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Cuffless blood pressure measurements: Promises and challenges

Thesis for the degree of Philosophiae Doctor (PhD)

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Selected abbreviations

24ABPM = 24-hour ambulatory blood pressure measurements

BMI	Body mass index
BP	Blood pressure
CV	Cardiovascular
DBP	Diastolic blood pressure
HR	Heart rate
ICG	Impedance cardiography
ICU	Intensive care unit
LOA	Limits of agreement
PAT	Pulse arrival time
PEP	Pre-ejection period
PP	Pulse Pressure
PPG	Photo-plethysmography
PTT	Pulse transit time
PWV	Pulse wave velocity
SD	Standard deviation
SBP	Systolic blood pressure

Summary in Norwegian

Måling av blodtrykk (BT) er viktig for både pasienter som er innlagt på sykehus og i utredning og oppfølging av pasienter med høyt BT (hypertensjon). Dagens metoder baserer seg på mansjettmålinger på overarmen, enten manuelt ved bruk av stetoskop for å detektere systolisk BT (SBT) og diastolisk BT (DBT) eller elektronisk med automatisk mansjettmåling. Mansjettbasert blodtrykksmåling ble oppdaget for over 100 år siden og det har vært lite utvikling foruten elektroniske målinger med mansjett som har muliggjort hjemmemåling og døgnmåling av BT. Selv om måling av BT på legekontoret, såkalt kontorblodtrykksmåling fortsatt regnes som gullstandard i diagnostikk og utredning av høyt BT, er døgnmåling vist å være bedre knyttet til risiko for hjerte- og karsykdom. Døgnmåling kan også avdekke viktige undergrupper av høyt BT som hvitfrakkshypertensjon, maskert hypertensjon og nattlig hypertensjon. Likevel er metoden begrenset til punktmålinger og pasienten bør være i ro under pågående måling ettersom metoden er sårbar for bevegelsesstøy. Mange pasienter synes også at mansjettmålinger er ubehagelige, spesielt på natten, og ønsker ikke å gjennomgå flere døgnmålinger. Hos pasienter som er innlagt på sykehus, overvåkes de fleste på sengeposter med punktmålinger av BT sammen med andre vitale målinger med varierende intervaller. Dette kan føre til at forverring av helsetilstanden oppdages for sent.

Med bakgrunn i svakheter og begrensinger ved dagens mansjettbaserte metoder for å måle BT, har interessen økt i senere år for å utvikle metoder som kan måle blodtrykk kontinuerlig, ikke-invasivt og uten bruk av mansjett. Kollektivt blir slike nye betegnet mansjettløs blodtrykksmåling. De mest lovende prinsippene baserer seg på måling av pulsbølgetider og bruk av disse som relative mål for endring av BT. Pulsebølgetider og endring av disse som følge av endring av BT er teoretisk forankret i teorier om pulsebølgehastigheter i arteriene. Et annet prinsipp er måling av fotopletysmografi (PPG), som detekterer en pulsatil komponent fra kappillærnivå gjennom huden ved bruk av lys med en bestemt bølgelengde og en fotodetektor. Ved å anta at denne pulssynkrone bølgeformen inneholder informasjon om systemisk BT, kan man bruke endringer av denne til å følge endringer i BT.

Et sensorbelte bestående av EKG elektroder, PPG sensorer, et akselerometer og en impedanskardiografisensor har blitt utviklet av SINTEF Digital. Målet med dette forskningsprosjektet var å undersøke pulsbølgetidbaserte målinger som en mulig metode for mansjettløs blodtrykksmåling og utvikle og teste algoritmer for å måle mansjettløst BT med sensorbeltet ved døgnmåling av blodtrykk og på pasienter innlagt på sykehus.

I artikkel I undersøkte vi sammenhengen mellom pulsbølgetider, definert som tidsintervallet fra en R-bølge i et EKG-signal til et PPG-signal, og BT under isometrisk og dynamisk trening hos 75 deltakere med et bredt aldersspenn og variert inklusjons-BT. Både friske deltakere og deltakere med en

hypertensjonsdiagnose (43,7 %) ble inkludert. Referanseblodtrykket ble målt manuelt med mansjett og auskultasjon av Korotkoff lydene. Studien avdekket sterke korrelasjoner innad hos individer mellom SBT og pulsbølgetider, men dårlig korrelasjon mellom DBT og pulsbølgetider. Det var også betydelige variasjoner i forholdet mellom pulsbølgetider og SBT avhengig av treningsmetode og noe variasjon i regresjonskoeffisientene mellom individer. Resultatene fra den første studien ble brukt til å utvikle algoritmer for å måle BT uten mansjett med sensorbeltet ved døgnmåling av BT og på pasienter på en intensivavdeling (artikkel III og IV).

I artikkel II undersøkte vi, på samme måte som i artikkel I, sammenhengen mellom pulsbølgetider og SBT ved en maksimal oksygenopptakstest i en liten gruppe godt trente mannlige syklister. Referanseblodtrykket ble målt med en elektronisk automatisert treningsblodtrykksmansjett som ved hjelp av en mikrofon detekterte Korotkoff-lydene. I tråd med funnene fra artikkel I viste resultatene sterke korrelasjoner mellom pulsbølgetider og SBT på individnivå, og det var noe variasjon i individuelt beregnede regresjonslinjene mellom individer.

I Artikkel III var hensikten å sammenligne det mansjettløse blodtrykksmålinger fra sensorbeltet, basert på en modell for å estimere BT fra pulsebølgetider utledet fra databasen i artikkel I, med oscillometriske (automatisk elektroniske) mansjettmålinger ved døgnmåling. Vi undersøkte også preferanser hos forsøkspersonene med hensyn til forstyrrelser av blant annet daglig aktivitet, søvn og foretrukket målemetode neste gang ved hjelp av et spørreskjema. I tillegg trente og testet vi en modell for automatisk estimering av søvntid ved hjelp av selvrapporterte søvn- og våkentider. Studien inkluderte 95 deltakere med variert aldersspenn, hvorav nesten halvparten hadde en hypertensjonsdiagnose. I motsetning til vår hypotese om at den mansjettløse metoden kunne estimere blodtrykket i rimelig overensstemmelse med konvensjonelle mansjettmålinger ved døgnmåling, overestimerte sensorbeltet døgnblodtrykket og klarte ikke å detektere nattlig dipp i BT. Det var ingen forskjell med hensyn til nøyaktigheten til den pulsbølgetid-baserte modellen mellom gruppene med og uten en tidligere hypertensjonsdiagnose. Deltakerne foretrakk det mansjettløse sensorbeltet på grunn liten påvirkning av daglige aktiviteter og søvn, og de foretrakk sensorbeltet ved en eventuell ny måling. Søvnanalysene viste at automatisk beregning av søvntid ved bruk av sensorbeltet er lovende.

I artikkel IV sammenlignet vi mansjettløse målinger fra sensorbeltet med kontinuerlige intra-arterielle (invasive) blodtrykksmålinger på pasienter innlagt på en intensivavdeling. På grunn av dårlige resultater i Artikkel III, ønsket vi å utvikle og teste mer komplekse modeller ved bruk av maskinlæring. Vi brukte derfor første halvdel av hver enkelt deltakers data til å trene en individuelt tilpasset maskinlæringsmodell som benyttet andre parametere fra sensorsignalene enn pulsbølgetider. Hver

deltakers siste halvdel av data ble brukt til å estimere blodtrykk med både den pulsbølgetid-baserte modellen og maskinlæringsmodellene. Begge disse ble sammenlignet med det invasivt målte blodtrykket. Studien inkluderte 25 deltakere med median observasjonstid (interkvartilbredde) på 4.0 (3.1-4.6) timer. Resultatene viste at pulsbølgetid-modellen ikke hadde god nøyaktighet og at maskinlæringsmodellene var signifikant bedre og fanget opp vesentlig mer av variasjonen av blodtrykket. I tillegg så vi indikasjoner på at pulsbølgetid-modellen korrelerte med hjerterate i tilfeller der blodtrykket var fallende og hjerterate stigende. Dette var i vesentlig mindre grad tilfelle med maskinlæringsmodellene.

Forskningsprosjektet viste at mansjettløse blodtrykksmålinger basert på pulsbølgetider målt på brystet med et sensorbasert belte ikke hadde tilfredsstillende nøyaktighet. Dette ble vist i en studie som sammenlignet pulsbølgetid-baserte blodtrykksmålinger med konvensjonelle mansjettmålinger ved døgnmåling av BT og på intensivpasienter sammenlignet med intra-arterielle blodtrykksmålinger. Årsakene er sannsynligvis knyttet til flere konfunderende faktorer som påvirket pulsbølgetidene. Pulsbølgetider målt på denne måten inkluderer et tidsintervall (fra R-bølgen i EKG til åpning av aortaklaffen) som er avhengig av hjertes elektromekaniske egenskaper og dermed ikke nødvendigvis er korrelert med endringer i systemisk BT. Pulsbølgetider er også avhengig av radius på blodårene som kan reguleres uavhengig av systemisk blodtrykk i mindre muskulære arterier og arterioler. I tillegg kan det se ut som at pulsbølgetider er avhengig av hjerterate. Maskinlæringsmodeller med bruk av andre parametere enn pulsbølgetider viste lovende resultater og fremtidig forskning bør tilnærme seg problemet på den måten.

Summary in English

Blood pressure (BP) measurements are fundamental for diagnosing and managing hypertension, as well as for monitoring patients during hospitalization. The technique to measure BP using an inflatable cuff to compress the brachial artery and detect systolic and diastolic BP by auscultating the Korotkoff sounds dates back to over a century. In management of hypertension, auscultatory cuff-based BP measurements remains the gold standard method, with little change except for the development of the electronic oscillometric method. Ambulatory blood pressure (BP) measurements are considered state-of-the art for out-of-office BP measurements and are shown to be superior to office BP in predicting cardiovascular events. Additionally, continuous BP monitoring of hospitalized patients is reserved for the critically ill by intra-arterial BP measurements in intensive care units (ICU), during surgery or post operatively. There are, however, limitations to cuff-based BP measurements. Cuff-based measurements can only provide snapshot measurements, which may not detect important fluctuations during ambulatory monitoring or deterioration of hospitalized patients. Furthermore, many find the cuff measurements uncomfortable which can affect compliance to monitoring and follow-up in hypertension management.

Therefore, novel methods to measure BP continuously, without the need for a cuff, have emerged in recent years. The most promising methods are based on the theoretical relationship between pulse wave velocity (PWV) and pressure in the arterial circulation as described in the Moens-Korteweg equation. PWV is related to arterial wall elasticity, which in short-term measurements is dependent on the pressure within the artery. If BP increases, PWV will increase and vice versa. A feasible approach is to measure pulse wave transit times, which is inversely related to PWV. Pulse wave transit times can be measured using an ECG signal or an impedance signal to indicate the start of a pulse wave in the arterial circulation, and a photo-plethysmography (PPG) signal to indicate its arrival at a distal location. Another potential method, but not founded in any known physiological theory, is to assume that the PPG waveform which captures blood volume changes at the capillary level contains information related to BP. From this, complex pulse wave analyses can be used to estimate BP changes based on changes in the PPG waveform.

A prototype cuffless multi-sensor device (Cuffless BP device) based on ECG, impedance cardiography (ICG) and PPG signals has been developed by SINTEF smart sensor and microsystems. This research project is part of a multidisciplinary consortium supported by the Norwegian Research Council. The aim of this thesis was to investigate the ability of the Cuffless BP device to measure pulse wave transit times and develop algorithms to estimate BP from the transit times and the PPG signal recorded with the Cuffless BP device. BP estimates using these aforementioned algorithms were both compared to

24-hour ambulatory oscillometric BP measurements (24ABPM) and to intra-arterial measurements in ICU patients.

In Paper I we investigated correlation between pulse arrival time (PAT) (the most promising pulse wave transit time measurement), defined as the time interval from an R-wave in an ECG signal to the PPG signal, and BP during isometric and dynamic exercise in 75 participants with a broad age range and inclusion BPs. Both healthy participants and participants with a hypertension diagnosis (43.7 %) were included. Reference BP was measured using auscultatory sphygmomanometry. The study revealed strong intra-individual correlations between systolic BP (SBP) and PAT, but not between diastolic BP (DBP) and PAT. There was also significant variation in the relationship between PAT and SBP between exercise methods and variation in the regression coefficients between individuals. The results from the first study were used to develop prototype cuffless BP estimation algorithms to be tested in pilot method comparison studies (Paper III and IV).

In Paper II we investigated, similarly to Paper I, the correlations between PAT and SBP during a maximal oxygen consumption test in a small group of well-trained male cyclists. Reference BP was measured with an electronic automated exercise BP cuff using a microphone to detect Korotkoff sounds. In agreement with the results from Paper I, PAT and SBP had strong correlations and there were some variability in the slope of the individually calculated regression coefficients between individuals.

Paper III was a method comparison study aimed at comparing the Cuffless BP device, using a PAT-based BP model derived from the database in Paper I, to oscillometric 24ABPM. Additionally, we investigated device acceptability with a questionnaire and trained and tested a model to predict sleep times using self-reported sleep and awake times as references. The study included 95 participants with a broad age range of which almost half had a hypertension diagnosis. Contrary to our hypothesis that the Cuffless BP device could estimate BP in reasonable agreement with oscillometric cuff BP measurements during 24ABPM, the PAT-based model was not able to track BP changes across 24 hours. There was no interaction regarding the subgroups of participants with a prior hypertension diagnosis and without a prior hypertension diagnosis on accuracy of the PAT-based model. The participants favored the Cuffless BP device as there was less interference of daily activity, sleep quality and participants expressed a greater willingness to follow up measurements. The sleep analyses showed promise towards automated sleep time prediction.

In Paper IV, a method comparison study was performed on critically ill ICU patients. Due to the unsatisfactory results regarding BP estimations of the Cuffless BP device in Paper III, we aimed to develop more complex models based on machine learning methods. Both the PAT-based model and

the complex machine learning models were compared with continuous intra-arterial BP measurements. Twenty-five participants were included with a median (Interquartile range) observation time of 4.0 (3.1–4.6) hours. Each patient's first half was used to individually fit a machine learning model that utilized other aspects of the sensor signals than PAT. Both the PAT-based model and the machine learning models were tested on each patient's second half of data. The study showed that the PAT-based model performance was unsatisfactory and outperformed by the complex individualized models. Additionally, it was observed that the PAT-based BP model was dependent on HR changes. In cases where hypotension was associated with an increased HR, the model was correlated with HR rather than BP, which was not the case for the machine learning models (in most patients).

In conclusion, PAT measured at chest level was not an adequate alternative measurement method to enable cuffless BP measurements. This was likely because of several confounding factors. Firstly, PAT includes the pre-ejection period, defined as the time interval from the electrical onset of systole to the opening of the aortic valve, which can change independently of systemic BP. Secondly, local arterial wall tension is regulated independently of systemic BP in small muscular arteries and arterioles which may have introduced changes in PAT that are not related to systemic BP. Lastly, we observed some dependency of PAT on HR rather than BP. Future research will require building on the results from Paper IV to develop more complex models to enable accurate cuffless estimation of BP.

Articles in the thesis

I. Heimark, S., Rindal, O. M. H., Seeberg, T. M., Stepanov, A., Boysen, E. S., Bøtker-Rasmussen, K. G., Mobæk, N. K., Søraas, C. L., Stenehjem, A. E., Fadl Elmula, F. E. M., & Waldum-Grevbo, B. (2022). **Blood pressure altering method affects correlation with pulse arrival time**. Blood pressure monitoring, 27(2), 139–146. https://doi.org/10.1097/MBP.0000000000000577

II. Heimark, S., Eitzen, I., Vianello, I., Bøtker-Rasmussen, K. G., Mamen, A., Hoel Rindal, O. M., Waldum-Grevbo, B., Sandbakk, Ø., & Seeberg, T. M. (2022). **Blood Pressure Response and Pulse Arrival Time During Exercise Testing in Well-Trained Individuals**. Frontiers in physiology, 13, 863855. https://doi.org/10.3389/fphys.2022.863855

III. Submitted to Blood Pressure on 29th of August 2023. Heimark, S. Hove, C., Stepanov, A., Boysen, E.S., Gløersen, Ø., Bøtker-Rasmussen K.G., Gravdal H.J., Narayanapillai, K., Fadl Elmula, F.E.M., Seeberg, T.M., Larstorp, A. C. K., Waldum-Grevbo, B. (2023): **Accuracy and User Acceptability of 24-hour Ambulatory Blood Pressure Monitoring by a Prototype Cuffless Multi-Sensor Device Compared to a Conventional Oscillometric Device**

IV. Heimark S, Bøtker-Rasmussen KG, Stepanov A, Haga ØG, Gonzalez V, Seeberg TM, Fadl Elmula FEM and Waldum-Grevbo B (2023) **Accuracy of non-invasive cuffless blood pressure in the intensive care unit: Promises and challenges.** Front. Med. 10:1154041. doi: 10.3389/fmed.2023.1154041. https://doi.org/10.3389/fmed.2023.1154041.

Introduction

What is blood pressure?

Blood pressure (BP) is a physical force exerted on the arterial walls by the volume of blood within the arteries (1). There is no clear definition of BP because it depends on how and where it is examined. A complete understanding and mathematical modelling of the pressure waves generated by the cyclic contracting heart in the arterial circulation is complicated and currently not possible to model accurately. A key concept to consider when discussing BP is that humans (and mammals) are pressure regulated (1, 2). Numerous control mechanisms ensure that the pressure is tightly regulated around a set point. Short-term control is mainly provided by the autonomous nervous system via baroreceptors in the arterial circulation. Baroreceptor feedback to the autonomic nervous system elicits acute vasodilatory or vasoconstrictor responses and changes in cardiac output. Long-term control of BP is regulated by the renal blood volume pressure control mechanism, i.e., pressure diuresis and pressure natriuresis. This system interacts with the renin-angiotensin-aldosterone system which affects vasoconstriction and the sodium balance. Short and long-term control of arterial blood pressure tightly around a set point allows for a pressure gradient from arterial to venous circulation and organs to autoregulate blood flow depending on metabolic demands.

BP measured at a single point in the circulatory system is a complex function of the stroke volume, the total peripheral resistance and kinetic energy (energy from blood flow) in interaction with elastic energy (the recoil force from the arterial walls on the volume of blood within) and potential energy from the gravitational effect on the mass of the blood (2, 3). In addition, reflected waves play an important role in determining particularly systolic BP (SBP) and the rate of emptying of blood from peripheral vessels is important in determining diastolic BP (DBP). Elastic recoil energy, i.e., resistance to stretching (elastance) from the arterial walls is the most important force (2, 3). Kinetic energy (energy from the flowing blood) only contributes about three percent and is usually neglected. Finally, the gravitational effect is important to consider as it greatly impacts assessment of the pressure at various places in the circulation due to the weight of blood.

Why measure blood pressure?

Measurements of BP is paramount in medical care and there are two principally different areas of which BP measurements are used. First, BP is a key vital sign and part of the routine assessment of any hospitalized patient. Second, hypertension is one of the most important modifiable risk factors for premature morbidity and mortality globally (4). BP is also used as a surrogate endpoint in trials because it is a major risk factor for cardiovascular (CV) and cerebrovascular diseases.

BP as a vital sign is a surrogate measurement of organ perfusion. What matters when considering the state of the CV system is blood flow to organs and that local metabolic demands are met. However, local organ blood flow is hard to measure and not feasible in clinical practice. To allow for tissue perfusion, adequate pressure gradients must be present so that blood flow can be regulated locally according to local metabolic demands. In this way, systemic arterial BP as a vital sign taken together with other indirect assessments of organ perfusion such as urine output or lactate from anaerobic metabolism, is an important indicator of organ perfusion. Few hospitalized patients are monitored continuously which is research-intensive and require intra-arterial cannulation. Therefore, most hospitalized patients are monitored intermittently by snapshot cuff measurements at varying intervals.

In the field of hypertension, substantial efforts are dedicated to developing guidelines for diagnostic thresholds and BP lowering targets (4). A tremendous body of evidence shows that reducing BP below defined targets reduces risk of stroke, myocardial infarction, progression of renal disease and other hypertension mediated organ damages (4). Hypertension as a risk factor is dependent on methods to measure BP in a standardized and reproducible way. Thus, office BP measured by a cuff remains the gold standard in hypertension management. However, out-of-office BP measurements such as 24-hour ambulatory BP monitoring (24ABPM) and home BP measurements are increasingly recognized to be better predictors of CV events and can detect important BP phenotypes such as white coat hypertension, masked hypertension and night-time hypertension (5, 6).

A brief history of blood pressure measurement

The rate and pulsatile characteristics of the palpable pulse were recognized as insights to the status of the human body several millennia ago (7). However, the modern way of measuring BP began in the eighteenth century. The first direct BP measurement was famously performed by Reverend Stephen Hales in 1733 (Figure 1) (8). Hales repeatedly cannulated the femoral artery of several horses (tied to the ground) with a brass pipe connected to a glass tube. He observed that column of blood rose 8-9 feet above the heart and had pulsatile characteristics. He also observed the mechanical characteristics of the blood in the glass tube during bleed out of the horses. He noted that after a large amount of blood was let out, all horses experienced sweats, “like that of a dying man”. Later advancements did not proceed until physician physicist Jean Léonard Marie Poiseuille introduced the mercury manometer in the early 19th century (9, 10). The mercury manometer allowed for height displacement against gravity of mercury to measure pressures and is to date the standard unit of BP measurements. Poiseuille studied direct arterial pressure in animals by connecting his mercury manometer to cannulated arteries. Poiseuille’s principles were improved by Carl Friedrich Wilhelm Ludwig with the kymograph (from the Greek words “Kyma”, meaning wave and “grapheion”, meaning

write, “wavewriter”), allowing graphical presentation of pulse waves recorded from cannulation of arteries (11). The first direct measurement of BP in humans were performed by French surgeon Jean Faivre, who, during a lower limb amputation in 1856, cannulated a lower limb artery (12, 13). Repeatedly he demonstrated the SBP in the lower limb to be about 120 mmHg.

Figure 1. A contemporary illustration of Stephen Hales famous experiment. The illustration indicates that the carotid artery was cannulized. In reality, the femoral artery was used. *Reprinted from Journal of Veterinary Cardiology, Vol 15 /issue 1, Buchanan, James W., The history of veterinary cardiology /, Copyright (2013), with permission from Elsevier. License number: 5618351332961*

The next significant advancement occurred in 1855 when Karl Von Vierordt measured the amount of counterpressure needed to cease pulsation in an artery. His cumbersome sphygmograph (from the Greek word “sphygmo”, meaning pulse) was the first mechanism to non-invasively estimate BP in humans by applying weights on a lever that pressed down on the radial artery (9, 14, 15). Improvements by French physiologist Jules Etienne Marey made the device portable and pulse

recordings became more detailed, providing graphical representations of pulse recordings and pressure measurements by a manometer (16). Marey's developments are also regarded as the first use of the oscillometric principle, which is the analysis of amplitude of oscillations during various counterpressures. In the 1870s, Samuel Sigfried Karl Ritter von Basch introduced a water filled inflatable bladder to transmit the pressure from a rubber bulb compressing the radial artery on a clamped arm (9). This is considered a key development towards the modern sphygmomanometer due to its simplicity and miniaturization. Basch's apparatus was the first to describe elevated BP readings in patients with CV disease and lower BP in patients with a fever.

Building on previous developments, Italian paediatrician Scipione Riva-Rocci invented the modern sphygmomanometer in 1896 (17, 18). Riva-Rocci's sphygmomanometer consisted of a circumferential cuff to be inflated around the upper arm of which the pressure at palpable pulselessness distally could be read from the connected mercury manometer to determine SBP. In 1905 Russian surgeon Nikola Korotkoff famously described distinctly audible sounds when listening with a stethoscope on the artery distally during cuff deflation from supra systolic pressures (17, 19). Undoubtedly, this most famous discovery remains highly relevant at present.

Current methods for blood pressure monitoring

An overview of current methods available to measure BP is presented in figure 2.

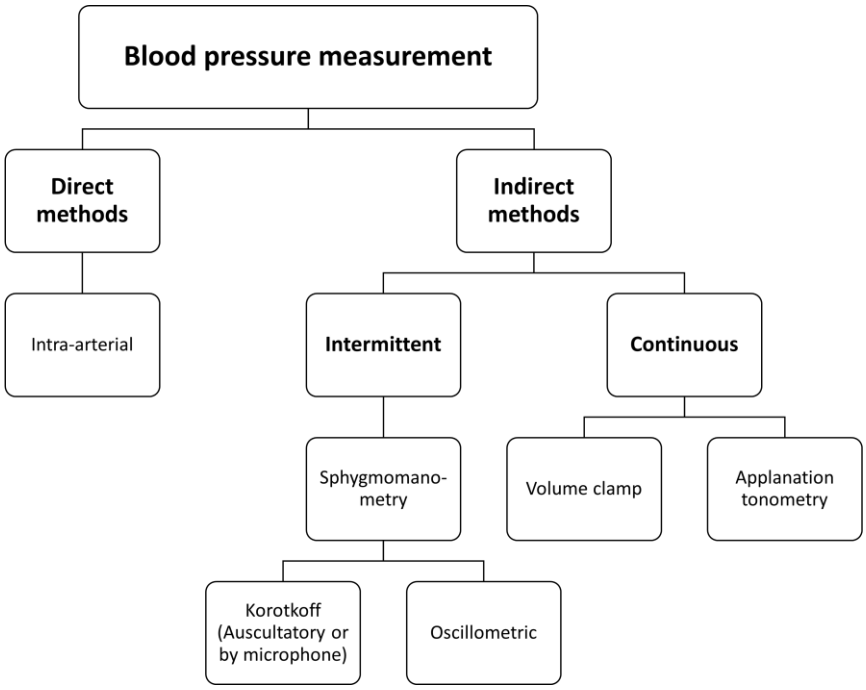

Figure 2. Overview of current methods to measure blood pressure.

Direct methods

Direct measurement of BP is only possible through arterial cannulation. The pressure from the artery is transmitted to a pressure sensor through a fluid filled tubing. The pressure sensor is usually a Wheatstone bridge electrical circuit that can translate the pressure fluctuations into electronic signals (20). The tubing is further attached to a pressurized fluid filled bag to prevent backflow and clotting. Intra-arterial BP monitoring allows for continuous beat to beat BP and inspection of the obtained waveforms in real-time and is considered the gold standard when it comes to measuring pressure within an artery of interest (21). However, it is only accurate if its operating conditions are met. The pressure transducer must be zeroed to the pressure inside the room, levelled according to a point of interest, and the tubing must have adequate damping properties (22, 23). Zeroing refers to exposing the pressure transducer to atmospheric pressure in the room and setting this to be zero, such that all following pressure readings (from inside an artery) are relative to the atmospheric pressure. This must be performed at repeating intervals since atmospheric pressure changes with time. Levelling refers to adjusting the pressure transducer height to a point of interest. The phlebostatic axis is commonly used, which is an approximation of the right atrium and the aortic root and thought to be a level which is unaffected by the changing hydrostatic pressures when the body changes postures (24). Lastly, since the system is a harmonic oscillator, over and under damping can occur. Under damping is the amplification of the pressure waveforms and can occur if the tubing's own resonance frequency is too close to the pressure waveform frequency, and is caused by faulty tubing material, length or radius. Over damping occurs due to compression of the waveforms from air, soft tubing or clotting. The mean arterial pressure (MAP) is less affected by inappropriate damping.

Indirect methods

Intermittent blood pressure measurements

Auscultatory sphygmomanometry

Cuff-based auscultatory BP measurements remain the gold standard method in hypertension management and is the reference (gold standard) method when new sphygmomanometers are validated for clinical use (25). The mercury sphygmomanometer is at present replaced (due to mercury toxicity) in most countries by the aneroid (from the Greek words "a", meaning without, and "nēros", meaning water, "without liquid"). The air pressure in the cuff is transmitted to metal bellows that are connected to gears which drive a gauge to display the pressure. The pressure levels corresponding to SBP and DBP are derived from the Korotkoff sounds auscultated with a stethoscope placed over the brachial artery distally to the cuff (Figure 3). During the deflation, the first appearance of pulse synchronous tapping sounds indicates SBP. The disappearance of sounds indicates DBP. Limitations of the cuff-based auscultatory method relate to operator dependency and

inter-operator variability. The patient needs to be physically in the same place as the operator, which limits the flexibility of measurements and may induce the white coat effect. Accuracy is also dependent on each operator's placement of the stethoscope and interpretation of the Korotkoff sounds in addition to the terminal digit preference phenomenon (26).

Oscillometric sphygmomanometry

Oscillometric BP devices are the most abundant type today due to their electronic and automated nature. They also utilize the principle of upper arm cuff inflation and deflation. However, in contrast these detect the amplitude of oscillations during cuff deflations (Figure 3). Interestingly, these are the same oscillations as described by Etienne-Jules Marey in the 1870s. Maximum amplitude of the oscillations are shown to correlate accurately to MAP (27). Proprietary algorithms are used to detect SBP and DBP from the change of oscillation amplitudes throughout deflation. Although the electronic oscillometric method has enabled automated office BP, ambulatory and home BP monitoring, it has limitations. Automated detection of and estimation of BP from the oscillations recorded is vulnerable to noise from movement in addition to an inability to detect the oscillations accurately if BP is changing too much during measurement.

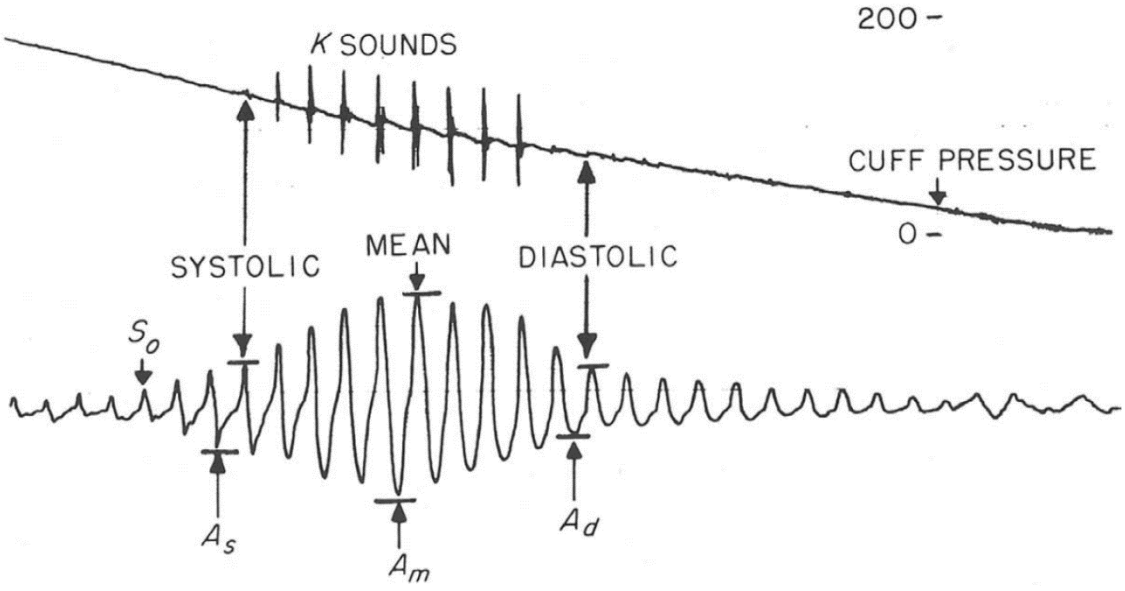

Figure 3. Graphical representation of Korotkoff sounds (K SOUNDS) (upper graph) and oscillations recorded by the oscillometric method (lower graph) during cuff deflation. A_s represents the systolic detection, A_m the maximum of oscillations and A_d the diastolic detection.

Continuous indirect blood pressure measurements

Volume clamp

The volume clamp method (also known as the vascular unloading technique) was first described by physiologist Jan Penaz in 1973 (28). By placing a cuff around a finger in combination with a photoplethysmography (PPG) sensor, it utilizes the principle of zero transmural state of the arterial wall (29). Zero transmural pressure is the state where the pressure on the inside of an artery equals the pressure on the outside (unloaded state). The PPG sensor emits light at a fixed wavelength and measure the amount of light reflected using a photo detector and can capture the pulsatility of the artery. The system first finds maximum pulsatility during a cardiac cycle and clamps the pressure at the unloaded state to calibrate. To obtain continuous BP measurements, the cuff pressure is tightly servo controlled to maintain a constant PPG amplitude corresponding to the unloaded state throughout a cardiac cycle. The pressure changes in the servo-controlled finger cuff thereby correspond to the arterial pressure waveform. The pressure waveform must be further reconstructed to resemble the brachial arterial waveform (29).

The volume clamp method requires bulky equipment and is dependent on the measurement site to remain at the same height or use a fluid filled column for height correction or a mathematical transformation of the finger waveform to correspond to the brachial BP waveform (30, 31). Also, conditions affecting peripheral circulation will affect quality of the PPG signal and device ability to trace BP. A meta-analysis including 919 patients across 28 studies found the accuracy to be outside of acceptable criteria when compared to continuous intra-arterial measurements as reference (32). For these reasons, the volume clamp method is hardly ever used in clinical practice, but often used in research settings were many of the factors contributing to decreased accuracy can be controlled.

Applanation tonometry

Applanation tonometry (developed in the 1960s) compresses an artery against the underlying bone and records the pressure waveform transmitted directly back to a pressure transducer in the apparatus (33, 34). By steadily increasing the applanation pressure, the amplitude will increase before starting to decrease again. The maximum amplitude is shown to correlate with MAP. SBP and DBP must be derived from mathematical transfer functions. Accuracy is limited by the strict operating conditions (33). The tonometer is dependent on being centred on the artery, and deviations of less than a millimetre will disrupt measurement accuracy. In addition to deriving the mean pressure, the displacement of the tonometer records a waveform, but it cannot estimate absolute values unless calibrated and converted via some transfer function with a known pressure recording.

Novel methods for blood pressure measurement

More than a century after its invention and with little advancements, sphygmomanometry (either auscultatory or by the oscillometric method) remains the gold standard BP measurement method in hypertension management and for most hospitalized patients. The intermittent nature with measurements taken at varying intervals can delay detection of clinical deterioration of hospitalized patients and hypotensive episodes may go undetected (35). 24ABPM for out-of-office monitoring in hypertension remains limited to snapshot measurements during resting conditions which may not capture all ambulatory BP fluctuations. Furthermore, patients often find the cuff measurements uncomfortable which may limit compliance to follow up (36).

The lack of methods to measure BP non-invasively without interference and in a more continuous manner has led to an abundance of research on methods to enable non-invasive cuffless BP measurements. In part, this is facilitated by the miniaturization and improvements of sensors. The most popular methods are based on the use of well-known principles of ECG and photo-plethysmography (PPG) incorporated in wearable devices. The most popular principle to estimate BP from sensor signals is the use of the theoretical relationship between BP and pulse wave propagation times. Furthermore, it is assumed that the PPG signal contains information on BP which can be used to estimate BP.

Photoplethysmography

PPG is based on the principle of measuring the amount of light that is absorbed and reflected. The principle of PPG is well-known from measurements of peripheral oxygen saturation (37). Pulse oximetry utilizes that oxygenated and deoxygenated haemoglobin absorb light of different wavelengths. Light is emitted at these different absorbance wavelengths, and the ratio of absorbance after passing through for example the finger is used to calculate against calibrated values the percentage of oxygenated haemoglobin.

PPG measurements used in the thesis are based on reflective PPG. Light of a fixed wavelength is emitted from a light emitting diode into the underlying skin. A photodetector placed in proximity on the same device measures the amount of light returned. The main absorbent of the emitted light is haemoglobin. Consequently, pulsatile variation in the unabsorbed light originates from volume changes in blood at the place of sensing. The origin from which the PPG signal arises is not well understood. The latest theories suggest that the pulsatile nature of the waveform originates from displacements of the capillary beds (which is the depth green LED light reaches) caused by pulsations in the underlying arteries and arterioles (38).

The use of PPG in cuffless BP research is based on two different aspects of the signal. First, the pulsatile component can be used to define the arrival of a pulse wave distally (described in detail below). A second method is to assume that the pulsatile component of the PPG signal contains information on BP or the change in BP over time. There is no consensus regarding exactly what the nature of the signal is, i.e., what mechanisms in the tissue and vessels contribute to the pulsatile component recorded and thus there is no a priori physiological knowledge or explanation that describe factors of the signal in relationship to BP (38). Methods to estimate BP from the pulsatile component of the PPG signal vary from defining certain characteristics of the PPG waveform and investigate correlation between changes in the characteristics of the PPG waveform with changes in BP, to utilizing machine learning methods to derive relationships between changes in the PPG signal to changes in BP (39).

