Cuffless Blood Pressure Monitoring Promises and Challenges

Jay A. Pandit,1 Enrique Lores,2 and Daniel Batlle2

Abstract
Current BP measurements are on the basis of traditional BP cuff approaches. Ambulatory BP monitoring, at 15- to 30-minute intervals usually over 24 hours, provides sufficiently continuous readings that are superior to the office-based snapshot, but this system is not suitable for frequent repeated use. A true continuous BP measurement that could collect BP passively and frequently would require a cuffless method that could be worn by the patient, with the data stored electronically much the same way that heart rate and heart rhythm are already done routinely. Ideally, BP should be measured continuously and frequently during diverse activities during both daytime and nighttime in the same subject by means of novel devices. There is increasing excitement for newer methods to measure BP on the basis of sensors and algorithm development. As new devices are refined and their accuracy is improved, it will be possible to better assess masked hypertension, nocturnal hypertension, and the severity and variability of BP. In this review, we discuss the progression in the field, particularly in the last 5 years, ending with sensor-based approaches that incorporate machine learning algorithms to personalized medicine.

BP Measurement in Common Practice
Office-Based Cuff Measurement
Most outpatient clinics use a cuff to acquire either an auscultated or an automated measurement of BP. According to the recent American Heart Association (AHA) statement on BP measurement (13), the available devices...
are reliable only when multiple physician- and patient-related variables are done according to standard.

Even when accurate, the fundamental issue with the office-based cuff BP measurement is that it is still a snapshot (14). The recommended averaging of several readings during a visit, usually three, is an improvement, but only a small piece of the full picture of the patient’s BP. This is apparent when considering the increasingly recognized importance of white coat and masked hypertension (15–18) and interest in chronotherapy (19). Masked hypertension, in particular, is now considered a very strong predictor of cardiovascular disease (17,20–22). As suggested by the USPSTF, multiple measurements out of clinic are needed to support the office-based BP measurement for it to be clinically relevant (3).

**Ambulatory BP Monitors**

These are BP cuffs that are powered by a wearable pump that can be programmed to provide measurements as frequently as every 15 minutes for 24–72 hours. Ambulatory BP monitoring (ABPM) has been around for over 30 years (23). In more recent years, several groups (7–9,17,24) have argued that ABPM should replace the office measurement for diagnosis of hypertension given that it provides an average over a longer period. Studies have shown that ABPM is superior to the clinic and home BP measurement approaches in predicting clinical outcomes (6,9,25,26). Cost-effectiveness analyses demonstrate that adopting an ambulatory approach for hypertension diagnosis would reduce hypertension costs despite the cost of the devices (9). ABPM allows for measurement of both white coat and masked hypertension (27) in a noninvasive manner. However, even with the latest wearable Omron HeartGuide (28) ambulatory BP monitor, design continues to hinder adherence. It still requires arterial compression, causing sleep disruption, which is a common reason for patient nonadherence (29). Also, the devices are significantly more expensive than the BP cuffs, and this has been a barrier for widespread clinic adoption (7,29). Ultimately, although more data clearly provide a better picture than the office-based BP, reimbursement had been an issue in the United States, although the documentation for this procedure has recently been relaxed by the Centers for Medicare and Medicaid Services (CMS) (30). Importantly, we are clearly due for more innovation to come.

**Home BP Measurement**

This approach relies on patients using a cuff-based device of their choice and keeping a log for the physician to review. There is a validation methodology for such devices that seek to measure BP with an agreed upon level of accuracy (31), and there are guidelines for patients to follow. For instance, it has been recommended that home BP measurement should be done in a quiet room after 5 minutes of rest in the seated position, with the back and arm supported (13,32). Given that this measurement is patient driven, it is difficult for physicians to confirm that the measurements were obtained correctly. Guidelines also suggest measuring home BP four times a day (twice a day with a repeated measurement) (32), which is difficult for patients to adhere to. Literature reviews of home BP measurement suggest that there is conflicting evidence for its value compared with other approaches (32,33). Advantages of the approach are that it is low cost and easily accessible, it gets patients involved in their own care, and many of the new devices are also compatible with smartphone applications (33). Disadvantages are concerns about accuracy of existing devices, validation of available devices by a recognized body, and reliance on patient adherence to proper measurement techniques (13). Regardless, this continues to be a commonly used method of follow-up for elevated BPs measured in the clinic to identify white coat hypertension and masked hypertension.

