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Challenges Presented by Cuffless Measurement of Blood Pressure if Adopted for Diagnosis and Treatment of Hypertension

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Abstract
The global health burden presented by hypertension is providing increased motivation for improved means of collection of blood pressure (BP) data. A growing area of research and commercial activity is the use of wearable devices to provide BP data using non-invasive cuffless techniques. The accelerated progress in recent years, particularly relating to connectivity of smartphone technology, has promoted the availability of consumer devices that provide values of BP. The main types of devices are wrist-worn, watch-type devices with sensors that typically record a photoplethysmography (PPG) signal, sometimes also with an electrocardiography (ECG) signal. The general underlying concept of the cuffless BP measurement in most device types is the association of BP and the travel time of the arterial pulse between two locations, determined from the time delay between the ECG and PPG signals. Other methods may involve additional analysis of the PPG waveform features. Experimental data are presented to illustrate the challenges presented by cuffless BP techniques in obtaining reliable BP measurements when the change in BP is caused by different stimuli affecting cardiac and vascular mechanisms. These effects influence the association of the measured and physiological BP change, thus presenting significant challenges and potential limitations in the use of cuffless BP devices for the diagnosis and treatment of hypertension.

Introduction

Of all sectors in modern society undergoing profound change due to the ubiquitous digital transformation, healthcare is amongst the slowest. In healthcare, of the most significant of all modifiable risk factors that could benefit from the technological advances, hypertension is perhaps the one that has made the least progress in all aspects, featuring low awareness, no progress in novel drug discovery, and low rates of treatment and control [1]. Hence, serious transformation is required for the health benefits of detection and treatment of hypertension to translate to global cardiovascular risk reduction [2]. A critical component of this transformation, with the aim

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to increase awareness and improve rates of treatment, is the trend to transfer blood pressure (BP) measurement from the clinician to the individual, such that the close engagement will result in the individual's better understanding of the risk implications of elevated BP, better compliance with medication, and better collection of BP data by having an increased number of measurements.

In evaluating screening for hypertension, the US Preventive Services Task Force issued a Class A recommendation that initial screening for hypertension in adults (>18 years) should be performed with office BP measurements, and diagnostic confirmation to be obtained with BP measurements outside the clinical setting before commencement of treatment [3]. To date, BP measurement outside the clinical setting mainly involves 24-h ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM). Both ABPM and HBPM deliver increased number of BP readings and can provide information on circadian BP variation. However, they still suffer from the inherent limitations of the brachial cuff sphygmomanometer with intermittent readings and essentially obtrusive operation. And all of this is in the context of large, randomized trials advocating more intense management of hypertension to lower thresholds across all age groups [4]. Recent developments in theory and technology for cuffless BP measurement [5] hold the promise to bypass these limitations and potentially alter the way BP is understood in daily living [6] by obtaining BP information which is continuous, unobtrusive and can contribute to the "big data" approach in harnessing analysis on digital platforms for improved and individualized treatment of hypertension [2, 7–9].

The entry of healthcare into the digital age and the recognition of the potential benefits of continuous BP measurement have accelerated the adoption of wearable devices that measure vital signs to include BP. Whilst vital signs such as heart rate (HR), respiration, and oxygen saturation are readily measured with acceptable degree of accuracy, BP measurement has been essentially elusive. However, there is an explosion of wearable devices (mainly wrist-worn, watch-type devices) that are now available on the market that purport to measure arterial BP. This, in itself, is potentially problematic, because, with consumer devices being readily available and affordable, and the emphasis of increased individual participation in BP measurement, the individual could be falsely empowered to titrate medication based on device readings or cause unwarranted concern. The problem being that there is no way of knowing if the readings are reliable, or if, indeed, they relate at all to the physiological BP.

This presents a dilemma for both clinicians and patients. On the one hand, the technology would make it easier to obtain unobtrusive BP measurements for better monitoring, and so elimination of artefactual situations such as operator-dependent readings. On the other hand, most available devices have not been clinically validated, and most also have no regulatory approval. This is because most are sold as consumer devices and so are not subject to the strict regulatory requirements as mandated for diagnostic devices. However, the consumer (patient) can still present data to the clinician as if the wearable device BP was similar to that provided by the conventional brachial cuff device from HBPM or ABPM measurements.

Challenges

The field of wearable devices for cuffless BP measurements is at a critical point. The clinical need is driven by the transformation required for the future of hypertension management [2, 7], particularly for global reduction of cardiovascular risk in middle- and low-income countries [1]. This is resulting in the perception that because a watch-type device has a feature for BP measurement, it is as trustworthy as the other vital signs from the watch, such as HR or blood oxygen saturation. This misconception is due mainly to poor or inadequate understanding of the differences in the modalities of measurement for different vital signs. For example, accurate measurement of HR simply requires the counting of events related to the heartbeat and not based on any underlying physiological principle of inference. This measurement does not require any calibration procedure. On the contrary, noninvasive BP measurement is based on external signals with an association to intra-arterial BP that does require calibration. And additionally, there should be consideration of the fundamental difference between cuff and cuffless BP measurement.