Pulse wave propagation times

Pulse wave propagation in the arterial circulation is not a new discovery. Pulse wave velocity (PWV), the speed at which a pulse wave generated by a heart contraction propagates along the elastic arterial tree, was of great interest in the early 20th century and found to increase with age and be related to the instantaneous pressure at the time of measurement (40). Although more complicated models exist, a commonly used theoretical relationship between PVW and BP is described by the Moens-Kortweg equation (41), which was independently derived by both Adriaan Isebree Moens and Diederik Korteweg in the late 19th century:

$$PWV = \sqrt{\frac{hE_{inc}}{2pR}}$$

Where h is wall thickness, E_{inc} is the young's modulus of wall elasticity, p is blood density and R is vessel radius. By making some simplifying assumptions, the Moens-Kortweeg equation describes the relationship between pulse wave velocity (PWV) and stiffness of the arterial wall in addition to blood viscosity and radius of a vessel and thickness of the wall. On the assumption that blood density, thickness of the arterial wall and radius are relatively constant, changes in PWV will be related to changes in BP that affect wall stiffness. PWV is commonly measured as carotid to femoral PWV to assess central PWV as a risk factor (42). Measurements of pulse arrival time (PAT) is a simplification of the PWV with the inverse relationship:

$$PAT = \frac{D}{PWV}$$

Where D is the length of the arterial segment of which PWV is measured. PAT is commonly measured from the R peak of an ECG signal, as the proximal timing reference, to a PPG signal as a distal timing

reference (Figure 4) (39). Hence, a limitation of PAT is the inability to provide an absolute measurement of PWV. However, the important aspect of PAT as a potential surrogate BP measurement is the measurement of relative short-term changes which could reflect BP changes. PAT or PWV cannot provide absolute measures of BP unless they are calibrated against a known BP measurement. Thus, relative changes from the point of calibration can provide measurements of BP.

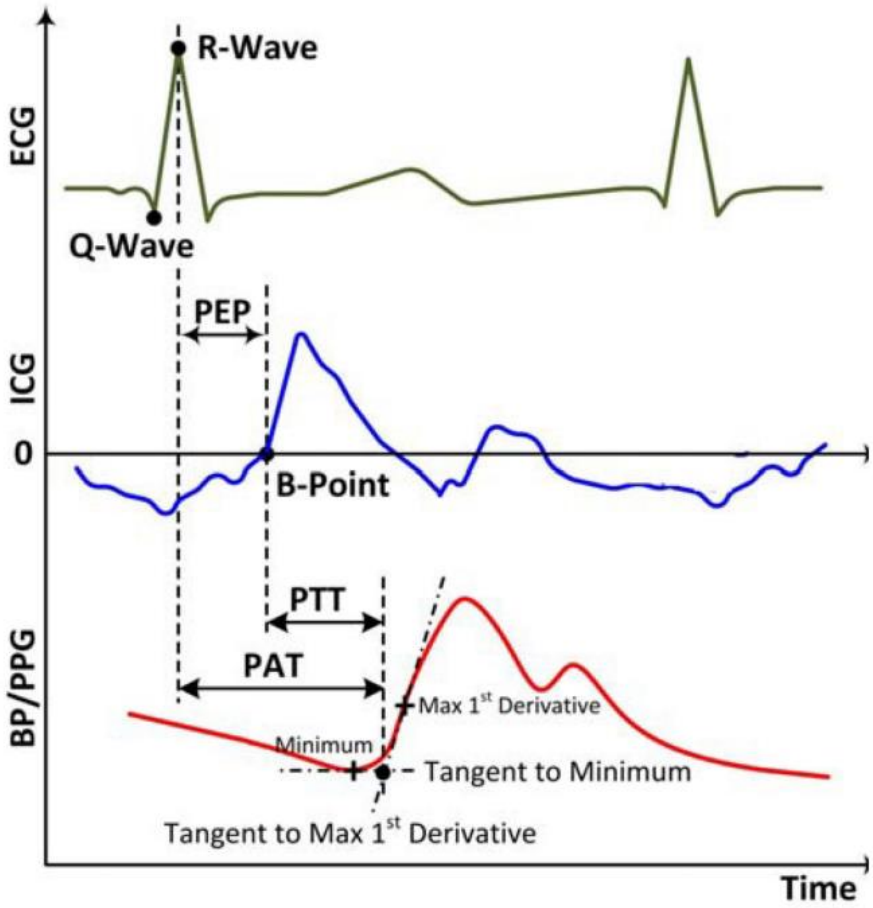

Figure 4. Illustration of pulse arrival time (PAT), pulse transit time (PTT) and the pre-ejection period (PEP) using ECG, impedance cardiography (ICG) and photoplethysmography (PPG). *© [2015] IEEE. Reprinted, with permission, from [R. Mukkamala, J. O. Hahn, O. T. Inan, L. K. Mestha, C. S. Kim, H. Töreyin, S. Kyal, Toward Ubiquitous Blood Pressure Monitoring via Pulse Transit Time: Theory and Practice, IEEE Transactions on Biomedical Engineering, Aug/2015].*

Another important aspect of PAT is the inclusion of the pre-ejection period (PEP), defined as the time interval from the R wave, which indicates the onset of electrical activity of the cardiac cycle, to the opening of the aortic valve (Figure 4) (39). Therefore, inclusion of PEP in PAT as a surrogate measure of BP can disrupt the relationship between PAT and BP because PEP may not be related to systemic BP in the same way as the pulse wave propagation in the artery.

A proposed workaround is to measure pulse transit time (PTT), defined as PAT minus PEP, by incorporating a measurement that corresponds to the onset of the pulse wave in the arterial tree.

One such method is impedance measurements to obtain an impedance cardiography (ICG) signal (43). ICG measures voltage changes in the thoracic cavity by applying a weak current between externally placed electrodes. Since blood is a good electric conductor, the major changing event in the obtained waveform corresponds to movement of blood through the thoracic cavity. The B-point (Figure 4) has been shown to correlate with the ejection of blood into the aorta, and thus correspond to the onset of a pulse wave in the arterial tree (44). Using non-invasive measurements of ECG, ICG and PPG, PAT, PTT and PEP can be estimated for each cardiac cycle as illustrated in Figure 4.

Recall that according to the Moens-Korteweg equation, PWV is also dependent on vessel radius and wall thickness. Thus, PWV (and both PAT and PTT), may be less affected by changes in vessel radius and wall thickness in central elastic arteries compared to peripheral muscular arteries (43). Measurements of PAT or PTT that have a significant amount of propagation time along arteries that have more smooth muscle and smaller diameter may disrupt the assumption that changes in PWV relates to changes in wall stiffness (BP). It has therefore been proposed to obtain the distal timing reference centrally at chest level to decrease this effect (45).

Although the theoretical relationship between PWV and BP has been known for a long time, it has not been feasible to assess in wearable devices until recently due to advancements in technology. Particularly miniaturization of sensors and components as well as performance of sensors and digital components have been central to the technological improvements. Feasibility studies in laboratory settings with devices under development have shown promise regarding pulse wave propagation methods (45-51). However, it is still uncertain whether a wearable Cuffless BP device can provide acceptable accuracy in relevant clinical settings such as ambulatory BP monitoring and in-hospital BP monitoring.

A prototype cuff less chest belt BP device has been developed and tested by SINTEF Digital (Figure 5). It is designed as a chest belt and has sensors placed on the skin of the thoracic cavity to obtain a one lead ECG, ICG and a PPG, thus capable of estimating pulse wave propagation times continuously (for each cardiac cycle). Generation 0 of the device was shown to have a high degree of correlation between PTT and MAP in 4 participants during isometric hand grip (52). The device was also investigated in 23 patients with non-alcoholic fatty liver disease and large variations in body composition where PTT showed strong correlations with SBP and MAP but varying correlations with DBP during seated dynamic exercise on a cycle (53). A consortium research project, funded by the BIA program of the Norwegian research council (282039), was established in 2018/2019. The research project was a collaborative effort between Oslo University Hospital, Ullevål, SINTEF Digital, Aidee Health AS and Sandefjord Helsepark AS.

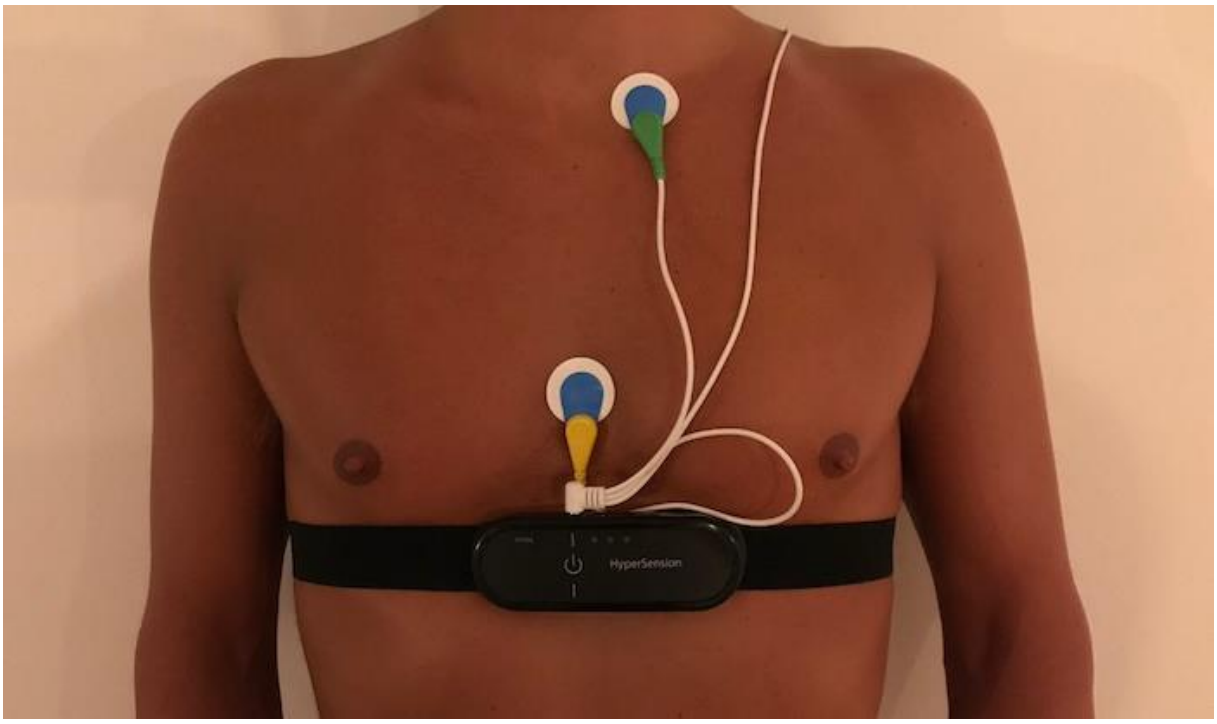

Figure 5. Generation 1 of the cuffless device.

Thesis aims

The overall aim of the thesis was to investigate potential cuffless surrogate BP measurements using the chest belt Cuffless BP device and develop algorithms to estimate BP that would match the conventional 24ABPM and intra-arterial BP measurements in patients in an ICU. Additionally, we aimed to investigate acceptability of the Cuffless BP device compared to conventional cuff 24ABPM and investigate automatic sleep detection as an additional feature.

The specific aims of the thesis were:

I. To investigate, in a cohort reflecting the general population, sensor-based measurements of ECG, ICG and PPG to calculate non-invasive continuous BP surrogate measurements during two differing BP altering methods and at rest, and explore the relationship between reference BP and potential cuffless surrogate measurements. In addition, data from this study would act as a database to develop and test algorithms to estimate BP with the device in other populations (Paper I).

II. To investigate device feasibility and PAT as a potential cuffless surrogate measurement of SBP during exercise testing in an athletic population (Paper II).

III. To investigate agreement and patient acceptability of the cuffless chest belt device during 24-hour ambulatory measurements compared to standard (state of the art) 24ABPM (Paper III) using a BP estimation model derived from the database from Paper I. Additionally, we aimed to investigate automatic sleep detection as an additional feature.

IV. To investigate agreement of BP estimation in critically ill patients in an intensive care unit compared to continuous invasive BP measurements as reference (Paper 3), using a BP estimation model derived from the database in Paper I. We further hypothesized that complex, individualized machine learning models would improve the agreement between the cuffless BP device and intra-arterial BP.

Materials and methods

Paper I

Study design population

The study population aimed to reflect a general population cohort similar to that of the most up to date consensus protocol on validation of BP measurement devices (25). Exclusion criteria were subjects defined as special populations regarding BP measurements; children, pregnancy, ongoing atrial fibrillation, and old age (above 79 years). Patients with a baseline SBP above 180 mmHg or DBP above 120 mmHg were excluded because of risk (of a CV event) regarding exercising with severely elevated BP. In addition, we aimed to include participants that was either healthy or had uncomplicated hypertension, but without comorbidity. Participants were screened on co-morbidities by taking a medical history at inclusion. Eighty participants were recruited as either healthy volunteers from Oslo University Hospital and collaborators in the research project or from a local hypertension registry (HYREBI REK 2017/477).

Study protocol and methods

The study protocol was designed to prospectively measure reference BP and device sensor signals during two different BP changing interventions and during resting conditions. Two different exercise methods, isometric exercise of large muscle groups and dynamic exercise seated on a cycle ergometer, were chosen because they induce large BP increases, but with differing hemodynamic responses (54). The study protocol is illustrated in Figure 6. Each participant completed an isometric exercise period and a dynamic exercise period with resting periods prior to, in between and after. Reference BP was measured by the cuff based auscultatory method, taking Korotkoff I as SBP and

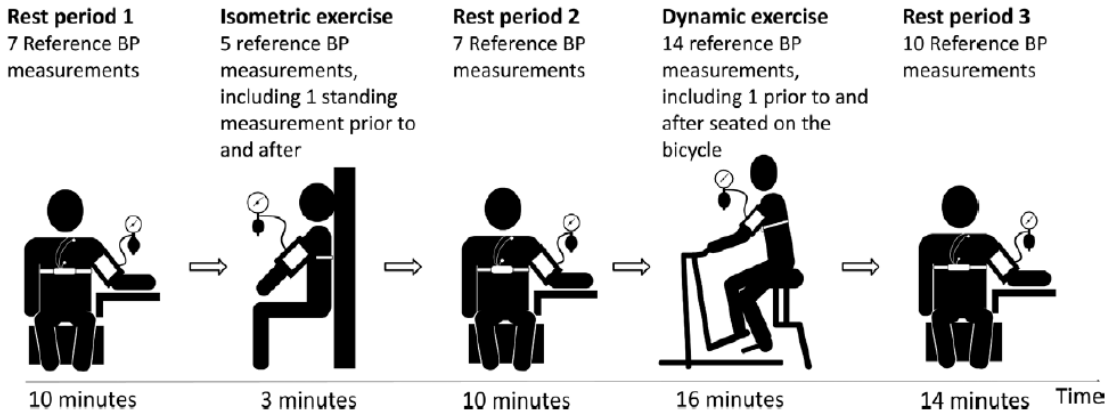

Figure 6. Illustration of the test protocol. *Reproduced under the CC-BY-NC-ND creative commons licence from Heimark, S., Rindal, O. M. et al. Blood pressure altering method affects correlation with pulse arrival time. Blood Pressure Monitoring 27(2): p 139-146, April 2022.*

Korotkoff V as DBP. If Korotkoff V was undefinable during exercise, Korotkoff IV was used to determine

DBP (55). An aneroid sphygmomanometer (Maxi-Stabil 3; Welch Allyn, Skaneateles Falls, New York, USA) which was tested to have satisfying pressure recordings prior to the study was used. Each reference SBP and DBP measurement was recorded to the nearest second. The Cuffless BP device was fitted as illustrated in Figure 5; a chest belt configuration with three standard electrodes. The device recorded a 1-channel ECG signal, an ICG signal and a PPG signal from a sensor located at the black box facing the skin. All signals were recorded with a sampling rate of 1000 hertz.

Data analysis and statistical methods

Data was recorded and analysed offline in a custom-made study database using the Python programming language. The data were inspected for normality using histograms and the Kolmogorov-Smirnov test. PAT was calculated from the R-peak in the ECG signal to the foot of the PPG waveform (tangent intersect between the minimum tangent and the tangent of the first upstroke as illustrated in Figure 4). PAT values were calculated for each measurement of SBP and DBP. A window of 10 cycles prior to and after the exact notion of the systolic and diastolic BP were used and filtered with a moving median filter with a window size of 30 cardiac cycles. Within this window, PAT values with a larger difference than 20 % from the median PAT value within the window were discarded. The relationship between PAT and BP were explored in each participant using Person's correlation and linear regression analyses. Mean of correlation coefficients across exercise interventions and mean of regression coefficients across exercise interventions were compared using the Wilcoxon sign rank test.

Statistical methods used in unpublished data (presented in the results section)

Potential cuffless features other than PAT as described above, were analysed using repeated measures correlation to account for repeated measures within different participants (56). Training and validation of different BP prediction models were performed internally in the project using the database created from the first study (Paper I). At random, 40 participants were selected to act as training group to develop an empiric model from the data to predict changes in BP based on changes in PAT. Subsequently, 10 participants were selected at random as a validation group to test the models developed in the first group. Both linear regression and multiple linear regression models (taking age, height, sex, hypertension status etc. as covariates) were tested in addition to multiple polynomial regression and multilayer perceptron (a feed forward artificial neural network). The model performances were compared numerically on mean and median absolute error and the standard deviation of the mean absolute error. All BP predictions were calibrated against a reference measurement during the first resting period; a correction for the offset of the b term in a simple linear equation $y = ax + b$.

Paper II

Study design and population

The Cuffless BP device investigation was a secondary investigation included in a study to assess the BP response in a cohort of well-trained male athletes. Therefore, the SBP response, maximal oxygen consumption and lactate threshold results will not be considered in this thesis. The study aimed to test the BP response in a cohort of well-trained male athletes during a lactate threshold test and a maximal oxygen consumption test. PAT was measured simultaneously using the Cuffless BP device during all test procedures with the aim to compare PAT calculations with reference BP measurements taken by an exercise BP cuff. Male cyclists were recruited from cycling clubs in Oslo. They had to meet pre-defined criteria related to being "well-trained"; a minimum of eight hours of weekly exercise, with at least five of these as cycling, and prior experience with high intensity cycling. Eighteen participants completed the study. the small sample size of only male participants was a result of the study being a pilot investigation to assess the BP response to maximum exercise testing and PAT as a potential SBP surrogate measurement during exercise testing with a limited time frame of test-lab availability. Eighteen participants completed the study. Fifteen were available for assessment of PAT measurements. Three participants could not be used in the PAT analyses because of excessive noise in the signals acquired. The cuffless BP chest belt was fitted in the same way as in study I and had the same sensor configurations.

Prior to exercise testing, participants had to abstain from exercise on the same day, caffeine three hours prior and food 1 hour before. The test protocol was designed to test both lactate threshold and maximal oxygen uptake (VO2max). Reference BP was measured using a standard exercise cuff with automated and ECG gated microphone-based detection of Korotkoff sounds (Schiller BP200+, Schiller AG, Baar, Switzerland). After 10 minutes of seated rest, reference BP measurements were taken at minute 5 and 7. Subsequently, the participants completed a warmup period of 10 minutes with three reference BP measurements followed by a lactate threshold test and a VO2max test. The lactate threshold test consisted of 5-minute steps with 30W increases. Reference BP was measured at the end of each step. The VO2max test had 1-minute intervals with 30W increases and repeated until exhaustion. Reference BP was taken every 2nd minute.

Data analysis and statistical methods

PAT was calculated and filtered in the same way as described in Paper I. Additionally, very high exercise intensity introduced noise in the sensor data. Therefore, measurement pairs of SBP and PAT were PAT calculations that did not have valid sensor data in reasonable proximity (in time) to the SBP measurement were excluded. Furthermore, a measurement pair having a probability of less than 2.5

% of occurring based on the Gaussian distribution within each participant was removed. The relationship between PAT and SBP was investigated in each participant with simple linear regression.

Paper III

Study design and population

The study was a prospective method comparison study aimed to compare BP estimations from the Cuffless BP device with state-of-the-art oscillometric cuff BP as reference. Additionally, user acceptability was investigated with a questionnaire and automated sleep time prediction was investigated as an additional feature. We included both healthy volunteers and patients with hypertension, but no other co-morbidities. Inclusion criteria were age > 18 years and signed consent. Exclusion criteria were any form of CV, renal or pulmonary disease, diabetes mellitus of any type, interarm BP difference > 10 mmHg, inability to obtain cuff BP measurements, resting BP > 220/120 mmHg or difficulties with understanding Norwegian. In addition, populations considered special populations with regards to cuff BP measurements were excluded; pregnant, ongoing atrial fibrillation and old age (> 70 years). Participants were recruited from both Oslo University Hospital, Ullevål and from a general practitioner practice participating in the collaborative research project (Sandefjord Helsepark). Oslo University Hospital recruited both healthy volunteers and patients with a hypertension diagnosis from the same local hypertension registry as in Paper I. Sandefjord Helsepark recruited patients with an indication of 24ABPM.

Initially we aimed to include 85 patients, similar to the most up to date consensus protocol regarding BP devices (25). However, during the research project it became evident that more data were needed to develop more complex models for BP estimation. After approval from the regional ethics committee, the purpose of the study was changed to involve both pilot testing of potential cuffless BP methods and creation of a database in order to develop more complex BP algorithms. The analyses in this paper were a pilot investigation of the first 153 patients included using the current BP algorithm of PAT derived from the database in Paper I.

Study protocol and methods

Participants were fitted with the Cuffless BP device to obtain continuous measurements in ambulatory conditions. Reference BP was measured with a validated oscillometric ambulatory BP device (Oscar 2, SunTech Medical, Morrisville, North Carolina, USA) fitted with appropriate cuff size on the non-dominant arm. The device was programmed to take a measurement every 20 minutes during daytime (07:00-23:00) and every 30 minutes during night-time (23:00-07:00). The participants were asked to log sleep and awake times in a diary to allow for accurate daytime and night-time BP

calculations. Participants were thoroughly instructed to stop any ongoing activity and have the arm relaxed at heart level during cuff measurements. Prior to the ambulatory measurements, standardized office BP measurements were taken. Participants rested in a seated position for five minutes. Thereafter, three measurements were taken bilaterally, starting on the dominant arm. If the difference exceeded 7 mmHg between any of the first three measurements, a total of five measurements were taken. Standardized orthostatic BP measurements (standing after one and three minutes) were also taken to include different postures and BP related to postures.

Device acceptability of both devices were assessed with a self-developed questionnaire. Parts of the questionnaire were based on the “device assessment form” published with the British Hypertension Society validation protocol for BP devices in 1993 (57). The questions were translated to Norwegian and translated to a 7-point Likert scale. Pain and discomfort were investigated using a visual numeric rating scale. In addition, questions tailored to assess aspects of the Cuffless BP device were developed.

Cuffless BP estimations were calculated and averaged on two-minute windows corresponding to the timestamp of the reference cuff measurements. A-priori quality criteria to determine any participant's 24ABPM as valid or non-valid were; at least 70 % valid measurement pairs between the Cuffless BP device and the oscillometric device. A valid reference pair was defined as at least 70 % valid cycles from the Cuffless BP device within the 2-minute window. Cycle classification as valid or non-valid were based on complex data analysis performed by SINTEF Digital and Aidee health. However, due to unforeseen amounts of noise in the sensor data and periods of lost ECG contact, the initial criteria only yielded 7 valid participants. It was therefore decided to reduce the criteria to at least 40 % good reference pairs of which a good measurement pair was defined as at least 40 % valid cycles within the 2-minute window. Next, as PAT showed considerable variance resulting in non-physiological BP predictions, non-physiological values were considered outliers (SBP > 280 mmHg, SBP < 50 mmHg, DBP > 150 and DBP <30) and removed. Lastly, participants with < 25 valid measurement pars (approximately half of the mean number of ambulatory measurements) and participants with no valid night-time measurement pairs were excluded.

Both generation II and III of the Cuffless BP device was used in Paper III (Figure 7). Compared to generation I (which was used in Paper I), the device was miniaturized, and the ECG electrodes were incorporated in the belt. The PPG sensor was upgraded for improved signal quality. Generation III was similar to generation II, but had better belt quality, improved ECG sensors and further improved PPG sensors.

Figure 7. Generation II (left side) and generation III (right side) of the cuffless device.

Data analysis and statistical methods

Data processing was performed offline in a custom-built database by SINTEF Digital and Aidee Health. The classification of PAT measurements as valid or non-valid were based on more complex signal analysis tools compared to that of Paper I and II and is not included here. Processed data was further analysed using STATA (Statacorp., Texas, USA). The best linear fit PAT-based algorithm from the isometric exercise data from study I was implemented to estimate BP. Calibration, i.e., correction for the Y-axis intercept offset, was performed according to the average of the office BP measurements, minus the first, taken on the non-dominant arm.

Mean 24-hour, daytime and night-time values were calculated for each participant for the oscillometric BP device and the Cuffless BP device to compare the overall estimations. Normal distribution was assessed by visual inspection of histograms. Comparison of means were performed with paired t-tests. Agreement between the Cuffless BP device and reference BP was calculated using Bland-Altman plots with bias and 95 % limits of agreement (LOA). Correlation between cuffless BP estimations and reference BP measurements were computed with a repeated measures correlation analysis as proposed by Bland and Altman (58). Diagnostic accuracy according to 24-hour, daytime and night-time hypertension thresholds defined by the 2018 ESC/ESH Guidelines for the management of arterial hypertension (4) was investigated with sensitivity and specificity analyses. Comparison of patient acceptability of devices were presented with numerical and visual representation of the distribution of the answers. Based on the lack of correlation between PAT and BP, we formulated and

tested the following post hoc hypothesis: were the PAT calculations biased from ambulatory changes in the PPG signal? We assumed that the slope of the first upstroke in the PPG waveform could affect the PAT calculations by causing temporal shifts of the detection point (The crossing between the first minimum and the tangent of the first upstroke). Hourly averaged slopes were calculated for the same 2-minute windows as the BP predictions and compared with ANOVA with repeated measurements and by visual inspection. Hourly average PAT values were also computed for visual representation. An automated sleep and awake classification algorithm was trained using a decision tree classifier with optimal decision tree depth of 1-25 using leave one out cross validation. Each patient's self-reported sleep and awake times were used as reference in the training and validation. Input parameters in the model were accelerometer data and R-R intervals (various heart rate variability parameters) from the electrocardiogram.

Paper IV

Study design and population

The study was an observational method comparison study aiming to compare Cuffless BP estimations with that of continuous intra-arterial BP measurements in ICU patients. In addition, we aimed to investigate whether individualized and more complex methods to estimate cuffless BP compared to a general PAT-based model could improve cuffless BP estimations. Patients older than 18 years admitted to a general ICU were prospectively considered for inclusion. Inclusion criteria were an indication of invasive arterial catheter for BP monitoring and signed informed consent. Exclusion criteria were irregular RR intervals or any contraindication to having a chest belt fitted. Initially we aimed to include approximately 30 valid participants to evaluate the device performance and feasibility. Ongoing research in the project made it clear that more data was needed to allow for building more complex models and the study aims were changed, after approval from REK, to allow for more data to develop better cuffless BP models. The study aim for Paper IV was therefore also changed to investigate more complex individualized models in addition to the cuffless BP estimation based on PAT derived from Paper I.

Study protocol and methods

After having the Cuffless BP device fitted, included patients could be observed for a minimum of 1 hour and a maximum of 12 hours. Reference BP was measured continuously with a catheter inserted in the radial artery connected to a pressure transducer (Xtrans; Codan, Forstinning, Germany) via a saline filled tubing which had a counterpressure saline flush bag set to 300 mmHg connected. The pressure transducer was levelled at the phlebostatic axis by ICU staff and zeroed to atmospheric pressure every eight hours according to ICU procedures. The data collection was observed by an

investigator to reliably exclude periods of which the pressure transducer and phlebostatic axis moved relative to each other.

Data analysis and statistical methods

Data processing was performed offline in a custom-built database by SINTEF smart sensor systems and Aidee health. The classification of PAT measurements as valid or non-valid were based on more complex signal analysis compared to that of Paper I and II and is not considered here. Processed data was further analysed using STATA (Statacorp., Texas, USA). Two different BP estimation models were tested; A linear PAT-based model derived from the database of Paper I (generalized PAT-based model), which included a PAT-based model with a HR term as proposed in the literature (59), and a PAT-based model without a HR term (the same as in Paper III). The second model was an individually fitted and more complex model which was trained (using machine learning methods) on each patient's first half of data (complex individualized models). The second half of each patient's dataset was used to test accuracy of both models. Each model was calibrated with invasive reference BP at the beginning of each patients test period. If transducer levelling was altered during data collection, periods where the transducer was out of level was excluded. Additionally, if the levelling was altered during a patient's data collection, the models were re-calibrated with reference BP. Reference BP and both model predictions were averaged and compared on 15-second epochs.

Accuracy of the two models were assessed using mean absolute error and Bland Altman plots with bias and 95% limits of agreement. The correlation between model predictions and reference BP was investigated with repeated measures correlation coefficients. Comparison of the two different predictive models was done in several steps. First, we compared their error statistics numerically. Second, each participants average predicted BP was calculated and fitted in a linear regression model with average reference BP. The linear model for the generalized PAT based model was compared with the linear model from the complex individualized models numerically and with Akaike's and the Bayesian information criterion. Finally, we compared the models using the Diebold Mariano test. Since patient time series glued together may violate the stationarity assumption of this test, the Diebold Mariano test was also performed on each patient's data. The overall significance of the p values were tested using Fisher's method (60).

Results

Paper I

We investigated the ability of a cuffless chest belt device to measure PAT continuously during rest and two different exercise interventions and assessed its correlation with reference auscultatory cuff BP.

Of 80 participants, five participants were excluded because of difficulty with auscultation of Korotkoff sounds (n = 2), excessive noise in the acquired cuff less device signals (n = 1), vasovagal reaction during the test protocol (n = 1) and SBP at baseline above 180 mmHg.

We demonstrated that PAT was strongly and linearly correlated (mean (SD) of individual Pearson's correlation coefficients) to SBP during the full protocol (-0.82 (0.14)), isometric exercise (-0.79 (0.27)) and dynamic exercise (-0.80 (0.18)). Correlation with DBP varied from 0.25 (0.35) for the full protocol to -0.74 (0.23) during isometric exercise and 0.39 (0.41) during dynamic exercise. The individual regression coefficients calculated on an individual level between BP and PAT showed a clinically significant degree of variation, indicating that generalizability may be a challenge. In addition, mean of individual regression coefficients between PAT and SBP were significantly different between the two exercise methods.

Unpublished data from Paper I

Repeated measures correlation coefficients with 95 % confidence intervals are presented in Table 1. Slope transit time is defined as the time interval from start of first upstroke to first peak in the PPG waveform (59). PPG width at 80 % is the width of the PPG signal at 80 % of its height. PPG width at 40 % is the width of the PPG signal at 40 % of its total height. Diastolic time of the PPG signal is the time interval from peak to second minimum. Ratio of width at 80 and 40 is the ratio between the width at 80 % and 40 % of its height. Photoplethysmogram intensity ratio is the value of the peak of the PPG signal divided by the value of the minimum of the same PPG signal. The results illustrate how different potential cuffless surrogate measurements were correlated to changes in SBP during the test protocol, of which PAT proved to be superior. Mean absolute error and its standard deviation of the internal validation data from the linear regression and multiple linear regression models are presented in Table 2. The simple linear regression models were marginally less accurate in all test protocols regarding both SBP and DBP except during rest. The polynomial regression model and multilayer perceptron model (a feed forward neural network) were less accurate compared to the linear and multiple linear models and are not considered here. These results were not considered for publication due to the confidentiality of potential BP prediction models (unpatented). It was considered at the time being best to not publish data directly related to models. However, as these models are not part of confidential BP models at present time, they fit well in the thesis to provide a better understanding of the progression of the research project.

Table 1. Correlation between potential cuffless surrogate measurements and systolic blood pressure (unpublished data).

Surrogate measurement	Repeated measures correlation coefficient between surrogate measurement and systolic blood pressure (95 % CI)
Pulse arrival time	-0.79 [-0.80, -0.78]
Slope transit time	-0.57 [-0.59, -0.55]
PPG width at 80 %	-0.26 [-0.29, -0.23]
PP width at 40 %	-0.44 [-0.46, -0.41]
Diastolic time of the PPG signal	-0.63 [-0.65, -0.61]
Ratio of width at 80 and 40	0.14 [0.11, 0.17]
Photoplethysmogram intensity ratio	0.41 [0.38, 0.43]

Table 3. Validation results of the linear regression model and the multiple linear regression model. Unpublished data.

Protocol	Seated rest only		Isometric exercise only		Dynamic exercise only		Full protocol (periods of seated rest, isometric exercise and dynamic exercise)	
Regression model	Linear	Multiple linear	Linear	Multiple linear	Linear	Multiple linear	Linear	Multiple linear
SBP, mean absolute error (SD), mmHg	6.06 (5.76)	6.11 (5.06)	18.77 (5.31)	17.89 (4.4)	18.29 (8.52)	16.39 (6.13)	11.73 (4.64)	11.03 (4.09)
DBP, mean absolute error (SD), mmHg	4.3 (1.85)	4.59 (1.89)	12.96 (4.75)	12.59 (5.51)	10.6 (4.84)	9.92 (5.03)	7.51 (1.97)	7.37 (2.01)

Paper II

We investigated PAT as a potential cuffless measurement to enable continuous measurements of BP during lactate threshold and maximal VO2 exercise cycle ergometry testing in well trained male athletes (age 32.4 ±9.4 years; maximal oxygen uptake 63 ± 10 ml/min/kg). Three participants had to be excluded from the PAT analyses due to device failure (n=1) and excessive noise (n=2). PAT showed

very strong linear relationships with SBP, with a mean (SD) of individually calculated coefficients of determination (R^2) of 0.81 (0.17). Similarly, to the results from Paper I, the regression slopes varied between individuals, reflected in the mean of -0.72 ms/mmHg with an SD of 0.37 ms/mmHg. The results from the main aim of the study supported the body of literature that has indicated exaggerated SBP responses in athletes. Peak aerobic exercise SBP showed a mean (SD) of 231 (18) mmHg at workloads of 403 (61) watts during the final step of the Vo2 max test.

Paper III

We investigated accuracy of the Cuffless BP device (using a PAT-based model) against standard cuff-based BP measurements during 24ABPM, patient acceptability and automated sleep time predictions. Additionally, post-hoc analyses were performed to investigate if changes in the PPG signal during ambulation could explain the observed poor agreement during ambulation and particularly night-time. Sixteen patients were excluded due to interarm BP difference > 10 mmHg, 33 patients were excluded due to having less than 40 % measurement pairs of adequate quality between the Cuffless BP device and reference BP, seven participants were excluded due to having less than 30 measurement pairs and finally two patients were excluded because of no valid night-time measurements.

Results of mean Cuffless BP device measurements compared to mean of reference BP during 24-hour, daytime, and night-time for all participants and in the subgroups of participants with and without a previous history of hypertension are shown in table 3. The PAT based model consistently and significantly overestimated BP, particularly night-time BP. Bland Altman bias [95 % LOA] between the Cuffless BP device SBP and the oscillometric cuff SBP were 7.9 mmHg [-23.3, 39.2 mmHg], 3.9 mmHg [-26.7, 34.6 mmHg] and 18.8 mmHg [-20.9, 58.4 mmHg] for 24-hour, daytime, and night-time respectively. Corresponding results regarding DBP were 6.9 mmHg [-10.8, 24.5 mmHg], 3.3 mmHg [-14.3, 20.9 mmHg] and 16.7 mmHg [-6.1, 39.5 mmHg]. Repeated measures correlation coefficients for 24 hours were 0.06 ($p < 0.001$) and -0.01 (p 0.51) regarding SBP and DBP respectively. Additionally, repeated measures correlation was calculated between PAT and HR for the thesis (unpublished data), which showed a coefficient of 0.20 ($p < 0.001$). Sensitivity and specificity analyses, taking the European hypertension guidelines as diagnostic threshold for hypertension, showed a sensitivity of 85.7 % and 96.0 % regarding SBP and DBP for 24 hours and a specificity of 60.0 % and 65.7 %. Specificity of night-time diagnostic accuracy was only 44.9 % and 23.3 % for SBP and DBP respectively.

Table 3. Mean of reference blood pressure measurements compared to mean of estimated blood pressure from the Cuffless BP device.