**Beyond Brachial Cuff–Based Approaches**

The Omron HeartGuide and the relaxation of the CMS reimbursement for ABPM reflect a movement toward more comprehensive BP measurements over longer time periods. The objective is to record a patient’s BP through activities of daily living without the patient being aware of the measurement. Much of this drive comes from the remarkable expansion of the wearables market, which now has the ability to continuously measure almost every single vital sign except BP. Acknowledging this trend, we feel that it is particularly important to confirm or rule out the individual variability in BP by a continuous measurement that is reproducible. As it stands right now, often we do not know if the variability is real or operator and device dependent. Notably, even the widely used BP cuff measurements lack a true gold standard for comparison.

Theoretically, invasive arterial BP measurement could provide a platform for comparison, but this is usually not done due to practical reasons in the ambulatory context. Although this has been used for comparison by new devices in some studies, we think that it is not the ideal gold standard because it requires a hospital setting for monitoring and is subject to its own set of limitations, such as calibration error, over- or underdampening of the waveform, and reliance on pulse volume (34). Further, a properly done, AHA-approved, seated brachial cuff measurement using a validated device may not be the perfect standard, but it is the standard used so far and what has been used in all BP trials of importance. Therefore, at the moment, any effort to develop a cuffless continuous BP device is stuck with either the cuff as a gold standard (as required by the Food and Drug Administration [FDA]) or the arterial line (as expected by some in the medical community). We surmise that there has to be a more practical and representative control and that ABPM may be a preferable gold standard.

For the foregoing discussion, we have separated the cuffless continuous BP approaches into active and passive. Active approaches require the need for a noticeable obtrusive intervention, such as compression or applanation pressure, for the sensor to derive a BP measurement. Passive approaches require only sensor application, with no further intervention needed to derive a BP measurement. Although we do not have enough data to suggest that continuous measurements are better than frequent intermittent measurements, the ability to obtain and store electronically a patient’s BP measurement continuously and without the patient noticing during sleep and diverse activities has become the ultimate target.
Active Approaches

Vascular Unloading Time Technique. In this approach, the cuff is moved from the arm to the finger to obtain an indirect measurement of beat-to-beat systolic and diastolic pressure (Figure 1). The finger cuff is used as a counter-pressure to keep a constant volume of blood in the finger. Photoplethysmography (PPG) is used at the tip of the finger to obtain a pulse waveform signal that is fed into the circuit to control the finger cuff pressure to maintain a constant pulse waveform amplitude. The assumption is that, because the amplitude of the pulse waveform is largely generated by pulse volume and the blood volume in the digit is finite, then any changes required to maintain a constant volume should mostly be due to peripheral arterial resistance. Hence, the deduction is that the finger cuff pressure required to counter the pressure should correlate (with correction factors) to BP (35,36).

Studies have validated this approach in the perioperative (36,37) and ambulatory setting (38). However, compressing the finger has led to concerns about digital ischemia, and therefore, this approach is not as practical for frequent measurements in the ambulatory setting.

Applanation Pulse Tonometry. In this approach, a pressure sensor is placed directly onto the artery of interest to obtain a measurement (Figure 2). It allows for non-invasive recordings of the arterial pressure waveform and amplitudes in both central and peripheral arteries (39,40). However, as implied by this statement, applanation tonometry can be limited by different pulse waveforms for each artery and difficulty with direct applanation for a given body habitus (41). There has been success in integrating tonometry with other modalities in order to get PWV as a measure of arterial stiffness (42). Devices using this approach still require continuous calibration with a brachial BP cuff.

Passive Approaches

Given the interest in identifying an unobtrusive continuous approach, the most recent work in the space has largely focused on the pulse waveform obtained by various sensors, such as optical, seismic (43), or radar (44), with the most common being PPG-acquired optical signals. PPG waveforms are easily obtainable and do not require an active intervention. Most of these approaches are variations of the PWV theory.

Pulse Wave Velocity. PWV is defined as the velocity at which the pressure waves, generated by the systolic contraction of the heart, propagate along the arterial tree (45) (Figure 3). PWV is a known way to estimate vascular stiffness (46) and central arterial pressures (47) using the Moens–Kortweg and Hughes equations (12). The ability of PWV to predict future hypertension (48) and link to BP autoregulation (49) adds to its relevance.

