure is defined as a systolic pressure <120 mmHg and 90 mmHg and diastolic pressure <80 mm Hg and 60 mm Hg). Diastolic pressures of 80 to 89 mm Hg and systolic pressures of 120 to 139 mmHg are considered prehypertension. Hyper-

tension is defined as diastolic or systolic pressures ≥90 or 140 mmHg, respectively [12], [3]. Hypertension can be hereditary, can reflect abnormal response to stress, and is very common in obesity and diabetes – this is defined as essential hypertension and represents approximately 90% of cases. It can also be a sign of more severe conditions, like renal disease, aortic coarctation, Cushing syndrome, among others – this is called secondary hypertension. For most people who have essential hypertension, the cause is unknown, so it cannot be targeted for correction. Whichever the cause behind it, chronic hypertension needs to be managed, since it can damage the heart, the blood vessels and other organs, such as the kidneys or the eyes [3].

2.4.3 Heart Failure

Heart failure is defined as reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress. It is characterized by typical symptoms – e.g. shortness of breath, fatigue, ankle swelling – that may be caused by a structural and/or cardiac abnormality [14].

The Frank-Starling mechanism is an intrinsic cardiac autoregulatory way to ensure that stroke volume and preload change in proportion. The Frank-Starling curve reflects the contractility of the heart – the larger the preload, the greater the contraction of the heart. When in heart failure conditions, it is possible to observe a change in the normal Frank-Starling curve. As the stroke volume decreases, the left-ventricle ejection end-diastolic pressure (LVEDP) increases, as a method of compensation (see Figure 2.5). This happens because the body is trying to maintain stroke volume, even when heart loses its inotropy [3].

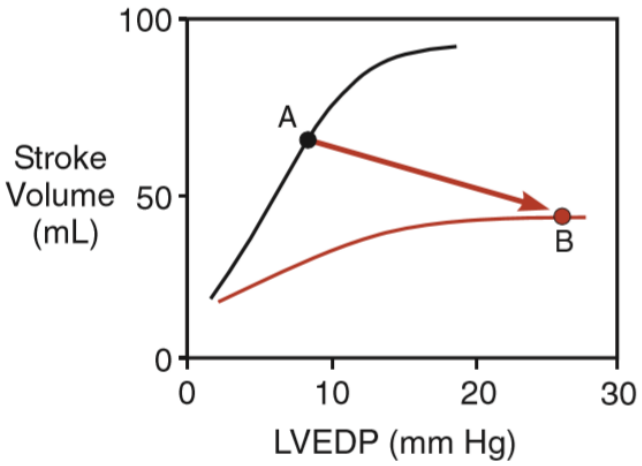


Figure 2.5: Frank-Starling curve in heart failure. Point A is control and point B is heart failure. Adapted from [3].

3

Literature Review

In this chapter, the current assessment of blood pressure in clinical practice is reviewed. Both invasive and non-invasive methods are used in different contexts, and a global analysis of the techniques is made. Only methods that are standardized and recommended for clinical practice are included in this review.
Concepts on photoplethysmogram and its potencial in contributing to BP assessment are also mentioned at the end of the chapter.

3.1 Invasive Assessment of Blood Pressure

Invasively measured blood pressure, via an artery catheter, is considered as gold standard blood pressure monitoring technique, offering close tracking of blood pressure with a high resolution in time and pressure. It is a commonly used technique in high acuity settings, such as the Intensive Care Unit (ICU) or during surgery, allowing rapid diagnoses of cardiovascular insufficiency and close track of patient's response to treatment.
The arterial line setup consists of a column of fluid that directly connects the arterial system to a pressure transducer. The pressure waveform of the arterial pulse is transmitted via the column of fluid, and it is then converted into an electrical signal. The pressure tubing must be positioned on the same level that the patients heart, to eliminate the influence of hydrostatic pressure exerted by the fluid. The arterial BP waveform is composed by the different sections of the cardiac cycle (Figure 2.4). The systolic, mean and diastolic BP are provided on a beat by beat basis, through a continuous pressure curve. Also, the analysis of the waveform allows further information about the patient's cardiovascular status to be gained (pulse contour analysis). The shape of the arterial waveform is conditioned by the closure of the atrioventricular valves, the differences in compliance/stiffness of the artery and wave reflections. These parameters vary among population according to age and/or physiological conditions such as hypotension, obesity or artery stiffness, and therefore can add significant value to diagnoses [15].
Invasive monitoring is required when patients are likely to have sudden changes in their hemodynamic status. This scenario could happen, for instance, during a vascular surgery, in high acuity settings or when treatment involves drugs that have an impact on blood pressure, like inotropes. This technique allows accurate BP readings during hypotensive

state, and on patients that are not suitable for non-invasive measurements, as morbidly obese patients or patients with gross peripheral oedema [16]. The implementation of this method needs trained personnel, requires significant time to get operational and poses the risk of infections, as well as compromises patient comfort. For these reasons, its use tends to be minimized and non-invasive techniques are preferably used [16].

3.2 Non-invasive Assessment of Blood Pressure

Non-invasive assessment of blood pressure can be done both manually, by palpation or auscultation, and automatically, using oscillometric method or cuffless techniques. Automated techniques are becoming the preferential procedure, because they are less prone to human reading and interpretation errors, they do not require calibration and because they allow patients to measure blood pressure outside clinical settings. This is especially significant in chronic hypertensive patients, whose tension profile is an important feature to track the evolution of their clinical condition. The possibility to monitor blood pressure without needing clinical professionals also facilitates the management of human resources in medium and high acuity clinical settings. Besides, it contributes to improve significantly the accuracy of BP readings in low and middle-income countries, where there is a lack of access to both affordable devices and qualified staff.
The most common blood pressure monitoring method in clinical practice is the oscillometric, that is automated or semi-automated, intermittent and non-invasive. An air-filled cuff is positioned in the upper arm and is inflated, until the artery occludes (Figure 3.1). At this point, a slow deflation starts, the blood flow returns, and the resulting cuff pressure oscillations are recorded, from which systolic, diastolic and mean blood pressures values are estimated. These estimations are made using a large variety of algorithms, that are usually secret and vary across devices' brands. This method is easy to apply, is non-invasive, and provides an estimation of mean blood pressure, just to name a few advantages. On the other side, its accuracy can be compromised by movement artifacts, and even by some clinical conditions, like hypotension or arrythmia [17], [18].

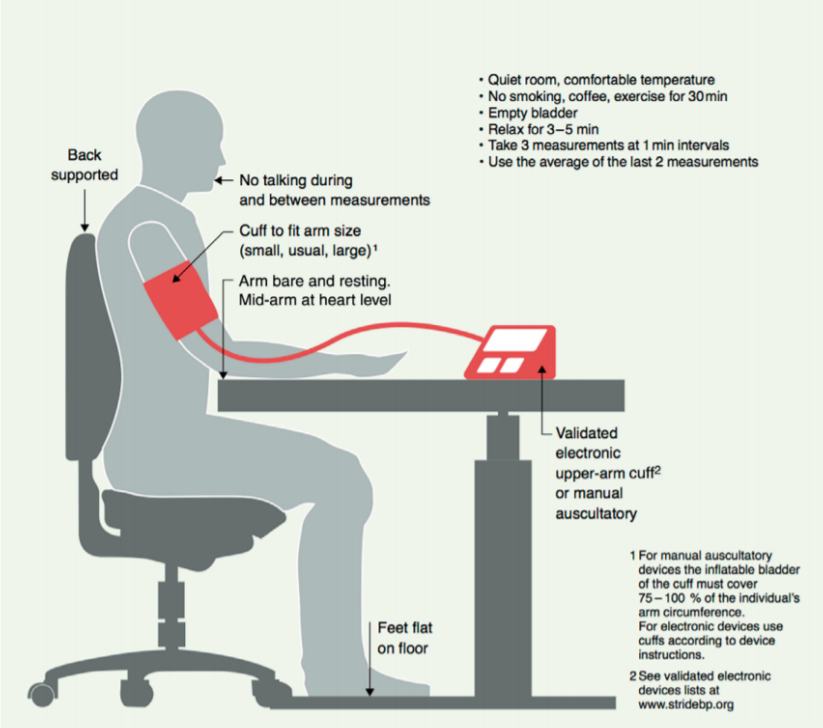


Figure 3.1: Instructions on how to measure blood pressure. Adapted from [5].

There are also automated devices that use Korotkoff sounds to estimate BP, containing a microphone that is positioned against the compressed artery. This auscultatory methods provide more accurate readings of SBP and DBP when compared to oscillometry. However, the technique is very sensitive to noise and movement artifacts, depending on silent environments and requiring more complex signal processing [19], [20], [21].

Whichever method is being used to assess blood pressure, its safety and accuracy are the priority concerns. An inaccurate device can compromise both diagnosis and treatment, having serious human and financial consequences. Non-invasive techniques are less accurate than the invasive ones and besides they only provide intermittent readings, which could lead to miss important BP oscillations and consequently the right time of intervention.

To commercialize devices and algorithms and use them in clinical practice, quality management must be ensured. There are institutions responsible for standardization and regulation, namely The International Electrotechnical Commission (IEC), the International Organization for Standardization (IOS), the American National Standards Institute (ANSI), the Association for the Advancement of Medical Instrumentation (AAMI), the European Society of Hypertension (ESH), among others. The World Health Organization (WHO) refers in its most recent report on the subject "WHO technical specifications for automated non-invasive blood pressure measuring devices with cuff" [22], that the pursuit of accuracy of BP measuring devices has been an issue for the past 100 years. According to AAMI/ESH/IOS, *"a device is considered acceptable if its estimated probability of a tol-*

erable error (≤10 mmHg) is at least 85%" [23].
Alternatives for blood pressure measuring devices with cuff have been suggested in the past few years and a lot of researchers are working on its development and improvement [24], [25], [26]. None of these new technologies have been regulated nor standardized, so they cannot yet be recommended for clinical use [22].

3.3 Photoplethysmography and BP assessment

Photoplethysmogram (PPG) is a non-invasive method for measuring the amount of light that is absorbed or reflected by blood vessels in living tissue. The PPG signal is responsive to changes in the volume of the blood, rather than the pressure of the blood vessels. By measuring the light absorption, it is possible to estimate the volume of blood in the sensor coverage area. This estimation is based on the Beer-Lambert law - if a homogenous layer of blood lies perpendicular to a beam of light, light intensity decays exponentially as a function of distance [27]. The sensor area includes both arteries and veins, so a raw PPG signal is composed by pulsatile and non-pulsatile blood volume [28]. The pulsatile component corresponds to arterial blood and its synchronous with heartbeat, so it is the most interesting component in terms of monitoring. In clinical practice, PPG is routinely used in peripheral body sites, usually in the finger, as the approximation may be more reasonable given a relatively uniform, diffuse vascular bed [29].
Photoplethysmography is commonly seen in the clinical settings of the anesthesia, critical care and emergency medicine, where pulse oximeters are widely used to infer arterial oxygen saturation (SaO2) [27], [30].
The PPG signal is morphologically similar to an arterial blood pressure waveform. In fact, for each cardiac cycle, the characteristic PPG waveform does seem modelled from the arterial pulse wave - it exhibits a dominant peak emerging from an onset/foot point, a dicrotic notch and a secondary peak (Figure 3.2).

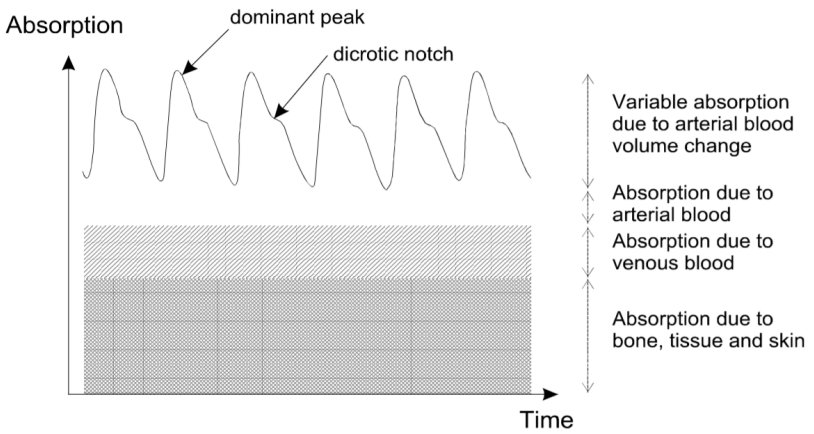


Figure 3.2: Typical aspect of the PPG signal. Adapted from [6].

Because it is a non-invasive monitoring technique, the use of PPG to estimate blood pressure has been a popular interest on research. Inspired in the palpatory method, PPG can be used to estimate SBP.
The palpatory method is a simple method that can be used to estimate systolic blood pressure. The cuff is placed on the patient arm and inflated until the pressure inside the cuff is 30 to 40 mmHg higher than pressure where no pulse can be felt. Then, the cuff is slowly deflated, and the systolic pressure is taken as the pressure point where pulse wave can be felt again. This technique requires a clinical professional to detect the pulse reappearance and read the corresponding pressure value. When inflating a pressure cuff, the PPG signal disappears as the artery occludes. This suggests that this pulse can be detected automatically using signal processing techniques.

3.4 Concluding Remarks

BP assessment is a challenging research field, and several aspects have to be considered when choosing the most appropriate technique. Although invasive methods are the most accurate, the risk of infection and need of trained personnel to its correct application are still major drawbacks for its widespread. Non-invasive measurement techniques have less complications associated, are easier to apply and are more accessible. However, its accuracy is still in need of improvement, in order to extend its use.
In the next chapter, the principal gaps and needs in clinical practice regarding non-invasive blood pressure monitoring are discussed.

4

Intermittent Non-Invasive Blood Pressure Measurement: Gaps and Clinical Needs

4.1 Intermittent NIBP Monitoring in Clinical Practice

Compared to ABP, NIBP methods are associated with lower patient risks, can be applied easily by less educated clinical staff and therefore are the routine measurement method preferred in clinical practice. ABP is typically used for high acuity patients only. Several NIBP methods are available, that can be continuous or intermittent. Continuous techniques (such as arterial applanation tonometry and volume clamp method using finger cuffs) are not commonly used because they are more expensive, difficult to apply, and e.g. susceptible to patient movements, which makes the monitoring of conscious patients challenging. Intermittent NIBP methods found widespread use regularly in clinical practice, using an air-filled occluding cuff. They can be implemented manually, by palpation or auscultation, or automated, using oscillometry. The auscultatory sphygmomanometry is considered as more accurate than the oscillometric method, being used as a reference for validation of automated algorithms. However, the use of automated methods has become more popular, since they offer the possibility of tracking BP in clinics and at home, by the patient himself, free of white coat effect [31], [32].