	All participants (n=95)			Subgroup with hypertension (n = 45)			Subgroup without hypertension (n = 50)		
SBP, mean (SD), mmHg	Reference BP	Cuffless BP (PAT-based BP model)	P	Reference BP	Cuffless BP (PAT-based BP model)	P	Reference BP	Cuffless BP (PAT-based BP model)	P
24-hour	125.4 (14.8)	133.3 (21.1)	<0.001	131.4 (14.9)	143.5 (21.3)	<0.001	120.0 (12.6)	124.2 (16.3)	0.016
Daytime	129.7 (13.8)	133.6 (20.9)	0.017	135.5 (13.4)	143.8 (21.0)	0.003	124.6 (12.1)	124.5 (16.1)	0.967
Nighttime	113.1 (16.5)	131.9 (23.4)	<0.001	120.1 (17.9)	141.7 (24.4)	<0.001	106.8 (12.3)	123.0 (18.6)	< 0.001
DBP, mean (SD), mmHg									
24-hour	74.3 (9.0)	81.2 (12.5)	<0.001	77.2 (9.2)	85.6 (13.1)	< 0.001	71.7 (8.2)	77.1 (10.5)	< 0.001
Daytime	78.0 (8.5)	81.3 (12.6)	<0.001	80.5 (8.7)	85.8 (13.2)	0.001	75.7 (7.8)	77.3 (10.5)	0.132
Nighttime	63.8 (10.0)	80.5 (13.2)	<0.001	67.9 (10.0)	84.8 (14.2)	<0.001	60.1 (8.5)	76.6 (11.1)	< 0.001

The Cuffless BP device was more accepted by the participants. The majority indicated that the Cuffless BP device did not disturb sleep or interfered with daily activities, while the majority indicated the opposite regarding the cuff device. Approximately 91 ± 5 % would have chosen the chest belt for a repeat 24ABPM. The sleep time classifier was 91 ± 5 % accurate and kohens kappa was 0.78 ± 0.14. The predicted sleep windows were overestimated by a median 10 minutes with interquartile range from –32 - 43 minutes. Contrary to our hypothesis, the slopes of the PPG signal were steeper during night-time, ($p < 0.001$, ANOVA), and could not explain the inability of the PAT-based model to estimate BP during ambulation.

Paper IV

Accuracy and agreement of the Cuffless BP device's PAT based algorithm was investigated in critically ill patients admitted to ICU with invasive BP measurements as reference. As an effort to improve the Cuffless BP device beyond that of using PAT-based algorithms, individually fitted and more complex models utilizing other aspects of the PPG signal were computed and compared to the PAT-based algorithm.

Twenty-five of 44 patients were included in the study analyses. Six patients were excluded prior to the formal study analyses due to excessive noise (n=2), arterial catheter failure (n=2), irregular RR intervals (n=1) and erroneous vital recorder data capture (n=1). In the formal analyses, further 18 patients were excluded by criteria defined to ensure valid data to develop the machine learning

models (n=18). These criteria were defined to ensure enough training data and enough BP variation both in the training part of each dataset.

The individualized machine learning models utilizing aspects of the PPG signal rather than PAT, showed significantly better predictions regarding SBP (p = 0.001) and MAP (p = 0.006), but not DBP (p=0.14). Mean absolute errors and SD of the errors for the PAT based model compared to the individualized machine learning models were 7.6 (7.2) mmHg vs. 6.5 (4.8) mmHg regarding SBP, 3.3 (3.1) mmHg vs. 3.1 (3.0) mmHg regarding DBP and 4.6 (4.4) mmHg vs. 4.0 (4.0) mmHg regarding MAP. Importantly, the repeated measures correlation coefficients favoured the individualized machine learning models compared to the PAT-based models; 0.39 vs. 0.23 regarding SBP, 0.33 vs. 0.29 regarding DBP and 0.37 vs. 0.25 regarding MAP. The PAT-only model (without a HR term) provided almost identical results to the model that included a HR term, indicating that the HR term did not affect the model significantly. Agreement between the PAT-HR model and the PAT-only model revealed a bias of -0.4 mmHg with 95 % LOA of -2,9 to 2.7 mmHg. It became apparent during data inspection that the PAT-based models appeared to be affected by HR changes during periods of increased HR and decreased BP. In contrast, the individualized machine learning models were not similarly affected.

Discussion of main findings

General results aspects

"True" PTT from central arteries has been demonstrated to correlate strongly with changes in BP in experimental animal models (50, 61). Furthermore, non-invasive measurements of PWV or pulse wave propagation times showed promise towards cuffless BP measurements (62-64). Thus, we hypothesised that PTT could be measured at chest level using ECG, ICG and PPG and that chest level PTT could track changes in BP after initial calibration. However, the current research project could not develop methods to reliably estimate PTT using an impedance cardiography signal. PAT measured at chest level showed strong correlations with SBP during exercise induced BP changes in Paper I and II. Despite variation of the individually calculated regression slopes between PAT and SBP between individuals and between exercise modalities, a BP estimation model based on PAT showed promising results regarding SBP when trained and validated on the database from Paper I (unpublished data presented in this thesis). Contrary to our hypotheses, a PAT-based BP model derived from the database in Paper I was not able to track BP changes measured by standard 24ABPM cuff. There was almost no correlation between PAT and BP during 24ABPM and the PAT-based model failed to detect nightly dipping patterns. The participants, however, favoured the Cuffless BP device compared to the cuff device. The PAT-based algorithm also failed to achieve accurate results compared to continuous

intra-arterial BP measurements in ICU patients. Of particular interest was the PAT-based models' tendency to correlate with HR in both in Paper III (unpublished data) and Paper IV (Both the model with and without a HR term). Although we did not formally test this in this thesis, our results indicate a lack of ability to detect clinically relevant episodes of hypotension accompanied by tachycardia. The combined results of this thesis suggest that PAT (measured at chest level) is not a robust cuffless surrogate measurement for 24ABPM and monitoring of hospitalized patients. However, in Paper IV, machine learning models utilizing other aspects of the PPG signal outperformed the PAT-based model. Thus, more advanced models utilizing machine learning could overcome the limitations we found investigating a PAT-based model. Additionally, our sleep prediction analyses in paper III indicated that cuffless BP devices can provide additional features such as automated sleep detection to improve hypertension management.

Paper I and II

Difficulties in calculating PTT has been demonstrated by others (64, 65). Proença et al. concluded that the measurement uncertainty of PTT calculated using ICG was unsatisfactory with respect to the magnitude of BP error these uncertainties would correspond to (65). There is also a substantial amount of research that has shown difficulties in detecting the fiducial points in the ICG waveform that corresponds to the opening of the aortic valve (44). In addition, publication bias likely exists in which research unable to calculate PTT with sufficient accuracy remain unpublished. Furthermore, difficulties of robust calculations of PTT have likely contributed to conflicting results regarding PTT as a surrogate BP measurement (64, 66). The short duration of PEP of around 100 milliseconds limits measurement accuracy of non-invasive sensor-based methods because of measurement error. Conversely, studies have reported promising PTT-based BP estimations in a laboratory setting using continuous wave radar to detect aortic valve opening (67) and thoracic impedance signals (68), and studies have also investigated seismocardiogram (accelerometer-based detection of the aortic valve opening) or phonocardiogram (sound-based detection of the aortic valve opening) (69).

Due to the simplicity and availability of PAT measurements compared to PTT, many studies have investigated PAT as a potential cuffless surrogate feature. Our results of strong intra-individual correlations between PAT and SBP are similar to most studies (66, 68). Regarding DBP, many reported strong correlations however with more variability compared to SBP (66). A strength in Paper I was the demonstration of inconsistent results regarding DBP compared to the majority of similar studies who often reported good correlations between PAT and DBP. The changing relationships between PAT and SBP across different hemodynamic conditions have also been shown by others. In one study, a hysteresis effect was found in which the PAT-SBP relationship showed a significant y-axis intercept shift between dynamic exercise and recovery, meaning that for the same SBP, PAT measurements

were shorter during recovery (70). Post hoc inspection of individual data from Paper I revealed that there might be such an effect present during recovery after the cycle ergometry, in which for the same SBP, PAT was shorter. Although not investigated by us nor in (70), this effect could be explained by an elevated HR post-exercise, possibly in combination with altered vasomotor tone.

One study that used cycle ergometry to induce BP changes reported a repeated measures correlation coefficient of 0.83 between estimated (based on PAT) and measured SBP (manual auscultatory) (46). This was stronger than our mean of individually calculated Pearson's correlation coefficients of 0.77 during dynamic exercise in Paper I and repeated measures correlation coefficients would have been lower compared to calculating Pearson's correlation coefficient in each individual and taking the mean. However, in paper II, the mean R^2 was 0.81 (= mean Pearson's correlation coefficient of 0.90). We interpreted the better correlations between PAT and SBP observed in Paper II compared to Paper I to possible be a result of the increased exercise intensity in addition to the larger increases in SBP in Paper II. The increased exercise intensity likely affected PAT to shorten by exercise intensity dependent shortening of PEP (71) and by increased sympathetic tone during maximal exercise compared to submaximal exercise in Paper I. Contrary to us, (46) found a better fit with non-linear functions which we did not see in our data in Paper I and II. Non-linear functions were also reported in other studies (72, 73) and in experimental animal models of aortic PTT measurements (50). On the other hand, studies have also reported linear associations (68, 74). Similarly to us, (46) trained a BP prediction model on one cohort and tested it on a different cohort using the same method (cycle ergometry) to induce BP changes both in the training and testing data. Their agreement regarding SBP of +/- 19.8 mmHg was comparable to our SBP predictions made in a similar way on 10 participants selected at random. We found a mean absolute error (SD) regarding SBP of 18.29 (8.52) mmHg during the dynamic test and 11.73 (4.64) mmHg for all datapoints in the protocol (rest, isometric exercise and dynamic exercise).

The use of pulse wave propagation times to non-invasively estimate BP has extensively been researched in the last decade. The results, mainly from small studies in laboratory settings, reflect the complexities involved in this research field; variations in sensor signal type and locations, signal processing methods, reference BP method, study population and method or methods (or the lack of) to induce BP changes. Thus, comparing methodologies and results between studies is difficult. One study also demonstrated a differential response of PAT measured simultaneously at three locations (ear, finger, and toe) to various BP altering methods (75). While both finger PAT and toe PAT decreased during a cold pressor test, finger PAT decreased and toe PAT increased in response to nitro-glycerine. Although the theory, animal models and some human experiments (76) suggest that central aortic PWV or pulse wave propagation times could be a robust surrogate BP measurement,

the main challenge is the lack of accurate methods to obtain robust central aortic measurements. Furthermore, the effect of HR on PWV needs to be further elucidated.

Paper III

Based on the findings from Paper I of strong correlations between PAT and SBP (and DBP during isometric exercise), we investigated if a PAT-based model could be used in tracking BP changes in 24ABPM (Paper III). During ambulatory conditions compared to conventional cuff 24ABPM, the Cuffless BP device was unable to track BP changes. Although the PAT-based algorithm estimated BP accurately in some individuals, it failed to detect the nightly dip and there was no correlation between estimated BP from the Cuffless BP device and cuff BP on a group level. This was surprising as both BP and HR decrease during the night, and therefore we expected correlations with ambulatory changes in BP and HR. Additionally, PEP is reported to lengthen during sleep (77), which corresponds to lower BP predictions. This means that night-time changes in PEP could not explain the observed ambulatory PAT measurements. We further investigated (post hoc) if ambulatory changes in the PPG signal, reflected in the slope of the first upstroke, could explain this finding. Contrary to our hypothesis that a less steep slope during night-time could cause biases in the PAT calculations, we found that steepness of the first upstroke of the PPG signal increased during night-time. Thus, we interpret the changes in slope not to affect the PAT calculations. Our findings during 24ABPM were in agreement with most other research that has investigated cuffless BP devices compared to oscillometric cuff measurements during 24ABPM (78-83). All except from the device from (81, 83) failed to detect night-time hypotension, including devices that utilize a PAT-based algorithm (82) and waveform analysis of the PPG signal alone (78). Although they did not report correlation coefficients corrected for repeated measures, we postulate that their results would have been similar to ours. Study populations were similar, including both healthy volunteers and patients with uncomplicated hypertension. We performed subgroup analyses regarding healthy volunteers and patients with a previous diagnosis of hypertension and found no interaction with respect to accuracy.

Device preference was in favour of the Cuffless BP device during 24ABPM. Patients reported minimal disturbances during daily life and sleep but reported the cuff to disturb both during sleep and daily activities. More than 90 % would prefer a repeat 24ABPM with the Cuffless BP device. Although these findings were not surprising and potentially biased by wearing both devices at the same time, it is important to recognize that patients find the cuff uncomfortable which can affect compliance to follow up. In addition, there is likely stigma associated with having to wear a bulky and noisy cuff device that inflates throughout the day. Others have also found that patients strongly prefer wearable devices that can measure without disturbance and interference (84).

Paper IV

The PAT-based algorithm achieved better results in hospitalized ICU patients compared to the results in 24ABPM in Paper III. Ninety-five % limits of agreement regarding SBP were [-21.5, 21.1 mmHg] compared to [-23.3, 39.2 mmHg] and repeated measures correlation coefficient of 0.39 versus 0.06. This difference emphasises that device signals and estimations of BP based on PAT calculations are difficult to infer from controlled settings such as in Paper I, II and IV, to the ambulatory conditions of Paper III. It should also be taken into consideration that cuff measurements are more susceptible to erroneous readings during ambulatory conditions compared to cuff measurements or invasive measurements in more controlled settings. It is for example unlikely that cuff measurements are at the same height relative to the heart throughout 24 hours.

Our results regarding agreement between the Cuffless BP device and continuous intra-arterial BP in hospitalized patients were comparable to the few existing similar studies (85-88). The Cuffless BP device investigated in the thesis achieved the least narrow LOA, but direct comparison of results is difficult. Study populations vary along with the number of included participants and length of observation in each participant. Most importantly, none of the comparable studies reported any statistic reflecting the degree of correlation between reference and estimated BP within participants. This is rather important as all devices at present need calibration at start, thus tracking of BP across time is what matters. Collectively, the results from our study on ICU patients together with similar research, there is an indication that cuffless BP may provide satisfactory accuracy in the future.

To shed light on future aspects of cuffless BP monitoring we performed a proof-of-concept analysis on the data collected on ICU patients. More complex aspects of the PPG signal were trained using machine learning methods using each patient's own data. One might argue that the comparison was unreasonable since we compared a PAT-based algorithm derived from a different dataset with individually fitted models. However, the machine learning training were also provided PAT as a parameter, but it was never included in the models, indicating that individually fitted PAT models would not achieve better results. However, this was not formally tested. Agreement between predicted BP and reference BP was improved to a smaller degree, but the overall correlation between predicted and measured BPs were significantly improved. We believe this can partially be explained by calibration. After initial calibration, if you have two parameters with little variation, statistics will provide excellent bias and narrow LOA. The individually fitted machine learning models showed better co-variation with the underlying BP variations. Importantly, the machine learning models were less dependent on HR.

Machine learning approaches have been extensively applied in the field cuffless BP research, but most often in publicly available vital signs databases such as the Multiparameter Intelligent Monitoring in Intensive Care databases and the Vital Recorder Database (89, 90). Although they allow for big data computing of recorded signals, there are some major limitations. Equivalent signals of ECG and PPG to assess for cuffless BP is heavily processed and filtered by automated algorithms and raw unfiltered signals are not available. This makes inference of features and associations found in such databases to cuffless devices difficult. Further, there are many unknown variables in the databases. For example, movements of the pressure transducer may introduce false BP alterations which will heavily influence the data analysis.

Potentially serious limitations in PAT-based algorithms were observed in the ICU data from study IV. While not formally investigated in the thesis, we observed that PAT-based predictions correlated more strongly with changes in HR than with changes in BP in cases where BP decreased while HR increased. Therefore, it is important to mention because of the potential implications in the use of pulse wave transit time-based approaches to cuffless BP. In Paper I, HR was not better correlated with PAT than BP, and in the 24ABPM study we did not clearly observe this effect, although PAT correlated more strongly with HR than BP in the dataset (unpublished data). Repeated measures correlation coefficient between PAT and HR was -0.20 compared to -0.06 between PAT and SBP. There is a growing body of literature in support of a BP independent effect from HR on PWV, investigated both in animal models and humans (91-95). The mechanisms are poorly understood. Proposed explanations attribute change in elastic recoil time and change in arterial wall viscoelastic properties with changes in HR. The effects of HR on PWV have been studied because of the implications on PWV as an independent CV risk factor (96) and thus HR as a potential confounder is important. Although there is conflicting evidence (94), this effect may have confounded our use of PAT as a surrogate BP measurement. Thus, we would have expected better results during 24ABPM because of expected correlations between PAT and both HR and BP during 24ABPM in Paper III. It has also been demonstrated in animal models that increased HR or stroke volume is associated with shortening PEP (97). Schaanning et al. investigated the ability of PAT to track changes in BP in an online database consisting of ICU monitoring signals and pointed out that PAT could be confounded by this in cases where increased HR or stroke volume compensate for vasodilatory or volume depleted states (98). It is likely that the same effects were observed in our ICU data. This effect, in addition to the HR effect on PWV, limits the use of PAT as a surrogate measurement to track changes in BP. Several confounding effects possibly contributed to very strong correlations observed between PAT and BP during BP alteration induced by exercise where BP, HR, PEP and sympathetic activation all contribute to a shortening of PAT.

Methodological considerations

General methodological considerations

Sample size considerations

A limitation of the research in this thesis is the lack of sample size calculations. Sample size calculations are important in research for two reasons. First, to ensure that the null hypothesis is accepted or rejected accurately and thereby detect the effect size. Rejecting the null hypothesis when it is true is called a Type I error. Alpha level, or significance level, is the probability level of which we are willing to falsely accept a null hypothesis, and is typically set to 5 %, i.e., there is a 5 % risk that the results are due to chance and not the intervention. Accepting the null hypothesis when it is not true is called a type II error and its risk of happening is referred to as power, or 1-beta. The power of a study depends on the effect size and sample size and describes the probability that a true difference will be detected. Second, appropriate sample prevents too many participants to be exposed to any risk associated with a study and an adequate use of resources.

The main reasons for not calculating sample sizes were the non-interventional design and pilot nature of the studies. Thus, effect sizes and their standard deviations were not clear in the planning phase. Large uncertainties of the input variables (the effect estimate and its SD) in the mathematical sample size calculations have large impacts on the calculated sample size and they assume some cut-off of acceptable vs not acceptable power and alpha levels, while it is in reality a continuum of probabilities. Furthermore, Paper III and IV classify as method comparison studies comparing a potential new method of BP measurement to a reference method (99, 100). J. M. Bland and D. G. Altman published their first paper on how to investigate agreement in method comparison studies in 1986 using bias and LOA (101). This method has been widely accepted as the appropriate statistical method. Their work was inspired by the widespread and faulty use of correlation and regression to determine agreement between methods.

Agreement as proposed by Bland and Altman is relevant to method comparison of BP measurements because due to inherent limitations of all BP measurement methods, the true value must be assumed unknown and varying. Thus, quantifying the agreement between methods is more relevant than assuming that the new method is compared to a true value. Bland and Altman also stated that in method comparison, a quantification of the agreement is the appropriate approach rather than hypothesis testing using such methods as a t-test comparison of means (99). Ideally, acceptable limits for agreement should be decided in advance, and sample size calculations could be based on assumptions regarding SD of the differences between the methods and the clinically accepted confidence intervals of the 95 % LOA (102). However, sample size calculations in agreement studies

following the 1986 publication were given little consideration resulting in most studies not performing any sample size calculations (103, 104). Bland and Altman considered 100 participants a good sample size (102) which may have contributed to many studies approximating 60-100 participants (104). Methods to calculate sample size in method comparison studies have since then gained more attention (105).

Study I (Paper I) was a pilot study to assess possible cuffless surrogate measurements by the Cuffless BP device and to develop models to estimate BP from these features. Thus, determining a clear effect size and its standard deviation was difficult. There were few similar studies identified at the planning phase. We found one study with a similar aim of both developing and testing a PAT based BP algorithm using exercise to induce BP alterations (46). They did not perform any sample size calculations and included 63 participants. The justified sample size was determined to be 80 participants in study I. This was a result of the time available to include participants, consensus agreement within the study regarding testing of multiple cuffless surrogate measurements and development and testing of cuffless BP models.

In Paper II, the main aim was to investigate the SBP response during a maximal VO2 test in well trained male cyclists and the sample size was determined regarding this aim, and not the secondary aim of assessing correlations between PAT and SBP. The sample size of 18 was a pragmatic consideration within the time frame available of the study with respect to the main aim.

Paper III was a pilot method comparison study between a PAT-based model, derived from the data in Paper I. Only one similar study existed at the planning phase of study III (82). It included 71 participants, and no sample size calculations were performed. Originally, sample size was determined to be 85 participants to reflect the most up to date consensus protocol regarding non-invasive BP measurement devices and compare results using their acceptance criteria (25). Although these considerations were based on the comparison of a potential new cuff method with that of dual auscultation during seated rest, we considered that in a pilot investigation, it was appropriate to extrapolate these considerations to our study design. There are however some caveats to this approach. Cuffless BP methods are at present dependent on calibration with a known BP value, and it is the estimation of relative changes that is considered. Thus, validation methods applicable to cuff-BP devices are not appropriate for cuffless BP devices. This is also recognized by the protocol developers, but no consensus regarding cuffless BP devices existed at the time of the research conducted in the thesis. Furthermore, statistical considerations regarding measurement variability of seated rest compared to ambulation may be too strict. This is illustrated by a recent study examining

simultaneous 24-ABPM in both arms which showed large LOA between the two cuff devices (over 35 mmHg for daytime and over 27 mmHg for nighttime SBP) (106).

It became evident during the research project that simple models based on PAT were inaccurate. After approval from REK, the aim of the study was changed to include more participants to build a database for model development and pilot testing of models. Thus, Paper III included the first 153 participants in the database to test the PAT-based algorithm developed from Paper I.

Paper IV was also a method comparison study aimed to compare a PAT-based cuffless BP estimations with continuous intra-arterial BP in ICU patients. Effect sizes and their variations were not clear and more importantly, no prior considerations regarding acceptable agreement (bias and 95 % LOA) existed regarding non-invasive in-hospital BP monitoring in ICU patients. At the time of the study planning, only one similar study existed which had included 31 participants (85). Therefore, the justified sample size was originally decided to be approximately 30. This was based on the time frame of the study, availability of eligible patients in the ICU, the pilot observational nature of the study and the possibility to compare with similar studies. However, the aim of this study was also changed after realizing that more data was needed to develop more complex models and the analyses in Paper IV was a pilot investigation of the first 44 included participants with the added aim to investigate more complex models beyond that of PAT using machine learning methods.

Repeatability

We did not assess repeatability of the reference BP methods used or the cuffless BP surrogate measurements and BP estimations based on the PAT-based model. Validity of method comparison using Bland and Altman agreement is dependent on each methods repeatability (101). If one or both methods compared have poor repeatability, agreement will be poor. This is particularly important regarding the reference method. Although reference BP methods are generally considered to have acceptable repeatability, it is dependent on the method used and clinical setting. The method with the lowest repeatability of those used in the thesis was exercise DBP, while exercise SBP is considered to have acceptable repeatability using both auscultatory and automated electronic Korotkoff sound detection (4, 107). Office BP measurements are generally considered less reproducible compared to out of office BP measurements using home BP or 24ABPM (4, 108-110). Intra-arteria BP measurements, investigated during 24ABPM have also shown satisfactory repeatability (109, 110).

A retrospective analysis of repeatability was performed to investigate this methodological aspect. Repeatability of a method can be assessed using the agreement method as proposed by Bland and Altman (101). The two last office BP measurement pairs from Paper III were considered to have steady state and repeated measurements within a short time span. The mean SBPs of these two

measurements for both the reference device, and the PAT-based BP estimations were plotted against their differences along with bias and limits of agreement (Figure 8). Considering the underlying variability of the true value of SBP, of which we cannot measure, and the reproducibility of office BP known to be limited, repeatability of the reference cuff device was acceptable and comparable to the repeatability in a similar setting reported by other studies (111). The 95 % LOA of the PAT-based repeatability was worse and included some obvious outliers. However, the difference in reproducibility in the PAT-based estimates likely explain some of the agreement results from Paper III and IV.

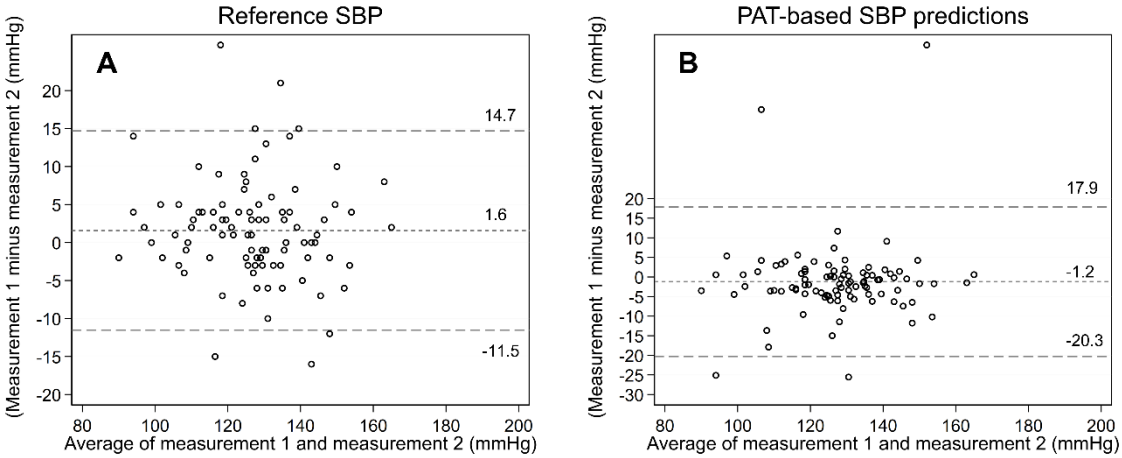

Figure 8. Bland Altman bias and 95 % limits of agreement between the two last office blood pressure measurements in Paper III. A is the results from the oscillometric reference BP device, and A is the results from the cuffless BP estimations.

Reference blood pressure measurements

Accuracy and reliability of BP measurements depend on the method used and setting of measurement. Each method has strengths and limitations, and they do not necessarily measure the same. Therefore, a strength in this thesis was the use of several reference BP methods in different measurement settings. This allowed for thorough assessment of the possible relationship or lack of relationship between PAT and PAT-based BP estimations compared to the different reference BP methods and clinical settings.

Considering the known heterogeneity of BP measurements, the comparison of BP estimates from signals recorded on the chest with that of measurements taken indirectly at the brachial artery (Paper I, II, III) and directly from the radial artery (Paper IV) may have introduced biases in the results. We could have assessed this by also recording PAT to the brachial artery level, optimally at the same arm, or the contralateral arm. However, this was not possible. In Paper III, the effect of differing BP measurements across various places in the CV system was minimized by excluding participants with an inter-arm BP difference larger than 10 mmHg.

In Paper I, auscultatory sphygmomanometer was used. There is no consensus regarding optimal reference BP method during exercise. Both the 2018 and 2023 European guidelines on arterial hypertension recommend that only SBP can be measured during exercise (4, 112). SBP has been shown to have acceptable repeatability during cycle ergometry (107, 113). Still, SBP is consistently under-estimated compared to intra-arterial measurement during cycle ergometry (114). DBP remains the least accurate method during exercise of methods other than intra-arterial BP measurements. In this light, it should be noted that the newly published recommendations regarding validation of cuffless BP devices recommend dual auscultation as reference during cycle ergometry to measure both SBP and DBP (115). There is little research regarding accuracy of manual auscultatory measured SBP and DBP during isometric exercise compared to intra-arterial BP as a reference. Theoretically, accuracy should be better during isometric exercise compared to cycle ergometry or treadmill exercise due to less movement and less noise. One small study found both SBP and DBP to be in reasonable agreement compared with intra-arterial BP measurements (116). There is a myriad of small studies comparing various methods with each other, of which all tend to produce fairly large LOA. This is likely a reflection of methodological differences and measurement method specific imitations. For example, auscultatory measurements compared to intra-arterial measurements in 25 patients during anaesthesia showed large limits of agreement of +/- 22 mmHg for SBP and +/- 19 mmHg for DBP (117).

Nonetheless, the use of auscultatory BP as reference in Paper I introduces some limitations, particularly regarding the accuracy of DBP during cycle ergometry. We argue that it was appropriate within the aim of the study as a pilot investigation and that the conclusions would not be different with the use of an intra-arterial reference. Intra-arterial BP as reference was not possible due to ethical considerations. In addition, intra-arterial measurement accuracy is dependent on optimal operating conditions, as is discussed earlier in this thesis. Prior to the data collection of Paper I, the research project collected data during repeated isometric handgrip using a volume clamp (vascular unloading) device (118), but it was not possible to use due to drift (the measurements trended towards lower BPs which could not reflect the participants BP) in the continuous non-invasive volume clamp measurements (unpublished data).

The auscultatory reference measurements were performed by the same investigator, which is a strength. Reliability of this investigator's measurements were tested by comparing measurements during exercise (on the same participant, but at different times) with that of a colleague prior to the study measurements. The BP device with accompanying cuffs of all sizes were verified to produce accurate pressure recordings throughout a wide range of pressures compared to a standardized pressure instrument prior to its use in the study.

In study II, a dedicated exercise cuff using a microphone gated to the R-wave in an ECG to detect Korotkoff sounds was used. This is at present the standard equipment used to measure the BP response during cardiac stress testing. Still, only the SBP measurements are considered valid. The findings of PAT and reference SBP and DBP was reproduced in Paper II, but with a different method.

In study III, the reference BP method was an oscillometric electronic cuff apparatus intended for ambulatory measurements (119). The strength of this study was a thorough comparison with state-of-the-art out of office BP measurements. A limitation with all ambulatory cuff devices is their validation only during steady state conditions at rest and not during 24 hours of ambulatory use (25, 119). Validation during 24ABPM is not feasible, and this limitation is therefore considered acceptable.

Blood pressure models

PAT is one variable, measured from each cardiac cycle and averaged over a number of cardiac cycles, while BP is reported as the SBP and DBP, corresponding to the maximum and minimum detected by the flow phenomenon of Korotkoff sounds, detection points by proprietary algorithms from the oscillometric signal, or the arithmetic peak and bottom of the pulse wave recorded by a pressure transducer connected to an intra-arterial catheter. In addition, MAP (the arithmetic mean of the intra-arterial waveform) is often used with intra-arterial BP measurements. If PAT could estimate all BP variables, an underlying assumption would be that all BP parameters that we commonly use (SBP, DBP and MAP) were linearly correlated. However, they are not. It is not clear whether PWV or pulse wave transit times, assuming that all parameters that affect these measurements expect BP remain unchanged, is more closely related to MAP, SBP, DBP or if PP plays a role. It is difficult to study these relationships because of the complex nature of the CV system in combination with difficulties in measuring all relevant variables. Conflicting results are found in the literature. One study with the aim to determine which hemodynamic variables was most closely related to changes in PWV found MAP in addition to HR and systemic vascular resistance to be most important (120). Another study assessed correlation in a large database perioperative data and found PP followed by SBP and MAP to have the strongest correlations with pulse arrival time (121).

For the purpose of exploring the feasibility of PAT, a linear correlation was assumed in the models, meaning that the difference in estimations of DBP rather than SBP were the coefficient in a linear $y = ax + b$ model. The offset, i.e., intercept was adjusted for by calibration and were thus not meaningful. Comparable studies do not disclose how they model PAT to both SBP and DBP, but we assume that they predict DBP from the same PAT measurement as used to predict SBP (81, 82). Based on the findings from Paper I, one could assume that PAT-based BP measurements would depend on individually calibrated BP models, such that any individual's relationship between PAT and BP had to

be fitted into the algorithm. However, not only is this impractical, but the results from Paper III and IV indicate that individualized PAT models would not work. In Paper III there was almost no correlation regarding PAT and BP, and in Paper IV, correlation was small and potentially biased by a confounding HR effect.

In Paper IV, two different PAT-based models were evaluated of which one included a HR term. Although this as a proposed method in the literature (59), it is obvious that this will create a dangerous bias in the model when used in hospitalized potentially unstable patients. In Paper IV, we also tested individually fitted machine learning models. A limitation is that we could not report, due to confidentiality of BP models, which parameters were used.

Cuffless blood pressure device development

The Cuffless BP device was undergoing development throughout the course of the research project. These were pre-planned developmental milestones to optimize the device in terms of design and sensor performance. The major difference between generation I and generation II and III was the removal of the ICG module. This decision was taken by the developers because it was not possible to use the ICG signals in any meaningful way within the time frame and expertise available. It should be noted that a considerable effort on this matter was made by the data analysts and engineers at SINTEF Digital. It was difficult to retain only one type of device during each study expect from Paper I and II in which generation I was used. Both Paper III and IV started with generation II and switched to generation III during the study time. It was considered unreasonable to not implement a newer generation when ready to use as the design and sensor performance was improved. The data collection for both Paper III and IV were prolonged due to the pandemic, while the development of the Cuffless BP device was not delayed to the same extent. In addition, generation II suffered from design issues related to ECG electrodes causing loss of contact which favoured transition to generation III where these issues were resolved. We did not see any clear differences in PAT calculations, except from when ECG was missing due to loss of contact, between generation II and III. There was, however, a difference in quality of the PPG signal when assessing other features as done in Paper IV.

Signal processing

It should be mentioned that processing of the sensor signals recorded with the Cuffless BP device was paramount to the realization of the research project. Signal processing were performed by data scientists at SINTEF Digital and Aidee Health and is not considered in detail in the thesis. This includes the processing of raw sensor signals by different filtering methods and development of algorithms to automatically detect fiducial points in the signals such as the R peak in the ECG, the foot of the PPG

signal or much more complex methods applied to develop the individualized machine learning models in Paper IV. Large efforts were also aimed towards classification of signals as either valid or non-valid. These methods became more sophisticated with the advancement of the research project.

Paper I

The aim was to explore potential cuffless surrogate measurements of which PAT was selected to explore more in depth. In contrast to our hypothesis, it was not possible use the ICG measurements due to large variations in the signal and therefore large variation of the fiducial points to be detected (data not published). On the contrary, preliminary analyses revealed that PAT was potentially a robust feature, and it was decided to investigate PAT in detail. Other features reported in the literature (122-125) were investigated but did not show adequate robustness compared to PAT. A strength in the methodology was the inclusion of two different BP altering methods with a known differing BP response. In this way, we could explore strengths and weaknesses of PAT and other potential features. The auscultatory BP reference method was a limitation as discussed above, but we argue that the conclusions would be the same if an intra-arterial reference was used; that PAT showed strong correlations with SBP on an individual level, and uncertain results regarding DBP. It was also considered that inference to the use case of 24ABPM was better if a cuff reference was used as intra-arterial measurements measure different BPs compared to the cuff. The study could have benefited from including other interventions to alter BP. There is a myriad of ways to alter BP ranging from pharmacological to cold pressor test and mental arithmetic test. The addition of more interventions could have helped identify poorer correlations between SBP and PAT. Still, we argue that it was appropriate for pilot testing and BP alterations across general population cohort as defined by (25).

The BP altering interventions used in this study did not conform to standardized exercise protocols often used, such as the STEEP protocol (126) or 40 % of maximal isometric handgrip (127). However, the aim of the interventions was not to assess the hemodynamic response but to measure cuffless BP surrogates during BP alterations compared to reference BP. The standardisation of workloads was based on self-reported fitness and calculation of metabolic equivalents during the final dynamic exercise step. Thus, we cannot exclude the possibility that exercise intensities may have influenced the variance in slopes but probably not the difference between protocols in slopes that we observed. Only one repetition of each modality was included, and the dynamic method always followed the isometric method. Therefore, we cannot exclude an effect of the isometric exercise on the measurements during the dynamic exercise.

To assess the association between PAT and BP, linear correlation and simple linear regression were calculated individually. Correlation and regression analyses cannot determine causality, and thus the

study design was not appropriate to determine causal relationships between cuffless surrogates and BP. However, the relationship between vascular transit times were assumed causal based on previous knowledge and theory. Mean values were calculated and presented as indications of the correlation on a group level. A repeated measures correlation coefficient, as used by Gesche et al (46), could have better reflected the average association between PAT and BP on a group level (56). On the contrary, the repeated measures correlation method is not a robust estimate of "average" within participant correlation on a population level if the individual slopes vary considerably between participants. In Paper I, the slopes varied, but likely not enough to cause concern regarding a repeated measures correlation estimate (56). Nonetheless, we believe that correlation and regression analyses, although simple, was appropriate to demonstrate the relationships between BP parameters and PAT in this paper.

We did not standardize possible biases such as prior exercise, food, nicotine and caffeine. Thus, we cannot exclude that some variation in the slopes were a result of this. However, a "general" PAT-based BP model should not depend on these variables to function during 24ABPM, and it would not be feasible to perform a 24ABPM study with standardized for such variables.

