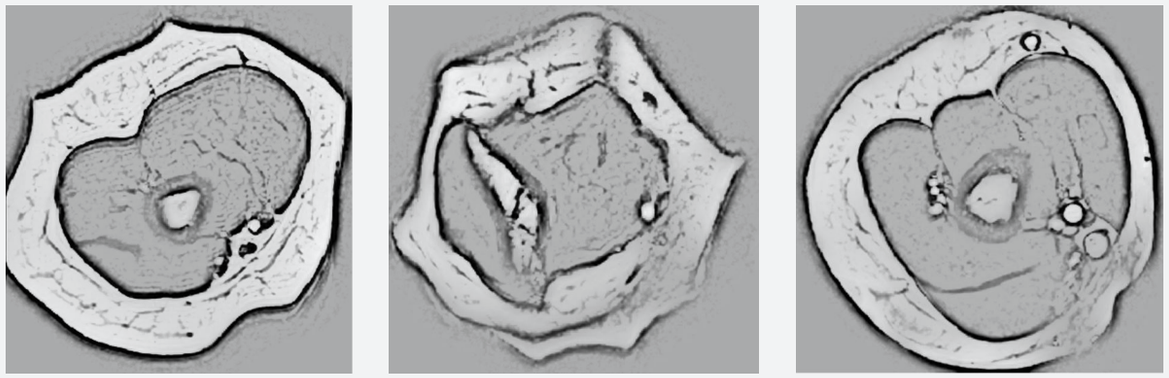
Enhanced model-based assessment of the hemodynamic status by noninvasive multi-modal sensing



ENHANCED MODEL-BASED ASSESSMENT OF THE HEMODYNAMIC STATUS BY NON-INVASIVE MULTIMODAL SENSING

LAURA BOGATU

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus prof.dr.ir. F.P.T. Baaijens, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op donderdag 9 juni 2022 om 16:00 uur

door

Laura Ioana Bogatu

geboren te Bacău, Roemenië

Dit proefschrift moet worden goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

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Het onderzoek of ontwerp dat in dit thesis wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

Summary

Assessment of the hemodynamic function plays an essential role in the treatment of patients at risk of deterioration. Monitoring technologies are evolving continuously, and a large number of bedside monitoring options are becoming available in the clinic. In the past decade, methods such as echocardiography, electrical bioimpedance, techniques based on calibrated/uncalibrated analysis of pulse contour have become increasingly common. At the same time, use of invasive monitoring by e.g. pulmonary artery catheterization has been declining, paving the way for safer, more continuous and accurate non-invasive measurements of blood pressure (BP), cardiac output (CO) and other standard hemodynamic parameters.

Yet important limitations in hemodynamic monitoring remain that stem from the need for accessing more complete hemodynamic information, in addition to standard indices. For example, there is still uncertainty in the interpretation of widely-used variables such as BP. Moreover, even when an accurate BP estimation is available, the BP value is a late indicator of deterioration and controversy exists in the clinical community regarding the definition of a healthy BP range. Additional hemodynamic information would help identify the original causes leading to instability – e.g. differentiating between heart related factors or vasodilation. In addition to this, it has been found that the micro- and macro-circulation can become dissociated, especially in the presence of sepsis, and additional measurements are needed to identify such complex hemodynamic states. It is also recognized that patient deterioration is detected too late in low-acuity monitoring settings; the wards requiring the most urgent improvement. At the same time, however, the existing ward measurements (typically aggregated in early warning scores) lead to frequent unspecific alarms, with a false alarm rate of 90%. This emphasizes the challenge of managing hemodynamically unstable patients with limited and unspecific information.

This PhD work addresses these limitations by proposing a new theoretical framework and experimental tests so as to broaden the set of parameters that can accurately be monitored with standard clinical equipment. In order to determine the limitations of the state-of-the-art monitoring technology in relation to the clinical needs, we first reviewed and evaluated the main trends and advances in critical care for the measurement of new hemodynamic parameters. The current research approaches, opinions, and protocols are analyzed from both a clinical and a technical perspective. This review confirms that the existing patient monitoring devices might not be used up to their full potential and that several opportunities exist for acquiring additional hemodynamic information with standard hospital equipment. Such additional information can also contribute towards improving the specificity and accuracy of existing measures, such as BP. Standard equipment is preferred over advanced novel technologies to favor and accelerate the clinical translation and uptake of the developed methods. Following this review work, the rest of the thesis is divided in two parts.

In Part I, we explore a number of underutilized arrangements of standard sensors which could be of use to reveal additional information on compensatory mechanisms of the circulation. We first investigate arterial stiffness/compliance parameters

which are extensively researched in the context of cardiovascular disease management, but largely overlooked in hemodynamic monitoring. Nevertheless, critical-care clinicians have expressed interest in such indices. In particular, short-term changes in arterial properties can be indicative of vascular tone and of compensatory responses preceding hemodynamic instability events. In principle, estimation of arterial compliance can be achieved either via analysis of arterial volume vs. pressure changes or via inference from the pulse wave velocity (PWV). Since the typical critical care monitoring system has access to both these information sources, we propose a new measurement strategy to assess brachial arterial compliance by fusion of arterial pressure-volume data (acquired via cuff-based oscillometry) and PWV (estimated via combination of electrocardiographic and photoplethysmographic signals). The method consists of modulating arterial transmural pressure and pulse propagation along the artery via occlusion-based perturbation controlled via the cuff. The sensor fusion is intended to minimize the measurement uncertainty and inaccuracy that is expected in a hemodynamic monitoring environment. The method is based on Bayesian analysis principles combined with physiological insights acquired via non-invasive measurements performed on healthy subjects. Alternative methods for assessment of brachial arterial properties (compliance, viscosity, collapse characteristics) are also explored via non-parametric processing of cuff signals and external pressure oscillometry.

Moreover, we further advance our understanding of the vasculature response to occlusion-based perturbations by analyzing BP waveforms acquired invasively downstream from the cuff in hemodynamically monitored patients. We find that highly-dynamic and patient-specific effects occur in the distal arm as a result of cuff inflation. These observations can lead to improved interpretation of the measured signals, which enable further access to hemodynamic information: artery-vein interaction, limb peripheral resistance, distal arterial and venous compliances. In addition, we also show how information on non-standard parameters such as arterial compliance can lead to improved estimation of standard parameters, such as BP.

In Part II, aspects concerning the implementation of the proposed measurement strategies are addressed. More specifically, while simulation frameworks, theoretical models and physiological insights obtained from patient data are essential to develop effective measurement strategies, the implementation of these measurements in clinical practice requires in-depth understanding of the cuff transducer characteristics and patient-specific, arm-tissue properties. These characteristics and properties are typically assumed to be ideal, with negligible impact on cuff-based measurements; as a result, they are largely overlooked in the literature about oscillometry. We therefore verify the validity of the assumptions that are typically made on cuff transducer and arm tissue characteristics, gaining insights into the oscillometric process via a series of studies involving MRI imaging, tensile tests conducted on typical cuff materials, and measurement of the cuff response to mechanically simulated arm pulsations under various conditions.

In conclusion, we have found that the common BP cuff is largely underutilized while it offers ample possibilities to modulate the blood flow and pulse propagation along the artery, revealing dynamic/compensatory mechanisms of the circulation. With our proposed setup, we obtained a more advanced characterization of the circulatory system response to occlusion perturbations and, based on this, developed several measurement strategies to enable the estimation of previously inaccessible parameters (vascular tone, peripheral resistance, artery-vein interaction, vascular collapse mechanics,

arterial viscosity). We have also gained an in-depth understanding of a number of oscillometric model assumptions related to cuff transducer and patient-specific arm tissue behavior, enabling for a more reliable implementation of the measurements and improved interpretation of the acquired signals. An important aspect is the possibility to implement the proposed methods via standard clinical equipment, which facilitates uptake of the provided new parameters in clinical practice. Future work will be aimed at investigating whether the availability of more parameters providing a better description of the hemodynamic status can effectively result in improved patient outcome.

Contents

CHAPTER

01

INTRODUCTION

1.1. **Motivation**

Several limitations which exist in hemodynamic monitoring today can be tackled by acquiring a more complete picture of the hemodynamic status of patients at risk of deterioration. Looking at the example of blood pressure (BP), there is clear correlation between hypotension and poor outcomes, and the likelihood of cardiovascular events increases when BP decreases [1]. However, even in the case of accurate, continuous BP measurements, controversy exists in the clinical community regarding the exact threshold value for hypotension. While recent findings suggest that a 65-mmHg mean arterial pressure (MAP) threshold should be regarded as an absolute minimum to prevent harmful hypotensive conditions, the trend towards personalized BP thresholds in fluid/vasopressor therapy is in contradiction with this fixed threshold [2, 3]. This leaves the use of BP as a therapeutic target open for discussion. In addition to this, the moment when clinical hypotension becomes evident does not correspond to the moment when hemodynamic instability occurs. Usually, low BP is a sign that compensatory mechanisms have already failed (Fig. 1). At this point, action can be taken to reverse hypotension; however, limited hemodynamic information can hinder the correct choice of therapy: administration of inotropes, vasoactive drugs or fluid. From a therapeutic perspective, it is important to identify the original cause that led to instability – e.g. differentiate between heart related factors or vasodilation. In many cases, the BP value in itself is not specific enough. There is need to complement the BP value with further data possibly related for example to the vascular tone, level of constriction of arteries, changes in arterial-venous interaction, or other parameters representative of compensatory mechanism activation.

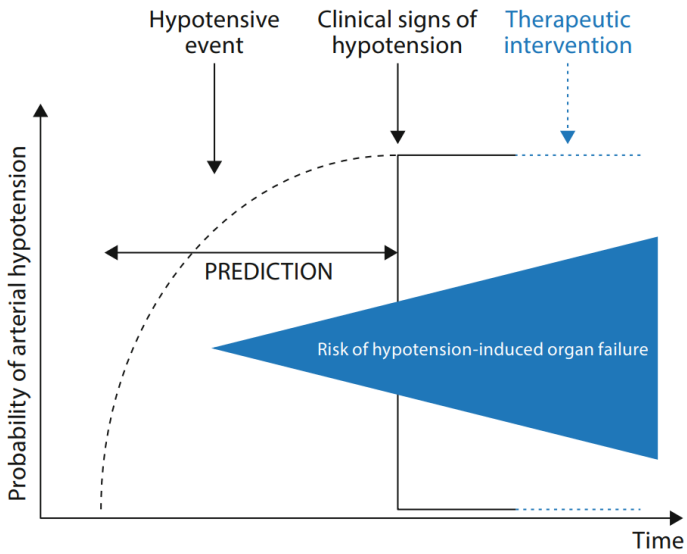

Figure 1. BP can be a late indicator of hemodynamic instability. Picture obtained from 2018 Annual Update in Intensive Care [4].

The need for additional data, the issues regarding thresholding and usage as therapeutic target apply to all other hemodynamic indices, such as cardiac output (CO) [6] and pulse pressure variation ("Applicability of pulse pressure variation: How many shades of gray" [5]).

"For example, because blood flow varies to match metabolic requirements, which in turn can vary considerably, there is no one specific value of cardiac output or oxygen delivery that can be defined as 'normal'." [6]

Such uncertainties are particularly severe in low-acuity monitoring settings, where access to hemodynamic information is even more limited, with the wards requiring the most immediate improvement. Missed patient deterioration as a result of insufficient ward monitoring is considered one of the main factors in the 4.2 million cases worldwide per year in which patients died within 30 days after surgery [7]. At the same time, however, the existing ward measurements (arterial BP, peripheral arterial oxygen saturation SpO2, and cardiac rhythm via electrocardiogram ECG) lead to frequent alarms, which are unspecific and have a false alarm rate of up to 90% [8]. Another aspect is that recent findings related to the microcirculatory function have shown how capillary-level and systemic level circulation can sometimes become dissociated, especially in cases of sepsis [9], and that tissue (microvascular) hypoperfusion may exist under conditions of normal systemic BP or CO. Managing hemodynamically unstable patients with limited and unspecific information leads to suboptimal decision-making.

Overall, the current situation underlines the need for complementing the existing standard parameters with additional hemodynamic information, so as to achieve earlier and more accurate assessment of the hemodynamic status and enable timely deployment of optimal, patient-specific treatment.

1.2. **Research questions**

Motivated by the current situation and clinical needs, this PhD work aims at addressing the following research questions with the aim of contributing to an improvement of the current methods and sensor settings employed for the assessment of the hemodynamic status.

- Which are the key aspects, challenges, and the clinical value of measuring new hemodynamic parameters in critical care?
- To what extent can standard sensors be used for more complete assessment of the hemodynamic status? In other words, can new measurement strategies be developed to achieve improved assessment of the hemodynamic status of a patient using the available standard sensors?
- Which are the requirements and main challenges for a robust implementation of the proposed measurements in clinical practice? In particular, which are the main sources of noise and uncertainty (also accounting for sensor/transducer device characteristics and patient-specific aspects) that affect the measurement accuracy, and which are the best implementation strategies to achieve robust and accurate

estimation of the key hemodynamic parameters?

1.3. **Thesis outline**

Chapter 1 presents the complexity of hemodynamic monitoring today and provides a background on the key aspects, challenges and clinical value of measuring novel hemodynamic parameters in critical care. Work being carried out on this topic is well-founded and it stimulates new, innovative research that is essential to advanced understanding of vascular physiology. However, a general pattern is that extensive developments are being realized in research, yet these are slow to find their way into standard clinical diagnosis and treatment procedures. Extensive clinical trials are needed to standardize the interpretation of new data and link it to diagnosis and therapy. A potential solution for near-future impact is to obtain additional hemodynamic information via more advanced interpretation of physiological signals acquired from standard hospital equipment. Our analysis (Chapter 2) suggests that several opportunities for this exist. For example, new advancements in the field of cardiovascular disease therapy have enabled measurements of arterial properties (e. g. compliance, vascular tone, collapse characteristics) via analysis of ECG, PPG, cuff signals. This improved understanding of vascular regulation mechanisms is potentially of great relevance to hemodynamic monitoring; the findings should be translated to critical care domains. Another application, management of venous thrombosis, has also been researched in depth via standard sensors and via models involving parameters related to peripheral resistance, arterial/venous compliance, mean systemic filling pressure, artery-vein interaction. The applicability of such models should also be investigated in the context of critical care, where the parameters can potentially be interpreted for detection of compensatory effects. Another aspect is the increasing interest in functional hemodynamic parameters, which are designed to quantify the response of the circulation to a well-defined perturbation. However, such measurements are currently limited to very specific patient groups or measurement situations. Many opportunities exist to further analyze variations of functional measurement principles (e. g. the response of the vasculature to cuff induced perturbations can reveal highly dynamic and patient specific effects).

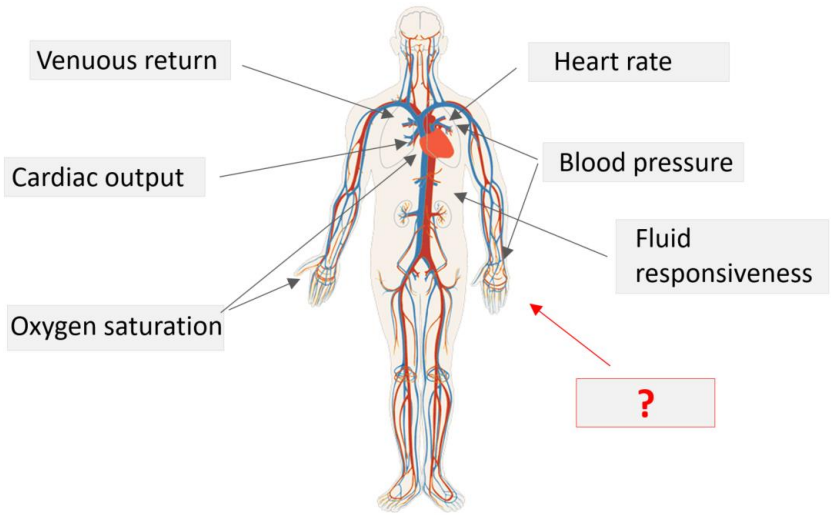

Figure 2. Additional information is needed to complement standard hemodynamic parameters.

Based on this analysis, in **Part I**, we therefore explore underutilized arrangements of standard sensors which could be of use to reveal additional information on compensatory mechanisms of the circulation.

In Chapter 3, the focus lies on arterial compliance, stiffness, and vascular tone. These properties have been extensively researched in the context of cardiovascular disease management but have been largely overlooked in critical care. Changes in vascular tone could potentially precede changes in BP and cardiac output. Taking the example of hemorrhage, compensatory mechanisms activation (e. g. via the autonomic nervous system) can sometimes hinder detection of blood loss, because parameters such as BP remain constant until the moment of hemodynamic instability [12]. Measurement of the vascular tone/arterial compliance might help identify when such compensation occurs, therefore potentially predicting deterioration. In addition, arterial compliance is a key parameter in hemodynamic measurements requiring calibration (e. g. beat-to-beat pulse arrival time - based BP estimation). Such measurements are needed for less invasive, more continuous monitoring, especially on the wards [15]. Also, knowledge of arterial compliance may facilitate model-based inference of other parameters (e. g. peripheral resistance, artery-vein interaction, venous compliance).

Intensive care clinicians have expressed interest in measuring short-term, dynamic regulation of arteries [10]; however, methods for estimating and interpreting arterial compliance, stiffness, and vascular tone with standard monitoring equipment are not yet available.

In principle, estimation of arterial compliance can either be achieved via a direct measurement of the ratio between arterial volume and pressure changes or via inference

from the pulse wave velocity (PWV). The typical critical care monitoring system has access to both these information sources:

- Arterial volume-pressure data can be acquired via the BP cuff. The measurement principle (oscillometry) consists of inflating a cuff usually placed at the brachial site in order to alter the transmural pressure (Ptm) across the arterial wall. The resulting arterial volume oscillations travel through arm tissue and appear in the cuff pressure signal.

- PWV information can be acquired via a combination of electrocardiogram (ECG) and photoplethysmogram (PPG) sensor combination. In addition, the travel of the pulse along the artery can be modulated via occlusion-based perturbation controlled via the cuff.

We propose a robust measurement strategy to assess brachial arterial compliance by fusion of the two information sources: arterial pressure-volume data and PWV. The method is tailored to critical care and the sensor fusion is intended to minimize the measurement uncertainty and inaccuracy that is expected in a hemodynamic monitoring environment. The algorithm is based on Bayesian analysis principles combined with physiological insights acquired via non-invasive measurements performed on healthy subjects. Parameters of a model describing brachial arterial collapse mechanics are inferred. Chapter 4 presents an alternative method based on non-parametric processing of cuff signals for estimation of arterial compliance. Benefits and drawbacks of parametric vs. non-parametric processing thus become evident. Chapter 5 presents a method for accessing arterial viscoelastic properties via the principle of “external oscillometry”. This involves measurement of the arterial volume response to externally generated controlled pressure pulsations, as opposed to standard oscillometry, which involves assessment of volume response to internal BP oscillations. Note that the methods aim to estimate local arterial compliance at brachial/distal site, as opposed to global, Windkessel arterial compliance, as presented by Westerhof et al [13].

In Chapter 5, we further advance our understanding of the vasculature response to occlusion-based perturbations by analyzing BP waveforms acquired invasively downstream from the cuff in patients monitored in the operating room. We find that highly dynamic and patient-specific effects occur in the distal arm as a result of cuff inflation. Ample hemodynamic information is expressed in the signals. The observations lead to improved interpretation of the ECG, PPG and cuff signals, which enable further access to vascular properties: artery-vein interaction, limb peripheral resistance, distal arterial and venous compliances. Moreover, it is shown how information on non-standard parameters such as arterial compliance can lead to improved estimation of standard parameters, such as BP.

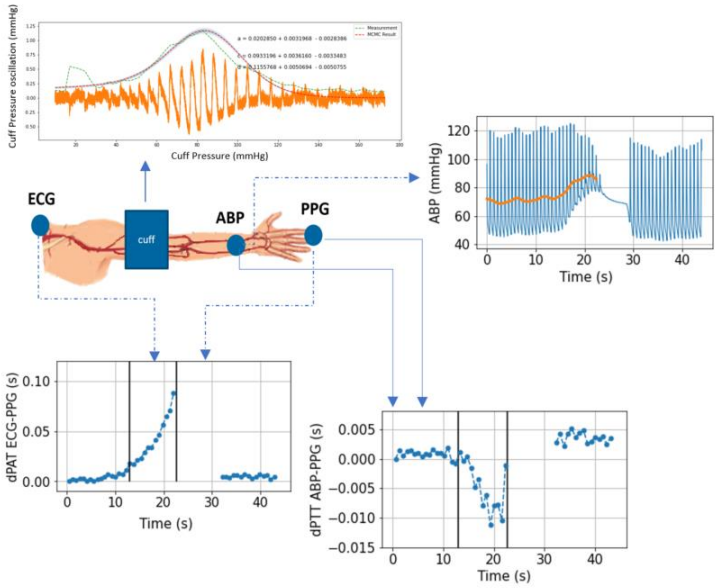

Figure 3. Visualization of main signals investigated in this thesis.

Part II of this thesis tackles aspects concerning the implementation of the proposed measurement strategies. More specifically, while simulation frameworks, theoretical models and physiological insights acquired from patient data are essential for the development of novel measurement strategies, the implementation of measurements in clinical practice requires an in-depth understanding of cuff transducer device characteristics and of patient-specific arm tissue properties.

The cuff-based oscillometric measurement principle has been used clinically for more than 100 years. However, in standard practice, the signals recorded via the cuff are still processed via empirical methods to infer BP values. Such empirical methods have been developed based on observations that cuff pressure oscillations at certain amplitude ratios are the same as reference clinical BP measurements (invasive, auscultatory) [11]. While empirical methods are generally accurate in normotensive patients, large errors in BP values have been reported in hypotensive and hypertensive patients. In addition to this, the empirical processing hinders further interpretation of the cuff pressure signal, and arterial volume amplitude/waveforms are difficult to extract for inference of additional hemodynamic parameters. Theoretical models describing oscillometry beyond empirical evidence have been developed; however, these models often overlook aspects related to transducer device characteristics and to patient-specific cuff-arm tissue interaction, assuming idealized behavior of these components. "*The occlusive arm-encircling cuff is probably one of the most widely used instruments in the measurement or blood pressure. Yet, its function as a mechanical device has not been explored. It is a device that has been developed more out of practicality than of engineering design.*" [14]

Figure 4 illustrates the oscillometric process decomposed into a number of basic steps: pressure pulsations in the artery cause the arterial wall to distend; this distension propagates through arm tissue and finally results in volume change at the exterior of the arm being measured as cuff pressure oscillations. In the following chapters we verify the validity of assumptions concerning several of these individual steps and we gain insights into the oscillometric process via a series of experimental studies.

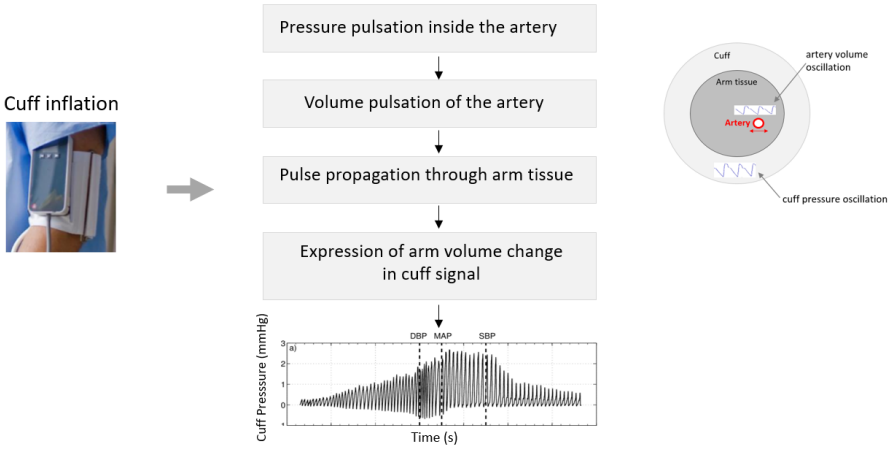

Figure 4. The oscillometric measurement can be decomposed into a number of basic steps.

Chapter 7 is focused on the investigation of the isolated cuff. More specifically, the study explores the cuff "transfer function" TF_{cuff}, which is the relationship between the input and output signals (i.e., the arm volume oscillations and the recorded cuff pressure oscillations). Knowledge of the TF_{cuff} is an essential step in the measurement of arm volume oscillations and, consequently, in measurement of artery volume oscillations. While several characterizations of TF_{cuff} exist, cuff-related uncertainties still remain, and there are no mechanical models which can accurately describe the behavior of the standard air cuff.

We first attribute this limitation to the fact that the existing studies are mostly qualitative, assume idealized nonrealistic, purely elastic material properties, ignore the frequency dependence of material stresses in the cuff wall, and experimental characterization is often missing or is incomplete. Because of this, we attempt to provide a more detailed mechanical characterization of the cuff properties. A dedicated experimental set-up is used, and air effects and viscoelastic cuff material effects are studied in depth. A number of relevant insights are acquired. Based on these insights, we then realize that the cuff properties depend on many factors, such as inflation speed, time passed since previous inflation, tightness of wrapping, unpredictable cuff folding during inflation; it is unlikely that mechanical characterization of typical cuffs, even when additional model complexity is added, would enable practical translation of arm volume oscillations.

In Chapter 8, an approach alternative to mechanical modelling is used to tackle

cuff-related uncertainties. The impact of the cuff behavior variability on the accuracy of cuff measurements is assessed via a specialized experimental set-up. We demonstrate a potential solution to eliminate cuff-induced measurement inaccuracies by using a simple calibrator device for real-time identification of TF_{cuff}. The presented solution is appealing from a clinical perspective. Embedding of a calibrator device within existing cuffs is feasible and it required only minimal changes to standard clinical equipment. While studying the isolated cuff is an essential part to improved cuff-based measurements, it solves only part of the oscillometric model uncertainties. Cuff-arm tissue-artery interaction along the length of the cuff is complex and requires further investigation.

To tackle this, in Chapter 9, the oscillometric process is studied by means of magnetic resonance imaging (MRI) of the upper arm during cuff inflation. Up until now, oscillometry has been studied via methods such as computer analysis, ultrasound measurements, ex-vivo analysis of arterial collapse, ECG/PPG-based PWV measurements, and mechanical characterization of cuff devices. MRI provides a new perspective over the oscillometric process, by enabling simultaneous visualization of artery, surrounding tissue, veins and the cuff over the entire length of the upper arm during cuff inflation. Images acquired from participants belonging to different demographic groups are used to verify common assumptions related to tissue compression due to cuff inflation and to provide further insights into the oscillometric process.

In Chapter 10 the findings of this thesis are summarized and discussed, along with the future perspectives.

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CHAPTER

02

BACKGROUND

New hemodynamic parameters in peri-operative and critical care – key concepts, characteristics, and challenges

Based on:

- Bogatu L.I., Turco S., Mischi M., Schmitt, L., Woerlee P., Bezemer R, Bouwman A., Korsten H. H., and Muehlsteff J.; New hemodynamic parameters in peri-operative and critical care – a review of key concepts, characteristics, and challenges. - Submitted

Abstract

Hemodynamic monitoring technologies are evolving continuously - large number of bedside monitoring options are becoming available in the clinic. Methods such as echocardiography, electrical bioimpedance, calibrated/uncalibrated analysis of pulse contour are increasingly common. This is leading to declining use of highly invasive monitoring and is allowing for safer, more accurate and continuous measurements.

The new devices mainly aim to monitor the well-known hemodynamic variables (e.g. novel pulse contour, bioreactance methods are aimed at measuring widely-used variables such as blood pressure, cardiac output). Even though hemodynamic monitoring is now safer and more accurate, a number of issues remain due to the limited amount of information available for diagnosis and treatment. Extensive work is being carried out in order to allow for more hemodynamic parameters to be measured in the clinic.

In this review we identify and discuss the main strategies aimed at obtaining a more complete picture on the hemodynamic status of a patient, namely, (i) measurement of circulatory system response to a defined stimulus, (ii) measurement of the microcirculation, (iii) technologies for assessing dynamic vascular mechanisms and (iv) machine learning methods. By analyzing these four main research strategies, we aim to convey key aspects, challenges and clinical value of measuring novel hemodynamic parameters in critical care.

2.1. Introduction

In peri-operative and critical care, assessment of hemodynamic function plays an essential role in the treatment of patients at risk of deterioration [1]. The principle of hemodynamic monitoring consists of interpreting a number of observations, or measurements with reference to a model which encompasses the overall current understanding of cardiovascular physiology. For example, information on parameters such as cardiac output (CO), blood pressure (BP) and central venous pressure (CVP) is usually interpreted with respect to the Guytonian view of the circulation [103]. This enables a general assessment of cardiac function and fluid responsiveness based on a limited number of physiological measurements, supporting clinicians in detecting patient deterioration and monitoring therapy effectiveness [104].

In practice, the way in which measurements are performed for the purpose of hemodynamic assessment can differ greatly in terms of clinical context: pathophysiology and progression of disease, the type of procedure and level of acuity, further patient-specific requirements and restrictions. These factors determine the required level of measurement accuracy and frequency for adequate clinical decision support, which in turn determine the level of monitoring invasiveness, measurement location, and degree of automation [1]. Invasive methods involving arterial, venous, and pulmonary artery catheters enable accurate, continuous measurement of hemodynamic parameters. However, their clinical benefits are in many cases outweighed by the probability of complications associated with invasive lines, the dependence on resources and trained staff, and by the uncertainty whether invasive monitoring would actually lead to better patient outcomes when compared to non-invasive, intermittent, or less accurate monitoring [106].

To tackle the compromise between the reliability of measurements and their invasiveness, various low-risk hemodynamic monitoring technologies are being developed [2, 105]. A large number of bedside monitoring options are becoming available in the clinic [61], including echocardiography, technologies involving electrical bioimpedance and bioreactance, techniques based on calibrated and uncalibrated arterial pulse contour analysis are increasingly common [2]. Such methods are allowing for more continuous, accurate minimally invasive hemodynamic management; this has led to a declining use of highly invasive monitoring such as by pulmonary artery catheterization.

The new devices mainly aim to monitor the well-known hemodynamic variables which have been previously validated and extensively used in clinical practice. For example, novel pulse contour or bioreactance methods aim to measure widely-used macrocirculatory variables such as central arterial BP, CO and related indices – preload, afterload, contractility. As a result, even though monitoring technologies are evolving continuously, the parameters most-frequently used in standard practice remain largely unchanged. This applies especially to general wards, where it is difficult to reliably measure additional hemodynamic parameters beyond arterial BP, peripheral arterial oxygen saturation (SpO2), and cardiac rhythm via electrocardiogram (ECG) [62].

While hemodynamic monitoring has developed greatly over the last decade, a number of issues still remain due to the limited amount of information available for diagnosis and treatment.

For example, there is still uncertainty in the interpretation of the widely-used variables such as BP [3, 4, 5, 6]. Even in the case of accurate, continuous BP measurements, the BP value is a late indicator of deterioration and controversy exists in the clinical community

regarding what is considered a “healthy” BP range. While recent findings suggest that a 65-mmHg mean arterial pressure (MAP) threshold should be regarded as an absolute minimum to prevent harmful hypotensive conditions, this contradicts with the movement towards personalized BP thresholds in fluid/vasopressor therapy protocols [3, 72]. This leaves the use of BP as a therapeutic target open for discussion. One aspect to this discussion is that recent findings related to the microcirulatory function in critically-ill patients have shown how micro- and macrocirculation can sometimes be dissociated, especially in cases of sepsis [7], and that tissue hypoperfusion may exist under conditions of normal and high BP. Monitoring the microcirculation, however, is a cumbersome task to date and not part of standard clinical guidelines or protocols. Another recognized need is earlier detection of deterioration in low-acuity settings; the wards requiring the most immediate improvement [8, 9]. Missed patient deterioration as a result of insufficient ward monitoring is considered one of the main factors in the 4.2 million cases worldwide per year, in which patients died within 30 days after surgery. At the same time, however, the existing ward measurements lead to frequent alarms, which are unspecific and have a false alarm rate of 90% [73]. This further presses the issue of managing hemodynamically unstable patients with limited and unspecific information.

In addition to this, it is believed that our fundamental understanding of cardiovascular physiology encompassed via Guytonian models might be incomplete and insufficient under the clinical conditions encountered in peri-operative and critical care. Early experiments underpinning such models are still being debated [110, 119]. At the core of Guytonian models lies the interaction between cardiac function and the return of blood to the heart. This provides an important, but simplistic construct for assessing hemodynamic (in)stability and response to therapy. The limited amount of information available via standard hemodynamic measures could be one of the factors limiting our ability to further apply our developing understanding of cardiovascular physiology in clinical practice and to expand existing models of potential value to peri-operative and critical care patients.

While the work aimed at refining measurements of standard parameters is unarguably of great relevance for peri-operative and critical care, a pressing need exists for complementing such established parameters with additional hemodynamic indices. This is important both for improvement of patient management in standard practice, as well as for further developing our fundamental understanding of the (patho)physiological processes that underlie cardiovascular complications.

A majority of efforts aimed at obtaining more complete information on the cardiovascular system via bed-side measurements rely on four main strategies:

1. Interpretation of the widely used parameters via functional hemodynamic monitoring. This is based on measuring response of the circulatory system to defined stimulus [1].
2. Measurement of the microcirculation [7] – direct assessment of the pathways of oxygen delivery and of the primary site at which oxygen exchange takes place.
3. Emerging technologies for characterization of dynamic vascular regulation – recent cardiovascular research is focused on study of natural compensatory mechanisms. Changes in vascular properties (compliance, viscosity, artery-vein interaction [19, 31, 33]) can precede changes in commonly measured hemodynamic indices such as BP, CO.

4. Data-driven, machine learning (ML) assessment of physiological signals. Statistical methods are used to identify complex interactions between physiological signal characteristics to predict adverse hemodynamic events or to estimate variables which are not directly measured.

Focusing on these four main strategies, this review identifies key aspects, challenges and clinical value of measuring novel hemodynamic parameters in critical care.

A general pattern across the work carried out on this topic is that extensive developments are being realized in research, however the findings are slow to find their way to standard clinical diagnosis and treatment procedures. An analysis is needed to reveal different approaches, points of view, from perspectives of clinical research as well as technology/sensor development. By conveying the complexity of hemodynamic monitoring today as well as envisioned future directions, this review intends to provide insights in identifying what is needed to accelerate the translation of research findings into meaningful implications for patient care.

2.2. Interpretation of the widely used parameters via functional hemodynamic monitoring

Functional hemodynamic monitoring consists of measuring the circulatory system's response to a well-defined stimulus. While these approaches measure the same well-known hemodynamic parameters such as CO, BP, SPO2, additional interpretation is given to the measurement by accounting for a controlled perturbation - offering extra information and a more complete picture on the status of a hemodynamically unstable patient [74, 1]. For example, the passive leg raise technique which has been the focus of many recent studies [75], measures CO with respect to a sudden blood shift towards the heart. The response of the CO parameter with respect to this blood volume shift reveals whether the patient is fluid responsive in the case of suspected need for fluid administration.

Compared to static measurements, functional (dynamic) measurements can better reveal when compensatory mechanisms of the circulatory system are activated, thus enabling earlier detection of deterioration and proactive interventions.

Measurements already employed in some clinical settings are based on interpreting heart-lung interaction for the purpose of assessing fluid responsiveness. An example is the pulse pressure variation (PPV) parameter, which quantifies the changes in arterial pulse pressure during mechanical ventilation [108]. Other measurements include stroke volume variation (SVV), end-expiratory occlusion test and tidal volume challenge. Some heart-lung interaction parameters can also be measured non-invasively via transesophageal echocardiographic approaches or via pulse contour analysis [113].

Other measurement strategies involve analyzing the response of the vasculature to cuff-based occlusions. Across applications, this principle has been used to investigate a multitude of conditions (e.g. venous thrombosis [33] and endothelial dysfunction [96, 97]). In critical care, cuff-based perturbations have mainly been used in combination with near infrared spectroscopy devices [65, 98] to obtain information on tissue metabolic function.

Variations of the same concept can be adapted to a large number of monitoring settings. For example, the ECG signal morphology response to an increase in heart rate can

be analyzed to reveal coronary artery properties [65], the arterial pressure response during a Valsalva maneuver can predict fluid responsiveness [107] and the microcirculatory function has also been studied with respect to thermal challenges [79]).

Current challenges

Functional hemodynamic monitoring has been gaining increasing interest from clinicians for its ability to enable more proactive patient management with existing clinical technologies. Especially when it comes to personalization of fluid management, dynamic measurements (PPV, SVV, passive leg raise, fluid challenge) are recommended over combinations of static measurements (such as BP, HR, CO, urine output, central venous oxygen saturation, lactate).

However, functional measurements share similar limitations with standard vital sign measurements. There are uncertainties regarding the interpretability of the measures - it is unclear how to achieve more personalized targets. For example, PPV is unarguably valuable for predicting fluid responsiveness. However, in some cases, a clear distinction between fluid responders and non-responders is difficult to define. For this reason, the spectrum of PPV values has been categorized into three zones: PPV values expected from responders, PPV values expected for non-responders and a PPV value "gray zone" where a patient and context-specific levels of uncertainty exist in the interpretability of the measure. (e.g. "Applicability of pulse pressure variation: How many shades of gray" [20]). This limitation is similar to the extensively studied difficulty of defining a threshold BP value to avoid hypotensive events.

Also, similarly to standard measures such as BP and CO, a compromise exists between degree of invasiveness/obtrusiveness and ability to perform continuous/repeatable functional measurements. This compromise is particularly evident in stop-flow measurements where a cuff is kept inflated for extended duration of time on a patient's arm to reliably measure dynamic tissue oxygen saturation. Also, the usefulness of PPV and SVV is questioned when lung-protective, low-tidal volume mechanical ventilation is used [140].

In addition to this, functional measurements pose extra challenges compared to standard measurements, mainly due to their novel nature. For example, the passive leg raise involves bed adjustments and possibly other actions which might differ from standard clinical workflow of managing the general patient population. The passive leg raise is generally limited to particular patients and clinical cases, e.g. it is typically performed to assess fluid responsiveness prior to resuscitation for the already hemodynamically unstable patient. Other well-known functional parameters such as SVV/PPV are mainly intended for the invasively monitored, mechanically ventilated patients in deep sedation, thus limiting applicability to the OR/ICU [135]. Functional measurements are not yet standard for prediction/detection of adverse events in the general patient population (for example in the wards). Automation, or inclusion of functional measurements in standard detection of deterioration spot-check might be found impractical in the near future.

2.3. **Develop technology specifically designed to assess microcirculation**

Inadequate tissue perfusion results in insufficient oxygen supply of cells. One way of identifying alterations in supply of oxygen is to assess the microcirculation - the primary site at which oxygen exchange takes place. Significant regulation mechanisms occur at the microcirculatory level and this was first observed via direct visualization of the capillaries [68]. Parameters such as capillary density, heterogeneity of capillary distribution, proportion of stopped or intermittently perfused capillaries were found to be linked to various conditions. For this reason, in the past three decades, hand-held microscopy at bedside underwent major technological advancements to allow for in-depth study of the microcirculation. By overcoming device limitations (such as motion artifacts, calibration requirements, measurement depth, temporal resolution, automated feature extraction, device bulkiness) it was possible to assess the relevance of measurement locations and the specificity of different morphological parameters. Visualization of the pathways of oxygen delivery improved the understanding of tissue oxygenation, capillary alterations in relation to progression of disease, pathophysiology of septic, cardiogenic and hemorrhagic shock [12] and expected patient outcomes [66, 69].

In parallel to the development of direct capillary visualization, other optical technologies such as near-infrared spectroscopy were adapted to measure tissue oxygenation as a surrogate for microcirculatory function [67, 63]. These technologies have been found particularly relevant in the assessment of cardiovascular reserve and tissue metabolic function via analysis of reoxygenation/deoxygenation rates in relation to occlusion-based perturbations. Interesting physiological [101] and pathophysiological [65] mechanisms have been observed via measurement of tissue oxygenation response to vascular occlusion tests.

Current challenges

Despite their significant contribution to advanced understanding of regulation mechanisms, the devices designed for measurement of microcirculation face a range of challenges in terms of inclusion in clinical hemodynamic monitoring practice in the general patient population [83]. The measurements are very localized and only reflect the quality of the microcirculation at pre-defined sites. For example, it is not known if sublingual microcirculation reflects other sites, such as the gut [136]. Also, peripheral locations such as the limbs might be influenced by factors such as temperature, which can impair the interpretability of microcirculatory measurements. It is not yet clear how to make use of existing microcirculation measurements for prediction of hemodynamic instability or therapy guidance. Ongoing research aims to solve uncertainties around microcirculatory response to systemic macrocirculatory changes [72] and differences between measurement sites in the body [22, 99, 100]. There are remaining questions that still need to be answered to achieve standardization and formal technology assessments are required to determine the precise role of these devices in critical care [21, 68].

Inevitably, further development of optical measurement techniques will take place to enable observations related to structural and functional characteristics of the microcirculation. Optical methods that are currently being investigated involve technologies such as laser Doppler imaging, laser speckle contrast imaging [85] and optical coherence tomography [86]. It is argued that optical measurements are limited to easily accessible surfaces, such as skin, muscle and tongue [22] and therefore, it is unlikely that optical

measurements alone will achieve comprehensive understanding of microcirculatory alterations (such as in different organs) [70, 68, 84].

"Despite their high spatial and temporal resolutions, optical imaging modalities are still not widely used for clinical imaging of the microcirculation due to their limited tissue penetration. Diffuse optical imaging techniques such as NIRS ameliorate this to some extent, but at the expense of spatial resolution. "[84]

For this reason, microcirculatory measurement devices intended for hemodynamic monitoring will likely involve optical methods complemented by other technologies such as ultrasound (US) and magnetic resonance imaging (MRI). Recent studies have made use of US to identify renal microcirculation alterations [71] and hybrid technologies involving photo-acoustics are currently being investigated [88]. Such studies together with novel developments of thin-film, wearable ultrasound transducers [114] may open up new possibilities for bed-side measurement of microcirculatory function. In addition to this, insights acquired from applications such as coronary disease management [111] will likely serve as basis for applying MRI to better understand oxygen delivery mechanisms in different organs and under different pathological states.

2.4. **More advanced assessment of vascular properties**

2.4.1. Cardiovascular research and its relevance for critical care

Cardiovascular diseases are a leading cause of death worldwide. Global efforts are aimed at understanding cardiovascular disease prevention, treatment and management [88]. Emerging insights have contributed to the development of models, devices, measurement procedures for cardiovascular indices, therapy standardization, as well as the discovery of new research trajectories. The solutions developed for cardiovascular disease management have enabled understanding of the arterial system, including arterial wall-blood interface, coupling between heart and vasculature, local and systemic arterial properties.

In particular, significant evidence on the importance of active arterial regulation mechanisms has been found. Studies are revealing complex, dynamic behavior of arteries on local as well as systemic levels [115, 31]. Since early observations on the ability of vessels to constrict/distend, evidence about other mechanisms has been found: pulse propagation, systemic resistance, local flow, wave reflection are controlled via factors such as non-linear properties of the arterial wall, viscosity, damping properties, frequency-dependent behavior, and strain-dependent activation of the smooth muscle tone [31]. Because of this, a more integrative approach to physiology is nowadays being encouraged, in which vascular compensatory mechanisms are studied. Methods for observing and measuring these compensatory mechanisms are being developed.

"When modeling blood circulation, the heart is usually considered the main element, the only one which has an actual relevance in the operation of the system, thus neglecting blood vessels, which are considered simple conduits that connect the cardiac pump with the organs. Such a basic approach underestimates the prominent role shown by blood vessels in general and by arteries in particular", "The active stress developed by smooth muscle has been overlooked as a contributor to the mechanic behavior of vessels, although it has been demonstrated that the activation of smooth muscle changes the stress–

strain relationship towards high levels of stress", "This is very important when studying the cardiovascular system given the active participation of the nervous system in hemodynamic regulation." [31]

Short-term, dynamic regulation of arteries are especially relevant in hemodynamic monitoring. Therefore, it is worth investigating how to adapt the recent findings in cardiovascular disease management to overcome limitations in patient monitoring. Changes in vascular properties can precede changes in commonly measured hemodynamic indices such as BP and CO.