In clinical practice it is even more relevant to have the possibility to track BP automatically, especially if it is possible to have the BP fluctuations compared with a relevant clinical threshold, triggering an alarm that alerts the physicians about the patient degradation. The oscillometric method uses a pressurized cuff wrapped around the arm or the wrist. The cuff is inflated until the pressure is higher than the maximum blood pressure, which will cause the complete occlusion of blood circulation. Afterwards, the cuff is deflated down to a value where the blood flows freely. From the cuff pressure oscillations, mean, systolic and diastolic arterial pressure values are inferred. A measurement can take up to a minute to be complete [33], [34], [35].

The cuff measurements are done on a regular pre-defined time interval, that can be every

5, 15, 30 minutes up to 4 or 8 hours, or even only 1-2 times a day only. The frequency of measurement depends on the severity of the patient condition, on the drugs that are being administrated, among other factors. The wrong choice of this fixed time ratio can lead to missed critical phases of hypotension and/or hypertension. With that in mind, the intermittent NIBP, an often-used measurement technique, can be described/analyzed from an engineering perspective as a sampling problem.

4.2 Clinical Research - Methods

In order to assess current clinical practice of BP monitoring, interviews were conducted with medical staff, aiming to understand clinical requirements, current gaps, most relevant use cases and clinical implications. The investigation took place in a Cardiology Department. The investigation took place in Coimbra Hospital and University Centre (CHUC), namely in its Cardiology Department, between November and December of 2019, and it was approved by the Health Ethics Committee of the CHUC.
The units that integrate the Cardiology Department and that were analyzed in this study are:

- General Ward of Cardiology A (GWA) – this unit is aimed at chronic patients, namely patients with mild cardiac insufficiencies, dilated cardiomyopathies, hemodynamic alterations, among others, at patients that are recovering from a cardiac surgery or that no longer need intensive care but do not have the conditions to be discharged;
- General Ward of Cardiology B (GWB) – this unit is aimed at cardiac patients who need complementary diagnostic exams or treatments that require hospitalization. Some examples are catheter ablation of atrial fibrillation, pacemaker insertion, electrophysiological studies, just to name a few;
- Advanced Heart Failure Treatment Unit of Cardiology B (AHFTU) – this unit receives patients with advanced heart failure, i.e. patients whose condition in no longer treatable with conventional therapies and where symptom management are no longer working. These patients show symptoms like shortness of breath or palpation even at rest;
- Intensive Care Unit (ICU) – this unit is divided into intermediate and advanced care, for patients with severe heart complications, such as acute arrhythmias, heart infarction or cardiogenic shock. Usually these critical conditions are followed by organ failure, such as lung or kidney failures.

The interviewees were chosen based on the hierarchical system of the cardiology department. The selection was made with the purpose of covering all functions in the different care units of the cardiology department. A total of 12 interviewees participated in the study: 2 cardiologists and 2 nurses from GWA, 1 nurse from GWB, 2 cardiologist and 1

nurse from AHFTU and 4 cardiologists from ICU.
The interviews were semi-structured, which means that although a set of questions were prepared to guide the conversation, the sequencing and wording of those were modified to best fit the interviewee, and the space for additional comments or in-sights on participant thoughts and experiences was considered. Emphasis was taken on formulating questions in an open ended, neutral and clear way [36], [37].
The questions selected were:

1. **Decision between ABP and NIBP monitoring**

- Which patients should be monitored invasively/non-invasively for diagnosis and for therapy/intervention?
- Are there protocols to be followed?
- When is the decision to transfer between ABP and NIBP taken?
- What are the consequences for early/late decision?
- How is BP measured in low cardiac output situations?

2. **NIBP monitoring**

- How is the sampling frequency defined?
- Under which conditions do clinicians trust NIBP reading?
- What does it mean to have clinically significant blood pressure changing?
- What are the current gaps in NIBP assessment that lead to ABP monitoring?
- Are there differences between day and night monitoring?

The interviews were conducted during labor hours in a quiet room isolated from patients. Each interview lasted on average 15 minutes. During the research, it was also possible to observe several current procedures, the patients' environment, the different types of monitoring, the decision process, among others. Notes were taken on the operations in all units covered by this investigation.

4.3 Results – Current clinical practice on NIBP/ABP Monitoring

The blood pressure of all patients in the Cardiology Department is regularly measured, by default with a pre-defined standard operation protocol in each care unit. The NIBP monitoring, namely the cuff oscillometry, is the preferred method, and its regularity is pre-defined in each unit. In GWA and GWB, BP assessment is done twice a day, by nurses. In AHFTU it is done in intervals of 1 hour, in ICU in intervals of 15 minutes, and the cuff inflation is automated in both units. Both doctors and nurses can take the

decision to modify the pre-defined NIBP sampling frequency, which happens whenever a relevant clinical event occurs that suggests closer surveillance of a patient is needed. Some examples of these events are signs of decompensation (shortness of breath, cold sweated extremities, dizziness), alterations on heart rate, on blood pressure or other vital signs. There is no fixed protocol followed to measure these alterations, besides the thresholds defined in guidelines (e.g. SBP=90 mmHg).

There are also some drugs that require a more frequent BP monitoring while being administrated, in particular the ones that can have an effect in the hemodynamic response. Examples of drugs that require close surveillance are vasoconstrictors, among which stand out noradrenaline, vasopressin and angiotensin.

Invasive ABP monitoring is available in ICU and AHFTU. Patients need to be invasively monitored when they are hemodynamically unstable, either for clinical conditions or administration of drugs. Hemodynamic instability is defined as a clinical state when perfusion failure represented by clinical features of circulatory shock and/or advanced heart failure [38]. That instability is currently being assessed through vital signs and surrogates of organ specific perfusion such as capillary refill time, urine output, presence of cyanosis of the ear lobes, nose and fingertips, and of the extremities, including mottling of cool and moist extremities. According to the European Society of Cardiology (ESC), patients with acute heart failure can be classified based on levels of congestion and perfusion – warm-dry, warm-wet, cold-dry and cold-wet. Those levels from ESC guidelines are currently used in clinical practice to describe the symptoms used to assess both congestion and hypoperfusion [14].

Invasive ABP is also useful during treatment, as mentioned previously. Any drug that influences blood pressure implies its monitoring, so that the effects can be controlled, and the patient remain stable. One good example are the inotropes, whose function is to change the force of heart contractions. Inotropes are indicated in acute conditions, where there is low cardiac output (CO), such as cardiogenic shock following myocardial infraction, acute decompensated heart failure and low CO states after cardiac surgery [39]. Continuous monitoring of blood pressure allows to detect hemodynamic changes and address them rapidly, which is required to ensure patient stability.

Clinicians mentioned that the consequences for missing the right time of decision could be, in case of transition from ABP to NIBP, hemorrhagic complications (especially in the ICU) and overstay on high monitoring settings. If the decision concerns the transition from NIBP to ABP, the consequences could be cardiogenic shock, several side effects derived from prolonged hypotensive state or more complex interventions due to longer time of instability. It is clear that delaying the transition implies significant human and financial costs in both situations.

4.4 Discussion – Current Gaps and Opportunities for Intervention

From the shadowing work at the hospital and the interviews conducted with medical staff, it was possible to identify some of the principal gaps in the current clinical practice related with BP monitoring.

4.4.1 Reliability of NIBP reading

Results show that clinicians find surrogate measurements, like urine output or signs of unconsciousness, more relevant than BP variations/trends to assess patient stability in critical situations. Being BP such an important vital sign that it is always being monitored, why is it not being used to support clinical decision, particularly when to transfer a patient from NIBP to ABP or vice-versa?
It is, then, important to understand how this decision would be made based on BP trends or values alone. According to clinicians, the transition from ABP to NIBP would happen once the patient is stabilized, i.e., when the patient's blood pressure regulation is able to guarantee normal perfusion and tension values. On the other hand, the insertion of an arterial line would take place first, when blood pressure dynamics suggest relevant changes in the hemodynamic state, and second when NIBP measurements are no longer reliable. Hereupon, when can NIBP reading be trusted, or not?
In cases of low cardiac output, the body compensates by leading the blood vessels to constrict. Constriction of venous (capacitance) vessels increases venous blood pressure and consequently the cardiac preload and output. Due to this response, physicians prefer ABP measurement in these cases, considering that there are no metrics to ascertain the reliability of NIBP reading.
Besides the aforementioned, according to Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO), *"a device is considered acceptable if its estimated probability of a tolerable error ($\leq$10 mmHg) is at least 85%"* [23]. That means that even when nothing else is affecting the accuracy of the measurement, oscillometric measurements exhibit an intrinsic accuracy limitation. In situations close to critical thresholds, this error can be highly significant. It would be extremely valuable to improve NIBP accuracy, in order to extend its use and to delay or even avoid the transition to ABP.

4.4.2 Relevant changes in BP dynamics

According to most interviewees, variations of $\pm$20mmHg relatively to the normal tension profile of the patient require close surveillance. Nevertheless, there are situations where events with lower amplitudes than 20mmHg need to be taken into consideration as well. For instance, if the patient is decompensating close to a relevant value of considerable unstable blood pressure, hypotensive events can be critical, and therefore clinicians need

continuous BP monitoring.

In Figure 4.1 it is shown an intermittent NIBP measurement with a fixed-time interval of 10 minutes, compared to continuous invasive BP monitoring. It reflects the zero-order-hold approach that is currently being used in clinical practice, which means that the value read is considered continuous until the next measure. It is possible to see that there are BP drops clinically relevant that remain undetected. Thus, it is here demonstrated the need for adaptive sampling that follows the changes in BP dynamics, i.e., that adapts to the dynamics of blood pressure regulation.

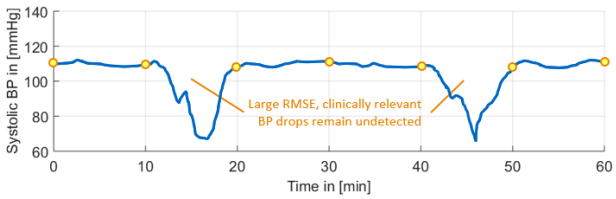


Figure 4.1: Illustration of NIBP spot-checking as a zero-order-hold sampling problem. Yellow dots represent NIBP measurements and blue line represents invasive BP monitoring.

In Figure 4.2 it is shown the impact that having adaptive sampling frequency could have, both on detecting BP dynamic changes more accurately, but also on contributing for patient comfort, by having longer intervals with no measurements when the BP is considered stabilized. Both Figure 4.1 and Figure 4.2 do not represent real measurements, being used for illustrative purposes only.

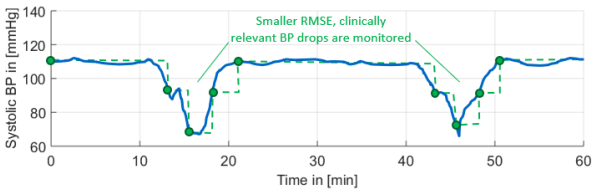


Figure 4.2: Illustration of how using adaptive sampling frequency would improve BP tracking. Green dots represent NIBP measurements and blue line represents invasive BP monitoring.

4.4.3 Personalization of thresholds

There are several thresholds for generating alarms already defined in the guidelines (e.g. MBP=65mmHg, SBP=90mmHg), which are certainly valid, and their importance is widely recognized. Nevertheless, during this research it was frequently mentioned that relevant thresholds are patient specific and hence there is a need for personalization. This means that there are individual factors that can influence the normal BP profile of a patient, namely comorbidities, drugs that are being administrated, performed procedures, among others. Indubitably, professionals are aware of this individualization and are dealing with

it, keeping records of clinical history of the patient and trusting in previous experience. Nurses, especially, are the ones responsible for knowing the patient history and to identify potential decompensations using this knowledge. For instance, if a patient has been diagnosed as hypertensive, they acknowledge that the SBP threshold for hypotension is probably higher than 90 mmHg in that particular case.
The alarms are programmed within the guidelines' values. It would be extremely valuable to have these personalized thresholds automatically defined, leading to better definition of the right time of intervention, not only for decision between monitoring methods, which would contribute for improving diagnose and treatment on its own, but also for predicting decompensations.

4.4.4 Other findings

It was found that there are no standard protocols defined to alter the sampling frequency of NIBP monitoring - changes are empirically made, i.e., they are performed based on clinician's experience and, therefore, are clinician dependent. Furthermore, the need for trained staff to apply an artery catheter can also delay the transition from NIBP to ABP, which urges the need to detect dynamic changes.
Every so often the pressure on clinical staff and the inherent bustle of the emergency unit may cause that the monitoring is not applied in the most adequate mode, or that the right timing of intervention is missed. This could also happen during night monitoring where, according to this investigation, fewer human resources are available, and the sample frequency is shortened.

4.5 Conclusion

The goal of this work was to identify current gaps and needs in clinical practice regarding the BP monitoring. Several interviews with healthcare professionals were performed, followed with shadowing of clinical procedures and decisions processes. Some opportunities of intervention came up as results from this research, which are summarized in Table 1. Working on these opportunities would be extremely valuable for supporting the decision on transferring from NIBP to ABP and vice-versa, this being clinically relevant both in diagnosis and in treatment.

Gap	Opportunity
NIBP measurements are being made with fixed-time intervals. This leads to missing rapid dynamic changes in BP, which can cause delay in medical intervention, resulting in patient deterioration. On the other hand, unnecessarily short sampling intervals has an impact on patient comfort and stress.	Adaptive sampling frequency.
There are individual factors that can influence the normal BP profile of a patient, namely comorbidities, drugs that are being administrated, performed procedures, among others.	Identify potential decompensations e.g., using BP monitoring profiles.
Alarms are programmed with values from guidelines.	Patient-specific and patient-safe thresholds automatically and interactively defined.
Oscillometric measurements exhibit an intrinsic accuracy limitation.	Improve NIBP accuracy.
Wrong timing of decision between methods can lead to hemorrhagic complications(especially in ICU), overstay on high monitoring settings, cardiogenic shock or other dangerous conditions, more aggressive interventions.	
The need for trained staff to apply an artery catheter can delay the transition.	

Table 4.1: Current gaps and opportunities of intervention in clinical practice.

5

Signal Processing - NIBP Methods

After literature review and after the clinical research reported in Chapter 4, it is evident that accuracy of NIBP monitoring methods is one of the principal concerns of health professionals, and its improvement still needs to be addressed by researchers. In light of this, a comparative analysis of different algorithms was performed. Three oscillometric methods and two variations of a palpation method were tested to estimate blood pressure, using invasively BP measurements as reference. In this chapter, the methodological steps implemented in this thesis are detailed. Furthermore, the data used in the implemented experiments is also thoroughly presented.