Paper II

This was a small study with a main aim to assess the BP response during exercise in well trained individuals. Only males were included to ensure a homogenous population with respect to the main aim of the study; to assess associations between exercise BP response and VO2 max. Although they had to fulfil certain fitness criteria, some overestimated their fitness level which led to larger than expected variance in VO2 max. BP measurement method was a standard electronic exercise BP cuff which utilize a microphone to detect Korotkoff sounds. Although the exercise protocol is not directly comparable to that of Paper I, the results were similar regarding SBP and DBP correlations with PAT. Also in this paper, simple linear regression for each participant was used and the mean taken as a study population average. Repeated measures statistics could have provided a better estimate for population mean. Many measurement pairs of SBP and PAT were classified as invalid. Although this is a limitation regarding the validity of the regression analyses, it is also showed how the sensor signals are vulnerable to noise during exercise. In this study, variables such as prior exercise, caffein intake and food were controlled.

Paper III

The aim was to test a PAT-based BP model derived from the cohort in Paper I during 24ABPM compared to conventional oscillometric 24ABPM. A strength of this study was the test of a PAT-based algorithm which was derived from a different cohort, which excluded overfitting from training and

testing in the same conditions. Additionally, the model did not depend on any demographic or anthropometric input. Due to the lack of correlation between PAT and DBP during dynamic exercise, the model was derived from the isometric exercise part of the data from Paper I. The PAT-based model was derived from a relatively small sample and could be erroneous. However, the raw PAT data indicated poor correlations with ambulatory oscillometric cuff measurements, which means that the model was not the issue. Another limitation regarding the model is the assumed linear correlation of PAT with both SBP and DBP, which is not true for the true variation of SBP and DBP within individuals. However, due to the lack of better methods at the time, it was decided to test this approach.

A strength in the statistical methods was the use of repeated measures correlation analyses, as proposed by Bland and Altman (58). However, these methods are less valid when the slope of the relationship vary between individuals as discussed above, of which they did considerably more in Paper III compared to Paper I and II (data not shown). In this case, multilevel modelling with methods to handle varying intercepts and varying slopes are proposed (56). Nonetheless, panel data regression with both fixed and random effects showed equally poor results (data not shown). The Bland Altman limits of agreement would have benefitted from taking into account repeated measures instead of aggregated means because omitting this aspect generally leads to underestimation of the LOA (99). However, because all comparable studies calculated LOA based on aggregated means, this method was chosen for comparative purposes. It is also evident in the Bland Altman plots that there was some dependency of the differences on the mean. This however, tends to give LOA that are too far apart compared to correction by log transformation or modelling the level of agreement as a function of the level of measurement (99).

It became clear that more data was needed to develop more advanced models and thus the aim and sample size was changed. We could have aimed to perform the study analyses on the first 85 participants included to adhere to the original aim. However, difficulties in recruiting participants to fulfil the baseline BP distributions and large number of excluded participants made it difficult. It was therefore decided to perform a pilot analysis of the first 153 participants included. The paper suffered from many excluded participants. However, the majority were due to unforeseen issues with sensor signal quality during ambulation in addition to the pre-determined criteria of large interarm BP differences, but we cannot exclude selection bias.

The questionnaire used was not validated, i.e., it has not been specifically investigated whether the questionnaire measures what it is intended to measure by finding out that a sufficient number of respondents understand and interpret the questions in the same way. The two monitoring methods (chest belt and cuff) were evaluated together, and this may have influenced the respondents (128,

129). Hsee & Leclerc show that when two choices are evaluated simultaneously instead of separately, that the user evaluates each of the products in relation to each other to a greater extent than evaluating the individual product in itself (129). If the participant perceives belt monitoring as more positive than cuff monitoring, there is thus a possibility that belt monitoring was given a higher score, or the cuff a lower score, than if they had been evaluated separately. In the context in which this survey was carried out, it was not an option to carry out a separate assessment of each of the products. A better research design to evaluate how each device was perceived independently of each other could have been randomization to device with a crossover design. This was however not possible within the scope of study at time.

The sleep predictions provide valuable insight into the possibilities of wearable cuffless devices. However, the results must be interpreted in light of the lack of a gold standard sleep time measurement.

Paper IV

The aim to assess the general PAT-based BP model from the study database from Paper I and to test in a proof-of-concept analysis of individually trained machine learning models. A strength in this study was the investigation in hospitalized ICU patients which de-masked potential serious limitations of using PAT to predict BP. On the other hand, ICU patients are heterogenous. Thus, some of the inaccuracy of the cuffless BP models probably resulted from large variations in ECG signal and peripheral PPG signal in addition to large variations in the state of the CV system, i.e., some received vasopressors or vasodilators, while others were stable. Some participants also received non-invasive ventilation support which can affect the PPG waveform (130). Additionally, the MAP based model predictions were based on calculating MAP from the auscultatory SBP and DBP measurements in Paper I. Different MAP formulas from the literature were tested, and the best fit formula from (131) were implemented.

Accuracy of intra-arterial BP measurements are dependent on correct operating conditions (132). We did not calculate damping coefficients, but considered the quality adequate if the ICU staff considered the measurements of sufficient quality. Additionally, MAP is not affected by inappropriate damping. However, some error could have been introduced by not formally checking damping coefficients. On the other hand, all data collection were closely monitored by the investigator to exclude data in which the pressure transducer was not levelled at the phlebostatic axis. A limitation also in this Paper was the exclusion of many participants and we cannot exclude selection bias. The reasons for exclusion were mostly related to signal quality and criteria to ensure adequate training and testing data for the complex individualized models.

Because there was no straight forward statistical method to test the hypothesis that the PAT-based BP estimations were equal to the individualized machine learning models, we compared the two methods in several steps, including numerical comparison of various error statistics and comparison of linear regression models of aggregated data. Finally, we borrowed a statistical test, the Diebold-Mariano test, from forecasting statistics to compare "forecasts" or estimations made by the two models. Because the stationarity assumption may be violated by gluing together participants in a time series, we also performed the test for each individual and tested for overall "significance" using the Fisher method. However, we believe that the significance testing is not the most important aspect. The combined statistics demonstrated the superiority of the individualized machine learning models. Particularly the improved repeated measures correlations indicated what was most obvious from inspecting all the data; that the complex models captured more of the true reference BP variation.

Male sex category was overrepresented in the study population. ICU populations are found to consist of 60 % males (133). Due to our small sample size, the observed 72 % males were probably due to chance.

Ethical considerations

All studies were performed in accordance with the declaration of Helsinki and included participants after informed consent. All studies, expect paper II, were approved by the regional ethics committee (number 65844). The data collection in Paper II were considered not applicable to a regional ethics evaluation because it did not involve creation of new knowledge regarding health and disease, only feasibility testing of the sensor. This was reviewed in a "fremmleggingsvurdering", in which the regional ethics committee (REC) review if there is a need to apply for ethical approval and found that there was not. The same interpretation was originally meant to be implemented in Paper I, but after the study was changed to involve both healthy participants and participants with a known hypertension diagnosis, we applied for a REC approval.

The proportionality principle, i.e., benefits outweigh potential harms of patients were considered well preserved. The studies were observational in nature and no procedures or drugs with potential harmful side effects or complications was used. Furthermore, no patients were being retained from usual care. As a safety measure in Paper I, II and III, participants with severely elevated BP at inclusion was to be excluded and referred to immediate care if needed. All participants in study I, II and III had their BPs thoroughly measured and received recommendations on how to follow up if needed by the investigator.

One aspect to consider is the involvement of a company seeking to make economic profit from the device in the future. This was a symbiosis necessary for the realization of the project. Financial involvement is always a potential risk when interpreting results. However, the study personnel at Oslo University Hospital, including the PhD candidate did not have any ties to the financial aspects of the project. Some results related to potential confidentiality issues regarding models to predict BP were not considered for publication because of the involvement of a company, but we do not believe that the involvement affected the studies, results or the conclusions reached.

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Conclusions and future perspectives

This research showed that PAT-based cuffless BP monitoring with a chest belt device was not a feasible method. This novel approach was thoroughly investigated across several studies including 24ABPM and in patients in an ICU. A general PAT-based model was derived from the study population in Paper I. This model was compared to conventional cuff 24ABPM in Paper III but was unable to estimate BP during 24 hours of ambulation. There was almost no correlation between cuffless estimated BP compared to the reference cuff measurements, BP was over-estimated and the nightly dip was not detected. In ICU patients in Paper IV, accuracy was not satisfactory and concerning dependencies on HR was observed. However, in Paper IV, individualized machine learning methods utilizing aspects of the PPG signal showed promising results, indicating that more complex modelling of the PPG signal may enable cuffless BP estimation in the future. Although changes in PWV in central elastic arteries may reflect changes in BP, PAT measured by a wearable chest belt using ECG and PPG were likely confounded. Contributing factors include the inclusion of PEP, noise and variations in the PPG waveform and the inclusion of peripheral arterial pathways in which local vasomotor regulations, independent of systemic BP, affect the measured transit times.

To enable cuffless BP measurements in the future, it seems that PWV/PTT based methods must overcome the challenge of measuring either PWV or PTT in the aorta. However, the possible confounding effect of HR must be elucidated. On the other hand, more data to allow complex modelling of the PPG signal to changes in BP is a potential approach based on the findings from Paper IV. Based on this, the research project has been expanded with a second PhD thesis that further

investigate other aspects in more new studies. The aim is to build models to predict BP based on complex modelling of changes in the PPG waveform with changes in BP during multiple BP altering interventions, not limited to exercise-only and with continuous BP as reference. This is in line with research in the field, in which pulse transit time methods measured by wearable devices have been found unreliable leading to explorations of more complex methods. At present, all cuffless BP methods utilizing pulse wave transit times, the PPG signal or a combination are dependent on calibration with a known BP measurement. Nonetheless, accurate BP tracking during for example 24ABPM where cuff measurements are obtained only when fitting and calibrating the cuffless BP device at the clinician's office is still a major advancement for patients.

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I

Blood pressure altering method affects correlation with pulse arrival time

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Objective **Pulse arrival time (PAT) is a potential main feature in cuff-less blood pressure (BP) monitoring. However, the precise relationship between BP parameters and PAT under varying conditions lacks a complete understanding. We hypothesize that simple test protocols fail to demonstrate the complex relationship between PAT and both SBP and DBP. Therefore, this study aimed to investigate the correlation between PAT and BP during two exercise modalities with differing BP responses using an unobtrusive wearable device.**

Methods **Seventy-five subjects, of which 43.7% had a prior diagnosis of hypertension, participated in an isometric and dynamic exercise test also including seated periods of rest prior to, in between and after. PAT was measured using a prototype wearable chest belt with a one-channel electrocardiogram and a photo-plethysmography sensor. Reference BP was measured auscultatory.**

Results **Mean individual correlation between PAT and SBP was −0.82 ± 0.14 in the full protocol, −0.79 ± 0.27 during isometric exercise and −0.77 ± 0.19 during dynamic exercise. Corresponding correlation between PAT and DBP was 0.25 ± 0.35, −0.74 ± 0.23 and 0.39 ± 0.41.**

Conclusion **The results confirm PAT as a potential main feature to track changes in SBP. The relationship between DBP and PAT varied between exercise modalities, with the sign of the correlation changing from negative to positive between type of exercise modality. Thus, we hypothesize that simple test protocols fail to demonstrate the complex relationship between PAT and BP with emphasis on DBP.**
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Introduction

Many studies have confirmed that monitoring blood pressure (BP) during a 24-hour period in ambulatory conditions is superior to office BP in predicting future disease [1]. Still, state-of-the-art 24-hour methods are considered by many as unsatisfactory. Intermittent measurements cannot capture the true hypertensive load, which is also masked by patients being instructed to rest during measurement as motion artifacts and non-steady-state hemodynamic situations easily disrupt the oscillations. Moreover, many find the cuff measurements painful and stressful, especially during night or if BP is elevated, which may affect compliance to monitoring and possibly increase the BP during measurement [2]. Thus, innovation in BP monitoring is motivated by the aim to improve hypertension management.

Cuff-less BP assessment has received increasing research attention in the past decade [3–5]. Pulse wave propagation times such as pulse arrival time (PAT) and pulse transit time (PTT) are commonly used surrogate measurements. The theoretical basis behind PAT as a BP surrogate marker is described in the arterial wall and pulse wave propagation models [6]. In short, if the pressure within a vessel increases, the pulse waves travel faster. This is detectable as a decrease in the measured pulse wave propagation time. PAT, defined as the time interval from an R-wave in an electrocardiogram (ECG) signal to a fiducial point in a peripheral photo-plethysmography (PPG) waveform, is particularly popular due to measurement simplicity, only requiring a simple ECG signal as a proximal timing reference and a second continuous bio-signal such as PPG as a distal timing

reference. However, it includes the pre-ejection period (PEP), defined as the time delay from the electrical onset of systole to the mechanical onset of the pulse wave transit time initiated by aortic valve opening. Whether or not exclusion of PEP is necessary for satisfactory accuracy in estimation of BP remains unknown. While some studies argue that simple PAT measurements are inaccurate due to PEP variability [7] others have demonstrated better accuracy of PAT compared to PTT [8]. Extensive research on PAT has demonstrated its relative dependency on BP changes [4,5,9,10]. Still, a key challenge is the transformation of PAT as a single parameter to both SBP and DBP. Most studies investigated PAT and its ability to predict or track both SBP and DBP in experimental protocols where both BP parameters change in the same directions [4]. Thus, test protocols with simple BP altering methods have potential pitfalls. BP regulation and its variations are complex. SBP and DBP may not always covary, for example during different exercise states [11] or in individuals with increased arterial stiffness where pulse pressure (PP) amplification more easily causes isolated rises in systolic pressure [12]. Current evidence indicates a strong correlation between SBP changes and PAT [4]. On the contrary, there is insufficient knowledge on the association between PAT and DBP and on how PAT is affected when SBP and DBP do not change in the same direction [7,13–15].

A differing BP response in isometric compared to dynamic exercise is well known [11]. Isometric exercise generally produces a 'pressor effect' causing both SBP and DBP to increase. Dynamic exercise generally introduces a large PP, where SBP increases markedly while DBP is less affected.

Thus, as a step to enable continuous, cuff-less SBP and DBP measurements, the aim of the present study was to utilize the differential BP response in isometric versus dynamic exercise to investigate the effects of differing BP alterations on PAT on an individual level.

Methods

Subjects and recruitment

This study included subjects reflecting the general adult population with a broad range of age as well as inclusion BPs. Subjects with atrial fibrillation, pregnancy or any contraindication to standard cardiac stress testing were excluded [16]. From December 2019 to September 2020, 80 subjects 18–79 years of age were recruited among volunteers and from a local hypertension registry after approval from its steering committee. Five subjects were excluded from the test protocol for the following reasons; inaudible or difficult to auscultate Korotkoff sounds during exercise (n = 2), poor signal quality (n = 1), baseline SBP >180 mmHg (n = 1) and vasovagal reaction (n = 1).

Test device and estimation of pulse arrival time

The test device is a fully wearable and easy-to-use chest belt with three standard electrodes for ECG and a PPG sensor with potential for seamless integration with clinical applications. Technical details on the device have been published previously [17,18], and an upgraded version (new casing, a higher sampling rate of 1 kHz, new PPG sensor) was used in the present study. PAT was calculated for each cardiac cycle from the R-peak in the ECG to the foot in the PPG waveform. Corresponding PAT measurements for each reference SBP and DBP measurement were calculated by finding the median PAT value from 10 valid cardiac cycles before and after. The PAT values were filtered using a gliding filter with a window size of 30 cycles, only keeping the cycles where the PAT value was within a 20% difference from the median value within the window. Subjects were fitted with the test device and an appropriately sized cuff on the non-dominant arm for reference auscultatory BP measurements.

Study protocol

The test protocol (Fig. 1) consisted of an isometric leg exercise, an incremental cycle ergometer test and seated periods of rest before, in-between and after. Prior to the isometric exercise, subjects were instructed to adjust the ankle, knee and hip angle to endure for 3 minutes. The cycle ergometer test was performed on a standard cardiac stress test ergometer cycle (Ergoline Ergoselect 200, GmbH, Bitz, Germany) and consisted of four increments lasting 4 minutes each. The three first increments had stepwise increasing workload and the fourth was a recovery period with equal workload to the first increment. The cycle ergometer test aimed for submaximal exertion during the third increment. Standardization of cycle workload was achieved by each subject determining their fitness level by the rating of perceived capacity tool, which rates maximum exercise capacity for 30 minutes based on metabolic equivalents [19]. Subsequently, the maximum workload during the third increment was calculated to two to three metabolic equivalents below the rating of perceived capacity.

A trained physician measured reference auscultatory BP every 1 to 1½ minute throughout the protocol with an aneroid sphygmomanometer (Maxi-Stabil 3; Welch Allyn, Skaneateles Falls, New York, USA). Korotkoff I determined systolic pressure and Korotkoff V diastolic pressure. In case of inaudible Korotkoff V during exercise, Korotkoff IV was used. Reference BP was measured 43 times in each subject; seven measurements during the first rest period, three measurements during the isometric exercise, seven reference measurements during the second rest period, 12 measurements during the dynamic exercise and 10 measurements during the third rest period. In addition, standing measurements were taken prior to and after the isometric exercise, and seated on the cycle prior to and after the dynamic exercise. PAT

Fig. 1

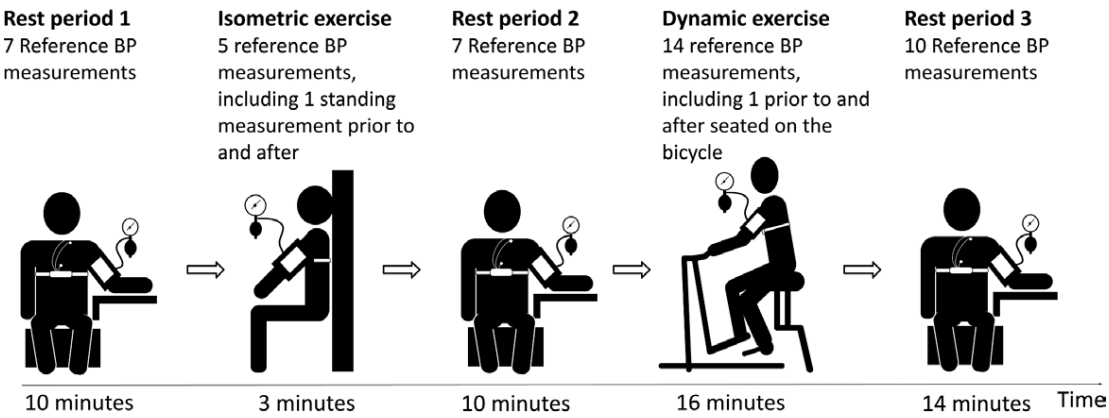


Illustration of the test protocol with isometric exercise, dynamic exercise and rest periods. The dynamic exercise consisted of four 4-minute increments with increasing workload from the first through the third and a fourth recovery increment.

measurements from the test device were obtained continuously throughout the test protocol. Because SBP and DBP from the reference BP measurements were separated in time and not from the same cardiac cycle, each SBP and DBP was noted to the nearest second to allow for PAT calculations from 10 cardiac cycles before and after the exact time when SBP or DBP was measured. Five subjects with corrupted test-device signals detected in the offline analysis were invited back for re-test to differentiate between subtypes of observable waveforms in the PPG and ECG signals and noise and were included in the analysis with data from the second attempt.

Data and statistical analyses

All analyses were performed offline using the Python programming language using the following packages: NumPy (1.18.2), SciPy (1.4.1), NeuroKit2 (0.0.40), Pandas (1.0.3) and Plotly (4.7.1) [20–24]. Continuous variables were evaluated for normality by visual inspection of histograms and the Shapiro-Wilk test. The strength of the association between BP variables and PAT was investigated in each subject using Pearson's correlation. Since it was not possible to measure more than three reference BP measurements during the isometric exercise, two measurement pairs taken standing prior to and after exercise were included for increased statistical power. However, a control analysis including only the three measurements during active isometric exercise was performed, and showed a non-significant reduction in the correlation coefficients and still a significant difference between the regression coefficients for PAT and SBP between the two exercise modalities (data not shown). Correlation coefficients were classified in strength in the following way; r = 0–0.19 was considered very weak, 0.2–0.39 as weak, 0.4–0.59 as moderate, 0.6–0.79 as strong and 0.8–1 as very strong [25]. Further analysis of the relationship between PAT and BP parameters was performed with simple linear regression per individual with PAT as the dependent variable and BP parameters as independent variables. Mean of both individual Pearson's correlation coefficients and regression coefficients were compared between exercise modalities with Wilcoxon Sign Rank Test after assessing for test assumptions. Unless otherwise specified, all continuous variables are presented as mean ± SD, while categorical values are presented as absolute numbers with percentage in parentheses and $P < 0.05$ was chosen as significance level.

Table 1 General characteristics

Characteristic	Quantity
Sex, male (%)	35 (46.7)
Age, years (range)	47.9 ± 15.5 (18–79)
BMI (kg/m^2)	25.6 ± 5.2
Hypertension diagnosis	32 (43.7)
Antihypertensive medication	31 (41.3)
Baseline SBP (range) (mmHg)	124.4 ± 15.5 (92.5–168)
Baseline DBP (range) (mmHg)	75.9 ± 9.6 (55–104)
Baseline PP (mmHg)	50.0 ± 11.8
Baseline PAT (ms)	180.8 ± 23.2
SBP distribution at baseline (%)	
≤100 mmHg	3 (4.0)
≥160 mmHg	1 (1.3)
≥140 mmHg	17 (22.7)
DBP distribution at baseline (%)	
≤60 mmHg	4 (5.3)
≥100 mmHg	2 (2.7)
≥85 mmHg	12 (16.0)

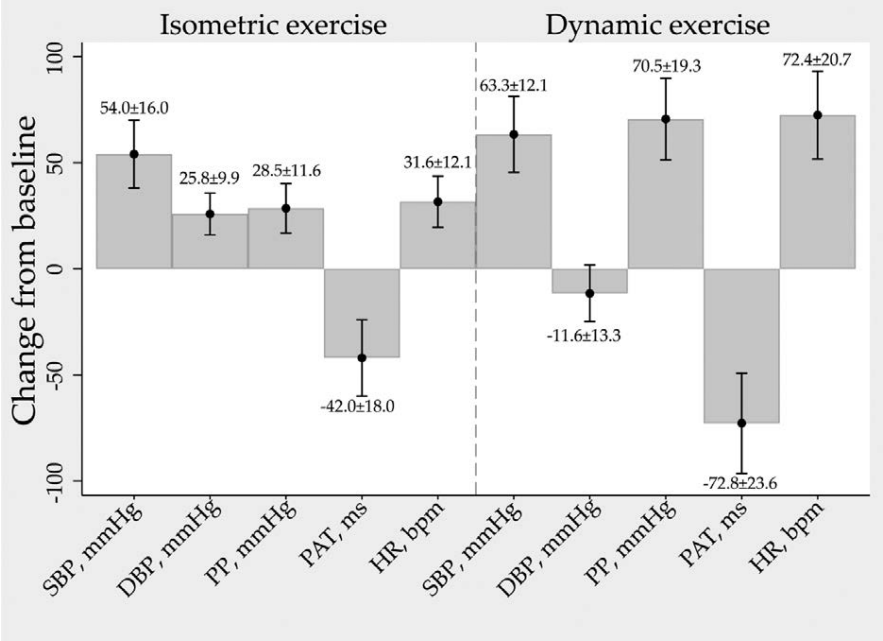
Values are presented as absolute numbers with percentages in parentheses or mean ± SD. Baseline values were defined by averaging the two last measurements during the first rest period.
PAT, pulse arrival time (ms); PP, pulse pressure (mmHg).

Results

General characteristics and group average change in measured variables during exercise

General characteristics of the test subjects are presented in Table 1. Group average change from baseline (defined as the average of the two last measurements during rest period 1) to maximum or minimum for all parameters

Fig. 2



Group average change from baseline in measured physiological variables during the two exercise modalities. Values are presented as mean ± SD. HR, heart rate (bpm); PAT, pulse arrival time (ms); PP, pulse pressure (mmHg).

during the two exercise modalities are presented in Fig. 2. SBP, DBP, HR and PP increased while PAT decreased during isometric exercise. During dynamic exercise SBP, HR and PP increased while DBP decreased slightly and PAT decreased.

Correlation between pulse arrival time and blood pressure

Based on one typical subject, Fig. 3 illustrates how the measured physiological variables varied throughout the experimental protocol (Fig. 3a) and visualizes the correlation analysis for the full protocol (Fig. 3b), isometric exercise (Fig. 3c) and during dynamic exercise (Fig. 3d). The correlation analyses and univariate linear regression were performed separately for the full protocol, the isometric exercise period and the dynamic exercise period. The results of the correlation analyses are presented in Fig. 4.

Differences in the pulse arrival time/blood pressure relationship between exercise modalities

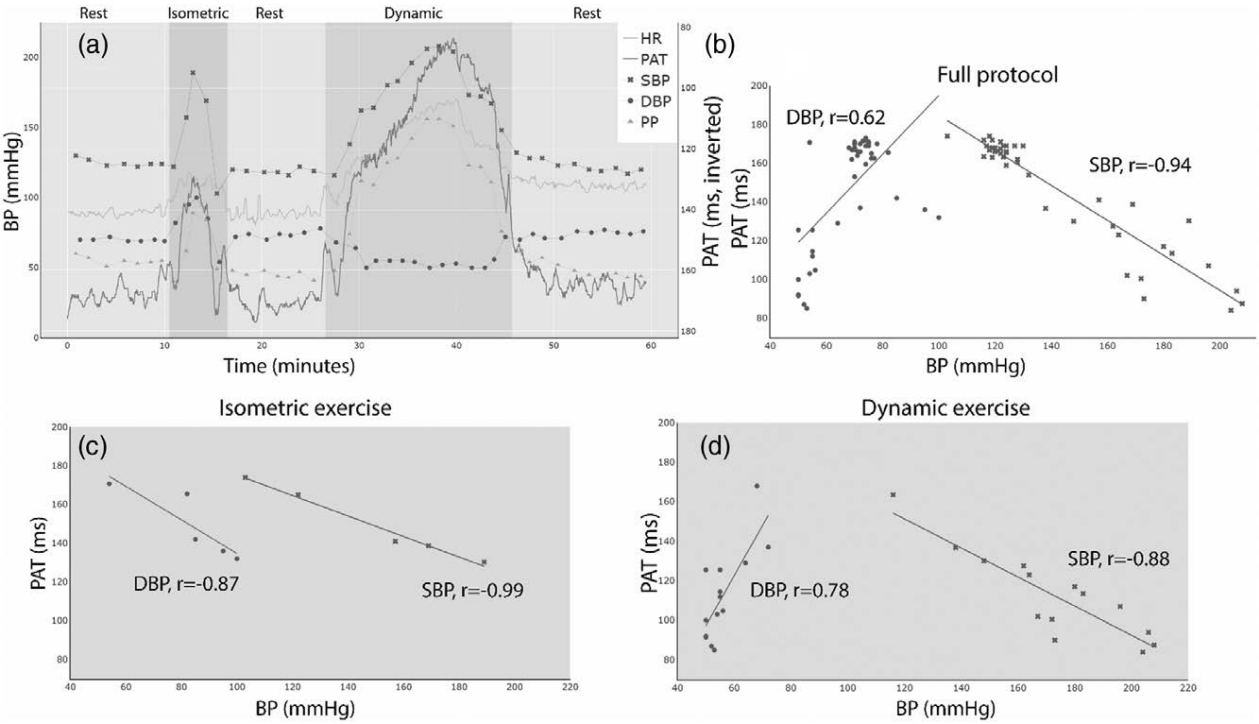
Simple linear regression was performed to determine the equation with the best fit between PAT and BP parameters for each subject for the full protocol and in the isometric and dynamic exercise periods. The results are presented in Fig. 5 as the mean of the individual regression coefficients to allow for a visual representation of the change in PAT per one-unit change in BP as well as comparisons of the regression coefficients between exercise modalities. The mean of individual regression coefficients between PAT and SBP were significantly different when comparing the isometric and dynamic exercise periods (–0.55 ± 0.29 ms/mmHg versus –0.79 ± 0.34 ms/mmHg, $P < 0.001$).

Discussion

As a step to enable continuous, cuff-less SBP and DBP measurements, the present study investigated the effects on PAT from distinctly different BP changes during isometric and dynamic exercise. Included subjects represented the general population with broad ranges of age and baseline BPs. The study presents two main findings. First, the lack of a clear association between PAT and DBP was demonstrated by the inconsistent correlation between the parameters in the two exercise modalities. Second, the PAT/SBP slope differed significantly between exercise modalities. A secondary finding was the confirmation of previously known very strong individual correlation between PAT and SBP. To our knowledge, this is the first study to clearly demonstrate the uncertainty of using PAT alone as a surrogate DBP measurement in the same cohort.

Our results demonstrated a strong negative correlation between PAT and DBP in isometric exercise, a weak positive correlation in dynamic exercise and consequently a weak positive overall correlation. A clear demonstration of this discrepancy in a comparable cohort, is previously unreported. A weak association between PAT and DBP has previously been reported [7,14,15], but stand in

Fig. 3

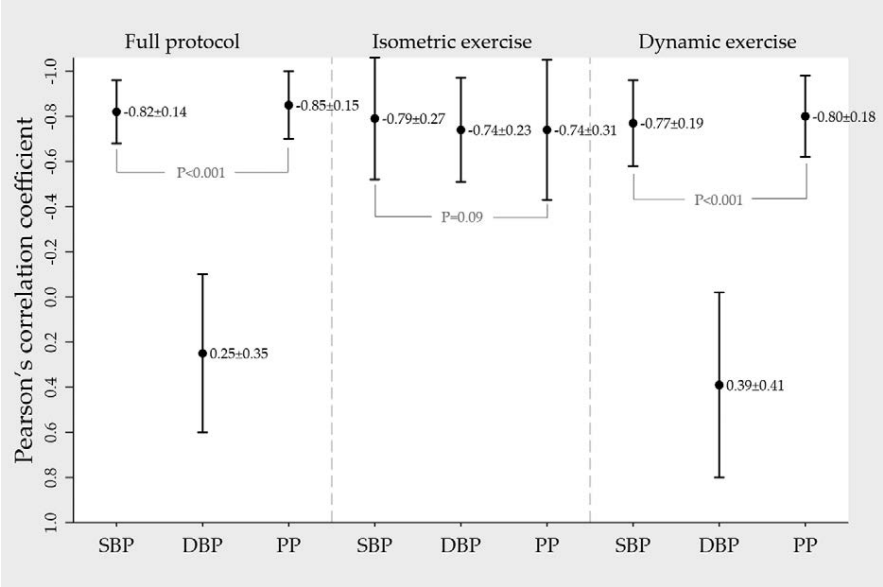


Measurements during the experimental protocol and correlation analysis for one typical subject. (a) All measured physiological variables throughout the test protocol. PAT is inverted on the Y-axis for illustrative purposes. Darker blue background indicates the isometric exercise period and green background indicates the dynamic exercise period. (b) Scatter plot and Pearson's correlation coefficients of PAT and BP during the full protocol in the same subject as in (a). (c) Scatter plot and Pearson's correlation coefficients of PAT and BP during the isometric exercise in the same subject as in (a). (d) Scatter plot and Pearson's correlation coefficients of PAT and BP during dynamic exercise in the same subject as in (a). HR, heart rate (beats per minute); PAT, pulse arrival time (ms); PP, pulse pressure (mmHg).

contrast to the strong correlations reported by the majority of research [4]. In Wibmer *et al.* [14], a weak association between PAT and DBP was found in patients with an indication of cardiopulmonary exercise testing. Only dynamic exercise was investigated and similarly to us they observed small fluctuations in DBP during dynamic exercise and still a very strong correlation between PAT and SBP. In Marie *et al.* [15], isometric and dynamic exercise-induced BP changes were studied in the same protocol in five healthy young male subjects with an invasive BP reference. A strong correlation between PAT and DBP was observed during isometric exercise and a moderate correlation during dynamic exercise. Similar to our findings, PAT correlated strongly with SBP changes across all interventions. The results are not directly comparable because exercise intensities and BP changes were of much lower magnitude in Marie *et al.* [15], and isometric handgrip exercise was performed during the last minute of cycling. Thus, we hypothesize that simple test protocols fail to capture the complex relationship between PAT and BP. This finding is important for ongoing and future research on new methods for BP measurements based on PAT.

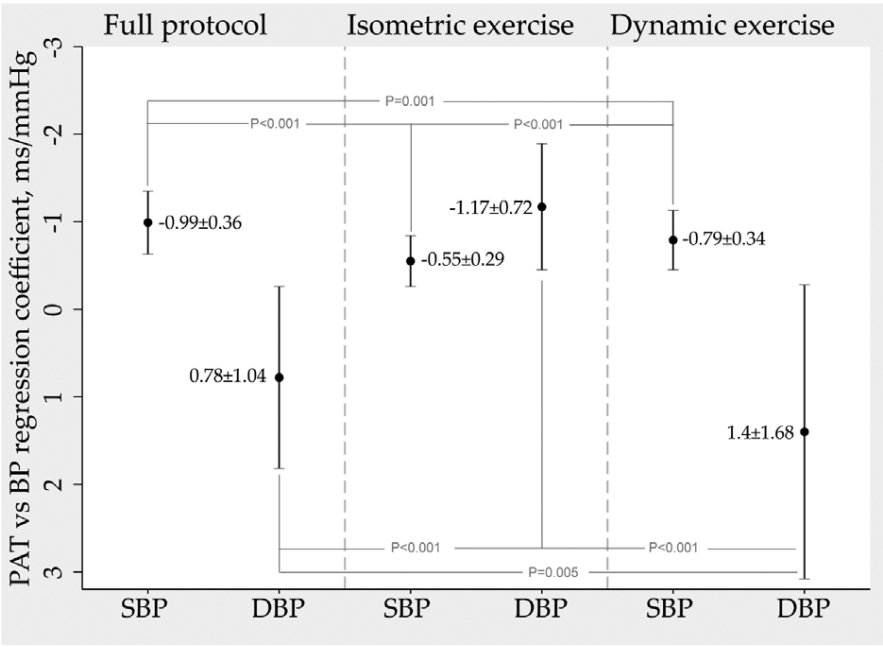
The linear relationship between PAT and SBP differed significantly between exercise modalities, suggesting that PAT is dependent on the characteristic of the BP change or other physiological changes. One previous study also indicated that the PAT/BP slope is altered across different BP changes in the same subject [26]. The inclusion of the PEP, a known source of error in PAT measurements [7] shown to decrease more in dynamic exercise compared to isometric exercise [27], is one possible explanation. Furthermore, in our study PP demonstrated significantly stronger correlation with PAT compared to SBP for both the full protocol and dynamic exercise, indicating that the maximum exerted pressure on the arterial wall is more important compared to an increase in both SBP and DBP. However, this contrasts with previous hypotheses stating that PAT is more dependent on the mean arterial pressure [28]. The role of PP changes on PAT is scarcely researched, but showed superior correlation compared to SBP in one study from a large bio-signal database [8]. Lastly, there is evidence of a BP independent effect of HR on pulse wave velocity (PWV), where increasing HR increases PWV [29,30]. The effect of HR on PWV is difficult to investigate

Fig. 4



Mean ± SD of individual Pearson's correlation coefficients between PAT/SBP, PAT/DBP and PAT/PP. Analyses were performed for the full protocol and then separately for the isometric exercise period and dynamic exercise period. PAT, pulse arrival time (ms); PP, pulse pressure (mmHg).

Fig. 5



Mean ± SD of the individual regression coefficients between PAT as the dependent variable and SBP and DBP as the independent variable. The analysis was performed for the full protocol and then separately for the isometric exercise period and dynamic exercise period. The presented numerical data in the graph represents change in PAT per one-unit change in BP (ms/mmHg). PAT, pulse arrival time (ms).

because HR and BP often change in the same direction and existing research also show conflicting results [29]. Future research needs to investigate the above-discussed physiological parameters and the implications on PAT accuracy.

Regarding SBP, our results are consistent with established evidence of a very strong negative correlation with PAT with most studies reporting correlation coefficients between –0.8 and –0.9 [4]. These findings indicate that PAT is a potential main feature in surrogate measurement of SBP in ambulatory monitoring. All associations between PAT and BP variables discussed in this article represent individual associations between PAT and BP. The current use of PAT as a BP surrogate requires calibration with a cuff measurement [4] to adjust for individual offsets [4,6].

A strong negative correlation between PAT and DBP shown during isometric exercise is similar to findings in previous studies [4,15,31], as well as studies applying a BP changing method where SBP and DBP change in the same directions, such as the cold pressor test [32], mental arithmetic stress test [32] or the Valsalva maneuver [33]. This suggests that DBP can be predicted from PAT during specific conditions, however, it is unlikely to be able to capture all DBP variations during ambulatory conditions.