In the brachial cuff sphygmomanometer, there is an absolute measurement of pressure, that is, the air pressure in the pneumatic cuff, and this is associated with underlying physiological mechanisms and signals such as audible sounds originating from turbulent flow in a collapsed artery (Korotkoff sounds) or time-dependent changes of the pulsations in the cuff during inflation/deflation (oscillogram). The calibration that is required for a cuff device is that of the pressure transducer (a requirement which is non-existent if a well-maintained column of mercury is used). For cuffless BP measurement, there is

generally no actual measurement of pressure, but rather arterial hemodynamic signals that are related to BP. The calibration required for cuffless BP devices is not the same as that for the cuff device. The calibration is essential to relate the output of the algorithm used to estimate BP from the measured signals to a fiducial measurement of BP, which is usually done by a validated cuff device. The algorithms for BP estimation are based mainly on measurement for pulse transit time (PTT) from two separate simultaneous arterial signals, or more commonly for most wearable devices, pulse arrival time (PAT) obtained from the time delay between the electrocardiogram (ECG) and an arterial pulse signal. It is important to note that PAT includes both PTT and the cardiac isovolumic contraction time (IVCT; PAT = IVCT + PTT), which has the capacity to influence the relationship between arterial BP and transit time of the arterial pulse [10].

The challenges that are currently presented by cuffless BP devices are underpinned by the broadly related aspects described above. In the context of using cuffless BP devices for diagnosis and treatment of hypertension, the important question to answers is: "*Can the conventional brachial cuff sphygmomanometer be reliably replaced by a cuffless BP device, and does the cuffless BP device give sufficiently reliable information to be able to make diagnostic and treatment decisions*"? To date, there is no answer to this question, and most likely will not come in the near future, as it would require large scale studies to investigate if hypertension treatment using a cuffless BP device is inferior, similar, or superior to the conventional use of office, home, and ABPM cuff devices.

The drive to improve detection and management of hypertension in the community has generated medical, consumer, and commercial imperatives for the deployment of cuffless BP devices as part of the broad spectrum of vital signs monitoring that can be integrated in telemedicine platforms, electronic medical records, and approaches to improve precision medicine. In this context, the following sections highlight the fundamental areas that present specific challenges related to sensor technology, device calibration, and validation.

Sensor Technology

Most cuffless BP devices that would be used for hypertension management are wrist-worn, watch-type devices with ECG electrodes and a photoplethysmography (PPG) sensor. These optical sensors measure the reflectance of light to sense the change in blood volume pulse in the peripheral cutaneous vessels, and when coupled with an ECG are used to determine PAT and which is subsequently used to estimate BP based on suitable calibration [11]. PPG sensors are robust and have been shown to have stable optical properties that make them suitable for clinical applications [12]. However, the PPG signal can be affected even by slight sensor movement, which can result in altered wave amplitude and shape due to changes in contact pressure and so alter the BP reading [13]. Hence, it is not possible to obtain continuous beat-to-beat BP measurement with sufficient accuracy during daily activities, although movement can be detected by accelerometers, and algorithms can be developed to obtain a reading during the time when there is no movement of the device. This is not a major issue during sleep. However, with possible reduction of HR and stroke volume (SV) during sleep, the peripheral volume pulse can become reduced in amplitude, thus affecting the parameters related to BP, such as waveform features or transit time. This could produce erroneous pressure profiles such as misdiagnosis of nocturnal BP dipping patterns, even with attempts at software improvements [14]. Substantial misdiagnosis of nocturnal dipping profiles in hypertensive patients has also been reported with wrist-worn devices using tonometric sensors, with large differences compared to the cuff device which was used for reference [15].

Dealing with changing PPG waveforms presents formidable challenges to distinguish changes that are related to physiology from artefact, and how these changes affect the calibration relationships between BP and measured parameters. It is thought that with increased acquisition of data under a range of static and dynamic conditions, machine learning algorithms can provide a means to address these issues [16, 17]. However, the efficacy of machine learning techniques is generally determined by the type of training data presented to the system and is reliant only on broad associations of parametric changes with physiological mechanism. In essence, data-driven techniques would undoubtedly perform well when dealing with large cohorts, in part due to the phenomenon of "convergence to the mean," but that does not imply they would perform well in individuals where waveform changes will need to be distinguished as being due to artefact or physiology. This would have important implications with diagnosis and treatment of hypertension.

Calibration

The general understanding of calibrating a cuffless BP device is to obtain a relationship of the parameters measured by the device (mainly PTT or PAT in most wearable devices) and the value of BP measured by a validated cuff. Thus, a calibration factor is determined such that it con-