Given that advances in the field of cardiovascular disease management are not usually discussed in the context of critical care, this section will require a more complex overview. For this reason, this section has been subdivided to allow for inclusion of more in-depth background information related to cardiovascular disease management parameters and their potential relevance for hemodynamic monitoring.

2.4.2. Arterial stiffness

Extensive studies on arterial stiffness have been conducted up until now. Many of these studies are aimed at understanding the strong link between the level of distension of the arteries and BP, with the aim of developing continuous, non-obtrusive (cuff-less) BP measurements. Beat-by-beat BP fluctuations throughout the day as well as long-term trends in BP over years can reveal the impact of lifestyle and pathological conditions on cardiovascular function. The most promising solution for monitoring BP continuously and non-invasively involves measurement of arterial stiffness (or compliance).

"*An important overarching concept underlying* cuffless *measurement of blood pressure is the fundamental relationship between transmural pressure and mechanical properties of the arterial wall which influence wave propagation phenomena. This is the pressure dependency of the material stiffness of all blood vessels. This property is present in all species with pressurized circulatory systems and is a fundamental evolutionary property of arterial design" [19].*

The level of distension of the arteries can be deduced from studying the speed at which the wave propagates along an artery (pulse wave velocity, PWV, pulse transit time, PTT), or by studying the artery volume amplitude/waveforms [143]. Since arterial stiffness is influenced by blood pressure, it can thus be assumed that a change in wave propagation is caused by a change in BP. For this reason, a large number of technologies have been designed to acquire information on PWV/ arterial distension (ultrasound, tonometry, radar, photoplethysmography, phonocardiography, impedance cardiography, seismocardiography, electrical impedance tomography, ballistocardiography [19]).

"*PTT is a measure for arterial stiffness. When blood pressure increases, the vascular tone increases and the arterial wall becomes stiffer, causing the PTT to shorten." – [19]*

However, major limitations have been identified such as the uncertainty of arterial stiffness being influenced by other factors besides BP (e.g. smooth muscle activation via hemodynamic regulation mechanisms) and the difficulty in approximating BP value– surrogate value relationship (e.g. a change in wave propagation speed of x ms reveals a change in BP of y mmHg). Frequent re-calibrations by means of simultaneous measurement of BP and PWV can in principle solve such issues. Initialization algorithms are also

employed to reduce the number of obtrusive re-calibrations or to increase the accuracy of the estimates. Solutions based on empirical knowledge and physiological models combined with demographic data (age, sex, weight, height) have been attempted. Despite the various proposed solutions, at the moment there is still no clear optimal method for linking PWV to BP, as many other items remain unsolved: location for surrogate measurement, distance travelled by pulse, inability to assume artery uniformity over large distances, peripheral arterial beds being significantly affected by regulation mechanisms, re-calibration intervals etc.

"Is "Cuffless" the Future of Blood Pressure Monitoring? There have been many patent submissions, start-up companies, and scientific publications, but to date there is no device that is universally accepted by the wider community beyond research laboratories and company boardrooms." [19].

A. Insights on vascular regulation mechanisms

Even though the non-obtrusive, or minimally obtrusive BP measurement is still considered an open question, the large-scale nature of the research resulted in a collection of extensive data related to arterial properties, regulation mechanisms, vascular hemodynamics. For example, PWV and arterial volume waveforms have been studied in the context of exercise, rest [120], sleep [121], or administration of vasoactive medication [36, 37]. Studies have also been conducted to understand arteries at local sites (brachial, radial, finger site) vs regional sites (PWV measured from heart to finger, or heart to femoral, toe or combinations) and peripheral vs. central regulation [112]. Other studies are dedicated to analysis of PWV as function of different mean lumen diameters [58]. Measurements involving pulse arrival time (PAT) or pulse transit time (PTT) confirm long-standing data that smooth muscle is sparser at the aorta, while in smaller arteries, smooth muscle can contract enough to impact pulse transit independently from BP [122]. PAT/PTT models have also revealed interesting processes of the circulatory system, such as blood redistribution during digestion in the context of ambulatory BP measurements [40, 42, 43]. This is relevant for identifying when to trigger a recalibration of BP value - PAT surrogate relationship.

B. Insights on technology requirements

Besides aiding in making observations on regulation mechanisms, the large number of studies have also contributed to identifying technology requirements for measurement of arterial properties. Device characteristics such as PPG sensor contact impact on PTT [41], hydrostatic effects [44], BP cuff size/shape/design properties [76, 77, 78], different cuff inflation strategies [112, 124, 124], measurement of cardiac factors [144] have been investigated and processes for validating devices have been improved [44]. Motion artifacts, signal-to-noise ratio have also been thoroughly investigated [55]. Several cuff and cuff-less device prototypes have been built and many measurement strategies have been tried out to sample arterial beds. Some examples involving variations of cuff, ECG, PPG, tonometric technologies are:

Device	Measurement procedure
Arteriograph	A cuff placed at brachial site is pressurized suprasytolically, therefore removing effects stemming from vasculature under the

(TensioMed, Budapest, Hungary) [123]	cuff and distal from the cuff. Arterial pulsations occur at the upper edge of the cuff. The resulting cuff signal is processed to obtain information such as central pulse wave velocity, aortic pressure values, wave reflection characteristics.
Mobil-O-Graph (IEM Gmbm, Stolberg, Germany) [124]	A cuff placed at brachial site is used; the cuff pressure is recorded with the use of a high-fidelity pressure sensor. The inflation process includes several seconds where the cuff pressure is held at diastolic vale. The waveform is analyzed to estimate aortic pressure values, wave reflection characteristics.
Complior (ALAM, Vincennes France) [125]	The method uses two non-invasive tonometric sensors to simultaneously record pulse waves in the carotid and femoral arteries to measure carotid-femoral pulse wave velocity for assessment of arterial stiffness.
PTT - BP calibration based on cuff modulation [127, 128, 81]	A cuff is used to alter transmural pressure across the brachial artery for the purpose of modulating PTT. The change in PTT with respect to the controlled transmural pressure is measured via ECG and PPG and analyzed in order to calibrate the BP-PAT relationship for the purpose of beat-to-beat PAT-based BP estimation and arterial stiffness estimation.
Chronos TM-2771 (A&D Company, Tokyo, Japan) [78]	Arterial diameter at brachial site is measured via a device consisting of four adjacent cuffs. The cuffs are designed of soft and hard materials such that the resulting cuff pressure oscillation reflects brachial artery volume oscillation as accurately as possible.
Water-filled cuff [16]	A water-filled blood pressure cuff is used to allow the brachial artery to be simultaneously imaged via ultrasound. The aim is to obtain an accurate measurement of brachial arterial volume during cuff-based occlusion.
Hydraulic coupling (UP-MED, recently merged with Philips Medizin Systeme Boeblingen, Germany) [146]	A revisited cuff measurement method involving hydraulic coupling to the upper arm by means of a semirigid conical shell incorporating a hydraulic sensor pad with a pressure transducer. This enables a high-fidelity measurement of tissue pressure pulse contour.
SphygmoCor (AtCor Medical, Sydney, NSW, Australia) [126]	Brachial and femoral cuffs or, alternatively, applanation tonometry of the carotid and femoral sites are used together with specially developed algorithms to acquire central aortic pressure waveform and carotid-femoral arterial PWV for the purpose of estimating cardiovascular risk.

Aktiia SA Aktiia SA, Neuchâtel, Switzerland [44]	Optical sensors perform green reflective photoplethysmography (PPG) measurements on the skin vasculature of the wrist to measure BP.

In addition to prototypes aiming to improve, adapt, or re-interpret typical cuff, ECG, PPG, tonometry technologies, several research groups and start-ups have attempted out of the box measurements, also providing unique technology insights – glasses with PAT sensors [129], BP measurement underwear [137], weighing scale BP estimation involving ballistocardiogram and PPG signal measured from the sole of the foot [130], other wearables [131], phone solutions [132], elaborate measurement settings involving technologies such as electrical impedance tomography [133], contactless transdermal optical imaging [134].

C. Value for critical care

It is important to assess whether the arterial tone can be re-interpreted for assessing the short-term adjustments in arterial properties for applications in critical care. Knowledge of smooth muscle tone (arterial compliance/stiffness) could be of high clinical interest as will be outlined below. ICU clinicians have expressed interest in these parameters [2], vascular compliance having a significant impact on CO estimations. However, measurements of arterial compliance in critical care are scarce. Methods for quantifying and interpreting short-term, dynamic regulation of arteries have yet to be investigated and developed.

Value for recalibration of standard measurements

As a first application in critical care, arterial stiffness estimates can be used for measurements requiring calibration. Devices which use pulse waveform as surrogate of cardiac output (PiCCO), require re-calibration whenever changes in arterial compliance occur as result of hemodynamic regulation mechanisms, vasoactive drug administration or in cases of development of vascular edema [2].

"The major weakness of all these devices is the drift in values whenever there is a major change in vascular compliance, as, for example, in vascular leak syndrome with increased vessel wall edema leading to decreased arterial compliance. " [2]

Therefore, identifying when such devices require re-calibration can be a first relevant application to introduce arterial property measurements in clinical hemodynamic monitoring practice. Such application can serve as basis for developing better understanding of arterial regulation for tackling other unmet clinical needs.

Value as predictive parameter and improvement of blood pressure estimation

Changes in arterial properties might precede changes in blood pressure and flow, and may be used for early warning of hypotension and hemodynamic instability. Moreover, information on arterial compliance can aid in interpretation of blood pressure values. Complementing the BP value with more information could make the measurement more specific.

For example, arterial compliance measurements can be used in principle to differentiate between heart related factors or vasodilation to identify the cause of a BP drop, thus facilitating improved fluid management. In addition to this, insights on the dissociation

between BP (or other macrocirculatory variables) and microcirculation could possibly be acquired from assessment of arterial compliance at central vs. peripheral vascular beds.

Another application likely to benefit from the recent findings related to arterial compliance is the accuracy of the cuff-based non-invasive BP measurement (NIBP). NIBP is still based on an empirical interpretation of the cuff pressure signal, which leads to large systematic errors in BP estimations especially in cases of hypo and hypertension. An in-depth characterization of the vasculature response to occlusion-based perturbation (such as cuff-induced arterial collapse and resulting effects on pulse propagation) can lead to better understanding of the cuff measurement principle, possibly leading to more accurate NIBP [40, 41, 116].

Current challenges

Despite the plethora of health data related to arterial properties available for interpretation, development is still needed for implementation of arterial compliance measurements in critical care. Concrete findings and standardized measurement setups are still lacking and controversy exists in the community. In many cases, the studies involving PAT/PTT are performed on small numbers of subjects, allowing for interesting qualitative insights, hypothesis identification and discovery of new research directions; at the same time the scarce nature of the measurements and variability in non-standardized measurement setups lead to uncertainty. There are evident and exhaustively discussed conflicting results regarding usage of PAT for BP monitoring [45, 46, 47]. As another example, the study of vasoactive drug effects on specific vascular beds is also not conclusive [36, 37]. Zong et al [36] reveals that vasoactive drugs do not influence arterial wall elasticity in the arm, while Banks et al [37] concludes the opposite – significant smooth muscle relaxation at brachial site is measured after administration of vasoactive drugs. However, the two studies are realized via very different methods – in the work by Zong et al [36] the PAT measured over a large distance via ECG and ABP (heart to radial site) is analysed in ICU patients. In the work by Banks et al [37] localized ultrasound imaging is employed to measure artery size at the brachial site in healthy subjects.

Another example of un-resolved conflicting findings is the effect of PPG contact pressure on finger vasculature. In two studies [41, 51], different findings are reported about the shape of PAT as function of PPG contact pressure, and it is recognized that the difference in the findings cannot yet be explained.

Comparing seemingly disagreeing studies or interpreting individual studies within a bigger picture is difficult to accomplish without the existence of standardized databases to validate assumptions, to account for error sources and for validation of signal processing algorithms (e. g. such as the MIMIC database). Many aspects of arterial compliance are currently being investigated [145, 37, 36, 45, 46, 47, 120, 121], further studies are required to converge the various research modalities and findings.

"The direct effect of smooth muscle relaxation on arterial elastic properties is controversial."" In human subjects, the contribution of smooth muscle to arterial elastic mechanics has been limited by difficulty in separating the direct effects of a vasodilator drug on the arterial wall from the indirect effects due to reduced blood pressure." [37]

More dedicated studies are required for re-interpretation of cardiovascular disease research in the context of hemodynamic monitoring. Preliminary, on-going research is tackling the challenge of establishing a standardized setup and overcoming some of the patient monitoring device uncertainties [80]. The setup presented in [80] aims to reduce the variability in existing BP cuffs and to determine whether compressibility of the arm due to cuff inflation is a significant source of error in cuff-based arterial compliance measurements. Besides this, a measurement setup involving existing hemodynamic monitoring devices (ECG, PPG and BP cuff), together with a dedicated signal processing algorithm have recently been proposed for measurement of arterial stiffness in critical care [81] and feasibility has been demonstrated via computer simulations and limited patient data.

2.4.3. Beyond arterial stiffness

An example of cardiovascular research topic to be re-interpreted for critical care applications is detection of venous thrombosis [33]. In [33], a parametric hemodynamic model describes the interaction between arterial and venous beds in partially occluded limbs; the model parameters are representative of clinically relevant indices related to thrombosis. The model however also includes parameters such as systemic resistance and blood vessel compliance, which are also relevant to hemodynamic monitoring, as stated by the author:

"*Finally, it is particularly important to note that changes in the compliance and resistance deduced with the aid of the model exhibit a dependency on pressure and flow, respectively, which is characteristic of the compliance and resistance of blood vessels. This suggests that a particularly appropriate application for the model is to use changes in the model parameters to monitor circulatory changes of the limb, such as those, for instance, that may occur during clinical anaesthesia."* [33]

Similar artery-vein interactions are studied in the context of endothelial function assessment [96]. Parameters such as arterial flow or venous distention are measured following induced ischemia of the limb to detect the extent to which regulation mechanisms are activated in response to tissue hypoxia. Such measurements are well-established in assessment of cardiovascular health and extensive efforts are aimed at further developments to enable standardization across disciplines, including critical care [97, 98].

Another example of relevant research involves the study of non-linear properties of arterial collapse [17, 18, 16, 15, 31]. Such properties are studied by estimating arterial cross-sectional area or compliance under different transmural pressures across the arterial wall. There is interest in finding whether such non-linear vascular parameters adapt due to vasoactive medication or due to activation of regulation mechanisms.

Many other regulation mechanisms linked to viscosity, damping properties and strain-dependent activation of the smooth muscle tone are being investigated [34, 31, 35]. Such dynamic behaviors can be studied on local as well as systemic levels [48, 49]. The studies give an outlook on the large amount of research still needed to characterize the intricate mechanisms of the cardiovascular system. Such research is currently difficult to perform in-vivo, however, further developments are being enabled by rapid technological advancements, such as continuous measurement of vascular flow and diameter by means of wearable, operator independent ultrasound patches [135, 141].

Current challenges

Modelling "beyond arterial stiffness" is important from a research perspective for obtaining physiological understanding. However, limitations exist in terms of clinical implementation; it is recognized that a very in-depth modelling is unlikely to have practical applicability, since the circulatory system is far too complex and patient/context specific. Accurate measurement of many parameters such as pressure, flow waveforms, pulse travel across arterial segments might not be realistic in standard patient care.

"It is well known that hemodynamics of large arteries is too complex to be apprehended using only non-invasive measurements and medical imaging techniques.", "As 3D models can only be used in small portions of the cardiovascular system due to their high modelling and computational costs, reduced-order models have gained attention to reproduce complex wave propagation behaviors in large networks of arteries.", "Although arterial pressure is easy to measure, the precise measurement of blood pressure requires highly invasive techniques."[31] "In cases where it is not possible to develop physical models it becomes necessary to use shortcuts based on empirical, statistical, or even simple profile models." [59]

2.5. **Data-driven approaches**

The arterial pulse signal contains ample information regarding complex homeostasis processes and this knowledge has been documented as early as in the 2nd century [52]. In traditional Chinese and Greek medicine, the pulse is seen as an important source for understanding health and disease. Reading of the pulse has always been recognized to have potential in aiding medical practice. First observations were based on a qualitative assessment on rhythmicity, pulse variation, elasticity of the artery.

"*How can one tell whether a pulse is 'full', 'rapid' or 'rhythmical'? Is there a perceptible pause when the artery has reached the limit of its contraction and, again, of this expansion? Is there also a pause when the artery returns to its normal size? Such questions Galen resolved partly historically, by referring to earlier authorities, and partly from experience. His own enthusiasm for studying the pulse, which has been with him since youth, and his hours of practice had given him, he claimed, a most sensitive touch, an example worth imitation"* [139]

Today, advances in sensor technology and physiological models have allowed for development of reliable HR, BP, and blood oxygenation estimations based on pulse measurements. In some cases, measurement of CO, SV and estimation of some arterial properties is also possible via the pulse, although such measurements come with several assumptions and controversy.

It is evident that the pulse contains far more information than currently exploited; lately, data-driven approaches have been used to attempt extracting this additional information from the pulse. Such methods are based on statistics and have the potential to pick up on subtle signal characteristics in large datasets while bypassing the need for circulatory system physiological characterization.

As an example, the Hypotension Prediction Index algorithm (HPI; Edwards Lifesciences, Irvine, USA) uses supervised learning to processes high fidelity arterial pressure waveforms and to estimate the likelihood that a hypotension event will occur 5-15 minutes in the future [89]. The algorithm is trained to detect which interactions between

thousands of potentially informative waveform features reveal compensatory mechanisms preceding a drop in blood pressure. The aim is to use the HPI and related information to act before hemodynamic instability occurs.

A great variety of other ML methods have been applied to process information encoded in signals acquired via PPG, ECG, intra-arterial line, cuff and volume clamp sensors. In fact, most of the existing ML algorithms have been adapted to process such physiological signals: variations of regression approaches, decision trees, support vector machines, different types of neural networks [53, 40, 93]. Methods such as regression models and decision trees require complex handcrafting of potentially informative features, while methods based on neural networks are usually applied when minimal signal pre-processing takes place. In the latter case, the algorithm automatically discovers features from data.

Such ML techniques are designed for example to predict deterioration events, such as sepsis, hemorrhage, unplanned intubation [90], or to estimate variables which are not directly measured (e.g. BP estimation via PPG/ECG waveform analysis [53, 102]). It is not clear up to this point which of the ML algorithms are most suitable for such applications. For this reason, some studies include thorough comparisons between performance of different statistical methods [91].

However, the choice of algorithm might play a secondary role in comparison to other factors, such as defining the information source that is most relevant for a given application. For example, in [89] the relevant information source for prediction of hypotension is defined as the pulse waveform – subtle adjustments and interactions in waveform features are identified when changes in compensatory mechanisms take place. In [91] however, the algorithm for prediction of hypotensive events does not take waveforms into account, arguing that the resulting features are too reliant on signal quality (waveform quality depends on hardware, filtering and digital signal processing). Instead, minimal information regarding the pulse (e.g. absolute values of vital signs) and ample context information (medications, ventilator data, demographics) are defined as relevant information sources. Both approaches are considered promising [92].

Current challenges

Despite the large number of identified opportunities, extensive research and great variety of investigated algorithms, ML has not yet been established as a standard clinical tool in hemodynamic monitoring [82]. In other fields, ML algorithms are found to be as beneficial as theoretical models, and in some specific applications, ML algorithms are found to even surpass the performance of conventional methods for signal processing and analysis. For example, deep learning has clearly surpassed standard approaches in image processing segmentation tasks [117]. Also, ML-based reconstruction of MRI images can be achieved by entirely bypassing the inverse Fourier transform, opening doors to interesting developments of image acquisition strategies [118]. There are several factors which could explain the limited usage of ML in hemodynamic monitoring.

One such factor is the difficulty of accessing good quality data due to the variety of measurement setups and medical procedures, the dependency on operator skills to place sensors, the transport of patients which usually involves changes from one recoding system to another (e.g. OR to ICU to ward). Also, in many cases it is difficult to document procedures and patient history or outcome. It is still unclear how to fully document

context.

In addition to this, many sensor effects are not fully understood or characterized. PPG contact pressure, cuff size and placement, wrapping tightness have recently been found to affect signal quality and interpretability [41, 76, 77, 78, 55]. In certain cases, even sensor effects of invasive measures such as arterial line can make the data unusable (e.g. inaccurate damping). Waveform signal quality depends on hardware, filtering and digital signal processing, if these steps are not known in depth then ML methods can be unreliable. Besides sensor effects, physiological effects are also not fully understood. Tissue compression and pressure transmission effects in cuff inflation [80] or volume clamp devices are particularly difficult to account for in ML models which lack transparency and interpretability [64]. Improved standardization of the measurement procedures is needed to enable data-driven methods.

In terms of databases available for algorithm training, in machine vision applications, performance of deep learning is strongly dependent on large amounts of annotated images collected over years. This might not be as feasible for 1D signals. Manual annotation is more difficult for 1D signals and few clinicians are available for completing annotation tasks. For example, in radiology, clinicians annotate X-ray images by default, in hemodynamic monitoring it does not occur in regular practice to annotate PPG/ECG/cuff signals in detail.

Even in the case of a well-annotated database, human biology and pathology can vary considerably. Applying ML to find the inverse function of a sensor vs. applying ML to understand physiological data are very different tasks. It is difficult to assess whether a database is sufficiently rich to represent the full variability of the underlying pathophysiology. Most existing algorithms are developed based on single-center studies. For this reason, algorithms usually work well on retrospective data, or in controlled environments, but they fail when they are applied to new patient groups or contexts. This poses a fundamental problem of the generalizability of the results and obtained ML models. For example:

- Cuff-based non-invasive BP measurement algorithms are optimized for normotensive patients and significant errors in clinical BP readings are being reported in hypo- and hypertensive patients [14].
- An algorithm for predicting kidney injury (DeepMinds [56]) was trained on data collected mainly from patients in a veteran hospital - a demographic not representative of the general population.

Another aspect is that, in most cases, defining a well-posed problem suitable to ML interpretation in hemodynamic monitoring is difficult. For example, is hypotension defined at 60 mmHg, 65 mmHg or personalized for every patient? [3, 4, 5, 6, 72].

Ultimately, there is no clinical interest in simply predicting parameters such as BP. ML is only relevant when data can be linked to actions that are relevant for clinical practice, adding a level of complexity compared to other fields where ML has been used.

ML methods are not yet standard in clinical practice [94]. While it is known that the information contained in arterial pulsations is underutilized, it is still unclear to what extent additional information can be extracted via ML.

Future possibilities involving data infrastructures and explainable artificial intelligence

There have been efforts aimed at increasing the quality of ML algorithms via data infrastructures across research centers. The focus is placed on standardized collection and annotation of data, facilitating re-utilization of databases and validation of algorithms. Other parallel work is aimed at overcoming hemodynamic monitoring sensor limitations to allow for more reliable recording of hemodynamic signals. In some cases, ML itself is used to solve for sensor limitations, for example, in overcoming inter-operator variability and motion sensitivity in ultrasound image acquisition [142].

Innovation in the field of big data will also likely enable development of frameworks compatible with different information sources, such as complex pulse waveform data as well as patient and context-specific information. This is relevant especially in view of the large variety of emerging technologies aimed at measurement of microcirculatory properties, vasculature response to controlled perturbations, regulation mechanisms linked to elasticity, viscosity and smooth muscle characteristics. Innovative frameworks aimed at aggregation of large amounts of information will be necessary to identify correlations between parameters and development of improved hemodynamic models.

At the same time, new perspectives on development of more 'interpretable' ML models [57, 95] might play a role in the future applications of artificial intelligence for hemodynamic monitoring. Also, the increasing interest in the concept of 'digital twin' across fields of research might help re-evaluate the way ML algorithms are applied to understand physiology.

2.6. **Discussion**

This review presented current trends and main outlooks for advances in critical care via measurement of new hemodynamic parameters: reinterpretation of the widely used parameters via functional hemodynamic monitoring (measuring response of the circulatory system to defined stimuli), technology aimed at observing the microcirculation, adapting knowledge acquired from cardiovascular disease research, and machine learning approaches. All four identified research directions are well-founded and they unarguably stimulate new, innovative research that is essential to advancing our understanding of vascular physiology.

However, the four research directions do differ in terms of near-future impact on standard hemodynamic monitoring practice. Several aspects need to be taken into account in order to achieve effective translation of technology into clinical practice. On a practical level, it is important to consider the extent to which the proposed equipment differs from existing hospital equipment, the dependence on operator, standard practice, training of staff [60]. *"The major issue going forward will not be the sensitivity or specificity of any new index, since most are quite sensitive and specific, it will be the ease to which they can be assessed continuously or repeatedly and their level of invasiveness."* [65]. On a more fundamental level, great difficulty comes from the challenge of evaluating the performance of a hemodynamic monitoring system. Access to additional hemodynamic parameters might not guarantee improved patient outcome and the process of assessing the usefulness of advanced monitoring is complex [138]. "*no monitoring tool, no matter how accurate, by itself has improved patient outcome"* [1], *"Hemodynamic monitoring systems are measurement tools and their effects on outcomes are only as good as the protocols they are used to drive."*[138]. It is likely that relatively slow, incremental changes to existing medical equipment and protocols will take place to allow for

such evaluation of usefulness. A measurement strategy which does not differ to a large extent from standard practice is arguably easier to include in large scale extensive clinical studies designed to assess impact of the monitoring system.

Therefore, ideal solutions for near-future implementations will be based on standard, existent hospital equipment [60]. Due to this, functional parameters and several parameters adapted from cardiovascular research will be more immediately investigated in a clinical setting.

Regarding longer-term advances, the large-scale, world-wide effort aimed at understanding cardiovascular diseases combined with improved solutions for microcirculation assessment will point towards much more complex analysis of the vascular system (e.g. viscoelastic effects, inclusion of capillary activity, artery-vein interaction). In terms of research, machine learning, big-data statistical tools will likely be employed to help synthesize the large amounts of measurements and context information, helping to achieve more in-depth understanding of the circulatory system and the dynamic interactions between different hemodynamic parameters.

Exceedingly complex modelling of the arterial system is unlikely to have practical applicability beyond research. The circulatory system is far too complex, patient and context-specific, requiring highly invasive measurements for accurate, real-time characterization. For this reason, big-data tools will also help in determining a finite, but optimized number of measurements and intelligent combinations of sensors most informative, safe and practical for patient monitoring clinical practice. Relatively simple, but well-understood theoretical structures, aided by empirical evidence will be used to interpret such measurements in clinical decision-support.

2.7. **Conclusion**

Hemodynamic monitoring has developed greatly over the last decade, many new technologies are becoming available in the clinic and the measurements are safer and more accurate. However, the new devices are designed for improved measurement of the commonly used indices (e.g. BP, CO). Extensive research is aimed at obtaining a more complete picture of the hemodynamic status of a patient, but the findings are slow to find their way to clinical practice. In this review we revealed that inclusion of new hemodynamic parameters in standard practice presents unique and complex challenges.

To overcome such challenges there is need to complement technological/sensor advancements with improved standardization of measurement setups, development of big data frameworks compatible with different information sources and larger clinical studies. However, more fundamental questions might need to be tackled in parallel, such as how to evaluate the usefulness of a hemodynamic monitoring system and how interpret new hemodynamic information with reference to existing models encompassing current understanding of cardiovascular physiology.

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PART

1

CHAPTER 03

Assessment of arterial compliance by fusion of oscillometry and pulse wave velocity information

Based on:

- Bogatu, L.I., Turco, S., Mischi, M., Woerlee, P., Bouwman, A., Korsten, E.H. and Muehlsteff, J., 2020. A modelling framework for assessment of arterial compliance by fusion of oscillometry and pulse wave velocity information. *Computer Methods and Programs in Biomedicine*, *196*, p.105492.
- Bogatu, L.I., Turco, S., Mischi, M., Woerlee, P., Bouwman, A., Korsten, E. and Muehlsteff, J., 2020, July. Method for measurement of arterial compliance by fusion of oscillometry and pulse wave velocity. In *2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)* (pp. 469-472). IEEE.
- Laura Bogatu, Jens Muehlsteff, Maarten Kuenen, Erik Bresch. Control Unit for Deriving a Measure of Arterial Compliance. 2018. Published as: CN113226161A; EP3669762A1; EP3897363A1; JP2022512449A;US2022071496A1;WO2020126576A1.
- Laura Bogatu, Jens Muehlsteff. Method and apparatus for estimating reliability of cardiac output measurements. 2020. Published as: EP3964124A1; WO2022048959A1.

Abstract

Measurement of arterial compliance is recognized as important for clinical use and for enabling better understanding of circulatory system regulation mechanisms. Estimation of arterial compliance involves either a direct measure of the ratio between arterial volume and pressure changes or an inference from the pulse wave velocity (PWV). In this study we demonstrate an approach to assess arterial compliance by fusion of these two information sources. The approach is based on combining oscillometry as used for blood pressure inference and PWV measurements based on ECG/PPG. Enabling reliable arterial compliance measurements will contribute to the understanding of regulation mechanisms of the arterial tree, possibly establishing arterial compliance as a key measure relevant in hemodynamic monitoring. Methods: A measurement strategy, a physiological model, and a framework based on Bayesian principles are developed for measuring changes in arterial compliance based on combining oscillometry and PWV data. A simulation framework is used to study and validate the algorithm and measurement principle in detail, motivated by previous experimental findings. **Results**: Simulations demonstrate the possibility of inferring arterial compliance via fusion of simultaneously acquired volume/pressure relationships and PWV data. In addition, the simulation framework demonstrates how Bayesian principles can be used to handle low signal – to – noise ratio and partial information loss. **Conclusions***:* The developed simulation framework shows the feasibility of the proposed approach for assessment of arterial compliance by combining multiple data sources. This represents a first step towards integration of arterial compliance measurements in hemodynamic monitoring using existing clinical technology. The Bayesian approach is of particular relevance for such patient monitoring settings, where measurements are repeated frequently, context is relevant, and data is affected by artefacts. In addition, the simulation framework is necessary for future clinical-study design, in order to determine device specifications and the extent to which noise affects the inference process.

3.1. Introduction

Up until now, research on measurement of vascular wall properties has mainly been conducted with the aim of identifying long-term impact of lifestyle, ageing or pathological conditions on cardiovascular function. In particular, studies related to long-term changes of arterial wall stiffness have contributed to better understanding of cardiovascular health and risks associated with cardiovascular disease. As a result, recent international efforts have been made to achieve standardization of arterial stiffness measurements as complementary to blood pressure measurements [1, 2, 3].

However, short-term, dynamic regulation of arteries is also relevant, especially in the context of hemodynamic monitoring. Wall stress and lumen diameter, adjustments of the smooth muscle tone are important for regulation of blood pressure (via the balance of stressed and unstressed volume and shifts of blood volume within the circulatory system). Changes in these vascular mechanical properties can precede changes in blood pressure and cardiac output; knowledge of arterial compliance could be of high clinical interest. Critical care, trauma, ICU clinicians have expressed interest in these parameters [8], however, measurements are scarce. Methods for measuring and interpreting short-term changes in arterial compliance have yet to be investigated and developed.

Changes in smooth muscle tone have been identified as particularly relevant in hemodynamic measurements requiring calibration. Devices which interpret pulse wave velocity as surrogate for blood pressure changes [5,6], or devices which use pulse waveform as surrogate of cardiac output (PiCCO [7]), require re-calibration whenever changes in arterial compliance occur as result of hemodynamic regulation mechanisms, vasoactive drug administration or in cases of development of vascular edema [8]. Therefore, identifying when such devices require re-calibration can be a first relevant application to introduce arterial compliance measurements in clinical hemodynamic monitoring practice.

Such application can serve as basis for developing better understanding of smooth tone regulation and tackling other unmet clinical needs:

1. Earlier warning of patient deterioration; changes in arterial properties might precede changes in blood pressure, flow and may be used for early warning of hypotension and hemodynamic instability.

2. The uncertainty in interpretation of blood pressure (BP) values in hemodynamic monitoring [9-12]; complementing the BP value with more information could make the measurement more specific (e.g. identify the cause of a BP drop – differentiate between heart related factors or vasodilation).

3. The dissociation between micro and macro circulation [13, 14]; reliable measurement of arterial compliance might give insights into regulation mechanisms at micro vs macro level.

4. The recognized need of including functional variables [15]; the cuff inflation could induce short-term changes in arterial properties, which might reveal information about the hemodynamic status of a patient [32].

5. Guidance of fluid management through addition of extra hemodynamic parameters related to arterial properties.

6. Research on oscillometric non-invasive BP measurements is needed to improve accuracy of the measurement especially for hypo- and hyper tension [31]. Understanding of arterial property expression in the oscillometric signal can improve accuracy of the BP measurement [19].

3.1.1. Measurement of arterial stiffness

There are two existing methods of measuring arterial stiffness: either based on analysis of arterial cross-sectional area with respect to arterial pulsatile pressure or based on analysis of wave propagation along regions of the arterial tree [16]. Below we describe how these two methods can be implemented.

1. A suitable modality for measuring arterial cross-sectional area is via imaging techniques such as ultrasound [17] or MRI [18, 28]. However, such techniques are not practical in clinical care settings. Alternatively, the arterial size can be obtained more indirectly via oscillometry. Oscillometric measurements are based on varying transmural pressure across the brachial arterial wall by inflation of a pneumatic cuff. A pressure sensor inside the cuff gives indication on the amplitudes of the arterial volume pulses via the resulting cuff pressure pulses, as transmural pressure over the artery is varied.

The data obtained from oscillometry is usually processed to derive blood pressure values. Mean arterial pressure is found by identifying the cuff pressure at which maximum volume pulses occur, while systolic and diastolic pressures are found at cuff pressures where certain empirical ratios in the pressure signal occur. Oscillometric data can also be interpreted for the purpose of obtaining information on arterial size as function of transmural pressure. Figure 1 shows simulated examples of this relationship, illustrating how arterial properties can vary from person to person and with time. As shown by Bank et al [17], administration of vasoactive drugs influences the relationship. Several studies have investigated methods of measuring the arterial cross-sectional area - transmural pressure relationship by means of oscillometric measurements [19 - 21]. Arterial properties such as compliance under a range of transmural pressures, as well as collapse characteristics can be obtained from this measurement.

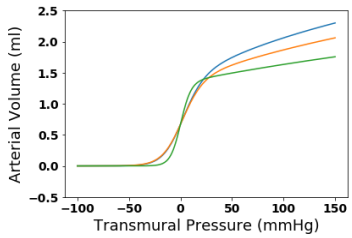

Figure 1. Illustration of varying arterial volume under the cuff (simulated).

2. Pulse wave velocity (PWV) measurements of arterial compliance are based on elastic principles of pressure pulse wave propagation in compliant vs. rigid tubes. Pressure pulses generated by the heart travel faster along stiffer arteries than compliant arteries. Formulas such as Bramwell-Hill or models based on transmission line principles [22] are used to relate PWV to arterial compliance as

$$PWV(P_{tm}) = \sqrt{\frac{\mathrm{V}(P_{tm})}{\rho * \mathrm{C}(P_{tm})}}, \quad (1)$$

where P_{tm} is transmural pressure across the arterial wall, ρ is the blood density, $V(P_{tm})$ is the arterial volume as a function of P_{tm}, and $C(P_{tm})$ is the arterial compliance as a function of P_{tm}.

PWV can be measured directly or it can be inferred from pulse travel time (i.e., the time of travel of the pressure pulse over a distance in the arterial tree). Imaging technologies such as Doppler ultrasound and MRI have been used [23, 24]. A more accessible way to measure PWV which does not involve imaging, is based on measuring pulse arrival time PAT – the time delay between the R-peak of the electrocardiogram ECG signal and a fiducial point in the photoplethysmogram (PPG) signal at the finger site or other peripheral location.

3.1.2. Arterial stiffness measurement in hemodynamic monitoring

Usual patient monitors include ECG, PPG and blood pressure cuffs. Therefore, it would be advantageous to infer brachial arterial compliance by assessment of arterial volume changes with respect to pressure changes through oscillometric measurements or by inference via pulse wave velocity derived from ECG/PPG based on data collected by the already available signals.

A source of uncertainty in the extraction of arterial properties from ECG/PPG-derived PWV is that vessel properties can differ significantly from central to peripheral locations. Therefore, assuming uniformity of the arterial properties is unrealistic. A complex transmission line model, together with the possibility to measure pulse arrival time at several locations between the heart at the finger PPG would be necessary to extract location-specific arterial properties. Drawbacks of measuring PWV based on ECG/PPG-derived PAT include the difficulty of approximating heart pre-ejection period (PEP), as well as measuring the exact distance that the pulse travels between the two sites.

A strategy to overcome these uncertainties can be derived from work concerning calibration techniques for BP surrogates [25]. Recording PAT changes during the inflation of a cuff placed on the upper arm enables estimation of arterial properties specifically at the cuff location. This is due to the localized change in transmural pressure over the arterial wall at brachial site. Therefore, this approach uses the cuff inflation to provide: 1) oscillometric data and 2) PAT changes induced by local changes in transmural pressure. A setup to simultaneously record oscillometric data and PAT based on this concept is shown in Fig. 2. A cuff is placed on the upper arm to obtain brachial artery volume oscillations from pressure oscillations in the cuff dependent on the transmural pressure. Simultaneously, PAT is recorded by means of computing the delay between the R-peak of the ECG signal waveform and a fiducial point of the PPG waveform (which is obtained at the finger site of the same arm as where the cuff is placed).

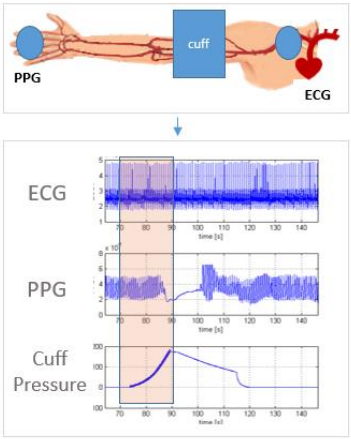

Figure 2. Arterial compliance measurement setup. ECG, PPG and cuff pressure signals are recorded on the same arm during cuff inflation.

As a follow up of this experimental work, in this paper we present an algorithmic framework for joint processing of volume/pressure data and PWV changes to robustly infer arterial compliance. The presented measurement method is designed to detect changes in arterial compliance at the brachial location. Arterial changes of systemic nature are detected at this site; this information complements the BP value extracted at the same brachial site through the cuff-based measurement. Our hypothesis is that this local information is also relevant for systemic changes in the vascular system.

Firstly, a forward model is presented which expresses the oscillometric and PAT data based on the mechanical properties of the artery. This is followed by introduction of a simulation framework to infer arterial compliance using a Bayesian fusion technique. The obtained results are discussed with emphasis on their clinical relevance.

3.2. **Methodology**

Information obtained from PAT and oscillometry measurements can be jointly processed by considering dynamics of arterial collapse and how such arterial mechanics are expressed in the two signals. More precisely, collapse mechanics are represented through a mathematical model describing arterial cross-sectional area changes as transmural pressure is varied [21]. The model parameters are expressed either in cuff pressure oscillations, in pulse wave velocity, or in both. The model reads as:

$$A(P_{tm}) = \mathrm{d} * \frac{\ln(\mathrm{a} * P_{tm} + \mathrm{b})}{(1 + \mathrm{e}^{-\mathrm{c} * P_{tm}})}, \qquad (2)$$

with parameter a representative of arterial compliance at normally occurring transmural pressure values (when cuff is fully deflated, transmural pressure varies between systolic and diastolic values), a and c representative of non-linear volume changes of arterial collapse around 0 mmHg transmural pressure, d representative of absolute arterial sizes. This equation fits experimental data of vessel collapse for both circular (P_{tm}>0) and non-circular (P_{tm}<0).

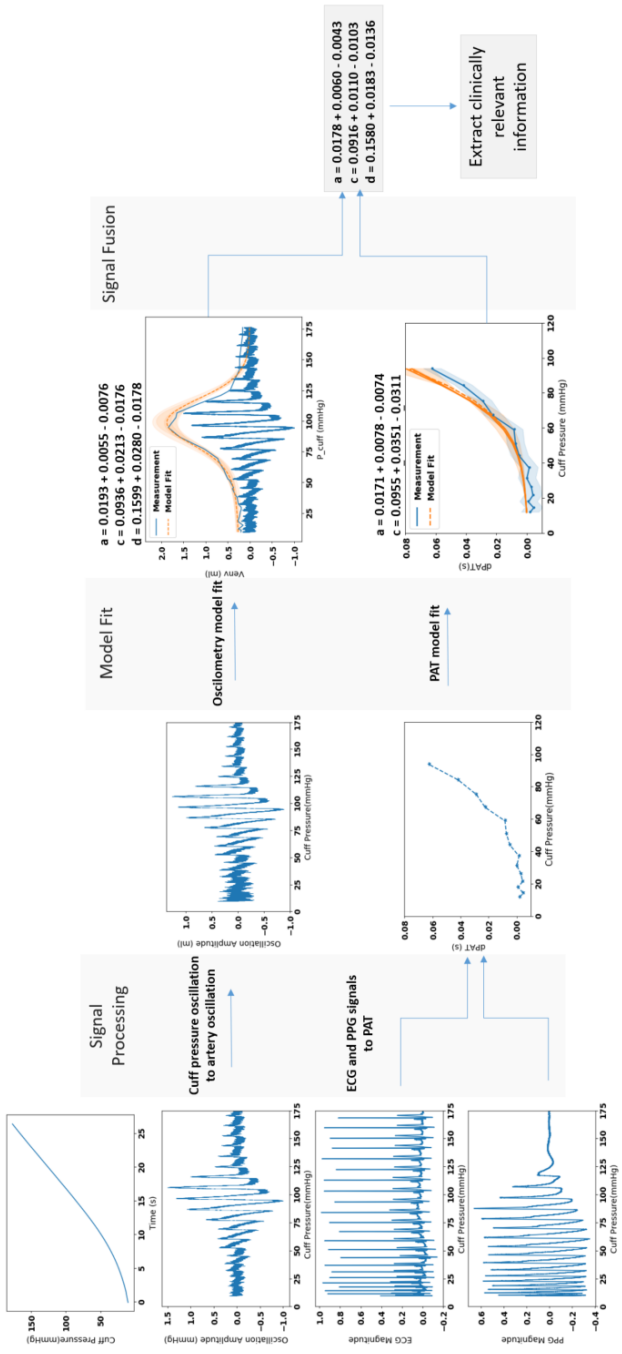

Figure 3. Signals acquired from a healthy volunteer through the measurement method shown in Fig. 2.

Differently from [21], here the free parameter b is set to an empirically chosen constant value of 3.3. From a practical perspective, this is justified by the possibility to express such arterial characteristics with adjustments in the parameters a, c and d only.

Here we propose an algorithm for the analysis of oscillometry and PAT recordings in order to infer values of the arterial collapse model parameters a, c and d. This algorithm is illustrated using data from an early experimental test of the method (see Fig. 3). Fig. 3 shows an example of acquired signals from a measurement on a healthy volunteer. Significant gain in robustness is observed when comparing parameter values obtained via oscillometry vs. parameter values obtained via fusion of oscillometry and PAT recordings. In this example, inference via fusion decreases the uncertainty in estimation of parameter a by 20%, parameter c by 80% and parameter d by 40% (compared to inference via oscillometry alone). The approach has been tested on more than ten volunteers and the results are encouraging. However, extraction of arterial parameters from oscillometric data requires further work. Therefore, parallel ongoing work is tackling cuff-related uncertainties (the Signal Processing step illustrated in Fig. 3 involving translation of cuff pressure signal to arterial volume signal [29]). For this reason, a simulation environment has been created where these uncertainties can be removed to test and validate the sensor fusion approach.