The present study measured PAT and BP during active exercise to investigate the effects of BP on PAT during large BP fluctuations. Previous comparable studies have investigated dynamic exercise-induced BP changes, most commonly cycle ergometry or treadmill running. However, BP measurements were mainly registered post-exercise or when exercise was intermittently stopped [34–36]. As BP changes rapidly towards 'normal' level immediately after stopping the exercise [11,37], the actual BP during the active exercise may have been masked. This may in part explain why strong negative DBP correlations have been previously reported from dynamic exercise-induced BP changes.

In this study, PAT was measured from a vascular pathway different from the brachial artery reference cuff measurement site. PAT measured at chest level detects pulse waves that propagate from the aorta to the skin vasculature via a mixture of central elastic arteries and the muscular internal thoracic arteries, and it is not known if this PAT reflects central BP rather than brachial BP.

PPG as well as ECG signals are susceptible to corruption by artifacts from noise. After retrospect visual inspection of seven outliers with a correlation between SBP and PAT less than –0.70, it is likely that this is a result of motion artifacts and noise in the PPG and ECG waveforms. Still, we did not omit them from the analysis as algorithms that could identify all artifacts are currently not available. These findings emphasize the importance of signal processing and robust methods to detect corrupt waveforms.

Limitations

The BP measurement method is the major limitation in all studies with protocols involving exercise and is a matter of debate and conflicting evidence regarding accuracy and appropriate noninvasive method [38–40]. Invasive measurements are generally considered as the gold standard during exercise but were not an available alternative in this study due to ethical considerations. Particularly DBP is difficult to measure during exercise and is known to either increase slightly, decrease slightly or remain unchanged during dynamic exercise [11]. The magnitude and direction of DBP change during dynamic exercise differ depending on study population, exercise modality and body position as well as workload intensity [37,39,41]. In one study, auscultatory measurements during dynamic exercise compared to an invasive reference showed a −5 ± 7 mmHg difference [42]. On the contrary, the auscultatory method is considered acceptable during exercise [38]. Although we acknowledge that high precision noninvasive BP measurements during exercise are not possible, it is unlikely that the uncertainty from the BP measurement method would have affected the study conclusions; that PAT is not consistently and strongly correlated to DBP changes across various hemodynamic states. The correlation and regression analyses were performed for each individual subject. With only three measurements during isometric exercise, a standing measurement immediately prior to and after was included to increase statistical power.

Conclusion

The present study demonstrated the lack of a clear association between PAT and DBP, enabled by an experimental protocol that included two different BP-altering exercise interventions. In addition, the change in PAT per unit change in SBP differed significantly between exercise modality. Thus, we raise concern regarding PAT alone as a surrogate BP measurement across various hemodynamic settings and argue that simple test protocols may fail to capture the complex relationship between PAT as a single parameter and both SBP and DBP. Future research should focus on additional parameters to improve the robustness of cuff-less BP estimation and include various BP altering methods. Despite this, our study showed consistent very strong negative correlations on an individual basis between PAT and SBP, suggesting that PAT is a potential main feature in cuff-less BP measurements.

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Conflicts of interest

N.K.M. is with Datek Next AS, a project partner involved in the development of the device prototype. For the remaining authors, there are no conflicts of interest.

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ORIGINAL RESEARCH
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Blood Pressure Response and Pulse Arrival Time During Exercise Testing in Well-Trained Individuals

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Introduction: There is a lack of data describing the blood pressure response (BPR) in well-trained individuals. In addition, continuous bio-signal measurements are increasingly investigated to overcome the limitations of intermittent cuff-based BP measurements during exercise testing. Thus, the present study aimed to assess the BPR in well-trained individuals during a cycle ergometer test with a particular focus on the systolic BP (SBP) and to investigate pulse arrival time (PAT) as a continuous surrogate for SBP during exercise testing.

Materials and Methods: Eighteen well-trained male cyclists were included (32.4 ± 9.4 years; maximal oxygen uptake 63 ± 10 ml/min/kg) and performed a stepwise lactate threshold test with 5-minute stages, followed by a continuous test to voluntary exhaustion with 1-min increments when cycling on an ergometer. BP was measured with a standard automated exercise BP cuff. PAT was measured continuously with a non-invasive physiological measurements device (IsenseU) and metabolic consumption was measured continuously during both tests.

Results: At lactate threshold (281 ± 56 W) and maximal intensity test (403 ± 61 W), SBP increased from resting values of 136 ± 9 mmHg to maximal values of 219 ± 21 mmHg and 231 ± 18 mmHg, respectively. Linear within-participant regression lines between PAT and SBP showed a mean r^2 of 0.81 ± 17.

Conclusion: In the present study focusing on the BPR in well-trained individuals, we observed a more exaggerated systolic BPR than in comparable recent studies. Future research should follow up on these findings to clarify the clinical implications of the high BPR in well-trained individuals. In addition, PAT showed strong intra-individual associations, indicating potential use as a surrogate SBP measurement during exercise testing.

Keywords: blood pressure response, continuous cuff-less measurement method, diastolic blood pressure (DBP), endurance athletes, pulse arrival time (PAT), systolic blood pressure (SBP)

INTRODUCTION

Blood pressure (BP) measurement is included as a regular component of exercise stress testing, in order to evaluate the physiological status of the individual and detect subclinical cardiovascular disease (CVD) (Schultz et al., 2012; Miyai et al., 2021). The normal BP response (BPR) to an increase in intensity during dynamic exercise includes a rise in systolic blood pressure (SBP) as well as decreasing total peripheral resistance (TPR), whereas the diastolic blood pressure (DBP) remains stable or reveals a slight decrease (Bjarnason-Wehrens and Predel, 2020). Exaggerated BPR to exercise has been reported as a prognostic factor for incident hypertension or cardiovascular disease in the general population (Schultz and Sharman, 2013; Caselli et al., 2019; Mariampillai et al., 2020). This so-called hypertensive response to exercise has been defined as an SBP ≥ 210 mmHg for men and ≥ 190 mmHg for women (Schultz and Sharman, 2013). However, these thresholds and the subsequent clinical interpretation of what should be regarded as a normal or abnormal BPR during exercise are under debate (Bauer et al., 2021), and The European Society of Cardiology states in its latest guideline that there is currently no consensus on what is to be defined as a 'normal' BPR during exercise (Williams et al., 2018). Thus, there is a strong need for information related to the clinical value of exercise-related BP in the general population (Bjarnason-Wehrens and Predel, 2020).

With regard to BPR to exercise in well-trained or athletic populations, data are even more sparse, and ambiguity is inherently even larger. Even though exercise testing plays a pivotal role in sports cardiology, few studies have evaluated the magnitude and distribution of exercise-induced BPR in athletic populations. Due to the high cardiac output achieved by athletes, the upper limit of 'normal values' for peak exercise SBP may differ from other populations. While an exaggerated exercise BP is increasingly regarded as a risk factor for cardiovascular disease in the general population (Schultz et al., 2017), the clinical importance of exercise BPR in athletes remains uncertain. A recent review by Richard et al. (2021) states that existent guidelines cannot be adapted when evaluating BPR in endurance-trained individuals and underlines that elevated SBP in this population might reflect adaptive responses to training rather than a pathological sign. Furthermore, comparison of results from the studies involving athletes that do exist is challenging, due to differences in reported exercise testing methods and protocols, BP measurement methods, and determinations of SBP at maximum or sub-maximum workloads (Pressler et al., 2018; Caselli et al., 2019; Bauer et al., 2020). Hence, a consensus on what is a normal BPR response to exercise in well-trained individuals, as well as direct causation linking high-graded exercise testing and SBP to pathology, is lacking.

Another obstacle in estimating BPR during exercise is caused by limitations in validated non-invasive measurement methods, which are usually cuff-based and may be impractical, intermittent, and give discomfort to patients (El-Hajj and Kyriacou, 2020). As a result, cuff-less BP monitoring with different bio-signal approaches has gained increasing attention (Pandit et al., 2020; Welykholowa et al., 2020). One of the signals regarded as promising for estimation of BP is the extraction of pulse arrival time (PAT) (Lee et al., 2019). PAT measured using an electrocardiography (ECG) sensor and a photo-plethysmography (PPG) sensor and is calculated as the time interval from an R-wave in an ECG signal to a fiducial point in a peripheral PPG waveform (Welykholowa et al., 2020). PAT is inversely related to pulse wave velocity (PWV) and the relationship between PWV and BP has been recognized since the late 19th century (Callaghan et al., 1984). When investigating BPR during exercise, a continuous cuff-less approach would be superior compared to cuff-based measurements, to avoid discomfort and inaccuracy caused by movement. However, PAT is a single parameter, and its relationship to different parameters of BP is not yet fully understood (Heimark et al., 2021). Still, the correlation coefficient (on an individual basis) between PAT and SBP in a recent review by Welykholowa et al. (2020) was shown to be $r = 0.84$ (range 0.42–0.98) in studies utilizing the ECG + PPG modality. Thus, it is reasonable to assess PAT as a potential cuff-less surrogate SBP measurement during exercise testing in athletes.

The present study aimed to investigate the BPR in a population of well-trained individuals during a lactate threshold and maximal exercise test on a cycle ergometer, utilizing both an auscultatory technique with an upper arm inflatable cuff with an integrated microphone designed for exercise, and a novel device aimed for cuff-less BP measurements to extract PAT as a potential surrogate BP measurement. The study will add to current knowledge on BPR during exercise testing in an athletic population by addressing the following two aims: 1) To investigate the systolic BPR during a lactate threshold and maximal cycle ergometer test in a population of well-trained male cyclists, and 2) To assess whether PAT measured with a novel cuff-less device can be used as a continuous SBP surrogate during exercise testing in the athletic population.

MATERIALS AND METHODS

Participants

Well-trained male cyclists over 18 years of age, free of any chronic and cardiovascular disease and not under any form of pharmacological treatment, were eligible for inclusion. Candidates were recruited from cycling clubs in Oslo and surrounding areas. Qualifying performance criteria were; experience in high-intensity bike exercise and a minimum of 8 hours of exercise per week, of which a minimum of 5 hours of cycling. In line with the Helsinki declaration, all participants were informed about the test procedure and signed a written informed consent form before final inclusion. The participants were instructed to be fully recovered on the test day, which included avoiding training earlier on the same day and accomplishing only light training on the day before. They were further encouraged to ensure an adequate food and fluid intake on the day before and earlier during the test day, and to avoid intake of any food during the last hour and caffeine drinks

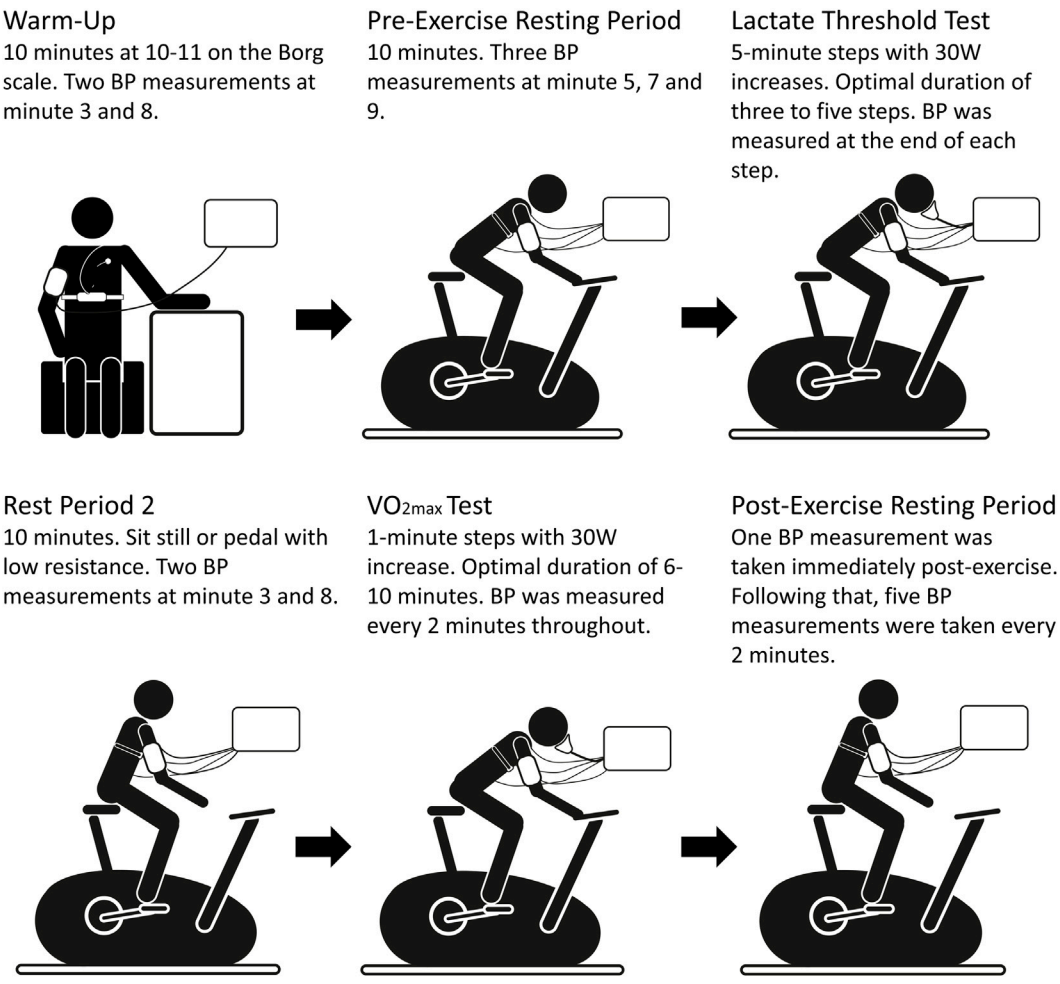

FIGURE 1 | Illustration of the test protocol. BP, Blood pressure.

the last 3 hours before the test. During the test, participants were shirtless, wearing only padded cycling tights and cycling shoes. If needed, the areas on which the electrodes were applied were shaved free of hair.

Equipment

BP at rest and during the exercise test was measured utilizing an auscultatory technique with an upper arm inflatable cuff with an integrated microphone designed for exercise tests (Schiller BP-200+, Schiller AG, Baar, Switzerland). The auscultatory technique BP device was calibrated by certified service personnel the day before the testing started (Diacor, Oslo, Norway), and the following settings were used: max inflation pressure of 300 mmHg, and a deflation rate of 3 mmHg/s. This setup for measuring BP also consists of a 3-channel ECG sensor (Schiller Cardiovit AT-104 PC, Schiller AG, Baar, Switzerland) that were used by Schiller BP-200 + to identify heart cycles (QRS triggering) to provide more accurate BP measurements.

Respiratory variables were measured continuously during the exercise test using a metabolic analyzer (Cosmed K5, Cosmed srl, Rome, Italy, software Omnia 1.6.5) and data was automatically synchronized with the Schiller ECG data. Prior to each test, the metabolic analyzer was calibrated in accordance with the user guide. This calibration included flow calibration by a 3 L calibration syringe (Cosmed ref C00600.01.11), CO_2 zeroing (shrubbery) and reference gas calibration, O_2 = 16.0% and CO_2 = 4.0% (CareFusion, Yorba Linda, CA, United States). Finally, blood lactate concentration (BLa) was measured with Lactate Scout, a portable analyzer (Lactate Scout+, EKF Diagnostics, Cardiff, United Kingdom).

A Garmin sports watch (Garmin Forerunner 920XT, Olathe, KS, United States) with a chest belt for measuring heart rate (HR) was used to give real-time measures to the investigators during the whole protocol. In addition, the Garmin device provided a master timeline for the protocol.

A prototype, wearable device, IsenseU (SINTEF, Oslo, Norway), capable of measuring a one-channel ECG, PPG, impedance cardiography, and movements (3D-acceleration, 3D-angular rate) in the chest area was used to extract PAT

from the ECG signal to the PPG at chest level. The PPG sensor was mounted on the case (12.5 cm × 4.5 cm) facing the body and ECG was measured using two standard electrodes placed on the anterior chest wall. Details on the devices have been published previously (Seeberg et al., 2017). An upgraded version with a higher sampling rate of 1,000 Hz was used in the present study. Raw signals were inspected in real-time via bluetooth connection to a custom-made software (SINTEF, Oslo, Norway).

Study Protocol

Set-Up and Subject Preparation

The test protocol is presented in **Figure 1**. All tests were performed in an exercise laboratory (Kristiania University College) on a cycle ergometer and comprehended a lactate threshold test followed by a maximal intensity test. The test protocol used in the present study is identical to the protocol utilized by the Norwegian Olympic and Paralympic Committee and Confederation of Sport at the time of planning the study. Participants' anthropometric measurements (birth date, height, weight, body mass index (BMI), and body fat percentage) were recorded prior to the test. The cycle ergometer (Lode Excalibur Sport, Lode B.V., Groningen, Netherlands) was calibrated 3 months before testing by certified personnel (Timik, Oslo), and adjusted prior to each test subject in accordance with their anthropometric data. The temperature in the laboratory was 20.1 ± 0.9°C.

The BP cuff was placed on the upper left arm of the subject (at heart level), with bladder size adjusted to the arm circumference and with the microphone positioned on the brachial artery. For some participants, a towel was placed between the lower arm and the handlebar so that the subject could be more comfortable. The IsenseU sensor was kept fixed on the chest by an elastic chest belt with three standard ECG electrodes positioned on the upper chest, as described by Seeberg et al. (2017). The Garmin chest belt HR monitor was positioned just below the IsenseU sensor. Continuous HR was measured throughout the whole test protocol. The 3-lead ECG was fitted with three standard electrodes; two were placed below the clavicle at the right and left upper part of the chest and the third at the lower left part of the chest.

Pre-Exercise Resting Period

Prior to the exercise test, the participants rested for 10 min seated in a chair while synchronized continuous data collection was initialized for the IsenseU, Garmin watch, and the 3-lead ECG. Resting BP was measured at the 5th, 7th, and 9th minute. The lowest recorded value of the three was defined as the resting BP value. After the last resting BP measurement, BLa at rest was recorded.

Warm-Up

After rest measurements, the participants performed a 10-minute warm-up period on the cycle ergometer at a controlled self-selected intensity corresponding to a rate of perceived exertion (RPE) of 10–11 on the Borg Scale (Borg, 1982). Two BP measurements were recorded at the 3rd and 8th minute. The warm-up period was followed by a short break, during which the mask for the metabolic recording was placed and checked for leakage (Hans Rudolph 7450 Series V2 mask with 2600 non-rebreathing *Y*-valve; Hans Rudolph Inc, Shawnee, KS, United States).

Lactate Threshold Test

Oxygen uptake was recorded throughout the test. The starting intensity of the threshold test was set between 60 and 90 W below the presumed lactate threshold at the nearest predefined unit with 30 W intervals. It was assumed that the participants knew their approximate anaerobic threshold load (W). In case this was not known, the starting load was at RPE of 11, with HR and RPE feedback from the warm-up period. Cadence was kept at 85-95 revolutions per minute (RPM) throughout the test.

The lactate threshold test consisted of 5-minute steps with an incremental increase in the workload of 30 W and an optimal duration between three and five steps. The BLa was measured by a finger capillary sample at the last 15 s of each increment. In cases where the BLa had reached a level between 3 and 4 mmol/L, the subsequent incremental increase was 15 W instead of 30 W. When the BLa reached a level above or close to 4 mmol/L the test was concluded. The reason for the conclusion at levels close to 4 mmol/L was that the addition of one more increment would spike the BLa significantly above 4 mm/L and potentially disrupt performance during the subsequent maximal incremental test. BP was measured starting 1 min and 40 s prior to the end of each incremental step and without pause in the test, in order to have an adaptation of the BP to the exercise intensity.

Rest Period two

After completion of the threshold test, the mask was taken off and all participants had a resting period of 10 min. Participants could decide whether to sit still on the bike or to pedal at a very low intensity to avoid an undesired stiffening of the legs. Two BP measurements were taken at the 3rd and 8th minute.

VO_{2max} Test

At the end of the break, the mask to measure the metabolic consumption was re-mounted. The VO_{2max} test started at the same intensity as the threshold test in cases where the anaerobic threshold was reached at the 4th or 5th incremental step. Otherwise, it started at 30 W lower if the threshold was reached earlier, or at 30 W higher if the threshold was reached later. The optimal duration of the VO_{2max} test was between 6 and 10 min. The incremental steps had a duration of 1 min with an increase of 30 W. The cadence was kept at 85–95 RPM throughout the test. The test continued until exhaustion was reached by the subject; defined as a voluntary interruption or by the cadence falling below 60 RPM, despite a strong encouragement to hold on to the given intensity. After completion, the mask was removed, and the metabolic recording turned off. BLa was measured 1-minute post-exercise. BP measurements during the test were recorded starting from the first minute of exercise at every second minute until exhaustion. IsenseU-data, metabolic capacity, and HR were recorded throughout the test.

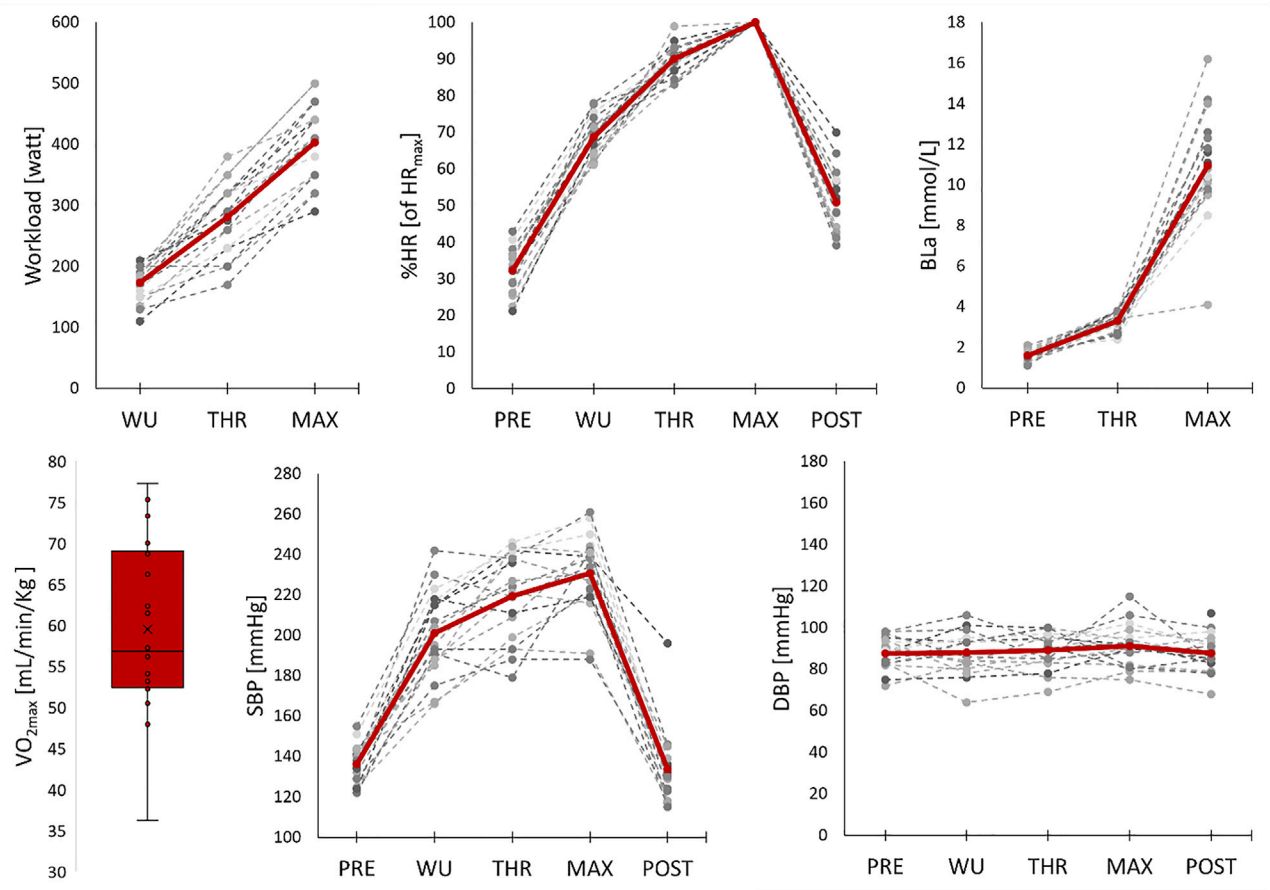

FIGURE 2 | VO_{2max} is presented as a box and whisker plot with median, interquartile range, and minimum and maximum value, otherwise Individual (dotted lines) and mean (red line) values for workload, percentage of maximal heart rate (%HR), blood lactate (BLa), systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the protocol. PRE = values at rest before the cycling, WU = values during warm-up, THR = values at the threshold, MAX = values at maximal intensity (except for BLa which was measured directly after the maximal intensity), POST = values measured 10 min after the test.

Post-Exercise Resting Period

A post-exhaustion BP measurement was taken immediately after completion of the VO_{2max} test when the subject was recovering seated on the cycle ergometer. Following the BP measurement, participants were seated on a chair while five post-exercise BP measurements were taken every second minute for 10 min.

Data Processing and Statistical Analyses

Synchronization of Sensor Data

First, the IsenseU-data was attached to the master-timeline (i.e. the time of the Garmin watch) by using manually noted times for the start/stop of the sensor. Then data from the metabolic analyzer (which was automatically synchronized with the Schiller ECG data), was synchronized to the master-timeline by accomplishing maximum correlation of RR-peaks in the two ECG signals (IsenseU and Schiller). Finally, the open-source software platform Activity Presenter, a software module created to simplify the process of visualizing, synchronizing, and organizing data and video from multiple sources (Albrektsen et al., 2022), was used to fine-tune and verify correct synchronization.

Performance Characteristic and Variation of Physiological Measurements Between Participants

To be able to compare data across participants, five characteristic physiological states were defined and the corresponding data at those points were extracted from the dataset (presented in **Figure 2**):

- PRE: value at rest before the cycling. The measurement point with the lowest SBP was used with the corresponding HR.
- WU: value during warm-up. The last BP measurement (after 8 min) was used as the subject-dependent intensity was adjusted and the physiological parameters were stabilized to the intensity demand.
- THR: values at 4.0 mmol/L as an indication of lactate threshold. The last completed BP measurement with the corresponding HR and watt values before passing BLa of 4.0 mmol/L was extracted.
- MAX = Watt at the last completed stage in the maximal test and maximal HR reached in the test. For the BP measurements, the point with the highest completed

valid measurement was chosen. It should be noted that this was lower than the maximal W reached during the max-test because the BP measurement took longer than each increment and it was difficult to obtain valid measurements during maximal intensity. BLa was measured directly after the maximal test.
- POST = SBP with the corresponding HR measured 10 min after completion of the maximal test.

Calculation of PAT and SBP-Corresponding PAT Values

PAT was calculated for each cardiac cycle from the R-peak in the ECG signal to the foot in the PPG signal recorded from the skin vasculature at chest level (Heimark et al., 2021). The PAT values were filtered by applying a moving median filter with a window size of 30 cycles, only keeping PAT values within 20% of the median of the window. Subsequently, a second median filter was applied to calculate the median PAT value from 10 cycles prior to and after the corresponding SBP value. SBP values were noted manually at the time of recording and synchronized to IsenseU as described earlier. To ensure that the PAT was not calculated too far away from its corresponding SBP measurement, PAT values calculated more than 20 s apart from the SBP measurement were discarded. If less than 5 valid PAT values existed in the window, the PAT measurement was discarded. DBP was not considered in the present analysis due to a lack of relationship between the two variables (Heimark et al., 2021).

Participant Selection

All participants (n = 18) were included in the analysis of performance and variation of physiological response during the lactate threshold and maximal dynamic exercise test. For the analysis of PAT, three subjects had to be excluded due to a low signal-to-noise ratio in the PPG, and thus only 15 were available for analyses of the relationship between PAT and SBP.

Statistical Analyses

Raw data processing and statistical analyses were performed using the Python programming language with these packages; NumPy (1.18.1), SciPy (1.4.1), NeuroKit2 (0.0.32), Pandas (1.3.3), and Matplotlib (3.1.1) (Hunter, 2007; McKinney, 2010; Harris et al., 2020; Virtanen et al., 2020; Makowski et al., 2021). Prior to the linear regression analysis, all PAT SBP pair outliers were filtered in the following way: If the probability of the pair occurring was less than 2.5% based on the normal Gaussian distribution from all samples from the same subject, the measurement pair was considered an outlier and removed from the data analysis. The 2.5% cut-off was selected due to increasing levels of noise in both the raw signals from the IsenseU and the BP cuff with increasing levels of exercise intensity. The relationship between PAT and SBP was analyzed using linear regression for each subject. All valid measurement pairs for each participant throughout the test protocol, including rest periods and warm-up, were used. For the performance characteristics of the five defined physiological states, mean and standard deviations were calculated.

RESULTS

Participant Characteristics

General characteristics of the 18 participants were; mean age of 32.4 ± 9.4 years, height of 182.7 ± 6.6 cm, body mass of 75.4 ± 8.2 kg, BMI of 22.6 ± 1.5 kg/m^{2,} and a body fat percentage of 9.3 ± 3.9%. The participants rode an average of 14,130 ± 7240 km/year and had 7.9 ± 4.8 years of experience in active cycling.

Performance Characteristics and Blood Pressure Response

To highlight the test protocol, physiological measurements for one typical participant are displayed in **Figure 3**. Performance parameters and BP response extracted from the pre-exercise resting period (PRE), warm-up (WU), at threshold (THR), at maximal intensity (MAX, except for BLa which was measured directly after the maximal intensity), and 10 min after the test (POST) are presented in **Table 1**. In brief, the participants had a mean VO_{2max} of 63 ± 10 ml/min/kg and maximum workload in the maximal performance test at 403 ± 61 W. Resting BP was 136/88 ± 9/7 mmHg and SBP at MAX was 231 ± 18 mmHg. Individual data and mean values for performance and BP characteristics for the participants during the protocol are given in **Figure 2**.

Table 2 shows the results from the linear regression between SBP and PAT. The mean r^2 of all individual regression analyses was 0.81 ± 0.17 with a mean of individual regression slopes of −0.72 ± 0.37 ms/mmHg.

DISCUSSION

At present, few studies have described the BPR in well-trained individuals and athletes, and it is not known whether an exaggerated BPR represents a warning sign, or rather is an expression of adaptive responses to training in these populations (Richard et al., 2021). The primary aim of this study was, therefore, to add to the current knowledge by investigating the BPR during a maximal cycle ergometer test in well-trained male cyclists. Our results indicate, similarly to previous studies, that the systolic BPR during maximal aerobic exercise in well-trained subjects is exaggerated compared to normative values from a general population. Notably, the SBP at peak aerobic intensity from our cohort was even higher than in recent similar studies. Furthermore, cuff-less approaches are suggested to overcome the current limitations of cuff measurements during exercise testing. Thus, as a secondary aim, we investigated PAT as a potential non-invasive cuff-less measurement method. Here, our results strengthen previous findings of strong associations between PAT and exercise SBP on an individual level.

Blood Pressure Response in Well-Trained Individuals

In our study, the mean (SD) value for SBP at peak aerobic exercise was 231 (18) mmHg, with a mean difference from baseline of 95 mmHg. There is no consensus on the exact definition for what

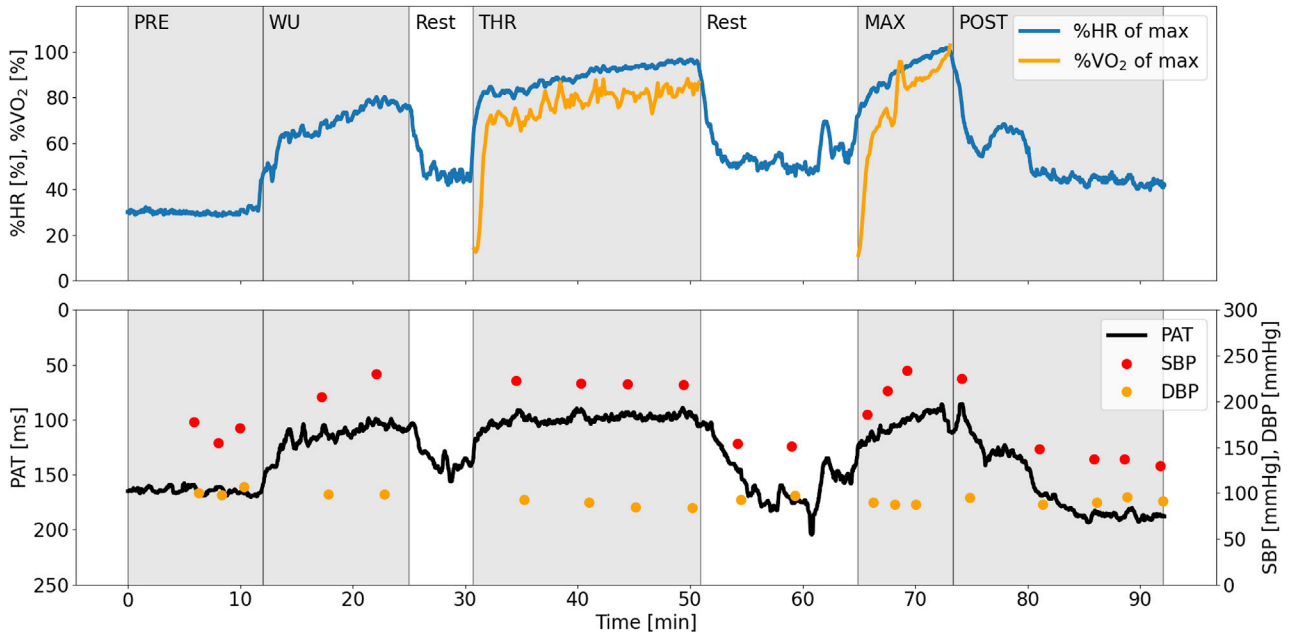

FIGURE 3 | Physiological measurements during the experimental protocol, exemplified with data from one typical subject. PAT is inverted on the *y*-axis to better visualize the co-variation with SBP. PAT, pulse arrival time (ms); SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); HR, heart rate (beats per minute).

TABLE 1 | Mean values and standard deviation for workload, VO_2, $\%VO_2$, HR, %HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood lactate (BLa) during the protocol.

	PRE	WU	THR	MAX	POST
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Workload [Watt]		174 (28)	281 (56)	403 (61)	
VO2 [ml/min/kg]			49 (9)	63 (10)	
%VO2 [of VO2max]			82 (12)	100 (0)	
HR [bpm]	59 (11)	125 (12)	164 (10)	182 (9)	93 (18)
%HR [of HRmax]	32 (6)	69 (5)	90 (4)	100 (0)	51 (8)
SBP [mmHg]	136 (9)	201 (21)	219 (21)	231 (18)	134 (18)
DBP [mmHg]	88 (7)	88 (10)	89 (9)	91 (10)	88 (9)
BLa [mmol/L]	1.6 (0.4)		3.3 (0.5)	11.0 (2.5)	

PRE = values at rest before the cycling, WU = values during warm-up, THR = values at the threshold, MAX = values at maximal (except for Bla which was measured directly after maximal intensity), POST = values measured 10 min after the test

should be regarded as an exaggerated BP response to exercise in general, even though SBP at peak aerobic exercise exceeding 210 mmHg for men and 190 mmHg for women has frequently been reported as exaggerated (Schultz and Sharman, 2013; Sabbahi et al., 2018; Percuku et al., 2019). An alternative suggested cut-off in several studies is a difference of 60 mmHg between baseline (resting) and peak SBP for men and 50 mm Hg for women (Percuku et al., 2019). Caselli et al. (2016) tried to accommodate the shortcoming of reference values specifically for the athletic population by assessing BPR in highly trained Olympic athletes and suggested a cut-off for males of 220 mmHg peak SBP. From recent similar studies listed in **Table 3**, Pressler et al. (2018), Caselli et al. (2019) and Bauer et al. (2020) reported mean peak aerobic SBPs somewhat lower than in the present study, but close to the suggested cut-off values in athletes. As a consequence, a large number of athletes still have an exaggerated systolic BPR. Importantly, the data from Caselli et al. (2019) are extracted from a cohort also including 27% women, and separate values for men were not given. As men consistently are reported to reveal a more pronounced SBP response than women (De Buyzere and Rietzschel, 2018; Song et al., 2020), the value for men-only would likely be higher. Comparably high maximum dynamic exercise BPR to our findings has previously been reported in similar populations. Karjalainen et al. (**Table 3**) reported a peak aerobic SBP of 228 (16) mmHg in elite male orienteers and long-distance runners aged 26 (±3) (Karjalainen et al., 1997). Compared with age and gender-matched normative data in apparently healthy general

TABLE 2 | Linear regression between systolic blood pressure (SBP) and pulse arrival time (PAT) for participants with valid pulse arrival time (PAT) measurements. The *p* value indicates the test of the null hypothesis that the coefficients are equal to zero.