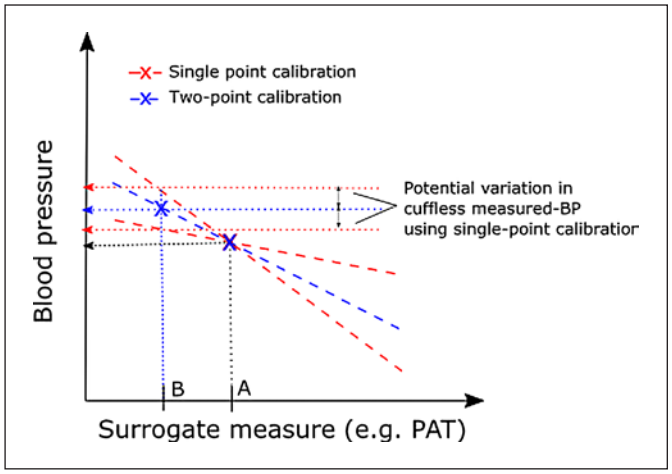

Fig. 1. Schematic showing possible increased error using single-point calibration compared to two-point calibration. With single-point calibration determined at point A, any calibration slope could be fitted; with a two-point calibration, the calibration slope is defined using two measured points (A and B). A single-point calibration can result in a higher or lower BP reading at point B compared to the measured reading, depending on the calibration slope used by the specific device.

verts the measured quantity (e.g., milliseconds) to a BP value (mm Hg). If a single measurement is made, it is implicit that the single-point calibration would theoretically be valid only at the value at which the BP was taken. If a different value of the measured parameter is obtained which is different from the calibration value, the device would give a different BP based on a predefined slope. However, there would be many different slopes that would intersect with the calibration point and, in addition, there is no way of knowing if the particular slope used in the device slope is valid at different levels of BP for a specific individual, or indeed for different individuals with similar calibration values. Figure 1 illustrates the single-point calibration and the potential errors in BP that can be present when compared to a two-point calibration. This, clearly, would have implications on the relative accuracy of BP measurements at different levels of BP, and the error would depend on how different the estimated BP values were from the calibration value. It is possible that in practical devices a correction might be made to the slope and intercept to account for the known average relationship of BP and transit times in adults.

Improvements on a single-point calibration can be achieved by obtaining values of the measured parameter at two different BP values (Fig. 1). However, the slope is only truly defined in the range of the measured BP with a conventional brachial cuff sphygmomanometer. Clinic-based measurements performed in 20 participants with a device that required a two-point calibration based on PAT for BP estimation has shown poor correlation with cuff-based BP ($r = 0.36$ for systolic BP; $r = 0.044$ for diastolic BP). However, when averaged across all participants, the device provided accurate directional BP changes with exercise [18]. Hence, for use of cuffless BP devices in hypertension management, the range of multipoint calibration is significantly important to ensure that it covers the range of potential variability with change in daily activity or with treatment. Yet, practically, a large variation in BP can be difficult to achieve, especially in terms of decreasing BP below an individual's normal resting BP.

Validation

At present, there are no complete and universally accepted standards for validation of cuffless BP devices. The *IEEE Standard for Wearable, Cuffless Blood Pressure Measuring Devices - Amendment 1* [19], amended in 2019, is the most advanced to date. It is based on tolerances and accepted ranges that are described in other standards for cuff-based devices [20] and provides additional guidance on a range of relevant issues related to sample sizes, mitigation of errors with reduced sample size and pressure ranges for different types of cohorts. However, there is no explicit specification on the application of intervention required for producing acceptable changes in BP over which cuffless BP devices can be compared with cuff sphygmomanometers. This is an important issue, and a significant point of difference with accepted standards for cuff-based devices.

Since most cuffless devices rely on the peripheral PPG signal for estimation of BP, the interventions that are used to elicit a BP change will also affect the PPG signal. The difficulty arises when changes in BP affect the specific parameter being measured, such that a similar change in BP is associated with different values of the estimating parameter, such as PTT or PAT. This has been convincingly demonstrated when comparing changes in PTT and PAT with PPG signals detected in different locations (finger, forehead, ear) with different conventional interventions that increased BP (cold pressor test, handgrip [HG], and bicycle exercise) [21]. In this study, PTT and PAT changes did not consistently detect BP changes that were associated with cold pressor test or HG interventions, but did so with exercise, even though BP changes were similar for all interventions [21]. Regional differences in PTT or PAT relationships with cuff-based BP were also observed with other interventions to change BP (slow breathing,

mental arithmetic, cold pressor, and sublingual nitroglycerin) [22].

A significant misconception in the use of standards for validation of BP devices is that the standards that are used for cuff-based sphygmomanometers can be used for cuffless BP and that testing under stable and static conditions is sufficient. That is, as long as the mean difference and standard deviation between cuffless BP device and reference (cuff) device are shown to be 5 ± 8 mm Hg as required by the standards for cuff-based devices [20], the cuffless BP devices are deemed acceptable [23, 24]. These problems are also exacerbated by the potential errors made in data presentation when evaluating the accuracy of devices where relationships are affected by parameters that are not dependent on the measured BP, such as age [25].

Experimental Studies

This section will provide quantitative examples of experimental studies to illustrate the variability and inconsistency of BP and transit time (PTT or PAT) that constitute the underlying problems of the challenges that can be presented by cuffless BP devices for estimation of BP for reliable management of hypertension.