3.2.1. Forward *model*

A. Expression of arterial properties in oscillometric data

Oscillometry consists of analyzing arterial volume as transmural pressure across the brachial wall is varied by means of inflating a pneumatic cuff. An illustration of transmural pressure and arterial volume pulsations, together with arterial volume amplitudes (volume envelope) over the course of a complete oscillometric measurement is shown in Fig. 4.

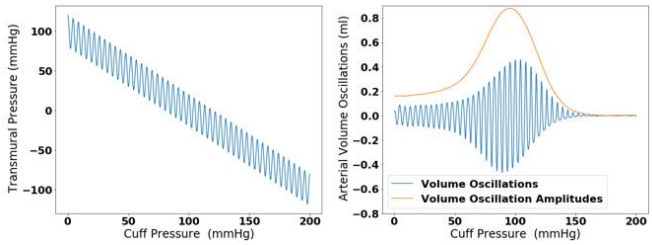

Figure 4. Illustration of the changes in a) transmural pressure and b) arterial volume as the cuff is gradually inflated.

The parameters of the arterial volume – transmural pressure relationship described by Eq. 2 influence the shape of the arterial volume envelope:

- a is reflected in the volume pulse amplitudes at low cuff pressures,
- a and c are reflected in the volume pulse amplitudes for cuff pressure reaching mean arterial pressure values and
- d has a scaling effect on the shape of the volume envelope.

The arterial volume oscillations cause pressure oscillations in the cuff. These are recorded with a pressure sensor. The magnitude of the pressure oscillations depends on the

cuff properties. Cuff transfer function (TF) as function of cuff pressure is necessary to recover amplitudes of arterial volume oscillations from cuff pressure oscillations. Figure 5 shows an illustrative example of the effect of cuff TF on the measured cuff pressure signal.

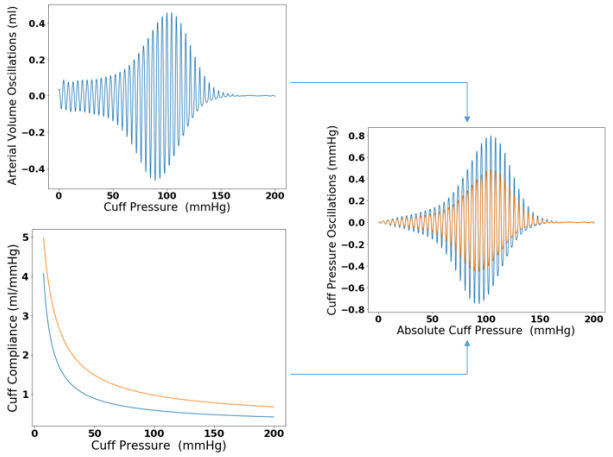

Figure 5. Cuff pressure signal is influenced by arterial volume oscillations and cuff TF. Blue and orange cuff pressure signals correspond to blue and orange cuff TF functions. It is observed how the two pressure signals differ significantly even though arterial oscillations are identical.

B. Expression of arterial properties in pulse arrival time data

The time delay between the R-peak of the ECG signal and a fiducial point in the PPG signal at finger site is used to compute PAT. Based on this measurement, the PWV can be obtained as:

$$\mathrm{PWV} = \frac{\mathrm{L}}{\mathrm{PAT}-\mathrm{PEP}} \qquad (3)$$

where L refers to the distance covered by the pulse and PEP is the heart pre-ejection period.

For this application, PAT is assessed during an oscillometric measurement. As cuff pressure increases, the arterial transmural pressure over the length of the cuff is altered, thus changing PAT values by $\Delta\mathrm{PAT}$. These changes are indicative of the artery characteristics for a range of transmural pressures. Relating PAT to PWV is necessary in order to quantify these characteristics. As PEP and L are difficult to measure, the assumption that PAT changes are primarily created under the cuff can be used to relate $\Delta\mathrm{PAT}$ to PWV [25] as:

$$\Delta\mathrm{PAT}(P_{tm}) = \left(\frac{1}{\mathrm{PWV}(P_{tm})} - \frac{1}{PWV_{ref}}\right) L_c \,, \qquad (4)$$

where PWV_{ref} is PWV at 0 cuff pressure and L_c is cuff length.

The PWV can reveal information on arterial properties by means of the Bramwell-Hill model (Eq. 1). To illustrate this model, Fig. 6 shows a simulation of the arterial size in relation to transmural pressure and the resulting compliance. PWV is estimated based on Eq. 1. From this, $\Delta\mathrm{PAT}$ is computed via Eq. 4. Since the PPG signal becomes distorted

as the cuff reaches mean arterial pressure values, the PAT and PWV simulations are shown in the relevant cuff pressure/transmural pressure ranges (0 to 100 mmHg transmural pressure in a typical subject).

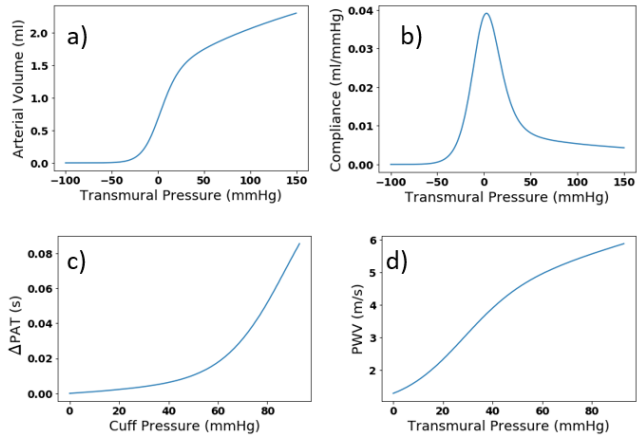

Figure 6. a) Illustration of arterial size with respect to transmural pressure and b) corresponding arterial compliance, c) PWV and d) PAT.

Parameters a and c in Eq. 2 influence the shape of the resulting PAT data. Parameter a mainly impacts the PAT curve in absolute terms, while parameter c influences the nonlinearity of the curve. Parameter d, which is representative of arterial absolute size does not have an effect on the PAT data. This can also be seen when combining Eq. 2 and Eq. 1, which results in cancelling out parameter d.

3.2.2. Parameter estimation

A dedicated estimator is introduced to extract the arterial collapse model parameters that are expressed in oscillometry and PAT measurements. As the recording setup involves several noisy sources that are present in a clinical environment where measurements are repeated frequently, a method based on Bayesian principles is found suitable for parameter inference. This rationale facilitates the interpretation of data fusion, quantification of uncertainty and detection of deviation from prior knowledge [26]. The two signal sources are processed in this Bayesian approach in order to determine parameters of the brachial artery pressure-area relationship.

A. *Parameter inference from oscillometric data*

The inference process is based on measuring arterial volume pulsations via the cuff. Amplitudes of arterial volume oscillations (volume envelope) translated from cuff pressure oscillations recorded during an oscillometric measurement are processed for inference of the parameters a, c, d (from Eq. 2) by means of a sampling approach.

The proposed algorithm receives as input a recording of cuff pressure of length determined by the duration of the oscillometric measurement and the sampling rate of the data acquisition system.

The pressure signal is:

- High-pass filtered to obtain pressure oscillations (P_{osc}) caused by arterial volume pulsations under the cuff. The cuff pressure oscillations are divided by cuff compliance, C_{cuff}, for calculation of the arterial volume oscillations (V_{osc}) as:

$$V_{osc} = \frac{P_{osc}}{C_{cuff}}. \quad (5)$$

The signal V_{osc} is processed for obtaining the volume envelope V_{env}.

- Low-pass filtered to obtain absolute pressure in the cuff, P_{cuff}. The transmural pressure across the arterial wall, P_{tm}, oscillates in the ranges $P_{sys} - P_{cuff}$ and $P_{dia} - P_{cuff}$ for every value of P_{cuff}. P_{sys} and P_{dia} values can be obtained by standard processing the P_{osc} signal. It is assumed in the inference process that P_{sys} and P_{dia} stay constant throughout the measurement duration.

A Markov chain Monte Carlo (MCMC) sampling process runs a pre-set number of iterations and generates a posterior distribution of arterial collapse parameters $P(\boldsymbol{\theta}|D)$, where $\boldsymbol{\theta}$ represents the parameter set $[a, c, d]$ and D represents the measured data $V_{env}(P_{cuff}), P_{sys}, P_{dia}$.

The posterior distribution $P(\boldsymbol{\theta}|D)$ is influenced by the observed data D and prior knowledge $P(D|\boldsymbol{\theta})$:

$$P(\boldsymbol{\theta}|D) \propto P(\boldsymbol{\theta})P(D|\boldsymbol{\theta}). \quad (6)$$

Given the lack of existing studies on arterial compliance in the context of critical care, a minimally informative prior $P(\boldsymbol{\theta})$ is used in the presented simulation framework. Parameter sets that satisfy the conditions $a > 0$, $b > 0$, $c > 0$, $aP_{tm} + 3.3 > 1$ are considered equally likely, while parameter sets that do not satisfy this condition have probability 0. These conditions enforce general physiological properties such as the arterial volume being larger than 0 and absolute arterial volume decreasing with cuff inflation.

The log-likelihood function $P(D|\boldsymbol{\theta})$ computes the probability that the measured data points $V_{env}(P_{cuff})$ could be generated by the model with parameter values $\boldsymbol{\theta}$. This gives as

$$P(D|\boldsymbol{\theta}) = \sum_{P_{cuff}=0}^{\max(P_{cuff})} \log\left(\frac{1}{\sqrt{2\pi\sigma^2}}\right) - \frac{\left(V_{env}(P_{cuff}) - V_{env\boldsymbol{\theta}}(P_{cuff})\right)^2}{2\sigma^2} \quad (7)$$

where $V_{env\boldsymbol{\theta}}(P_{cuff})$ is the expected volume envelope that would be obtained with the sampled arterial parameters $\boldsymbol{\theta}$ and measured P_{sys} and P_{dia}. This is computed by the same procedure as described in Section 3.2.1.A:

- The arterial volume under the cuff (V_{art}) is computed as function of P_{tm}. This depends on the proposed parameter values $\boldsymbol{\theta}$ and cuff length L_c, as:

$$V_{art}(P_{tm}) = L_c d \frac{\ln(a P_{tm}+3.3)}{(1+e^{-c P_{tm}})} \quad (8)$$

- For every absolute cuff pressure, P_{cuff}, the transmural pressure across the artery P_{tm} varies between $P_{sys} - P_{cuff}$ and $P_{dia} - P_{cuff}$ (Fig. 5). The transmural pressure-volume relationship computed in the previous step is used to obtain the arterial volume oscillation at every cuff pressure as

$$V_{env\boldsymbol{\theta}}(P_{cuff}) = V_{art}(P_{sys} - P_{cuff}) - V_{art}(P_{dia} - P_{cuff}). \quad (9)$$

Since the number of noise sources possibly affecting the measurement is not yet established (research on cuff transfer function, tissue compression is ongoing [27, 28]) a least informative noise model is used in this study. For this reason, the likelihood function in Eq. 7 assumes the measured samples of the volume envelope to be generated from a normal distribution with mean at the true value of the volume envelope and variance σ. The variance parameter is representative of expected measurement noise. This measurement noise is dependent on the accuracy of blood pressure measurement ($\mathrm{P_{sys}}$ and $\mathrm{P_{dia}}$), the accuracy of cuff transfer function characterization, arm tissue effects, number of recorded beats, or quality of interpolation between recorded volume oscillations (volume envelope of Fig. 5) or motion/breathing artefacts. These effects can be studied by characterization of the measurement setup, as well as identification of application-specific required measurement accuracy. In our simulations, the variance parameter value is set to 0.1 mL or 0.25 mL, corresponding to an accurate measurement and a measurement performed in a clinical setting respectively. For reasons explained in Appendix 1, only half of the volume envelope is considered for the inference algorithm - the volume envelope values corresponding to cuff pressures larger than mean arterial pressures are discarded.

B. Parameter inference from PAT data

The MCMC sampling process runs a set number of iterations and generates a posterior distribution of arterial collapse parameters $\mathrm{P}(\boldsymbol{\theta}\,|\mathrm{D})$, where $\boldsymbol{\theta}$ represents parameter set $[\mathrm{a, c, d}]$ and D represents the measured data $\mathrm{PAT}(\mathrm{P_{cuff}})$, $\mathrm{P_{MAP}}$ (mean arterial pressure MAP is used to link transmural pressure P_{tm} to P_{cuff}). The resulting posterior distribution is described by Eq. 10. The prior is identical to the one described in Section 3.2.2.A and the log-likelihood function given as

$$\mathrm{P(D|\boldsymbol{\theta})}=\sum_{\mathrm{P_{cuff}}=0}^{\max(\mathrm{P_{cuff}})}\log\left(\frac{1}{\sqrt{2\pi\sigma^2}}\right)-\frac{\left(\Delta\mathrm{PAT}(\mathrm{P_{cuff}})-\Delta\mathrm{PAT}_{\boldsymbol{\theta}}(\mathrm{P_{cuff}})\right)^2}{2\sigma^2} \tag{10}$$

where $\Delta\mathrm{PAT}_{\boldsymbol{\theta}}(\mathrm{P_{cuff}})$ is the data that would be obtained with the arterial parameters $\boldsymbol{\theta}$ and measured $\mathrm{P_{MAP}}$. This is computed by the same procedure described in Section 3.2.1.B:

- The relationship between P_{tm} and V_{art} is computed via Eq. 7. The derivative of V_{art} is the arterial compliance, C_{art}.
- Equation 1 is used to compute $\mathrm{PWV}(P_{tm})$.
- Equation 4 is used to compute $\Delta PAT(P_{tm})$, which is linked to $\mathrm{P_{cuff}}$ by

$$P_{tm} = P_{MAP} - P_{cuff}\ . \tag{11}$$

The likelihood function assumes the measured samples of volume envelope to be generated from a normal distribution with mean at the true value of $\Delta\mathrm{PAT}$ and variance σ set to 1 ms. The value of 1 ms assumes little measurement noise, but can be adjusted given characterization of measurement setup – MAP measurement accuracy, fiducial point extraction from PPG signals in presence of breathing and vasomotion, number of recorded beats or quality of artefact removal.

C. Parameter inference from fusion of PAT and oscillometry

PAT data can be considered an information source additional to the oscillometric measurement. In this way, the posterior distribution is computed based on prior knowledge, oscillometric and PAT data. The same MCMC method is used to simultaneously take into account both information sources. An algorithm combining the implementation of Sections 3.2.2.A and 3.2.2.B is used for fusion of the two information sources. Conditioned on the arterial collapse model parameters, the two observations are assumed to be independent, hence the posterior distribution can be characterized by

$$\mathrm{P}(\boldsymbol{\theta}\,|\mathrm{D}) \propto \mathrm{P}(\boldsymbol{\theta})\ \mathrm{P}(\mathrm{D}_{\mathrm{Oscillometric}}|\boldsymbol{\theta})\ \mathrm{P}(\mathrm{D}_{\mathrm{PAT}}|\boldsymbol{\theta}), \tag{12}$$

where the prior $\mathrm{P}(\boldsymbol{\theta})$ is the same as in Eq. 6, $\mathrm{P}(\mathrm{D}_{\mathrm{Oscillometric}}|\boldsymbol{\theta})$ is described in Eq. 7 and $\mathrm{P}(\mathrm{D}_{\mathrm{PAT}}|\boldsymbol{\theta})$ is described in Eq. 10.

3.2.3. Implementation

Implementation of the three algorithms described in Sections 3.2.2.A, 3.2.2.B and 3.2.2.C was realized in Python using the emcee library [29]. The representativeness of the posterior distribution on the parameters is checked for accuracy by Gelmen-Rubin chain convergence test; the algorithm is run to produce an effective sample size (ESS) of at least 10,000 for all presented simulations. For efficiency purposes related to computing power, Markov chains are clustered by the method described in [30]. To demonstrate the functionality of the algorithms and show possible clinical use cases, simulated data is regarded as real measured data.

A. ***2.3.1 Oscillometric data simulation framework***

A framework is implemented to simulate oscillometric data and to process this artificial signal by means of the MCMC algorithm (Fig. 7). Several simulations are performed to evaluate the clinical significance of the inferred parameter values and on the interpretablity of the additional information provided through Bayesian inference (such as confidence in the accuracy of the measurement, or deviation from prior knowledge).

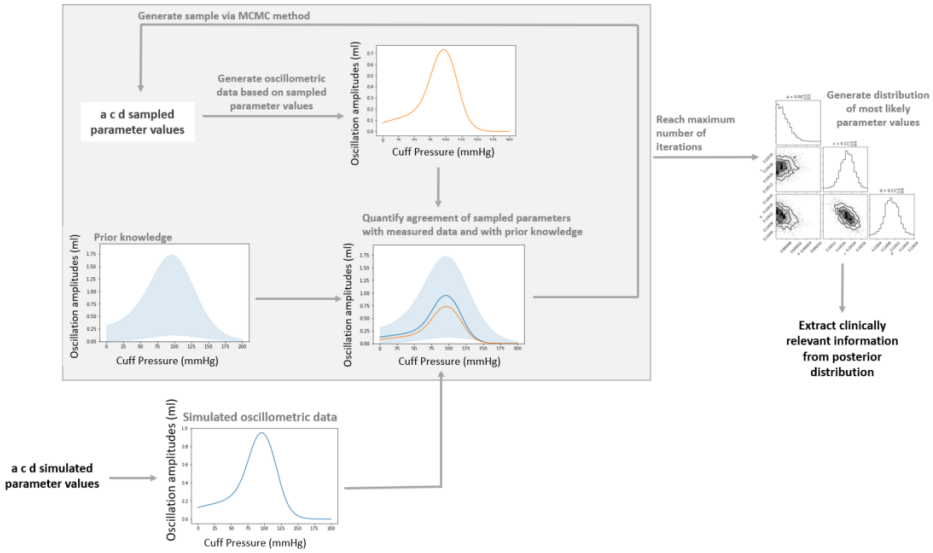

Figure 7. Overview of oscillometry simulation framework.

1. A volume envelope is simulated with parameter set [0.03, 0.1, 0.08]. P_{sys} and P_{dia} values are simulated as 120 mmHg and 80 mmHg, respectively, cuff length is set to 14 cm, and cuff pressure is simulated as gradually increasing from 0 to 200 mmHg. The measurement includes 32 beats which can be achieved with a measurement duration of about 30 seconds at 70 beats per minute heart rate. Expected measurement noise is set to 0.1 mL.

2. To enable a discussion on detection of arterial properties adjustments, vascular constriction is simulated. Absolute arterial size is decreased (parameter d is set to 0.06), compliance at normal transmural pressures is also decreased (parameter a is set to 0.02) and collapse characteristics are changed (parameter c is set to 0.11).

3. A different simulation is run for the purpose of studying a non-ideal case. The expected noise of the oscillometric measurement is increased to 0.25 mL (which could be expected for example in a setup where cuff compliance cannot be accurately characterized) and some minor breathing artefacts are simulated.

B. PAT data simulation framework

By the same approach, simulated PAT data regarded as real measured data are processed (Fig. 8). Two simulations are run:

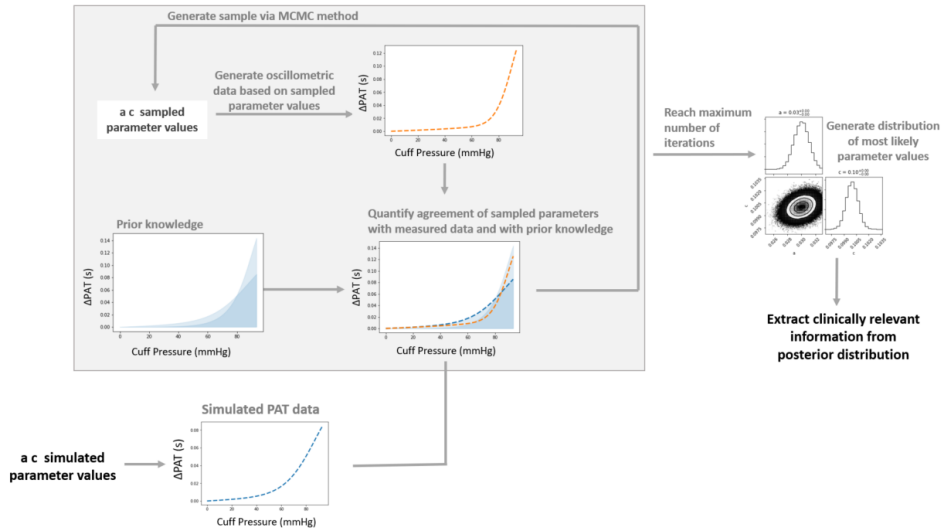

Figure 8. Overview of PAT simulation framework.

1. PAT data is simulated with parameter values a = 0.03, c = 0.1. Mean arterial pressure is simulated as 100 mmHg, cuff length is set to 14 cm, and cuff pressure is simulated as gradually increasing from 0 to 200 mmHg.

2. To obtain more realistic PAT data, a measurement where only 10 reliable samples are acquired during a cuff inflation is simulated. This choice is justified by the fact that PAT computing can be significantly affected by difficulty to measure at the peripheral site where PPG is recorded. Extracting reliable PPG waveform features can be challenging, especially as cuff pressure reaches mean arterial pressure values, at which point significant waveform distortion occurs and only a few PAT points can be obtained.

C. *Oscillometric and PAT data fusion simulation framework*

The framework is used to illustrate the possibility of simultaneous processing the two data sources. The realistic (non-ideal) oscillometric and PAT simulated data is provided as input to the MCMC inference algorithm. A pre-set number of sampled parameter values are compared to both input signals with consideration of prior knowledge. The output is a posterior distribution of parameter values. Simulations are run for the purpose of comparing results of processing individual simulated measurements to results of fusing the two measurements.

3.3. **Results**

A. *3.1. Parameter inference from oscillometric data*

An illustration of the oscillometric data simulated with parameter set [0.03, 0.1, 0.08] is shown is Figure 9.

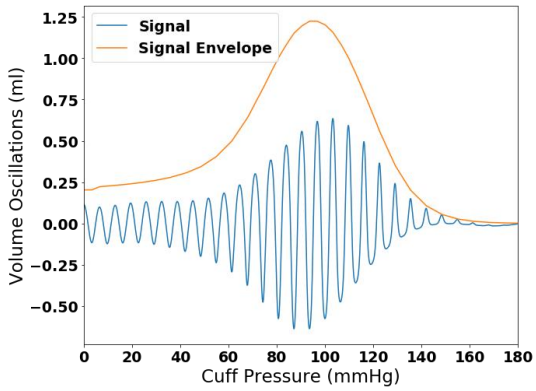

Figure 9. Simulated oscillometric data regarded as real measurement.

The simulated oscillometric data is fed into the MCMC sampling algorithm, which after a set number of iterations outputs posterior distributions for the three model parameters a, c and d (this process is illustrated in Fig. 7).

The posterior distribution can be summarized by the 95% highest density interval (HDI), which contains the 95% most probable parameter values, together with the distribution's central tendency [17]. Figure 10a shows the HDI of the posterior distribution obtained by processing the simulated oscillometric data.

The results indicate that the central tendency computed as median of the posterior distribution of the distribution approaches simulated parameter values.

Results of processing data from another simulated measurement (parameter values [0.02, 0.11, 0.06]) is shown with relation to the first simulated measurement in Figure 10b. The changes in the central tendency of the distribution can be interpreted as adjustments in arterial properties (in this case the detected change is indicative of vascular constriction).

A source of information complementary to the central tendency is the width of the HDI. If a large number of parameter values are likely to describe the data, then high levels of noise might be present - indicating that the cuff inflation should be repeated. Also, in the case of complex patients where unusual volume envelopes might be obtained (volume envelopes that cannot be fitted by the model of arterial mechanics), more invasive monitoring techniques could be suggested.

A non-ideal case is also simulated. A volume envelope is created with parameter set [0.03, 0.1, 0.08], minor artefacts are simulated and expected noise is increased to from 0.1 mL to 0.25 mL. The inaccuracy in the central tendency is expected given the simulated artefact. The uncertainty in cuff compliance estimation is reflected in the large width of the HDI.

A. Parameter inference from PAT data

PAT data is simulated with parameter values a = 0.03, c = 0.1. The results indicate that the central tendency of the distribution approaches simulated parameter values (Figure 10c).

A non-ideal case is simulated, where only 10 PAT data points are available. The uncertainty in parameter inference in this case is due to the small amount of data available for processing.

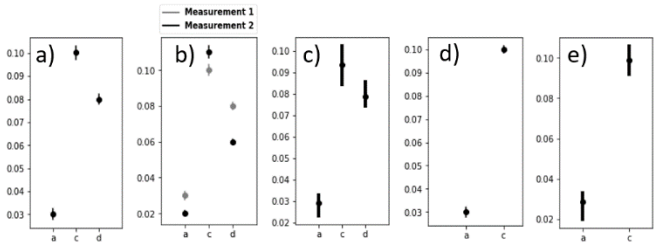

Figure 10. Figure showing parameter estimates – the vertical black bars indicate the 95% HDI. The point is indicating the median of the posterior distribution (a quantification of central tendency).a) Results of processing oscillometric data simulated with parameter set [0.03, 0.1, 0.08]; b) Detection of arterial constriction scenario – possibility of displaying changes in arterial properties from consecutive oscillometric measurements; c) Results of processing non-ideal oscillometric signal. d) Results of processing PAT data simulated with parameter set [0.03, 0.1]; e) Processing of PAT simulation with only 10 data points available for processing.

	Central Tendency			HDI width		
	a	c	d	a	c	d
Figure 10a	0.03007	0.1000	0.0799	0.0043	0.0054	0.0040
Figure 10b Measurement 2	0.0200	0.1101	0.0599	0.0028	0.0067	0.0026
Figure 10c	0.02939	0.0939	0.0786	0.0097	0.0176	0.0112
Figure 10d	0.0299	0.1000	-	0.0041	0.0028	-
Figure 10e	0.0284	0.0989	-	0.0126	0.0135	-
Figure 11 Fusion Result	0.0306	0.0979	0.0774	0.0060	0.0101	0.0070

Table 1. Central tendency values and HDI width of posterior distribution results illustrated in Figures 10 and 11.

B. *Parameter inference from fusion of PAT and oscillometry*

The simulated realistic, non-ideal oscillometric and PAT data are used for parameter inference by the fusion method described in 3.2.3.C. Results of this simultaneous processing are shown in comparison with results of individual processing of oscillometry and PAT (Fig. 11). The posterior distribution computed through simultaneous processing leads to a decrease in the uncertainty of parameter estimates compared to individual processing.

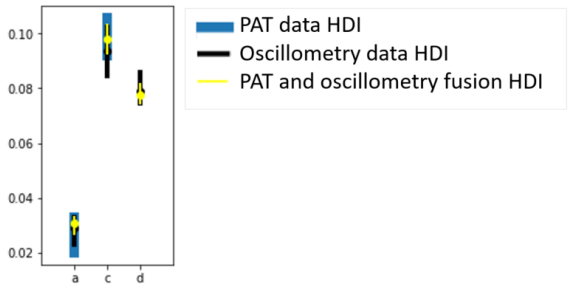

Figure 11. When simultaneously processing the noisy volume envelope measurement together with the small number of reliable PAT samples, the algorithm outputs a posterior distribution with the median for parameter a of 0.0306 (with HDI width 0.0060), parameter c of 0.0979 (with HDI width of 0.0101), and parameter d of 0.0774 (with HDI width 0.0070).

3.4. **Discussion**

This study presents an inference approach based on Bayesian principles for fusion of two measurements (oscillometry and PAT) with the goal of obtaining a robust estimate of arterial compliance in a realistic hemodynamic monitoring scenario with access to PAT and arterial volume envelope obtained from oscillometry. The inference modality is first demonstrated on the individual measurements via simulations (Fig. 10 a, b, d). No artefacts are simulated in the oscillometric signal and expected oscillometric measurement noise is assumed to be very low (0.05 mL variance). In this case the output of the inference is accurate and shows high degree of confidence.

A 0.05 mL variance, would enable very precise estimation of arterial properties. However, for a clinical context, a larger variance such as 0.25 mL would still allow for detection of major changes in arterial compliance, this being beneficial in applications such as identification of need for re-calibration of pulse waveform analysis devices. This value was chosen with consideration of expected absolute artery volumes under the cuff which can be in the range of approximately 2.5 mL at small cuff pressures [17].

To study such a non-ideal case, the expected noise of the oscillometric measurement is increased to 0.25 mL variance, artefacts are simulated, and some information is excluded from the PAT data (Fig. 10 c, e). Individual processing of the two measurements in this case is less accurate, and the confidence level decreases. However, the posterior distribution computed through simultaneous processing (Fig. 11) leads to a decrease in the uncertainty of the parameter estimates; the number of parameter values likely to describe the data decreases in view of additional information. This result is influenced by many factors: the information expressed in the two measurements, the expected measurement error, the number of data points (number of heart beats recorded in each measurement), prior knowledge and correlation between model parameters. Another parameter correlation effect is observed when limiting the number of possible values for parameter a and c – this also decreases the uncertainty in the inferred value of parameter d (even though information about parameter d is only expressed in one of the information sources).

The value of the central tendency, computed as the median of the posterior distribu-

tion, brings attention to the difficulty of summarizing the inference result. Clinically relevant and easy to interpret information needs to be extracted from the posterior distribution. This example shows how the range of likely parameter values is decreasing with simultaneous processing, while the true parameter values remain highly likely (are within the HDI limits). However, the central tendency itself does not correspond to the true parameter values – which brings the question of the most correct way to display the output of the algorithm for clinical interpretation.

Clinical investigations are necessary to identify regions of practical equivalence (ROPE) [26] which depend on measurement setup, clinical setting and application specific necessary accuracy. The ROPE would enable for more correct interpretation of the posterior distribution. For example, it can serve as a way to identify if the measurement needs to be repeated (in the case the HDI width is greater than ROPE width), or as a way to more easily quantify a change in arterial properties (assessing if the HDI of two consecutive measurements lies within the same ROPE, as opposed to comparing central tendency values).

Another question related to clinical interpretation is the inclusion of prior knowledge. In this study, a minimally informative prior is used. In a clinical scenario, prior knowledge on the expected spread of parameter ranges could be based for example on demographics. A more informative prior could also be personalized based on previous measurements performed on the same patient.

However, such interpretations of the HDI width and prior information would only be possible after investigation of arterial compliance measurements in a clinical setting. This would allow for identification of patient groups and clinical relevance in parameter changes, as well as characterization of noise sources in the measurement setup. Current ongoing work is tackling such questions [27, 28], with preliminary results showing cuff compliance and arm tissue compression playing a significant role in expression of artery volume change in oscillometric data. For example, the variance parameters in the model might have to be adjusted throughout the duration of the measurement instead of being set to a constant value e.g. cuff compliance is difficult to be accurately measured at low cuff pressures.

Still, the presented work demonstrates the concept of processing both arterial volume changes and pulse wave velocity information for the purpose of inferring arterial compliance. The current implementation can be adjusted based on new findings - the measurement procedure, clinical considerations and principles of signal fusion remaining valid.

3.5. **Conclusion**

The presented simulation framework illustrates the feasibility of a data processing approach for obtaining information on arterial compliance by signal fusion of two data sources (PAT and oscillometry). The results show the basic feasibility of the concept, this being a first step towards improved patient monitoring via measurement of hemodynamic parameters related to arterial compliance. The framework allows for illustration of clinical scenarios and transparent interpretation on how the two measurements contribute to parameter inference in the presence of noise or available prior knowledge. Characterization of the measurement setup and investigation of arterial compliance measurements in a clinical setting, together with identification of measurement requirements tailored to specific applications and patient groups are needed as a next step.

Appendix 1 – Cuff edge effect

An oscillometric volume envelope measurement can be processed in two ways to obtain the arterial size-transmural pressure relationship: either via a parametric approach (described in Section 3.2.2), or via a non-parametric approach.
The parametric approach is based on Eq. 2 which has been developed with consideration of arterial collapse mechanics [21]. Therefore, the parametric treatment can be interpreted as a fitting procedure of the mechanical model on measured data.

The non-parametric approach of computing the arterial size-transmural pressure relationship is based on integrating volume envelope data with consideration of cuff pressure and systolic, diastolic BP values. This modality does not use knowledge of arterial mechanical collapse properties.

A systematic effect is observed when comparing arterial volume – transmural pressure relationships obtained via the parametric approach versus ones obtained via the non-parametric approach. At negative transmural pressures the arterial volume obtained by non-parametric processing is larger than the arterial volume values inferred with consideration of arterial collapse mechanics. Such phenomenon could be explained by the "knocking effect", or cuff edge effect – as the artery under the cuff collapses, volume changes are still detected. This effect could appear as blood ejected from the heart hits against the closed portion of the artery. Since it is not certain at which point in the cuff inflation such phenomenon becomes prominent, all volume envelope values obtained at cuff pressure larger than mean arterial pressure are discarded.

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CHAPTER 04

A non-parametric method for assessment of arterial compliance

Based on:

- Bogatu, L.I., Turco, S., Mischi, M., Woerlee, P., Bouwman, A., Korsten, E.H. and Muehlsteff, J., 2020. A modelling framework for assessment of arterial compliance by fusion of oscillometry and pulse wave velocity information. *Computer Methods and Programs in Biomedicine*, *196*, p.105492.
- Laura Bogatu, Jens Muehlsteff, Erik Bresch, Maarten Kuenen, Pierre Woerlee. Control Unit for Deriving a Measure of Arterial Compliance. 2019. Published as: EP3760109A1; WO2021001336A1

Abstract.

The circulatory system's ability to compensate for deterioration has a direct impact on surgical outcomes - operative mortality, complication rates, functional health status, length of hospital stay. During procedures, or when recovering from procedures, patients are at risk of hemodynamic instability – difficulty of the circulatory system to maintain homeostasis.

This can manifest in multiple ways - blood pressure drops, changes in cardiac output, abnormal heart rates, etc. Regardless of what the manifestation is, if not treated in time, hemodynamic instability ultimately causes diminished organ perfusion, which can lead to complications or death. Multiple measurement techniques are employed for monitoring vitals of patients at risk of hemodynamic instability. The measurements reveal information about blood pressure, heart activity, concentration of carbon dioxide in lungs and peripheral perfusion. While this data is important in detecting hemodynamic instability, there is underutilized information that can be extracted from these vital sign measurements for the purpose of more accurate and faster detection of patient deterioration.

This chapter presents a solution for obtaining information about the arterial smooth muscle tone (or arterial compliance) via a non-parametric method of processing the BP cuff signal. The advantage is that pressure and volume data is obtained non-invasively from the same site (brachial artery), as opposed to the method presented in Chapter 3, which relies on the finger site waveforms. Therefore, the inferred hemodynamic information describes the systemic, rather than peripheral vascular function. In addition, the non-parametric method can be used to access insights on the oscillometric measurement process, thus complementing information acquired via the parametric method presented in Chapter 3.

Arterial compliance is defined by (1):

$$C_a(p_{tm}(t)) = \frac{dV_a(t)}{dP_a(t)} \quad (1)$$

Therefore, arterial compliance can be obtained if arterial volume V_a and pressure waves P_a are available. Means of acquiring pressure waves can involve arterial line at radial or brachial site or volume clamp at finger site. Volume waves can be deduced by PPG at finger site or by oscillometry at upper arm level. This ID describes an alternative approach of obtaining arterial compliance by means of the blood pressure cuff alone.

A simulation of an oscillometric measurement has been implemented to explain the proposed process of computing arterial compliance.

Figure 1 shows transmural pressure (P_{tm}) across the arterial wall as a cuff is inflated during a simulated oscillometric measurement. Figure 2 shows the corresponding arterial volume V_a under the cuff (simulated with the arterial-transmural pressure function in Equation 2 [1]).

$$V_a(P_{tm}) = 0.08 * log(0.03 * P_{tm} + 3.3)/(1 + e^{-0.1*P_{tm}}) * 10 \quad (2)$$

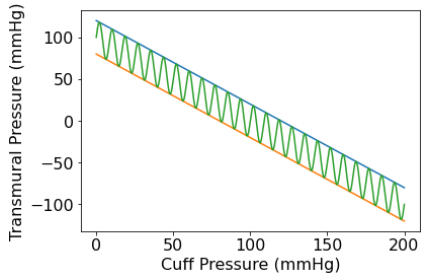

Figure 1. Transmural pressure (P_{tm}) across the arterial wall as a cuff is inflated during a simulated oscillometric measurement

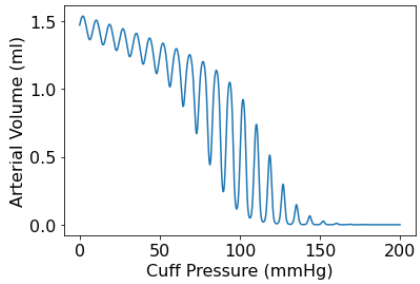

Fig 2. Simulated arterial volume $\mathbf{V_a}$ under the cuff as absolute pressure in the cuff increases from 0 mmHg to above systolic pressure.

Given the volume oscillations, the pressure sensor inside the cuff would record the data shown in Fig. 3.

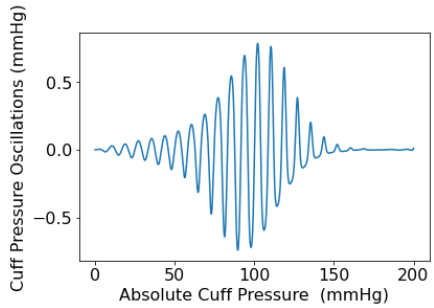

Figure 3. Simulated recording of cuff pressure oscillations as absolute pressure in the cuff increases from 0 mmHg to above systolic pressure.

If translation from cuff pressure is performed correctly (if cuff compliance is known), then the de-trended arterial volume $Va_{Measured}$ can be obtained (Figure 6). The volume envelope represents the total volume change at the corresponding cuff pressures.

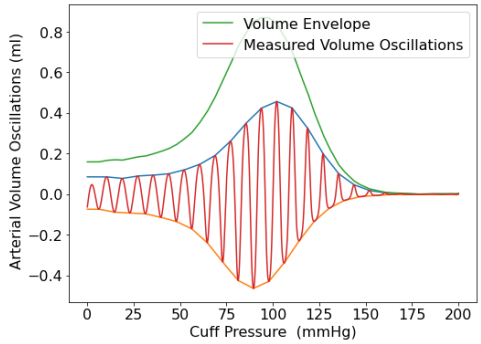

Figure 4 – Data about arterial volume obtained from a cuff pressure recording.

The arterial volume measurement can be used together with an arterial pressure measurement in order to obtain arterial compliance. However, the only information about arterial pressure that is obtained from oscillometry are the systolic (P_{sys}) and diastolic (P_{dia}) values. Given that the total volume change at each cuff pressure is caused by a chance in pressure of $P_{sys} - P_{dia}$ (pressure pulse), an approach to obtain compliance would be to divide the volume envelope by the pulse pressure. However, this method fails when taking into account the non-linearity of the arterial volume across transmural pressures (Fig. 5) and the typical pulse pressure of 40 mmHg.

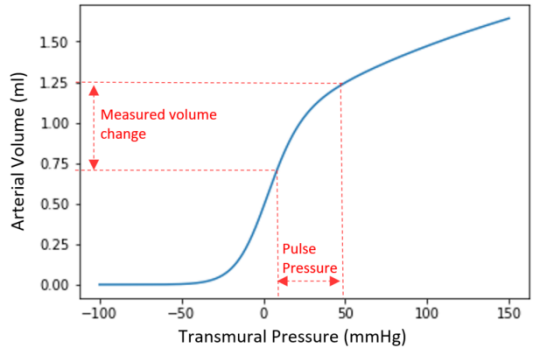

Figure 5. The typical arterial volume - transmural pressure relationship is non-linear.

To address this, a different approach of processing the volume envelope is considered.

The measured volume envelope is the result of multiple pressure pulses generating volume pulses in the artery over the duration of the cuff inflation. With every beat, the transmural pressure varies between $P_{sys} - P_{cuff}$ and $P_{dia} - P_{cuff}$. This results in volume pulsations of amplitudes which depend on the arterial volume – transmural pressure relationship.

Given that the change in P_{cuff} is relatively slow compared to changes in arterial pressures, multiple beats will cover similar ranges of transmural pressures (Fig. 1). The changes in volume envelope from one pulse to another can be attributed to the small differences in transmural pressures covered by consecutive beats.

With this reasoning the volume envelope can be processed starting from large cuff pressures, where arterial volume is close to 0 ml. As described in Fig. 6, every succeeding pulse will cover a slightly different range of transmural pressures in comparison to the previous pulses. This information can be used when analysing the difference in volume envelope from one pulse to another. In this way, the change in volume can be more precisely attributed to the correct change in transmural pressure, eliminating the uncertainty of dealing with pressure changes as large as $P_{sys} - P_{dia}$.

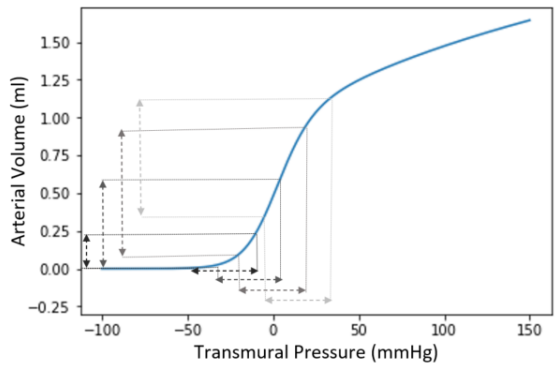

Figure 6. As cuff pressure is varied, consecutive pulses can be processed together to obtain better approximation of arterial compliance.

This reasoning has been implemented in an algorithm (Fig. 7) which receives as input a volume envelope, the corresponding systolic, diastolic and absolute cuff pressures and computes the arterial volume over a range of transmural pressures.

The volume envelope can be processed in terms of a chosen step pressure dP. The change in volume (dV) caused by a change in pressure dP is computed for absolute transmural pressures.

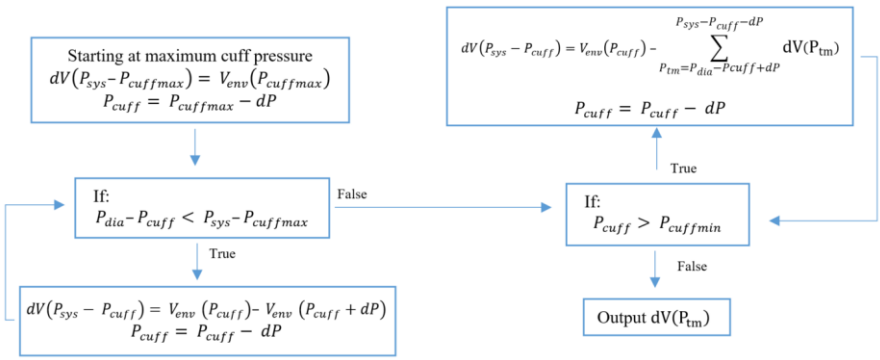

Figure 7. Overview of algorithm.

The output of this algorithm is the array $dV(P_{tm})$ which represents the volume changes caused by a set pressure change of value dP at different transmural pressures. The arterial volume as function of transmural pressure is obtained by numerically integrating the values of this array.

A successful processing of the volume envelope simulated in Fig. 4 is shown in Fig. 8.

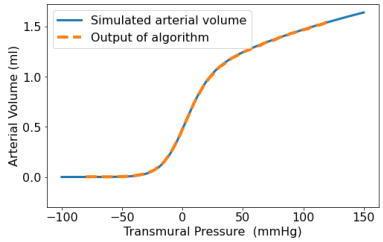

Figure 8. Simulated arterial volume and result of processing the volume envelope via the proposed method.