Study Dataset

The data used in this study were collected at the Elisabeth-Tweesteden Ziedkenhuis hospital in Tilburg, NL, from 15 patients (5 females), during surgery in the OR. The access to the data was provided by Philips Research, in Eindhoven, NL. The data acquisition was prior to this research.
The patients had an age range from 23 to 91 years (μ=62.0, σ=21.4). The surgeries were vascular (8) and neuro (7), with lengths between 1.4 and 7.6 hours (μ=5.3, σ=1.8). All patients had their BP monitored using both intermittent non-invasive and continuous invasive methods. Signals recorded were ABP, pressure from the inflatable cuff used to measure BP non-invasively and PPG. Data were recorded at a sampling rate of 125Hz. The recordings were started immediately after the arterial line was placed, when the patient was fully anesthetized and ventilated. All signals span the duration of the entire surgery until the patient is either woken up, extubated, undraped, or prepared for transport to the recovery room, whichever occurred first. The total recording duration is 79 hours [40]. A detailed description of some characteristics is presented in Table 1.

	Age	Gender	Mean HR (bpm)	Mean ABP(mmHg)	Type of surgery
Patient 1	66	F	75,43	80,43	Neuro
Patient 2	57	M	67,9	92,88	Vascular
Patient 3	68	M	65,4	99,99	Vascular
Patient 4	88	M	55,38	123,02	Vascular
Patient 5	69	M	60,53	100,03	Vascular
Patient 6	81	M	80,74	89,95	Neuro
Patient 7	44	F	79,53	89,46	Neuro
Patient 8	23	F	62,42	98,7	Neuro
Patient 9	65	M	81,18	88,78	Neuro
Patient 10	33	F	65,56	87,68	Neuro
Patient 11	70	M	56,61	86,37	Vascular
Patient 12	91	M	50,93	94,99	Vascular
Patient 13	78	M	64,03	91,31	Vascular
Patient 14	26	F	89,1	86,43	Neuro
Patient 15	71	M	52,71	109,5	Vascular

Table 5.1: Dataset.

5.1 Overview

The main methodological steps performed in this thesis are described in Figure 5.1. The fundamental steps are detailed in the next subsections.

5.2 Methods

5.2.1 Pre-processing

The goal of the pre-processing stage is to remove signal components that do not represent fundamental features or that can compromise their assessment. Following Liang [41], a 4th order low-pass Chebyshev II filter with a 20 Hz cut-off frequency was applied to PPG signal to remove high frequency components not physiologically related with PPG waveform. A 2 seconds window moving average filter was also applied to derive an approximation of the PPG signal baseline, which was subtracted from the original PPG signal. The same low-pass filter was applied to the ABP signal, considering the morphological similarities with PPG.

The first 20 minutes and the last 45 minutes of each patient recordings were discarded, since these are periods with many artifacts due to manipulations at the patient (placement of devices, turning/positioning the patient, etc.).

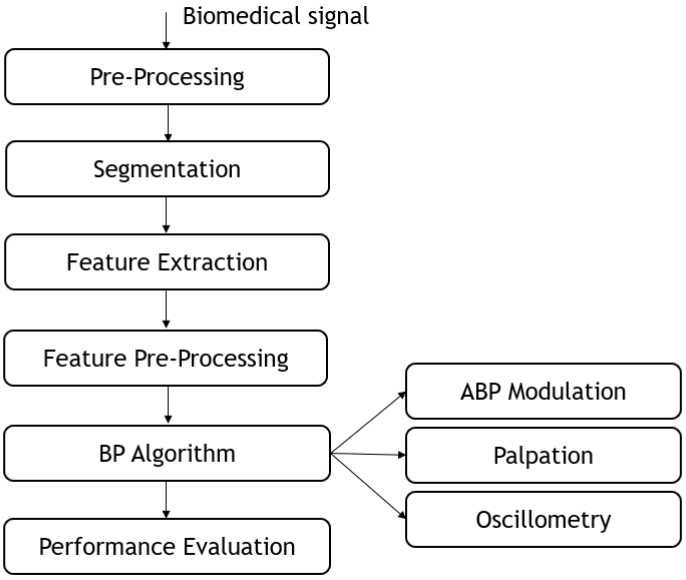


Figure 5.1: Methodological steps

5.2.2 Segmentation

As this study intends to assess non-invasive blood pressure measurement (NIBP) methods, the pressure signal was segmented into cuff inflations, each segment representing a NIBP measurement. Local maxima with minimum prominence of 100 mmHg were selected as maximum inflation points. From those points, closest minimum values were defined as onset and final moments of a measurement (Figure 5.2). Maximum points closer than 30% of the mean distance between all inflations were discarded, since they usually corresponded to noisy peaks of pressure.

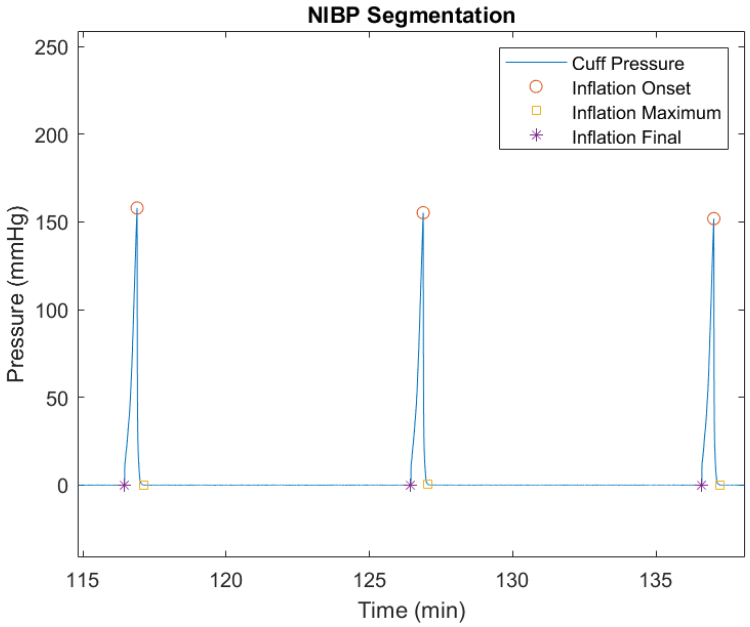


Figure 5.2: Non-invasive Blood Pressure signal – Segmentation

A visual inspection was made in order to detect outliers – inflations where the signal was corrupted with visual artifacts were not considered to be relevant for the results and were discarded. These outliers can be a result of muscle contraction, other motion artifacts during surgery or even a default in the data acquisition system.

5.2.3 Feature Extraction - ABP Modulation

5.2.3.1 Systolic Blood Pressure (SBP)

Hemodynamic pressure is the energy imparted to the blood by contraction of the left ventricle. The maximum value of this energy is measured by SBP, corresponding to the force of blood against the artery walls immediately after a heart contraction. The SBP is determined by the stroke volume, the velocity of left ventricular ejection (an indirect indicator of left ventricular contractile force), systemic arterial resistance, the distensibility of the aortic and arterial walls, the viscosity of blood, and the left ventricular preload (end-diastolic volume) [42], [43], [44]. It is, therefore, an important metric used to assess hemodynamic function of a patient. To extract this feature, ABP signal was divided into segments defined between consecutive final and onset inflation points of NIBP measurements. In each segment, local maxima were defined as SBP values.

5.2.3.2 Mean Arterial Pressure (MAP)

Mean arterial blood pressure (MAP) is the average of all values that arterial blood pressure shows during an entire cardiac cycle. MAP is defined as the product of cardiac output and systemic vascular resistance, being a clinically relevant blood pressure feature because

it measures the pressure necessary for adequate perfusion of the organs of the body. It is sensed by baroreceptors located in the carotid sinuses and the arch of the aorta. These receptors control arterial pressure mainly by adjusting heart rate and arteriolar vessel radius. MAP is also the basis for autoregulation by some organ systems such as the kidney, heart, and brain [3].
MAP is generally closer to diastolic pressure, since diastole represents about two thirds of the cardiac cycle. This relationship is expressed in 5.1 and 5.2. However, the proportion of diastole in the cardiac cycle changes with changes in heart rate. These formulas must be used with caution, since they provide a good estimate of MAP only when the heart rate is close to 60bpm.

$$MAP = DBP + \frac{SBP - DBP}{3} \tag{5.1}$$

$$MAP = \frac{SBP + 2 * DBP}{3} \tag{5.2}$$

As observed in Table 1, mean heart rate is not only patient dependent as also several times different than 60bpm. Therefore, the integration of the pressure curve corresponding to a cardiac cycle is a more accurate approach than the rule of thumb and should be preferred when invasive arterial line is available. The equation 5.3 was used, where a and b are the beginning and the endpoint of a pulse, respectively, and area is the area under curve in interval [a, b].

$$MAP = \frac{1}{b - a} * area \tag{5.3}$$

5.2.3.3 Diastolic Blood Pressure (DBP)

In spite of systolic blood pressure has been considered more relevant to diagnose hypertension and increased CVD risk, DBP has a wide clinical relevance in what concerns vascular system assessment [45]. For instance, DBP is a very important indicator of artery stiffness, a physiological condition that can contribute to a wide variety of cardiovascular and metabolic problems, like cardiac and vascular hypertrophy or target organ dysfunction. In a rigid aorta, the absence of elastic recoil causes the full stroke volume to be delivered through the resistance arterioles during systole. There is minimal or no diastolic flow, resulting in decreased diastolic pressure [46].
Diastolic blood pressure is the minimum pulsatile pressure in the arteries, the minimum occurring just before the next ventricular contraction. For each segment between two cuff inflations, the minimum value between two consecutive SBP indexes was defined as DBP. Figure 5.3 illustrates these features marked on the ABP signal.

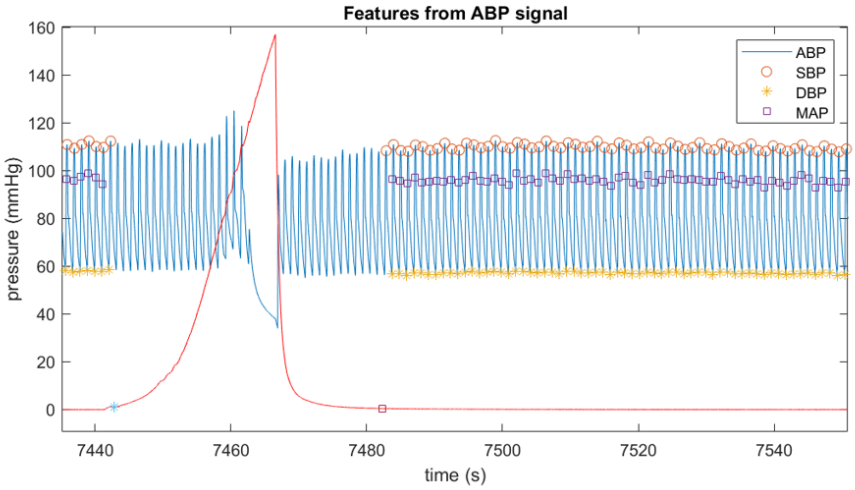


Figure 5.3: Invasive Blood Pressure Signal - Features

5.2.3.4 Blood Pressure Variability

The estimation of BP is subject to two sources of uncertainty: the first due to measurement system inaccuracy and the second due to physiological variability [47].
Arterial blood pressure shows constant fluctuations in heart rate, caused by the effects of ventilation and muscle contraction (Figure 5.4). BP variability is principally determined by the sympathovagal balance of cardiovascular regulation and it can be investigated using continuous recording of the arterial pulse waveform. These fluctuations can be easily used to augment the accuracy of NIBP measurements. Not only they can provide a confidence interval and the standard deviation to the inferred SBP and DBP, but also can be useful to detect wrong measurements and generate alarms to repeat them, if it is the case [48].

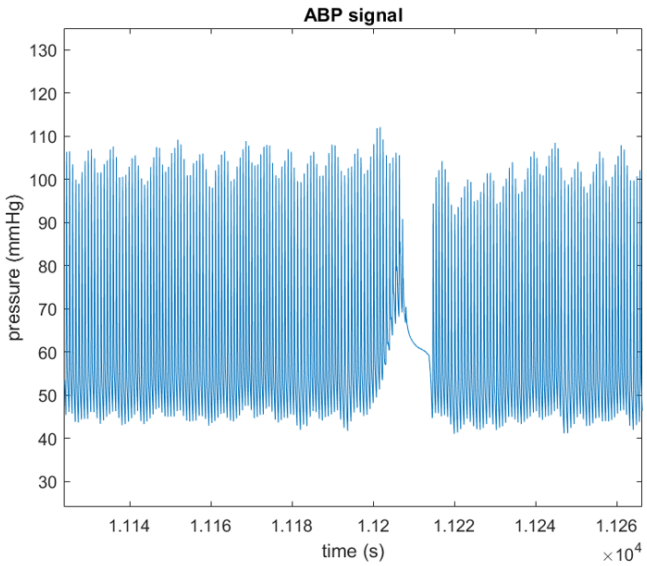
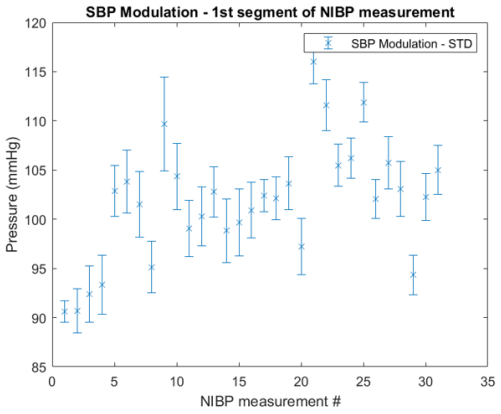
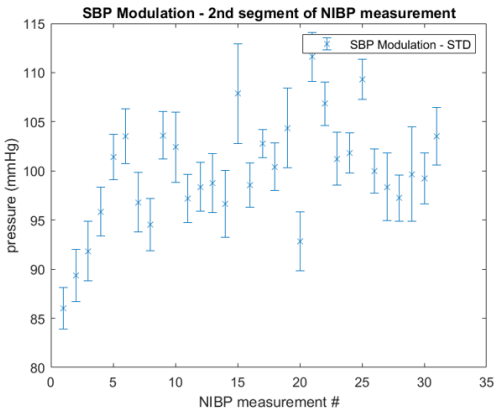


Figure 5.4: ABP Modulation - SBP fluctuations due to normal respiration and muscle contraction.