Physiological Considerations Related to Changes of BP

Mean BP (MBP) is the product of SV, HR, and total peripheral resistance (TPR):

$$\mathrm{MBP} = \mathrm{SV} \times \mathrm{HR} \times \mathrm{TPR} \quad (1)$$

Relative changes in the parameters that contribute to changes in MBP are additive,

$$\frac{\Delta \mathrm{MBP}}{\mathrm{MBP}} = \frac{\Delta \mathrm{SV}}{\mathrm{SV}} + \frac{\Delta \mathrm{HR}}{\mathrm{HR}} + \frac{\Delta \mathrm{TPR}}{\mathrm{TPR}}. \quad (2)$$

The implication of Equation (2) is that changes in MBP from a reference point are brought about by changes in cardiac function (ΔSV, ΔHR) and in vascular function (ΔTPR). The transit time methodologies (PTT, PAT) for BP estimation are based on the intrinsic relationship of BP and arterial stiffness, which is also an intrinsic determinant of pulse wave velocity (PWV), as measured by the travel time of the pulse over a given path length [5]. Since BP is a function of PWV and PWV is a function of 1/PTT, BP has a reciprocal relationship with PTT. That is,

$$\mathrm{BP} = F\left(\frac{1}{\mathrm{PTT}}\right). \quad (3)$$

Hence, when a metric of transit time is obtained (PTT or PAT), different calibration functions (F) can be obtained for mean, systolic, and diastolic BP.

Equations (2) and (3) imply that for PTT or PAT to be uniquely related to BP, the measurement of PTT or PAT should not be affected by factors that can cause changes in BP due to cardiac (ΔSV, ΔHR) or vascular (ΔTPR) factors. For example, if an increase in BP is due to increase in SV which in turn is associated with a change in IVCT (IVCT is included in the PAT measurement), a physiological increase in BP could be associated with no changes in PAT if there is a prolongation of IVCT (since PTT is reduced due to the increase in PTT); hence, the device would register no change in BP. Similarly, if an increase in BP were due to increase in TPR (due to elevated sympathetic activity), peripheral vasoconstriction associated with arteriolar smooth muscle contraction could affect the PPG measurement through changes in waveform morphology or amplitude [26]. If these changes alter the reliability of transit time measurements, the estimated BP would not be related to physiological changes in BP. The result being that a change in BP would not be registered by the device, or indeed, a real increase in BP could be registered as a decrease in BP by the device. Clearly, these effects would present significant consideration in the diagnosis and treatment of hypertension, particularly when there are frequent BP variations. The following three experimental examples illustrate the potential effects of the physiological correlates described above on the reliability and consistency of cuffless BP devices to register changes in BP that can be used in the diagnosis and treatment of hypertension.

Different Relationship of BP and Metrics of Transit Time with Different Interventions to Change BP

Whenever there is a change in BP, a basic requirement of a cuffless BP device is that it should deliver a consistent BP reading that is independent of the mechanism that has caused a change in BP. Generally, if PTT or PAT is the metric that is measured, the sensitivity of the device should not vary such that any change in BP should result in a proportional change in PTT or PAT (assuming a linear calibration).

A sensitivity parameter was calculated from results of a previous study that assessed changes in PTT and PAT with interventions that caused an increase in BP [21]. The study included 20 participants (age 24–34 years). BP was measured continuously with a finger cuff device (Finometer) and PPG sensors used to measure PTT and PAT at three different anatomical locations: finger, ear, and fore-

Table 1. S (ms/mm Hg) calculated for PTT and PAT values that show a significant difference from control with change in MBP (mm Hg)

S		Ear		Forehead		Finger		IVCT
test	MBP	S-PTT	S-PAT	S-PTT	S-PAT	S-PTT	S-PAT	S-IVCT
REST	85.7	Control	Control	Control	Control	Control	Control	Control
CPT	101.8	ns	0.9	ns	1.3	0.6	1.3	0.5
HG	96.6	ns	0.9	ns	0.9	ns	1.4	0.5
CYC	94.7	3.3	6.1	4.4	6.7	3.3	5.6	2.0

ns, measurement for which the change of PTT or PAT was not significant for a significant change in MBP for the tests. S, sensitivity.

head. PAT was measured from the PPG pulse delay in reference to the R wave of the ECG and PTT was determined from the PPG pulse delay in reference to a seismographic signal that registers the time of opening of the aortic valve. Change in BP was obtained by three separate tests: (i) cold pressor test (CPT): 2-min right-hand immersion into a bowl with water at 3–5°C; (ii) HG: 3-min isometric HG contraction at 30% of maximal voluntary contraction; (iii) cycling (CYC): 5-min pedalling on a recumbent cycle ergometer with a 75 W workload. Control measurements were obtained during a 5-min initial sitting rest period (REST) and each test was followed by a 5-min recovery period. Sensitivity (S) was calculated from the MBP change for each test as the ratio of change of magnitude of transit time metric to change in BP (S-PTT = ΔPTT/ΔBP; S-PAT = ΔPAT/ΔBP; S-IVCT = ΔIVCT/ΔBP ms/mm Hg). IVCT was calculated as IVCT = PAT – PTT for each site.