The described method analyses arterial volume changes detected during an inflation of the blood pressure cuff. As the cuff pressure reaches systolic values the artery under the cuff collapses. In practice, after the moment of arterial collapse, volume changes are still detected with the cuff setup – this effect appears as blood ejected from the heart hits against the closed portion of the artery. This effect needs to be quantified when analysing data collected by means of oscillometric measurements.

When used in combination with models which describe mechanical principles of arterial collapse, the output of the method presented in this ID can be interpreted for the purpose of quantifying this “knocking effect”, or “cuff edge effect”. An example of such an arterial mechanics model is described in [1]. The parameters of this model can be fitted to the output of the described algorithm. The differences between the parametric and the non-parametric computation of arterial volume at negative transmural pressures is indicative of the knocking effect.

Figure 10 shows the result of parametric and non-parametric processing of four volume envelopes obtained via oscillometric measurements on a healthy volunteer. The figure highlights the difference between the parametric and the non-parametric evaluation. This information can be used when interpreting data recorded by means of oscillometric measurements for the purpose of reading blood pressure or for obtaining true arterial volume under the cuff.

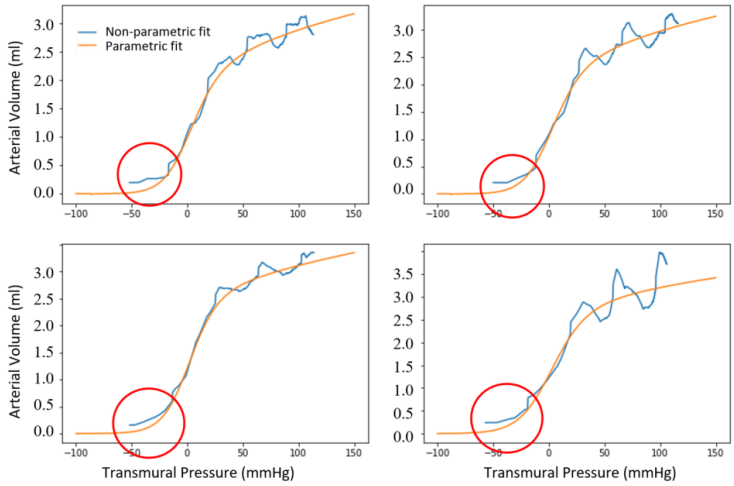

Figure 10. Arterial volume obtained from oscillometric measurements performed on a healthy volunteer. Non-parametric processing vs. parametric processing. Red circles indicate regions which are affected by the “cuff edge effect”, or “knocking effect”.

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CHAPTER 05

Arterial compliance and viscosity measurement via external pressure oscillometry

Based on:

- Laura Bogatu, Jens Muehlsteff, Pierre Woerlee; System and method to non-invasively measure properties of arteries by external pressure oscillometry; Filed 2021.

Abstract

Overcoming limitations in current patient monitoring requires measurement of regulation mechanisms of the circulatory system. As an example, it is important to detect circulatory system compensation mechanisms (such as arterial constriction) in order to prevent hypotension. A hypotensive event occurs when compensation mechanisms have failed. Therefore, organ perfusion might already be compromised when a drop in blood pressure is measured. For this reason, measurement of regulation mechanisms is essential for proactive patient management. Research on this topic is revealing evidence of complex, dynamic behaviour of arteries on local as well as systemic levels. New regulation mechanisms are being found. These mechanisms impact the elasticity properties of the arterial wall, non-linearity properties of the arterial collapse, viscosity, damping properties, existence of a cut-off frequency and strain-dependent activation of the smooth muscle tone [8, 9, 10].

Because of this, methods for observing and measuring these compensatory mechanisms are being developed. However, up until now, proposed methods for obtaining such complex regulation measurements involve invasive measurements, or ex-vivo studies of arteries, or inference via complex physiological models involving uncertainties and many assumptions.

We propose a non-invasive method for measuring viscoelastic arterial properties of the artery via a blood pressure cuff. The method does not require an estimation of blood pressure, which is one of the most significant sources of error in estimation of arterial properties non-invasively. This is achieved by measuring the response of the artery to external, controlled pressure perturbation, as opposed to standard methods, which are based on assessing the arterial response to internal (undefined and difficult to measure) blood pressure pulsations. Another benefit of the proposed methods vs. state-of-the-art is that it enables measurements in non-pulsatile states e.g. when blood flow is intendedly suppressed.

The measurement method can be used to obtain local regulation mechanisms (e.g. at brachial site), or information regarding systemic mechanisms (such as mean-systemic filling pressure). The method and its embodiments apply external pressure oscillations to the artery via a system consisting of a cuff and defined volume changes by appropriate means e.g an oscillator attached to the cuff/internal to the cuff. An algorithm controls the oscillator movements and processes the oscillator movements and pressure signal of the cuff to obtain response of an artery to different frequencies. The measured response can be processed to obtain elastic arterial collapse parameters and viscosity parameters. Different embodiments can be used to obtain information about local regulation mechanisms (via a single cuff embodiment) or systemic regulation mechanisms of the circulatory system (via a two-cuff embodiment).

5.1. **Introduction**

An underestimated and underutilized source of information in current clinical practice is the vascular compliance, which plays a fundamental role in circulatory integrity. It adjusts with respect to changes in blood pressure, circadian rhythms, physical activity, stress, as well as with respect to longer term changes caused by age, lifestyle etc. Compliance, and in particular, arterial compliance can reveal a considerable amount of information regarding health status. However, continuous measurement of compliance is hardly feasible.

Besides the arterial compliance, or the elasticity properties of the arterial wall (which enable constriction/distension), new regulation mechanisms of the circulatory system have been discovered: non-linearity properties of the arterial wall, viscosity, damping properties, existence of a cut-off frequency, strain-dependent activation of the smooth muscle tone. Because of this, methods for observing and measuring these compensatory mechanisms are being developed. However, up until now, proposed methods for obtaining such complex regulation measurements involve invasive measurements, or ex-vivo studies of arteries, or inference via complex physiological models involving uncertainties and assumptions [8, 9, 10].

Arterial properties

Arterial compliance represents the ability of arteries to distend and contract in response to changes in pressure. Consequently, arterial compliance $C_a$can be expressed as Eq. 1. This equation is also the basis for externally applied changes of transmural pressure.

$$C_a(P_{tm}) = \frac{dV_{art}}{dP_{tm}} \tag{1}$$

Where $\mathrm{V_{art}}$ is the arterial volume, P_{tm} is transmural pressure across the arterial wall. $P_{tm} = P_{art} - P_{ext}$, where P_{art} is the arterial blood pressure and P_{ext} is pressure outside the artery (atmospheric pressure or cuff pressure, if cuff is placed on the arm). The maximum of P_{art} is the systolic blood pressure (SBP) and the minimum of P_{art} is the diastolic blood pressure (DBP). Ca, the arterial compliance, is a highly nonlinear and person-specific function of the transmural pressure P (i.e., the pressure across the arterial wall).

Viscosity parameters can be obtained by analysing the response in volume $\mathrm{V_{art}}$ to transmural pressure pulsations of different frequencies.

Measurement of arterial properties

In principle arterial volume can be measured by means of high resolution imaging (e.g. ultrasound), which can reveal changes in arterial diameter as arterial pressure varies between systolic and diastolic values. In practice however, difficulties are caused by the fact that the procedure is not automatic – it requires highly skilled operators and is prone to errors [1]. Besides this, if information about arterial properties is necessary over a wider range of transmural pressures, then imaging technologies would have to be incorporated into cuff setups, further complicating the measurement.

A different approach to arterial volume measurements over a wide range of transmural pressures involves the use of the already existing BP cuff. The pressure oscillations inside the cuff are representative of arterial volume changes due to the pulsating nature of systemic blood pressure. However, in order to extract arterial properties from this signal, accurate knowledge of arterial pressure is necessary. Such accuracy can be obtained invasively via arterial line. For a non-invasive measurement, the blood pressure value can be obtained via typical cuff-based oscillometric measurement. However, the oscillometric measurement has

been found to be inaccurate in certain patient groups (such as hypo and hypertensive patients). In addition to this, especially in hemodynamically unstable patients, BP can change within a very short time span, and there are beat-to-beat variations caused by breathing. Measuring blood pressure at one time and arterial volume change at a different time might not give correct arterial property values.

A solution to solve this uncertainty can be developed from the concept of blood pressure measurement involving external perturbation. With an external oscillation set-up, the arterial volume is measured as response to external, well defined pressure changes resulting in changes in transmural pressure. Knowledge of internal arterial pressure is not necessary.

In addition to this, the arterial response to different frequencies (beyond heart rate) can be measured via external perturbations. This can give information regarding viscosity properties of the artery.

5.2. Description of the method

5.2.1. Arterial compliance and viscosity measurement

A typical, expected pulsation of arterial volume dV_{art} under the cuff during a cuff inflation is illustrated in the figure below:

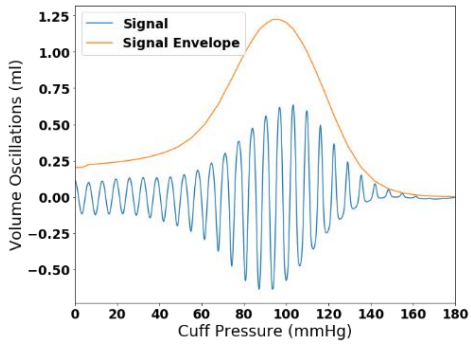


Figure 1. Arterial volume $\boldsymbol{dV_{art}}$ under the cuff during a cuff inflation

A system that measures arterial volume response to external pressure can be implemented by artificially generating well-defined volume oscillations inside a cuff placed on the upper arm of a subject. A possible embodiment consists of inflating the cuff to different absolute pressures P_{abs} (e.g. 0 to 200 mmHg). Volume pulsations dV_{osc} are generated artificially within the cuff. If cuff compliance C_{cuff} is well-defined, then the pressure response dP_{osc} of the cuff to artificial volume changes is known ($dP_{osc} = dV_{osc}/C_{cuff}$). The arterial volume dV_{art} responds to pressure pulsation dP_{osc} and to internal pressure pulsation dP_{art} (which occurs between systolic and diastolic values). The measured cuff pressure signal P_{cuff} will be influenced by both dV_{art} and dV_{osc}. Arterial volume pulsations can be can be obtained from a measurement of P_{cuff} via the equation:

$$dV_{art} = \left(P_{cuff} - P_{abs}\right) * C_{cuff} - dV_{osc} \quad (2)$$

Expected dV_{art} magnitude is in the order of 0.25 ml at low cuff pressures and in the order of 1.25 ml as cuff pressure reaches mean arterial pressures (as shown in Fig. 1). In general, maximum amplitude of dV_{art} is expected to be in the range of 1 to 3 ml. This volume change occurs as a result to an arterial pressure change in the order of 40 mmHg (pulse pressure, or the difference between systolic and diastolic values).

To achieve this range of controlled pressure amplitudes, the oscillator is used with consideration of C_{cuff} to generate cuff pressure pulsations in the order of 20 - 40 mmHg (e.g. if cuff compliance is 0.5 ml/mmHg, then artificial volume amplitudes of 10 ml will cause cuff pressure pulsations of 20 mmHg). The resulting cuff pressure signal P_{cuff} can be processed via Eq. 1 to obtain artery volume response to the well-defined 20 mmHg pressure changes. To illustrate the measurement process in more detail, a simulation framework has been established.

A system of equations characterizes the system:

$$P_{cuff} = P_{abs} + (V_{osc} + V_{art}) * C_{cuff}; \quad (3)$$

$$V_{art}(P_{tm}) = 0.08 * \frac{\ln(0.03 * P_{tm} + 3.3)}{1 + e^{-0.1 * P_{tm}}} L_{cuff}; \quad (4)$$

V_{art} is arterial volume under the cuff as function of transmural pressure across the arterial wall. $P_{tm} = P_{art} - P_{cuff}$, P_{art} is arterial pressure which oscillates between systolic and diastolic values. The function describing arterial collapse $V_{art}(P_{tm})$ and parameter values are described from [11]. The cuff length L_{cuff} is set to 14 cm.

The cuff is simulated to inflate from 0 to 200 mmHg (P_{abs} gradually increases). P_{art} oscillates between 80 mmHg and 120 mmHg at 1 Hz frequency. V_{osc} oscillates at 10 Hz, 10 ml amplitude. Cuff compliance is set to 0.5 ml/mmHg.

As P_{abs} increases, P_{art} and V_{osc} oscillate, the cuff pressure signal illustrated in Fig. 2 is generated. Figure 3 shows arterial volume oscillations occurring due to resulting transmural pressure P_{tm} pulsations. As compared to the signal illustrated in Fig. 1 (which is caused by internal arterial oscillations), the arterial volume pulsations in Fig. 4 are caused by a combination of internal arterial pressure and external cuff pressure pulsations.

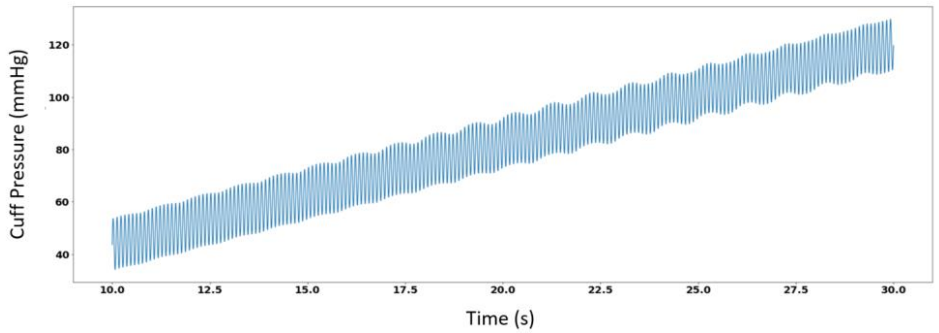


Figure 2. Cuff pressure signal pulsations as result of arterial and controlled external volume pulsations

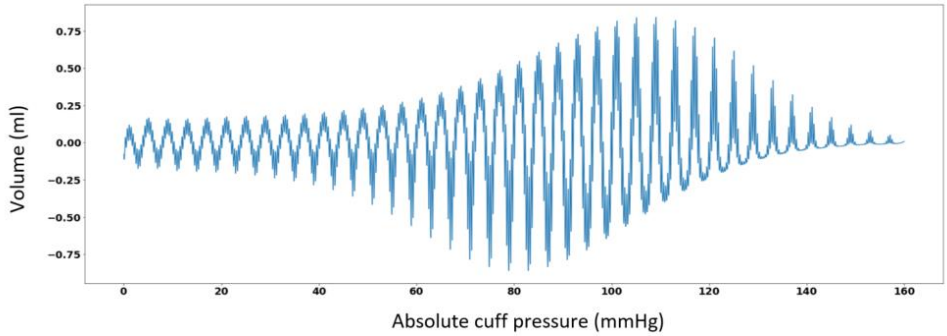


Figure 3. Arterial volume pulsations resulting due to controlled external pressure pulsations and internal blood pressure pulsations.

During a measurement, the cuff pressure signal in Fig. 2 would be recorded and oscillator volume would be known. The arterial volume pulsations can be obtained by using Eq. 1, the recorded cuff pressure signal and known oscillator volume pulsation. Fig. 4 shows the reconstructed volume pulsations (orange) plotted together with the original arterial volume signal (blue, which is also shown in Fig. 3).

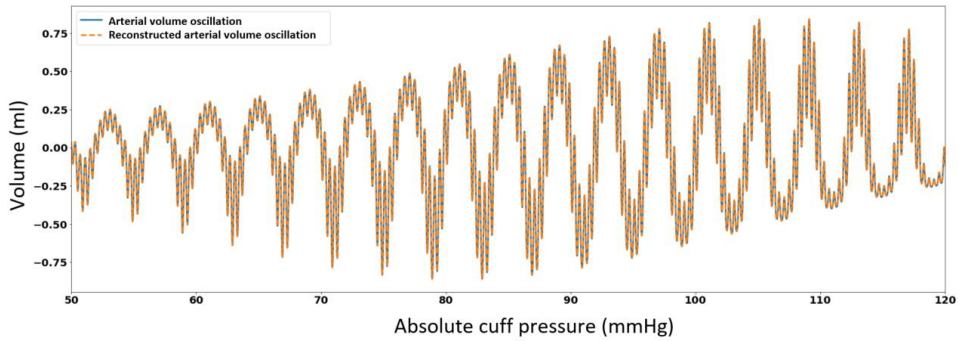


Figure 4. Reconstructed arterial volume oscillations based on cuff pressure and oscillator data.

Arterial compliance and arterial collapse characteristics can be obtained by re-constructing the arterial volume vs transmural pressure function. This can be done by obtaining the arterial volume response to the artificial pressure pulses of amplitude 20 mmHg. For example, in Fig. 5 (zoom in of Fig. 4), the larger amplitude, low frequency pulses are generated by internal arterial pressure. The fast, smaller volume oscillations are the ones occurring due to the 20 mmHg artificial pressure pulsations. Arterial dVart as response to 20mmHg pressure change can be obtained at several cuff pressures. To minimize impact of arterial internal pressure oscillation, it is important to process a specific portion of the waveform. This is illustrated in the figure as an example - the top of the arterial pressure pulse, where arterial pressure pulse is always systolic value. The arterial compliance values at different cuff pressures can be processed parametrically, or non-parametrically to obtain arterial volume vs transmural pressure function.

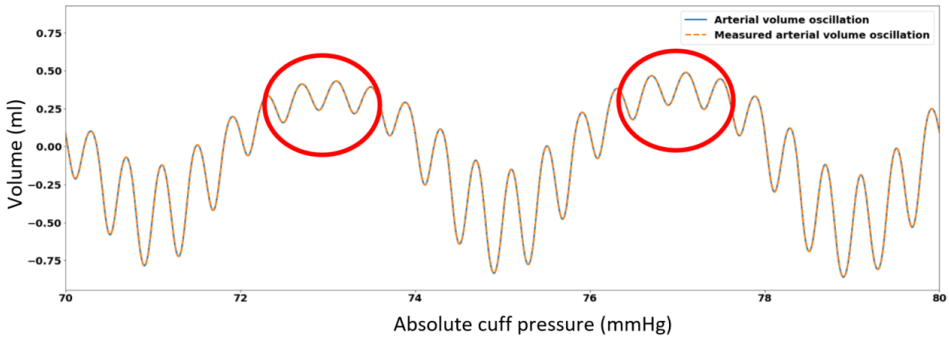


Figure 5. Zoom in to segments of interest for estimation of arterial properties.

An important benefit of the external pressure measurement is that artificial oscillations of multiple frequencies can be generated. In this way, information regarding viscous properties of the artery can be obtained. Up until now, this information was only available via invasive, or ex-vivo methods, of via inference through complex physiological models involving uncertainties and assumptions

5.2.2. Mean systolic filling pressure measurement

The mean systemic filling pressure (Pmsf) is defined as the mean pressure that exists in the circulatory system when there is no blood in motion. Pmsf is influenced by the volume of blood and the smooth muscle tone. Pmsf can be derived by measurement of stop-flow forearm arterial and venous equilibrium pressures. Occluding the vein and the artery at the brachial site causes the flow of blood at the lower arm site to stop. Therefore, measurement of blood pressure at the lower arm site during occlusion gives Pmsf.

The Pmsf value can be interpreted to infer intravascular volume status, which contributes to the assessment of fluid responsiveness [6][7].

However, this method requires invasive pressure measurements. We propose solution for non-invasive measurement of the blood pressure in the occluded, non-pulsatile region of the limb.

In this method Cuff 1 (illustrated in Fig. 6) is inflated such that stop-flow conditions are reached. Cuff 2 applies external pressure oscillometry to the non-pulsating artery and measures volume response of the artery. Maximum compliance of the artery occurs when pressure inside the artery equals external pressure. Therefore, the cuff pressure at which maximum arterial compliance occurs is equal to arterial pressure. Since there is no blood flow due to the occlusion at the site of Cuff 1, then the measured arterial pressure at Cuff 2 equals Pmsf.

This embodiment enables for fully non-invasive mean systemic filling pressure measurement. Besides this, information about arterial compliance obtained via external pressure oscillometry can improve the estimation of intravascular volume, thus leading to a better quantification of fluid responsiveness.

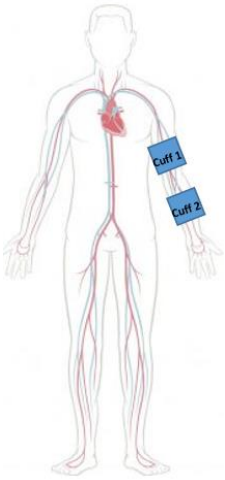
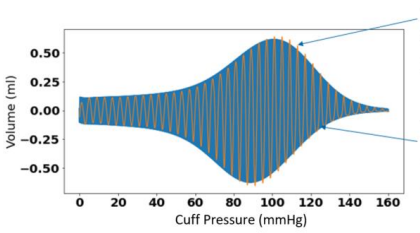


Figure 6. Illustration of the Pmsf measurement two cuff arrangement.

A simulation framework was used to show that the same arterial volume signal can be measured via internal vs external pressure pulsations (Fig. 7). This proves how the same arterial properties and mean arterial pressure can be obtained if the pressure oscillations are external, rather than internal when using the two cuff system (applying external pressure with Cuff 2 on the non-pulsating portion of the artery).



Orange: envelope obtained from internal oscillation (40 mmHg, frequency 1 Hz) by usual cuff compliance multiplication with pressure signal.

Blue: envelope obtained from external pressure oscillation of 40 mmHg at frequency 10 Hz. Pressure in the artery is constant at 100 mmHg.

The processing requires cuff pressure signal and artificial volume signal. Artificial dP is controlled with artificial dV which causes pre-defined dP = dV/cuffC.

Figure 8. Volume envelope measured via the external pressure method compared to envelope measured via standard oscillometry.

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CHAPTER 06

Modulation of Pulse Propagation and Blood Flow via Cuff Inflation–New Distal Insights

Based on:

- Bogatu, L.I., Turco, S., Mischi, M., Schmitt, L., Woerlee, P., Bresch, E., Noordergraaf, G.J., Paulussen, I., Bouwman, A., Korsten, H.H. and Muehlsteff, J., 2021. Modulation of pulse propagation and blood flow via cuff inflation—new distal insights. Sensors, 21(16), p.5593.
- Bogatu, L.I., Turco, S., Mischi, M., Schmitt, L., Woerlee, P., Bresch, E., Noordergraaf, G.J., Paulussen, I., Bouwman, A., Korsten, H.H. and Muehlsteff, J., 2021. Modulation of pulse travel and blood flow during cuff inflation- An experimental case study. In 2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). IEEE.

Abstract

In standard critical care practice, cuff sphygmomanometry is widely used for intermittent blood pressure (BP) measurements. However, cuff devices offer ample possibility of modulating blood flow and pulse propagation along the artery. We explore underutilized arrangements of sensors involving cuff devices which could be of use in critical care to reveal additional information on compensatory mechanisms. In our previous work, we analyzed the response of the vasculature to occlusion perturbations by means of observations obtained non-invasively. In this study, our aim is to 1) acquire additional insights by means of invasive measurements and 2) based on these insights, further develop cuff-based measurement strategies. Invasive BP experimental data is collected downstream from the cuff in two patients monitored in the OR. It is found that highly dynamic processes occur in the distal arm during cuff inflation. Mean arterial pressure increases in the distal artery by 20 mmHg, leading to a decrease in pulse transit time by 20 ms. Previous characterizations neglected such distal vasculature effects. A model is developed to reproduce the observed behaviors and to provide a possible explanation of the factors that influence the distal arm mechanisms. We apply the new findings to further develop measurement strategies aimed at acquiring information on pulse arrival time vs. BP calibration, artery compliance, peripheral resistance, artery-vein interaction.

6.1. Introduction

In standard hemodynamic monitoring practice, the cuff measurement principle consists of altering the transmural pressure across the brachial arterial wall; the resulting brachial arterial volume oscillations are measured and interpreted via an empirical method to estimate blood pressure (BP). This measurement is performed at intervals between five minutes to several hours depending on the patient's condition.

A hypothesis is that the cuff is underutilized in clinical practice and that other measurement strategies can be developed based on occlusion-based modulation of flow and pulse propagation along the artery, in combination with standard monitoring equipment (e.g. electrocardiogram ECG, photoplethysmogram PPG). For this reason, in our previous work we explored how to adapt the cuff measurement principle to obtain further information, in addition to the intermittently acquired BP values.

- In [18], the cuff is used to alter the transmural pressure across the brachial artery for the purpose of modulating Pulse Arrival Time (PAT). The change in PAT with respect to the controlled transmural pressure is analyzed in order to calibrate the BP-PAT relationship for the purpose of beat-to-beat PAT-based BP estimation.

- In [17] both the brachial artery volume oscillation and the PAT response to cuff-based perturbation are interpreted in order to estimate brachial arterial compliance and collapse mechanics. Changes in these vascular properties can precede changes in BP and cardiac output [17]. Intensive care clinicians have expressed interest in measuring short-term, dynamic regulation of arteries [24], however, methods for detecting such regulation mechanisms are not yet available, mainly due to the difficulty of measuring vascular properties with standard hemodynamic monitoring hospital equipment.

The two studies [17, 18] involved modelling of the localized change in transmural pressure and its impact on pressure pulse propagation: as the cuff inflates, the arterial transmural pressure over the length of the cuff is decreased, thus increasing the time it takes for the pulse to propagate down the brachial artery. These studies demonstrated this effect by means of non-invasive measurement setups (consisting of BP cuff, ECG, PPG), complemented by computer simulations.

Due to the noisy nature of the non-invasive measurements, it was not possible to thoroughly study the effects occurring downstream from the cuff. This led to the development of a model which characterized the brachial vasculature, but excluded effects occurring in the distal limb vasculature (under the assumption that distal BP and distal pulse transit time do not change significantly throughout cuff inflation) [17, 18]. Other previous studies involving cuff-based modulation of PAT also lack experimental characterization of distal vasculature effects, leading to unverified assumptions and development of unrealistic models [25, 26]. In general, numerous studies tackle the brachial artery collapse caused by cuff inflation (for example, via ex-vivo studies [9], ultrasound measurements [8], computer simulations [28]), however, effects of cuff inflation on the distal artery are not being thoroughly investigated.To further advance our understanding

of vasculature response to occlusion-based perturbations, in this study we measure blood pressure downstream from the cuff invasively in two patients monitored in the operating room (OR). We observe highly dynamic and patient specific effects occurring in the distal arm as a result of cuff inflation. The observations lead to improved interpretation of the cuff measurement. We develop a model in order to reproduce the observed distal vasculature behavior. We apply the new findings to improve the measurements presented in [17], [18]. In addition to this, we demonstrate that information on parameters such as distal arterial compliance, artery-vein interaction, mean systemic filling pressure, changes in arm peripheral resistance (possibly representative of changes in systemic resistance), can be extracted from the distal BP response to cuff inflation. The presented measurement strategy, data and model-based analysis are aimed at establishing a basis for further investigations of occlusion-based perturbations applied to the circulation and of the resulting activation of compensatory mechanisms.

6.2. Materials and Methods

6.2.1 Measurement procedure

A sensor arrangement consisting of ECG, brachial BP cuff, radial intra-arterial line (ABP) and finger PPG (Fig. 1) is used to collect data from two anesthetized and mechanically ventilated patients undergoing non-cardiac surgery. All sensors are standard devices common in clinical practice: Philips Comfort Care Adult Cuff [2], Edwards Lifesciences TruWave disposable pressure transducer (Edwards Lifesciences, Irvine, CA) [3] and Philips PPG model M1191B [2].

The data is recorded using a Philips MP50 patient monitor [2] and custom data logging software. The ECG is sampled at 500Hz, and the ABP, PPG, and cuff pressure is sampled at 125Hz. The data collection is approved by the MEC-U ethical committee (St. Antonius Ziekenhuis, Koekoekslaan 1, 3430 EM Nieuwegein, NL. Approval W19.046) and the data is collected at the Elisabeth-TweeSteden Ziekenhuis, Tilburg, NL. Written informed consent was obtained from the patients. For reasons of clarity, the two patients are distinguished as $Patient_1$ and $Patient_2$. For both patients, cuff inflations are performed at arbitrary intervals across 7 hours before, during and after a surgical procedure. Cuff pressure, ECG, ABP and PPG signals are simultaneously recorded during cuff inflations. Changes in PAT and pulse transit time (PTT) due to cuff inflation are computed over two vascular segments:

- **Heart to finger site**: : $\Delta PAT_{ECG-PPG}(CuffP)$ is computed as the change in delay between the R-peak of the ECG signal and the foot of the PPG waveform as cuff pressure $CuffP$ increases.

- **Radial to finger site**: $\Delta PTT_{ABP-PPG}(CuffP)$ is computed as the change in delay between the foot of the ABP waveform and the foot of the PPG waveform as cuff pressure $CuffP$ increases.

Note that invasive surgical procedures are performed on the patients, abrupt hemodynamic alterations are induced and motion artifacts are present in the signals. For this reason, 12 out of 48 cuff inflations had to be removed from *Patient*$_1$ data. 21 out of 68 cuff inflations had to be removed from *Patient*$_2$ data. Removal criteria include presence

of motion artifacts causing the pulse to be indistinguishable over portions of the signal, flushing of the arterial line, pressure pulse change greater than 20 mmHg at 20 s after the cuff inflation compared to the start of the cuff inflation (indicative of significant hemodynamic events, which hider the analysis of cuff-induced effects). Throughout each cuff inflation, changes in ABP and in distal PTT are observed.

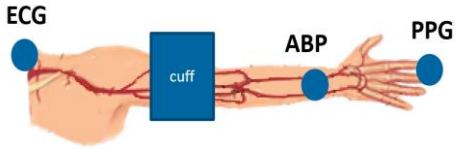

Figure 1. Sensor arrangement consisting of electrocardiogram ECG, blood pressure cuff, radial intra-arterial line ABP and photoplethysmogram PPG.

6.2.3. Model

A model is developed to identify the factors that influence the observed dynamic behaviors. The model is then used to further develop the methods presented in [17, 18] and to explore opportunities for deriving additional hemodynamic parameters.

The model presented by Seagar et al in [5] was adapted for our experimental condition. The study in [5] was aimed at the detection of venous thrombosis; patient data on limb volume and venous pressure was collected at the distal side of a cuff while the cuff was held inflated at a constant pressure to stop the blood flow out of the limb. The data was then fitted via a parametric model of the limb circulation; the model parameters were representative of clinically relevant indices related to thrombosis. The model however included parameters such as systemic resistance and blood vessel compliance, which are also relevant to hemodynamic monitoring, this fact being stated by the author: *"… a particularly appropriate application for the model is to use changes in the model parameters to monitor circulatory changes of the limb, such as those, for instance, that may occur during clinical anaesthesia "* [5]

The venous thrombosis model in [5] is therefore adjusted to characterize our critical care data. Figure 2 shows an overview of the adapted model. Systemic arterial pressure, cuff pressure and several parameter values are considered as input to the model. The model outputs are the distal arterial pressure and distal venous pressure. R_a represents the resistance to blood flow over the brachial artery. Its value is estimated via the Poiseuille equation,

$$R_a(P_{tm}) = \frac{8\eta L}{\pi\, r(P_{tm})^4}, \quad (1)$$

, where η is the blood viscosity, L is the length cuff length and $r(P_{tm})$ is brachial-artery radius as function of transmural pressure P_{tm} across the arterial wall:

$$P_{tm} = P_{art} - P_{cuff}, \quad (2)$$

where P_{art} is the arterial pressure under the cuff. Physiological ranges of absolute value of radius r is obtained from ultrasound measurement of brachial artery performed by Bank et al in [8].

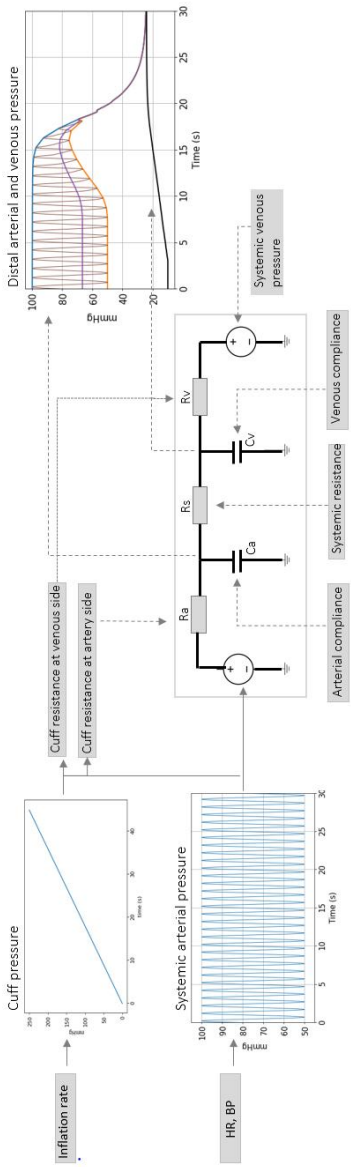

Figure 2. Overview of arm circulation model including a change in R_a due to cuff inflation.

As cuff pressure P_{cuff} increases, the artery radius decreases as function of transmural pressure. The function is defined via the equation describing arterial collapse mechanics from [9, 17]:

$$A(P_{tm}) = d \frac{\ln(a\,Ptm + 3.3)}{1 + e^{-c\,Ptm}}, \quad (3)$$

where A is arterial cross sectional area and a, c, d are parameters describing arterial collapse. The resulting R_a (illustrated in Fig. 2) as function of transmural pressure is proportional to the fourth power of the radius. R_v represents the resistance to blood flow over the brachial vein.

During fast inflations R_v does not influence the arterial BP behavior significantly - evidence on vein collapse behavior ([12, 13], including MRI images collected as part of our previous studies [4, 11]) confirm that the vein collapses at approximately -10 mmHg venous transmural pressure. The physiologic venous pressure range is between 5 mmHg and 15 mmHg [12], from which it can be concluded that the vein collapses in the very first part of the inflation (before cuff reaches 30 mmHg).

R_s represents the arm peripheral resistance. Physiological ranges for peripheral resistance in the arm were obtained from a study aimed at assessing hemodialysis access sites [10]. The study reports direct measurements of resistance via flow rate and pressure acquired *in-vivo* in the upper arm. Resistance values of about 100 $\mathrm{mmHg.\,s/mL}$ are reported. C_a and C_v represent arterial and venous compliance respectively. In [10] arterial compliance C_a in the arm is approximated in the order of 0.03 $\mathrm{mL\ mmHg^{-1}}$. C_v is approximated as about 30 times larger than C_a [14].

Simulations conducted via the model (Fig. 3) with parameters within ranges close to the reported values mimic effects observed in the patient data, showing that the model can be used to represent changes in distal arterial pressure during cuff inflation and that some physiological meaning can be attributed to the model parameters.

6.2.4. Parameter inference

The model is used to:

- Improve the inference method of brachial artery compliance presented in [17].
- Assess the estimation of PAT-BP calibration by further development of the method presented in [18].
- Infer distal arm circulation parameters.

A. Brachial artery compliance inference

In [17, Section 2.2.2] a method to obtain information on smooth muscle tone/compliance of the artery located under the cuff is proposed. The method involves modulation of pulse propagation along the arm via inflation of a cuff placed at the brachial site. The resulting PTT with respect to cuff inflation is processed to obtain the parameters **a** and **c** describing the brachial artery volume with respect to arterial transmural pressure $V_{art}(P_{tm})$. $V_{art}(P_{tm})$ is expressed via the brachial artery area (Eq. 3) multiplied by the

cuff length.

PTT was measured via ECG and finger PPG. The method assumed that the only portion of the artery where changes in PTT occur are along the length of the cuff, and that the transit time in the distal artery remains unaltered during cuff inflation. This assumption was based on preliminary results involving non-invasive measurements. Our new invasive measurements, however, reveal that significant changes do occur in the distal artery.

Simulation framework

To improve the method presented in [17, Section 2.2.2], a simulation framework is used. A distal BP signal is generated according to the model in Fig. 2. Systemic arterial diastolic pressure is set to 50 mmHg and systemic arterial systolic pressure is set to 100 mmHg. Heart rate is set to 1 Hz and cuff inflation speed is set to 25 s. The model parameters are chosen based on the values reported in the literature: systemic venous pressure is set to 10 mmHg [12], peripheral resistance Rs is 106 mmHg.s/mL [10], arterial compliance Ca is 0.03 mL/mmHg [10], venous compliance Cv is 0.9 mL/mmHg [14]. BP-PWV relationship is expected to be approximately linear over transmural pressure regions above 50 mmHg [3][8][9]. Therefore, a linear relationship between distal MAP and pulse wave velocity (PWV) is fitted to obtain PTT changes of similar amplitudes as the ones observed in the patient data.

The simulated signals are analyzed in order to assess the impact of distal artery effects on the correctness of the inference process described in [17] (which assumed that no change takes place in distal PTT) and to investigate mitigation solutions.

Inference of brachial artery parameters from patient data

The findings obtained at point a) are applied to the patient data in order to infer brachial artery compliance. Over the course of each inflation, changes in PTT occurring over the length of the cuff ($\Delta PTT_{Brachial}$) are obtained via Eq 4:

$$\Delta PTT_{Brachial}(CuffP) = \Delta PAT_{ECG-PPG}(CuffP) - 2 \cdot \Delta PTT_{ABP-PPG}(CuffP) \quad (4)$$

The drop in ΔPTT over the entire length of the distal arm is assumed to be twice the drop in $\Delta PTT_{ABP-PPG}$, due to the arterial line being placed halfway between the distal edge of the cuff and the fingertip. Note that this is a simplified model, which assumed a homogeneous artery segment. $\Delta PTT_{Brachial}$ is then processed via the inference modality described in [17, Section 2.2.2] to obtain brachial artery volume with respect to arterial transmural pressure $V_{art}(P_{tm})$ at the time of each inflation.

B. Estimation of PAT-BP calibration from patient data

The inferred $V_{art}(P_{tm})$ is used to estimate the calibration at the time of each inflation. First, the Bramwell-Hill equation (Eq. 5) is used to compute PWV with respect to P_{tm}.

$$PWV(P_{tm}) = \sqrt{\frac{V_{art}(P_{tm})}{\rho * C_{art}(P_{tm})}} \quad (5)$$

where P_{tm} is the transmural pressure across the arterial wall, ρ is the blood density, $V_{art}(P_{tm})$ is the arterial volume as a function of P_{tm}, and $C_{art}(P_{tm})$ is the arterial compliance as a function of P_{tm} (derivative of $V_{art}(P_{tm})$).

For a time segment between two consecutive cuff inflations, the beat-to-beat PAT value is calculated as the time delay between the R-peak of the ECG signal and the foot of the PPG signal. For each heartbeat, Eq. 6 is used to estimate PWV based on the measured change in PAT.

$$PWV = \frac{1}{dPAT_{measured}/_{L} + 1/_{PWV(P_{SysRef})}} \quad (6)$$

Where $dPAT_{measured}$ is the PAT change with respect to the reference PAT value measured at the beginning of the time segment, P_{SysRef} is defined as the systemic systolic pressure at the moment of cuff inflation, and L is the length travelled by the pulse (heart to finger site), approximated as 1 m [18]. It is assumed that the heart pre-ejection period (PEP) does not change over the time segment. The transmural pressures corresponding to each computed PWV value is found via the $P_{tm} - PWV$ relationship previously obtained via Eq. 5. This resulting transmural pressure is assumed to be the systolic pressure value of the corresponding heartbeat. In this way, the beat-to-beat systolic value is estimated over the time segment between two consecutive cuff inflations. For validation, the estimated systolic value is compared to the invasively measured systolic value.

C. Inference of distal arm circulation parameters

Time constant and mean systemic filling pressure

The response of BP to cuff inflation (Fig. 4) is complex; the signal contains many features from which physiological meaning could be derived. However, artifacts and interference between multiple effects are also present. The portion of the signal which is influenced by the least number of factors is the exponential decline occurring after complete arterial collapse. In this region, the signal is not influenced by cardiac activity, breathing artifacts, or by blood flow in/out of the limb. This portion of the signal is investigated first.

The exponential decline can be characterized by two parameters: the value towards which arterial and venous pressures tend to ($\boldsymbol{P_{Equilibrium}}$), and time constant ($\boldsymbol{\tau}$) . When cuff inflation is very fast (when artery and vein collapse simultaneously) $\boldsymbol{P_{Equilibrium}}$ can be defined as the mean systemic filing pressure P_{msf}. P_{msf} is the mean pressure in the circulatory system when there is no blood in motion. This value is of great interest to clinicians because it holds information on the fluid status of a patient [20]. There is a great need for reliable P_{msf} measurements in the clinic. Previously investigated cuff-based P_{msf} measurement modalities involve complete vascular occlusion of about ~30 s to allow for venous and arterial pressures to reach an equilibrium value [22]. We investigate if the distal arm model (Fig. 2) can be used to estimate P_{msf} via a ~5 s arterial occlusion.

The time constant $\boldsymbol{\tau}$ is a non-standard parameter, but it is potentially valuable to hemodynamic monitoring as it holds information on the artery-vein interaction (the rate at which arterial and venous pressures tent towards the equilibrium value).

To demonstrate a measurement strategy aimed at estimation of τ and $\boldsymbol{P_{Equilibrium}}$, a simulation framework is used. τ and $\boldsymbol{P_{Equilibrium}}$ values are inferred by fitting an exponential function to a signal generated via the model in Fig. 2. Analytically derived parameter values are compared to exponential fit results.

The patient data is then processed to infer τ and $\boldsymbol{P_{Equilibrium}}$ values at each cuff inflation. The results are analyzed qualitatively to identify correlations between different hemodynamic parameters.

Systemic resistance and distal vascular compliance

Several other parameters can be inferred by taking into account the complete BP signal recorded over the entire cuff-inflation duration. A dedicated estimator is introduced to infer distal circulation parameters of the model shown in Fig. 3 – arterial compliance C_a, arm vasculature resistance R_s and venous compliance C_v. The algorithm is based on standard Bayes Markov Chain Monte Carlo (MCMC) processing [19]. This method is chosen due to the complex interference between multiple physiological effects affecting the signal – brachial artery collapse (influenced by parameters *a*, *c*, *d*), artery-vein interaction (parameters $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$), arterial venous collapse, heart and lung activity. Usage of prior knowledge and transparent interpretation of the inference results are needed.

The algorithm receives as input the systemic arterial pressure waveform and cuff pressure. To determine the systemic arterial pressure throughout the cuff inflation without introducing a second invasive arterial line, it is necessary to assume that prior to the cuff inflation, the systemic arterial pressure equals the distal arterial pressure and that the systemic arterial BP stays constant throughout the cuff inflation.

A sampling process is repeated over a pre-defined number of iterations in order to represent the posterior distribution of arterial collapse parameters characterized by Eq. 7 and Eq. 8. With every iteration, a set of parameter values, C_a, R_s, and C_v, are sampled from the posterior and used as input to the model presented in Fig. 3 to compute a distal arterial pressure signal. Agreement of sampled parameter values with measured data and with prior knowledge is evaluated via Eq. 7 and Eq. 8. An illustration of the sampling process is shown in Fig. 3.

$$\mathrm{P}(\boldsymbol{\theta}\,|\mathrm{D}) \propto \mathrm{P}(\boldsymbol{\theta})\mathrm{P}(\mathrm{D}|\boldsymbol{\theta}), \tag{7}$$

where $\mathrm{P}(\boldsymbol{\theta}\,|\mathrm{D})$ represents the posterior distribution, $\boldsymbol{\theta}$ represents the parameter set $[\mathrm{C_a}, \mathrm{R_s}, \mathrm{C_v}]$ and D represents the measured data $\mathrm{P_{cuff}}$ and $\mathrm{BP_{env}}(\mathrm{P_{cuff}})$. $\mathrm{BP_{env}}$ is defined as the lower envelope of the distal BP signal (illustrated in Fig. 3). $\mathrm{P}(\mathrm{D}|\boldsymbol{\theta})$ is defined as:

$$\mathrm{P}(\mathrm{D}|\boldsymbol{\theta}) = \sum_{\mathrm{P_{cuff}}=0}^{\max(\mathrm{P_{cuff}})} \log\left(\frac{1}{\sqrt{2\pi\sigma^2}}\right) - \frac{\left(BP_{env}(\mathrm{P_{cuff}}) - \mathrm{BP_{env\boldsymbol{\theta}}}(\mathrm{P_{cuff}})\right)^2}{2\sigma^2} \tag{8}$$

Where σ, the expected measurement noise is set to 2 mmHg, according to measurement device specifications [3].