Essentially, these approaches are on the basis of a variation on the velocity equation. Every patient’s BP changes, however, differently to hemodynamic maneuvers, and therefore, calibration is necessary and usually has to be done with a BP cuff (50). PWV has a strong physiologic underpinning; however, the challenge initially was to derive pulse travel distance and pulse arrival time (in order to calculate velocity) and to calibrate to each individual. The calibration challenge has led to the development of multiple algorithm improvements, and several studies have evaluated PWV-based approaches that are promising (51–53). The drawbacks to the PWV approach that have been acknowledged include site specificity and better prediction of central BPs than peripheral BPs (47).

In summary, PWV is generally considered the best connector of pulse waveforms to BP. As mentioned, in order to derive PWV, a distance and a time are required. In the early stages of developing a cuffless continuous BP measurement approach, a constant was used as a surrogate for distance in almost all approaches, and most of the innovation was focused on deriving an accurate time. This gave rise to the focus on PTT, which is discussed below.

Pulse Transit Time. PTT refers to the amount of time required for a pulse that stems from each cardiac cycle to travel from the heart to a distal point in the cardiovascular system with a known distance (12,54) using an electrocardiogram
and a PPG sensor (Figure 4). The goal with PTT is to obtain this time and correlate it to BP or use it to calculate velocity, which in turn could be used to derive BP. Although the list of references on PTT-based approaches is by no means exhaustive, there has been and continues to be an explosion of PTT-based research (55–61). Since 2015 alone, there have been a myriad of conference papers not yet developed into full publications.

There are, however, consistent limitations to overcome in this approach. Inherent limitations of the PTT approach are that the method makes some indefensible assumptions or approximations regarding important parameters, such as the elasticity of the arterial wall, the pre-ejection period of the heart (time between peak of QRS on the ECG and actual systolic contraction of the left ventricle), and blood density (viscosity). Technical limitations of the approach are that in order to acquire an accurate derivation, the ECG and PPG signals need to be noise free, and the patient needs to be immobile to minimize motion artifact, suggesting that PTT can be inaccurate during activity. These challenges are known, and several groups are working to overcome them using curve-fitting techniques (62–69).

Device form factors include wrist wearables, ear wearables, armchair sensors, and bathroom scale–type sensors (56,70). Many of these approaches have demonstrated mean errors that fall within standards of recognized validation organizations, suggesting that these approaches are waiting for full validation and clinical trials.

Pulse Wave Analysis and Machine Learning

Much of the recent work has now focused on improving raw signal accuracy, incorporating machine learning into the derivation algorithms and creative modeling techniques (43,44,62–68,71–92). It is important to note that, although the majority of the publications are using optical light-emitting diode sensors to obtain a pulse waveform, there have been other attempts, such as using seismic (43) and radar (44) sensors. Ultimately, the goal has been to obtain a pulse waveform and use this waveform to derive BP. We have provided some differences between PTT and pulse wave analysis in Table 1.

The pulse waveform was initially felt to be directly correlated to the opening and closing of the heart valves and the elasticity of the artery (46). There are, however, other factors that need consideration. The shape of the pulse waveform also depends on the pressure of blood in arteries itself and the amplitude of reflected waves from curves and takeoffs in the arterial highway, as well as the contractile force of the heart, among other things. Because pulse wave analysis takes all of these variables into account, it is likely a more comprehensive source of vascular health information than the isolated systolic and diastolic numbers derived from arterial compression.

Our group (93), along with many others (92,94–96), has attempted to collect a dataset of these pulse waveforms in order to develop an algorithm using machine learning to derive BP. There is tremendous activity in curve fitting and algorithm development such that The Handbook of Cuffless
Blood Pressure Monitoring: A Practical Guide for Clinicians was published in 1997 (97,98). Despite the activity, large-scale clinical trials in patients with varying systolic and diastolic BPs are missing.

**Challenges**

Despite the search for an accurate cuffless continuous BP monitoring approach, all current noninvasive BP measurement devices on the basis of any method will likely not give the same exact absolute BP value. This is compounded by the inherent dynamicity of BP. There are consistent challenges that have faced attempts to move away from the cuff, and we present a few of them below.