In order to consider BP variability, in this work two segments were defined for each NIBP measurement – the first segment corresponding to the 10 seconds before inflation onset and the second segment to the 10 seconds after the inflation final. For both segments, mean and standard deviation of SBP, MAP and DBP were calculated.
As an example, in Figure 5.5 is described the SBP variability of a patient in a perioperative scenario, where 31 NIBP measurements were performed. Because it is considered an interval of 10 seconds before and after an inflation to measure SBP, instead of a random moment in time, it is possible to observe that the value of SBP inferred has an STD associated, even being invasively assessed. Furthermore, it can be observed that there are NIBP measurements being performed during moments of high BP variability, which can be translated on a high STD (e.g. NIBP measurement 9) or a considerable difference between the first and the second segment of the same inflation (e.g. NIBP measurement 15).
The mean and standard deviation of SBP, MAP and DBP obtained 10 seconds before each cuff inflation will be used as a reference value to test performance of several NIBP methods. Also, the delta between the first and the second segment will be used to assess how BP variability can impact the accuracy of a NIBP measurement.



(a) Mean and STD of SBP 10 seconds before each cuff inflation.



(b) Mean and STD of SBP 10 seconds after each cuff inflation.

Figure 5.5: ABP Modulation - SBP.

5.2.4 Feature Extraction - Oscillometry

Oscillometry is based on sensing the pressure pulsations within a cuff wrapped around a patient's bicep or wrist. The cuff is inflated until the pressure is higher than the maximum blood pressure, which will cause the complete occlusion of blood circulation. From the cuff pressure oscillations, mean, systolic and diastolic arterial pressure values are inferred, for which several methods can be applied. A measurement can take up to a minute to be complete. Unlike auscultatory technique, oscillometry can be repeatedly performed by patients at home and is possible to perform it in noisy environments. These are

advantages that in clinical practice can improve both diagnosis and treatment of several conditions, which lead researchers from different areas to search for more accurate and low-cost solutions [49].

5.2.4.1 Oscillometric Waveform and Amplitude Envelope

Most oscillometric methods extract BP features over the curve obtained during the deflation period. However, in this work, the inflation period was used instead, as the signals were recorded in a perioperative scenario. Over the inflation period, the recorded pressure waveform forms a signal known as cuff inflation curve. This curve is composed of two main components: the slow-varying component resulting of the applied cuff pressure and the pulsations derived from the arterial pressure. To extract this arterial pressure – called oscillometric waveform (OMW) – a high-pass filter was used, with a cutoff frequency of 0.5 Hz [50], [51]. An illustrated example of this processing is provided in Figure 5.6, where the blue line represents the cuff inflation curve and the orange line represents the corresponding OMW.

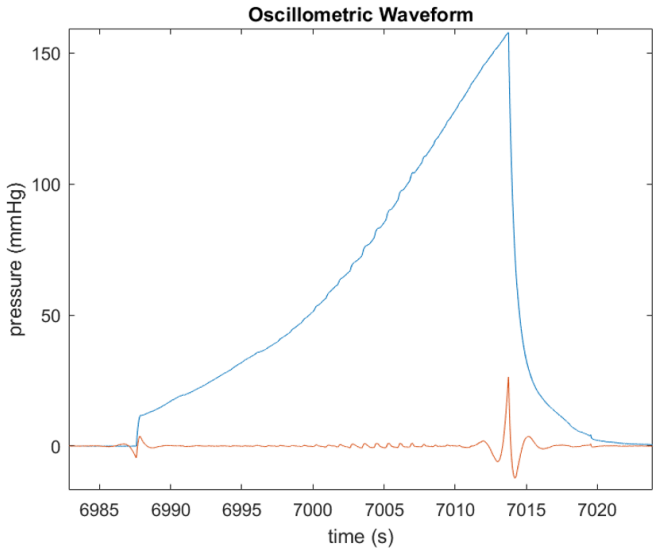


Figure 5.6: Cuff inflation curve (blue line) and extracted OMW (orange line). A close-up of the OMW is illustrated in figure 5.7.

Since most of the BP information is carried by oscillation amplitudes, the oscillometric amplitude envelope (OWE) is the most common used feature extracted from OMW [52], [53]. Following the work of Chen *et al.* [54], the envelope was obtained by subtracting the consecutive peaks and troughs of the OMW, ignoring the last three peaks, that correspond to the maximum inflation point (illustrated in Figure 5.6, in time interval [7010-7020]s). To correct for erroneous peak values that could be present in OMW, OWE was smoothed using a 5-point moving average filter [54]. In Figure 5.7) it is possible to observe an example of the OMW and the extracted OWE.

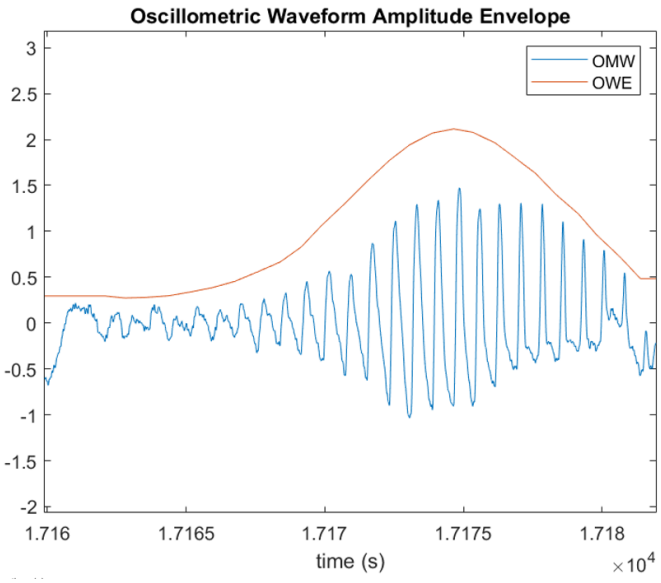


Figure 5.7: OMW (blue line) and extracted OWE (orange line).

5.2.5 BP Estimation Algorithms

5.2.5.1 Oscillometric Methods

In this work, three different oscillometric methods were analyzed, based on Chen *et al.* 2009 [54]: maximum amplitude, linear approximation and points of rapidly increasing/decreasing slope. These methods were used to extract systolic and diastolic blood pressures. The comparative analysis here described has the purpose of highlight the principal features that affect algorithm's performance, and not to select the best algorithm. The idea is to collect relevant information that could lead to design an improved algorithm using the advantages and avoiding the problems already known.

Maximum Amplitude Algorithm

The Maximum Amplitude Algorithm (MAA) assumes that arterial compliance is maximum when the cuff pressure equals the mean arterial pressure, that is, when the arterial wall is maximally distended. Based on that, the MAP is defined by locating in time the point on the cuff pressure inflation which corresponds to the maximum point of the OWE. The SBP and DBP can be identified when the amplitude of the oscillations reaches a specific fraction of the maximum oscillation amplitude. Empirically derived coefficients are used in most replications of this method, with range defined between 0.45 to 0.73 for SBP and 0.69 to 0.83 to DBP. Chengyu Liu *et al.* [55] mentioned that the maximum oscillometric pulse peak amplitude from cuff inflation was significantly higher than the obtained from cuff deflation. It was also proven that, for both normotensive and hypertensive patients, pressure widths of OWE higher than 30%, 50% and 70% of maximum amplitude obtained from inflation curve were significantly different than when obtained from deflation curve. Hereupon, in this work were tested different coefficients, and the

ones that lead to measurements better correlated with ABP were systolic coefficient 0.70 and diastolic coefficient 0.55.

Linear Approximation Algorithm

The Linear Approximation Algorithm (LAA) works under the same principle as the MAA, with the difference that the OWE is approximated by two lines of best fit – one for the systolic side and another for the diastolic side. The same characteristic coefficients of MAA are applied, this time using the lines of best fit instead of directly the OWE. This is done with the purpose of smoothing any eventual artifacts of the OMW that could lead to less accurate SBP and DBP inferences.
The LAA is performed in two iterations. In the first one, all points from OWE are used, and pairs of line of best fit are found for points 1 2 and 3 to N, with N the total number of points. Then the pair of lines for points 1 to 3 and 4 to N, until points 1 to N-2 and N-1 N. As pairs of lines are being found, the intersection point between them is recorded. After the first iteration is complete, the highest intersection point recorded is defined as MAP. In the second iteration, points of OWE smaller in amplitude than half the MAP are discarded, and the method described above is repeated for all remaining points. The new highest intersection point is defined as MAP and respective lines are also recorded (Figure 5.8). SBP and DBP points are located on these lines, using the coefficients mentioned in MAA, and then time-mapped in cuff inflation curve.

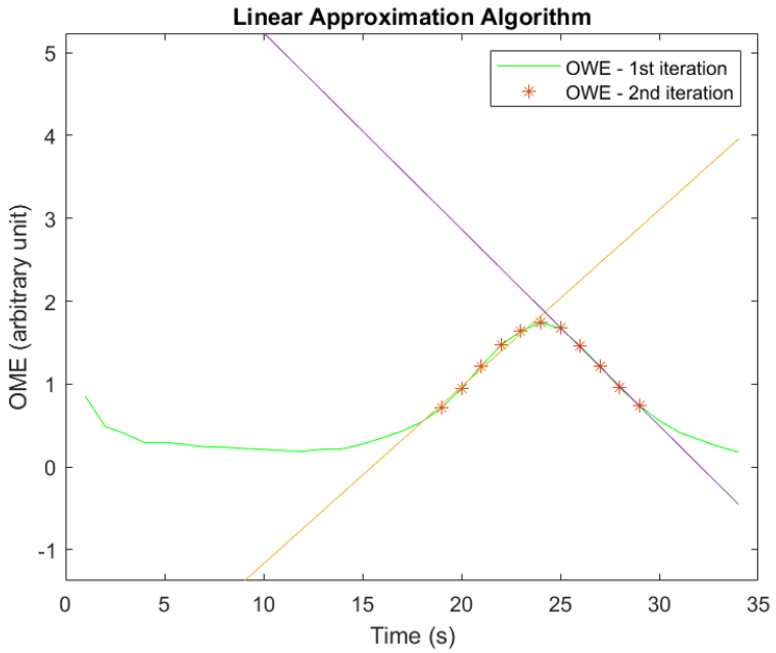


Figure 5.8: Linear Approximation Algorithm - 2nd iteration where some points are discarded, and pair of best fit lines is recorded.

Points of Rapidly Increasing/Decreasing Slope

This 3rd algorithm also uses the OWE to infer SBP and DBP but this time its slope is analyzed, instead of using characteristic coefficients – the systolic point is taken to be where the slope decreases the fastest and the diastolic point where it increases the fastest (inversely when cuff deflation curve is being used).
The points of rapidly increasing/decreasing slope correspond to the zeros of OWE second derivative or to the maximum and minimum of OWE first derivative. Hereupon, OWE was differentiated using a five-point digital differentiator (equations 5.4 and 5.5), where f represents the OWE time series, t the time index and h the sampling time, resulting in first and second order derivatives (D1, D2).

$$D1 = f'(t) = \frac{f(t-2h) - 8f(t-h) + 8f(t+h) - f(t+2h)}{12h^2} \tag{5.4}$$

$$D2 = f''(t) = \frac{-f(t-2h) + 16f(t-h) - 30f(t) + 16f(t+h) - f(t+2h)}{12h^2} \tag{5.5}$$

In this work, zeros from the second derivative are considered first and, in cases where only one or even no crossing zeros were found, maximum and minimum points from first derivative are used to replace them.
Figure 5.9) shows a plot of second derivative of the OWE in red line and the OWE in blue line. The corresponding zero crossings are represented in dashed lines. Although more zeros of second derivative may occur, only the closest to maximum OWE amplitude are selected as valid. The two points selected correspond to the index in time of DBP and SBP, being DBP the closest zero by the left side and SBP the one by the right side.

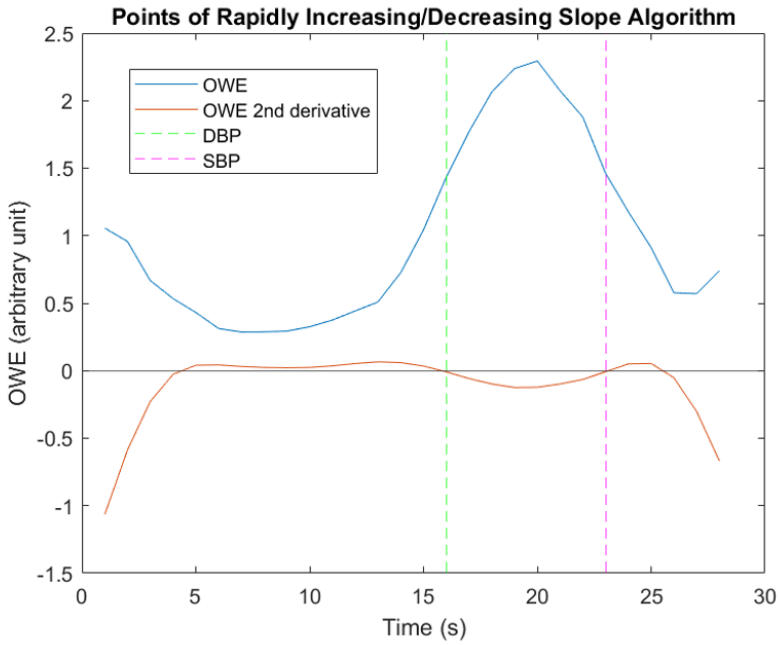


Figure 5.9: Points of Rapidly Increasing/Decreasing Slope - SBP and DBP described as zeros from second derivative of OWE.

The principal advantage of this algorithm when compared to the others described before is that it does not require any empirical coefficients. However, it is very sensitive to noise and artifacts such as movement and muscle contractions, being highly dependent on good quality signal to perform accurately.

5.2.5.2 Palpation Method

Photoplethysmography (PPG) can be used to measure systolic blood pressure at the brachial artery [56]. There is the volume clamp method, where a finger pressure cuff with a photoplethysmographic probe under it is used, and the cuff pressure is varied in time to counter the changing arterial BP during the cardiac cycle, keeping the blood volume constant. This method can provide BP pulse waveform and beat-to-beat SBP and DBP, but the accuracy of the absolute values is limited [57], [58]. Researchers have been working on another PPG-based technique, inspired on the well-known palpation method. In this method, a cuff pressure is inflated while a clinician is sensing the pulse of the patient at the radial artery - the level of pressure at which the pulse disappears and subsequently reappears during deflation is noted as systolic blood pressure [59]. PPG signal can be used to perform palpation method automatically and by non-professionals: a pressure cuff is inflated while a photoplethysmographic probe is on a distal finger; the cuff pressure correspondent to the moment where last pulse is detected during cuff inflation or the moment where the first pulse appears during cuff deflation is taken as systolic blood pressure [60]. In this work, an algorithm by Nitzan *et al.* [43] is analyzed to detect the moment immediately before the PPG signal disappears and use it to infer SBP. Nitzan *et al.* use two PPG

signals: one in the finger distal to the cuff and the other on the free hand. The second PPG signal is used to predict where the time-segments in the occluded signal would appear. In the dataset used in this work, only the PPG signal from the distal finger was recorded. In future work, the available ECG signal could be used as a signal of comparison.