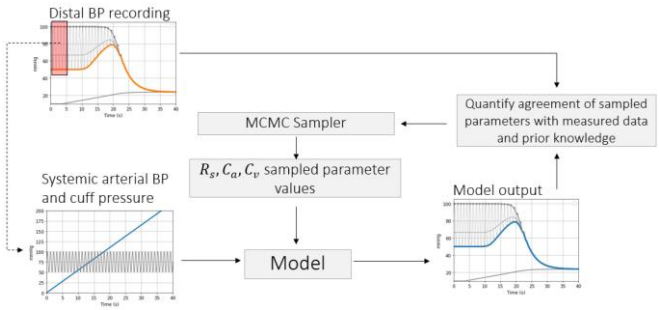

Figure 3. Sampling process to be repeated over a number of iterations to determine the posterior distribution of model parameters.

The resulting posterior distribution is interpreted to obtain the 95% most probable parameter values, (also known as highest density interval HDI), together with the distribution's central tendency.

To demonstrate the feasibility of the inference method, the algorithm is run on simulated BP signals generated via control parameter sets [C_a, R_s, C_v]. Inferred parameter values are compared against the control parameter values.

The prior $\mathrm{P}(\boldsymbol{\theta})$ is used in the simulation framework to enforce that the parameter sets satisfy the expected physiological properties (compliance parameters cannot take negative values, the output BP signal is compatible with observations made on real data, e.g. the RC decay time constant is less than 10 s). This prior information is sufficient for correct inference in the simulation environment. However, it is possible that more complex priors will be needed when processing patient data.

Validation of this method is preliminary and limited for now to the simulation framework. The method cannot yet be applied to our patient data, as information on *d*, the arterial collapse value at brachial site (Eq. 3), is not available due to uncertainties regarding arm tissue compression and cuff compliance. This is currently being investigated as part of work conducted in parallel [11]. Nevertheless, the simulation framework does demonstrate that ample information regarding the hemodynamic status of a patient is contained within the distal BP response to cuff inflation and that opportunities for cuff-based measurement strategies should be explored further.

6.3. **Results**

6.3.1. Measurements

To give a visual impression of the cuff inflation effects on distal arm arterial pressure, Figs. 4.1.A and 4.2.A show a segment of the cuff pressure signal and Figs. 4.1.B and 4.2.B show the simultaneously recorded ABP signal . Effects of cuff inflation on the distal limb BP have previously been assumed as irrelevant for characterization of pulse propagation along the arm [17]. However, our data shows that large BP changes occur due to cuff inflation.

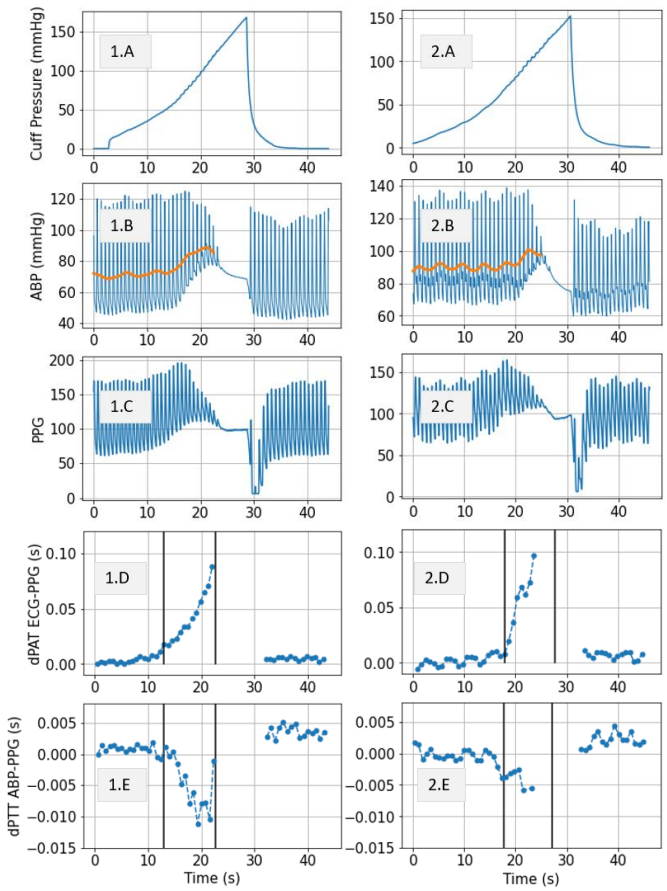

Figure 4. Example signals $Patient_1$ (left) and $Patient_2$ (right). Highly dynamic and patient specific effects are occurring in the distal arm as result of the cuff inflation. The plots show: A) Cuff pressure; B) Blue: Arterial pressure (ABP) measured invasively downstream form the cuff at radial site, Orange: MAP; C) PPG signal measured at finger site downstream from the cuff; D) $\Delta PAT_{ECG-PPG}(CuffP)$; E) $\Delta PTT_{ABP-PPG}(CuffP)$.

Simultaneously recorded ECG and PPG are used to compute changes in PTT due to cuff inflation over two vascular segments: Heart to finger site $\Delta\mathrm{PAT}_{\mathrm{ECG-PPG}}(CuffP)$ (Figs. 4.1.D and 4.2.D) and radial to finger site $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}(CuffP)$ (Figs. 4.1.E and 4.2.E).

Our previous model [18, 17] assumed that no significant changes in PTT occur in the distal arm during cuff inflation. Our current data however gives insights on the validity of this assumption. Figs. 4.1.E and 4.2.E show a decrease in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ over the radial site to finger length of about 10 ms and 6 ms for for *Patient*$_1$ and *Patient*$_2$, respectively; therefore, the drop in ΔPTT over the entire length of the distal arm (defined as $\Delta\mathrm{PTT}_{\mathrm{distal}}$) is expected to be approximately ~20 ms and ~12 ms, respectively.

Figure 6 summarizes the changes in distal BP across all inflations performed on *Patient*$_1$

and *Patient*$_2$, respectively. For each inflation, the maximum increase in diastolic pressure, the maximum decrease in systolic pressure and the maximum increase in mean pressure are calculated. Figure 5 illustrates how the reference BP values, maximum MAP, maximum P_{dia} and minimum P_{sys} are defined.

On average across all inflations performed on *Patient*$_1$, the diastolic pressure increases by 25 mmHg, the systolic pressure decreases by 29 mmHg and the mean arterial pressure increases by 16 mmHg. On average across all inflations performed on *Patient*$_2$, the diastolic pressure increases by 30 mmHg, the systolic pressure decreases 28 mmHg and the mean arterial pressure increases by 18 mmHg.

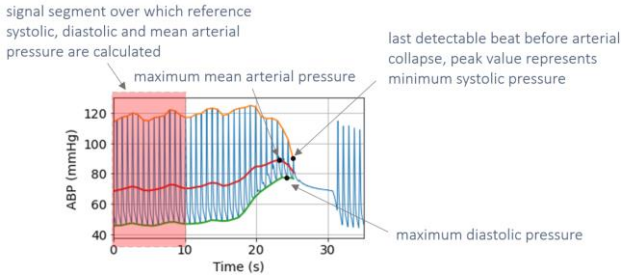

Figure 5. Illustration showing reference Psys, Pdia, MAP values and maximum MAP, maximum Pdia, minimum Psys.

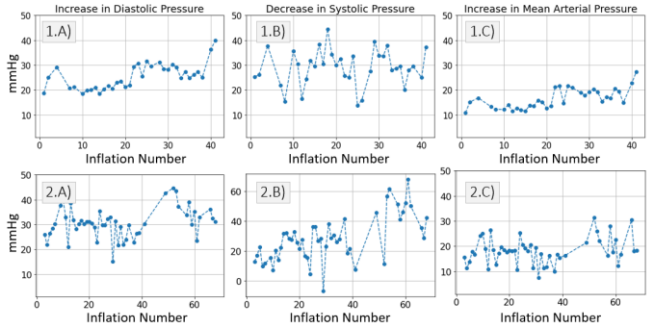

Figure 6. A) Maximum increase in distal diastolic pressure per inflation. B) Maximum decrease in distal systolic pressure per inflation. C) Maximum increase in distal mean arterial pressure per inflation. Results are displayed for *Patient*$_1$ data and *Patient*$_2$ data respectively.

We quantify the decrease in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ (Figs. 7.1.A and 7.2.A) for all cuff inflations performed on *Patient*$_1$ and *Patient*$_2$, respectively. On average $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ decreases by 10 ms for both patients. Standard deviation of $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ values is 2.5 larger in *Patient*$_2$ than in *Patient*$_1$.

Figures 7.1.B and 7.2.B show the cuff pressure at which the maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ occurs. It is found that the maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ occurs when the cuff pressure increases beyond diastolic value. From this it can be deduced that the cuff inflation (and resulting distal BP increase) systematically lead to a drop in distal PTT. Therefore, the effect cannot be attributed to other factors.

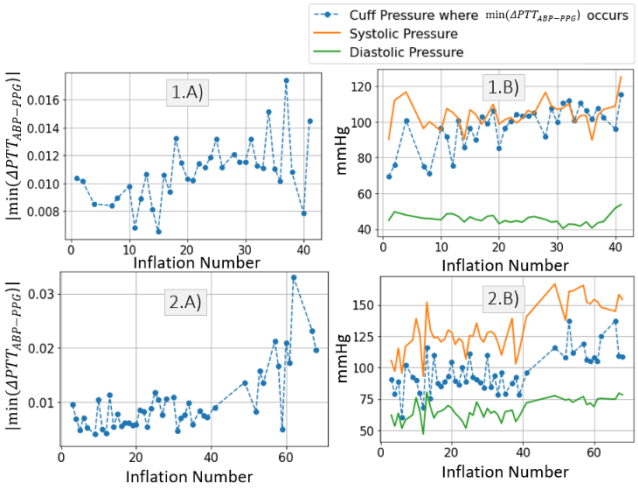

Figure 7. A) Maximum drop in $\Delta PTT_{ABP-PPG}$ per inflation. B) Cuff pressure at which the maximum drop in $\Delta PTT_{ABP-PPG}$ occurs, systolic and diastolic systemic values per inflation. Results are displayed for *Patient*$_1$ data and *Patient*$_2$ data respectively. Expected ΔPTT_{distal} is twice the value of $\Delta PTT_{ABP-PPG}$.

6.3.2. Model Simulations and Inference Results

A. Brachial artery compliance inference

Simulation framework

The model shown in Fig. 2 is used to simulate distal BP change with respect to cuff inflation. Figure 8.A shows systemic arterial pressure, cuff pressure and resulting distal arterial and venous pressure. The simulated MAP increases by almost 20 mmHg during cuff inflation. This is similar to a typical change in MAP are observed in the patient data (Fig. 4). The distal pulse transit effect is simulated (Fig. 8.B) by fitting a linear PWV-MAP relationship to obtain a ΔPTT_{distal} response to MAP increase similar to the observations on patient data (see Fig. 4). Figure 8.B also includes $\Delta PTT_{brachial}$ simulated with parameters a = 0.03 and c = 0.1 (as shown in [17]), and total ΔPAT (the summation of ΔPTT_{distal} and $\Delta PTT_{brachial}$).

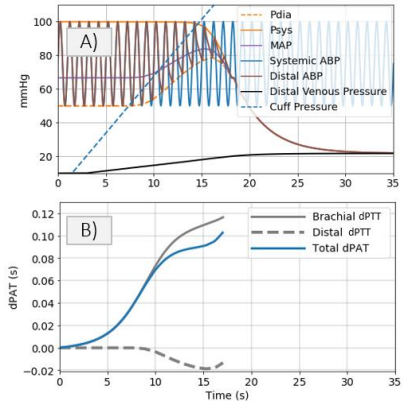

Figure 8. A) Simulated systemic arterial pressure, cuff pressure and resulting distal arterial and venous pressure. B) Simulated total ΔPAT, $\Delta PTT_{brachial}$, and ΔPTT_{distal}.

To assess the impact of distal artery effects on the correctness of the inference process, the total dPAT is fitted as described in [17], under the assumption that $\Delta\mathrm{PTT}_{\mathrm{distal}}$ is not influenced by the cuff inflation. Figure 9.A shows the fit result with a dotted black line. The inferred *a* value is 0.012 and the inferred *c* value is 0.08, corresponding to an error in *a* inference and *c* inference of over 50% and almost 20%, respectively. Therefore, changes in distal arm circulation are not negligible as assumed until now.

A simple mitigation involves disregarding ΔPAT values recorded at cuff pressures greater than diastolic pressure. Simulations show that, in principle, it is possible to infer correct *a* and *c* values by taking into account the first portion of a ΔPAT recording only. Figure 9.B shows the fit result with a dotted black line; the inferred *a* value is 0.027 and the inferred *c* value is 0.099, which are close to the true parameter values of 0.03 and 0.1, respectively. Figure 10 gives more information on the inference result by showing the 95% HDI, which contains the 95% most probable parameter values (more details in [17]). A larger uncertainty is present when disregarding ΔPAT data recorded at high cuff pressures.

Regarding our patient data, such small ΔPAT changes which occur in the first part of the inflation would ideally be recorded over much slower inflation speeds than we show in Fig. 4. Alternatively, if an invasive line is available as in Fig. 1, then the distal ΔPTT_{distal} can be accounted for.

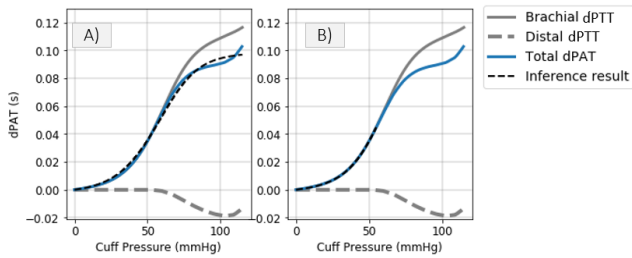

Figure 9. Inference of parameters *a* and *c* by A) taking into account the entire dPAT recording, B) discarding dPAT samples corresponding to cuff pressures greater than P_{dia}.

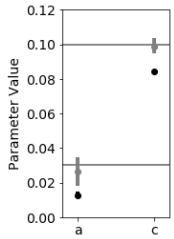

Figure 10. The parameter estimate are shown: the vertical bars indicate the 95% HDI. Black bars represent the HDI corresponding to the fit result shown in Fig. 9.A and gray bars represent the HDI corresponding to the fit result shown in Fig 9.B.

Inference of brachial artery parameters from patient data

The inference method is applied to our patient data as described in Section 6.2.4.A The results are shown in Fig 11.

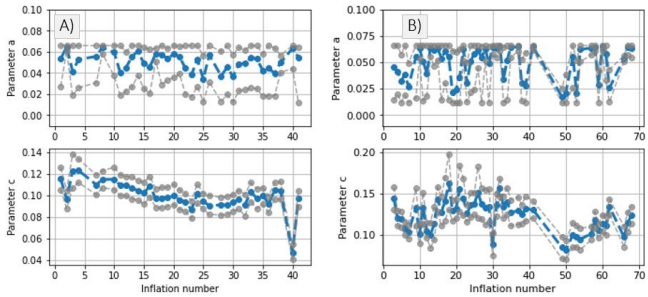

Figure 11. Inference results of the parameters *a* and *c* per inflation; A) $Patient_1$ data and B) $Patient_2$ data. Blue represents the central tendency of the posterior distribution, gray represents the 95% HDI.

A slight correlation between parameter *c* and the parameters shown in Fig. 16 (HR, maximum P_{dia} increase and maximum distal $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ decrease) can be noticed. In $Patient_1$, the *c* value decreases gradually up to inflation number ~ 25, after which a plateau is reached, followed by a slight increase. An opposite trend is observed in plots showing heart rate (HR), maximum P_{dia} increase and maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ (Fig. 15).

In $Patient_2$, a drop in the *c* value is noticed at inflation 50. Again, the opposite trend is observed in HR, maximum distal P_{dia} increase and maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ (Fig. 17). Such qualitative assessment suggests that the *c* parameter is to some extent linked to systemic changes in hemodynamic status.

B. Estimation of PAT-BP calibration

The inferred *a* and *c* parameter values (Fig. 11) are used to obtain the BP-PAT calibration. By the method described in Section 6.2.4.B, the ECG and PPG signals are processed over a number of time segments to estimate beat-to-beat P_{sys}. One time segment is defined as the duration between two consecutive cuff inflations.

To illustrate the algorithm performance, Figs. 12 and 13 shows examples of BP prediction over a total of six time segments obtained from *Patient*$_1$ and *Patient*$_2$ data, respectively.

Over the entire recording, we find the P_{sys} estimation to be generally accurate. To define a performance criterium, P_{sys} estimation is considered inaccurate when an error larger than 10 mmHg occurs over a duration longer than one minute. For *Patient*$_1$, the algorithm estimates P_{sys} inaccurately over two out of thirty-six time segments, and for *Patient*$_2$, the algorithm estimates P_{sys} inaccurately over five out of thirty-six time segments. Note that the PAT-based estimation of BP can only work when the pulse transit is undisturbed by motion. Figure 14 shows an example of a time segment where significant motion occurs due to the invasive nature of the procedure. For this reason, we did not account for 11 time segments from which breathing rate could not be distinguished (assuming that motion artifacts are minimal if breathing is expressed in the signal).

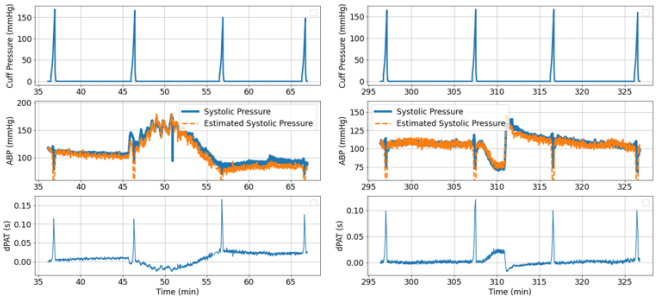

Figure 12. Example of PAT-based BP estimation in *Patient*$_1$.

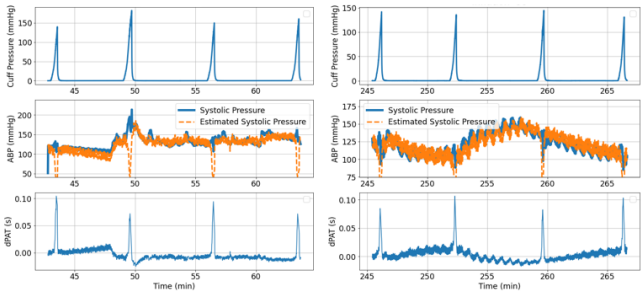

Figure 13. Example of PAT-based BP estimation in *Patient*$_2$.

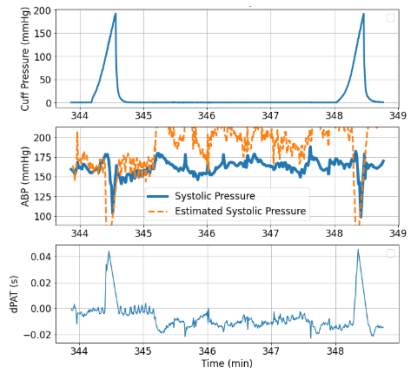

Figure 14. Example of time segment not included in the analysis.

C. Inference of distal arm circulation parameters

Time constant and mean systemic filling pressure

A distal BP signal is generated with the same parameter values as in Section 6.2.4.C. Figure 15 illustrates the 15 s segment of the BP signal where the artery is fully collapsed. Analytically (according to the series combination of arterial compliance, systemic resistance and venous compliance), the time constant of the exponential decline is equal to 3.08 s and the $\boldsymbol{P_{Equilibrium}}$ is equal to 23 mmHg (note that in this case $\boldsymbol{P_{Equilibrium}}$ does not equal $P_{msf,}$ because artery and vein do not collapse simultaneously). An exponential function is fitted to the selected segment and inferred values are $\boldsymbol{\tau}$ = 3.18 s and $\boldsymbol{P_{Equilibrium}}$ = 23 mmHg. This suggests that the inference method is feasible. However, our data contains fast inflations of about 30 s in total, with exponential decline segments of ~ 4 to 5 s long (Fig. 4). Therefore, it is important to check if $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$ inference is possible when short recordings are available. Figure 15 highlights the first 4 s of the exponential decline segment. Fitting an exponential decline function to this short segment results in $\boldsymbol{\tau}$ = 3.4 s and $\boldsymbol{P_{Equilibrium}}$ = 22 mmHg.

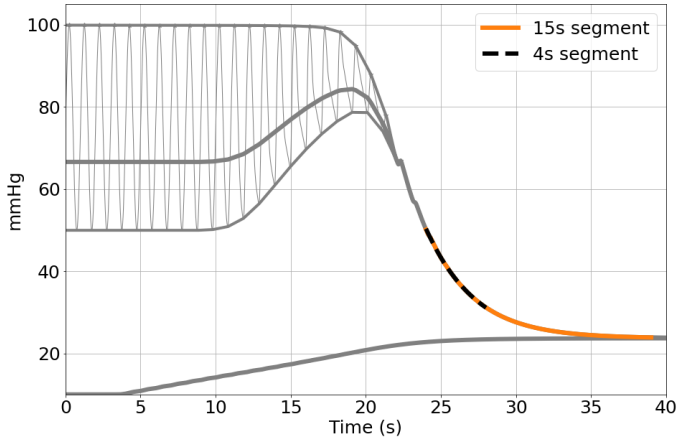

Figure 15. Feasibility of simulation-based time constant and $\boldsymbol{P_{Equilibrium}}$ measurement.

Ideally, a longer cuff inflation is necessary to infer the time constant parameter accurately. Nevertheless, the algorithm is applied to our patient data in order to obtain an approximation of the parameter values. Figures 16.A and 16.B show the $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$ inference results for each of the 35 cuff inflations performed on *Patient*$_1$. One clear trend is observed in the $\boldsymbol{P_{Equilibrium}}$ inference results. The $\boldsymbol{P_{Equilibrium}}$ value increases gradually up to inflation number ~25, after which a plateau is reached, followed by a slight decline. The same trend is observed in plots illustrating HR, maximum P_{dia} increase and maximum distal $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ decrease with respect to inflation number (Fig. 16), suggesting that systemic changes in the hemodynamic status are occurring. A plausible explanation to this correlation is that HR determines the amount of blood which is pumped by the heart into the arm throughout the 30 s inflation. Therefore, when HR increases, blood fills up the arm vasculature at a faster rate, leading to larger changes in distal diastolic pressure prior to arterial collapse, and also leading to an increase in $\Delta\mathrm{PTT}_{\mathrm{distal}}$ drop and $\boldsymbol{\tau}$.

Figures 17.A and 17.B show the $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$ inference results for *Patient*$_2$. A decrease in $\boldsymbol{\tau}$ is observed at inflation fifty. Significant changes in HR, maximum P_{dia} increase and maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ are also observed around inflation fifty. It is clear that at the time of inflation fifty, the hemodynamic status of *Patient*$_2$ is altered. However, the correlation between hemodynamic variables is slightly different from *Patient*$_1$. The change in the hemodynamic status is not clearly visible when analyzing the $\boldsymbol{P_{Equilibrium}}$ values. A distinguishable change in $\boldsymbol{\tau}$, however, is observed at inflation fifty.

Such correlations are interesting to observe, and they indicate that τ and $P_{Equilibrium}$ are to some extent affected by systemic alterations in the circulatory system.

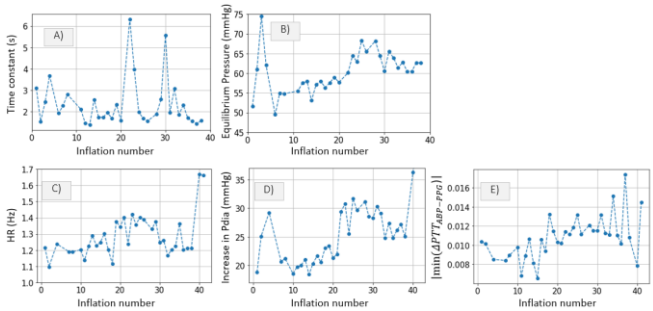

Figure 16. Time constant $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$ from *Patient*$_1$ data. HR, increase in P_{dia} and maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ are plotted for qualitative comparison.

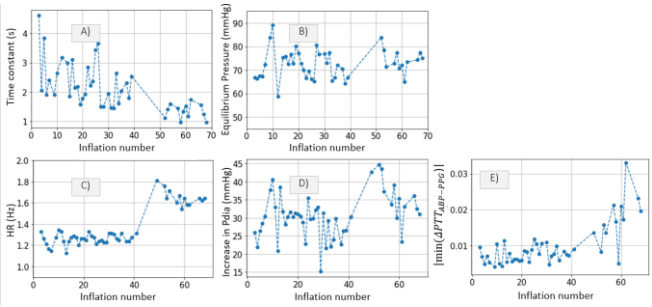

Figure 17. Time constant $\boldsymbol{\tau}$ and $\boldsymbol{P_{Equilibrium}}$ from *Patient*$_2$ data. HR, increase in P_{dia} and maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ are plotted for qualitative comparison.

Systemic resistance, distal vascular compliance

The distal BP signal simulation (generated with the parameter values described in Section 6.2.4.A is processed to infer distal arterial compliance, systemic resistance and venous compliance via the MCMC fitting method described in Section 6.2.4.C. The fit result, the HDI and central tendency of the resulting posterior distribution are shown in Fig. 18.

The correct estimation of the model parameter values from the simulated BP signal demonstrates the feasibility of the inference method and that the BP response to cuff inflation can be processed to obtain information on systemic resistances, arterial and venous compliances.

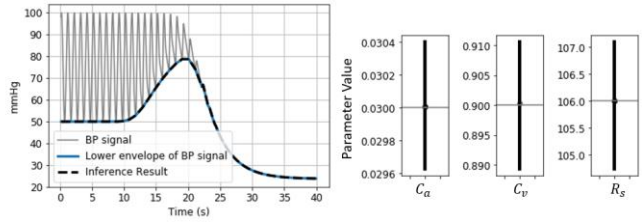

Figure 18. Simulated BP signal and inference result. The signal is simulated with control parameter values Ca = 0.03 mL/mmHg, Cv = 0.9 mL/mmHg, Rs = 106 mmHg.s/mL. The inferred parameter values (determined as the central tendency of corresponding posterior distributions) are equal to the control parameter values.

6.4. **Discussion**

Interesting dynamic effects occur in the vasculature as response to occlusion-based perturbations. Our goal is to understand these effects in depth. The insights are applied towards developing cuff-based measurement strategies for acquiring information on a number of hemodynamic parameters of potential interest to critical care.

We previously studied the response of the vasculature to occlusion perturbations via non-invasive modalities. In this study, we advance our understanding by invasively measuring BP downstream from the cuff. We observe highly dynamic effects occurring in the distal arm as result of the cuff inflation. Figure 4 shows the extent to which

distal BP is altered due to cuff inflation: P_{dia} increases by 30 mmHg, MAP increases by 20 mmHg. This effect is also evidenced by the 20-ms drop in $\Delta\mathrm{PTT}_{\mathrm{distal}}$. The cuff-induced effects on distal vasculature are systematic and are seen in both investigated patients across all cuff inflations (Figs 6, 7).

A model is developed to obtain an understanding of the factors influencing the observed behaviors (Fig. 2). Simulations conducted via the model with parameters within ranges close to values reported in the literature mimic the effects observed in the patient data. Five cuff inflation stages which are identified based on the patient data (Fig. 4) are also present in the model output (Fig. 2 upper right plot):

1. Cuff pressure value is below systemic venous pressure: arm circulation remains unaltered.
2. Cuff pressure increases beyond systemic venous pressure: vein collapses, flow out of the limb is stopped and buildup of blood begins to occur in the limb via the artery; arterial pressure is not visibly altered at this stage.
3. Cuff pressure increases beyond systemic diastolic pressure leading to increase in distal diastolic pressure.
4. Cuff pressure approaches systemic systolic pressure: minimal amount of blood flows into the limb at each heart-beat, a decrease in the distal systolic pressure is observed.
5. Eventually, blood flow is stopped - arterial and venous pressures tend towards an equilibrium value.

The model closely mimics all 5 stages of the cuff inflation process, meaning that the model can be used to represent changes in distal arterial pressure during cuff inflation and that physiological meaning can be attributed to the model parameters. With the help of the proposed model, we explore several measurement strategies.

6.4.1. Inference of brachial artery compliance

Via a simulation framework we show that the inference of brachial parameters *a* and *c* is inaccurate when distal PTT effects are not accounted for (Figs. 9, 10). Two mitigations are possible:

- Disregarding dPAT values recorded at cuff pressures greater than P_{dia}. This leads to accurate inference of the parameters *a* and *c*. One downside is in that a relatively high degree of uncertainty is present (Fig. 10). This method is not suited to our data, which includes fast inflation speeds and few PAT points recorded at cuff pressures below P_{dia}.
- Alternatively, if an invasive line is available as in Fig. 1, then the distal PTT can be accounted for. We apply this method to our data (Fig. 11).

We observe some correlation between the parameter *c* and other hemodynamic parameters: HR, maximum distal diastolic increase and maximum distal dPTT decrease. Such qualitative assessment gives indication that the *c* parameter is to some extent linked to systemic changes in the hemodynamic status. The relatively large HDI of the parameter *a* inference result and the outlier parameter *c* value occurring at inflation 40

of *Patient*$_1$ suggest that the measurement procedure needs to be further optimized, possibly via slower cuff inflation speeds, which can allow for the collection of more dPTT datapoints. Improved measurement devices with higher sampling rate, better PPG contact pressure will also likely enable better inference of parameters.

6.4.2. Estimation of PAT-BP calibration

The inferred *a* and *c* parameter values (Fig. 11) were used to estimate beat-to-beat P_{sys} over time segments following each processed inflation (Figs, 12, 13). We find the P_{sys} estimation to be generally accurate over the majority of time segments. This gives indication that the inferred *a* and *c* parameter values are in the correct range. In 7 of the 72 time segments, the estimation is inaccurate. It is not yet clear which effects cause this temporary drop in performance. It is likely that the model (Fig. 2) is not yet complete and that other dynamic mechanisms are taking place. The model also assumes a homogeneous artery segment, which might contribute to inference innacurracy. In addition, Eq. 3 [9] which characterizes arterial collapse has been developed based on insights acquired via ex-vivo methods of research. High resolution imaging and specialised setups are needed to further validate the arterial collapse mechanisms in-vivo [8]. Parallel work is also tackling uncertainties regarding cuff, arm tissue, artery interaction [11, 27].

Also, the presented PAT-based BP estimation is intended for patients that are not monitored invasively. The method might perform better during less invasive OR procedures, or during ICU monitoring, where hemodynamic alterations are expected to be less frequent and less abrupt, allowing for more accurate measurement of cuff-induced effects on the vasculature. Also, the absence of motion artifacts caused by invasive interventions would increase the reliability of the PAT-based BP estimation.

6.4.3. Inference of distal arm circulation parameters

Time constant and mean systemic filling pressure

We first investigate the RC decay BP segment following arterial collapse. This portion of the signal is influenced by the least amount of physiological effects, e.g. brachial artery collapse mechanics, and heart and lung activity does not affect the vasculature behavior at this stage. Via a simulation framework, we demonstrate the measurement of the time constant τ and $P_{Equilibrium}$ to be feasible. If the inflation speed is increased such that arterial and venous collapse occur simultaneously, then $P_{Equilibrium}$ would be identical to the mean systolic filling pressure P_{msf}. Previously investigated cuff-based P_{msf} measurement modalities involve complete vascular occlusion of about ~30 s [22]. Our simulation framework shows preliminary results that this occlusion duration can be reduced to ~5 s if RC decay principles are taken into account.

The proposed algorithm is applied to the patient data and a qualitative assessment is performed. In *Patient*$_1$, we observe a correlation between $P_{Equilibrium}$ and a number of other hemodynamic parameters: HR, distal P_{dia} increase, maximum drop in $\Delta\mathrm{PTT}_{\mathrm{ABP-PPG}}$ and parameter *c* (Fig. 16). However, in *Patient*$_2$, we observe a correlation between τ and the rest of the hemodynamic parameters (Fig. 17). This qualitative assessment of the

correlations between the inferred parameters and the hemodynamic measurements gives some indication of the link between distal vasculature parameters and systemic changes in hemodynamic status. Further investigation is possible with dedicated clinical studies designed to assess possible links between changes in distal vasculature parameters and hemodynamic instability events

Systemic resistance, distal arterial and venous compliance

A method accounting for all portions of the BP response to cuff inflation was developed in order to obtain information on arm vasculature resistance Rs, distal arterial Ca and venous compliance Cv. It is evident that the physiological meaning is approximate - for example, it is possible that Rs adapts to some extent throughout the inflation processTherefore, Rs can be perceived as an indicator of resistance, rather than as an exact measurement (this uncertainty applies also to the other parameters Ca, Cv, τ, $P_{Equilibrium}$, *a* and *c,* which might be affected by the cuff inflation itself). Further clinical evidence involving multiple patient groups can indicate if changes in arm vasculature resistance are linked to changes in systemic resistance and if there is a correlation between relative changes in parameters such as Ca, Cv and subsequent changes in blood pressure, patient outcome etc. It is likely that factors such as type of procedure, level of sedation, or conditions such as arteriosclerosis, endothelial dysfunction impact vasculature response to cuff inflation.

In our study, the validation of the method is preliminary and is limited to the simulation framework (Fig. 19). The method cannot yet be applied to our patient data, as information on the arterial collapse value at brachial site (Eq. 3), *d*, is not available due to uncertainties regarding arm tissue compression and cuff compliance. This is currently being investigated as part of work conducted in parallel [11]. Further development might be needed when applying the method to patient data. For example, a more informative prior might be necessary, due to the complex interference between multiple physiological effects influencing the signal.

Nevertheless, the proposed simulation framework does demonstrate that extensive information regarding the hemodynamic status of a patient is contained within the distal BP response to cuff inflation and that related opportunities for cuff-based measurement strategies should be explored further.

6.4.4. Outlook

The presented research method is intended to serve as a basis for further studies aimed at characterizing vasculature response to occlusion-based perturbations. Several strategies aimed at modulating blood flow and pulse propagation need to be further investigated: stepwise/continuous inflation/deflation, venous vs. arterial occlusion, varying duration of occlusion, inflation speed, frequency of occlusions, length over which occlusion is applied, site at which occlusion is applied.

In addition to this, studies which address occlusion-related effects via non-standard measurement setups might contribute to the development of improved models. For example, interesting pathophysiological mechanisms are being observed via NIRS-based

measurement of tissue oxygenation response to vascular occlusion tests [1] and cuff devices are being used for evaluation of endothelial function and nitric oxide regulation [23].

Many other emerging techniques which measure interactions between hemodynamic variables in response to defined perturbations will also facilitate further exploration of cuff-based measurement setups [21].

6.5. **Conclusions**

This study improves our understanding of vasculature response to occlusion-based perturbations. Initial characterizations [17, 18] neglected the changes occurring in the distal limb. However, our new experimental evidence shows that highly dynamic processes occur in the distal vasculature during cuff inflation. A distal arm model and a simulation framework were developed based on experimental evidence in order to explore cuff-based modulation of blood flow and pulse propagation along the artery.

We demonstrate new possibilities to interpret the cuff-induced changes and obtain information of potential value to critical care: PAT-BP calibration, brachial arterial compliance, distal vascular compliance, peripheral resistance, mean systemic filling pressure, artery-vein interaction. Feasibility of the measurements was mainly demonstrated via computer simulations and via qualitative assessment of limited patient data; this work is meant as basis for further clinical studies.

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PART

2

CHAPTER 07

An Experimental Study on the Blood Pressure Cuff as a Transducer for Oscillometric Blood Pressure Measurements

Based on:

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- Bogatu, L., Bresch, E., Muehlsteff, J., Smink, J. and Woerlee, P., 2019, July. Insights into oscillometry: An experimental study for improvement of cuff-based blood pressure measurement technology. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 7068-7071). IEEE.

Abstract

Non-invasive blood pressure (BP) measurements still rely on empirical interpretation of arterial oscillations recorded via cuff-based oscillometric methods. Extensive effort has dedicated to establishing a theoretical basis for oscillometry, aiming at more accurate BP estimations and measurement of additional hemodynamic parameters. However, oscillometry is still a heuristic method for BP inference. *Goal:* This study is focused on improving our understanding of the expression of arm volume pulsations in oscillometric signals. The aim is to identify main factors that determine the transfer function of arm volume to cuff pressure oscillations for existing cuff devices - this being an essential step in establishing a theoretical basis for oscillometry. Methods: The effects of air compression within the cuff and the influence of viscoelastic cuff material properties on the transfer function are studied by an experimental setup. Mechanical numerical modelling is used to interpret the results. Results: Air compression is found to be of adiabatic nature in the frequency range of interest. The cuff material exhibits viscous characteristics which is the cause of cuff response dependence on: inflation speed, tightness of wrapping, time passed since previous measurement, heart rate. Conclusion: It was found that typical cuffs used in clinical practice exhibit complex behavior. Cuff hardware needs to be improved to enable practical translation of pressure to arm volume oscillations. The presented characterisation method contributes to standardized development of new cuff prototypes and to identification of designs, techniques and materials with improved properties for enabling BP measurement accuracy and extraction of additional hemodynamic information.

7.1. Introduction

Blood pressure (BP) is a key, well-established parameter indicative of the hemodynamic status. For this reason, it is used in many care settings involving patient monitoring and cardiovascular disease management. Non-invasive, automatic BP measurement is currently based on oscillometry, which involves inflation of a cuff on the upper arm and recording of oscillations within the cuff. BP values are inferred based on an empirical interpretation of the recorded signal. It has been found that cuff pressures at certain ratios of oscillation amplitudes relative to the maximum amplitude are the same as reference clinical measurements (invasive, auscultatory) [21]. However, very large errors in BP values have been reported especially in hypo- and hyper-tensive patients [1, 11]. There is an urgent need for more accurate non-invasive blood pressure technologies.

Research on improving the accuracy of non-invasive BP measurement is focused on providing physical and physiological interpretation of the oscillometric signal, beyond empirical understanding. Physical modelling deals with the process by which pressure pulsations in the artery cause the arterial wall and arm surface to distend as cuff pressure is exerted on the arm surface. The exerted cuff pressure influences the transmural pressure across the arterial wall. The resulting arterial volume pulsations propagate through arm tissue and are measured as cuff pressure oscillations. An in depth understanding of this process could lead to more accurate BP estimations, waveform feature analysis and measurement of additional hemodynamic parameters (related for example to arterial properties [2], or heart and lung function [10]).

Some existing methods for interpretation of oscillometry involve special non-standard cuffs [4], or incorporation of extra features in the standard cuffs [3]. Such devices are not ideal for clinical use since they are not compatible with existing clinical equipment [22]. An ideal solution should be based on using standard air BP cuffs. However, detailed mechanical characterization of the cuff properties under inflation/deflation and under realistic arm pulsations is still lacking. From an engineering perspective, the “cuff transfer function”, which is the relation between input and output signals, i.e., the arm volume oscillations and the recorded cuff pressure oscillations, needs to found.

This transfer function has been studied in the past by means of mechanical models of different levels of complexity [2, 5, 7, 12, 13, 14, 19]. However, these studies are mostly qualitative, assume idealized non-realistic material properties, ignore the frequency dependence of material stresses and strains in the cuff wall and experimental characterization is often missing or is incomplete. For this reason, there is uncertainty in the level of complexity required in a realistic model describing cuff behavior.

For example, in previous studies there is uncertainty related to adiabatic or isothermal air compression behavior and material distension effects are either excluded or assumed to be purely elastic [2, 5, 13, 19]. In other studies, cuff behavior assumptions are based on simple observations on limited numbers of measurements, lacking a physics-based characterization. In [12], for example, the cuff compliance is estimated by measuring pressure during inflation with known flow rate. This gives the cuff volume-pressure relationship, which is used to obtain information on arterial volume changes. However, the

study does not investigate whether cuff response to inflation is different from cuff response to high frequency artery pulsations.

A more in-depth analysis of the cuff transfer function is performed in [14], where a measurement system including mechanically simulated artery pulsations is used to investigate cuff behavior. The study raises awareness on the importance of developing better hardware for the non-invasive BP measurement. The experimental set-up is used to show variability in the cuff transfer function depending on factors such as tightness of wrapping. Limitations of improving non-invasive BP measurement technology based on algorithm development alone become evident, especially in view of increasingly complex processing being applied to oscillometry signals (e.g. fuzzy logic [16], complex filters [17]). However, these studies do not attempt to characterize how the cuff functions as a transducer – how compression of air, distension of cuff material and time response of the system impact the expression of arm volume changes in cuff signal (e.g. the time response of the system is especially important to determine whether it is possible to use the cuff for arterial waveform feature analysis). Therefore, the cuff transfer function needs to be further investigated in order to identify which design aspects should be improved.

In [15] and [18] some issues related to cuff time response are raised by comparison of invasive brachial signals to simultaneously acquired cuff pressure signals in limited numbers of subjects. However, these studies are not focused on cuff characterization, and the presented measured cuff pressure oscillations are a combination of arm tissue effects and cuff effects.

Other studies tackle uncertainties related to cuff size (or cuff volume) required for accurate arterial volume pulsation measurement. Some studies provide qualitative estimations [8], but indicate that more quantitative research into cuff BP methodology is desirable. Issues related to standardization of cuff placement have also been tackled via observations of cuff measurements on a limited number of human subjects [9].

In view of the number of studies [2, 5, 7, 12, 13, 14, 19] which rely on unverified assumptions regarding cuff behavior to derive hemodynamic parameters or studies which partially investigate cuff behavior uncertainties, this work is dedicated to obtaining a more in-depth understanding of the cuff as a transducer. For a systematic study, this work is an in-depth analysis of the isolated cuff, without consideration of arm compressibility effects. Parallel work [6] is tackling the arm response separately. Future studies will combine arm and cuff behavior, to provide a complete theoretical understanding of oscillometry. Our work proposes an experimental setup and method for characterization of commercial cuffs using established methods of system response analysis. Here, the cuff transfer function is studied with an experimental setup which generates mechanical simulations of arm volume pulsations. Cuff response to the controlled volume pulses of different frequencies is measured and compared to cuff response to slow inflation by constant mass flow. This builds on our preliminary work, which indicates that assuming purely elastic behavior of cuff external wall material does not provide realistic description of cuff behavior [24]. The obtained measurements and interpretation of the

results are supported by dedicated material characterization and a first order model including viscoelasticity and hook and loop fastener properties. An investigation and comparison of two commercially available cuff models with the proposed procedure serves as illustration of how the experimental system is employed. The comparison also reveals the difference in behavior of two widely used cuffs. Results are discussed for understanding the extent to which it is possible to use standard blood pressure cuffs for theoretical treatment of oscillometry.

First, elastic and viscoelastic models for the cuff transfer function are derived (Section 7.2), followed by a description of the experimental setup and experimental procedure (Section 7.3). In Sections 7.4 and 7.5 results of the experiments are shown, and discussed and interpreted with reference to cuff elastic and viscoelastic model simulations.