**Accuracy of Control**

Developing a novel cuffless and continuous approach to BP requires comparison with an accepted standard. The arterial line remains the clinical gold standard but is not appropriate for ambulatory settings. There are some FDA-approved volume clamping devices that provide beat-to-beat BP, but all have their own limitations and are still not widely accepted in the clinical community. Currently, any effort to develop a cuffless continuous BP device is stuck with the cuff as the gold standard required by the FDA and the arterial line, neither of which provide an ambulatory beat-to-beat measurement. There has to be a more practical and representative model for comparisons.

**Need for Validation Standards**

The FDA requires continuous BP monitors to be compared with snapshots of a BP cuff. IEEE Standard for Wearable, Cuffless Blood Pressure Measuring Devices—Amendment 1 has now been published (98), and there is discussion of a new set of International Organization of Standardization guidelines to assist companies; however, none of these have been informed by clinical trials. This is direly needed to match the speed of innovation with the speed of regulation because patients already have access to the many cuffless BP devices that did not require FDA clearance due to being classified as recreational.

**Technical Issues**

BP, although simplified into a systolic and diastolic reading, is a complex physiologic parameter affected by age, sex, position, internal physiology, external context, time of day, and equipment used, among other things. Sensors, just like absolute measurements from BP cuffs, are affected by the structural and functional properties of both large and small arteries, which are quite different from patient to patient. For example, an optical-based device still might not be accurate in patients with severely stiffened arteries. We know that functional stiffness (determined by BP) and structural stiffness (dependent on compliance of vessel wall) are different from patient to patient. We know this to be a fact by seeing the inaccuracy of the BP cuff–based measurements in calcified vessels, but we need more studies to test optical approaches in these patients. They could be inaccurate, or they could be a novel solution. Development of a prototype is at the intersection of multiple disciplines, including physiology, signal processing, hardware and software engineering, and data analytics, just to name a few. This team needs to work together to iterate their prototype, addressing additional questions that come up at each stage.

**Calibration**

Finally, and probably the most important, is that any attempt at continuous measurement of BP requires constant calibration to an existing acceptable standard. There have been myriad attempts to get around the issue of calibration, but none have been able to replace the need for intermittent calibration with a cuff. With larger datasets to learn from, even this problem will be one that can potentially be overcome using machine learning.

These are the challenges that are faced while developing a cuffless continuous BP monitoring device. After the device is developed, there will be many more challenges in terms of incorporation into current workflows, including infrastructure, privacy, and liability in dealing with continuous BP data, just to mention a few.

Despite the undisputable value of BP using a cuff, a singular snapshot of BP just cannot tell the whole BP story (14). Frequent and, ideally, continuous measurements should better capture important aspects of BP dysfunction that underpin, among others, the clinical syndromes of masked hypertension and nocturnal hypertension. Even if continuous measurements by cuffless approaches will not necessarily be more precise than the cuff-based method, if reproducible for a single individual, they provide the unique advantage of continuity in assessing BP in that individual easily and under diverse conditions. Any newer cuffless continuous approach for BP measurement should have the intrinsic “potential,” justified by clinic considerations, to be user friendly and provide many more readings over time possibly prognostically better than the existing methods (i.e., office BP, home BP, and ABPM). Clearly, there is a long way to go, and many studies will be needed for cuffless BP to become the standard of care. On the other hand, there is no reason why the field could not move faster than in the past given the need for transformative approaches to hypertension diagnosis and care.

Despite the challenges, all key stakeholders (clinicians, medical device companies and patients, to name a few) recognize the need for continuous BP monitoring and its promise. This should also facilitate involvement of patients.
in their medical care. Having a large database for continuous BP's in the ambulatory setting with machine learning algorithms could help identify novel biomarkers for cardiovascular disease prediction and subclinical forms of multiple diseases and, ideally, further knowledge on the natural progression of existing diseases as a start. With our review, we hope to send the message that, technically speaking, the solution is not on the horizon but may be around the corner.

Disclosures
D. Battle is a coinventor of the patent “Active Low Molecular Weight Variants of Angiotensin Converting Enzyme 2” and founder of Angiotensin Therapeutics Inc. J. Pandit is a cofounder of Bold Diagnostics Inc. and is coinventor of the patent “Ambulatory Blood Pressure and Vital Signs Monitoring System and Method” (US20180279965A1). The remaining author has nothing to disclose.

Funding
D. Battle is funded by National Institute of Diabetes and Digestive and Kidney Diseases grant RO1DK104785.

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Published online ahead of print. Publication date available at www.cjasn.org.