PPG Pulse Segmentation and Validation

The signal was divided into time segments, from maximum derivative to maximum derivative, each suspected to contain a full PPG pulse. Equation (4) was used to differentiate the signal, this time with f representing the PPG time series.
In order to determine if a segment was indeed a valid PPG pulse, two parameters were considered: area and cross-correlation coefficient.
The area parameter intends to assess pulse waveform. Each segment was divided into sub-segments, corresponding to its first and second half. The area of the first sub-segment, *INT1*, and the area of the second, *INT2*, were calculated using the function *trapz* from MATLAB R2019b. According to Nitzan *et al.* [43], for a normal PPG pulse it is expected to have (INT1-INT2)>0. The segments that did not follow this condition were discarded. (INT1-INT2) was taken as the pulse pattern parameter PF.
The correlation coefficient (CC) was calculated between the signal in each segment and the signal in the two neighboring segments, using the function *corr2* of MATLAB R2019b. If two segments were not equal, the longer one was shortened until both have the same number of samples. PPG pulses were considered valid when CC was higher than 70% of the value of mean correlation for all segments.
Segments that followed both area and cross-correlation conditions were considered PPG pulses, marked in Figure 5.10) with yellow dots.

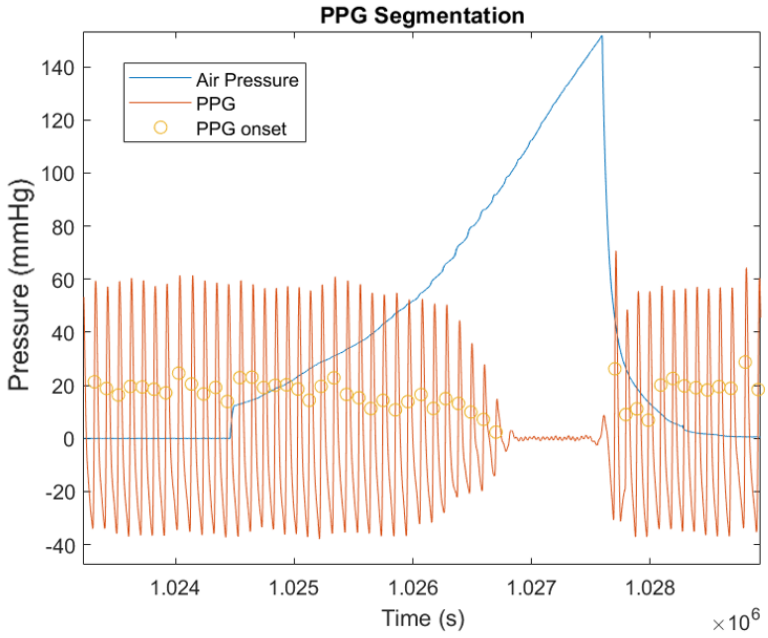


Figure 5.10: Palpation Method - PPG valid pulses.

PPG Pulse Selection

The goal is to select the last valid pulse during cuff inflation, before the signal is occluded. In Nitzan *et al.* it is argued that, according to former examinations, that pulse would be the last one of seven consecutive pulses complying with one of the following two conditions, obtained empirically:

- At least five segments had CC value higher than 0.85, and PF value higher than 1% of PI, the average value of PF for the distal finger before the inflation.
- At least five segments had CC value higher than 0.65, and for three of them PF value was higher than 7% of PI. For the other two segments, PF value was higher than 10% of PI.

Figure 5.11 illustrates an example of a PPG pulse selection after applying these conditions (pulse marked with a purple dot). The value on the cuff pressure that corresponded with the onset of the selected valid pulse was taken as SBP.

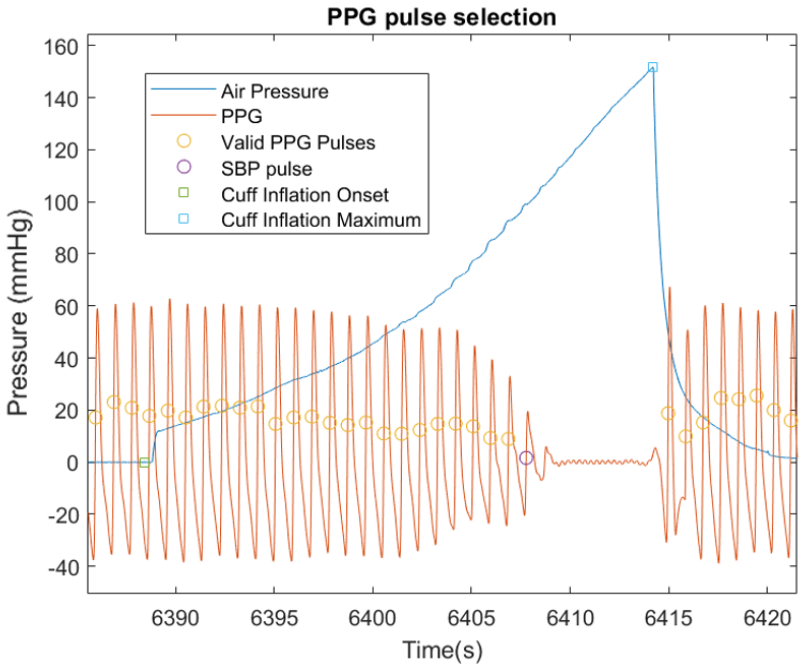


Figure 5.11: Palpation Method – Selection of the last valid pulse before artery occlusion.

5.2.5.3 Palpation Method – New Approach

When BP physiological variability is considered, a standard deviation is added to absolute values estimated with invasive arterial blood pressure, that is the gold-standard method and, therefore, it is used as reference (see Section 3.3.4.). In this dataset, the mean standard deviation of SBP estimated using ABP signal was found to be 3,34 ± 2,94 mmHg, resulting in a confidence interval [0,4-6,28] mmHg.

In Figure 5.12, a NIBP measurement is represented (blue line). On the cuff inflation curve, two values are marked – one corresponding to SBP estimated with the palpation method (Y=99,75 mmHg), and the other corresponding to SBP estimated using ABP signal (Y=112,50 mmHg). The error between the two estimations is 12,75 mmHg, that is not in the predicted confidence interval for STD of invasive estimations, [0,4-6,28] mmHg.

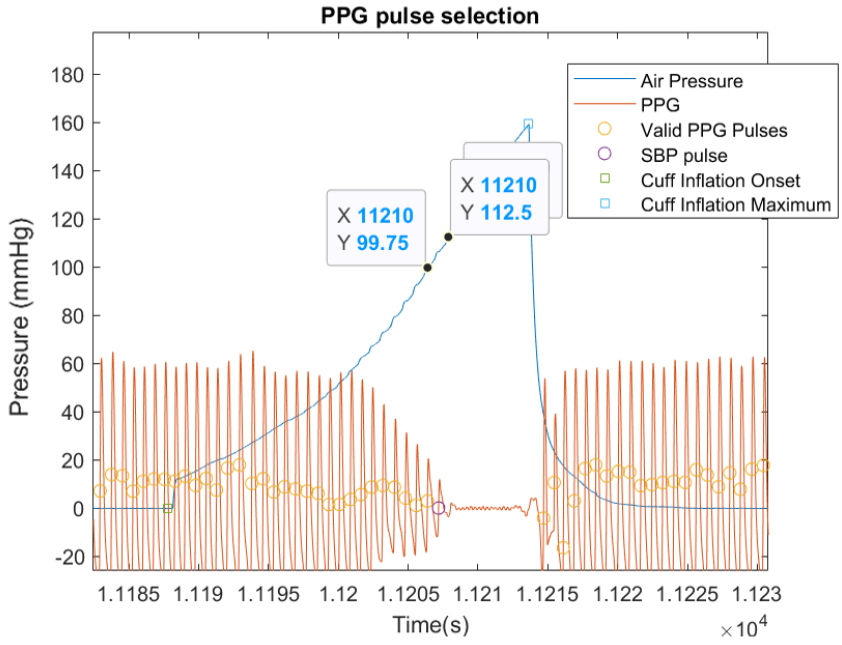


Figure 5.12: Palpation Method: Analysis of error between SBP predicted with invasive ABP and with original Palpation method.

This observation was a motivation to develop a new approach to improve the palpation method described in the above sections. The palpatory method used by clinicians is sustained on the theory that SBP would correspond to the value of the cuff pressure during inflation where the last pulse is detected before artery occlusion. As, in this algorithm, the segmentation of the PPG signal is based on maximum points of its derivative, the choice of the last valid pulse, used to time-map the SBP value on cuff inflation curve, in fact corresponds to the onset point of that pulse (purple dot in Figure 5.12). In practice, that point does not correspond to the occlusion of the artery, since an entire pulse is still detected after it. Hypothetically, the last point of the selected pulse would be more accurate to infer SBP.

To test this hypothesis, peaks of PPG pulses were interpolated, from onset of the cuff inflation curve until its maximum. The minimum point of PPG between onset of the last pulse detected and the intersection of the linear interpolation with the PPG signal would correspond to the moment in time right before the artery occlusion. In Figure 5.13 this approach is illustrated. The blue line represents ABP signal, the yellow line represents PPG signal and the green dot on PPG signal represents the point selected to time-map into cuff inflation curve. In the plot on the right side of the figure, three values are marked – one corresponding to SBP estimated with palpation method from Section 3.3 (Y=99,75 mmHg), another corresponding to SBP estimated with suggested approach of palpation method described in this section (Y=107,30 mmHg) and another corresponding to SBP estimated using ABP signal (Y=112,50 mmHg). The error between the later and the estimation that resulted from this new suggestion is 5,2 mmHg. The error of

this estimation, in particular, is approximately less 59% than the error obtained using the original palpation method and it fits into the predicted confidence interval [0,4-6,28] mmHg.

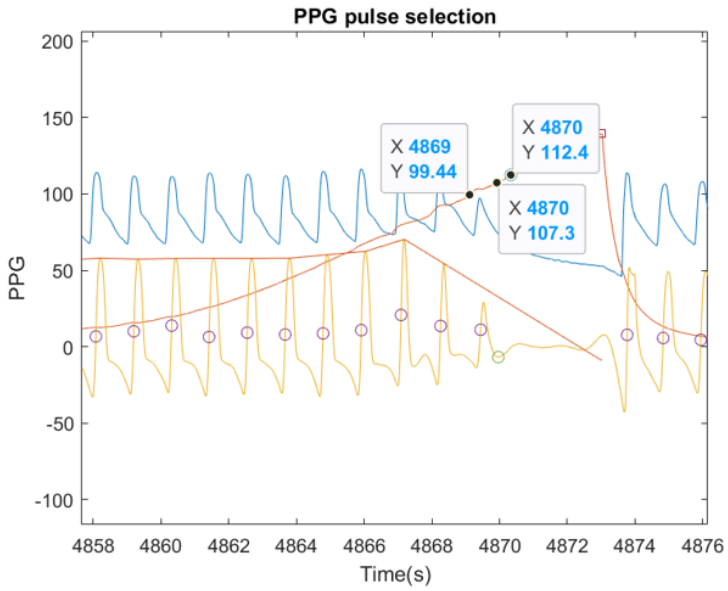


Figure 5.13: Palpation Method: Analysis of error between SBP predicted with invasive ABP, with original Palpation method and with suggested approach to Palpation method.

5.2.6 Performance Evaluation

The mean value of BP in the 10 seconds before each cuff inflation obtained from ABP signal (see Section 3.3.4) was used as reference to test the performance of all NIBP methods described above. In order to test the methods' global performance we choose standard assessment measures, i.e., the mean absolute error (MAE) and root-mean-square error (RMSE).

5.3 Summary

To summarize, for each patient, the following steps were implemented:

1. A 4th order low-pass Chebyshev II filter with a 20 Hz cut-off frequency was applied to PPG and ABP signal;
2. Segmentation of ABP and cuff pressure signals into cuff inflations, each segment representing a NIBP measurement;
3. Outliers detection and removal (inflations where signal was corrupted);
4. Mean and STD of SBP, MAP and DBP from ABP signal, obtained using intervals of 10 seconds before and after each cuff inflation;

5. Extraction of OWE from cuff pressure signal and application of a 5-point moving average filter;
6. Use of three different oscillometric algorithms to infer SBP, MAP and DBP from cuff pressure signal: Maximum Amplitude, Linear Approximation and Points of Rapidly Increasing/Decreasing Slope;
7. Segmentation of PPG signal into valid pulses;
8. Use of two different approaches of a palpation algorithm to infer SBP from PPG signal.
9. Evaluation of oscillometric and palpation algorithms performance, using BP variability extracted from ABP signal as reference.

6

Results of Algorithm Evaluation

6.1 NIBP Quality Assessment

As described in the previous chapter, a non-invasive blood pressure measurement using an inflatable cuff, is not an instant procedure. During the time that it takes for the cuff to inflate and deflate, blood pressure oscillates and can have a constant trend, as described in Section 5.2.3.4. Hereupon, the estimation of blood pressure using oscillometry or palpation methods actually corresponds to a mean value calculated over the time that the measurement lasted, instead of an instant measure as the one obtained by invasive monitoring.

Considering this, we wanted to assess how BP variability can impact the accuracy of the NIBP measurement. If we observe that the accuracy of a measurement deteriorates when it is made during a period when BP is significantly changing, that information could be relevant to conduct monitoring decisions in clinical practice.

We calculated the mean of MAP values (estimated from ABP signal, as described in Section 5.2.3.2) 10 seconds before the inflation onset and 10 seconds after the inflation final (points defined as inflation onset and inflation final are illustrated in Figure 5.2), for each NIBP measurement. Then, we defined delta as the absolute difference between the mean MAP before and after a cuff inflation. This delta intends to represent how much the BP changed in that period. To classify those periods as hemodynamically stable or unstable we built a histogram, representing the frequency of these deltas, using all NIBP measurements of all patients – a total of 420 measurements (Figure 6.1).