7.2. **Cuff transfer function model**

The cuff transfer function C_{TF} represents the cuff pressure response to arm volume changes. It depends on cuff pressure and is defined as

$$C_{TF} = \left(\frac{|\mathrm{d}V_{arm}|}{|\mathrm{d}P_{cuffA}|}\right)_{P_{cuff},\ dV_{arm}\nu}, \tag{1}$$

where the numerator $|\mathrm{d}V_{arm}|$ is the magnitude of the arm volume pulsation, the denominator $|\mathrm{d}P_{cuffA}|$ is the magnitude of the corresponding cuff pressure signal and $dV_{arm}\nu$ is the frequency of the arm volume change.

In order to obtain $|\mathrm{d}V_{arm}|$ from a measurement of cuff pressure change, air compression within the cuff and cuff external wall displacement need to be considered. A first order model of the cuff transfer function is described below. The models are used to give the reader more insight in cuff behavior. Therefore, the models are very simple. Figure 1 illustrates a cross-sectional and longitudinal view of the cuff placed on an arm, where V_{ext} is the total volume, consisting of cuff volume V_{cuff} and arm volume V_{arm} as

$$V_{ext} = V_{arm} + V_{cuff}. \tag{2}$$

The cuff is regarded as a thin-walled cylindrical tube of radius r, length l and wall thickness d. The wall strain ε as response to a change in wall stress due to a change in transmural pressure across the cuff wall is assumed to occur in tangential direction only; the change in strain leads to an increase in external radius. The transverse strain is neglected (i.e., length *l* remains constant). The force F_p projected on the horizontal plane generated by the transmural pressure $P_{cuff} - P_{atm}$ is balanced by the two elastic forces and other force components; their sum is proportional to the circumferential wall stress σ.

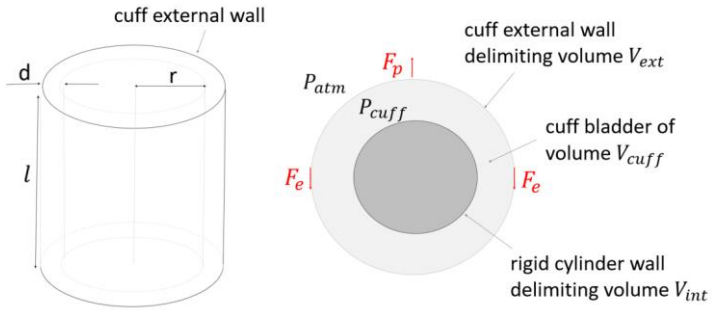

Fig. 1. Cuff illustration as a thin-walled cylindrical tube and balancing forces within the cuff.

Figure 2 shows a diagram of the changes in the cuff arm system due to a change in arm volume. An increase in arm volume causes the cuff volume to decrease. Due to air compression, the cuff pressure increases, deforming the external cuff wall due to (visco)elasticity of the cuff material. Hence, the final change in cuff volume is smaller than the change in arm volume due to the expansion of the external cuff wall. The change in cuff pressure follows from Boyle's Law.

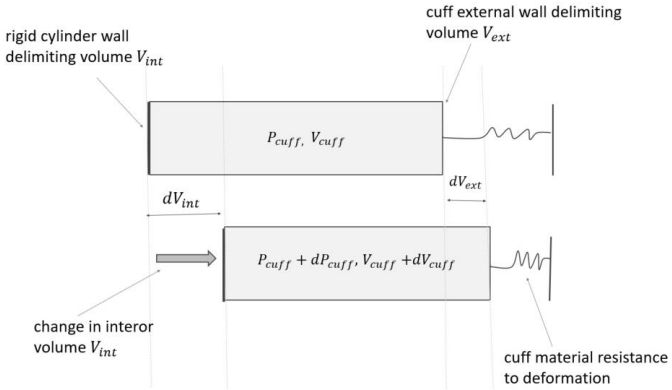

Fig. 2. Arm volume change effect on cuff pressure and volume

In the following, we first derive a model of the transfer function when the external cuff material consists of an ideal elastic material. Thereafter, we provide a model for a cuff with a visco-elastic wall material.

7.2.1. Ideal elastic model

Consider a cuff that is slowly inflated. The changes in arm volume are small and of low frequency. It is a reasonable assumption to neglect air temperature changes and effects of the mass of the cuff material (elastic force is much larger than inertial force, no pressure signal ringing observed). In the case of purely-elastic cuff material behavior, the frequency of pressure changes does not influence cuff wall response. For an elastic material, changes in wall stress and wall strain are in phase and do not depend on the frequency of the cuff pressure changes - the transfer function does not depend on frequency. Equation 2 can be differentiated with respect to the absolute cuff pressure and subsequently

be re-arranged as

$$C_{TF} = \frac{\mathrm{d}V_{arm}}{\mathrm{d}P_{cuffA}} = \frac{\mathrm{d}V_{ext}}{\mathrm{d}P_{cuffA}} - \frac{\mathrm{d}V_{cuff}}{\mathrm{d}P_{cuffA}} = C_m - C_{air} \ , \quad (3)$$

where C_{air} describes the air compliance which can be obtained from Boyle's Law and C_m is the compliance related to cuff material properties (wall thickness, radius and Young Modulus E_m). Therefore, the transfer function C_{TF} consists of two compliances, one related to the elastic deformation of the cuff wall material and the other to the compression of the air in the cuff. Note that in the case of an increase in $\mathrm{d}V_{arm}$, $\mathrm{d}V_{cuff}$ takes a negative value. For an ideal elastic material, the transfer function is a true compliance and can be calculated when the volume V_{cuff} - pressure P_{cuff} relation of the cuff is known. This relation can be obtained from Boyle's Law when the number of moles n of air in the cuff and the absolute pressure and temperature are known:

$$V_{cuff} = \frac{nkT}{P_{cuffA}} \quad (4)$$

Air compliance is described by Boyle's law and thermodynamics; therefore, given a measurement of the absolute pressure P_{cuffA}, and calculation of the cuff volume using the gas temperature and number of moles present in the cuff [23], we obtain:

$$C_{air} = -V_{cuff}/(P_{cuff}\alpha) \ , \quad (5)$$

with α being a parameter dependent on the frequency of the arm volume oscillations. For the assumed low frequency (<< 1 Hz), isothermal conditions are approached and α is equal to 1. For higher frequency oscillations (> 1 Hz), the adiabatic limit is approached and a limiting value for α is 1.4. The parameter α will be studied and discussed in later sections.

External wall compliance, $\mathrm{C_m}$, can be expressed as the change in cuff exterior volume $\mathrm{dV_{ext}}$ as a response to a change in cuff inner pressure $\mathrm{d}P_{cuff}$, in the absence of arm oscillations:

$$C_m = \mathrm{d}V_{ext}/\mathrm{d}P_{cuffA} = \frac{\mathrm{d}V_{cuff}}{\mathrm{d}P_{cuffA}} . \quad (6)$$

For a thin-walled tube, the relation between external wall stress σ, tangential wall strain ε, external wall radius r, and transmural pressure P_{cuff} can be derived using Hooke's Law and Laplace Law (Fig. 1) for a cylindrical structure:

$$\sigma = E_m(\varepsilon)\varepsilon; \ \varepsilon = \frac{P_{cuff}\, r}{d}; \ \varepsilon = \frac{(r - r_0)}{r} \ . \quad (7)$$

The wall thickness *d*, radius at zero transmural pressure r_0 and strain-dependent Young Modulus E_m are parameters that influence the external wall compliance C_m.

C_m can be derived by expressing V_{cuff} as function of P_{cuffA} via Eq. 7 . Differentiating this volume-pressure relation gives C_m. The compliance at small strain (unstressed volume $\pi r_0^2 l$) is approximately equal to:

$$C_m = \frac{2\pi r_0^3}{E_m(0)d} \tag{8}$$

The compliance increases with the third power of the radius and is inversely proportional to the Young Modulus E_m and external wall thickness d.

In the absence of arm oscillations, when pressure changes occur only due to slow changes in number of moles inside the cuff during inflation/deflation, the exterior volume change $\mathrm{d}V_{ext}$ is identical to the cuff volume change $\mathrm{d}V_{cuff}$. In this case, both C_{air} and C_m can be estimated by measuring cuff volume and absolute pressure during inflation/deflation with Eq. 5 and 6.

Alternatively, also in the absence of arm oscillations, total cuff compliance can be obtained by using the volumetric flow Q and time differential of the measured pressure:

$$Q\left(P_{cuff}\right) = C_{TF}\,\frac{\mathrm{d}P_{cuffA}}{\mathrm{d}t} \tag{9}$$

These two methods of obtaining total cuff compliance (Eq. 3 and Eq. 9) give identical results when isothermal air compression is assumed. This estimation of the transfer function in the form of a compliance obtained at very low frequency (quasi-static cuff compliance) can then be used in the presence of arm volume oscillations. Given a measured pressure change $\mathrm{d}P_{cuff}$ caused by an arm oscillation $\mathrm{d}V_{arm}$, then $\mathrm{d}V_{arm}$ is computed based on Eq. 3.

7.2.2. Viscoelastic model

Most cuffs are made from plastic materials. The mechanical behavior differs from ideal elastics; typically these materials exhibit complex and non-linear viscoelastic behavior. For a viscoelastic external cuff wall, cuff response to arm volume changes in the frequency range of arterial pulses cannot be determined from a measurement of cuff response to slow inflation. Due to material viscosity the strain rate is time dependent and a cuff material response $\frac{\mathrm{d}V_{ext}}{\mathrm{d}t}$ needs to be included. For stress rates that occur during arm volume pulsations, the viscous force increases the stiffness of the outer wall material and a reduction in cuff volume changes in comparison with the ideal elastic material is expected. The transfer function can be obtained with different methods, for instance by system characterization with small harmonic oscillatory stresses at the input side, by a step input etc. In the former case the transfer function will be equal to the inverse of the modulus of the ratio of output to input signals for a given frequency. When arterial volume or pressure waveforms are required, Fourier analysis is needed.

For a visco-elastic material, wall stress is expressed in terms of two components: elastic stress σ_e and viscous stress σ_v. A

lumped element model consisting of ideal (non-linear) springs and dashpots is used for a first-order qualitative model (see Eq. 10). The mass of the cuff material is neglected, under the assumption that the viscous force dominates the inertial forces (large damping ratio). Hence a first order model is proposed to illustrate the effect of visco-elastic material behavior. Assuming that the stress-strain relation of the visco-elastic wall material can be modeled by a Kelvin-Voigt model the total stress is given by:

$$\sigma = \sigma_e + \sigma_v = E_m \cdot \varepsilon + \eta \frac{d\varepsilon}{dt} , \quad (10)$$

where E_m is the cuff material Young modulus, η represents the cuff material viscosity coefficient, ε is the external cuff material strain in the tangential direction (Eq. 7).

Although the Kelvin-Voigt model might be too simple to describe the plastic materials used for cuff fabrication, in this study, the simple first-order model is used to show the main features of the time-dependent strain in the outer-wall material. The wall stress σ can be obtained from the transmural pressure from Eq. 7.

Tensile tests can be used to measure E_m and η of cuff materials at different strains and stress rates. When the cuff includes hook and loop fasteners, the fastener elastic properties can also be included by adding a spring in series with the described Kelvin-Voigt model. Spring properties are described by fastener-material Young-modulus E_V, which can also be obtained from tensile tests.

A non-linear differential equation links cuff pressure P_{cuff} to time dependent arm volume V_{arm} changes. The model outputs are pressure oscillations within the cuff given the measured material properties E_m, E_v, η and input volume pulsation waveform $V_{arm}(t)$ at several cuff pressure plateaus. The transfer function is then calculated using Eq. 1. Please note that in this case the transfer function is not a compliance although it has the same units. In fact, compliance is a parameter of an ideal elastic element and its value does not depend on frequency.

An implementation is based on Eq. 1, 2, 6, 7 and standard stress and strain distribution among a spring in series with a Kelvin unit. V_{ext} is expressed in terms of r. As shown later, pulsatile changes in cuff volume V_{cuff} are related to P_{cuff} through the adiabatic P-V equation by means of the constant K, which is defined as

$$K = P_{cuff} \cdot {V_{cuff}}^{1.4}. \quad (11)$$

Here, the value 1.4 corresponds to adiabatic approximation, which is shown in the paper to be appropriate for characterizing air compression in a volume shaped like a cuff for relevant frequencies

Values of K at specific cuff pressure values can be obtained from measurements of cuff pressure during inflation at known mass flow (Eq. 4). The equations can be processed via a Matlab/Python ODE solver.

7.3. **Experimental Details**

We realize three different experiments:

- Simulate arm volume changes by generating controlled volume oscillations in the cuff to infer a resulting cuff compliance for an artificial “rigid” arm,
- Quantify air compliance effects,
- Characterize cuff material properties.

7.3.1. Measurement of cuff transfer function

The experimental setup is shown in Fig. 4 - cuff inflation and cuff volume changes were applied to a cuff wrapped around a rigid cylinder of a diameter of 9 cm. A rigid cylinder was used to isolate cuff properties from those of arm tissue properties. Two cuffs typically used in clinical practice (re-usable and disposable models), with both tight and loose wrapping were studied. Loose-wrapping is defined as wrapping the cuff such that a 50% increase in cuff volume is achieved at 200 mmHg, compared to tight wrapping. Arm volume changes were generated by a proprietary device designed to simulate oscillometric volume pulsations at different cuff pressures. Electronically-controlled volume oscillations of magnitude and frequency content comparable to physiological arm volume pulsations were applied to the cuff/tube system (Fig. 4). A volume change is induced by changing the position of a small piston that is driven by a linear motor. In this study, both harmonic waves (0.5 Hz to 5 Hz) and step-function (duration 1 to 60 seconds) pulses with volume close to expected amplitudes of arm volume changes (in the range of 1 mL) were applied to the system. The cuff pressure is measured about 20 cm away from the cuff with a gauge pressure sensor (at sampling rate of 125 Hz). To avoid inertance effects we verified that the small lumen of the tubing and the length of the tubing do not play a role at frequencies below 5 Hz. The small-signal cuff compliance C_{sine} is obtained by dividing amplitudes of controlled volume changes $\mathrm{d}V_{arm}$ by corresponding measured pressure changes $\mathrm{d}P_{cuff}$:

$$C_{sine} = \frac{\mathrm{d}V_{arm}}{\mathrm{d}P_{cuff}} \tag{12}$$

C_{sine} is identical to C_{TF} shown in Eq.1, with the property that $\mathrm{dV_{arm}}$ is a pure sinusoid.

For computation of quasi-static (QS) cuff compliance, cuff inflation was done at constant 200 SCCM mass flow with a mass- flow controller (Brooks SLA5800). The advantage is that the number of moles of gas that flow into the cuff is known with high accuracy. Using Eq. 4, the cuff air volume V_{cuff} can be measured when the initial number of moles in the cuff prior to inflation is known. Before inflation, air was squeezed out of the cuff and the residual volume was assumed to be equal to that of the external tubing system.

The quasi-static (QS) cuff compliance C_{QS} (consisting of C_{air} and C_m) is obtained from Eq. 9 after conversion of the mass flow to volumetric flow [20] (via air density) and after computing the time derivative of the measured pressure curve. Alternatively, the quasi-static compliance could be obtained from the measured total system volume and pressure curves, and assuming either isothermal or adiabatic conditions (Eq. 3). To study the

QS compliance, the two cuffs were inflated at 200 SCCM for both tight wrap and loose wrap conditions.

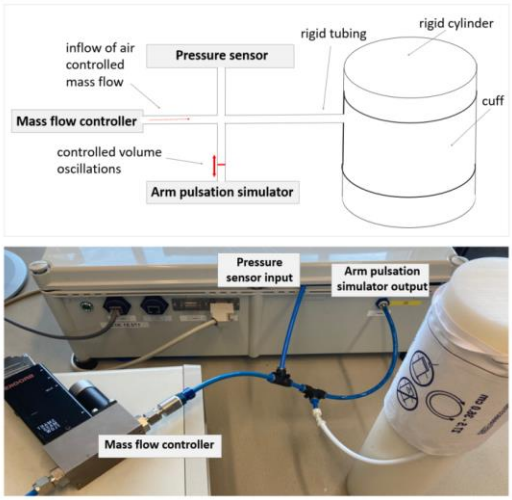

Fig. 4. Illustration and picture of the experimental setup for measurement of the cuff transfer function.

The cuff response C_{sine} to AC (harmonic) volume changes is analyzed against the quasi-static cuff response C_{QS} to slow-ramp inflation for identifying main effects occurring in the cuff during an oscillometric measurement.

7.3.2. Measurement of Air Compliance Properties

Air compression analysis is performed on two rigid wall structures: a rigid stainless steel (RVS) cube of volume 216 mL and a structure consisting of two rigid concentric PVC cylinders (0.4 cm separation between inner and outer radius). The rigid cube has a well-defined volume while the structure consisting of two concentric cylinders has a shape similar to that of a cuff.

The structure consisting of two concentric cylinders is used for studying air compression effects within a shape similar to that of a cuff, where heat transfer between the air and fixture walls might occur differently than for the cube volume. When volume compression heats the internal gas, heat will diffuse to the external walls. The thermal diffusion length from the warmer internal gas to the walls sets a time scale for the heat diffusion to the outer walls. When the wall distance is much larger than the thermal diffusion length, at a time scale of the volume pulsation, an adiabatic air compression is expected. A rigid structure consisting of two concentric PVC plastic cylinders has a shape and air volume similar to that of an inflated cuff, but with a small separation between the inner and outer walls and poor thermal conduction of the wall material. The cylindrical device is used to mimic the thermal diffusion time constants that occur in a cuff - finding the type of air compression (isothermal vs adiabatic) in a cuff.

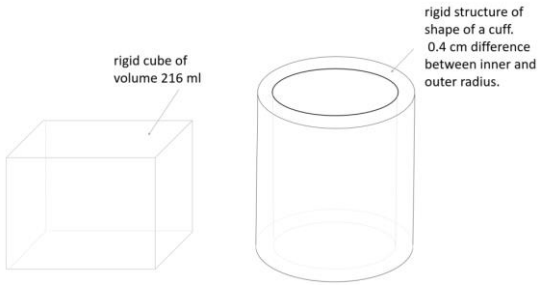

Fig. 5. Rigid structures for study of air compression and experimental setup validation.

7.3.3. Accuracy and precision of the transfer function measurement system

The accuracy and repeatability of the measurement system were verified by reference measurements on the rigid stainless steel cube (Fig. 5). The analysis was done via the following method: controlled harmonic and step volume pulses $\mathrm{d}V_{step}$ are generated and corresponding pressure changes dP_{cuff} are measured at several pressure plateaus in the rigid cube fixture of well-defined volume. For a step pulse, $\mathrm{d}P_{cuff}$ is computed as the difference between the pressure measured at 20 s after the volume pulse generation and the pressure measured before the volume pulse generation. This gives a measurement of compliance $C_{step} = \mathrm{d}V_{step}/\,\mathrm{d}P_{cuff}$. The duration of 20 s is chosen to avoid transient effects and to allow for heat transfer between the air and fixture walls to occur. This approach confirms whether C_{step} shows air compression effects of isothermal nature and quantifies sources of absolute errors in the system such as accuracy of piston displacement, pressure measurement, and air flow control. Sources of variability within the system, such as leaks, precision of pressure sensor and measured volume change, peak detection within the signal processing software are also studied by generating volume pulses for 40 s at frequencies between 0.5 Hz and 5 Hz at low, medium and high pressures within a rigid volume. This test is performed to evaluate the consistency of pressure responses.

It was found that sources of absolute errors in the system such as accuracy of piston displacement and pressure measurement cause an error of less than 0.01 mL/mmHg in computation of C_{sine}. Sources of variability within the system, such as leaks, precision of pressure sensor and measured volume change, peak detection within the signal processing software do not have a significant impact on C_{sine} estimation (less than 0.01 mL/mmHg).

7.3.4. Measurement of Cuff Material Properties

Cuff material elastic properties are characterized with a tensile test system (Zwick/Roell Z010) which applies controlled force on a 3-cm sample of cuff material (the stress direction is in tangential direction of the cuff wall) at 2 N/s (close to usual cuff inflation speeds) and 0.5 N/s. The corresponding strain is measured. The maximum applied force achieves a stress on the material sample approximately equal to the stress on the cuff walls at the end of inflation. Equations 7 and 10 are used to relate the stress

applied on cuff sample to the stress caused by transmural pressure over the cuff material:

$$\sigma_{sample} = \frac{F_{test}}{d \cdot w}; \tag{13}$$

where F_{test} is the controlled force applied on the cuff sample during the tensile test, and w represents the cuff width. The recording of stress-strain relationships is analyzed for computing material E and η as function of strain. This is done by using a system of equations based on the Kelvin-Voigt model, where values of strain, stress and strain rate are considered both in loading and unloading stages:

$$\sigma_{loading} = E \cdot \varepsilon + \eta \cdot \dot{\varepsilon}_{loading} \tag{14}$$

$$\sigma_{unloading} = E \cdot \varepsilon + \eta \cdot \dot{\varepsilon}_{unloading}$$

The material is stretched in consecutive cycles to reproduce inflation/deflation.

7.4. **Results**

7.4.1. Cuff Pressure-Volume Relations and Cuff Transfer Function

Pressure-volume relationships for the two cuffs and wrapping conditions are shown in Fig. 6. There is a large difference in the magnitude and shape of the V-P relations of the re-useable and disposable cuffs. The reusable cuff is stiffer and has smaller cuff volumes for comparable wrapping conditions. Furthermore, the shape of the V-P curve differs. At comparable cuff pressures, the volumes for the loose wrapping condition are much larger than for the tight wrapping condition. It is expected that these differences have a large influence on the cuff transfer functions for the two cuffs at different wrapping conditions.

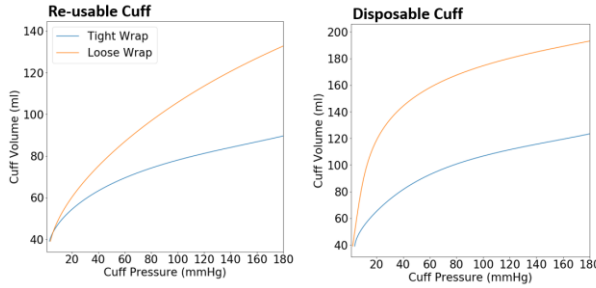

Fig. 6. Tight wrap and loose wrap cuff volume-pressure relationship

The total quasi-static compliances extracted from the volume-pressure relationships (computed via Eq. 3 and illustrated in Fig. 7) and from the volumetric flow (computed via Eq. 9 and illustrated in Fig. 7) for a reusable cuff at tight and loose wrapping are shown in Fig. 7. The isothermal air-compliances are included in the figure to illustrate the relative contribution of air compressibility to the total compliance. First, the excellent agreement of the total cuff compliance calculated from the measured volume-pressure curves via Eq. 3 (isothermal) and from the volumetric flow (Eq. 9, where no assumptions on temperature and residual volume were made) is noted. Secondly, the total compliance

depends strongly on cuff pressure and decreases with up to a factor five over the pressure range. The cuff is very compliant at low cuff pressures; the sensitivity to arm volume changes is low at these pressures. Furthermore, for loose wrapping the compliance is larger, i.e., the cuff pressure signals are reduced. Finally, at high pressures the contribution of air compliance to the total transfer function becomes more significant. The quasi-static compliance describes cuff behavior at very low frequencies because the measurements are obtained during slow inflation. The frequency content of arm volume pulsations is in the range between 1 Hz and 15 Hz, which is a factor 50 to 1000 higher than the slow ramp frequency. The effect of frequency is studied next.

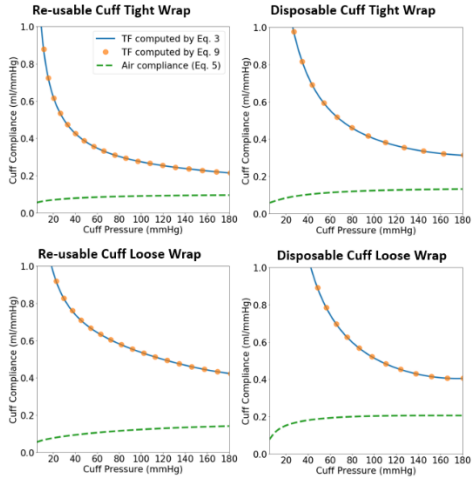

Fig. 7. The total quasi-static compliances extracted from the volume-pressure relationships (solid line, Eq. 3) and from the volumetric flow (open symbols, Eq. 9) for a reusable cuff at tight and loose wrapping. Air compliance (Eq. 5) is also plotted.

Results of the quasi-static and the small signal transfer function at different harmonic frequencies are studied next. Figure 8 shows slow-ramp compliances (C_{QS}) under isothermal and adiabatic assumptions (computed based on the data of Fig. 8) and the small signal transfer functions measured for harmonic volume pulsations (C_{sine}) with frequencies between 0.5 Hz and 5 Hz. There is a large difference in magnitude between cuff transfer function obtained from the quasi-static compliance during slow-ramp inflation (1-minute inflation corresponds with a frequency of ~0.016 Hz) and that obtained from the higher frequency volume pulses of 1mL in the frequency range (0.5 – 5 Hz). The frequency dependence of the transfer function obtained from the harmonic small volume pulses (between 0.5 Hz and 5Hz) is largest at low cuff pressures. At high frequencies, the decrease in cuff compliance with frequency is small. For loose wrapping, the frequency dependence is larger and also appreciable at higher cuff pressures. Please note that the frequency dependence is influenced by cuff type, cuff pressure and the degree of wrapping tightness.

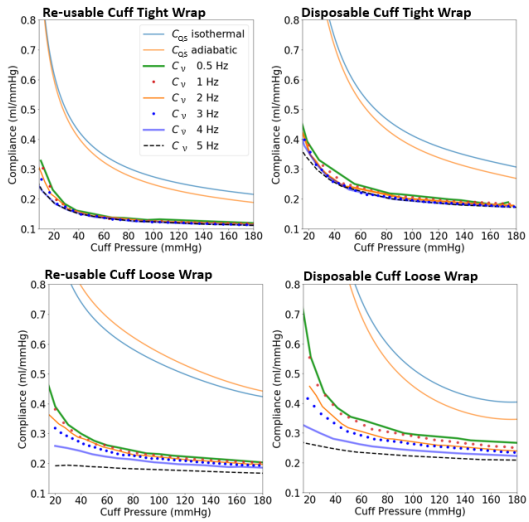

Fig. 8. QS and small signal compliance (0.5 Hz to 5Hz) plotted versus cuff pressure for two cuff types and tight and loose wrapping.

Note that both air compression and cuff material viscoelasticity can play a role in this frequency dependence. In the following section air compliance is studied using the rigid test structures where wall deformation can be neglected.

C. Rigid test structures - Air compression

Air compliance measurement results in the rigid cube are shown in Fig. 9. Isothermal and adiabatic air compliance (C_{air}) are calculated using Eq. 5 on a pressure recording realized during inflation at 200 SCCM. The solid curves represent the isothermal and adiabatic air compliances. The small signal pressure response to volume pulses in the range 1 to 5 Hz (C_{sine}) and pressure response at 20 seconds after a step volume pulse C_{step} is compared to the estimated isothermal and adiabatic air compliance. C_{step} shows expected isothermal behavior, while C_{sine} estimations show adiabatic behavior. This rigid cube is also used to tests the measurement accuracy and precision. It is estimated that absolute errors and sources of variability within the system cause an error of less than 0.01 mL/mmHg in computation of compliance.

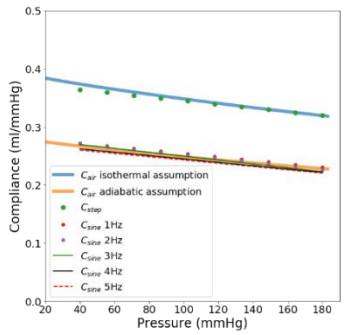

Fig. 9. Rigid cube - isothermal and adiabatic air compliance and measured air compliance for 1 - 5 Hz harmonic waves.

Air compression analysis performed on the rigid cylindrical structure in the shape of a cuff are shown in Fig. 10, where the measured response to volume pulses in the range of 1 to 5 Hz (C_{sine}) is plotted against the estimated isothermal and adiabatic air compliamce (C_{sine}). As the results suggest, the adiabatic approximation for the air compliance seem to be appropriate for frequency of 1 Hz (close to minimal heart rate frequency) and higher. This result can be linked back to previous studies where the uncertainty related to adiabatic or isothermal air compression behavior is relevant. In relation to the total cuff compliance, this result indicates that the large discrepancy between slow-ramp compliance computed under adiabatic assumption and AC compliances shown in Fig. 8 is due to frequency dependence of the exterior cuff material response.

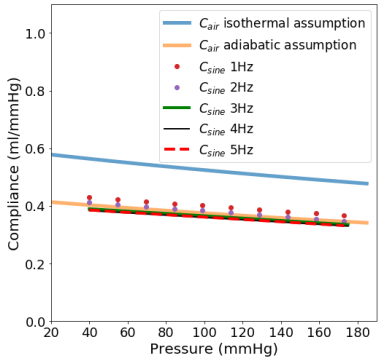

Fig. 10. Rigid structure in the shape of a cuff - Isothermal and adiabatic air compliance and measured air compliance for 1 - 5 Hz harmonic waves.

7.4.2. Measurement of cuff material properties

Stress-strain relationships of four consecutive cycles of loading/unloading of the material sample measured by tensile tests are plotted in Fig. 11. The sample material is obtained from a new unused cuff - to ensure that the cuff material properties resemble those of a typical cuff used in the clinic, which undergoes repetitive inflations. Creep, stress relaxation and hysteresis effects seems to be present, suggesting that indeed the cuff material behave in a viscoelastic fashion and that viscoelasticity needs to be considered for the estimation of the cuff transfer function.

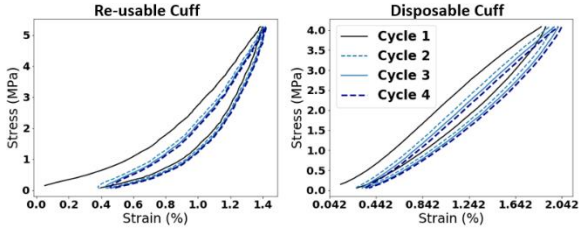

Fig. 11. Cuff sample stress-strain relationship

A large difference between the two cuff materials is observed. The stress-strain relationship recorded during 4 cycles of inflation/deflation is analyzed using the Kelvin-Voigt model (Eq. 14). The resulting material Young's Modulus E and viscosity coefficient η depend on strain (Fig. 12, Cycles 1-4). Besides this, material properties are history depend-

ent (presence of hysteresis) and values converge after consecutive inflation/deflation cycles. The time constant τ (also called retardation time) of the Kelvin-Voigt model can be extracted from the data and it varies from 0.5 seconds at low strains up to five seconds at the largest strains.

To study steady-state material behavior and history dependence of the cuff material, two additional stretches are performed after a delay of 15 minutes (Fig. 12, Cycles 5,6). The delay of 15 minutes is chosen based on typical duration between oscillometric BP measurements performed in the clinic on patients at risk of deterioration. Results show that cuff material properties depend on time elapsed since the previous inflation. However, it is again observed that successive inflations performed in rapid sequence result in similar cuff material parameters.

Figure 12. Material Young's Modulus E and viscosity coefficient as function of strain (cycle 1 to 4). Material parameters computed after a delay of 15 minutes plotted with reference to previous measurements (cycle 5, 6).

Figure 12. Material Young's Modulus E and viscosity coefficient as function of strain (cycle 1 to 4). Material parameters computed after a delay of 15 minutes plotted with reference to previous measurements (cycle 5, 6).

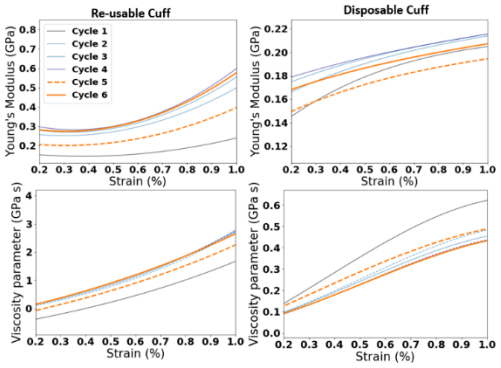

Figure 12. Material Young's Modulus E and viscosity coefficient as function of strain (cycle 1 to 4). Material parameters computed after a delay of 15 minutes plotted with reference to previous measurements (cycle 5, 6).

An additional tensile test is performed to study the cuff material elasticity parameters under a different inflation speed. The material is stretched at 0.5 N/s and 2 N/s. Young modulus and viscosity parameters derived from the two recordings are shown in Fig. 13. It is observed that speed of inflation has significant impact on extracted cuff material parameters.

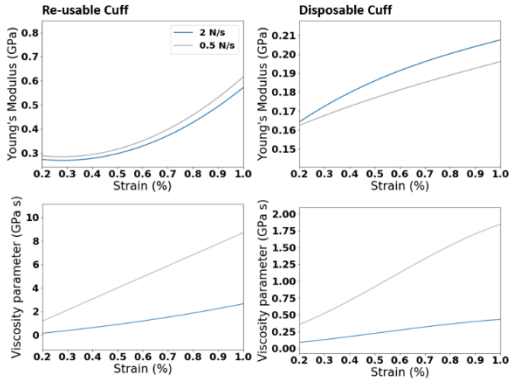

Figure 13. Elasticity and viscosity parameters under different inflation speeds of 0.5 N/s and 0.1 N/s and 2 N/s.

A tensile test at 2N/s is also performed on a portion of fastener material for measuring displacement between the hooks and loops of the material. The resulting Young's modulus varies between 0.10 GPa at 0.2% strain and 0.12 GPa at 1% strain, which is comparable to cuff material Young's modulus, so cannot be neglected.

7.4.3. Modelling results

The time constants extracted from the Kelvin-Voigt model indicate that for physiologically-relevant frequencies (1 Hz and higher) viscous effects will start to dominate the cuff material strain rates at all cuff pressures. The hypothesis that the viscous effects dominate exterior material deformation for the harmonic volume pulses in the range between 0.5 and 5 Hz is tested by model calculations using the values for E and η measured in the previous section. Figure 14 shows the modelled cuff compliance over a range of arm volume pulse frequencies – the values are computed by consideration of input arm volume pulse amplitudes and corresponding output pressure amplitudes. The model parameters were chosen to emulate conditions during real cuff inflations as closely as possible: K values relating P_{cuff} to V_{cuff} are derived from measurements of cuff pressure during inflation at known mass flow, while material properties E_m, E_v and η are derived from the tensile test measurements as function of strain and inflation speed. Input volume changes between 0.5 Hz and 3 Hz are similar to volume changes used to generate the results in Fig. 8.

Qualitatively, the modelled pressure response is in agreement with observations relative to Fig. 8 – the cuff transfer function is frequency dependent especially at low pressures and Q-S compliance differs significantly from AC compliance. However, differences in absolute values between Fig. 14 and Fig. 8 suggest that both a more complex material modelling and consideration of three-dimensional effects in cuff geometry are needed for a practical translation of pressure oscillations to volume oscillations. This would require finite element simulations and more complex material models.

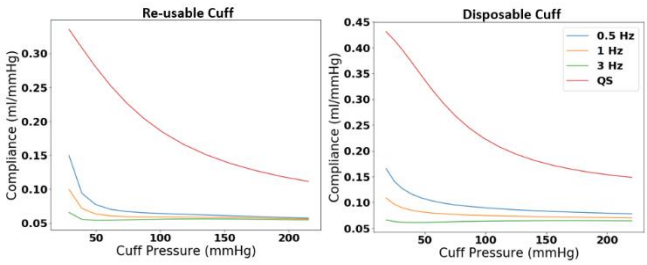

Figure 14. Modelled Q-S and small signal compliance (0.5 Hz to 3Hz) plotted versus cuff pressure for two cuff types.

7.5. **Discussion**

7.5.1. Factors that determine the cuff transfer function

Our results show that cuff response to slow inflation differs from cuff response to volume changes in the arterial pulse frequency range (Fig. 8). Therefore, a model based on quasi-static conditions cannot be used for translation of arm oscillations from cuff pressure changes. Both factors affecting cuff compliance, air compression and exterior wall material compliance, could in principle be the cause of such frequency dependence. However, our results reveal that for all frequencies of interest air compression occurs under adiabatic conditions (Figs. 9 and 10). It is therefore reasonable to assume that the adiabatic assumption also holds for the actual cuffs, hence air compression does not play a major role in the frequency dependence of the cuff transfer function.

7.5.2. Cuff Material Properties

The frequency dependence of the cuff transfer function is likely dominated by the visco-elastic mechanical properties of the external cuff material. This was further investigated by tensile tests of the cuff material on a test bench; it was observed that the stress-strain relation exhibited large hysteresis effects. This confirms that the materials are not purely elastic, are non-linear and material viscoelasticity needs to be considered for appropriate modeling of the cuff transfer function. The visco-elastic time constants for the cuff material can be estimated from the measured Young Modulus and viscosity parameters.

The material time constant for strain changes depends on cuff pressure and on wall strain. Estimated values are in the range between 0.5 seconds at small cuff pressure (10-20 mmHg) and 2 to 4 seconds at higher cuff pressures (> 40 mmHg). This result supports the observation that the cuff transfer function for the quasi-static frequency range during slow cuff inflation (frequency range of 0.1 to 0.01 Hz) is dominated by non-linear elastic material deformation. For the frequency range relevant for arterial volume pulses (1 Hz – 15 Hz) and especially during the short volume rise time (0.2 s), viscous material behavior will limit sudden wall strain changes at these short time scales and the cuff material will be much stiffer for these relatively fast changes in cuff pressure.

7.5.3. Modelling

Two-dimensional model calculations using a first-order visco-elastic model for the wall material were performed to study the frequency dependence of the cuff transfer function in more detail. Inclusion of measured Young's modulus and viscosity parameters in

the model leads to a simulation of cuff compliance that shows qualitative agreement with the measured cuff compliance (Figs. 8 and 14). The model describes main effects expected in the cuff during an oscillometric measurement, i.e., simulated Q-S compliance differs considerably from simulated AC compliance, and AC simulations are significantly dependent on at low pressures.

However, this more complex viscoelastic model still does not lead to a quantitative characterization of the cuff, leading to different absolute values for the modelled and measured compliances (Fig. 14 vs Fig. 8). Three-dimensional models and highly complex anisotropic and highly complex non-linear visco-elastic material models in combination with complex heat diffusion modelling may contribute to a more accurate simulation model of the cuff transfer functions. This is outside the scope of the present study, which was aimed at identifying the main effects that need to be included in a physical model of the cuff transfer function.

7.5.4. Development of improved cuff-based measurements and relevance of presented experimental setup

There is a wealth of physiological information present in the observed cuff pressure signal and waveform, which is currently not utilized in clinical practice. In principle, extraction of features from the measured pressure oscillations is possible; even extraction of arterial parameters has been proposed [3, 4]. Obtaining a theoretical foundation for treatment of oscillometry is important for improved BP estimation and measurement of new hemodynamic parameters. This requires in depth understanding of the cuff as a transducer. Results indicate that typical cuffs used in clinical practice require complex modelling for translation of pressure pulsations to arm volume oscillations. Discrepancy between model output (Fig. 14) and measurements (Fig. 8) indicate that aspects of the cuff inflation have been overly simplified. Such aspects could include the shape of the cuff being significantly different from a cylinder, or the shape of the cuff varying throughout the inflation (at the start of the inflation the material takes the form of a folded structure, with stress not being applied evenly, and only later the structure takes the shape of a cylinder); material deformation possibly occurring in the longitudinal direction, in addition to cross-sectional deformation; the viscoelastic model requiring a larger network of lumped elements. Moreover, tensile test results show significant variability of cuff material properties (Figs. 11 to 13). Young modulus and viscosity parameters depend on time passed since previous inflation, as well as inflation speed.

Arm tissue and arterial mechanical properties will also affect the observed pressure oscillations in the entire cuff pressure range. For example, cross-sectional visualizations of the upper arm compression during a blood pressure measurement [6] reveal that models developed by investigating cuff inflations on rigid cylinders need to be combined with models that describe arm tissue effects. Eventually, three-dimensional arm tissue and arterial compression effects will need to be included in patient-specific, mechanical models for a realistic characterization of oscillometry. Detailed knowledge of the cuff, arm and arterial material properties over the relevant frequency range at the specific moment of measurement is needed.

Nevertheless, this work presents a solution for studying the cuff by separating cuff effects from arm/artery effects. Characterization of the cuff wrapped around a rigid cyl-

inder is necessary and will be used as a reference for development of new cuff models/prototypes with alternate designs, for investigation of improved measurement techniques, or for studying of arm effects in future studies.

7.6. **Conclusion**

Development of a theoretical basis for oscillometry is essential for improving the accuracy of BP measurements and for obtaining additional hemodynamic parameters from cuff pressure signals.

An experimental setup and specific procedure were developed to improve knowledge of blood pressure cuff as a transducer for measurement of arm volume changes, this being a key step in development of a theoretical basis for oscillometry.

The transfer function of arm volume to cuff pressure pulses was studied using controlled small signal volume pulsations with frequencies up to 5 Hz. Air compression in the cuff and cuff material properties were characterized. It is found that the adiabatic assumption holds for air compression effects inside the cuff for frequencies higher than 1 Hz. Furthermore, external wall viscoelastic material properties impact cuff response to realistic arm volume pulsations.

Results also show that cuff properties depend on many factors such as inflation speed, time passed since previous inflation and tightness of wrapping, which suggests that alternative cuff designs should be considered for theoretical interpretation of the oscillometric measurement. It is unlikely that characterization of typical cuffs before being used in clinical practice, even when additional model complexity is added, would enable practical translation of arm volume oscillations. The experimental setup used in this study can be of use in the development of new techniques and alternative cuffs for the purpose of identifying designs and materials with more reproducible and predictable properties, as well as for investigation of dedicated methods to overcome arm tissue compression uncertainties. Extraction of more complex hemodynamic parameters and arterial pressure waveforms is an even greater challenge and requires detailed knowledge of cuff and tissue parameters at the actual time of measurement.

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CHAPTER 08

Air cuff transducer design for occlusion based hemodynamic measurements - An experimental and simulation study

Based on:

- Bogatu, L.I., Turco, S., Mischi, M., Schmitt, L., Woerlee, P., Bouwman, A., Korsten, H.H. and Muehlsteff, J., Air cuff transducer design for occlusion-based hemodynamic measurements - An experimental and simulation study – Submitted.

- Laura Bogatu, Jens Muehlsteff, Erik Bresch, Maarten Kuenen, Pierre Woerlee; Blood pressure measurement device and control method. 2020. Published as: EP3705033A1.

Abstract

In standard clinical practice, cuff devices are widely used for non-invasive blood pressure measurements (NIBP). However, cuff-based NIBP is prone to large errors especially in cases of hypo- and hypertension. In addition to this, the cuff measurement principle allows for estimation of a number of other hemodynamic parameters (e. g. cardiac output, arterial stiffness, augmentation index) by means of analysis of the pulse waveform and/or pulse amplitude recorded in the cuff pressure. However, in standard practice, the cuff is still only used for the measurement of BP.

A key reason for the observed measurement errors and the limited set of extracted parameters lies in our poor understanding of the cuff device as a transducer; the cuff pressure response to arm volume pulsations (the cuff transfer function TF_{cuff}) depends on a large number of factors. It is not yet clear to what extent the cuff contributes to the NIBP error, or if the cuff in its current format is reliable for measurement of arterial pulse waveform/amplitude.

In this study, we investigate the isolated cuff in order to gain a better understanding of the main sources of measurement errors. By using an experimental setup which measures the cuff response to mechanically simulated arm pulsations, we find that the cuff can explain part of the NIBP errors in cases of hypotension. Also, we find that pulse waveforms can be estimated using a standard cuff; however, measurement of the pulse amplitude is unfeasible.

We demonstrate that the observed inaccuracies can be eliminated by usage of a calibrator device which obtains real-time information on TF_{cuff}. These findings will enable further investigation of the effects related to the pulse travel along the compressed limb and the interaction between cuff, arm tissue, and arterial walls for the development of improved occlusion-based measurement strategies.