Table 1 shows the average changes in MBP with each test, which range from an increase of 9–16.1 mm Hg from REST (control). However, this increase in MBP did not result in the expected decreases in PTT or PAT. PTT did not change for CPT and HG test in all locations except in the finger for CPT, but PAT changed for all tests. When this was expressed in terms of sensitivity, the contribution to the PAT sensitivity came from changes in the cardiac parameter IVCT. It is important to note that if these interventions were used for calibration for a cuffless BP device (Eq. (3)), the calibration factor would be different for similar changes in BP depending on which test was used to elicit a change in BP. Clearly, this observation has implications beyond the changes presented in standardizing calibration, but also in the underlying circulatory and neurogenic mechanisms that are involved in causing changes in BP, which would be of relevance to the diagnosis and treatment of hypertension. In this study, the changes of sensitivity in the finger are of particular significance as the PPG in the finger is close to that of the wrist, where most cuffless BP devices sense the PPG signal.

Differences in Sensitivity with Different Magnitude of Changes in BP

Experiments were conducted in 15 participants (mean age 31 ± 15 years; 10 females) in whom PAT measurements were obtained in the finger with a PPG sensor and at the wrist of the same hand with a tonometric sensor. A cold pressor test (foot in iced water) was used to alter BP from baseline [27]. Participants gave written informed consent, and the study was approved by Macquarie University Human Research Ethics Committee (No. 5201700226), and participants gave written informed consent. The effect of the cold pressor test was not uniform across the participants, with brachial cuff MBP changes from an average increase of 14.6 mm Hg to a decrease of 4.9 mm Hg. Average PAT changes ranged from a decrease of 24 ms to an increase 2 ms for radial tonometry and decrease of 26 ms to an increase of 4 ms for finger PPG. However, the changes with BP were not consistent across participants and magnitude of BP changes.

Figure 2 shows the values of BP and corresponding PAT changes in the group of 15 participants plotted in ranking order of BP changes. Both tonometry and PPG measurement of PAT showed directional changes consistent with BP directional changes in 11/15 cases (73%). However, the magnitudes varied across BP differences. PAT calculated from tonometry and PPG signals showed similar directional changes in 10/15 cases (67%). BP values were grouped in high (T1, 8.8 mm Hg), medium (T2, 4.6 mm Hg), and low (T3, −2.3 mm Hg) tertiles with respect to average BP changes.

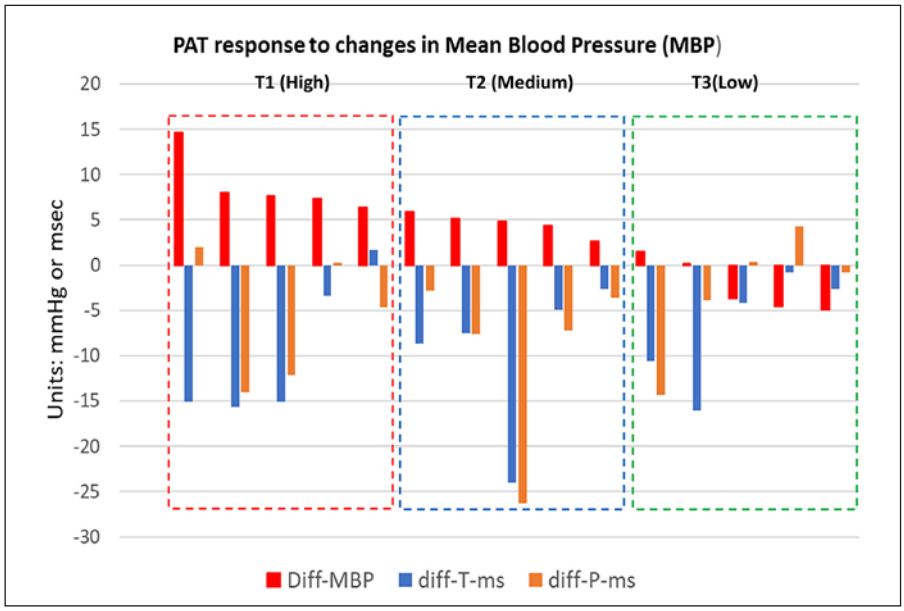

Fig. 2. Effect of cold pressor in 15 participants ranked on magnitude change of MBP (diff-MBP) with corresponding PAT differences obtained by tomometry (diff-T-ms) and PPG (diff-P-ms). The sections are in tertiles of average changes in MBP: T1-high (8.8 mm Hg); T2-medium (4.6 mm Hg); T3-low (−2.3 mm Hg).

Table 2. Average PAT-MBP S for tonometry and PPG measurements for tertiles of change of MBP with cold pressor test

Tertile of MBP change	S-tonometry	S-PPG
T1 (8.8 mm Hg)	1.03	0.79
T2 (4.6 mm Hg)	2.00	2.08
T3 (−2.3 mm Hg)	1.30	3.42

S, sensitivity (ms/mm Hg).

The observations described in Figure 2 illustrate that, in addition to the variation of individual response to the same stimulus intensity, the relationship of the average PAT change with MBP for each tertile is not consistent. Table 2 presents the sensitivity magnitude (S = ΔPAT/ΔMBP) averaged across measurements in each tertile of MBP changes (computed for measurements that showed a change of MBP of at least 1 mm Hg and PAT of at least 1 ms).