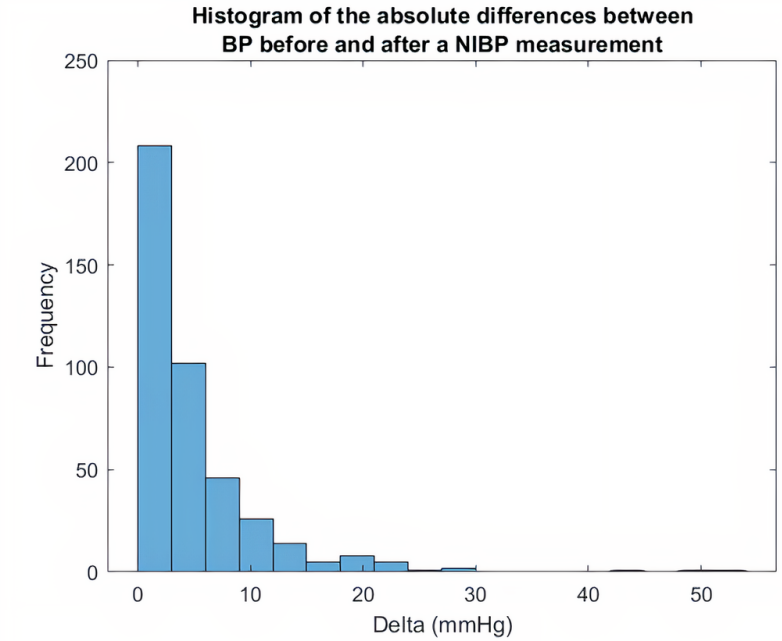
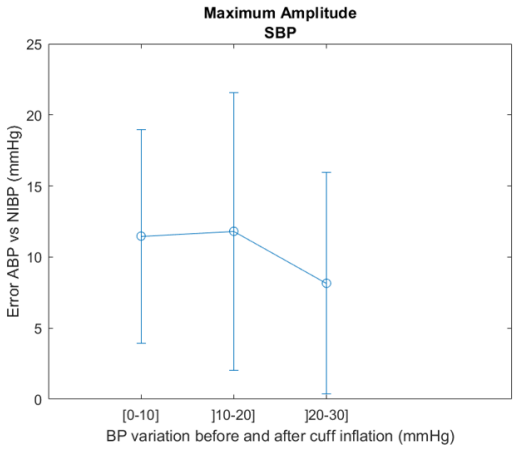
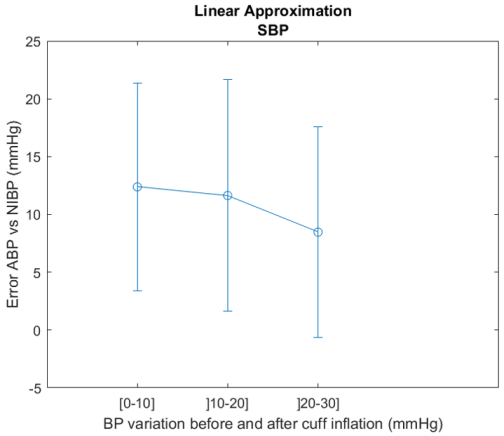


Figure 6.1: Histogram representing the frequency of the absolute differences between mean blood pressure 10 seconds before and 10 seconds after each cuff inflation (delta Δ), using estimations from ABP signal.

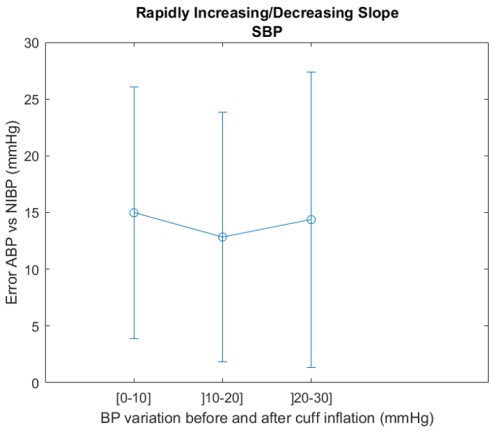
Based on the analysis of the histogram, we considered 3 intervals for delta: [0-10] mmHg,]10-20] mmHg and]20-30] mmHg. Delta values greater than 30 mmHg were considered outliers, because in the dataset used there were not enough samples in this interval to take significant conclusions (approximately 0,01%). As near 80% of the measurements presented a delta in the interval [0-10] mmHg, we consider this as stable measurements and the ones in interval]10-30] as unstable. In Figure 6.2 is illustrated the impact of BP variability in SBP estimation using oscillometry (a, b, c) and palpation (d) methods. In Figure 6.3 is illustrated the impact of BP variability in DBP estimation using oscillometric methods (a, b, c). The plots represent the MAE between NIBP estimation and ABP estimation (10 seconds before each NIBP measurement, as explained in Section 5.2.3.4) in function of delta. In diastolic blood pressure inference, unstable measurements show less accurate results. In what regards systolic blood pressure, the impact is not so clear. It is important to point out that, in the dataset used, the samples are not balanced – the number of stable measurements is considerably larger than the number of unstable. We believe that testing this hypothesis with a more balanced dataset would show more solid results. Nevertheless, we decided to present the global performance distinguishing between stable and unstable measurements. The results are introduced in the sections 6.2 and 6.3.



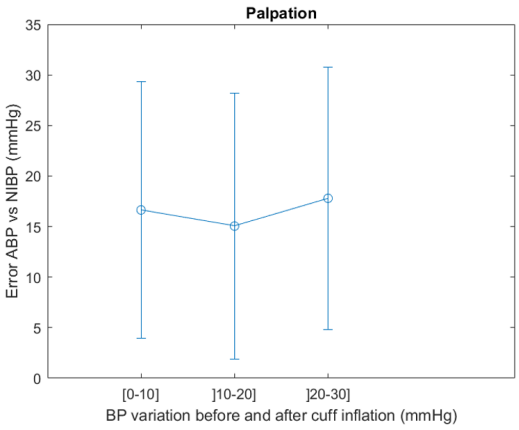
(a) Maximum Amplitude Algorithm.



(b) Linear Approximation Algorithm.

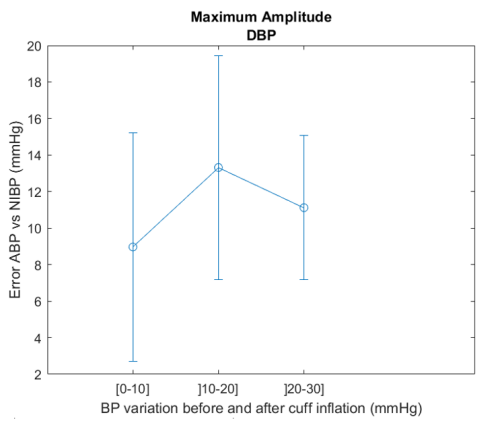


(c) Slope Variation Algorithm.

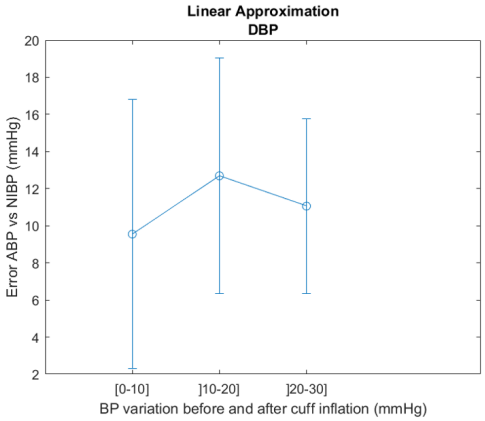


(d) Palpation Algorithm.

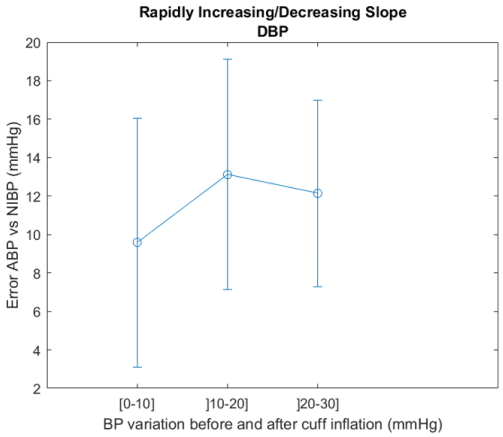
Figure 6.2: MAE between SBP inferred from ABP signal and using NIBP methods, in function of Δ.



(a) Maximum Amplitude Algorithm.



(b) Linear Approximation Algorithm.



(c) Slope Variation Algorithm.

Figure 6.3: MAE between DBP inferred from ABP signal and using NIBP methods, in function of Δ.

6.2 Oscillometric Methods

In this section the results for oscillometric methods' global and individual performances are presented, using ABP estimations as reference values.

In Table 6.1, the MAE and the STD of SBP and DBP estimations are displayed, for Maximum Amplitude Algorithm (MAA), Linear Approximation Algorithm (LAA) and Slope Variation Algorithm (SVA). Figures 6.4 and 6.5 illustrate Box and Whiskers analysis for SBP and DBP, respectively.

The MAA and the LAA show similar performances in SBP estimation, while SVA is approximately 40% less accurate. In what concerns DBP estimation, the three methods have close median values. However, from the Box and Whiskers analysis, we can see that the distributions vary among them, being the MAA the method that more often estimates DBP with a MAE lower than 10 mmHg. The elimination of the unstable NIBP

measurements did not present relevant changes in performance. In general, the DBP estimation is more accurate than the SBP estimation

		MAE ± STD (all Δ)	**MAE ± STD (Δ[0-10])**
Max. Amp.	SBP	11,88 ± 8,48	11,79 ± 8,06
	DBP	9,62 ± 6,50	9,08 ± 6,44
Lin. Ap.	SBP	12,56 ± 9,56	12,65 ± 9,43
	DBP	10,70 ± 6,52	10,44 ± 9,15
Inc. Dec. Slope	SBP	17,13 ± 17,58	17,30 ± 17,25
	DBP	11,19 ± 9,49	10,79 ± 9,76

Table 6.1: Global performance of oscillometric methods: MAE and STD for all NIBP measurements (all Δ) and for considered stable NIBP measurements only (Δ[0-10]), compared to ABP estimations.

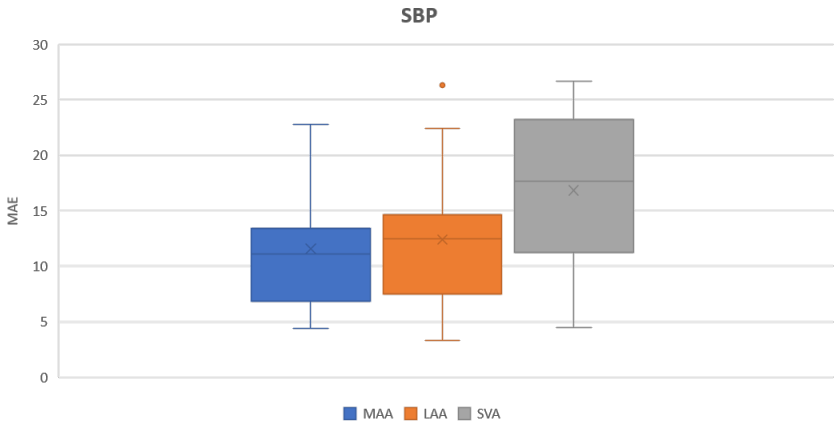


Figure 6.4: Box and Whiskers plot of SBP estimation' MAE from oscillometric methods.

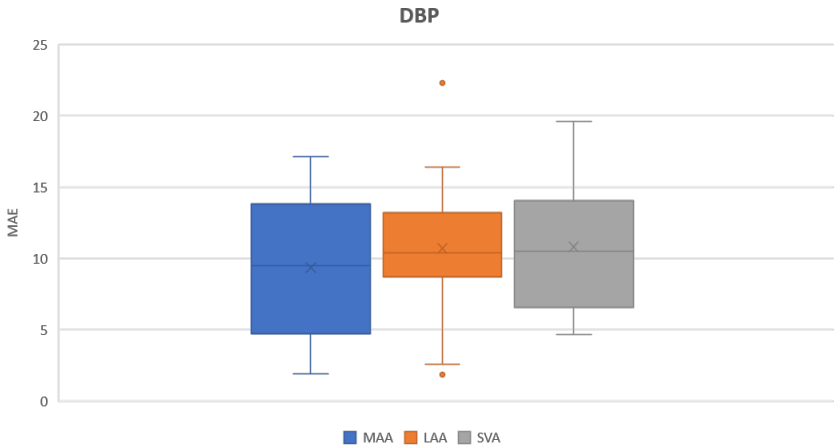


Figure 6.5: Box and Whiskers plot of DBP estimation' MAE from oscillometric methods

Results for each patient individually are presented in tables 6.2 and 6.3, using MAE and STD, and in tables 6.6 and 6.7, using RMSE. Reinforcing what is observed in global performance for SBP estimation, MAA and LAA present close values of MAE and STD, while SVA shows less accurate results. Even though, there is an evident individual pattern across the three methods. For SBP estimation (tables 6.2 and 6.6), patients 5, 7 and 9 exhibit a worse performance for all methods. Patients 1, 6, 8 and 12 have better performances than the average. For DBP estimation (tables 6.3 and 6.7), the results are better than for SBP, in general. Patients 4, 7 and 12 show the highest errors.
Visual representation of this analysis is described in figures 6.6 and 6.7, where it is possible to have a better insight of performance variability among patients.

	Max. Amp.		**Lin. Ap.**		**Inc./Dec. Slope**	
	MAE	**STD**	**MAE**	**STD**	**MAE**	**STD**
Patient 1	5,95	3,23	3,29	2,72	8,66	6,96
Patient 2	11,53	8,59	14,61	10,81	19,58	32,84
Patient 3	7,63	6,19	8,34	6,80	17,70	22,06
Patient 4	11,09	7,69	13,75	7,98	15,71	10,27
Patient 5	22,78	5,93	26,33	6,00	26,70	11,81
Patient 6	6,83	4,37	5,73	5,08	5,85	3,65
Patient 7	18,62	8,75	17,67	8,93	21,92	9,33
Patient 8	6,45	5,23	7,52	6,71	11,23	22,52
Patient 9	20,23	3,45	22,46	7,18	24,18	7,11
Patient 10	13,44	9,01	14,65	7,74	15,78	9,66
Patient 11	8,94	6,96	10,72	8,72	23,29	24,45
Patient 12	4,4	3,66	3,59	3,33	4,49	2,97
Patient 13	9,85	11,06	12,48	12,74	11,40	15,13
Patient 14	13,03	4,58	13,86	4,77	23,26	5,12
Patient 15	12,84	8,68	11,18	8,27	22,82	23,44

Table 6.2: Performance of oscillometric methods for each patient - SBP inference: MAE and STD for all NIBP measurements.