8.1. **Introduction**

The cuff-based noninvasive blood pressure measurement (NIBP) is key to hemodynamic monitoring and to assessment of cardiovascular health. The measurement principle (oscillometry) consists of inflating a cuff usually placed at brachial site in order to alter the transmural pressure (Ptm) across the arterial wall. Blood pressure (BP) oscillations inside the artery cause arterial volume pulsations of amplitudes which depend on the Ptm. The arterial volume oscillations propagate through arm tissue, generating arm volume pulsations, which in turn generate cuff pressure (P_{cuff}) pulsations in the attached cuff. The resulting cuff pressure oscillations are processed via empirical methods to derive systolic and diastolic BP values. Such empirical methods have been developed based on observations that cuff pressures at certain ratios of oscillation amplitudes represent reference clinical BP measurements (invasive, auscultatory) [1].

While empirical methods are generally accurate in normotensive patients, large errors in BP values have been reported in hypotensive and hypertensive patients [2]. There is an obvious need for more accurate noninvasive BP measurement technologies, especially in critical care, where patients are more likely to suffer from hemodynamic instability and severe variations in BP. Reliable NIBP measurement in the intensive care unit/operating room would also enable for reduced use of the intra-arterial line, which is invasive and risk-prone.

In addition to this, it is hypothesized that the cuff is underutilized in clinical practice and that other measurement strategies can be developed via occlusion-based modulation of arterial Ptm to extract additional physiological parameters. In principle, cardiac output [3], arterial stiffness [5], augmentation index [4], arterial viscosity, heart and lung function [6] might be estimated by analysis of the pulse waveform and/or pulse amplitude recorded in the cuff pressure. In standard practice, however, the cuff is still only used for measurement of blood pressure.

It is not yet clear if the standard air cuff in its current format is suited for more accurate NIBP measurement and for measurement of arterial pulse waveform/amplitude, or if hardware improvements are needed. In addition, it is not known what proportion of the measurement inaccuracies can be attributed to the cuff itself or to other factors such as effects related to the pulse travel along the compressed arm tissue [1, 7]. As stated by Drzewiecki et al:

"The occlusive arm-encircling cuff is probably one of the most widely used instruments in the measurement of blood pressure. Yet, its function as a mechanical device has not been explored. It is a device that has been developed more out of practicality than of engineering design." [8]

For these reasons, many efforts have been focused towards characterization of the cuff and, more specifically, the cuff "transfer function" which is the relationship between the input and output signals, i.e., the arm volume oscillations and the recorded cuff pressure oscillations, this being an essential step towards better interpretation of the oscillometric measurement principle. This led to development of mechanical models of different levels of complexity describing the cuff behavior [1, 10, 11, 12, 13, 14]. Despite the amount of work, cuff behavior is still not understood in sufficient detail. The existing studies are mostly qualitative, assume idealized nonrealistic, purely elastic material properties, ignore the frequency dependence of material stresses in the cuff wall. Experimental characterization is often missing or incomplete. In our previous study, we attempted to provide a more detailed mechanical

characterization of the cuff properties [15]. A dedicated experimental set-up was used to study the cuff transfer function including air compliance and viscoelastic cuff material effects. While a number of insights were acquired, physical characterization of the cuff was found to require much more complex modelling than expected. The cuff behavior was found to depend on factors such as cuff material time constants, pulse frequency content and patient-specific arm compressibility. In addition to this, our MRI results [7] show that the cuff changes in shape and folds in unpredictable ways during inflation i.e. it cannot be approximated by a cylinder most of the time, further revealing the unfeasibility of mechanical modelling without detailed knowledge of the cuff design and patient-specific tissue properties.

Therefore, from the practical perspective of improving BP estimation accuracy and introducing new parameters in clinical practice, two questions remain:

A. To what extent does the standard air cuff design and materials impact the BP measurement accuracy and the measurement of arterial pulse waveform/amplitude?

B. Can the standard air cuff be modified to solve the current inaccuracies?

In this study, we tackle the two questions as following.

A. Via an experimental setup, we measure the response of the cuff to mechanically simulated arm volume pulsations under a range of factors occurring under typical clinical circumstances i.e. varying cuff inflation speeds, different pulse frequency content and arm compressibility. In essence, we measure the dependence of the cuff transfer function TF_{cuff} on these factors. An analysis is performed to quantify the impact of the TF_{cuff} variability on the accuracy of the estimated BP, pulse waveform and pulse amplitude under different physiological conditions.

B. We overcome the current inaccuracies by means of the “cuff calibration” principle [9]. A hardware feature is added to the cuff in order to enable automatic real-time TF_{cuff} estimation. In this way, cuff response to arm volume pulsations is accurately measured regardless of the absolute cuff pressure, amount of air volume within the cuff, cuff material time dependance, arm compressibility, cuff folding during inflation. By using the experimental set-up described above, we validate the performance of this novel hardware feature.

The presented calibration approach is beneficial and practical because it solves the problem of cuff-related uncertainties by circumventing the need for complex, assumption-prone physical characterization of the cuff and patient arm characteristics. Moreover, the method enables for development of cuff features specifically aimed at overcoming the observed measurement inaccuracies. In this way, only minimal changes to standard clinical equipment are needed, favoring the clinical uptake of the method by employment of cuff devices that stay compatible with existing hospital equipment and clinical procedures [16].

8.2. **Methods**

8.2.1. Measurement accuracy of the standard cuff design

A. Cuff transfer function measurement

The realized experimental setup is shown in Fig. 1. A two-input standard air cuff is inflated via a mass-flow controller (Brooks SLA5800). During the inflations, sinusoidal arm volume variations of amplitude dV_{arm} are artificially generated via an electronically-controlled piston pump connected to the cuff input via a 25-cm length, 4 mm diameter air tube. dV_{arm} amplitudes and frequencies are chosen close to the expected values for arm volume changes: 1-mL volume at frequencies from 1 to 10 Hz. The cuff is inflated over 20 or 40 seconds. A 40 cm air tube connects the second cuff input to a gauge pressure sensor (sampling rate of 125 Hz). The cuff is wrapped around either a rigid phantom arm or around a compressible silicone phantom arm. Silicone is a material commonly used to simulate tissue behavior in phantom arms [14]. The rigid and silicone phantoms are meant to mimic two arms of different compressibility.

TF_{cuff} is defined as:

$$TF_{cuff} = \frac{dVarm}{dPcuff}, \quad (1)$$

where dP_{cuff} is the cuff oscillation as response to dV_{arm}. TF_{cuff} varies depending on dV_{arm} frequency, absolute cuff pressure, cuff inflation speed, arm compressibility.

TF_{cuff} is measured under the different conditions: volume oscillations of different frequencies, over a range of cuff pressures under the two different inflation speeds on both the rigid and the silicone phantom arms.

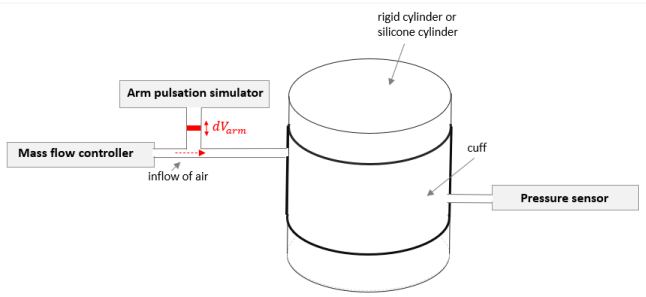

Fig. 1. Illustration of the experimental setup for measurement of the cuff transfer function.

B. Impact of cuff transfer function on BP estimation

The measured TF_{cuff} is then used as part of a proprietary simulation software which estimates the error in empirical BP estimation due to cuff behavior variability. The software framework enables analysis over a wide range of BP values, pulse pressures and control of arterial volume waveform according to non-linear arterial collapse principles.

In the simulation arterial volume V_{art} is modelled via Eq. 2:

Arterial volume V_{art} is simulated via Eq. 2:

$$V_{\mathrm{art}}(P_{\mathrm{tm}}) = L_{\mathrm{cuff}}\, \mathrm{d}\, \frac{\ln(\mathrm{a}P_{\mathrm{tm}}+3.3)}{(1+\mathrm{e}^{-\mathrm{c}\ P_{\mathrm{tm}}})}, \tag{2}$$

where a, c, d are parameters describing arterial collapse [11, 5]. P_{tm}, the transmural pressure across the arterial wall depends on the arterial pressure P_{art} and cuff pressure P_{cuff}:

$$P_{\mathrm{tm}} = P_{\mathrm{art}} - P_{\mathrm{cuff}}. \tag{3}$$

P_{art} is simulated to follow a typical arterial waveform, oscillating between systolic value, P_{sys}, and diastolic value, P_{dia}, at either 60 beats per minute (BPM) or 200 BPM. As the cuff pressure increases, the V_{art} oscillations adjust in amplitude according to the resulting P_{tm}.

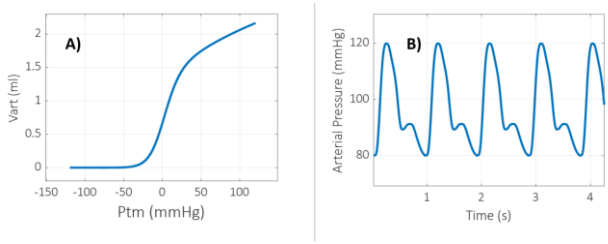

Fig. 2. A) Illustration of arterial volume with respect to transmural pressure across the arterial wall. B) Example of simulated arterial pressure.

It is assumed that dV_{art} equals dV_{arm}; transmission of volume pulse through arm tissue is outside the scope of this paper (although preliminary evidence is showing this could be of importance at lower cuff pressures).

The amplitude of the V_{arm} oscillations with respect to the absolute cuff pressure is defined as the volume envelope $Venv(P_{cuff})$; an example illustration of $Venv(P_{cuff})$ can be seen in Fig. 3.A.

The cuff pressure envelope is then simulated. Each V_{arm} frequency component corresponds to a TF_{cuff} value; the V_{arm} waveforms are processed in the frequency domain to obtain the resulting P_{cuff} waveforms (example in Fig. 3.B). Cuff pressure envelopes are simulated under hypotension, normotension, and hypertension conditions, different inflation speeds, and different heart rates.

For each simulated P_{cuff} envelope, $P_{sysPenv}$ and $P_{diaPenv}$ are computed and compared to reference P_{sys} and P_{dia} respectively. To achieve this, the P_{cuff} envelope is normalized. According to the common empirical method [1], the cuff pressure on the falling phase of the envelope at which the pulsation amplitude is about 50% of the maximum amplitude is the systolic BP $P_{sysPenv}$. Cuff pressure on the rising phase of the oscillation signal at which the pulsation amplitude is about 70% of the maximum amplitude is the diastolic BP $P_{diaPenv}$ [1]. However, the ratios are empirical, and their exact values depend on the specific implementation of algorithms in commercially available devices. It is important to understand whether the TF_{cuff} is relevant in selection of such ratio values. To achieve this, for each simulated Pcuff envelope, the ideal ratios that would lead to correct BP inference are computed.

In addition, we also give an illustration of the potential error that could result from empirical estimation of BP by fixed ratios which do not account for TF_{cuff} variability. For this, $P_{sysPenv}$ and $P_{diaPenv}$ are computed for each Pcuff envelope based on two often mentioned

sets of fixed ratios, which are likely to be encountered in practical algorithm implementations:

- 50% and respectively 70% respectively for P_{sys} and P_{dia} estimation,
- 55% and respectively 75% respectively for P_{sys} and P_{dia} estimation.

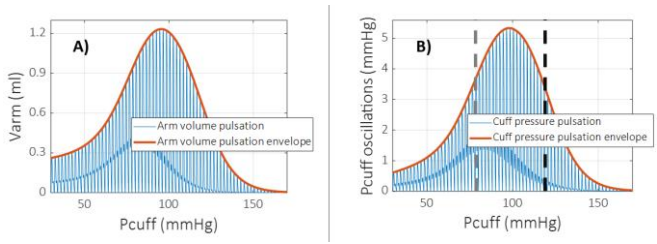

Fig. 3. A) Example of simulated arm volume pulsations with respect to absolute cuff pressure $Venv(P_{cuff})$. B) Example of corresponding simulated cuff pressure pulsations with respect to absolute cuff pressure $Penv(P_{cuff})$ under slow cuff inflation and rigid arm conditions. Dashed lines represent diastolic and respectively systolic values inferred via empirical processing of the signal envelopes. This example simulates normotension with P_{dia} = 80 mmHg, P_{sys} = 120 mmHg. Empirical ratios are typically optimized such that BP is estimated correctly under normotension conditions. In this example, $P_{diaPenv}$ = 80 mmHg and $P_{sysPenv}$ = 121 mmHg.

C. Impact of cuff transfer function on quantified volume pulse amplitude measurement

The variability of TF_{cuff} across different conditions (cuff inflation speeds, heart rate values, absolute cuff pressure, arm compressibility) is assessed. The degree of variability can reveal if translation of dV_{arm} absolute value by means of analysis of the corresponding dP_{cuff} oscillation is feasible.

D. Impact of cuff transfer function on pulse waveform measurement

The measured TF_{cuff} is used as part of a software framework to estimate the error in pulse waveform estimation due to variability in the cuff behavior. By the same method described in II.B), V_{arm} and the corresponding P_{cuff} oscillations occurring during a cuff inflation are simulated under different conditions. Each pulse in the V_{arm} signal is normalized and is compared to the corresponding normalized P_{cuff} pulse. The difference in waveform between the two pulses is quantified via the root mean square error metric.

8.2.2. Cuff calibrator device

A second piston pump generating controlled sinusoidal volume oscillations $dV_{calibration}$ is designed for real-time measurement of TF_{cuff} (Fig. 4). dV_{arm} is programmed to generate a waveform similar to the pulsations recorded in typical NIBP measurements performed on real arms. dV_{arm} can be set to 60 beats per minute (BPM) or 200 BPM.

The controlled volume oscillations $dV_{calibration}$ and dV_{arm} both generate cuff pressure

oscillations $dP_{calibration}$ and dP_{arm}. The frequency of $dV_{calibration}$ is designed such that it differs from the frequency components of dV_{arm}. Therefore, simple filtering can be applied to the P_{cuff} signal to measure the amplitude of $dP_{calibration}$. The amplitude of $dV_{calibration}$ is also well-defined; therefore, information on TF_{cuff} can be obtained in real time.

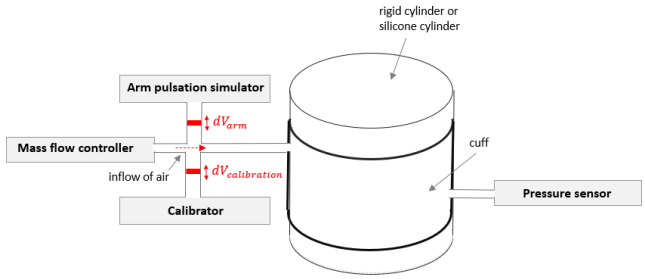

Fig. 4. Illustration of the experimental setup for validation of calibrator device.

For validation of the measurement strategy, dV_{arm} and $dV_{calibration}$ oscillations are generated. The resulting P_{cuff} signal is filtered to obtain the $dP_{calibration}$ amplitude, which is divided by the $dV_{calibration}$ amplitude to obtain TF_{cuff}. The amplitude of dV_{arm} is then computed based on dP_{arm} and TF_{cuff} information. Since the exact amplitude of dV_{arm} is known, the percentage error in the dV_{arm} amplitude estimation can be computed.

The validation of the measurement is conducted at 40-mmHg and 90-mmHg absolute cuff pressures, for 60 BPM and 200 BPM dV_{arm} heart-rate values, and for rigid and compressible phantom arms. For each of the absolute cuff pressure value, heart rate and arm compressibility conditions, the dV_{arm} estimation process is repeated 20 times. For each repetition, the percentage error between the estimated amplitude of dV_{arm} and the true value of dV_{arm} is calculated. The results are summarized by computing the percentage error mean and standard deviation.

Across all measurement conditions, the $dV_{calibration}$ is set to a predefined frequency of 8 Hz, which differs sufficiently from the frequency components of the dV_{arm} signal. Note that future developments will enable real-time adjustment of $dV_{calibration}$ frequency depending e. g. on the recorded patient-specific dP_{cuff} waveform frequency components, or changes in heart rate. Also, $dV_{calibration}$ composed of multiple frequency components is ideal for a more complete sampling and subsequent identification of the cuff response. However, this is outside the scope of this paper, which aims at conducting a first investigation of the TF_{cuff} measurement principle, along with the applicability and use of a calibrator device.

8.3. **Results**

8.3.1. Measurement accuracy of the standard cuff design

A. Cuff transfer function measurement

Figure 5 reveals that the cuff response varies significantly depending on arm compressibility, inflation speed, absolute cuff pressure. This finding suggests the need to quantify and possibly to correct the impact of TF_{cuff} on the accuracy of cuff-based hemodynamic measurements. TF_{cuff} cannot be predicted; in standard clinical practice, the TF_{cuff} is expected to change with every wrapping, depending on exact location on the upper arm where cuff is positioned, subsequent compression of the tisuse, wrapping tightness leading to unpredictable cuff folding, inflation procedure etc.

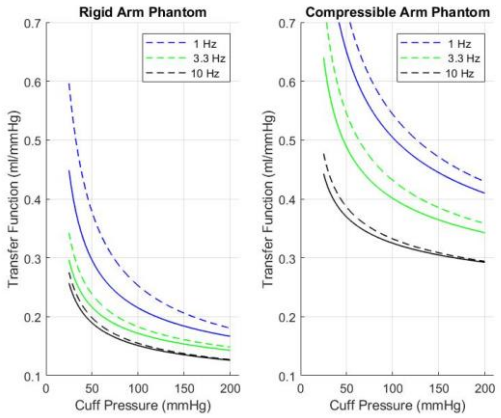

Fig 5. TF_{cuff} measured via the experimental setup (illustrated in Fig. 1). The cuff pressure response to mechanically generated arm volume pulsaitons of 1Hz, 3.3Hz and 10 Hz is plotted. TF_{cuff} is measured on rigid (left) and compressible (right) arm phantom respectivelly. The dashed lines represent TF_{cuff} measured under fast inflation, the solid lines represent TF_{cuff} measured under slow inflation (the cuff is inflated over 20 or 40 seconds).

B. Impact of cuff transfer function on BP estimation

P_{cuff} envelopes are simulated under different conditions: blood pressure values ranging across hypotension, normotension, and hypertension, different pulse pressures, for normal and high HR, for fast and slow inflation, and for compressible and rigid arms. For each of the conditions, V_{arm} oscillations are generated via the simulation framework and $Venv(P_{cuff})$ is computed. The V_{arm} oscillations are processed together with the corresponding TF_{cuff} (measured via the experimental setup) to generate $Penv(P_{cuff})$.

For each simulated Pcuff envelope, the ideal ratio values that would lead to correct systolic and diastolic values is computed. Fig. 6 shows that the ideal ratio for systolic value inference varies from 48% to 68% and the ideal ratio for diastolic value inference varies from 50% to 78%. This result reveals that fixed ratios might not be optimal, and that knowledge of TFcuff can contribute to improved selection of such ratio values.

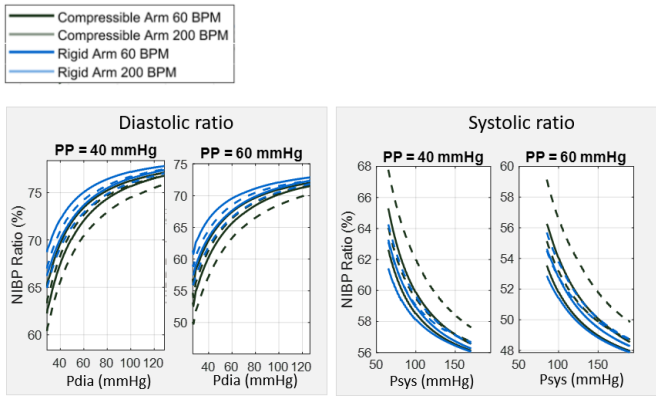

Figure 6. Ideal ratios for deriving correct BP values based on the pressure envelope for rigid and compressible arms, 60 BPM and 200 BPM, 40 and 60 mmHg pulse pressure values. The dashed lines represent BP ratios corresponding to fast inflation. The solid lines represent BP ratios corresponding to slow inflation.

In [2, Fig. 1] large errors in NIBP are reported in hypotensive and hypertensive patients. We quantify the error that could result from empirical estimation of BP by fixed ratios which do not account for TF_{cuff} variability.

Figures 7 and 8 show the NIBP errors defined as $P_{sysPenv}$ - P_{sys} and respectively $P_{diaPenv}$ - P_{dia} for blood pressure values ranging across hypotension, normotension, and hypertension, for different pulse pressures, for normal and high HR, for fast and slow inflation, and for compressible and rigid arms. $P_{sysPenv}$ and $P_{diaPenv}$ are computed based on:

- the 50% and respectively 70% ratios (Fig. 7).
- the 55% and respectively 75% ratios (Fig. 8).

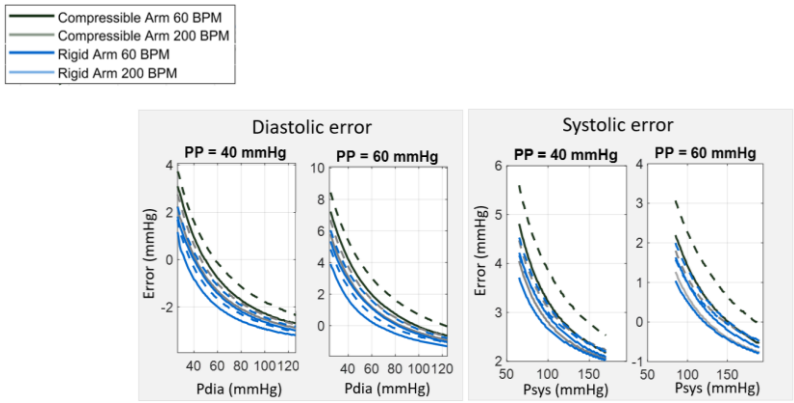

Figure 7. $P_{sysPenv}$ - P_{sys} and respectively $P_{diaPenv}$ - P_{dia} are plotted for rigid and compressible arms, 60 BPM and 200BPM, 40 and 60 mmHg pulse pressure values. The dashed lines represent BP erro r corresponding to fast inflation. The solid lines represent BP error corresponding to slow inflation. The $Penv(P_{cuff})$ envelopes are generated based on the simulated V_{arm} oscillations and the measured TFcuff (Fig. 5). $P_{sysPenv}$ and $P_{diaPenv}$ are obtained based on the 50% and respectively 70% empirical ratios.

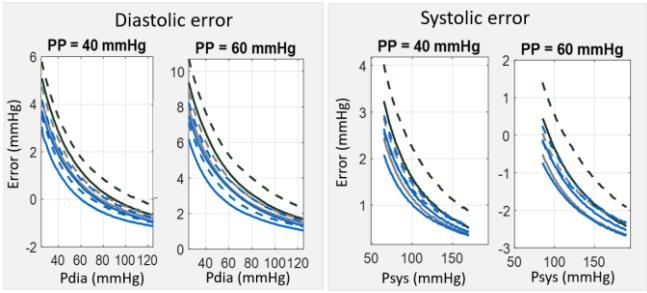

Figure 8. $P_{sysPenv}$ - P_{sys} and respectively $P_{diaPenv}$ - P_{dia} are plotted similarly to Fig. 6. $P_{sysPenv}$ and $P_{diaPenv}$ are obtained based on the 55% and respectively 75% empirical ratios.

Trends similar to the errors reported in [2, Fig. 1] are observed: the systolic and diastolic errors under hypotension are positive; as normotension is reached, the errors decrease. In [2, Fig. 1] BP inference in cases of hypotension is overestimated; BP inference in cases of hypertension is underestimated. Our results show that the cuff can contribute to BP overestimation during hypotension. In this simulation the cuff transfer function contributes by a negligible amount to BP underestimation during hypertension.

In terms of error absolute values, the results show that the cuff mainly impacts the inference of diastolic values in cases of hypotension, where a maximum in the order of 10 mmHg error is found. Note, these absolute error values depend not only on the cuff behavior, but also on the BP inference algorithm and chosen ratio (Fig. 6, 7).

In [2, Fig. 1], errors in the range of 25 mmHg are reported. This suggests that the TF_{cuff} variability and empirical processing of the P_{cuff} envelope can explain part of the reported errors in NIBP, while the rest of the error likely stems from arm tissue effects, pulse travel along the compressed arm, arm-cuff interaction or issues of the accuracy of the invasively

measured BP.

C. Impact of cuff transfer function on quantified volume pulse amplitude measurement

The TF_{cuff} variation (illustrated in Fig. 5) can lead to errors up to a factor ~4 in the estimation of the arm volume pulsation amplitude based on a measured cuff pressure oscillation. Therefore, this is a clear indication that the amplitude of the volume pulse cannot be measured via the standard cuff dependent on the situation- specific measurement conditions (cuff / arm tissue compression).

D. Impact of cuff transfer function on pulse waveform measurement

According to our simulation results, the cuff impact on the pulse waveform measurement is minimal. To give a visual impression, Fig. 9 shows examples of different simulated V_{arm} waveforms and corresponding *Pcuff* oscillations (computed based on Fig. 5 measurements). In Fig. 10, the difference between the two waveforms via the root-mean-square error (RMSE) metric for each of the simulated conditions is quantified (different pulse pressures, normal and high HR, fast and slow inflation, inflation on compressible and rigid arms). For each of the conditions, V_{arm} oscillation is generated via the simulation framework. The V_{arm} oscillation is processed together with the corresponding TF_{cuff} (measured via the experimental setup) to generate P_{cuff}.

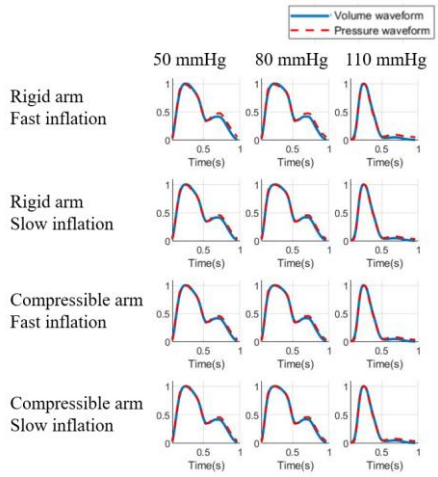

Figure 9. Simulated and normalized arm volume waveforms and corresponding cuff pressure waveforms. The cuff pressure waveforms are generated based on the simulated arm volume waveforms and the measured TFcuff (Fig. 5). Example waveforms at 50, 80 and 110 mmHg absolute cuff pressures are shown.

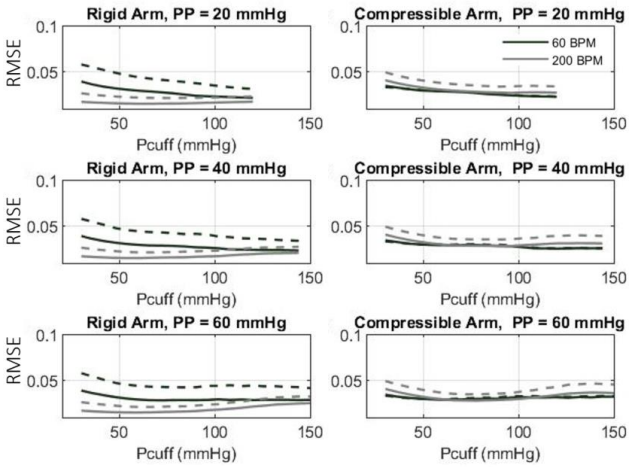

Figure 10. RMSE representing the difference between normalized arm volume waveform and corresponding cuff pressure waveform is plotted for rigid and compressible arms, 60 BPM and 200 BPM, various pulse pressure values. The dashed lines represent RMSE corresponding to fast inflation. The solid lines represent RMSE corresponding to slow inflation.

8.3.2. Cuff calibrator device

As shown in Fig. 5, large errors in estimation of arm volume pulsation amplitude can occur if TF_{cuff} is not known. We demonstrate the feasibility of the real-time TF_{cuff} measurement method via the experimental setup illustrated in Fig. 4.

Table 1 shows the mean and standard deviation of the dV_{arm} amplitude estimation percentage error for each of the measurement conditions.

	HR **Cuff Pressure**	**60 BPM, 40 mmHg**	**200 BPM, 40 mmHg**	**60 BPM, 90 mmHg**	**200 BPM, 90 mmHg**
Rigid arm	Mean	0.2%	0.3%	3.9%	1.6%
	Standard deviation	0.7%	0.2%	0.8%	0.6%
Silicone arm	Mean	4.2%	1.5%	2%	1.3%
	Standard deviation	1.8%	1.6%	1.5%	0.7%

Table 1. dV_{arm} amplitude estimation accuracy based on measured dP_{cuff} and calibrator data. Results acquired via the experimental setup illustrated in Fig. 4.

The dV_{arm} estimation percentage error is minimal and ranges from 0.2% to 4.2%. This demonstrates that the calibrator enables for accurate measurement of dV_{arm} amplitude and that measurement inaccuracies stemming from the cuff can be tackled via real-time measurement of TF_{cuff}.

8.4. Discussion

8.4.1. To what extent does the standard air cuff design impact BP measurement accuracy and measurement of arterial pulse waveform/amplitude?

Firstly, we find that the cuff contributes partially to the NIBP measurement error. TF_{cuff} needs to be taken into account for optimized selection of BP inference ratios dependent on (Fig. 6). Not accounting for TF_{cuff} variability can lead to error contribution up to 10 mmHg in the estimation of BP values in some cases of **hypotension**. However, the cuff contribution to NIBP errors occurring in **hypertension** is negligible based on our framework. TF_{cuff}, even though very variable in absolute terms (Fig. 5), does not cause significant distortion of the normalized $Venv(P_{cuff})$ signal, especially at high cuff pressures reaching systolic values. It is likely that other factors (arm tissue/pulse travel along the compressed arm, increase blood volume in distal arm during inflation, resistive drop over brachial artery) can explain the rest of the NIBP errors (as it was reported to be in the order of 25 mmHg in both hypo and hypertension [2]). Also it is relevant to note that the invasive BP measurement itself can sometimes be inaccurate. This could be another potential reason for the reported discrepancy between invasive and non-invasive measurements.

Secondly, we find that the standard cuff does not allow for a quantified estimation of the dV_{arm} absolute value.

Thirdly, our results indicate that the cuff behavior variability does not lead to significant errors in the measurement of the arm pulse waveform. Note that our results only reveal the impact of the cuff component on the arm volume waveform measurement. The arterial pulse waveform, however, might be distorted by the cuff – arm tissue – arterial wall interaction along the length of the cuff (arm tissue fat/muscle consistency, strain dependent young modulus of tissue, viscous properties). To illustrate this, Fig. 11 shows cuff pressure signals measured on a patient; this represents a typical example of cuff pressure waveforms acquired on humans. The waveforms appear damped when compared to typical arterial waveforms. This study focused on measuring the **arm volume** pulsation. Next studies will focus on accessing **arterial volume** information [17].

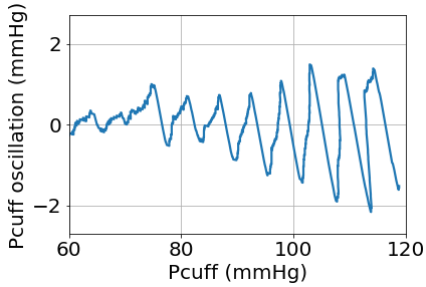

Fig. 11. Example of typical waveforms acquired via high-pass of the cuff signal obtained during cuff inflation performed on patient arm.

8.4.2. Can the standard air cuff be modified to overcome the observed inaccuracies?

measurement of dV_{arm} absolute value was found to be unfeasible due to variations in TF_{cuff}; this being the main limitation when investigating the cuff device, without taking into account cuff-tissue-artery interaction. In addition, a cuff-induced 10 mmHg error in the BP

estimation can occur in some cases of hypotension, this is dependent in the particular algorithms for oscillometry-based BP inference. Two potential solutions to these limitations exist:

a) Physics-based characterization of cuff behavior such that cuff pressure change with response to arm volume change is known.

b) Embedding of a hardware feature within the standard cuff as a method to obtain information on TF_{cuff} in real-time.

In this study we explored the latter solution and we made use of a piston-pump calibrator device to demonstrate the measurement principle for acquiring information on *TFcuff* in real time. We found that this solution can lead to accurate measurement of the arm pulsation amplitude. Therefore, it is suggested that cuff-induced NIBP error can also be improved by the same approach.

The presented solution is favorable from a clinical perspective. Embedding of a calibrator device within existing cuffs is feasible and it ensures that minimal changes to standard clinical equipment are made. Therefore, cuff devices stay compatible with existing hospital equipment and clinical procedures, while enabling for absolute dV_{arm} measurement. Another benefit is in that the real-time measurement of TF_{cuff} is not prone to effects related to unpredictable cuff folding occurring during inflation, or to unpredictable changes in cuff volume during inflation (caused by patient-specific arm tissue compression).

This study provides an understanding of the isolated cuff. The obtained findings will aid further studies to investigate the effects related to pressure/volume pulse travel along the compressed limb and the interaction between cuff, arm tissue, and artery. Our study suggests that integration of a calibrator in the cuff is a valid and adequate solution for conducting occlusion-based measurements; implementation adjustments and additional cuff features might be needed by new insights of the interaction between cuff, arm tissue, and vasculature are acquired.

8.5. **Conclusion**

The oscillometric measurement principle is very complex; the P_{cuff} signal is the result of interference between multiple effects related to cuff properties, arm tissue, and arterial walls. Analysis of the isolated cuff is an essential step towards NIBP improvement and towards estimation of additional hemodynamic parameters from cuff pressure signals.

Our results show that the typically unknown cuff transfer function can explain part of the NIBP error in certain cases of hypotension and that absolute volume pulse amplitude cannot be measured via the standard air cuff. We find that a practical solution to overcome these limitations consists of introducing a calibrator device. Given the presented framework, we also find that the cuff transfer function itself does not lead to substantial waveform distortion of the localized mechanically simulated arm volume pulse. Further studies are required to investigate the cuff – arm tissue – arterial wall interaction along the length of the cuff and its potential impact on the accuracy of occlusion-based hemodynamic measurements. The presented research approach, experimental setup, and validation method can serve as basis for such further studies.

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CHAPTER 09

On the value of MRI for improved understanding of cuff-based oscillometric measurements

Based on:

- Laura I. Bogatu, Jan Hoppenbrouwers, Harrie van den Bosch, Simona Turco, Massimo Mischi, Lars Schmitt, Pierre Woerlee, R. Arthur Bouwman, Hendrikus H.M. Korsten and Jens Muehlsteff, 2022. On the value of MRI for improved understanding of cuff-based oscillometric measurements - Submitted.

Abstract

Blood pressure (BP) is a key parameter in critical care and in cardiovascular disease management. BP is typically measured via cuff-based oscillometry. This method is highly inaccurate in hypo-and hypertensive patients. Improvements are difficult to achieve because oscillometry is not yet fully understood; many assumptions and uncertainties exist in models describing the process by which arterial pulsations become expressed within the cuff signal. As a result, it is also difficult to estimate other parameters via the cuff such as arterial stiffness, cardiac output and pulse wave velocity (PWV)-BP calibration. Many research modalities have been employed to study oscillometry (ultrasound, computer simulations, ex-vivo studies, measurement of PWV, mechanical analysis). However, uncertainties remain; additional investigation modalities are needed. In this study, we explore the extent to which MRI can help investigate oscillometric assumptions.

Four healthy volunteers underwent a number of MRI scans of the upper arm during cuff inflation. It is found that MRI provides a novel perspective over oscillometry; the artery, surrounding tissue, veins and the cuff can be simultaneously observed along the entire length of the upper arm. Several existing assumptions are challenged: tissue compression is not isotropic, arterial transmural pressure is not uniform along the length of the cuff and propagation of arterial pulsations through tissue is likely impacted by patient-specific characteristics (vasculature position and tissue composition). *Clinical Relevance*— The cuff interaction with the vasculature is extremely complex; existing models are oversimplified. MRI is a valuable tool for further development of cuff-based physiological measurements.

9.1. **Introduction**

Blood pressure (BP) is measured in various care settings involving patient monitoring and cardiovascular disease management. This key parameter is commonly acquired non-invasively via oscillometry, which consists of evaluating arterial volume (V_{art}) changes as the arterial transmural pressure (P_{tm}) is modulated. In practice, this is achieved by inflating a pneumatic cuff around the upper arm. As the cuff inflates, pressure is exerted on the arterial wall. The resulting V_{art} pulsations propagate through arm tissue and become expressed within the cuff pressure (P_{cuff}) signal. The recorded P_{cuff} oscillations are processed via algorithms to infer systolic, diastolic, and mean arterial pressure (MAP) values. Such BP inference algorithms are largely empirical; they are based on observations that cuff pressures at certain ratios of oscillation amplitudes are the same as invasive BP measurements [1]. This empirical approach is generally accurate in normotensive patients, however, large errors in BP values have been reported in hypotensive and hypertensive patients [2]. There is an urgent need for more accurate noninvasive BP estimation, especially in critical care, where patients are more likely to suffer from severe BP variations.

The issue is that oscillometry is not yet fully understood. Many assumptions are still needed to model the process by which arterial volume pulsations generate oscillometric signals. This also limits the usage of the cuff for more complete assessment of the hemodynamic status. In principle, cardiac output [3], arterial stiffness [5], and heart and lung function [6] can be estimated by analysis of the pulse waveform and pulse amplitude recorded via the cuff. Various other hemodynamic parameters can be extracted from the response of the vasculature to occlusion perturbations [7]. However, more advanced understanding of the artery and tissue interaction with the cuff are required to achieve practical implementation of such measurements.

For these reasons, significant research has been conducted for the purpose of interpreting oscillometry by means of physics and physiology mechanisms, beyond empirical evidence [1, 8, 9]. The aim is to characterize the process by which BP pulsations distend the arterial wall, propagate through arm tissue, and ultimately are measured as the P_{cuff} signal. This process has been studied up until now by means of computer simulations [1], ex-vivo studies of arterial collapse [8], ultrasound measurements of artery size [10], studies of pulse wave velocity over segments of the limb arterial tree [5, 7], mechanical analysis of cuff devices [11]. Despite the vast amount of research, several questions remain. For example, existing characterizations of the oscillometric process typically overlook arm compression effects, assuming the arm tissue to be incompressible [1, 12]. However, it is not known if the arm volume pulsations are equivalent to the arterial volume pulsations. Another assumption concerns the arterial P_{tm} modulation via cuff inflation. P_{tm} is typically defined as the difference between the blood pressure and the pressure inside the cuff. However, it is unclear if the pressure at the exterior of the artery equals the pressure at the exterior of the arm along the length of the cuff. Also, the arterial volume change under the cuff is defined as the arterial cross-sectional area at the mid-length of the cuff multiplied by the length of the cuff. This likely oversimplifies arterial collapse effects along the entire length of the cuff. Existing studies tackling these questions are lacking in-vivo observations of cuff pressure effects on tissue compression and on arterial collapse along the cuff length [13].

Additional research modalities are needed. In this study we explore the option of using MRI

to research the mechanisms by which oscillometric data is produced. MRI offers the possibility to simultaneously image the artery, surrounding tissue, veins, and cuff along the entire length of the upper arm, thus giving a novel perspective over oscillometry and providing additional insights, complementing existing research modalities.

9.2. Methods

9.2.1. MRI imaging of arm tissue

We performed 3D T1 weighted FFE sequence scans on 4 participants belonging to different demographics (F 20 years, M 45 years, M 60 years, F 40 years). This scan type allows for simultaneous acquisition of arm cross-sectional slices along the entire length of the upper arm. For each participant, the scans were acquired at 7 cuff pressure plateaus: 150, 125, 100, 75, 50, 25, 0 mmHg. The employed cuff was a standard two-tube Invivo single-patient model of 14 cm length. The in-plane resolution of the acquired images was 1x1 mm, with slice thickness of 5 mm. Due to overcontiguous slice setting, a 5-mm thick slice was reconstructed every 2.5 mm.

The images were processed via basic watershed segmentation algorithm to quantify arm cross-sectional area with respect to cuff pressure along the length of the upper arm (shoulder to elbow). The images were also processed to obtain skin reconstruction to visualize limb morphology alterations due to cuff inflation.

All experiments were performed on a 1.5T Ingenia, Philips with a dStream 8ch small extremity coil. Participant written informed consent was obtained. The data collection was registered with the Medical research Ethics Committees United (St. Antonius Ziekenhuis, Koekoekslaan 1, 3430EM Nieuwegein, Netherlands) and assessed as non-WMO (registration number W20.090). The study was approved by the Catharina Ziekenhuis (Michelangelolaan 2, 5623EJ Eindhoven, Netherlands) committee.

9.2.2. MRI imaging of the vasculature

Additionally, retrospective gated balanced-TFE CINE images of individual cross-sectional slices were acquired to study the vasculature (0.4x0.4mm in-plane resolution, slice thickness of 8.0 mm, 10 cardiac cycle phases). The scans were acquired according to the following protocol. Basic watershed segmentation algorithm was used to extract the artery area from all acquired images.

- A deflation consisting of 7 P_{cuff} plateaus **(150, 125, 100, 75, 50, 25, 0 mmHg)** was performed. Artery areas over 10 cardiac cycle phases were acquired at each cuff pressure plateau at the $\boldsymbol{S_c}$ cross-sectional slice (Fig. 1).

- A second deflation consisting of 7 P_{cuff} plateaus **(90, 80, 70, 60, 50, 40, 30 mmHg)** was performed. Similarly, artery areas over 10 cardiac cycle phases were acquired at each cuff pressure plateau at the $\boldsymbol{S_c}$ cross-sectional slice.

- A third deflation consisting of 7 P_{cuff} plateaus (**150, 125, 100, 75, 50, 25, 0 mmHg**) was performed. Artery areas over 10 cardiac cycle phases were acquired at each cuff pressure plateau at the $\boldsymbol{S_P}$ slice (Fig. 1).

- A fourth deflation consisting of 7 P_{cuff} plateaus (**150, 125, 100, 75, 50, 25, 0 mmHg**) was performed. Artery areas over 10 cardiac cycle phases were acquired at each cuff pressure plateau at the $\boldsymbol{S_D}$ slice (Fig. 1).

This protocol enables for in depth quantification of artery area at the center of the cuff and for identification of arterial collapse behavior close to the edges of the cuff.

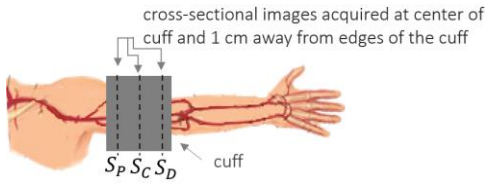

Fig 1. Cross-sectional slices (marked as $\boldsymbol{S_P}, \boldsymbol{S_C}, \boldsymbol{S_D}$) are acquired for high-resolution assessment of vasculature.

9.3. **Results**

9.3.1. Effects of cuff inflation on arm morphology

Figure 4 (left) illustrates skin reconstruction at 0 and 150 mmHg P_{cuff} and cross-sectional view of the arm (right) at the center of the cuff at 0 and 75 mmHg P_{cuff}. The figure facilitates visualization of the patient-specific characteristics and assessment of the cuff inflation impact on tissue morphology. Figure 2 shows the quantification of arm cross-sectional area with respect to P_{cuff} along the length of the upper arm. In Fig. 3, the entire volume of the arm tissue situated under the cuff with respect to P_{cuff} is quantified.

