Continuous Blood Pressure Measurement from Invasive to Unobtrusive: Celebration of 200th Birth Anniversary of Carl Ludwig

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***Abstract*—The year 2016 marks the 200th birth anniversary of Carl Friedrich Wilhelm Ludwig (1816–1895). As one of the most remarkable scientists, Ludwig invented the kymograph, which for the first time enabled the recording of continuous blood pressure (BP), opening the door to the modern study of physiology. Almost a century later, intra-arterial BP monitoring through an arterial line has been used clinically. Subsequently, arterial tonometry and volume clamp method were developed and applied in continuous BP measurement in a noninvasive way. In the last two decades, additional efforts have been made to transform the method of unobtrusive continuous BP monitoring without the use of a cuff. This review summarizes the key milestones in continuous BP measurement; that is, kymograph, intra-arterial BP monitoring, arterial tonometry, volume clamp method, and cuffless BP technologies. Our emphasis is on recent studies of unobtrusive BP measurements as well as on challenges and future directions.**

***Index Terms*—Carl Ludwig, Kymograph, Continuous, Unobtrusive, Cuffless Blood Pressure**

I. Introduction

HIGH blood pressure (BP) is the main risk factor for cardiovascular morbidity and mortality, accounting for 9.4 million deaths worldwide in 2010 [1]. In addition, high BP, or hypertension, is commonly considered a major modifiable factor for cardiovascular disease (CVD), which is the leading cause of death and disability globally. Hypertension is highly prevalent, with more than 1.5 billion (40%) of adults being affected worldwide. This number is expected to increase rapidly because of the aging population [2, 3]. The prevalence of hypertension is high because it is a "silent killer." Hypertension often develops without symptoms in early stages, with the diagnosis rate being as low as 46%. Furthermore, hypertension is controlled in less than 33% of patients undergoing treatment [3]. Reliable and timely BP measurement, hypertension diagnosis, and monitoring changes in BP are imperative for prevention of and early intervention in hypertension and its related CVD. Recent data from the study Systolic Blood Pressure Intervention Trail (SPRINT) have suggested the benefits of lower BP goals, which further increase the awareness regarding the importance of unobtrusive and ubiquitous monitoring for BP control [4-6].

Studies have reported that ambulatory BP and self-measured BP at home (home BP) are superior to clinical BP in predicting BP-related risks [7, 8]. Thus, they have been recommended as routine BP measurements for a majority of patients with known or masked hypertension [9]. The major advantage of ambulatory and home BP monitoring include obtaining BP information during daily activities and sleep. This information can be used to assess the lifestyle of patients with hypertension and thereby identify hypertension causes, monitor response to antihypertensive medication, and improve patient adherence with therapy. Devices for measuring ambulatory and home BP are commonly developed using the oscillometric approach. During measurement, an inflatable cuff is used, which may cause discomfort and pain to the user, particularly to those with hypertension and who require frequent repeated readings. For monitoring nighttime BP, the repeated inflation and deflation of the cuff can disturb the user during sleep. Moreover, conventional devices based on auscultatory and oscillometric techniques can provide only intermittent measurements; that is, snapshots of dynamic BP readings. Therefore, conventional devices cannot be used to monitor short- or long-term longitudinal continuous BP changes. These changes have been well-recognized as a more accurate determinant of cardiovascular risks because changes in systolic or diastolic BP and shape of BP waveforms over time reflect the evolution of arterial and arteriolar alterations.

Compared with snapshot BP, continuous arterial BP measurement provides additional information for diagnosis and treatment of hypertension through systolic, diastolic, and mean BP as well as through beat-to-beat variations (Fig. 1). In addition, arterial pressure waveforms indicate changes in the

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cardiovascular status, allowing the approximation of additional derived parameters such as stroke volume, cardiac output, arterial stiffness, and vascular resistance. For example, myocardial contractility can be assessed using the slope of systolic upstroke; cardiac output and total peripheral resistance can be derived from the slope of diastolic pressure decay over various ambulatory activities; and an adaptive transfer function deriving the central BP waveform from the peripheral waveform can be used to measure stroke volume. Furthermore, long-term rhythms can provide insights on hemodynamic control and fluid management.