Participant number	r^2	Slope (ms/mmHg)	*p* value	Number of measurement pairs removed based on poor signal quality
1	0.91	–0.51	0.001	10/17
2	0.69	–0.66	0.005	13/22
3	0.97	–0.65	< 0.001	1/20
4	0.84	–1.09	< 0.001	3/22
5	0.32	–0.18	0.014	2/20
6	0.90	–0.79	< 0.001	2/20
7	0.93	–0.76	< 0.001	6/20
8	0.93	–1.00	< 0.001	0/19
9	0.77	–1.59	< 0.001	0/20
10	0.86	–0.73	< 0.001	1/20
11	0.82	–0.44	< 0.001	3/23
12	0.90	–0.93	< 0.001	8/21
13	0.64	–0.69	< 0.001	4/22
14	0.82	–0.59	< 0.001	1/15
15	0.91	–0–86	< 0.001	3/22
Mean ± SD	0.81 ± 0.17 *n* = 15	–0.72 ± 0.37		

TABLE 3 | Overview of similar studies.

Study	Cohort, number of participants, age (SD)	Peak aerobic SBP (SD), mmHg	Maximal workload (SD), Watt	Difference from baseline, mmHg	Exercise method	BP measurement method	Test protocol
Present study	Well-trained male cyclists, 18, 32 (9.4)	231 (18)	403 (61)	95*	Cycle ergometry	Automated electronic exercise cuff	Threshold W followed by 30 W increases every 1 min
Bauer et al. (2020)	Male professional handball and hockey athletes, 142, 26 (5)	197 (20)	351 (79)	74 (20)	Cycle ergometry	Automated electronic exercise cuff	100 W followed by 50 W increases every 2 min until exhaustion
Pressler et al. (2018)	Professional athletes, 2419 (663 female), 26 (12)	204 (22)	305 (59)	80 (20	Cycle ergometry	Manual sphygmo-manometry	Varying; usually starting load of 50-100 W with 20-50 W increases and 3-minute durations
Caselli et al. (2019)	Male and female professional athletes, 141, 26 (6)	208 (22)	262 (61)	87*	Cycle ergometry	Manual sphygmo-manometry	0.5W/Kg with increases of 0.5W/Kg every 2 min
Karjalainen et al. (1997)	Male orienteer and long distance runners, 32, 26 (3)	228 (16)	333 (27)	97*	Cycle ergometry	Manual sphygmo-manometry	50 W followed by 50 W increase every 3 min

*SBP, systolic blood pressure. SD, standard deviation. W, watt. *SD unknown*

population cohorts, Hedman et al. (2020b) reported a peak SBP during exercise test of 202 (22) mmHg and Sabbahi et al. (2018) 179 (20) mmHg, with corresponding differences from baseline of 74 and 56 mmHg, respectively. In sum, our data indicate an exaggerated BPR in well-trained individuals compared to the general population and reflect an even higher peak SBP than in recent comparable studies on athletic populations.

One possible explanation for the observed high peak SBP values in our study compared to recent comparable studies is that our participants had a higher mean age. It has been shown that peak exercise SBP increases steadily with increasing age (Hedman et al., 2020b). However, in the study by Karjalainen et al., which demonstrated similarly high peak aerobic SBP, participant age was lower compared to our study. Another possible explanation is that cyclists compared to other athletes are shown to have a larger BPR during a maximal cycle ergometry test (Richard et al., 2021), and none of the other studies included cyclists-only. It is further important to bear in mind that there is no accepted gold standard exercise BP measurement method, which may impact the comparability across studies, particularly if the number of participants is small, as in our cohort. Another variable which differentiated our results from the afore discussed studies, was the higher achieved workload at peak aerobic exercise, presented in **Table 3**. All four comparable studies had test protocols that

consisted of cycle ergometry. Pressler et al. (2018), Caselli et al. (2019) and Bauer et al. (2020) had considerably lower achieved workloads. Also in the study by Karjalainen et al. (1997), which had the most comparable BPR, the athletes achieved lower a maximal workload; of 333 (27) W. Whether the maximum workload is causal towards the higher peak SBPs by physiological explanations such as differences in TPR, or a result of well-trained cyclists performing a cycle-ergometer test, is uncertain. However, novel approaches in interpreting SBP response to peak aerobic exercise include indexing maximum SBP to max achieved workload (Hedman et al., 2020a).

Interestingly, the suggested alternative cut-off of 60 mmHg from rest to peak aerobic exercise is exceeded not only in our study but also in all four comparable studies on athletes as well as the normative data. The uncertainty of what should be regarded as a potentially dangerous exaggerated response is further complicated by the variance in prevalence of an exaggerated BPR between studies, not only due to different definitions but also because the BRP must be seen in relation to the characteristics of different study populations (Schultz and Sharman, 2013). It is further crucial to interpret values from the level of exercise intensity. Both our findings and results from comparable studies (**Table 3**) suggest that a cut-off of 60 mmHg increase from rest to peak SBP for exaggerated BP response may be inaccurate. Another factor that must be taken into consideration when comparing findings between studies is how they have defined measurements at "rest". Body position may affect the measurements (Eser et al., 2007), and the white-coat effect should also be considered. For athletes, in particular, exercise testing may entail expectations of performance, which can lead to anxiety and an elevated stress level (Ford et al., 2017) which may influence their baseline data; in this context resting BP.

Although there is a growing body of studies indicating that an exaggerated BPR in athletes is a matter of physiological adaptation, there is a lack of longitudinal studies assessing if there is an increased risk of hypertension or cardiovascular disease. Caselli et al. (2019) showed that athletes with an exaggerated BPR compared to normal BPR to maximal cycle ergometry [max SBP 208 (22) mmHg vs. 185 (20) mmHg achieving maximal workloads of 262 (61) W vs. 257 (62) W] had a 3.6-fold hazard ratio of incident hypertension after 6.5 ± 2.8 years of follow up. These results highlight the need for future studies on athlete populations to define cut-off values and risk assessment.

Is PAT a Potential Non-Invasive, Continuous Surrogate Systolic Blood Pressure Measurement in Athletic Populations?

Our results demonstrated that, on an individual level, PAT has a strong association with SBP in well-trained individuals during a threshold and VO_{2max} test. This has not previously been assessed in an athletic population with corresponding exercise intensities. PAT has gained increasing interest in non-invasive, cuff-less BP monitoring to overcome cuff limitations. Gold standard BP measurements during exercise are limited to the invasive method, which is not ethically justifiable in routine exercise testing or even in most research settings. Cuff-based methods, either manually or electronically by using a microphone to detect Korotkoff sounds, are considered acceptable but remain unable to produce high precision non-invasive measurements. Cuff-based methods are further limited due to intermittent sampling and distortion caused by noise and motion artifacts. Previous studies have, similar to our findings, demonstrated that PAT is strongly correlated to SBP on an individual level during dynamic exercise (Wibmer et al., 2015; Heimark et al., 2021). However, the need for calibration against a cuff-measurement to correct for the unknown length of the pulse wave propagation in addition to other individual factors is still an unresolved limitation in PAT-based approaches. Wibner et al. (2015) achieved comparable coefficients of determination to our results using regression analysis in 18 patients referred to cardiopulmonary exercise testing, with a mean r^2 (SD) of 0.80 (0.22) vs. 0.81 (0.17) in our study. Wibner et al. further translated PAT to absolute BP values using multipoint calibration and achieved a Bland Altmann bias of –0.3 (12.4) mmHg with limits of agreement from –24.7 to 24.1 mmHg compared to the reference exercise BP cuff, which was considerably better than simultaneously measured continuous volume clamp method [bias 14.0 (28.5) mmHg)]. Thus, our results indicate that PAT may be a feasible continuous SBP surrogate measurement also in an athletic population. However, a major limitation to overcome, in addition to the need for at least one static calibration to adjust for individual offsets, is the significant between-individuals variation in the PAT/SBP slope. Wibner et al. were able to produce accurate SBP values for comparative purposes by multipoint calibration; however, this is not a practical approach in everyday use. Future research should focus on methods to predict the individual PAT/SBP slope.

Regarding DBP, no meaningful association with PAT was observed as DBP during dynamic exercise changed very little, which is expected from the underlying physiological adaptations. Similar indications have been reported in previous studies assessing PAT during dynamic exercise (Wibmer et al., 2015; Heimark et al., 2021). Although many studies report strong correlations between PAT and both SBP and DBP, we believe that PAT as a single parameter cannot be generalized to both SBP and DBP across various hemodynamic states.

It is an ongoing debate whether confounding of the pre-ejection period (PEP) limits the application of PAT as a BP surrogate measurement. PEP is defined as the electromechanical time delay from the electrical onset of the systole (observable as the R-peak in an ECG signal) to the actual opening of the aortic valve and true onset of the pulse wave propagation in the arterial tree, defined as pulse transit time (PTT). The PEP may not vary with the same magnitude and direction as the PTT and corresponding change in BP (Pour Ebrahim et al., 2019). However, during dynamic exercise, PEP is previously shown to display an intensity-dependent decrease from rest to exercise (Michael et al., 2017), potentially minimizing the confounding effect during exercise testing compared to non-exercise settings of BP measurement. Our study is limited to PAT only, and the potential confounding role of PEP should be clarified in future studies.

LIMITATIONS

The main limitations of the present study are the small study sample containing only males, and the lack of a control group. Most investigations examining exaggerated BPR during exercise are derived from Caucasian middle-aged men, and there is a lack of studies including younger individuals and specifically athletes and/or well-trained individuals. There is further a lack of studies including women. Our study only partly addresses this bias, as our material consists of Caucasian men with a mean age of 32.4 years and a VO_{2max} of 63 (10) ml/min/kg. In addition, peak aerobic SBP suffers from varying test protocols with different methods of BP measurements across and within studies. Thus, the aforementioned limitations warrant caution when interpreting the results and drawing conclusions in the context of data from comparable studies. An important consideration when assessing the BPR to exercise is the change in BP from baseline values, of which the validity is dependent on true baseline or resting values. We observed in the present study, despite sitting rest for 5 min prior to baseline measurements, unreasonably high resting BP values, which was the reason for choosing the lowest value. The most likely explanation for this high resting BP is the anticipation of the subsequent VO_{2max} test. Our PAT analysis was limited by significant amounts of noise in the PPG signal, which was attributable to movement artifacts and clipping of high amplitude PPG waveforms during exercise. However, strict criteria were applied to measure PAT from valid signals during high noise periods. A major challenge in future developments in the PPG-sensor technology and signal processing is improvements to account for noise.

CONCLUSION

The present study adds to existing data on the BPR in well-trained populations. The results suggest an exaggerated BPR compared to normative cut-off values and reveal a higher SBP at peak aerobic exercise compared to most similar studies. Our findings indicate that athletes may have different cut-off values than less trained populations, which could be a result of physiological adaptations. However, there is a need for more data to determine reliable cut-off values in addition to considering any possible risk factors associated with exaggerated SBP responses in athletic populations. Furthermore, the results suggest that PAT may be used as a potential non-invasive and cuff-less SBP surrogate measurement on an individual level. However, a measurement device with a more robust signal-to-noise ratio is required, and the varying individual relationship between PAT and SBP remains a challenge for future work.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: SH, IE, IV, ØS, BW-G, and TMS. Methodology: SH, IV, TMS, IE, and ØS. Data acquisition: IV, AM, and TMS. Software: OH and KGB-R. Formal analysis: SH, OH, KGB-R, and TMS. Writing—Original draft: SH, IE, and TMS. Writing—Review and editing: IV, KGB-R, AM, OH, BW-G, and ØS. Final approval of submitted manuscript: All authors.

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III

Accuracy and User Acceptability of 24-hour Ambulatory Blood Pressure Monitoring by a Prototype Cuffless Multi-Sensor Device Compared to a Conventional Oscillometric Device

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Keywords: cuffless[1], ambulatory blood pressure[2], pulse arrival time[3].

Abstract

Objective

24-hour ambulatory blood pressure monitoring (24ABPM) is state of the art in out-of-office blood pressure (BP) monitoring. Due to discomfort and technical limitations related to cuff-based 24ABPM devices, methods for non-invasive and continuous estimation of BP without the need for a cuff have gained interest. The mains aim of the present study was to compare accuracy of a pulse arrival time (PAT) based BP model and user acceptability of a prototype cuffless multi-sensor device (cuffless device) with a conventional cuff-based oscillometric device (ReferenceBP) during 24ABPM.

Methods

Ninety-five normotensive and hypertensive adults underwent simultaneous 24ABPM with the cuffless device on the chest and a conventional cuff-based oscillometric device on the non-dominant arm. PAT was calculated using the electrocardiogram (ECG) and photoplethysmography (PPG) sensors incorporated in the chest-worn device. The cuffless

device recorded continuously, while ReferenceBP measurements were taken every 20 minutes during daytime and every 30 minutes during nighttime. Two-minute PAT-based BP predictions corresponding to the ReferenceBP measurements were compared with ReferenceBP measurements using paired t tests, bias and limits of agreement.

Results

Mean (SD) of ReferenceBP compared to PAT-based daytime and nighttime systolic BP (SBP) were 129.7 (13.8) mmHg versus 133.6 (20.9) ($p = 0.017$) mmHg and 113.1 (16.5) mmHg versus 131.9 (23.4) mmHg ($p < 0.001$). Ninety-five % limits of agreements were [-26.7, 34.6 mmHg] and [-20.9, 58.4 mmHg] for daytime and nighttime SBP respectively. The cuffless device was reported to be significantly more comfortable and less disturbing than the ReferenceBP device during 24ABPM.

Conclusions

In the present study, we demonstrated that a general PAT-based BP model significantly overestimated ambulatory BP during 24ABPM. If sufficient accuracy can be achieved, cuffless BP devices have promising potential for clinical assessment of BP due to the opportunities provided by continuous BP measurements during real-life conditions and high user acceptability.

Plain Language Summary

- What is the context?
  - Hypertension is a major risk factor for cardiovascular and cerebrovascular end-organ damage, morbidity, and mortality world-wide.
  - Accurate measurement of blood pressure is essential for the diagnosis and management of hypertension.
- What is new?
  - Cuffless blood pressure devices that allow measurement of blood pressure without a pressure cuff is a promising and novel method of blood pressure estimation.
  - The objective of this study is to assess whether pulse arrival time alone can be used to estimate blood pressure accurately during 24-hour ambulatory blood pressure monitoring, using a prototype cuffless device placed on the chest.
  - Our analysis shows that a general model based on pulse arrival time overestimated ambulatory blood pressure, especially during nighttime.
  - User acceptability was higher with the cuffless device compared to a conventional cuff-based oscillometric device during 24-hour ambulatory blood pressure monitoring.
- What is the impact?
  - This study provides further evidence that accurate blood pressure estimations cannot be achieved by using pulse arrival time alone as a surrogate for blood pressure measurements.

Introduction

Accurate measurement of blood pressure (BP) is essential for the diagnosis and management of hypertension. Office BP has been used in every large outcome trial that has investigated the effects of lowering BP on cardiovascular outcomes, and thus remains the gold standard.

However, office BP is unable to detect clinically important hypertension phenotypes such as white coat hypertension, masked hypertension, and nighttime hypertension. 24-hour ambulatory BP monitoring (24ABPM) has been shown to better predict hypertension-mediated organ damage, cardiovascular events and death compared to office BP, and is therefore considered to be the state-of-the-art method for out of office BP measurements (1, 2). Standard ambulatory upper arm cuff-based oscillometric BP measurements have several limitations. The intermittent measurements from cuff devices only provide BP information during a certain, short time window, thereby ignoring BP fluctuations during real-life conditions. Furthermore, the cuff inflation itself may cause discomfort that can lead to both errors in measurements and falsely elevated BP (2). Also, incorrect cuff-size can lead to over- or underestimation of BP (3, 4), which is common in very thin and very obese patients (3). Finally, repeated 24ABPM investigations are limited by patients' high discomfort factor of cuff inflation, disturbed sleep and restriction of daily activities related to ambulatory BP monitoring (ABPM) (5-7).

Several efforts have been made in recent years to develop wearable cuffless devices that track changes in BP after initial calibration with a cuff measurement (8-14). In these devices, BP is predicted by measuring other physiological variables that are related to changes in BP and using algorithms, machine learning models or other data-driven techniques to convert these measurements to BP. Cuffless BP devices differ in several aspects (15-17). First, they use different principles and technologies for estimating changes in BP. Both the physiological variable and the sensors used to measure these variables vary between devices. Second, they differ in anatomical sensor location, e.g. wrist (18), chest (19), ear (14) and finger (20). Finally, they have different intended use (continuous vs. intermittent) and are implemented in different types of devices' e.g. smartwatch, smartphones, dedicated devices. Most cuffless BP devices are based on pulse wave analysis (PWA) of a photoplethysmography (PPG) signal, pulse arrival time (PAT) or a combination of the two (9-14, 20-23). Even though there has been an increasing amount of cuffless BP devices that claim to accurately estimate BP available on the market, none of these devices have yet been validated according to the recently released validation protocol for cuffless devices, ISO 81060-3:2022 standard, nor according to the European Society of Hypertension recommendations (24).

The present study is a pilot investigation of using PAT as a potential surrogate BP measurement to enable non-invasive cuffless 24ABPM, using a prototype cuffless multi-sensor device (cuffless device) placed on the chest. The study had three main aims. First, we aimed to compare BP predictions of the PAT-based BP model, derived from a general population cohort (25), with the measurements of a conventional cuff-based oscillometric BP device (ReferenceBP) during 24ABPM in subjects with and without hypertension. Second, we aimed to compare the user acceptability of the cuffless device with the ReferenceBP device. Third, we aimed to test feasibility of the cuffless device to predict sleep times using a machine learning method based on self-reported sleep data.

Materials and Methods

Study participants

We recruited 153 adults from Oslo University Hospital, Ullevål (n= 111) and from a general practitioner office, Sandefjord Helsepark (n= 42). At Oslo University Hospital, the subjects consisted of healthy volunteers, employees and patients registered in a local hypertension registry (HyReBi, REK 2017/477). At Sandefjord Helsepark, patients with an indication for 24ABPM were included. Inclusion criteria were age > 18 years and a written informed

consent. Exclusion criteria were a history of cardiac arrhythmia, pregnancy, possible extreme uncontrolled hypertension (resting office BP ≥ 220/120 mmHg), interarm BP difference > 10 mmHg, age > 70 years, known cardiovascular or cerebrovascular disease, pulmonary disease, renal disease or Diabetes Mellitus type I or II, inability to measure BP on one or both arms or inadequate Norwegian skills. Thus, the study aimed to include individuals that were either healthy or with uncomplicated hypertension. Participants recruited from the local hypertension registry were screened by examining the registry information in addition to their own knowledge of any new onset excluding disease history. Other participants were screened by their own knowledge of any excluding disease history. The study was approved by the Regional committee for medical and health research ethics (REK), project number 65844, prior to inclusion of the first study subject.

ABPM measurements

ReferenceBP measurements were performed using a conventional ambulatory oscillometric BP device (Oscar 2, SunTech Medical, Morrisville, North Carolina, USA) (26). The same ReferenceBP device was used at both centers. A detailed description of the cuffless device has been given previously (25, 27, 28). In short, it is a wearable chest belt that measures electrophysiological and optical signals in form of an ECG and a PPG and has an inertial measurement unit (IMU) consisting of a 3D accelerometer and a 3D gyroscope. Cuffless BP predictions were obtained by using PAT calculated from the ECG and PPG signals. The model to obtain BP values from PAT estimations was developed from a different dataset, considered a general population cohort, during isometric exercise induced BP changes (25). The model is a simple best-fit linear equation with an intercept term and a coefficient to determine either systolic BP (SBP) or diastolic BP (DBP) from measured PAT.

Both devices were mounted with the participants sitting in an upright position with back support and legs uncrossed. The dominant arm was fitted with an appropriately sized cuff. After 5 minutes of seated rest, inclusion BP measurements (office BPs) were taken on both arms starting with the dominant arm using the ReferenceBP device. Three consecutive measurements were taken on each arm with 1-minute intervals between measurements. If the difference between any of the first three BP measurements were > 7mmHg, two more measurements were taken. The first measurement taken on each arm was discarded. Inter arm BP differences were then calculated as the difference between the average remaining measurements on each arm. Following the seated measurements at rest, standing measurements were taken at one and three minutes to include orthostatic BP measurements.

The ReferenceBP was programmed for measurements every 20 minutes from 07:00 to 23:00 and every 30 minutes in the remaining period. The cuffless device measured signals continuously with 1000 Hz resolution. To be able to compare measurements from the two devices, only PAT-based BP predictions corresponding to the timing of the cuff measurements were used. PAT-based BP predictions were estimated in 2-minute windows corresponding to a reference measurement. Individual self-reported diaries were used to define awake and asleep BP values. If a participants sleep diary was missing, the default sleep window of 23:00-0700 was used, and the participant was excluded from the sleep analyses. The participants were instructed to engage in normal activities but stop any activity and keep the arm still at heart level during measurements and refrain from strenuous exercise, long car drives and taking the equipment off. Furthermore, participants were informed to stop moving and keep the arm still with the cuff at heart level when the cuff inflated.

A valid participant 24ABPM was defined as having at least 40 % good measurements pairs where a good reference pair was defined as at least 40 % valid data from the cuffless device within the 2-minute cuff measurement window. Valid sensor data was based on PPG and ECG quality criteria. Participants who did not meet these criteria were excluded. Furthermore, participants with less than 25 valid 24ABPM measurements and no valid night-time measurements were removed. Outliers predicted by the PAT-based algorithm were filtered in the following way: Within each participant extreme BP values defined as SBP above 280 mmHg or below 50 mmHg and/or DBP above 150 or below 30 mmHg. These values were considered non-physiological BP values.

Questionnaire

A self-developed questionnaire was used to evaluate the level of comfort, discomfort, activity, and sleep disturbance of both devices. Parts of the questionnaire were based on questions published in the "Device assessment form" from the British Hypertension Society BP device validation protocol (29). These questions were translated into Norwegian and transformed to a 7-point Likert scale. In addition, we assessed discomfort and pain with a verbal numeric rating scale (VNRS) (30, 31) and developed questions tailored to the chest belt design of the cuffless device.

Statistical analysis

Data processing was performed offline using the Python programming language. Data processing included processing and filtering of the raw signals from the cuffless device and we implemented algorithms to classify signals from a heart cycle as valid or non-valid. Statistical analyses were performed using Stata v. 17.0 (Statacorp., Texas, USA). Variables were assessed for normality by visual inspection of histograms. Continuous data are presented as means (SD), or median (interquartile range (IQR) if non-normally distributed). Mean BP were normally distributed and compared using paired t-tests. The level of absolute agreement between the ReferenceBP and the PAT-based BP model for daytime, nighttime, and 24-hour SBP and DBP were evaluated using Bland-Altman plots with bias and 95 % limits of agreement (LOA). Correlation analysis was performed using repeated measures correlation as proposed by Bland and Altman (32). Within participant change in BP was calculated by taking the highest reported ReferenceBP measurement minus the lowest reported ReferenceBP measurement during 24ABPM. We performed separate subgroup analyses stratifying for hypertension. In these subgroups, mean of reference compared to predicted BP was calculated as well as repeated measures correlation coefficients. Hypertension strata and sex category interaction on accuracy of the PAT-based model was investigated both in a linear regression model with mean BPs and in a panel regression model to account for within participant repeated measures. Diagnostic accuracy was investigated by computing 2 x 2 contingency tables to calculate sensitivity and specificity. ReferenceBP was considered the gold standard test and diagnostic thresholds were based on the European hypertension guidelines (33).

Because of the inability of the PAT-based BP model to estimate nighttime BP dip, we investigated hourly changes of PAT during 24 hours and tested (post hoc) whether changes in the PPG waveform during ambulation could alter the PAT calculations. During data inspection we observed some variation of this slope during ambulation. We assumed that the steepness of the slope of the first upstroke of the PPG waveform could introduce errors in absolute PAT calculations. A steeper slope could cause PAT to be longer, corresponding to a lower BP prediction, and vice versa. We therefore hypothesized that a less steep slope during

nighttime could cause an erroneous shortening of PAT calculations during nighttime. Average numeric values of the slope of the first upstroke of the PPG signal were calculated, i.e. the 1st derivative of the PPG waveform, in the same 2 minute windows as all BP measurements. Next, hourly averages were calculated and tested for changes over time using a one-way ANOVA repeated measures test. The slope values were log-transformed to achieve a normal distribution. A two-sided p value < 0.05 was considered statistically significant.

Sleep analyses

Sleep features

The accelerometer-based features Euclidean Norm Minus One (ENMO) and Locomotion Inactivity During Sleep (LIDS) were calculated as described by Sundararajan and colleagues (32). In addition, three new accelerometer and gyroscope-based features were defined: ChangeGravity, AccumRot and SleepPosture. ChangeGravity was defined as the angle between average accelerometer vectors in two successive epochs. This is an indication of posture change between two epochs. AccumRot was defined as the root-sum-square rotation about all three gyroscope axes. This serves as an indicator of overall rotational movement of the truncus within an epoch. Lastly, SleepPosture was defined as 1 if pose was classified as laying prone, supine or on the side. Heart rate (HR) and HR variability features were calculated from the ECG-signal after normalization of the RR-intervals, as described by Aktaruzzaman et al (33). Time-domain features were mean RR interval (meanRR) and standard deviation of RR-intervals (SDNN). Frequency-domain features were the low-frequency to high-frequency ratio (LF/HF).

Sleep wake classification

An automated sleep/wake classification algorithm was trained using the participants' sleep diaries as a reference. The algorithm was a decision tree classifier which used features derived from IMU data and R peak to R peak measurements from the ECG to derive HR frequency and HR variability measurements. The features were calculated over 5-minute epochs and are described in paragraph above. Optimal decision tree depth was determined by evaluating depths from 1 to 25 using leave-one-out cross validation of 10 subjects. Finally, decision tree classifiers with optimal depth were trained for each subject using leave-one-out cross validation. Classifier performance was evaluated by overall accuracy score (fraction of correctly classified epochs) and Cohen's kappa (34).

Sleep window determination and sleep efficiency

Sleep window was determined by finding the continuous time window that maximized sleep epochs and minimized wake epochs. Specifically, setting $s = 1$ in epochs classified as sleep and $s = -1$ in epochs defined as wake, the time points for sleep window onset (slept) and offset (woke) was determined by the following equation:

$$(slept, woke) = \text{argmax} \left(\sum_{i=slept}^{woke} s_i \right)$$

Sleep efficiency was defined as the fraction of epochs classified as sleep during the time spent in bed. Time spent in bed was defined from the last epoch with a non-sleep pose directly prior to onset of the sleep-time window, until the first epoch of non-sleep pose after the end of the sleep-time window.

Results

Participant selection, general characteristics and blood pressures

A flow chart of participant inclusion is presented in figure 1. Twenty-one observations were defined as outliers predicted by the PAT-based algorithm and removed. A total of 4010 measurement pairs were included in the analyses. All participants reported sleep times. Eight participants did not report sleep quality and was excluded from those parts of the sleep analyses. General characteristics are presented in Table 1. Median (IQR) age was 49.0 (39.0 – 61.0) years, 42.1 % were female and approximately half of the included subjects had a previous history of hypertension (47.4 %). Baseline mean (SD) SBP and DBP, defined as the average of the office BP measurements on the non-dominant arm excluding the first measurement, were 127.0 (15.2) mmHg and 78.4 (10.6) mmHg. Comparisons between ReferenceBP and PAT-based mean 24-hour, daytime and nighttime BP showed that the PAT-based model significantly overestimated BP (Table 2). Mean (SD) 24-hour ReferenceBP SBP was 125.4 (14.8) mmHg compared to the PAT-based SBP of 133.3 (19.8) mmHg ($p < 0.001$) and mean nighttime ReferenceBP SBP was 113.1 (16.5) mmHg compared to the PAT-based SBP of 131.9 (23.4) mmHg ($p < 0.001$). The results were similar regarding DBP and in the subgroups of participants with or without a prior history of hypertension (Table 2). To exemplify more result details, we included time series plots from a few selected participants in Figure 2. The plots defined as mediocre agreement (Panel A, B and C) were considered to be among the best and those defined as poor agreement (D, E and F) were considered representative of the majority of participants.

Agreement

Agreement between the PAT-based BP model and ReferenceBP is presented with Bland Altman plots with bias and 95 % LOA (Figure 3). Regarding SBP, bias [LOA] were 7.9 mmHg [-23.3, 39.2 mmHg], 3.9 mmHg [-26.7, 34.6 mmHg] and 18.8 mmHg [-20.9, 58.4 mmHg] for 24-hour, daytime, and nighttime respectively. Corresponding results for DBP were 6.9 mmHg [-10.8, 24.5 mmHg], 3.3 mmHg [-14.3, 20.9 mmHg] and 16.7 mmHg [-6.1, 39.5 mmHg]. Repeated measures correlation coefficients were 0.06 ($p < 0.001$) and -0.01 (p 0.509), demonstrating a weak but statistically significant correlation regarding SBP but no correlation regarding DBP. The results were similar when stratifying for hypertension and sex category. There was no interaction regarding hypertension strata in a linear regression model on aggregated mean 24-hour BPs ($p = 0.16$ for SBP and $p = 0.25$ for DBP), and no interaction in a panel regression model ($p = 0.81$ for SBP and $p = 0.68$ for DBP). There was also no interaction regarding sex category in a liner regression model ($p = 0.0.45$ for SBP and $p =$ 0.074 for DBP) and no interaction in a panel regression model ($p = 0.1$ for SBP and $p = 0.88$ for DBP).

Diagnostic accuracy

The sensitivity and specificity of the PAT-based BP model compared to ReferenceBP are presented in Table 3. Because of the tendency to overestimate BP, sensitivity was good regarding the PAT-based BP model. However, specificity was poor, only 44.9 % and 23.3 % for SBP and DBP during nighttime respectively.

Ambulatory changes in pulse arrival time

Hourly averages of PAT showed an opposite ambulatory variation compared to expected (Figure 4A). Contrary to our hypothesis that the slope would be less steep during nighttime

and steeper during daytime, potentially confounding the PAT calculations, our analyses showed the opposite (Figure 4B). There was a statistically significant hourly variation in slope ($p < 0.001$), as calculated by ANOVA repeated measures.

User acceptability

Ninety-two (97%) of the 95 participants answered the questionnaire. Results are presented in Figure 5. Questions related to comfort during 24ABPM of the cuffless device yielded high acceptance ratings with 58 (63 %) agreeing or strongly agreeing versus only 4 (4 %) for the ReferenceBP device. Response regarding disturbance of both daily routine and sleep also showed the cuffless device superior to the ReferenceBP device, 83 (90 %) versus 17 (18 %) subjects and 76 (83 %) versus 15 (16 %) responding with strongly disagree/disagree to being disturbed. Furthermore, the cuffless multi-sensor device had a higher rating for long term adherence with 85 (92 %) of the study participants answering that they would choose cuffless multi-sensor device as the monitoring method for their next 24ABPM.

Sleep detection

Eighty-seven (92 %) of the 95 participants answered the sleep diary. The decision tree classifier accuracy was 91 ± 5 % and Cohen's kappa = 0.77 ± 0.13, of which 1 is perfect agreement and 0 the expected agreement due to chance alone. Reported versus predicted sleep windows for all participants are presented visually in Figure 6A. The distribution of deviations between predicted sleep window and diary sleep window is presented as boxplots in Figure 6B. There was a median 10-minute overestimation of predicted sleep window compared to the sleep diaries, with the 25^{th} and 75^{th} percentile ranging from -32 to 43 minutes (Figure 6B, "SW duration"). The sleep window onset was more challenging to detect than the end of the sleep window (IQR 67 minutes vs 28 minutes, respectively, "SW onset" and "SW end" in Figure 6B). Sleep efficiency (fraction of epochs classified as sleep during the time spent in bed) was on average 85 ± 12 % and was unrelated to sleep quality in the diaries (Figure 6C).

Discussion

Our findings together with previously published studies suggests that PAT alone is not sufficient as a cuffless surrogate measurement to predict BP measurements accurately in 24ABPM. The PAT-based algorithm used to estimate BP, which was measured with a cuffless device and derived from general population cohort, significantly overestimated daytime, nighttime, and 24-hour ambulatory BP, with the largest discrepancy observed during nighttime. However, user acceptability was higher with the cuffless device compared to the ReferenceBP device and it showed promising results towards automatic sleep detection as an additional feature.

Our BP results are comparable to most similar studies that have investigated accuracy in a cuffless BP device compared to conventional cuff BP in adults for 24ABPM (11, 22, 35-39). Nyvad et al investigated a PAT-based device in 51 adults with essential hypertension and found that BP was generally overestimated with the largest discrepancies observed during nighttime (35). Compared to our subgroup of 45 patients with a hypertension diagnosis, nighttime SBP bias was smaller (21.6 mmHg compared to 11.6 mmHg) and LOA similar (± 48.0 mmHg compared to ± 47.1 mmHg). In our subgroup without a hypertension diagnosis, nighttime bias regarding SBP was 16.2 mmHg with LOA of ± 30 mmHg. Similar results were reported in other studies investigating 24ABPM accuracy of the same PAT-based device as

Nyvad et al (22, 36). Tan et al investigated a PWA-based cuffless wrist band in 41 normotensive and hypertensive adults and also found that particularly nighttime BP was overestimated (38). Nighttime SBP bias and LOA were 15.3 [-8.7, 39.3] mmHg. In contrast, Proença et al found good agreement between a cuffless wrist or upper arm worn device based on PWA of the PPG signal and conventional cuff measurements in 67 adults including healthy and hypertensives (23). Their daytime and nighttime SBP bias and LOA were -1.5 [-14.4, 11.4] mmHg and 0.4 [-14.4, 15.1] mmHg. Nachman et al investigated PWA of the PPG signal in combination with pulse wave transit times (PAT or pulse transit time not clearly specified) incorporated in a watch-like device in 28 participants both healthy and with stable chronic disease (8). This study is the only one to date to report high precision and accuracy with SBP LOA of [-6.9, 3.3 mmHg] and [-1.7, 2.6 mmHg] during daytime and nighttime respectively. All the cuffless devices in these studies were calibrated once when mounted using a brachial BP measurement.

The present study is the only one to date to report correlation coefficients that account for repeated measures within individuals. An important factor when evaluating accuracy of cuffless BP estimations is the degree of BP change within each individual after this initial calibration. A small intraindividual change in BP during data collection will result in a small bias and narrow LOA. Our participants had high within-subject variations in BP with mean SBP (SD) 55.6 (12.8) (Table 1). Within-subject variation in BP is not described in detail in the above-mentioned studies, but since they all describe standard 24ABPM settings we assume that within-subject variation is similar to our results, and thus, if the predicted BP values were accurate, high repeated measures correlation coefficients can be expected. In the present study, correlations corrected for repeated measurements within individuals showed no correlation for SBP or DBP. Other studies reported correlations of mean predicted BP vs mean ReferenceBP for each individual. In this way, predicted BP versus ReferenceBP show good correlation because of calibration at start of the measurement period and subsequently because there is a range in mean BP between individuals. We hypothesize that other studies that show discrepancies between reference and predicted BP that are similar to ours, also have poor repeated measures correlation. Even though the generalized PAT-based BP model did not achieve high accuracy results overall, the model was able to predict ambulatory BP changes in selected participants as displayed in figure 2.

A concerning finding in our results, as well as in most previous studies evaluating cuffless devices compared to conventional cuff-based 24ABPM, except from the study by Proença et al and Kachel et al, was the inability of the PAT-based BP model to predict nighttime BP (8, 22, 35, 38, 39). As shown above, agreements tended to be poorer for nighttime averages compared to daytime. A cuffless device utilizing the radial artery tonometry method also failed to detect nighttime dipping (37). Other PWA-devices, such as smart watches, showed a systematic bias toward a calibration point, overestimating low BPs and underestimating high BPs, in 40 normotensive and hypertensive subjects (11). Combining PWA and pulse wave transit time analyses seems to manage to overcome these difficulties and accurately predict nighttime BP (8). However, the findings from Kachel et al are yet to be reproduced in a manufacturer-independent clinical research study.