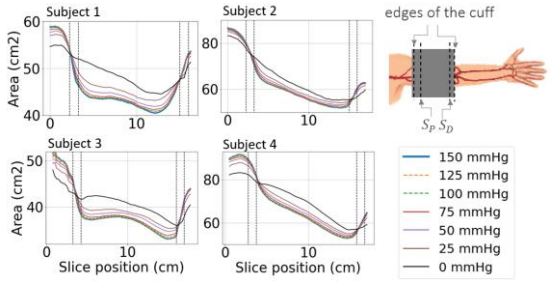

Fig. 2. Arm cross-sectional area vs. slice position at different P_{cuff} values. Dotted-line markers indicated (right).

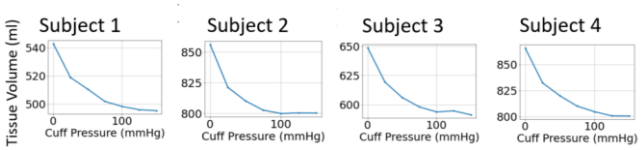

Fig. 3. Arm tissue volume situated under the cuff vs. P_{cuff}.

9.3.2. Effects of cuff inflation on the vasculature

Figure 4 (right) shows the cross-sectional slice corresponding to the center of the cuff; the arteries (in systolic phase) and veins are visible. Figure 5 shows the mean artery area computed across the 10 heart phases plotted with respect to transmural pressure for all 4 participants. The transmural pressure is defined as the difference between the MAP value and the

P_{cuff} value. MAP is found by identifying the cuff pressure at which the artery pulsation amplitude is maximum.

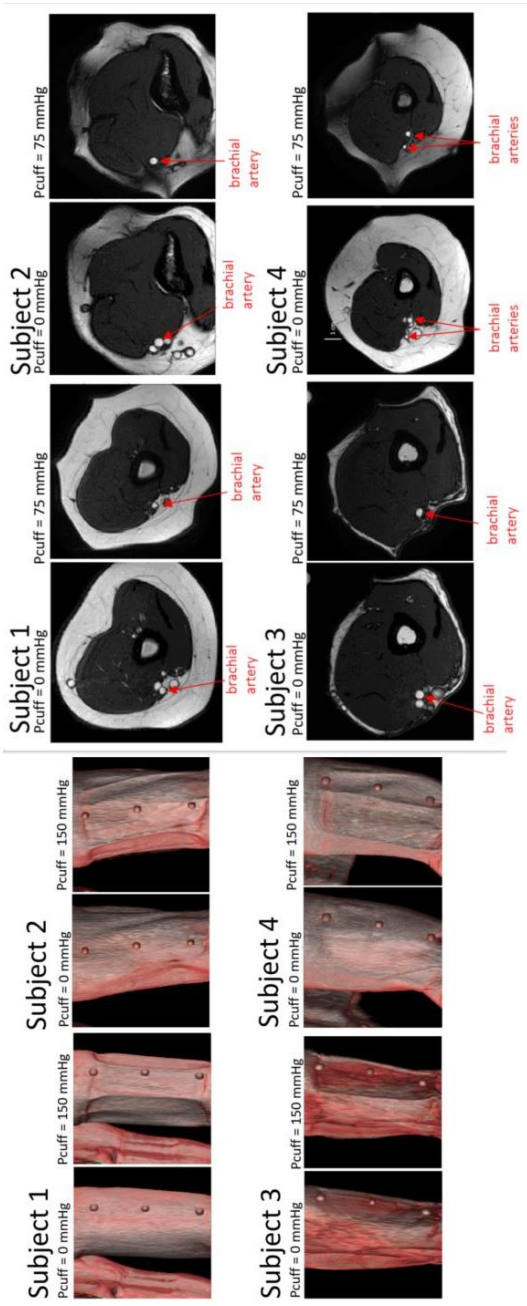

Fig. 4. Skin reconstruction for 0 and 150 mmHg P_{cuff} (left); central cross-sectional slice at 0 and 75mmHg P_{cuff} (right).

The artery is also imaged at distal and respectively proximal markers. Image quality de-

creases when imaging close to the edges of the body coil; for this reason, the artery size cannot be quantified at the distal and proximal markers. Nevertheless, open arteries can be differentiated from collapsed arteries for a qualitative assessment. Figure 6 shows the arterial collapse analysis performed on Subject 3.

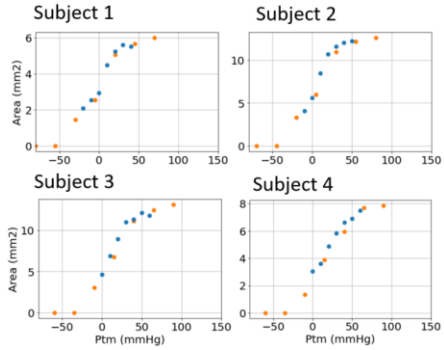

Fig 5. Mean artery area vs. P_{tm}. Orange: acquired during first deflation; Blue: acquired during second deflation.

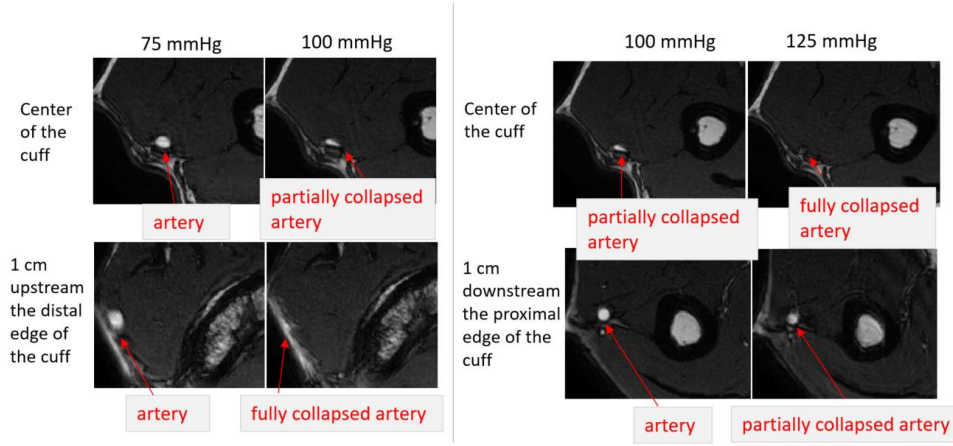

Fig 6. Analysis of arterial collapse at the cross-sectional slices illustrated in Fig. 1 (central, proximal, and distal).

9.4. **Discussion**

9.4.1. Effects of cuff inflation on arm morphology

It can be observed in Fig. 4 that the arm tissue is not homogeneous (as previously modelled in [13]) and that complex, subject-dependent muscle/fat distribution is present.

Also, the cuff folds in unpredictable ways during inflation. The arm is not compressed isotropically, and "pinching" of the tissue is observed. It is possible that this effect hinders accurate modulation of arterial transmural pressure, since the pressure applied outside the artery might depend on such cuff folding mechanisms. Also, from the perspective of the patient, the air cuff "pinching" effect might contribute to discomfort. Figure 2 shows the arm tissue being both compressed and displaced along the length of the cuff. The displacement effect becomes particularly noticeable at the 1 cm markers with respect to the edges of the cuff where the

cross-sectional area is increasing as the cuff is inflated. In Fig. 3 it is revealed that the tissue volume is altered even as the P_{cuff} reaches typical MAP values. The tissue is compressible between 0 and 100 mmHg P_{cuff}. It is likely that oscillometry performed during hypotensive states (MAP < 65 mmHg) is more prone to errors stemming from such arm tissue effects.

9.4.2. Effects of cuff inflation on the vasculature

It can be noticed (Fig. 4) that the artery location is subject dependent. In Subject 3, the artery is close to the exterior of the arm at 75-mmHg P_{cuff}. In Subject 1, significant tissue thickness is present between the artery and the exterior of the arm at 75-mmHg P_{cuff}. Some subjects can have more complex vasculature than others. Subject 4 even presents two arteries. In [14] it is reported that this can occur in 20% of the population. It is unclear to what extent such anatomical variations impact the expression of artery volume pulsation within cuff signal.

Figure 5 shows the artery area measured at the center of the cuff with respect to the transmural pressure. The absolute values are similar to previously reported values of brachial artery size [10], with the exception of Subject 1, which presents smaller than previously reported arterial size. The arterial collapse characteristics are also similar to previously reported observations: the approximately linear behavior of the artery at small cuff pressures (≤ 50 mmHg) followed by the non-linear arterial collapse as P_{cuff} reaches MAP values.

The second deflation consisted of different cuff pressure plateaus, such that additional points along the arterial volume-pressure curve were collected (Fig. 5). The results show that artery area sizes measured during the second deflation do not differ from the ones measured during the first deflation. This indicates that no significant changes in arterial properties occurred following the initial arterial collapse. It is therefore possible that in healthy subjects compensatory mechanisms are not activated due to cuff-based transmural pressure modulation.

The artery is also imaged at the 1-cm markers with respect to the two edges of the cuff. Figure 6 challenges the assumption that the arterial volume under the cuff equals artery area at the middle of the cuff multiplied by the length of the cuff. The artery at 1 cm downstream the proximal edge of the cuff is open at cuff pressures which lead to complete arterial collapse at the middle of the cuff. The opposite effect takes place distally: the artery at 1 cm upstream the distal edge of the cuff is fully collapsed at cuff pressures which do not cause the artery to fully collapse at the middle of the cuff. Such non-uniform collapse is observed in all participants. The effects are likely caused by a combination of non-uniform pressure distribution along the artery, complex tissue compression/displacement/folding and difference in internal blood pressure proximally vs. distally with respect to the cuff. The latter effect takes place due to the compressed artery and vein cutting circulation in/out of the limb. During the occlusion time, distal venous and arterial pressures equalize. As the cuff deflation starts, complex mechanisms occur [7]; blood flow in/out of the arm resume, however, with a distal arterial pressure that is lower than usual and a venous pressure that is higher than usual. The pressure drop over the cuff length is also altered due to blood flow effects in presence of strongly increased resistance during arterial collapse (resistance scales with 4th power

of artery radius).

In addition, Fig. 6 illustrates a further demonstration of the “knocking effect”, or cuff edge effect – as the artery under the cuff collapses, volume changes are still detected within the cuff signal. This effect appears as blood ejected from the heart flows against the closed portion of the artery. It is therefore difficult to detect at which cuff pressure the artery under the cuff has collapsed by just analyzing the cuff signal. Figure 6 shows that this effect is not only limited to the very edge of the cuff, but extends 1 cm along the proximal part of the cuff.

The compressed tissue exerts sufficient pressure at the center of the cuff to occlude the artery, however compression/ displacement effects lead to significantly lower pressure being exerted towards the edge of the cuff. The partially occluded artery in unloaded state along this proximal region of the cuff will also lead to particularly large local volume oscillation amplitudes.

The MR imaging protocol will be optimized in future studies such that vascular alterations close to the edges of the cuff can be quantified, rather than observed qualitatively. MRI will also be used to analyze flow and pulse wave characteristics during cuff inflation. Acquisition of data across additional demographic groups is also planned.

9.5. **Conclusion**

We find that MRI is a useful research tool for understanding tissue and vasculature response to occlusion-based perturbations. A number of insights were acquired on patient-specific vascular and tissue characteristics. In addition, the images enabled improved understanding of effects concerning arterial transmural pressure modulation and arterial collapse behavior along the length of the cuff. It becomes evident that existing oscillometric models are oversimplified. This study highlighted which mechanisms require more in-depth characterizations via further modelling and experimental studies. Since existing in-vivo data on cuff interaction with tissue and vasculature is scarce, the data acquired in this study will serve as an essential database for such future developments.

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CHAPTER 10

Discussion and outlook

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In this chapter the results of this PhD work are discussed in relation to the three research questions posed in the introduction of this thesis. In particular, the main achievement, along with their limitations and the future perspective are critically discussed.

10.1. Research question 1: Which are the key aspects, challenges, and the clinical value of measuring new hemodynamic parameters in critical care? (Chapter 2)

Hemodynamic monitoring is extremely complex; a great deal of risk and uncertainty is involved in treatment of patients at risk of hemodynamic instability. To mitigate this, significant improvement in the accuracy and safety of standard parameter measurements (e. g. BP, CO) has been realized [1, 2]. However, limitations remain because the standard parameters, even if measured accurately and continuously, are only few and do not convey sufficient information about the hemodynamic status of a patient. The main issue resides in that integration of new hemodynamic parameters at the bedside presents unique and complex challenges. The technological difficulties related to sensor development, modelling and signal analysis/interpretation represent only part of the challenge; clinical practice, integration of new measurements within clinical workflow also pose complex questions. Extensive clinical trials are required for the uptake of new hemodynamic parameters in routine clinical decision-making guidelines [3, 4].

The main outcome of our analysis (Chapter 2) is that near-future impact on patient monitoring is likely to be facilitated by advanced interpretation of physiological signals acquired via standard hospital equipment. A measurement strategy which relies on the standard technology and does not differ to a large extent from clinical practice is arguably easier to include in large scale clinical studies designed to assess impact of a monitoring protocol.

We find that opportunities for this do exist; the standard technology might currently not be used up to its full potential and that several additional hemodynamic parameters can in principle be accessed via existing hospital equipment.

- First of all, extensive studies on arterial compliance have been conducted up until now in the context of cardiovascular disease management [5, 6]. This led to many insights being acquired on vascular regulation mechanisms, as well as on technological aspects of arterial compliance measurement principles. Such findings have not yet been translated to critical care.

- Secondly, advances in other medical applications, such as detection of venous thrombosis, have led to development of circulatory models supported by patient data, which involve parameters related to peripheral resistance, arterial/venous compliance, mean systemic filling pressure, artery-vein interaction [7]. Such parameters are also relevant to hemodynamic monitoring, this fact being stated by the authors (Seagar et al.): *"… a particularly appropriate application for the model is to use changes in the model parameters to monitor circulatory changes of the limb, such as those, for instance, that may occur during clinical anaesthesia "* [7]. It is worth exploring how to advance such studies.

- Thirdly, the concept of functional hemodynamic monitoring has been gaining increasing interest among critical care clinicians due to it enabling better measurement of dynamic interactions between hemodynamic variables. It consists of analyzing the circulatory system's response to a well-defined stimulus or perturbation [8]. Several variations of this measurement principle have been investigated up until now. However, the response of the vasculature to occlusion-based perturbations has been largely underutilized in critical care. At the same time, the cuff is a key component of all patient monitoring set-ups, therefore potential measurement strategies should be investigated.

10.2. Research question 2: To what extent can standard sensors be used for more complete assessment of the hemodynamic status? In other words, can new measurement strategies be developed to achieve improved assessment of the hemodynamic status of a patient using the available standard sensors? (Part I)

From a physiological perspective, parameters such as arterial and venous compliances, peripheral resistance, mean systemic filling pressure, artery-vein interaction, response of the vasculature to a well-defined perturbation should reveal compensatory mechanism activation and enable better assessment of the hemodynamic status. Part I of this thesis explores the feasibility of the required developments identified in Chapter 2, with special attention on their applicability to critical care to make such hemodynamic information accessible via standard patient monitoring technology.

10.2.1. Brachial artery parameters (Chapters 3 and 4)

Information on arterial properties is particularly relevant for measurements requiring calibration; devices which interpret pulse wave velocity as surrogate for blood pressure changes [15, 16], or devices which use pulse waveform as surrogate of cardiac output [17] require re-calibration whenever changes in arterial compliance occur due to hemodynamic regulation mechanisms or vasoactive drug administration. In addition, determining the level of arterial distension can lead to improved interpretation of standard parameters (e. g. identify the cause of a BP drop – differentiate between heart related factors or vasodilation). Moreover, changes in arterial properties hold potential for early warning of hemodynamic instability as they might precede changes in standard pressure and flow parameters.

Therefore, in Chapter 3, a method for estimation of brachial artery volume – transmural pressure relationship, arterial compliance, arterial collapse parameters is developed based on ECG, PPG and cuff-based oscillometry. This is achieved by studying the localized change in transmural pressure (controlled via cuff) and modelling its impact on brachial artery collapse and on pressure pulse propagation (PAT, measured via ECG/PPG). As the cuff inflates, the arterial transmural pressure over the length of the cuff is decreased, thus altering the brachial arterial volume oscillation amplitudes and increasing the time it takes for the pulse to propagate down the brachial artery. Information obtained from PAT and from cuff signals can be jointly processed by modelling how arterial collapse mechanics are simultaneously expressed within the two signals. This is enabled by inference of the arterial collapse model parameters from the two information sources.

In Chapter 3, a non-parametric approach for arterial compliance estimation is explored. The non-parametric method does not allow for fusion of multiple information sources; it is solely based on processing the arterial volume oscillations measured via the cuff. However, the method directly computes arterial volume with respect to transmural pressure and is not constrained to a pre-defined mathematical model. In this sense, it can be argued that the non-parametric method is more suited to special cases of hemodynamic instability, where unique behavior of the vasculature might not be well represented by the model. In addition, the non-parametric method enables the analysis of effects which cannot be observed via parametric inference. For example, as the cuff pressure reaches supra-systolic values, the artery under the cuff collapses. In practice, after the moment of arterial collapse, volume changes are still detected within the cuff – this effect may be explained by blood ejected from the heart flowing against the closed portion of the artery. The impact of such effects on the measured signal can be quantified via the non-parametric approach, possibly leading to a more correct interpretation of the cuff signal. Nevertheless, implementation of the non-parametric method requires in-depth understanding of cuff transducer and tissue characteristics. These aspects might be less challenging when employing the parametric fusion modality, which is designed to identify the common information within multiple signals affected by different sources of noise. In short, the parametric and non-parametric approaches have inherent benefits and drawbacks. Further clinical studies, high-resolution imaging, FEM, or phantom-based investigations are needed to investigate the extent to which changes in arterial compliance are detected via the two modalities. The simulation framework will aid in identifying the causes of potential discrepancies in the inference results.

Main outcomes

- Improved understanding of brachial arterial volume – transmural pressure relationship and arterial collapse properties and how such properties become expressed within physiological signals acquired via standard hemodynamic monitoring sensors. Knowledge of arterial volume – transmural pressure relationship is essential to applications requiring re-calibration (PAT-based BP estimation, PiCCO).

- Brachial artery properties can be estimated by integration of two measurement principles: analysis of arterial volume vs. pressure changes and inference from the pulse wave velocity. This novel parametric approach appears more robust than state-of-the-art solutions as the two information sources are affected by different sources of noise; the developed algorithm identifies the common information within the data acquired via the two measurement principles.

- Non-parametric processing of the cuff signal is usually limited to assessing the response of the artery to internal pressure pulsations in the order of 40 to 60 mmHg, thus limiting the ability to observe non-linear effects. In Chapter 4, however, a new method is proposed for non-parametric processing, able to obtain the arterial response to small pressure pulsations (in the order of 1 -5 mmHg).

- The proposed parametric and non-parametric approaches can be used to provide insights into different occlusion effects. The methods can also be used together for a thorough assessment of brachial arterial properties.

10.2.2. Distal arterial and venous compliances, mean systemic filling pressure, peripheral resistance, artery-vein interaction (Chapter 6)

In Chapters 3 and 4, the impact of the cuff inflation on arterial volume oscillations and on pressure pulse propagation is investigated based on physiological insights obtained from data measured non-invasively on healthy participants. To advance our understanding of the vasculature response to cuff inflation, in Chapter 6, BP data is acquired invasively in hemodynamically monitored patients. It is found that interesting effects occur in the distal arm as response to the cuff inflation. Such effects cannot be observed via non-invasive measurement setups. Models developed for applications in venous thrombosis are adapted in order to understand the mechanisms observed in the invasively-acquired patient data.

Main outcomes

- Improved understanding of vasculature response to occlusion-based perturbation.

- The brachial artery volume-transmural pressure relationship inference method first presented in Chapter 3 is improved by more advanced characterization of cuff-induced changes in flow and pressure pulse propagation.

- We find that the inferred arterial transmural pressure-volume relationship can be used towards accurate beat-to-beat PAT-based BP estimation.

- The measurement of cuff-induced changes on the vasculature also reveals potentially valuable information on artery-vein interaction, distal arterial and venous compliances, mean systemic filling pressure, and peripheral resistance. Such parameters hold potential to enable more complete assessment of the hemodynamic status (e. g. fluid responsiveness, capillary activity, compensatory mechanism activation).

- A key component in the development of the measurement strategies presented in Part I is the design of a dedicated simulation framework, which can possibly be used to:
    - Provide possible explanations of the factors that influence the mechanisms observed in patient data. Physiological effects measured on participants/patients via non-invasive and invasive measurement setups are complemented by computer simulations to identify which hemodynamic parameters are expressed in the cuff/invasive BP/ ECG-PPG signals.

- Enable generation of synthetic data. This facilitates algorithm development due to control over the parameter space and ground truth. This framework therefore also enables first basic feasibility check of the measurement concepts.
- Illustrate different clinical scenarios and transparent interpretation on how multiple measurements contribute to parameter inference in the presence of noise or available prior knowledge.
- Facilitate iterative development of measurement strategies; enable analysis of vasculature property expression within physiological signals in absence of sensor-related inaccuracies. Once measurement principles have been developed, then focus can be aimed at in depth characterization of individual sources of potential error, such as cuff transducer non-ideal behavior, or patient-specific arm compression.

- In Chapter 6, in-vivo validation of the measurement approach and of the model is made possible beyond the simulation framework. It is shown how information on brachial arterial compliance led to accurate PAT-based beat-to-beat BP estimation in two hemodynamically monitored patients.

- In addition, interesting correlations were found among inferred parameters when processing the patient data. Vascular time constant, mean systemic filling pressure, heart rate, distal diastolic value response to cuff inflation and maximum drop in distal pulse transit time appear to follow similar trends.

10.2.3. Limitations and potential future developments

The findings of Part 1 were enabled mainly by study of the vascular response to relatively fast cuff inflations. Further access to hemodynamic information will likely be achieved via future studies of vascular response to other types of occlusion-based modulation . For example, more robust parameter inference might be achieved via processing the vascular response to both inflation and deflation. It is also important to understand if any of the vascular properties change depending on inflation/deflation speeds. It is expected that limb equilibrium pressure increases as cuff inflation speed decreases, however it is not certain if other parameters, such as compliance, resistance, artery-vein interaction adjust as response to increased amount of fluid in the limb. Also, study of the distal BP alterations due to cuff pressure plateaus might offer interesting insights; for example, during a cuff plateau of 50 mmHg the brachial vein is collapsed and the brachial artery size is minimally affected, enabling non-turbulent inflow of blood in the distal arm. Studies are required to observe the effects that occur as response to such modulation strategies. Other factors also enable interesting exploration e. g. length of the cuff, location on the limb where cuff is placed etc.

Dedicated clinical studies are also required to assess which of the measured parameters are the most informative depending on clinical context; e.g. how deterioration, hypotension, sepsis, fluid responsiveness become expressed within the vasculature response to occlusion perturbation at brachial/distal sites. It is also important to analyze how conditions such as

peripheral edema impact the measurement accuracy. Peripheral edema would increase interstitial fluid pressure, therefore compressing peripheral veins and elevating Pmsf [21]. This increase would in principle be possible to detect via the arm-Pmsf value. However, the increased transmural pressure across the vessel walls could also alter vasculature compliance, resistance unpredictably and non-homogeneously in which case the limb vasculature might not be a representative sample of the total circulation and arm-Pmsf might not be indicative of total Pmsf.

In addition, in Chapter 6, generally accurate BP estimation over a majority of time segments throughout the procedure gives indication that the inferred arterial compliance parameter values are in the correct range. However, in 7 out of 72 time segments, the estimation is inaccurate. It is not yet clear which effects cause this temporary drop in performance. The inference modality involved a large number of assumptions regarding cuff and its effects on arm tissue and vasculature; because of this, it is difficult to identify the main sources of the error. For this reason, Part II is dedicated to achieving more in-depth understanding of potential sources of noise stemming from cuff transducer device, patient specific aspects (e. g. arm characteristics), and cuff interaction with the limb. Many assumptions related to these factors exist in models describing oscillometry and the potential sources of error are not fully understood. Such uncertainties hinder further usage of cuff devices beyond empirical BP estimation.

10.3. Research question 3: Which are the requirements and main challenges for a robust implementation of the proposed measurements in clinical practice? In particular, which are the main sources of noise and uncertainty (also accounting for sensor/transducer device characteristics and patient-specific aspects) that affect the measurement accuracy, and which are the best implementation strategies to achieve robust and accurate estimation of the key hemodynamic parameters? (Part II)

10.3.1. The cuff as a transducer (Chapters 7 and 8)

The isolated cuff is investigated first with the goal of determining the impact of the cuff behavior on the expression of arm volume oscillations in the cuff pressure signals. On a practical level, it is important to identify what accuracy can be reached in the translation of arm volume pulsations from cuff pressure signals and if any changes to the standard air cuff are needed. Chapter 7 aims to investigate this via in-depth mechanical modelling of the cuff device. Existing cuff models lack experimental validation and might oversimplify aspects related to air compression and to frequency-dependent behavior of cuff material. The hypothesis is that a cuff mechanical model of a higher level of complexity, complemented by experimental validation, will enable improved investigation of cuff-related uncertainties.

Our results suggest that the cuff behavior, expressed via the cuff transfer function (TFcuff) depends on a large number of factors. Tensile tests reveal a complex viscous response of the cuff outer material as well as of the fastening hook-and-loop (Velcro) material. Also, absolute cuff pressure change as response to arm volume change is highly dependent on the amount of air present in the cuff, which can vary considerably based on tightness of wrapping, absolute cuff pressure, patient-specific arm tissue radius, tissue compressibility etc. In addition, the cuff folds in unpredictable ways during cuff inflation; thus it should not be modeled as a

cylinder. All this evidence indicates that parametric mechanical modelling, even at a higher level of complexity, does not have practical applicability; it is unlikely to enable practical translation of arm volume oscillations from cuff pressure data. The study ultimately reveals that an approach alternative to mechanical modelling is required to overcome cuff-related uncertainties.

In Chapter 8 it is found that a cuff calibrator approach (a method for measuring TFcuff in real-time) is more suitable for overcoming cuff-related uncertainties; in this way, the cuff response to arm volume pulsations can be accurately measured regardless of the absolute cuff pressure, cuff material time dependance, arm compressibility, and cuff folding during inflation. This is achieved by by-passing the complex physical characterization of the cuff, which unavoidably relies on strong assumptions. Our results suggests that integration of a calibrator within the cuff is a valid and adequate solution for conducting occlusion-based measurements. Note that the presented solution overcomes limitations stemming from the isolated cuff only. Additional cuff features might be found necessary as more advanced physiological understanding of the cuff interaction with the vasculature system is acquired.

Main outcomes

- Mechanical modelling, even at a higher level of complexity, does not have practical applicability; it is unlikely to enable practical translation of arm volume oscillations from cuff pressure data.

- An approach alternative to mechanical modelling of the standard cuff is required to overcome cuff-related uncertainties.

- It is found that measurement inaccuracies stemming from the isolated cuff can be tackled via dedicated calibration.

- It is shown, however, that the waveform acquired via combination of the cuff and the calibrator do not resemble typical arterial waveforms. This suggests that additional cuff features might be required to solve for uncertainties stemming not only from the isolated cuff, but also from the cuff – arm tissue – artery interaction.

10.3.2. The arm and artery interaction with the cuff (Chapter 9)

In Chapter 9, we therefore investigate the arm-artery interaction with the cuff. Oscillometry has up until now been researched via a large variety of modalities: computer simulations, ex-vivo studies of arterial collapse, in-vivo assessment of artery size performed by ultrasound, measurement of pulse wave velocity over segments of the limb arterial tree, and mechanical analysis of cuff characteristics. Nevertheless, additional observations and research modalities are needed to tackle remaining uncertainties. MR imaging provides a new perspective over the process by which arterial pulsations are expressed in cuff data. The images of Chapter 9 provide insights into several of the assumptions of existing oscillometric models:

- Arm consistency is not homogeneous; complex, subject-dependent muscle/fat distribution is present.

- Unpredictable cuff folding occurs during cuff inflation; therefore, the compression of the arm is not isotropic. It is possible that this effect hinders accurate modulation of arterial transmural pressure; the pressure applied at the exterior of the artery might depend on such cuff folding mechanisms.

- Some subjects can present much more complex vasculature than others; it is unclear how to model pulse propagation through tissue when for example two similarly sized brachial arteries are present, or when the venous component is pulsatile.

- The artery location is also subject dependent. It is likely that oscillations of superficial arteries are expressed differently within cuff pressure than oscillations of deeper arteries surrounded by subcutaneous fat.

- Complex, patient-dependent mechanisms involving tissue compression and displacement occur under the cuff. It is unlikely that arterial volume pulsation is equivalent to arm volume pulsation, especially at cuff pressures lower than typical MAP values.

- The arterial collapse characteristics described in [18] and later observed by [19] are accurate. The MRI measurements confirm the relatively linear behavior of the artery at small cuff pressures (<= 50 mmHg) followed by the non-linear arterial collapse as the cuff pressure approaches MAP values. The MRI scanner allows for observations of particularly small arteries, as well as of unusual vasculature consisting of more than one brachial artery.

- The images also confirm that no significant changes in arterial properties occur following the cuff-induced arterial collapse. It is therefore possible that in healthy subjects compensatory mechanisms are not activated due to transmural pressure modulation via the cuff at the brachial site.

- Arterial collapse is not uniform across the length of the cuff. Images acquired along the length of the cuff show how the artery collapses differently at proximal vs. middle vs. distal regions of the cuff. This disproves the assumption that the arterial volume change under the cuff is equal to the artery cross sectional area at the middle of the cuff multiplied by the length of the cuff.

- The images further demonstrate the extent of the “knocking effect”, or cuff edge effect, which occurs as far as 1 cm within the proximal side of the cuff. Awareness of this effect plays a significant role in correct interpretation of the cuff signal.

Main outcome

The cuff interaction with the arm and the vasculature is extremely complex and the majority of assumptions in existing oscillometric models are oversimplified and can be challenged via high resolution imaging.

10.3.3. Limitations and potential future developments

Further studies are needed, possibly by design of realistic FEM models and arm phantoms based on the obtained high-resolution MRI observations. Various distributions of muscle/fat, arm circumference, vasculature characteristics should be studied with respect to the principles behind cuff-based measurements.

It is important to note, however, that limitations exist in the extent to which detailed modelling of the oscillometric process has practical applicability. Evidently, the more findings acquired via MR imaging, modelling, mechanical cuff characterization, the more awareness of potential sources of noise and errors, and the more correct interpretation of the signals will be achieved. However, validation of complex models would require in-vivo measurements which are unfeasible (e. g. detailed flow, pressure data along the length of the upper arm, pressure levels inside the arm tissue etc.). In addition, patient-specific properties (muscle/fat distribution, artery, vein placement) are likely not possible to include in such models beyond general patient demographic characteristics. The limit of practical applicability of patient-specific models of increased complexity is a general issue in physiological modelling.

"It is well known that hemodynamics of large arteries is too complex to be apprehended using only non-invasive measurements and medical imaging techniques." [9]

"As 3D models can only be used in small portions of the cardiovascular system due to their high modelling and computational costs, reduced-order models have gained attention to reproduce complex wave propagation behaviors in large networks of arteries." [9]

"Although arterial pressure is easy to measure, the precise measurement of blood pressure requires highly invasive techniques." [9]

"In cases where it is not possible to develop physical models it becomes necessary to use shortcuts based on empirical, statistical, or even simple profile models." [10]

Nevertheless, even in the presence of such a large number of assumptions and uncertainties, promising results on the effectiveness of a measurement strategy for the assessment of arterial compliance are obtained in Chapter 6. It is likely that a number of uncertainties can be tackled via empirical evidence to enable practical implementation of measurement strategies. For this reason, next studies will involve a strong clinical component; further cuff, ABP, ECG, PPG patient data will complement mechanical/imaging based characterizations. It is possible that particularly interesting findings will arise from data acquisition during distinct hemodynamic states (e.g. awake vs. anesthetized, before/after nerve blocking, or administration of vasoactive drugs). Also, the physiological meanings of arterial/venous compliance, systemic resistance, artery-vein interaction are approximate; the parameters can be perceived as indicators of arterial properties, rather than as exact measurements. Further clinical evidence involving multiple patient groups might reveal that the measured indices are correlated to subsequent changes in patient outcome even in the case of signal interpretation which

relies on strong assumptions. It is also important to identify potential correlations among parameters describing limb circulation vs. parameters describing the global circulation, such as CO, total compliance, total peripheral resistance (inferred via e. g. Windkessel [20] analysis of the BP waveform).

Besides empirical evidence, advanced signal processing modalities can also be designed to overcome uncertainties that cannot be tackled via mechanical characterization alone. As an example, in Chapter 3, the fusion approach was designed to find the common information in two signals which are affected by different sources of noise, minimizing the need for in-depth characterization of arm tissue behavior or of pulse propagation along the artery. The algorithmic approach also involves the option to use prior knowledge, enabling empirical data collected via clinical trials to be used as an information source.

In addition, as more understanding of vasculature-tissue-sensor interaction is acquired, simulation frameworks will be needed to perform sensitivity analyses to quantify the contribution of different sources to the uncertainty on the parameter inference. This will enable for model reduction and for identification of the main effects which do require in-depth modelling.

Specialized hardware features can also contribute towards more correct interpretation of physiological signals in presence of uncertainty. This was demonstrated in Chapter 7, where uncertainty around cuff folding and patient-specific arm compression effects is tackled via the use of a simple piston-based calibrator. Additional hardware features can be implemented as further understanding of cuff interaction with the vasculature is acquired.

Ultimately, the basic measurement principles can be re-considered. For example, accurate knowledge of BP is required for the estimation of arterial compliance. However, accurate measurement of BP is difficult to obtain non-invasively. In Chapter 5, this uncertainty was tackled via external pressure NIBP, which measures the response of the artery to external, controlled pressure perturbations, rather than to internal arterial blood pressure oscillations, which can vary beat-to-beat. This alternative measurement strategy also gives access to arterial viscosity, as the arterial response to different frequencies (beyond heart rate) can be measured via external perturbations. In addition, the method potentially enables measuring response of the non-pulsatile (occluded) artery to pressure perturbations, therefore revealing information on parameters such as mean systemic filling pressure.

10.4. General conclusion

This thesis demonstrates that the standard patient monitoring equipment can be used to gain information on previously inaccessible parameters of interest to critical care. In particular, we find that the common BP cuff is largely underutilized. The cuff offers ample possibility of modulating blood flow and pulse propagation along the artery, revealing dynamic and compensatory mechanisms of the circulation that are of clinical, diagnostic relevance. We obtained a more advanced characterization of vasculature response to occlusion perturbations and, based on this, developed several measurement strategies to gain information on artery volume-transmural pressure relationship, PAT vs. BP calibration, brachial and distal arterial, venous compliances (representative of smooth muscle tone), systemic resistance, artery-vein

interaction, mean systemic filling pressure, vascular collapse mechanics, and arterial viscosity. The measurement strategies were demonstrated via simulation frameworks and partial validation was achieved on (small) patient datasets. To enable further validation, aspects related to practical implementation of the measurements (cuff transducer characteristics, potential error sources, patient-specific effects) were investigated. We find that arterial collapse along the length of the cuff and cuff interaction with arm tissue have largely been oversimplified up until now. Uncertainties cannot be tackled through physiological/mechanical modelling alone, especially given the existence of patient-specific characteristics. From a practical measurement implementation perspective, this thesis demonstrates that advanced algorithms, specialized hardware features, empirical evidence, and re-interpretation of the measurement principle can be used to cope with oscillometric measurement uncertainties.

Future work will focus on bringing the proposed measurement strategies closer to their clinical implementation. The response of the vasculature to occlusion-based perturbations under different hemodynamic states will be studied to find correlations between measured indices and subsequent changes and cardiovascular events. Further characterizations of the oscillometric measurement principle will also be conducted in parallel.

Clinical integration outlooks

The findings of this research will likely first benefit measurements requiring calibration. As shown in Chapter 6, the proposed measurements can be used towards improved calibration of pulse wave velocity as surrogate for blood pressure [11, 12]. Knowledge of vascular properties at brachial and distal sites can contribute towards more accurate beat-to-beat BP estimation. Another application example relates to devices using the pulse waveform as surrogate for cardiac output CO [13], which require re-calibration by thermodilution whenever changes in arterial properties occur as result of hemodynamic regulation/compensation mechanisms, vasoactive drug administration or in cases of development of vascular edema [14]. In practice, it is difficult to obtain a reliable estimation of CO between intermittent thermodilution measurements; a change in arterial properties from the moment of thermodilution calibration leads to incorrect interpretation of the arterial pressure waveform and, therefore, incorrect estimation of CO. There is no clinically implemented modality for identifying alterations in arterial compliance; as a result, there is uncertainty in the reliability of waveform-based CO measurements. This limitation is emphasized in consensus articles in the field of critical care and hemodynamic monitoring [1]:

"The advantages of these arterial pressure-based cardiac output monitoring systems over PAC-derived measurements are primarily their less invasive nature. The major weakness of all these devices is the drift in values whenever there is a major change in vascular compliance, as, for example, in vascular leak syndrome with increased vessel wall edema leading to decreased arterial compliance."

Information on the artery-vein interaction, vasculature compliance, arterial level of distension, peripheral resistance can be used to detect hemodynamic alterations and therefore indicate the reliability of the CO surrogate measurement.

Such surrogate-based applications can serve as basis for further development of the pro-

posed measurements as more extensive clinical trials are conducted. These potential developments can be aimed at tackling other unmet clinical needs, such as improved detection of deterioration. Given the principles underlying regulatory mechanism activation, changes in arterial properties might precede changes in blood pressure, flow and may be used for early warning of hemodynamic instability. Another relevant aspect relates to the recent trends in patient management, which have been focusing towards prevention of hypotension events due to extensive evidence supporting the link between hypotension and mortality/adverse clinical outcomes. Studies are suggesting that a 65-mmHg mean arterial pressure (MAP) threshold should be regarded as a minimum in prevention of harmful hypotensive conditions. However, while avoidance of hypotension will likely lead towards an overall decrease in mortality in the general population, a significant proportion of patients might suffer due to over administration of fluids and vasoconstrictors. The organ pressure-flow autoregulatory curve is subject dependent; there is need to obtain personalized BP thresholds and to distinguish situations where low BP is in fact caused by hemodynamic instability and therefore requiring resuscitation. Measurement of the arterial level of constriction, artery-vein interaction, analysis of vasculature response to cuff-induced perturbations might offer information on the onset and activity of the underlying compensatory mechanisms to better determine the risk of instability and its link to blood pressure for the individual patient.

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List of publications

Articles

Bogatu, L., Turco, S., Mischi, M., Woerlee, P., Bouwman, A., Korsten, E.H. and Muehlsteff, J., 2020. A modelling framework for assessment of arterial compliance by fusion of oscillometry and pulse wave velocity information. *Computer Methods and Programs in Biomedicine*, *196*, p.105492.

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Bogatu, L., Turco, S., Mischi, M., Schmitt, L., Woerlee, P., Bresch, E., Noordergraaf, G.J., Paulussen, I., Bouwman, A., Korsten, H.H. and Muehlsteff, J., 2021. Modulation of pulse propagation and blood flow via cuff inflation—new distal insights. *Sensors*, *21*(16), p.5593.

Bogatu L., Turco S., Mischi M., Schmitt, L., Woerlee P., Bezemer R, Bouwman A., Korsten H. H., and Muehlsteff J.; New hemodynamic parameters in peri-operative and critical care – a review of key concepts, characteristics, and challenges. - Submitted

Bogatu, L., Turco, S., Mischi, M., Schmitt, L., Woerlee, P., Bouwman, A., Korsten, H.H. and Muehlsteff, J., Air cuff transducer design for occlusion-based hemodynamic measurements - An experimental and simulation study – Submitted.

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Bogatu, L., Bresch, E., Muehlsteff, J., Smink, J. and Woerlee, P., 2019, July. Insights into oscillometry: An experimental study for improvement of cuff-based blood pressure measurement technology. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 7068-7071). IEEE.

Bresch, E., Bogatu, L., Smink, J. and Muehlsteff, J., 2019, July. Feasibility of in-vivo estimation of the brachial artery area-pressure relation from CINE and real-time MRI during upper arm cuff inflations. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (pp. 4012-4015). IEEE.

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Bogatu, L., Bresch, E., Muehlsteff, J., Smink, J. and Woerlee, P., (2019). Insights into oscillometry: A Study for Improvement of Cuff-Based Blood Pressure Measurement Technology. Presented at the National Day on Biomedical Engineering, Brussels, Belgium.

Bogatu, L., S. Turco, M. Mischi, P. Woerlee, A. Bouwman, E. Korsten, E. Bresch, J. Smink, Muehlsteff, J., (2019). A Study for Improvement of Cuff-Based Blood Pressure Measurement Technology. Presented at the Philips PhD Community Reflect Symposium, Eindhoven, Netherlands.

Bogatu, L., Hoppenbrouwers, J., van den Bosch, H., Turco, S., Mischi, M., Muehlsteff, J., Schmitt, L., Woerlee, P. H., Korsten, H., & Bouwman, R. A. (2022). MRI as research tool for cuff-based physiological measurements. *Critical Care*, 41st International Symposium on Intensive Care and Emergency Medicine, ISICEM, *26*(Suppl. 1), 11. [P027]. https://doi.org/10.1186/s13054-022-03927-z

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Laura Bogatu, Jens Muehlsteff, Erik Bresch, Maarten Kuenen, Pierre Woerlee; Blood pressure measurement device and control method. 2020. Published as: EP3705033A1.

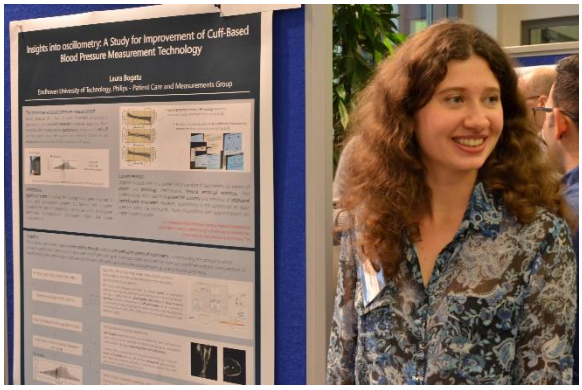
Laura Bogatu, Jens Muehlsteff, Erik Bresch, Maarten Kuenen, Pierre Woerlee. Control Unit for Deriving a Measure of Arterial Compliance. 2019. Published as: EP3760109A1; WO2021001336A1.

Laura Bogatu, Jens Muehlsteff, Maarten Kuenen, Erik Bresch. Control Unit for Deriving a Measure of Arterial Compliance. 2018. Published as: CN113226161A; EP3669762A1; EP3897363A1; JP2022512449A;US2022071496A1;WO2020126576A1.

Laura Bogatu, Jens Muehlsteff, Pierre Woerlee; System and method to non-invasively measure properties of arteries by external pressure oscillometry; Filed 2021.

Jens Muehlsteff, Erik Bresch, Lars Schmitt, Laura Bogatu, Pierre Woerlee. System and Methods to calibrate BP surrogate. Filed. 2021.

Curriculum Vitae



Laura Bogatu was born on the 29th of April 1994 in Romania. She attended high school at Colegiul Național Mircea cel Bătrân and graduated in 2012. Afterwards she attended University of Glasgow, Scotland and in 2017 she obtained a Masters degree 1st class in Electronic and Software Engineering. As part of her graduation project, she developed machine vision applications for congestive heart failure diagnosis in collaboration with Imec (Holst Centre), Netherlands. With an interest in interdisciplinary perspectives, she also worked on video compression applications in collaboration with Nallatech (BittWare), developed remote control software tools for IBM and participated in Glasgow University research projects involving compressive sensing for single detector imaging and cloud computing. In September 2017 she started a PhD supported by Eindhoven University of Technology, Philips Research and Catharina Hospital. Her PhD work consisted of developing patient monitoring solutions with a focus on measuring novel hemodynamic parameters via non-invasive technologies. From July 2022 she will continue the work started during the PhD as a scientist at Philips Research in the department of Patient Care and Measurements.