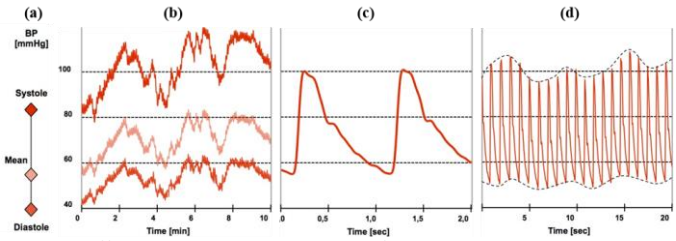


Fig. 1. Different blood pressure (BP) information: (a) snapshot BP; (b) beat-to-beat BP; (c) BP waveform; (d) long-term BP rhythms (figure adapted from [10]).

Continuous BP recording can be dated back to 170 years ago when Carl Ludwig devised the kymograph. Subsequently, intra-arterial BP measurement by using a catheter inserted into an artery has been used to detect continuous BP in real time and is often considered the gold standard for arterial pressure measurement. From the 1960s to 1970s, arterial tonometry and arterial volume clamp enabled continuous BP measurement in a noninvasive way. They are performed by compressing the artery to the optimal "applanation position" and keeping the arterial wall in an unloaded state so as to derive the continuous BP waveform. However, no method can forego the use of the occlusive cuff. Thus, their use is still restricted to research and specialist clinical settings. For this reason, significant investigations on continuous or beat-to-beat BP measurements without any interruption for unobtrusive application have been performed since the 2000s.

Thus far, the evolution of BP measurement devices has been well documented [11, 12]. In this review, we focus on key technological milestones of continuous BP measurement from invasive to unobtrusive techniques. In addition, we discuss the current techniques for cuffless continuous BP monitoring, followed by remaining challenges and future research and development directions.

II. Milestones of Continuous BP Measurement Techniques

Stephen Halls first discovered arterial BP in 1733. He used a long glass tube cannulating the artery of a horse and measured the pressure. At that time, only arterial pulsations could be observed. Intermittent BP could be measured only after Poiseuille invented the mercury manometer in 1828. In 1847, Ludwig developed the kymograph, which was a major breakthrough for obtaining continuous BP recording and other hemodynamic information [13]. In 1949, intra-arterial continuous BP measurement through cannulation was used in clinical settings. After that, researchers focused on developing noninvasive techniques for continuous indirect monitoring of arterial BP. Two major techniques, arterial tonometry and volume clamp method, were pioneered by Pressman *et al.* and Peñáz in 1963 and 1973, respectively [14, 15]. However, these two techniques are intrusive because they require the application of external force and the occlusive cuff. Therefore, the study on pulse transit time (PTT) and its relationship with arterial pressure in the early 1960s brought expectation of BP measurement without the intrusive cuff [16]. Unobtrusive BP measurement systems have emerged since the early 2000s when the functionality of cuffless BP devices was demonstrated on daily objects such as sleeping cushions [17]; chairs [18]; weighing scales [19]; and wearable objects including watches [20], rings [21], shirts [22], eyeglasses [23], mobiles [24], and cameras [25]. The key milestones of continuous BP measurement technologies from invasive to unobtrusive techniques are illustrated in Fig. 2 and further elaborated as follows.

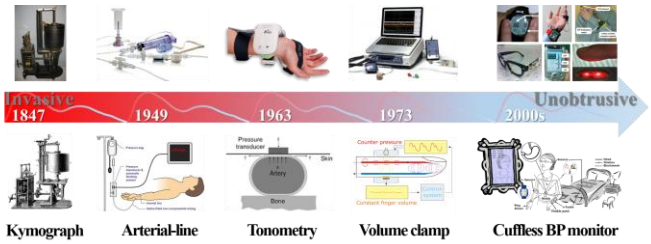


Fig. 2. Key milestones of continuous blood pressure (BP) measurement technologies.