Our post-hoc analyses of ambulatory changes in the PPG signal did not reveal any possible explanatory mechanism towards our unexpected results (Figure 4). Contrary to our hypothesis that a less steep slope during nighttime could cause shorter PAT calculations, we found that the slope steepness increased from daytime to nighttime. Thus, we interpret the slope of the PPG signal to not affect the PAT calculations. The pre-ejection period (PEP) is a known potential confounder. PAT includes PEP, defined as the electromechanical delay from the

electrical R wave to the actual onset of the pulse wave when the aortic valve opens (40). PEP is repeatedly shown to lengthen during sleep (41). Thus, PEP cannot explain the observed shortening of PAT during sleep in our study. The shortcomings of PAT as cuffless surrogate measurement remain incompletely understood. Both PAT-based and PWA-based devices have been shown to accurately predict BP in subjects under controlled conditions in the laboratory. Sola et al demonstrated accurate BP predictions in the most common body positions of daily life of a PWA based bracelet compared to auscultation in 91 subjects (18) and Bilo et al showed similar results in 33 adults in the sitting position using a PAT based device (42). There are, however, many potential sources of error. It is well known that the contact pressure of the PPG sensor markedly alters the PPG waveform amplitude (43, 44). This issues a clinically relevant problem since sensor movement can result in altered PPG wave amplitude and shape due to changes in contact pressure and thereby alter the PAT measurement (45). The theoretical relationship between changes in PAT and BP is based on the Moens-Korteweg equation, in which changes in pulse wave propagation times arise from pressure induced changes in vessel wall stiffness if diameter and wall thickness are held relatively constant (46). Although this may be true in central elastic arteries, wall thickness and vessel diameter changes frequently in the peripheral circulation due to both systemic autonomic signals and local autoregulatory blood flow demands. HR is also suggested to affect pulse wave propagation times. Increased HR is shown to cause increased wave propagations independently of BP (47, 48). We believe these issues make PAT-based BP estimations extremely challenging or even impossible.

Previous studies have found 24ABPM to cause significant discomfort and sleep disturbances (50, 51). This can lead to both errors in measurements and falsely elevated BP (52, 53), and poor acceptance for repeated 24ABPM due to discomfort has been shown (2). Our questionnaire results showed that the cuffless device was more comfortable for participants and less disturbing during both daily activities and sleep compared to the ReferenceBP device during 24ABPM. The cuffless device showed promising results in limiting the impact of discomfort associated with 24ABPM measurements, especially during sleep. These findings agree with previous studies evaluating user acceptability of cuffless BP devices (8, 14, 35, 54, 55). The 28 participants in the study by Nachmann et al (8) reported the wrist monitor significantly more comfortable, less disturbing and had a significantly higher rating for long-term adherence. Similar results were found by Nyvad et al (35), Zeng et al (55) and by McGillon et al (14).

As an additional feature we investigated the ability of the device to predict sleep times. To the best of our knowledge, this is the first study to investigate this as an additional feature in a wearable cuffless BP device. Predicted sleep times from the model trained on one part of the dataaset showed high accuracy. Sleep time is important to correctly distinguish between daytime and nighttime BP values. However, in clincal practise default sleep time between 23 and 07 is often used regardless of the patients actual sleep time. Although diaries to adjust for acutal sleep and awake times are recommended, they are often only utilized in 24ABPM in research settings. Thus, automated features could improve sleep and awake classifications.

Strengths and Limitations

A strength of the present study is the 24-hour recording time under routine clinical conditions. This allows for an interpretation of clinical utility and feasibility. Our study provides, to the best of our knowledge, the highest number of study participants to date with 95 individuals included in the analysis and a data set with a total of 4010 BP measurement pairs. The ability to automatically detect sleep window by measuring movement, HR and HRV is an advantage

of the cuffless device compared to the ReferenceBP device. Furthermore, we evaluated both healthy individuals and individuals with a prior hypertension diagnosis (47.4 %). This is important because any novel method must show satisfactory accuracy in both groups. The gender distribution was relatively equal (42.1 % females).

The study has several limitations. First, as with other conventional cuff-based 24ABPM devices, our ReferenceBP device (Oscar 2, SunTech Medical, Morrisville, North Carolina, USA) is only validated according to ISO 81060-2:2013 standard in the seated position, and with stable, relaxed conditions. Accordingly, this and other cuff-based BP devices are not validated in an ambulatory setting. Therefore, the accuracy of these cuff-based BP devices during 24ABPM is unknown, still, they are currently accepted as the best ambulatory method to collect BP readings and are found to be part of the standard of care for hypertensive patients. Second, we excluded many individuals (38 %) and cannot rule out selection bias. However, the majority were related to quality criteria for minimum acceptable good measurement pairs within an individual and reflect issues related to signal quality. The signals from the prototype chest belt had unforeseeable amounts of noise in combination with loss of ECG electrode contact during free ambulatory living. The reason for this seemed to be issues with the flexible belt, such as stiff material, which later has been improved in addition to loss of signal from the first generation of ECG electrodes which were changed. Originally, the quality criteria regarding a valid participant 24ABPM were defined a priori to be at least 70 % good measurement pairs, of which “a good pair” was defined as at least 70 % valid data within the 2-minute cuff measurement window. However, as these criteria only yielded seven valid participants, the criteria were modified. We did not include very old individuals or very obese individuals. Furthermore, we used the ReferenceBP device as the calibration measurement for the PAT-based BP model. The findings regarding PAT as a cuffless surrogate measurement must be interpreted in light of PAT being measured at chest level, which could differ from PAT measured at different anatomical locations or by other signals.

There are also important methodological considerations regarding the questionnaire to evaluate the user acceptability and the sleep analyses. A limitation was the lack of validation of the survey. Additionally, evaluating the two methods together may affect the user evaluation (56, 57). This means that the user evaluates each of the products in relation to each other to a greater extent than evaluating the individual method. If the participant perceives belt monitoring as more positive than cuff monitoring, there is thus a possibility that belt monitoring is given a higher score, or gives the cuff a lower score, than if they had been evaluated separately. Finally, as measurements were carried out with both devices mounted at the same time, we cannot conclude that patient sleep would be significantly better if measurements were carried out only with the chest belt. The sleep/wake classifier was trained using self-reported sleep diaries, which is a limitation. The sleep diaries did not include nighttime wake-periods nor daytime sleep-periods. It is likely that the sleep/wake classifier can be improved if it is trained on objective reference measurements of sleep/wake-state.

Conclusion

In the present study, we demonstrated that a general PAT-based BP model measured by a prototype cuffless multi-sensor device on the chest significantly overestimated 24-hour and nighttime ambulatory BP in normotensive individuals and individuals with a prior hypertension diagnosis compared to conventional cuff measurements. We interpret this as a need for more data to develop robust and more complex models that can accurately estimate BP across differing postures and daily activities. The prototype multi-sensor device was reported to be more comfortable and less disturbing during daily activities and sleep

compared to the reference device. Furthermore, the prototype device showed promising results in automatic sleep detection. If sufficient accuracy can be achieved, cuffless BP devices have promising potential for clinical assessment of BP due to high user acceptability and the ability to estimate BP continuously during real-life conditions in relation to context data, rather than providing mere snapshots of the dynamic BP profile.

Conflict of interest

TMS, KGBR and AS are employees of the company behind the prototype cuffless multi-sensor device. The remaining authors have no conflicts of interest to declare.

Author Contributions

SH, TMS, ESB, FEMFE and BWG contributed to conception and design of the study. ESB designed the questionnaire. SH, HJG and KN performed the data collection. SH, KGBR, AS, ØG and ESB organized the database. SH and in part CH performed the data analysis and statistical analysis. CH and SH wrote the first draft of the manuscript. ØG and ESB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Data Availability Statement

BP predictions from the PAT-based model and the reference measurements can be made available upon a reasonable request. Raw signals and data regarding model development may not be disclosed.

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Tables

Table 1. General characteristics of included participants.

Age, median (IQR), years	49 (39.0 – 61.0)
Female sex, no (%)	40 (42.1)
Body mass index, mean (SD), kg/m2	26.7 (5.6)
Cuff size, no (%)	
1 (range 18-26 cm)	9 (9.5)
2 (range 26-34 cm)	66 (69.5)
3 (range 32-44 cm)	19 (20.0)
4 (range 42-55 cm)	1 (1.0)
Baseline Systolic Blood Pressure, mean (SD), mmHg	127.0 (15.2)
Baseline Diastolic Blood Pressure, mean (SD), mmHg	78.4 (10.6)
History of hypertension, no (%)	45 (47.4)
Treatment with antihypertensive drugs, no (%)	44 (46.3)
Mean within-subject 24-hour change in SBP (SD), mmHg	55.6 (12.8)

Table 2. Comparison between conventional cuff-based oscillometric device (ReferenceBP) measurements and PAT-based blood pressure measurements. SBP, systolic blood pressure. DBP, diastolic blood pressure.

	All participants (n=95)			Subgroup with hypertension (n = 45)			Subgroup without hypertension (n = 50)		
SBP, mean (SD), mmHg	ReferenceBP	Cuffless BP (PAT-based BP model)	P	ReferenceBP	Cuffless BP (PAT-based BP model)	P	ReferenceBP	Cuffless BP (PAT-based BP model)	P
24-hour	125.4 (14.8)	133.3 (21.1)	<0.001	131.4 (14.9)	143.5 (21.3)	<0.001	120.0 (12.6)	124.2 (16.3)	0.016
Daytime	129.7 (13.8)	133.6 (20.9)	0.017	135.5 (13.4)	143.8 (21.0)	0.003	124.6 (12.1)	124.5 (16.1)	0.967
Nighttime	113.1 (16.5)	131.9 (23.4)	<0.001	120.1 (17.9)	141.7 (24.4)	<0.001	106.8 (12.3)	123.0 (18.6)	< 0.001
DBP, mean (SD), mmHg									
24-hour	74.3 (9.0)	81.2 (12.5)	<0.001	77.2 (9.2)	85.6 (13.1)	< 0.001	71.7 (8.2)	77.1 (10.5)	< 0.001
Daytime	78.0 (8.5)	81.3 (12.6)	<0.001	80.5 (8.7)	85.8 (13.2)	0.001	75.7 (7.8)	77.3 (10.5)	0.132
Nighttime	63.8 (10.0)	80.5 (13.2)	<0.001	67.9 (10.0)	84.8 (14.2)	<0.001	60.1 (8.5)	76.6 (11.1)	< 0.001

Table 3. Sensitivity and specificity of the PAT-based blood pressure (BP) model compared to conventional cuff-based oscillometric device (ReferenceBP) as the gold standard.

		PAT-based BP model	
		SBP	DBP
24-hour	Sensitivity, %	85.7	96.0
	Specificity, %	60.0	65.7
Daytime	Sensitivity, %	79.4	100.0
	Specificity, %	67.2	76.7
Nighttime	Sensitivity, %	92.3	90.9
	Specificity, %	44.9	23.3

Figures

Figure 1. Flowchart of participant inclusion/exclusion.

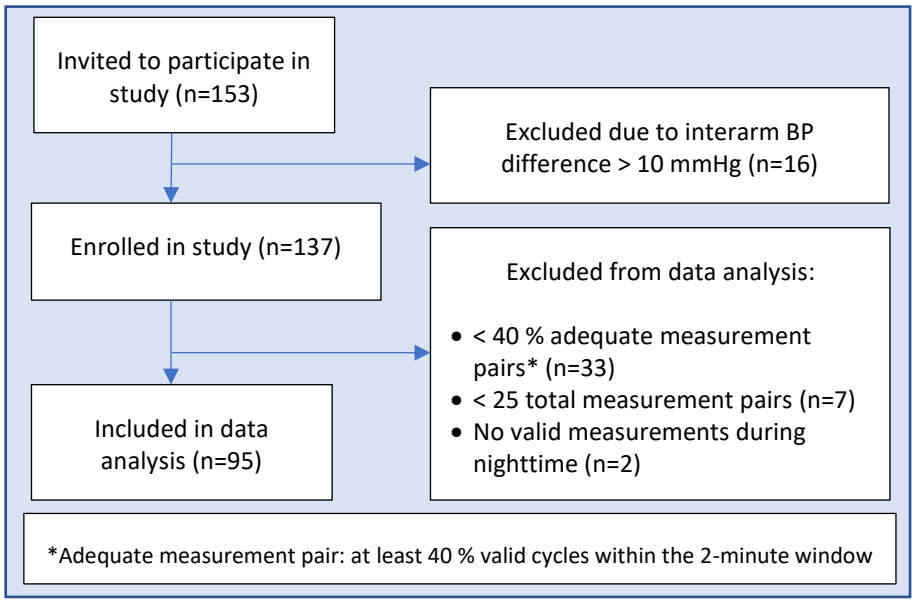

Figure 2. Time series plots from six different participants of systolic blood pressure (SBP) and diastolic blood pressure (DBP) from the cuff-based oscillometric device (ReferenceBP) and PAT-based blood pressure (BP) model (Predicted BP). Three subjects with mediocre agreement (A + B + C) and three subjects with poor agreement (D + E + F).

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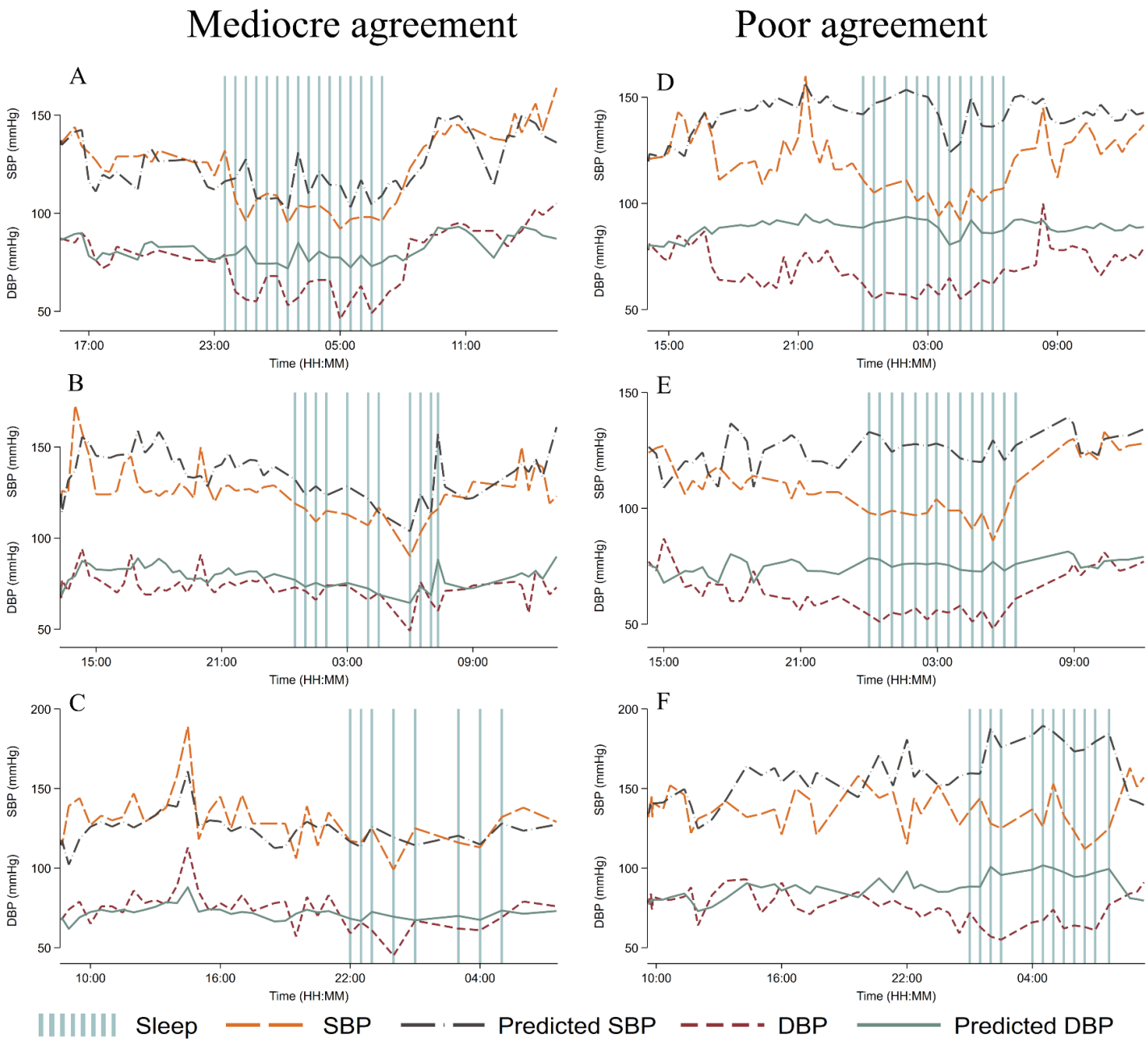

Mediocre agreement
Poor agreement
A
B
C
D
E
F
SBP (mmHg)
DBP (mmHg)
Time (HH:MM)
Sleep
SBP
Predicted SBP
DBP
Predicted DBP

749

750

Figure 3. Bland-Altman plots. Mean of measurements from the cuff-based oscillometric device (ReferenceBP) and PAT-based blood pressure (BP) model (x-axis) plotted against the difference between ReferenceBP and PAT-based BP model (y-axis). Horizontal lines indicate bias and upper and lower 95 % limits of agreement. Systolic blood pressure (SBP; left panels) and diastolic blood pressure (DBP; right panels) for the entire 24-hour measurement period (top panels), daytime measurements (mid panels) and nighttime measurements (bottom panels).

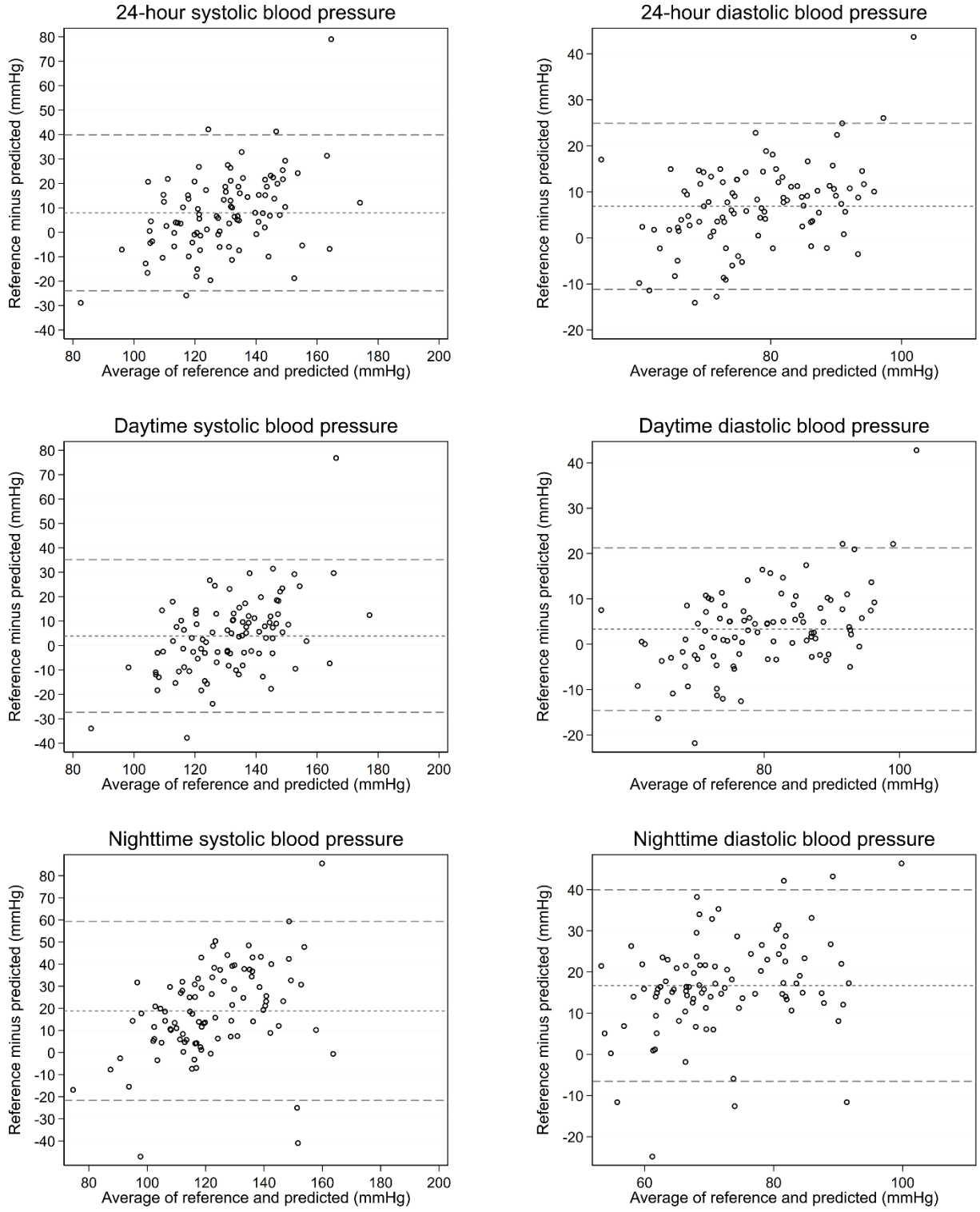


Figure 4. Hourly averages of pulse arrival time (A) and log transformed values of the first derivative of the photoplethysmography (PPG) waveform (B). A higher value of the log transformed first derivative indicates a steeper slope.

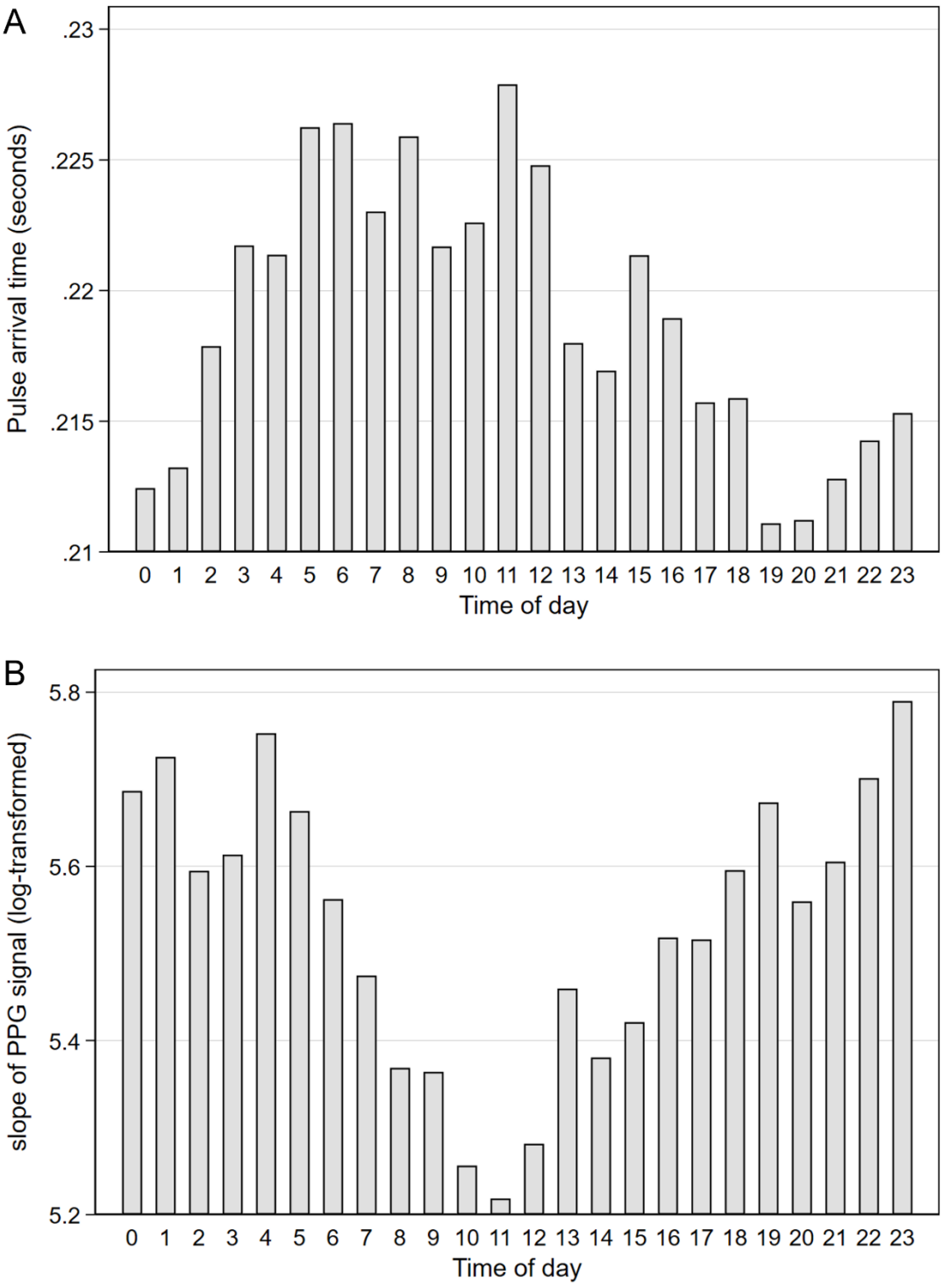


Figure 5. Participants' feedback regarding the use of the prototype cuffless multi-sensor device compared to cuff-based oscillometric device (ReferenceBP). Daily activity disturbance (A) and sleep disturbance (B) on a 7-point Likert scale or no answer, and prefered future monitoring method (C).

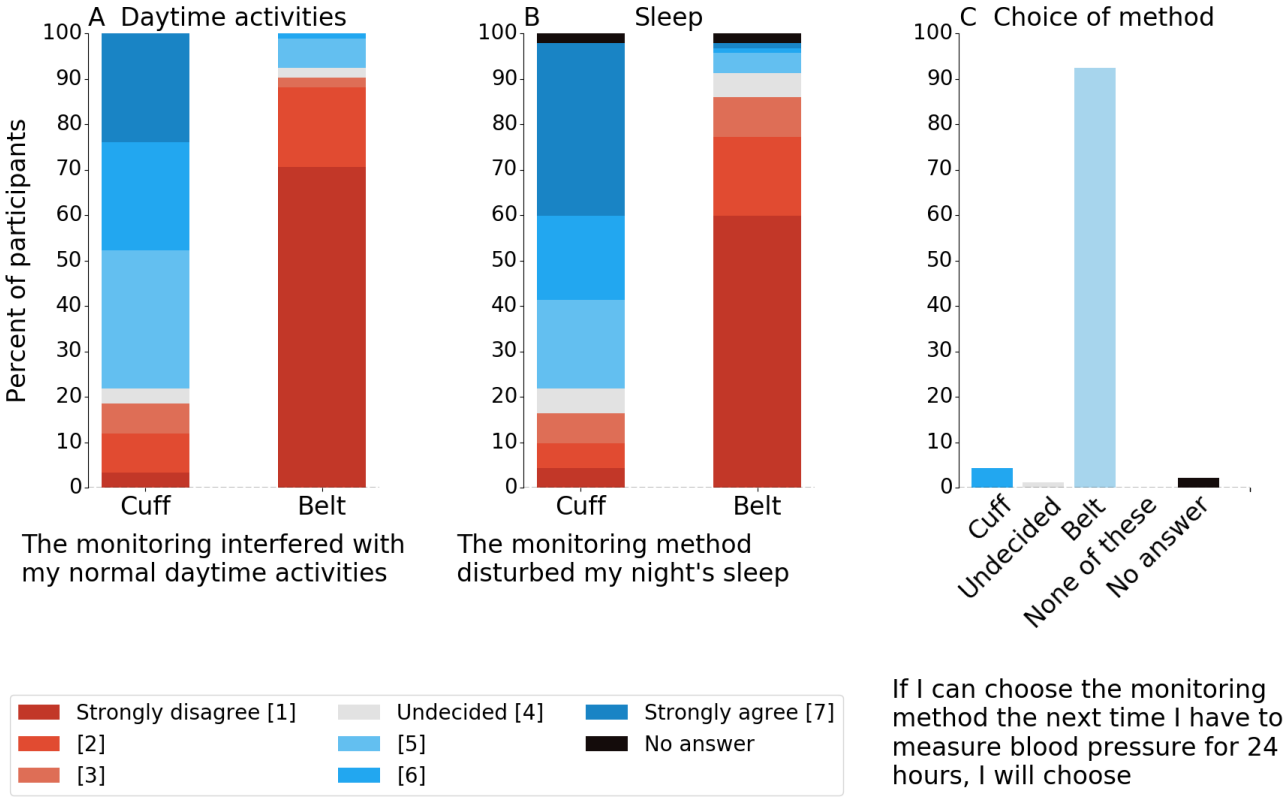
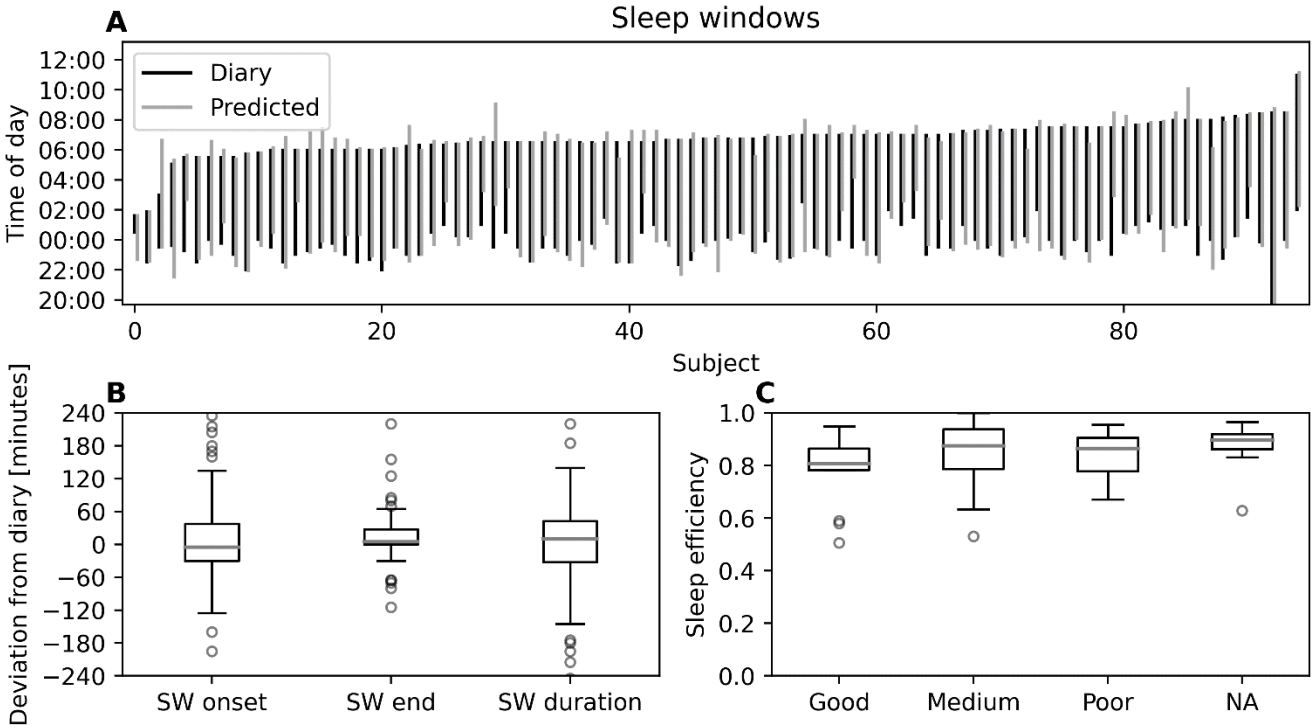


Figure 6.

(**A**) Reported (i.e. diary, black lines) versus predicted (gray lines) sleep windows (SW) for each participant. Numbering on horizontal axis represent participants. (**B**) Distribution of deviations between predicted SW and reported SW. The boxplots show interquartile range (box height) and median deviation (gray lines). “SW onset” and "SW end” indicates deviation between predicted and reported sleep window onset and end, respectively. “SW duration” indicate the deviation between predicted and reported sleep window duration. (**C**) Sleep efficiency (i.e. the fraction of time in bed classified as sleep) for the three self-reported sleep quality categories (“good”, “medium” and “poor”). “NA” indicates no response from the participant (*N*=8 occasions).



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Accuracy of non-invasive cuffless blood pressure in the intensive care unit: Promises and challenges

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Objective: Continuous non-invasive cuffless blood pressure (BP) monitoring may reduce adverse outcomes in hospitalized patients if accuracy is approved. We aimed to investigate accuracy of two different BP prediction models in critically ill intensive care unit (ICU) patients, using a prototype cuffless BP device based on electrocardiogram and photoplethysmography signals. We compared a pulse arrival time (PAT)-based BP model (generalized PAT-based model) derived from a general population cohort to more complex and individualized models (complex individualized models) utilizing other features of the BP sensor signals.

Methods: Patients admitted to an ICU with indication of invasive BP monitoring were included. The first half of each patient's data was used to train a subject-specific machine learning model (complex individualized models). The second half was used to estimate BP and test accuracy of both the generalized PAT-based model and the complex individualized models. A total of 7,327 measurements of 15s epochs were included in pairwise comparisons across 25 patients.

Results: The generalized PAT-based model achieved a mean absolute error (SD of errors) of 7.6 (7.2) mmHg, 3.3 (3.1) mmHg and 4.6 (4.4) mmHg for systolic BP, diastolic BP and mean arterial pressure (MAP) respectively. Corresponding results for the complex individualized model were 6.5 (6.7) mmHg, 3.1 (3.0) mmHg and 4.0 (4.0) mmHg. Percentage of absolute errors within 10mmHg for the generalized model were 77.6, 96.2, and 89.6% for systolic BP, diastolic BP and MAP, respectively. Corresponding results for the individualized model were 83.8, 96.2, and 94.2%. Accuracy was significantly improved when comparing the complex individualized models to the generalized PAT-based model in systolic BP and MAP, but not diastolic BP.

Conclusion: A generalized PAT-based model, developed from a different population was not able to accurately track BP changes in critically ill ICU patients. Individually fitted models utilizing other cuffless BP sensor signals significantly improved accuracy, indicating that cuffless BP can be measured non-invasively, but the challenge toward generalizable models remains for future research to resolve.

KEYWORDS

cuffless, blood pressure, pulse arrival time, machine learning, intensive care unit

1. Introduction

At present, blood pressure (BP) monitoring in hospitalized patients is limited to either intermittent cuff-based measurements or invasive arterial catheterization. Invasive arterial BP monitoring is the only method capable of accurate in-hospital continuous BP monitoring and is considered the gold standard given correct operating conditions. However, it is only available during surgery, post-operatively or in intensive care units (ICU) and requires specialized personnel. In addition, arterial catheterization carries risk such as bleeding, arterial occlusion and infection. For the remainder of hospitalized patients, BP is taken intermittently at varying intervals. Undetected hypotensive episodes may lead to organ damage such as acute kidney injury, and undetected clinical deterioration may delay adequate treatment and lead to adverse outcomes (1, 2). Studies indicate that adverse events are related to the intermittent nature of vital signs monitoring on hospital wards (3, 4). Thus, there is a clear need for non-invasive continuous cuffless BP monitoring in hospitalized patients to bridge the gap between intermittent cuff-based measurements and invasive arterial catheterization.

Despite substantial research on methods to enable non-invasive cuffless BP monitoring, its general accuracy remains uncertain, and few studies have investigated accuracy in critically ill patients. In addition, non-invasive cuffless BP methods use different approaches such as pulse wave propagation-based measurements (such as pulse arrival time (PAT)) and photo-plethysmography (PPG) waveform features. Studies, including research performed by our multidisciplinary team, have shown strong correlations between PAT and BP, particularly during various exercise methods (5–9) but its accuracy across differing populations and hemodynamic conditions are uncertain (6). New advances in non-invasive cuffless BP indicate that complex modeling by machine learning methods of sensor-based measurements are key toward improved results (6). In the present study, we aimed to investigate accuracy of two different BP-prediction models using the signals from a prototype chest belt BP sensor in critically ill patients. Specifically, we investigated a PAT-based model, derived from a general population cohort (generalized PAT-based model) compared to continuous invasive BP measurements and compared it with accuracy of individually fitted machine learning models (complex individualized models) that utilized other features of the signals obtained by the cuffless BP sensor.

2. Materials and methods

2.1. Subjects

Patients older than 18 years admitted to the general medical ICU at Oslo University Hospital, Ullevål were considered for inclusion. Inclusion criteria were signed consent and an inserted arterial line. Exclusion criteria were ongoing arrythmias generating irregular R-R intervals, failure to obtain adequate signals from the cuffless device or any medical contraindication to having a chest belt mounted. Each patient was monitored for a duration of 1–12 h, depending on length of stay, discontinuation of the intra-arterial catheter or other clinical interruptions.

2.2. Reference blood pressure

Reference BP was measured continuously with a radial artery catheter connected by a fluid filled tube to a pressure transducer (Xtrans; Codan, Forstinning, Germany). The pressure transducer was leveled at the phlebostatic axis and had a saline flush connected with a counterpressure of approximately 300 mmHg. The system was connected to a Philips IntelliVue MX 800 patient monitor (Philips, Böblingen, Germany). Zeroing was performed every 8-h according to the ICUs procedures. All vital signs, including the raw arterial waveform and the monitor-generated absolute BP values sampled every 5 s, were recorded directly to a laptop *via* an RS-232 connection using the Vital Recorder software (10).