Table 2 illustrates the potential problems that can occur when group averages of different individuals are used for calibration of cuffless devices that use transit time measurements for estimation of BP. Both tonometry and PPG show different PAT sensitivities with MBP. This means that if a single calibration is used for a device, the same change of PAT would correspond to a different change of MBP. The corollary of this observation is that using group averages with different responses to a BP change, the calibration factor would need to be pressure-dependent to be able to estimate reliable physiological BP changes.

Variability of Calibration Parameters over Time

When BP is measured by a brachial cuff sphygmomanometer with the arm in different positions such that the cuff is at a different vertical location in reference to the right atrium, measured BP values will change even when arterial BP is constant, with the difference being due to the hydrostatic effect of the blood column. This phenomenon has been shown to be a useful manoeuvre that can be used to calibrate BP changes with corresponding changes in PTT or PAT [28, 29]. This technique has been used to investigate the stability of calibration indices over time [30].

Experiments were conducted in seven participants (mean age 37 ± 18 years; 4 females). Participants gave written informed consent, and the study was approved by Macquarie University Human Research Ethics Committee (No. 5201700226) and participants gave written informed consent. BP was measured by a brachial cuff oscillometric sphygmomanometer, and PAT was determined from the time delay of the foot of the arterial pulse obtained at the radial artery by applanation tonometry in reference to the R wave of the ECG. Measurements were taken with the arm at 5 positions with the arm rotated through 180° from the vertical in angular segments of 45°. This produced a linear relationship between diastolic BP and PAT with an average change in diastolic BP of 39 ± 11 to 88 ± 12 mm Hg and corresponding change in PAT

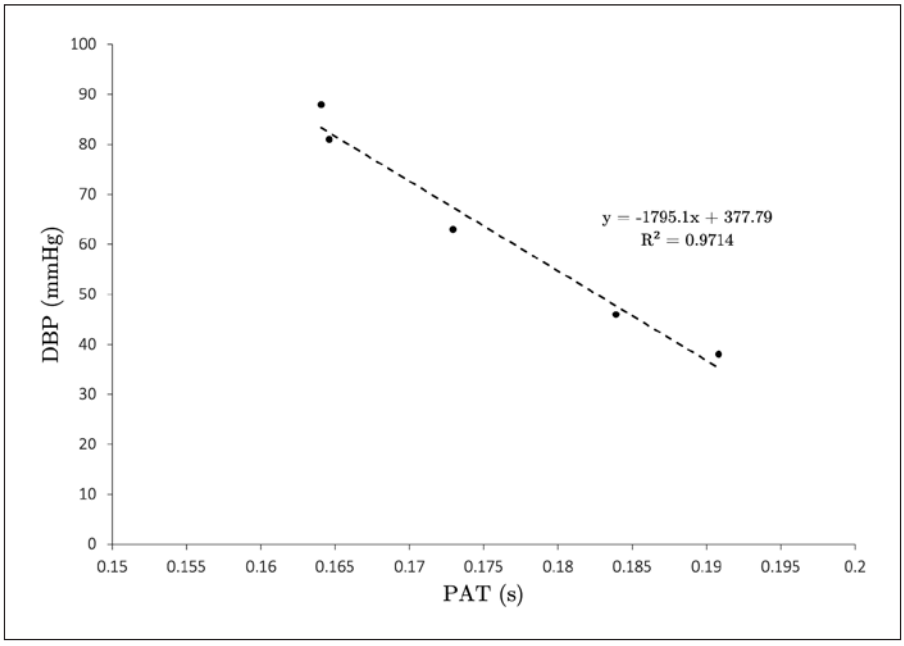

Fig. 3. Change of DBP and PAT with arm position rotated at 5 positions from 0 to 180° in reference to the vertical direction in an individual. This manoeuvre produces a consistent result with a high correlation enabling the computation of a slope and intercept for each measurement. DBP, diastolic pressure.

Table 3. Difference of slope and intercept between days 2, 7, 30, and 60 from the initial calibration measurement (day 1)

	Day 1–2	Day 1–7	Day 1–30	Day 1–60	*p* value
Slope, mm Hg.s^{-1}	847±1,576	194±996	110±742	−185±1,270	0.229
Intercept, mm Hg	−143±263	−29±169	12±131	38±228	0.233

Mean±SD.

from 197 ± 26 to 177 ± 11 ms. Figure 3 shows the linear relation in an individual with a slope of 1,795 mm Hg.s^{-1} and an intercept of 378 mm Hg.

The values of slope and intercept were used as calibration metrics and were compared in each participant over a period of 2 months with 5 separate measurements performed on Day 1, Day 2, Day 7, Day 30, and Day 60. Consistency of the calibration metrics was assessed by comparing consecutive measurements over time with measurements on Day 1.

Table 3 shows the range of variation of the slope and intercept after the first measurement (Day 1). There are large mean differences as well as larger differences in standard deviation. This gives a non-significant statistical difference (p = 0.23 for both), but this does not suggest that the calibration is stable over the period of months. Figure 4 highlights the fact that although a regression relation may be found for all the measurements in each individual participant, the regression line is very different to the line of unity for both slope and intercept, and there is also a significant inter-participant variability.