A. Kymograph

The kymograph ("wave writer" in Greek) was invented by the German physiologist Carl Ludwig (1816–1895) in 1847 (Fig. 3). The kymograph consists of a brass pipe cannula, a U-shaped mercury manometer tube, and an ivory float to which a stylus is attached to enable sketching on a revolving drum. The kymograph was first used to graphically record continuous oscillations of human arterial pressure through inserting the cannula into the artery. The introduction of this graphic recording of continuous arterial pressure as well as other hemodynamic measures in physiology remained as one of the great landmarks of science for over a century, making far-reaching effects on experimental physiology and scientific medicine development [26].

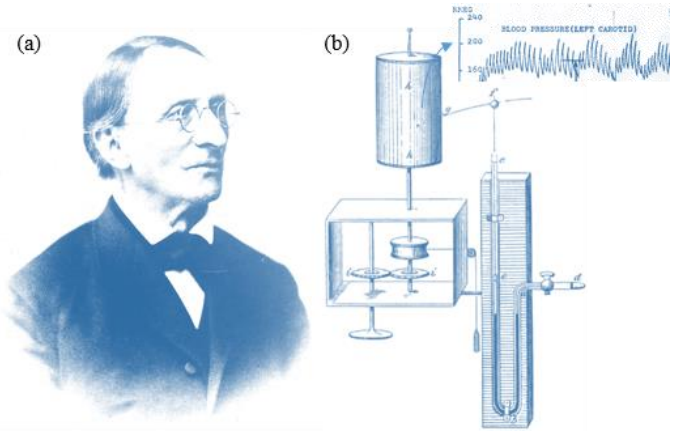


Fig. 3. (a) Carl Ludwig and (b) his kymograph [27].

B. *Intra-arterial BP Monitoring through an Arterial Line*

The first clinically useful placement of a plastic catheter into an artery for invasive BP monitoring was developed by Peterson *et al.* in 1949 [28]. The intra-arterial catheter ("arterial line") is usually a high-pressure plastic tube filled with a fluid column and directly connects the artery system to a pressure transducer. The arterial pressure waveform is transmitted from the fluid column to the transducer and converted into an electrical signal through hydraulic coupling. This electrical signal is then processed and displayed on a terminal (Fig. 4). The cannulation site can be peripheral arteries such as the radial, ulnar, brachial, femoral, or root aortic arteries. Percutaneous radial artery cannulation is a well-established procedure commonly used in operating rooms and intensive care units for critically ill patients.

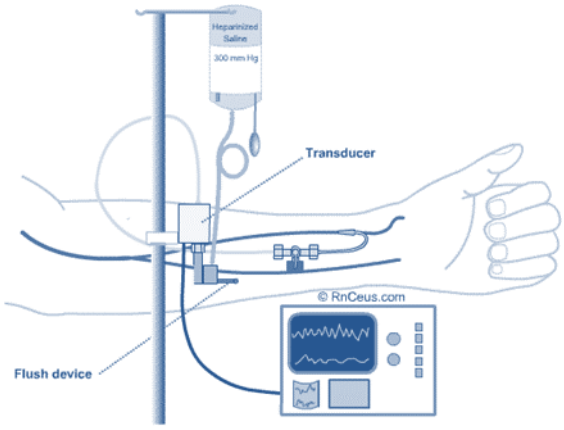


Fig. 4. Radial arterial line and transducer [29].

C. *Arterial Tonometry*

Although the intra-arterial method is the gold standard for continuous BP monitoring, it is invasive and can be used only in clinical environments. Attempts have been made to enable continuous measurement of the arterial pressure without cannulation. In 1963, Pressman and Newgard developed arterial tonometry inspired by the older technique of ocular tonometry [14]. Basically, tonometry is performed by applanating a superficial artery (e.g., radial artery) against a bone with an external transducer until the artery is flattened (Fig. 5). At this applanation state, the tangential arterial wall tension does not affect the vertical force measured using the transducer. Therefore, after some simplification and assumption, the measured arterial displacement due to arterial pulsation will be proportional to the intra-arterial pressure:

$$\delta = \frac{F_a}{k} \tag{1}$$

where δ, Fa, and k represent arterial displacement, force due to arterial pressure, and spring rate of the pressure transducer. Subsequently, the arterial waveform and continuous BP can be derived.