	Max. Amp.		Lin. Ap.		Inc./Dec. Slope	
	MAE	**STD**	**MAE**	**STD**	**MAE**	**STD**
Patient 1	8,96	2,04	8,70	2,96	11,58	5,86
Patient 2	11,2	5,33	13,18	9,91	14,07	13,92
Patient 3	9,47	7,95	10,06	8,22	10,50	9,76
Patient 4	14,33	6,65	11,57	6,63	19,61	16,92
Patient 5	4,14	2,14	6,28	6,36	4,67	3,17
Patient 6	2,39	2,01	2,59	2,65	6,54	8,43
Patient 7	17,15	4,41	22,29	12,34	15,83	4,95
Patient 8	4,69	2,09	9,07	14,36	6,20	3,11
Patient 9	10,23	3,42	12,19	6,80	8,19	4,03
Patient 10	7,9	4,84	10,41	10,36	9,08	6,07
Patient 11	13,8	1,83	15,58	4,27	13,02	2,82
Patient 12	15,3	1,90	16,43	2,46	16,93	2,00
Patient 13	11,44	2,34	10,62	2,37	13,48	2,50
Patient 14	1,87	2,03	1,83	1,92	4,72	4,59
Patient 15	7,41	6,88	9,76	6,13	7,59	10,96

Table 6.3: Performance of oscillometric methods for each patient - DBP inference: MAE and STD for all NIBP measurements.

	Max. Amp.	Lin. Ap.	Inc./Dec. Slope
Patient 1	6,75	4,23	11,04
Patient 2	14,33	18,11	37,92
Patient 3	9,76	10,68	27,97
Patient 4	13,42	15,83	18,67
Patient 5	23,48	26,96	29,01
Patient 6	8,09	7,62	6,87
Patient 7	20,54	19,77	23,79
Patient 8	8,17	9,90	24,38
Patient 9	20,51	23,54	25,16
Patient 10	16,07	16,49	18,39
Patient 11	11,25	13,71	33,40
Patient 12	5,61	4,78	5,30
Patient 13	14,64	17,65	18,69
Patient 14	13,79	14,64	23,80
Patient 15	15,38	13,79	32,31

Table 6.4: Performance of oscillometric methods for each patient - SBP inference: RMSE for all NIBP measurements.

	Max. Amp.	Lin. Ap.	Inc./Dec. Slope
Patient 1	9,19	9,18	12,94
Patient 2	12,38	16,43	19,68
Patient 3	12,27	12,9	14,21
Patient 4	15,76	13,28	25,71
Patient 5	4,62	8,76	5,57
Patient 6	3,11	3,68	10,59
Patient 7	17,70	25,43	16,57
Patient 8	5,10	16,51	6,88
Patient 9	10,76	13,89	9,09
Patient 10	9,21	14,53	10,85
Patient 11	13,91	16,14	13,31
Patient 12	15,41	16,59	17,04
Patient 13	11,67	10,87	13,70
Patient 14	2,74	2,64	6,54
Patient 15	10,00	11,45	13,12

Table 6.5: Performance of oscillometric methods for each patient - DBP inference: RMSE for all NIBP measurements.

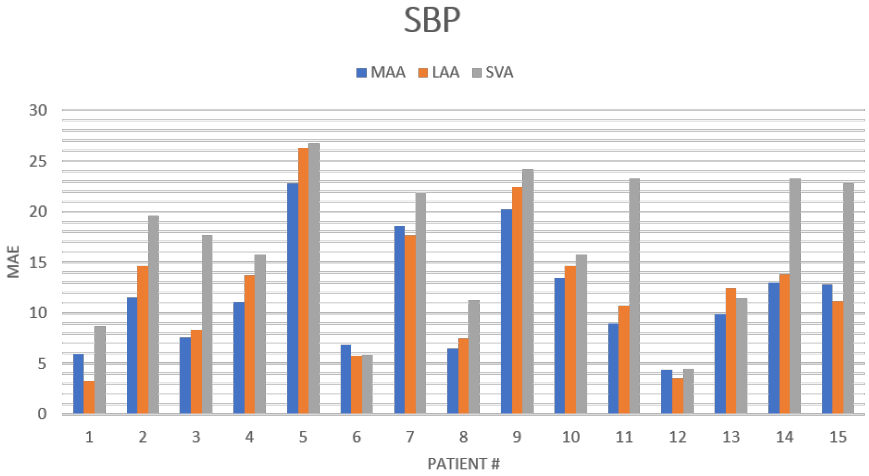


Figure 6.6: Column cluster chart for SBP estimation' MAE from oscillometric methods.

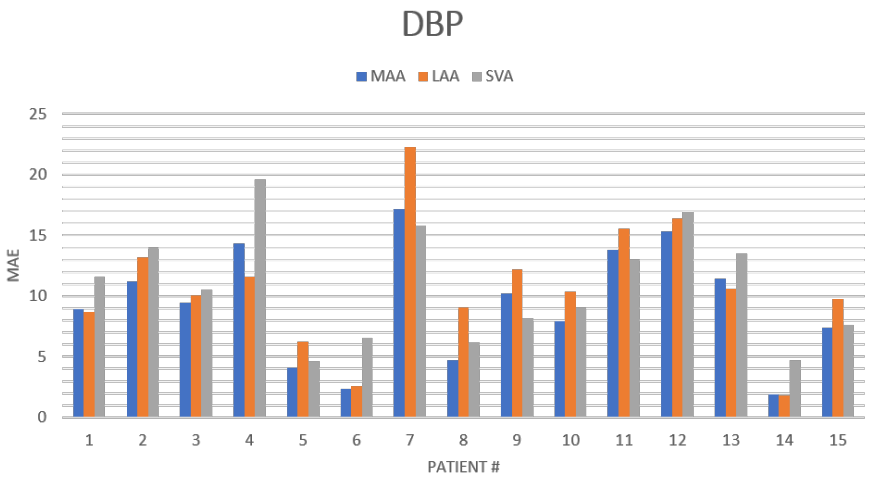


Figure 6.7: Column cluster chart for DBP estimation' MAE from oscillometric methods.

6.3 Palpation Method

The results for palpation method described in Section 5.2.5.2 are presented in table 6.6. As observed in oscillometric methods, performance is similar using NIBP unstable measurements and after removing them.

Figure 6.8 represents a Box and Whiskers analysis of the three oscillometric methods and the palpation method. The median value of palpation method estimation errors is close to MAA and LAA. SVA continues to show the worst general performance. Palpation' MAE is less dispersed than MAE from any other method, looking approximately like a normal distribution. However, MAA and LAA show more SBP estimations with error lower than 10 mmHg.

MAE ± STD (all Δ)	**MAE ± STD (Δ[0-10])**
16,56 ± 12,70	16,64 ± 12,68

Table 6.6: Global performance of palpation method: MAE and STD for all NIBP measurements (all Δ) and for considered stable NIBP measurements only (Δ[0-10]), compared to ABP estimations.

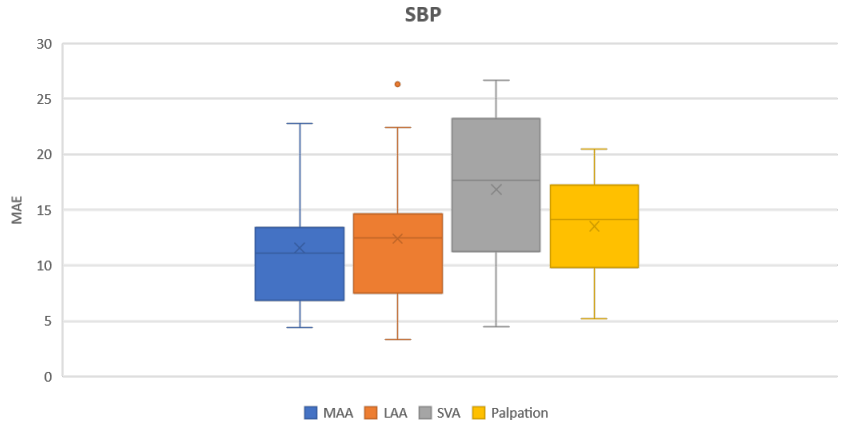


Figure 6.8: Box and Whiskers plot of SBP estimation' MAE from oscillometric and palpation methods.

Results for each patient individually are presented in table 6.7, using MAE and STD, and in table 6.8, using RMSE. Compared to oscillometric individual performance, palpation method shows a lower variability across different patients. Figure 6.9 illustrates a column cluster chart representing MAE of the four NIBP methods analyzed, across the 15 patients.

	MAE	**STD**
Patient 1	17,26	3,99
Patient 2	20,45	9,60
Patient 3	7,48	5,61
Patient 4	9,44	7,32
Patient 5	15,74	4,46
Patient 6	14,89	5,14
Patient 7	17,31	9,01
Patient 8	9,83	9,71
Patient 9	18,00	3,52
Patient 10	11,47	7,08
Patient 11	12,56	9,78
Patient 12	14,11	2,85
Patient 13	15,59	13,85
Patient 14	5,20	3,40
Patient 15	13,34	12,16

Table 6.7: Performance of palpation method for each patient - SBP inference: MAE and STD for all NIBP measurements.

	RMSE
Patient 1	17,70
Patient 2	22,54
Patient 3	9,29
Patient 4	11,87
Patient 5	16,31
Patient 6	15,73
Patient 7	19,48
Patient 8	13,55
Patient 9	18,33
Patient 10	13,40
Patient 11	15,79
Patient 12	14,37
Patient 13	20,66
Patient 14	6,19
Patient 15	17,81

Table 6.8: Performance of palpation method for each patient - SBP inference: RMSE for all NIBP measurements.

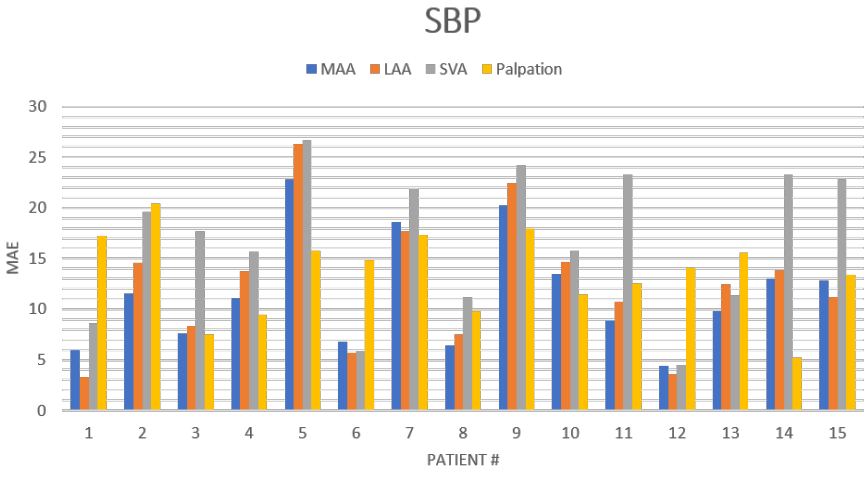


Figure 6.9: Column cluster chart for SBP estimation' MAE from oscillometric and palpation methods.

The results of suggested approach to palpation method, detailed in Section 5.2.5.3, are presented in table 6.9. The alterations to the method improved the global performance in approximately 16%.

MAE ± STD (all Δ)	MAE ± STD (Δ[0-10])
13,97 ± 8,99	13,74 ± 8,77

Table 6.9: Global performance of new approach to palpation method: MAE and STD for all NIBP measurements (all Δ) and for considered stable NIBP measurements only (Δ[0-10]), compared to ABP estimations.

6.4 Discussion - Tension profile and oscillometric methods' performance

Wax *et al.* [7] demonstrated that patients' tension profile can have an impact on NIBP accuracy. As illustrated in Figure 6.10, NIBP tended to be higher than radial ABP during periods of hypotension and lower than ABP during periods of hypertension.

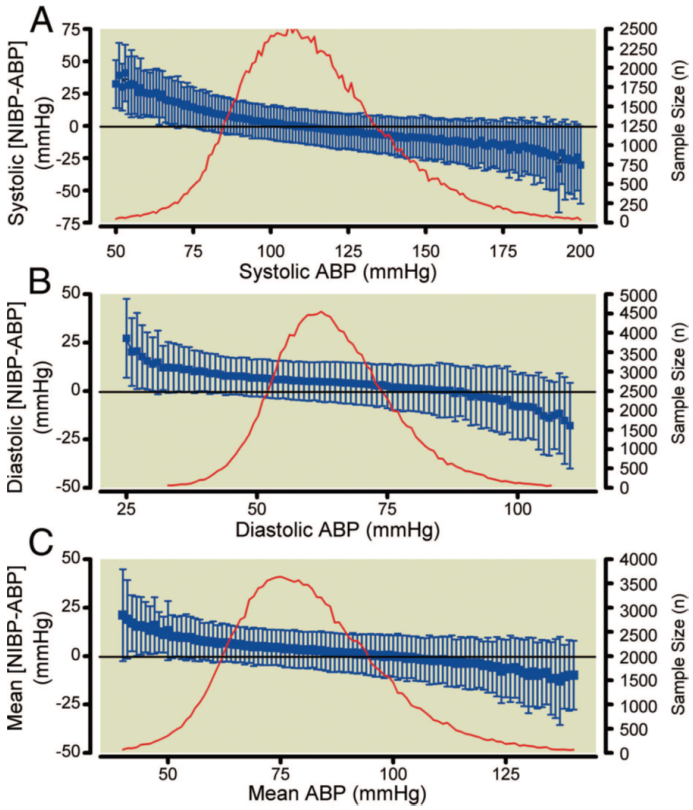


Figure 6.10: Difference between oscillometric cuff and radial artery catheter measurements of blood pressure. Adapted from [7].

From the analysis of the performance of oscillometric methods implemented in this work, it is also possible to notice a considerable discrepancy among different patients. In light of that, we wanted to test if patients tension profile *does* influence NIBP estimations' error. The null hypothesis formulated was: "All patients follow the same BP distribution.", with a level of significance considered to be 0,05. According to J. B. du Prel, *et al.* [61], *"The decision for a statistical test is based on the scientific question to be answered, the data*

structure, and the study design". As the endpoint of our data structure is continuous – BP values estimated using ABP signal – we started to test if it followed a normal distribution. The QQ plot in Figure 6.11 shows that both SBP and DBP do not follow a normal distribution. To validate these observations, we performed a Kolmogorov-Smirnov test, which result rejected the null hypothesis (normal distribution). Therefore, we concluded that a non-parametric test had to be chosen.