The implication of these findings is that if the same calibration were used for an individual participant on different days, the same measured PAT would give a BP which would be different to the arterial BP, and the difference would change on different days. This then suggests that a calibration should be done before each measurement when using a cuffless BP device based on PAT. Other studies conducted over a period of a year have shown that the calibration consistency may also be site specific [31].

Discussion

The quest for continuous and unobtrusive measurement of BP is not new. The relationship between arterial stiffness and BP was recognized in specific fields such as psycho-

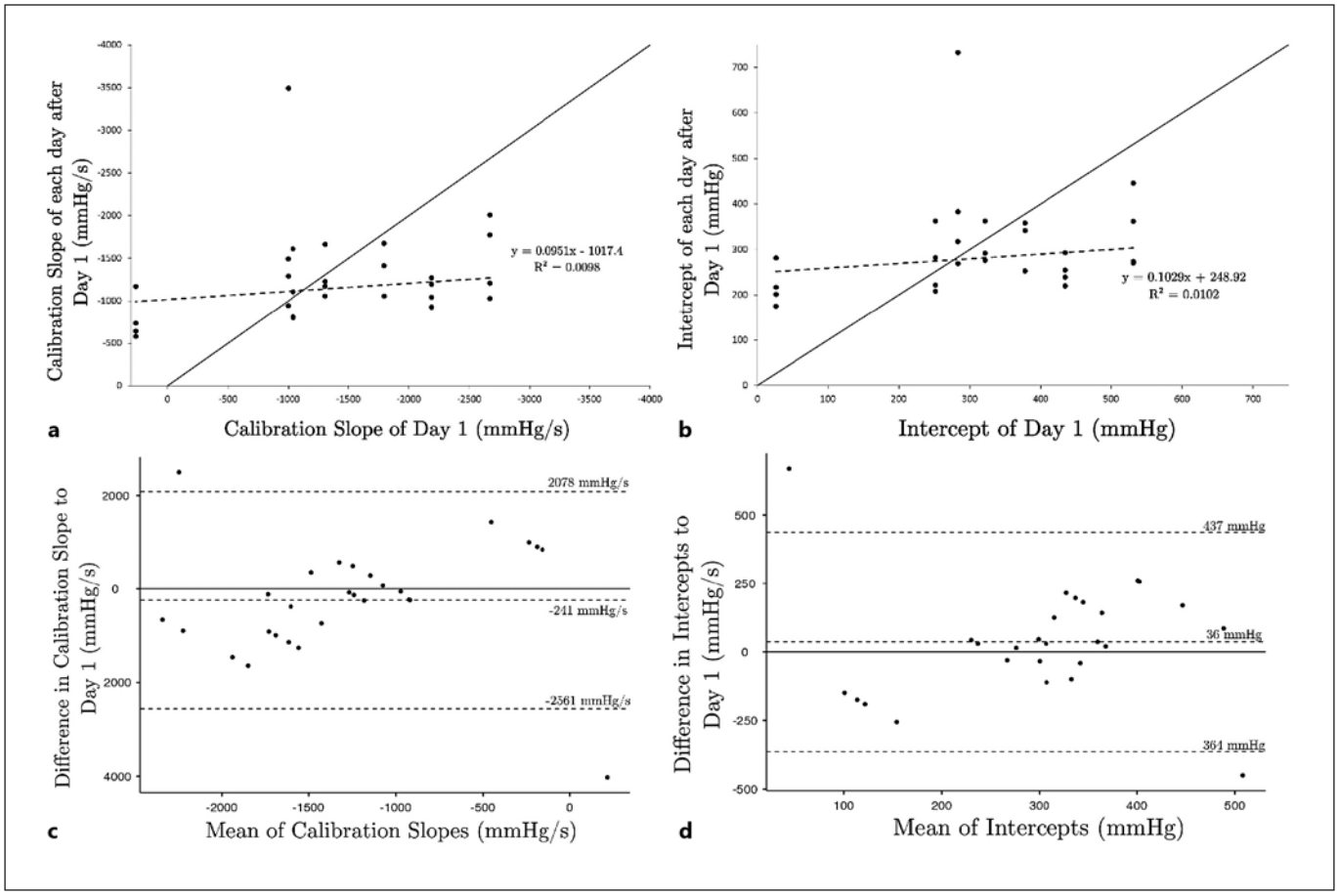

Fig. 4. Bland-Altman analysis of calibration factor and intercept. The agreement between calibration factors (**a**) and intercepts (**b**) attained during the initial and each subsequent visit. Dashed line: line of regression; solid line: line of unity. **c**, **d** are Bland-Altman plots depicting the degree of agreement between all days and the initial day. Dashed lines indicate 95% confidence intervals (mean ± 1.96 SD) and mean difference.

physiology some 50 years ago, where there was a necessary requirement for monitoring BP changes due to sensory stimuli which were not corrupted by the additional stimulus of brachial cuff inflation [32]. The first possible commercial cuffless watch-type device, the Casio BP-100 Digital Watch, was produced 30 years ago with an ECG and PPG sensor and dual-point calibration to give measurement of systolic and diastolic BP [18]. However, notwithstanding the progress made over the years in the theoretical and practical implementation of cuffless techniques, mainly based on the fundamental arterial property of pressure dependence of arterial stiffness [5], there is still no widely accepted cuffless BP device that can be shown to confidently replace the brachial cuff sphygmomanometer.