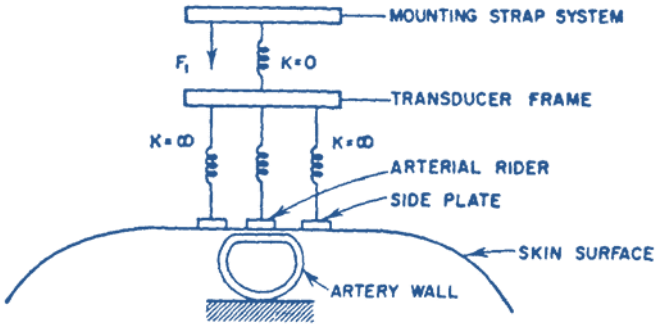


Fig. 5. The transducer artery system at the applanation state [14].

Arterial tonometry has been improved to be reliable and commonly used in the measurement of pulse wave velocity (PWV) for evaluation of arterial stiffness. However, because its validity of measuring arterial BP depends on the applanation of the artery, the requirement of external force means that it is partly invasive. In addition, practical problems of sensor positioning, motion artifacts, and calibration are still encountered.

D. *Volume Clamp Method*

Approximately 10 years after the development of arterial tonometry, Peñáz, a Czech physiologist, developed a continuous noninvasive BP measurement technique by introducing the volume clamp method on the finger [15]. The diagram of the system control loop is illustrated in Fig. 6. The system includes an inflatable finger cuff with a built-in photoplethysmograph (PPG) sensor, a fast pneumatic servo system, and a dynamic servo set-point adjuster. By using the fast servo system, a pulsating cuff pressure is applied to the finger arteries that are precisely opposite to the intra-arterial pressure. Through the process of unloading the arterial diameter to a set point, the artery is clamped at a constant size reduced from its elastically expanded and pulsating diameter to a smaller non-pulsatile diameter. When the cuff pressure equals the arterial pressure, the transmural pressure, which is the difference between the intra-arterial pressure and external applied cuff pressure, is zero. This indicates that $p_t = p_a - p_c$, in which p_t, p_a, and p_c represent transmural, arterial, and cuff pressure, respectively. Furthermore, $p_t = 0$ and $d = d_u$ follows $0 = p_a - p_c$; that is,

$$p_c = p_a \text{ and } d = d_u \tag{2}$$

Unloading of the artery until its diameter d equals the unstressed diameter d_u is crucial for the volume clamp method of Peñáz. To ensure this, the criterion for set point should be based on the physiological properties of finger arteries [30]. Although various criteria are used in practice, the Physiocal criteria proposed by Wesseling are the most widely used [31, 32].

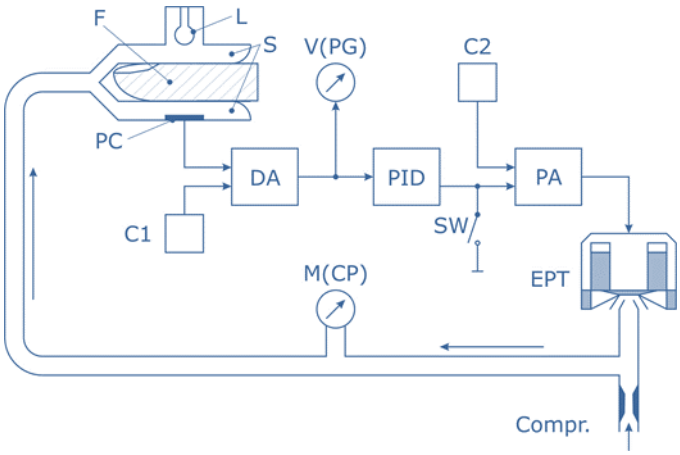


Fig. 6. Block diagram of Peňáz's system [15].

On the basis of the volume clamp method and the Physiocal criteria, Finapres™ was developed and introduced in the market in 1986. Finapres™ has been validated in several studies for measuring intra-arterial pressure; however, its accuracy remains controversial [33]. Moreover, the system is bulky and the finger cuff used in this system causes tight confinement and discomfort. Thus, this system is limited only to bedside uses.