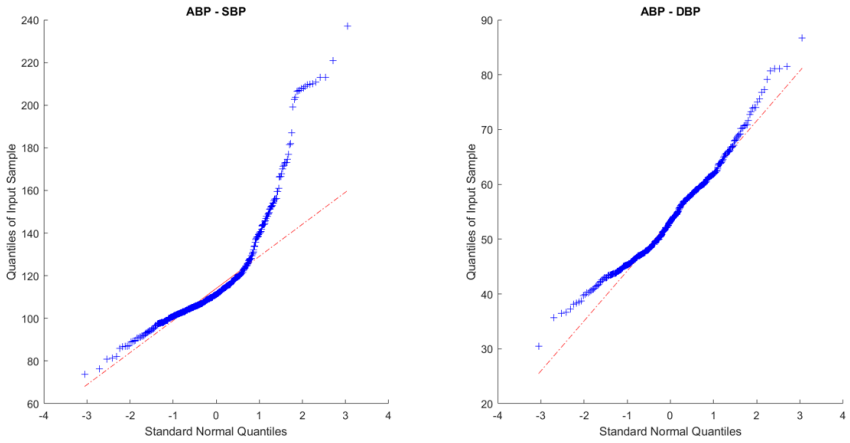


Figure 6.11: Test for normal distribution: QQ plot for SBP and DBP estimated from ABP signal.

As we are comparing BP values from different patients, our data is unpaired. The statistical test chosen based on this analysis was the Kruskal-Wallis test. The test was applied using the function *kruskalwallis* from MATLAB R2019b, with a group variable, since we had groups with a different number of observations (i.e. duration of surgery is variable among patients).
Figures 6.12, 6.13 and 6.14 illustrate the result of Kruskal-Wallis test for SBP, MAP and DBP, respectively. Plots show that the mean values and data dispersion is highly variable for different patients, which means that there are significant differences among their BP distributions. Furthermore, all p-values were lower than the significance level of 0,05. Hereupon, we conclude from this test that the differences between some of the means are statistically significant, and therefore we can use the mean BP value to cluster patients.

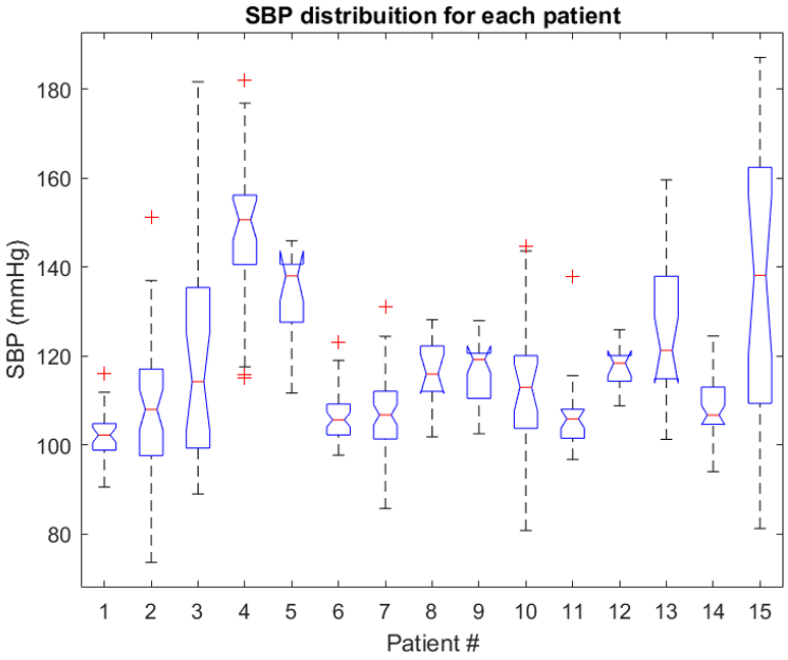


Figure 6.12: Kruskal-Wallis test for SBP estimated from ABP signal.

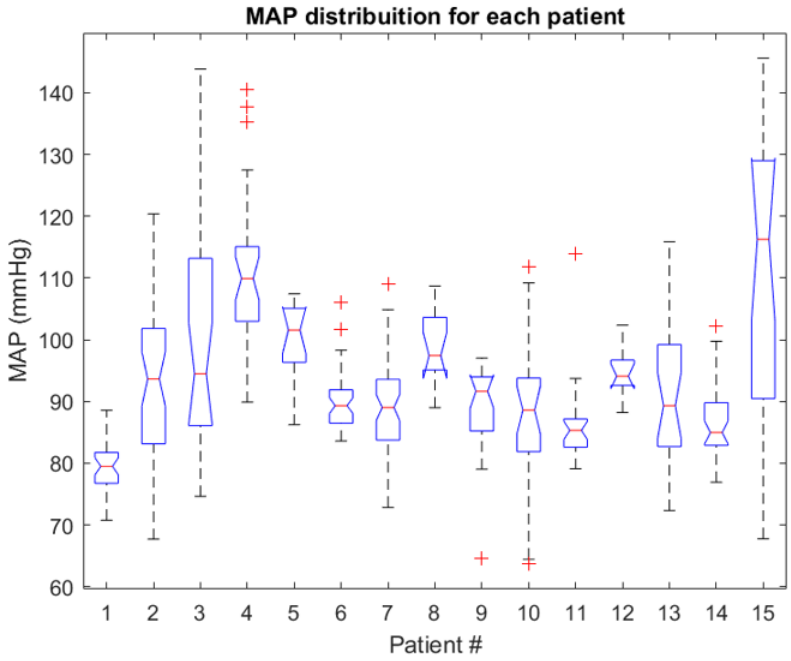


Figure 6.13: Kruskal-Wallis test for MAP estimated from ABP signal.

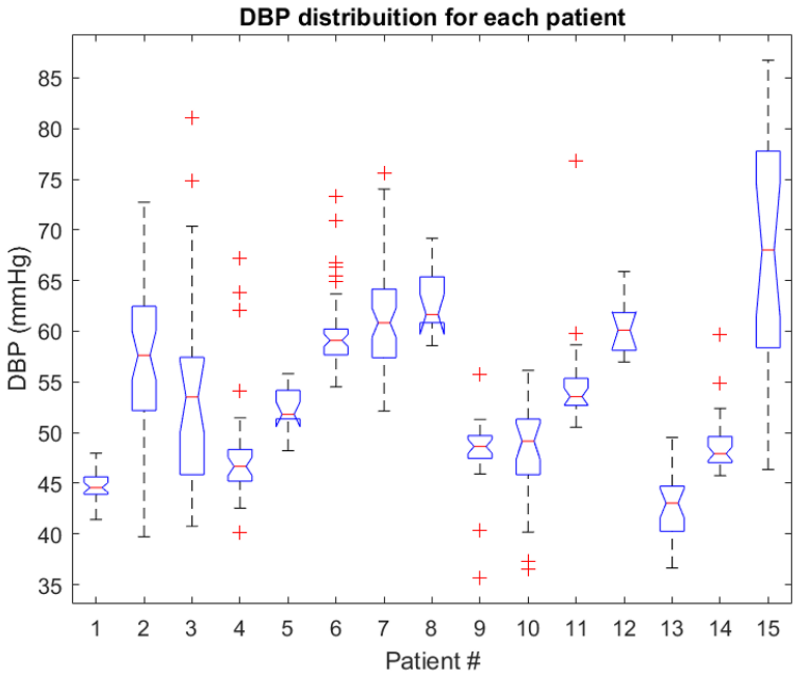


Figure 6.14: Kruskal-Wallis test for DBP estimated from ABP signal.

According to 2020 Global Hypertension Practice Guidelines from American Heart Association (AHA) [5], a patient is hypertensive if SBP>130 mmHg and/or DBP>85 mmHg (Figure 6.15). In this study, we only have access to patients' BP profile during surgery, and this table considers office measurements. As L. Meng, *et al.* [62] argue that, in intraoperative scenario, maintenance of BP to 90% of its baseline is recommended, we considered hypertensive the patients with mean SBP higher than 120 mmHg – patient 4, patient 5, patient 13 and patient 15.

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Normal BP	<130	and	<85
High-normal BP	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	≥160	and/or	≥100

Figure 6.15: Classification of Hypertension Based on Office Blood Pressure. Adapted from [5].

In Tables 6.10 and 6.11 is presented the global performance of the oscillometric method when applied to hypertensive and to normotensive patients, respectively. The results show that, when oscillometry is applied to hypertensive patients, the performance decreases approximately 15% for SBP estimation, when using Maximum Amplitude Algorithm, and 24% using Linear Approximation Algorithm, when compared to performance using all

patients (Table 6.1). For DBP estimation, the performance actually increases approximately 13% with Slope Variation Algorithm. For normotensive patients, there are not significantly changes in performance.

		All Δ	**Δ[0-10]**
Max. Amp.	**SBP**	13,72 ± 9,55	15,39 ± 9,54
	DBP	9,08 ± 4,54	8,22 ± 4,19
Lin. Ap.	**SBP**	15,56 ± 10,84	17,66 ± 10,36
	DBP	9,56 ± 5,37	9,58 ± 5,35
Inc./Dec. Slope	**SBP**	16,54 ± 14,19	19,24 ± 14,70
	DBP	9,69 ± 5,32	8,58 ± 4,86

Table 6.10: Global performance of oscillometric methods for **hypertensive and stable patients**: MAE and STD for all NIBP measurements (all Δ) and for considered stable NIBP measurements only (Δ[0-10]).

		All Δ	**Δ[0-10]**
Max. Amp.	**SBP**	11,51 ± 8,08	11,04 ± 7,28
	DBP	9,49 ± 6,82	8,88 ± 6,64
Lin. Ap.	**SBP**	12,62 ± 9,16	11,31 ± 8,97
	DBP	11,12 ± 6,93	11,01 ± 6,68
Inc./Dec. Slope	**SBP**	17,01 ± 18,60	16,32 ± 17,35
	DBP	11,21 ± 9,01	10,81 ± 9,17

Table 6.11: Global performance of oscillometric methods for **normotensive and stable patients**: MAE and STD for all NIBP measurements (all Δ) and for considered stable NIBP measurements only (Δ[0-10]).

We observed that excluding hypertensive patients from our dataset does not improve the global performance of methods. However, when looking at hypertensive cluster alone, we see a general deterioration of performance, indicating that tension profile has, indeed, a significant impact in NIBP accuracy. In addition, we conclude that the methods show different sensitivities to BP profile changes.

7

Conclusions

Blood pressure is an essential parameter to assess cardiovascular status. Its use in clinical practice spreads for all types of medical conditions, and its monitoring is mandatory in almost every clinical context, both for diagnose and treatment.
BP can be monitored invasively, via an artery catheter – in high acuity settings or whenever a continuous monitoring is needed – or non-invasively, usually with an inflatable cuff wrapped in the arm – in every other clinical situation, being the preferential procedure. Invasive monitoring provides more accurate readings, and that is why it is used in more severe clinical scenarios. Its use tends to be minimized as it is prone to infections and it needs trained staff to apply. On the other side, non-invasive monitoring application is easier and more comfortable for the patient. The principal drawbacks of this method are first, its lower accuracy, and second the inherent intermittence of the measurements, that could lead to miss relevant BP events and consequently the right time of intervention.
In this thesis, an investigation was performed in a cardiology department, aiming to analyse and interpret how BP is currently being monitored in different clinical contexts. Health professionals, both doctors and nurses, were interviewed and notes were taken on their work, based on observation. It was found that BP of all patients in the Cardiology Department is regularly measured, by default with a standard operating procedure in each care unit. The NIBP monitoring, namely the cuff oscillometry, is the preferred method, and its regularity is pre-defined in each unit. Patients need to be invasively monitored when they are hemodynamically unstable, either for clinical conditions or administration of drugs. Some opportunities of intervention came up as results from this research, among which stand out: the need for adaptive sampling frequency, the identification of potential decompensations using BP monitoring profiles, the definition of automatic patient-specific and patient-safe thresholds and the improvement of NIBP accuracy. All these opportunities of intervention are relevant for supporting the decision on transferring from NIBP to ABP and vice-versa, and consequently to improve diagnose and treatment of CVDs.
After finishing this clinical research and reported the main conclusions, we concluded that the NIBP estimation accuracy is a challenging topic, that still needs to be worked on. In light of this, we decided to implement and analyse three of the most well-know oscillometric algorithms, as well as a palpation algorithm. We then evaluated their performance, using BP extracted from ABP signal as reference. Results show that, in general,

DBP estimation is more accurate than SBP estimation. Also, that for all methods the performance is affected by the tension profile, and that it deteriorates with hypertensive patients. However, the methods show different sensitivities to BP profile changes. Compared to oscillometry, palpation method shows a lower variability of performance across different patients. Another observation is that the MAE values for palpation method are less scattered than for oscillometric methods, but oscillometric methods have a greater probability to estimate BP with errors lower than 10 mmHg, which is required from standards.

A new approach to the palpation method was suggested. This approach consists in choosing the last point of the pulse before artery occlusion to infer SBP, instead of the last pulse onset, as in the original method. This alteration improved the general performance of the method in approximately 16%. Although, we believe that it needs to be tested with a larger dataset in order to increase robustness of the results. Also, including ECG signal to predict the pulse disappearance could lead to a more accurate choice of the moment in time used to infer SBP.

The results achieved by implementing these algorithms evidence the huge variability that accuracy of NIBP estimations can present. The fact that some algorithms depend on empirically defined fixed-ratios makes it difficult to generalize their behaviour for every patient. The amplitude of OWE varies across patients and even across measurements of the same patient. This observation suggests that the ratios should be personalized, as they are intrinsically dependent on the definition of OWE.

There are features in NIBP algorithms that still need improvement. Although, it would be extremely valuable to have BP continuously monitored in a non-invasive way, which it is not feasible with an inflatable cuff. This would allow the improved assessment of BP variability, of nocturnal hypertension, and even predict severe BP events, having more time to manage them, probably using less aggressive interventions.

Research on continuous NIBP monitoring and alternative technologies has been ongoing for decades (*e.g.* [10], [63–66]). None of these new technologies have been regulated nor standardized, so they cannot yet be recommended for clinical use, and oscillometry is still the principal technique used in clinical practice. The development of cuffless techniques should continue to be improved, towards the widespread of its use globally. Furthermore, it is increasingly urgent to develop and implement health solutions that are integrable in systems of telemonitoring. The use of BP telemonitoring is becoming more frequent, allowing a closer relation between patients and professionals, contributing for a better management of diagnosis and treatment. Besides, it has been proven that the accuracy of the measurements is highly related with the environment where it takes place. In traditional office-based care, the reading can be overestimated due to white coat effect. These reasons, associated with patient increased comfort, sustain the high interest in developing cuffless monitoring technologies. The development of more user-friendly devices would increase the potential of this type of monitoring, as the current global health reality demands.

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