The association of BP and arterial stiffness is exploited by measurement of PWV [32], or more specifically by travel times of the arterial pulse over a fixed distance using PTT or more commonly PAT [5]. The electronics and digital technologies are now well advanced for robust implementation of signal detection and analysis techniques that make use of this relationship in wearable devices. Concomitant with this progress, the realization that hypertension is increasing the global health burden but with slow progress in risk mitigation [1] is causing concern that the conventional methods of managing hypertension are not adequate, and that the field should take advantage of modern advances in digital and communication technologies [2]. This convergence is resulting in the establishment of a perceived clinical need: *new devices are required to manage hypertension*, *and these should preferably be wrist-worn, watch-type devices*. This then defines the essential characteristics of the devices.

To achieve the perceived clinical need, it is implicitly assumed that the new devices will need to be at least as

reliable as the conventional brachial cuff sphygmomanometer for meaningful management of hypertension. It is also assumed that with additional diurnal and nocturnal measurements, management will be more efficacious. These notions have expanded the horizons of research and commercial endeavours [7, 8, 24, 33–35] to produce devices that enable measurement of BP outside the constraints and limitations of the conventional brachial cuff sphygmomanometers to encompass not only wrist-worn devices but other devices with other form factors [33, 36, 37] or those that make use of smartphone technology [38, 39]. Applications are also extended to contactless techniques, making use of optical imaging to detect cardiac related pulsations through skin colour change of the face and other locations [40, 41]. In most cases, the underlying technology is the use of the peripheral PPG, mainly associated with PTT or PAT measurement. Some PPG applications involve a normalized PPG amplitude [42, 43] which is purported to be a measure of vasoconstrictive activity of the peripheral microcirculatory beds [44].

Given the level of activity in the field of cuffless BP measurement, the ease of user acquisition of the devices, and the ubiquitous use of smartphones, professional societies are beginning to release official statements and position papers on use of these devices for hypertension management [45]. However, the high level of activity does not imply that cuffless BP devices are necessarily ready for diagnostic use. A potential misconception is that if a cuffless BP device is tested against a brachial cuff sphygmomanometer in a group of participants, and the mean and standard deviation are within the values of 5 ± 8 mm Hg, as required by regulatory standards designed for pneumatic cuff devices [20], then the device is acceptable [24, 33, 46]. This type of validation is generally static and does not guarantee that cuffless BP device will reliably track BP changes in an individual. This may be due to a range of factors involved in covariates that determine different levels of BP (such as age) and so opens up the controversial notion of accuracy of cuffless BP devices [25, 47]. This, of course, leads to the question of: *How accurate can cuffless BP devices expected to be when there is no actual measurement of force by the device sensors*?

In the context of broad areas (described above) that present challenges for cuffless BP devices for diagnosis and treatment of hypertension, experimental data have been presented to illustrate some of the potential pitfalls that may be encountered with the measurement of surrogate signals such as the cutaneous PPG to estimate BP without any actual measurement of pressure (as employed in the inflatable pneumatic cuff used in the conventional sphygmomanometer). Although not intended to be exhaustive, the data presented is meant to show the type of variability that is found with the use of cuffless BP techniques. The underlying problem that is relevant to diagnosis and treatment of hypertension is that the mechanisms that cause change in BP can be related to the heart (change in SV and HR), the vasculature (change in peripheral resistance) or vascular fluid volume, and these very mechanisms can affect the measurement of the parameters used to estimate BP. The response of PTT or PAT to a controlled protocol for a cold pressor test varies with different studies and cohorts and is also different between static and dynamics tests, even for similar change in BP [21, 27, 48, 49]. This implies a potentially variable sensitivity of the cuffless BP device with BP.

Conclusion

The universal acceptance of a reliable cuffless BP device that delivers meaningful readings of relevant physiological BP would undoubtedly contribute to a paradigm shift of BP assessment and could conceivably lead to increases in awareness of hypertension in society [7, 9]. The current surge in research, commercial, and clinical activity [8] suggests that there will be increased consumer adherence to wearable devices that include BP as the suite of measurements of vital signs. However, the underlying challenges that are presented by cuffless BP devices still beg the question whether they can reliably replace the brachial cuff sphygmomanometer for diagnosis and treatment of hypertension.

Statement of Ethics

The studies reported here were reviewed and approved by the Macquarie University Human Research Ethics Committee, approval number 5201700226. All participants gave written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare in relation to this manuscript. A.A. is an Associate Editor of the journal Pulse.

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Author Contributions

Alberto Avolio conceived the topic and wrote drafts of the manuscript; James Cox, Ahmad Qasem, Mark Butlin, and Isabella Tan provided critical feedback; James Cox, Kyrollos Louka, and Fatemeh Shirbani provided experimental data; Alberto Avolio, Mark Butlin, Isabella Tan, and Ahmad Qasem were involved in experimental supervision of studies and in data analysis.

Data Availability Statement

Parts of the data generated or analysed for the reported studies are included in this article as illustrative examples. Further enquiries can be directed to the corresponding author.

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