2.3. Cuffless blood pressure device

A prototype cuffless BP sensor (cuffless BP device) was used in this study (7–9). It consists of a one-channel electrocardiogram (ECG) sensor, a photo-plethysmography (PPG) sensor and an inertial measurement unit (3D accelerometer and 3D gyroscope) integrated in a wearable chest belt. Raw signals from the ECG and PPG sensors were sampled at 1,000 Hz, while accelerometer data was sampled at 208 Hz and gyroscope data that were sampled at 26 Hz. The gyroscope data was not used. The cuffless BP device was fitted as illustrated in Figure 1. The generalized PAT-based model was developed from BP changes during isometric exercise in a general population cohort (9), using PAT and HR as cuffless surrogates but not any demographic information. A linear best fit equation with a coefficient for PAT, a coefficient for interaction between PAT and HR (this term was negligible) and a coefficient for HR was used. Additionally, we computed a best fit linear model using only PAT. The complex individualized models, utilizing other signal features, were trained using the first half of each patient's data. Thus, the test period for both models were defined as the second half of each patient's data. The cuffless BP device was calibrated against the first three minutes of reference BP at the start of each test period. This was a simple static calibration to correct the offset between average reference BP and cuffless BP across the initial three minutes. Since the pressure transducer was mounted on a bracket next to the patient bed, temporary periods occurred of which the pressure transducer moved relative to the phlebostatic axis. To reliably exclude such periods, an investigator continuously observed all data collections. In addition, if the pressure transducer moved significantly during such a period and was relevelled by the ICU staff, the cuffless BP device was re-calibrated against reference BP during the test period. Recalibration occurred in 14 patients (once in seven patients, twice in four patients and three times in two patients). Reasons for recalibration were related to nursing care, changing from supine bed rest to seated position or temporary detachment from the invasive monitoring system because of imaging studies or bathroom visits. Recalibration was decided necessary to avoid systematic biases introduced during relevelling. For example, if the pressure transducer was relevelled one time during a patient's data collection with an offset of 5 cm relative to the previous leveling, a systematic bias of 3.7 mmHg would be introduced for the remaining observation time.

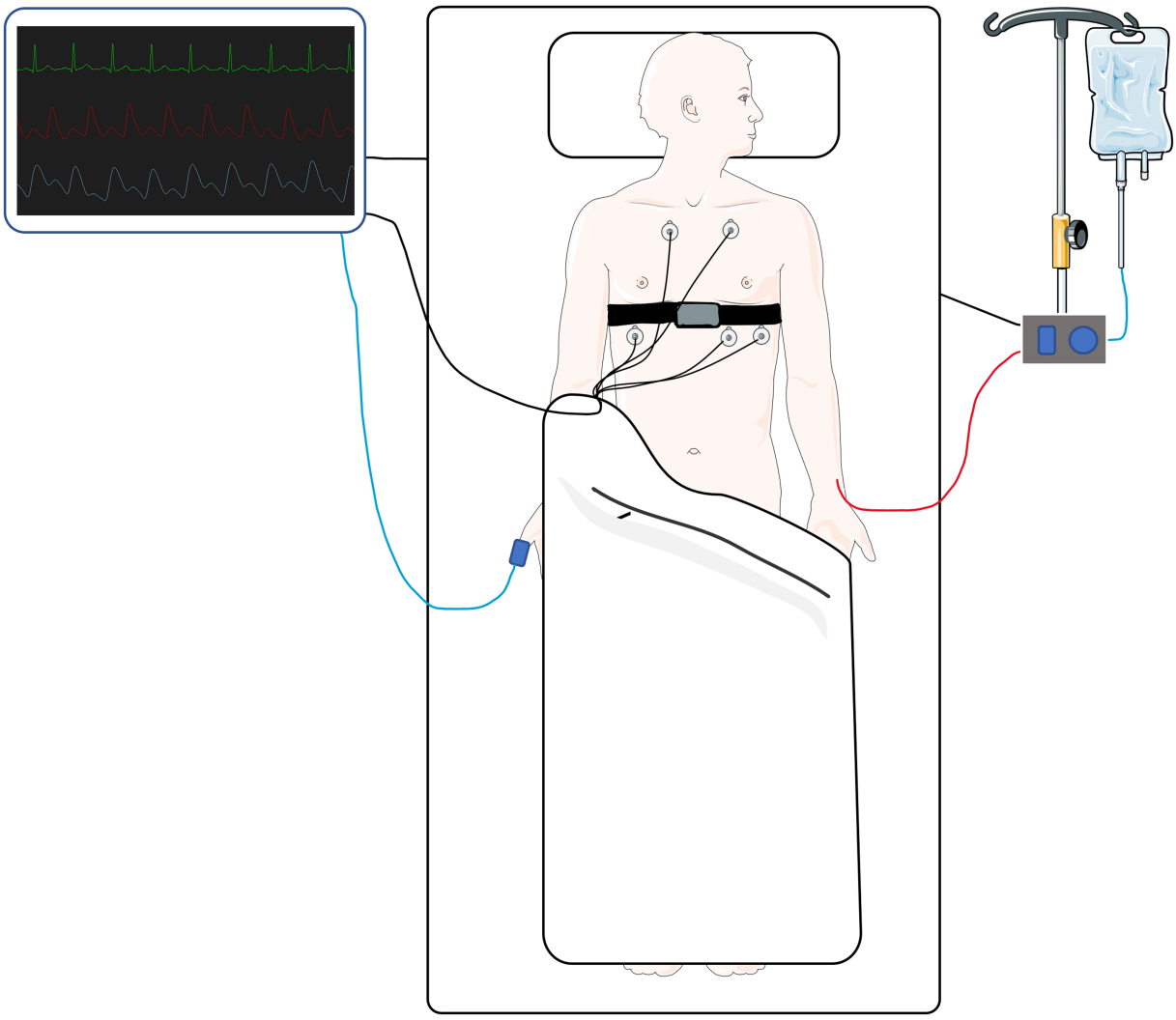

FIGURE 1
A simplified illustration of the chest belt device (cuffless device) fitted on a patient in the intensive care unit alongside basic monitoring equipment. Parts of the figure were created by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

2.4. Data analysis

2.4.1. Patient selection

Of 44 patients, 25 were available for the present study after exclusions (Figure 2). Prior to data analysis six patients were excluded due to the following reasons: (1) excessive movement causing the transducer to move relative to the leveling set point and excessive noise ($n = 2$), (2) arterial catheter failure ($n = 2$), (3) irregular RR intervals from pacemaker ($n = 1$) and (4) erroneous vital recorder data capture ($n = 1$). Thus, 38 patients were included in the formal data analysis. Next, the cuffless BP device data was processed to allow for proper training of the complex individualized models and 13 of the 38 patients were excluded because one or more of three criteria were met: (1) Ratio of valid device signals to reference data above 0.6 ($n = 9$), (2) short recordings (total number of reference and cuffless datapoints below 200) ($n = 11$) and (3) to ensure that adequate BP variation was available for the machine learning algorithm, the standard deviation of reference BP in the first half had to be at least 50% of the standard deviation of the reference BP for the whole duration of each individuals data ($n = 3$). Most patients met the criteria related to signal quality and number of reference and device measurement pairs.

2.4.2. Data filtering and processing

Filtering and processing of the data was performed post-hoc in a custom-made database using the Python programming language. Reference BP values were extracted from the raw arterial waveforms. The raw arterial waveform signals were filtered both manually and automatically to reliably remove artefacts from around arterial blood sampling, detachments and re-attachments to the arterial monitoring system, compression of waveforms from wrist flexion, cuff measurements taken at the same arm and high frequency noise. After filtering, reference BP and cuffless BP estimations from the two models were averaged on 15 s epochs. To allow for direct comparison between the two cuffless models, pairwise comparisons between cuffless BP and reference BP were made on the same data in each

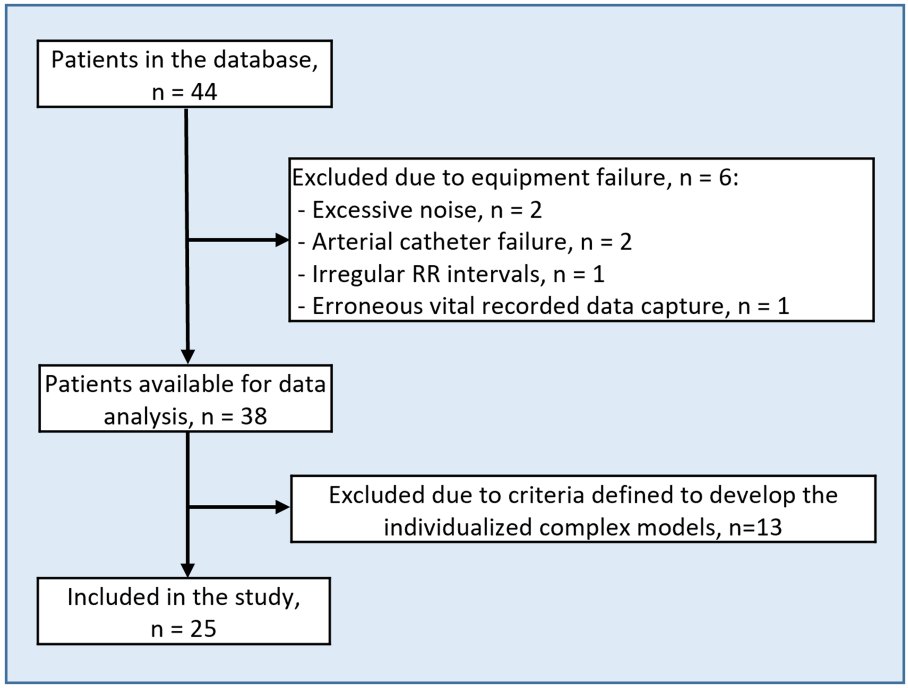

FIGURE 2
Flow chart of patient selection.

patient, i.e., the test period defined as the last 50% of data for each patient.

2.4.3. Statistical analyses

Statistical analyses were performed using Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Data is presented as mean (standard deviation (SD)) or median (interquartile range) if non-normal distribution. We computed mean errors, mean absolute errors (MAE), SD of errors and Bland–Altman plots with bias and 95% limits of agreement (LOA). We are aware that pooling all measurement pairs across all patients may violate the Bland–Altman assumption of independent measurements (11). However, all comparable studies have pooled all measurements in Bland–Altman analyses (12–15). Thus, we chose same methodology for comparative purposes. We also computed Bland–Altman bias and LOA using a proposed method for repeated measures (16) which resulted in bias and LOA (not reported) with negligible differences from the pooled analyses. Correlation analysis was performed using repeated measures correlation as proposed by Bland and Altman (17). In this way the dependency of repeated within subjects are correctly handled. To be able to compare with similar studies, Pearson's correlation coefficients were also calculated for all measurements across all subjects pooled together.

Comparison of model performance was analyzed in three steps. First, we compared error estimations to determine if they were different from each other. The absolute errors of all measurement pairs ($n = 7{,}327$) were compared by a non-parametric test for equality of means. Equality of the standard deviation of the errors were compared using a variance comparison test. Second, aggregated BP means per subject from reference BP, the generalized PAT-based model, and the complex individualized model were computed. These means were fitted with the corresponding reference values in a linear regression model for the two models. As these models are not nested, they could not be directly compared by any statistical test. Thus, they were compared numerically on the coefficient of determination (R^2), root mean squared error and Akaike's and the Bayesian information criterion. Finally, the predictive accuracy of the two models were tested using the Diebold-Mariano predictive accuracy test. The stationary assumption was tested using the augmented Dickey-Fuller test. Sensitivity of the predictive accuracy test, as the stationary assumption may not hold regardless of the result of the augmented Dickey-Fuller test because the data is comprised of different subjects, were tested by performing the Diebold-Mariano test in each subject separately. The overall significance was tested using Fisher's method of combining p values. To test the influence of HR as an additional parameter in the PAT-based model, we also predicted BP using a PAT-only model derived from the data as the PAT and HR-based model. A value of p below 0.05 was considered statistically significant.

3. Results

Patient characteristics are presented in Table 1 and distribution of reference BP across all patients are presented in Table 2. The average number of pairwise comparisons (SD) between reference and the cuffless BP device per subject were 293.2 (161.2), ranging from 124 to 754 with a total of 7,327. Median (Interquartile range) observation time was 4.0 (3.1–4.6) hours with a range from 1.4–8.0 h. Performance of the generalized PAT-based model compared to the complex individualized models are presented in Table 3. The complex individualized models were numerically superior to the generalized PAT-based model across all parameters. Particularly when comparing

the repeated measures correlation, more covariation was captured by the complex individualized models compared to the generalized PAT-based model for SBP and MAP where repeated measures correlation coefficients were 0.23 vs. 0.39 and 0.25 vs. 0.37. Results were more similar for DBP compared to SBP and MAP with correlation coefficients of 0.29 (generalized PAT-based model) vs. 0.33 (complex individualized models). Bland–Altman plots with bias and LOA are presented in Figure 3. Bias was close to zero for all BP parameters in both models; −0.2 mmHg vs. −1.4 mmHg, −0.2 vs. 0.0 mmHg and 0.1 mmHg vs. −0.9 mmHg for the generalized PAT-based model vs. the complex individualized models regarding SBP, DBP, and MAP, respectively. LOA favored the complex individualized models for SBP [−21.5, 21.1 mmHg] vs. [−19.2, 16.2 mmHg] and MAP [−13.4, 13.5 mmHg] vs. [−13.9, 11.4 mmHg] but were similar for DBP [−9.8, 9.8 mmHg] vs. [−9.6, 9.6 mmHg]. Percentages of absolute errors within 15, 10 and 5 mmHg (Table 4) also favored the complex individualized models where all percentages were numerically higher for the complex individualized models except for within 15 mmHg regarding DBP. The complex individualized models were significantly different from and outperformed the generalized PAT-based model for SBP and MAP. To the contrary, for DBP, the SD of the errors were not significantly different, and the Diebold-Mariano test of predictive accuracy was not significant. Comparison of the PAT and HR-based model to a PAT-only model showed negligible differences. Pearson's correlation coefficient and R^2 between the two models were 0.999 and 0.997, respectively.

An important difference between the generalized PAT-based model and the complex individualized models appeared during the detailed data inspection The generalized PAT-based model performed inadequately in cases of decreasing BP with corresponding heart rate (HR) increase. Therefore, we plotted four different timeseries plots (Figure 4) of four different patients where reduction in BP was coupled with a rise in HR. In the first case (upper left panel) both models were unable to predict the BP reduction, while for the remaining cases, only the complex individualized models correctly predicted the direction of change in BP. Importantly, regarding periods of reduction in BP coupled with a rise in HR, the generalized PAT-based model compared to the PAT-only model showed negligible differences.

TABLE 1 Patient characteristics.

Sex, male no (%)	18 (72)
Age, years (SD), range	62.0 (15.4), 27–89
Body mass index, Kg/m^2(SD)	27.1 (6.4)
Cardiovascular Disease, no (%)	10 (40)
Hypertension, no (%)	17 (68)
Diabetes mellitus type I or II, no (%)	9 (36)
Ongoing intravenous vasopressor treatment, no (%)	2 (8)
Ongoing intravenous vasodilator treatment, no (%)	4 (16)
Ongoing non-invasive continuous or bi-level positive airway pressure, no (%)	2 (8)

4. Discussion

Continuous and cuffless non-invasive BP monitoring may improve in-hospital patient monitoring by early detection of clinical deterioration and reduction of adverse outcomes (18). The present study investigated the accuracy of two different predictive BP models using sensor data from a prototype cuffless BP chest belt against intra-arterial measurements in a critically ill ICU cohort. Specifically, we compared a PAT-based model derived from a general population cohort to complex individualized models. The present study had two main findings. First, the generalized PAT-based model did not achieve high accuracy results, indicating that PAT-based BP monitoring in critically ill patients may not be possible, particularly when considering the inability to detect periods of hypotension and tachycardia. Second, the complex individualized models significantly improved accuracy of the cuffless BP device for SBP and MAP, but not DBP, and were able to better track BP changes during hypotension and tachycardia.

The significantly improved accuracy by the complex individualized models sheds light on important challenges regarding non-invasive cuffless BP devices. PAT is frequently cited as a potential non-invasive cuffless surrogate feature in recent years (5). Our results, however, suggests that PAT may not be adequate as cuffless surrogate measurement alone to achieve high accuracy non-invasive BP measurement in critically ill patients. An underlying assumption for general accuracy is stability of the relationship between changes in PAT and changes in BP across individuals, populations and across differing hemodynamic conditions. One or more of these factors likely affect generalizability of PAT as a cuffless surrogate measurement. Several studies have shown that varying between-individuals relationships between PAT and BP are a major limitation (9, 18, 19). The improved accuracy of the complex individualized models indicates that features extracted from ECG and PPG sensors can enable non-invasive cuffless BP monitoring, but these models are patient-specific (and potentially cannot be generalized for all subjects) and rely on machine learning without any *a priori* physiological knowledge. In addition to improved errors, an important finding was the ability of the complex individualized models to better track BP fluctuations, reflected by correlations corrected for repeated within subjects' measurements (0.23 for the generalized PAT-based model vs. 0.39 for the complex individualized models regarding SBP). It should

TABLE 2 Blood pressure distribution.

	Systolic blood pressure	Diastolic blood pressure	Mean arterial pressure
Mean (SD), mmHg	131.0 (25.7)	61.2 (14.6)	83.9 (18.1)
Range, min-max, mmHg	70.6–194.3	34–100.3	50.9–136.3
Within subject change, median (IQR), mmHg	29.3 (25.0–42.1)	13.4 (12.0–17.0)	18.6 (25.8–27.7)

TABLE 3 Performance of the generalized PAT-based model, the complex individualized models and comparison of the two.

	Generalized PAT-based model	Complex individualized models	*p* value for comparison
Systolic blood pressure			
Mean error, mmHg	−0.2	−1.4	
Mean absolute error (SD), mmHg	7.6 (5.3)	6.5 (4.8)	<0.001*
SD of errors, mmHg	7.2	6.7	<0.001**
Median of absolute errors (IQR), mmHg	5.3 (4.5–10.7)	5.8 (4.7–7.3)	
Repeated measures correlation coefficient	0.23	0.39	
Correlation coefficient, all subjects pooled	0.91	0.94	
Linear regression of aggregated data between model and reference***, R^2	0.91	0.96	
Akaike's information criterion***	173	154	
Bayesian information criterion***	175	156	
Diebold-Mariano comparison of predictive accuracy	Individualized model is significantly better		0.001
Diastolic blood pressure			
Mean error, mmHg	0.2	0.0	
Mean absolute error, mean (SD), mmHg	3.3 (3.3)	3.1 (2.2)	<0.001*
SD of errors, mmHg	−3.1	3.0	0.56**
Median of absolute errors (IQR), mmHg	2.7 (1.8–4.1)	2.2 (1.7–3.5)	
Repeated measures correlation coefficient	0.29	0.33	
Correlation coefficient, all subjects pooled.	0.94	0.94	
Linear regression of aggregated data between model and reference***, R^2	0.94	0.94	
Akaike's information criterion***	131	130	
Bayesian information criterion***	134	133	
Diebold-Mariano comparison of predictive accuracy	Individualized model is non-significantly better		0.14
Mean arterial pressure			
Mean error, mmHg	0.1	−0.1	
Mean absolute error, mean (SD), mmHg	4.6 (3.2)	4.0 (2.9)	<0.001*
SD of errors, mmHg	4.4	4.0	<0.001**
Median of absolute errors (IQR), mmHg	3.3 (2.4–6.4)	3.3 (2.5–4.5)	
Repeated measures correlation coefficient	0.25	0.37	
Correlation coefficient, all subjects pooled.	0.93	0.95	
Linear regression of aggregated data between model and reference***, R^2	0.93	0.95	
Akaike's information criterion***	146	138	
Bayesian information criterion***	149	140	
Diebold-Mariano comparison of predictive accuracy	Individualized model is significantly better		0.006

*Compared using non-parametric test of difference in means of all absolute errors between the two models. **Compared using variance comparison test of equality of standard deviations. ***Means of predicted BP from each model for each subject fitted in a linear regression model against reference BP.

be kept in mind that correlation across all the data is suppressed by the fact that there were stable periods where BP had low variation.

A concerning finding in our analyses was the inability of the generalized PAT-based model to predict BP changes during some periods of BP reductions coupled with elevation in HR (Figure 4). In our data, the complex individualized models estimated BP better in these situations. In the first scenario in Figure 4 (upper left panel) all models fail, whereas for the next three scenarios the complex individualized models predict the correct direction of BP change while the generalized PAT-based model and the PAT-only model predicts an increase in BP during reduction of reference BP and increases of HR. Our findings suggest that PAT is dependent on HR; an increase in HR causes PAT to decrease independently of the underlying change in BP (a decrease in PAT should always indicate an increase in BP according to the theory). Although conflicting results exists, HR has been shown to affect pulse wave propagation independently of BP similarly to our observations (20, 21). It is also possible that elevated HR is an indication of elevated sympathetic tone, which is shown to increase pulse wave propagation speed independently of central aortic BP (22). This can mask the true BP change in cases were HR and BP change in opposite directions. It should be noted that this was not a pre-specified analysis nor tested in

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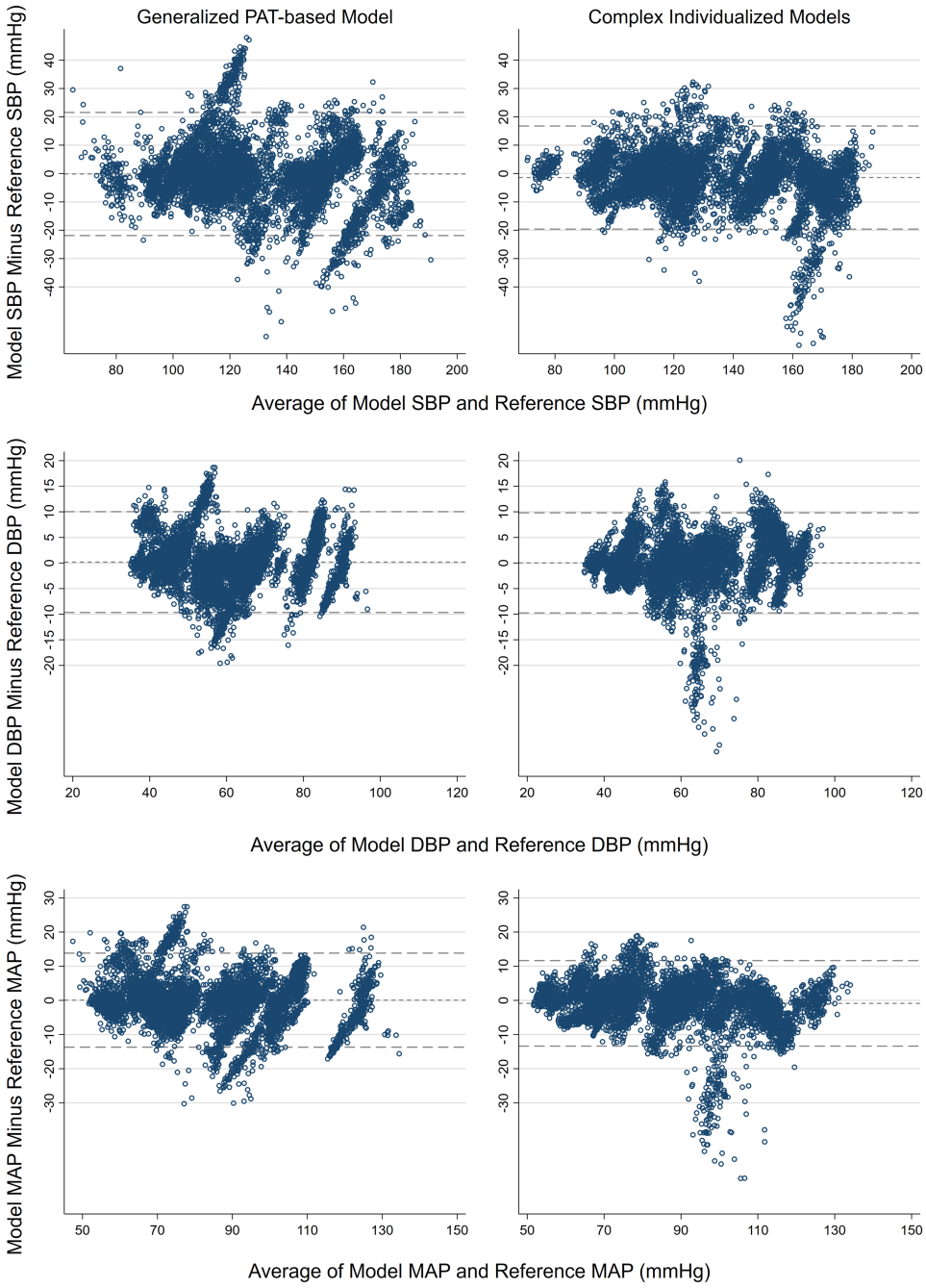

FIGURE 3
Bland–Altman plots. Mean of reference and model (*x*-axis) plotted against the difference between reference and model (*y*-axis). Horizontal lines indicate bias and upper and lower 95% limits of agreement. SBP, systolic blood pressure. DBP, diastolic blood pressure. MAP, mean arterial pressure.

any statistical model, merely, an indication of a potential serious limitation of cuff-based BP monitoring. We interpret this as a need for more data to develop robust models that can accurately estimate BP across differing hemodynamic conditions.

The generalized PAT-based model and complex individualized models achieved LOA of [−21.5, 21.1 mmHg] vs. [−19.2, 16.2 mmHg] regarding SBP and [−13.4, 13.5 mmHg] vs. [−13.9, 11.4 mmHg] regarding MAP. Corresponding results of MAE (SD of errors) were 7.6 (7.2) vs. 6.5 (6.7) and 4.6 (4.4) vs. 4.0 (4.0) regarding SBP and MAP, respectively. These results fall short of accuracy demands required in potentially unstable ICU patients. Particularly when considering the inability of the generalized PAT-based model to predict BP reductions coupled with elevated HR, which is critical in hospitalized patients as such circulatory changes may suggest onset of shock. On the other hand, considering more stable patients and that 78% (generalized PAT-based) and 84% (complex individualized models) of the absolute differences were below 10 mmHg regarding SBP, one may argue that our results are acceptable. It should also be kept in mind that the accuracy of the "gold standard" itself is dependent on appropriate damping as well as leveling and zeroing of the pressure transducer. In

TABLE 4 Percentage of absolute errors within 15, 10, and 5mmHg.

	Model	Systolic blood pressure	Diastolic blood pressure	Mean arterial pressure
≤5 mmHg	Generalized PAT-based model, %	53.1	78.9	69.2
	Complex individualized models, %	59.2	85.3	78.8
≤10 mmHg	Generalized PAT-based model, %	77.6	96.2	89.6
	Complex individualized models, %	83.8	97	94.2
≤15 mmHg	Generalized PAT-based model, %	87.9	99.7	95.9
	Complex individualized models, %	92.9	98.5	97.8

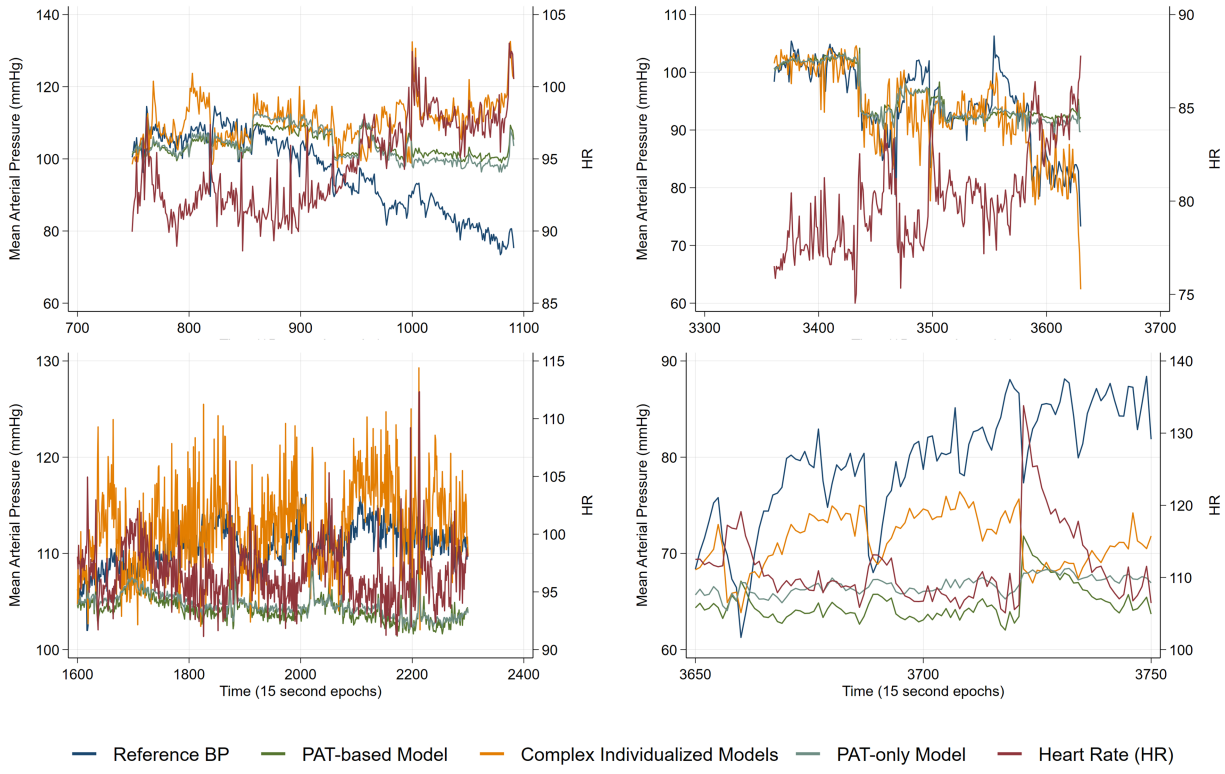

FIGURE 4
Time series plots from four different patients of reference mean arterial pressure (MAP), heart rate (HR) and predicted MAP from the two models in addition to predicted MAP from a PAT-only model.

everyday management of patients in the ICU, brachial oscillometric cuff BPs are taken regularly. Our LOA were considerably narrower compared to SBP LOA of [−30.2, 31.7 mmHg] revealed in a retrospective analysis comparing oscillometric cuff measurements to invasive measurements in 736 ICU patients (23).

We did not pre-specify any cut-off error statistic because we were evaluating a prototype of the cuffless BP device and the anticipated ISO 81060-3 validation standard applicable to cuffless BP devices was not completed at the time of study planning and data analysis. Acceptance criteria from validation standards aimed at cuff-based devices are not appropriate (24). As a consequence of lack of appropriate validation requirements regarding cuffless BP devices, many have compared against the Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) criterion; mean error less than 5 mmHg and SD of errors less than 8 mmHg regarding SBP (12, 14, 15). Both our models satisfy this criterion as all mean errors were close to zero. This criterion is, however, intended for standardized cuff measurements seated at rest. Thus, it is difficult to specify clinically accepted accuracy in the study setting. Validation of novel cuffless BP devices dependent on calibration, of which all are at present, should be performed according to the new AAMI/ESH/ISO consensus validation protocol (24). Cuffless BP devices that pass the cuff-intended AAMI/ESH/ISO criterion may not be interpreted as accurate until also passing the new protocol intended to validate initial stability, accuracy during BP changes and reproducibility of stability within the time window of intended use.

Our device performances were comparable to the few similar studies that have investigated accuracy in a cuffless BP device, based on either ECG and PPG or PPG alone, against invasive measurements (12–15). Three of these devices are available on the market (12–14)

and one is a prototype (15). It is however difficult to compare results from those directly due to heterogenicity. Our results demonstrated the least narrow LOA compared to SBP LOA of [−10, 10 mmHg] in 10 post cardiac surgery patients (Biobeat wrist watch) (13), [−11.9, 12.2 mmHg] in 23 ICU patients (Aktiia wrist band, PPG) (12), [−11, 16 mmHg] during cardiac catheterization in 17 patients (Senbiosys prototype finger ring, PPG) (15) and [−7.4, 12.8 mmHg] in 20 cardiac ICU patients during controlled short-term supine and in bed measurements (Vitaliti continuous vital signs monitor, ECG and PPG) (14). However, while not achieving as narrow LOA, our study had the most subjects, 25 vs. 10 (Biobeat, ECG and PPG), 23 (Aktiia), 17 (Senbiosys) and 20 (Vitaliti) and by far the largest number of pairwise comparisons of 7,327 compared to 4,000 (Biobeat), 326 (Aktiia), 708 (Senbiosys) and 120 (Vitaliti). Sampling rate also varied between studies from 10 s epochs by Senbiosys to 1-min epochs by Biobeat. All studies excluded a large proportion of patients of which the majority were related to signal selection by algorithms or noise. A particularly important factor regarding cuffless BP devices is the degree of BP change within each patient during data collection. As all devices are dependent on initial calibration, a low change in BP within subjects may result in narrow LOA but the actual ability of these devices to track changes in BP remains unknown. Vitaliti reported measurements only from a stable period immediately following calibration, and Biobeat reported that their subjects were relatively stable as a limitation (within subject ranges not reported). Our subjects had reasonable within subject variations in BP with median SBP (IQR) of 29.3 (25.0–42.1) mmHg with a maximum of 63.2 mmHg. A related issue is reporting of Pearson's correlation coefficients which are pooled across all subjects, particularly when the devices are calibration dependent and there are repeated measurements within individuals. For comparative purposes we also computed Pearson's correlation coefficients from all measurements pooled and achieved 0.91 (generalized PAT-based model) and 0.94 (complex individualized models) for SBP compared to 0.94 (Biobeat), 0.87 (Aktiia) and 0.93 (Senbiosys). However, Pearson's correlation coefficients in this setting does not reflect device accuracy. In contrast, one study found a cuffless BP device using ECG and PPG inaccurate during coronary angiography with SBP LOA of [−2, 70 mmHg] (25). The study was, however, criticized by the manufacturer for incorrect calibration (26).

5. Strengths and limitations

A strength in our study is that neither model used any demographic information. The use of demographic information in cuff less research is criticized (27) because demographics itself are known to correlate with BP. Thus, when evaluating accuracy, it is not known how much is related merely to demographics as input in a model. We also provided, to the best of our knowledge, the most datapoints to date in a study evaluating accuracy of a cuffless BP device against invasive arterial measurements. Testing on critically ill patients admitted to an ICU enabled us to reveal the weaknesses of a PAT-based model and the strengths of complex individually fitted models.

We excluded many subjects (43%). However, the majority were related to criteria for developing the complex individualized models and we had comparable proportions and reasons for exclusion to similar studies. Algorithm selection imposes potential limitations on which patients may benefit from cuffless BP in the future. Re-calibration during the data collection in 14 patients may have introduced some overestimation of accuracy. If the device estimation of BP had drifted from reference BP, recalibration would artificially improve error estimates. However, as stated in the methods section, not recalibrating could introduce systemic errors and since the majority only had one recalibration it was decided to recalibrate if the transducer was relevelled. We did not formally test quality of the arterial line by for example the square wave test and calculation of damping coefficients. Since the transducer is levelled on a bracket next to the patient, arterial line BP accuracy is vulnerable to patient movement. We cannot exclude that some variations in reference BP were introduced in this manner. To reliably exclude all periods of which the pressure transducer was out of system, all data collection were observed by an investigator. The critically ill cohort is heterogenous. With a limited number of subjects, we cannot determine which, if any, clinical parameters affected accuracy. PAT can be measured at various places and we are limited to infer our findings to PAT measured at chest level.

6. Conclusion

Cuffless BP monitoring is promising, but challenges remain. In the present study, we demonstrated that a generalized PAT-based model measured on the chest did not achieve high accuracy results in critically ill ICU patients and failed to detect clinically important situations. We further demonstrated that more complex and individually fitted models, utilizing more information from the ECG and PPG signals, significantly outperformed the generalized PAT-based model. More data is needed to build robust general models based on machine learning to enable cuffless BP in hospitalized patients.

Data availability statement

The datasets presented in this article are not readily available because raw signals and data regarding model development may not be disclosed. BP predictions from both models together with reference measurements can be made available upon a formal request. Requests to access the datasets should be directed to sondhe@ous-hf.no.

Ethics statement

The studies involving human participants were reviewed and approved by REK sør-øst (REC south-east), Oslo, Norway. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SH, TS, FF, and BW-G contributed to conception and design of the study. SH performed the data collection. KB-R, AS, ØH, and VG organized the database. SH, KB-R, AS, ØH, and VG performed the

data analysis and statistical analysis. SH wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

KB-R, AS, and TS were employed by company Aidee Health AS.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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