E. Unobtrusive Technique for BP Measurement

Recently, the demand for ubiquitous, unobtrusive, continuous BP monitoring without using a cuff for ambulatory and home BP measurement has been increasing. BP can be continuously measured through beat-to-beat measurement (i.e., continuous systolic/diastolic/mean BP, Fig. 9) or continuous arterial waveform calibration by using a BP-related indicator. The method based on PWV recording is an attractive alternative for measuring unobtrusive BP without using the intrusive intra-arterial, arterial tonometry, and volume clamp method. In principle, the method can be performed using PWV or its reciprocal, PTT. This method is based on the fact that PWV theoretically and experimentally depends on the property of the arterial wall, which varies with the arterial pressure [34]. PWV is usually assessed using the arrival time of a pressure wave propagating through the arterial tree in a certain distance between the proximal and distal arterial sites. Because of the complexity of distance measurement, PWV can be indirectly approximated using PTT, which can be easily derived from two pulse signals, namely ECG and PPG signals (Fig. 7). The usage of PTT can be dated back to 1964 or earlier in 1959 [16] when Weltman *et al.* devised the PWV computer by "utilizing the EKG complex and a downstream pulse signal to define pulse transit time over a known arterial length". By using a calibration procedure, the measured PTT can be translated into arterial pressure by using an appropriate model. Moreover, other cuffless solutions based on different mechanisms have also been studied in recent years.

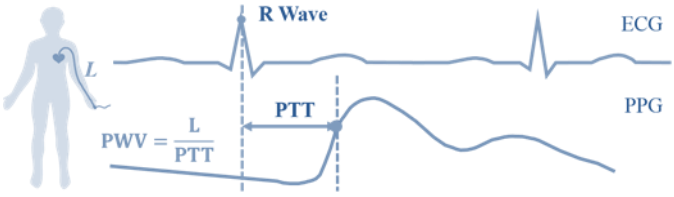


Fig. 7. Schematic diagram of the pressure pulse wave velocity (PWV) and pulse transit time (PTT).

Table 1. Comparison of techniques for continuous blood pressure measurement.

Technique	Ambulatory compliance criteria			Clinical compliance criteria	
	Unobtrusive	Supervision requirement	24 hours available	Periodicity	Accuracy
Kymograph (1847)	No	Yes	No	Continuous	
Intra-arterial (1949)	No	Yes	No	Continuous	Gold standard
Tonometry (1963)	Partly	No	Partly	Continuous	Controversial
Volume clamp (1973)	Partly	No	Fairly	Continuous	Controversial
Cuffless BP (2000s)	Yes	No	Yes	Continuous or beat-by-beat	Controversial

The overall comparison of each techniques for continuous BP measurement in terms of criteria of ambulatory compliance and clinical compliance is listed in Table 1.

III. Current Unobtrusive Techniques for BP Measurements

Extensive research has been performed to unobtrusively measure cuffless BP for mobile, smart, and connected health. The PTT method is one of the most widely used methods. In addition, other methods such as ultrasound/magnetic, tissue character-based approach, and machine learning have been studied.

A. PTT-based Techniques

PTT Calculation

PTT is generally defined as the time taken by a pulse wave to travel between two places in the cardiovascular system. PTT can be determined using different sensing approaches such as electrical, optical, mechanical, bioimpedance, magnetic, and radar. As illustrated in Fig. 8, PTT is usually calculated as time intervals between the R wave of electrocardiogram (ECG) and characteristic points of PPG/tonoarteriogram (TAG) [35], which includes the pre-ejection period (PEP), between impedance cardiogram (ICG)/ballistocardiogram (BCG)/seismocardiogram (SCG) [36, 37]/phonocardiogram (PCG) and PPG/TAG, between PPG and TAG, or between two PPGs/TAGs at different arterial sites. PEP has been a concern to PTT-based BP estimation. Nevertheless, several studies have confirmed the prominent role of PEP on PTT and its positive contribution to accurate BP estimation [38-40].

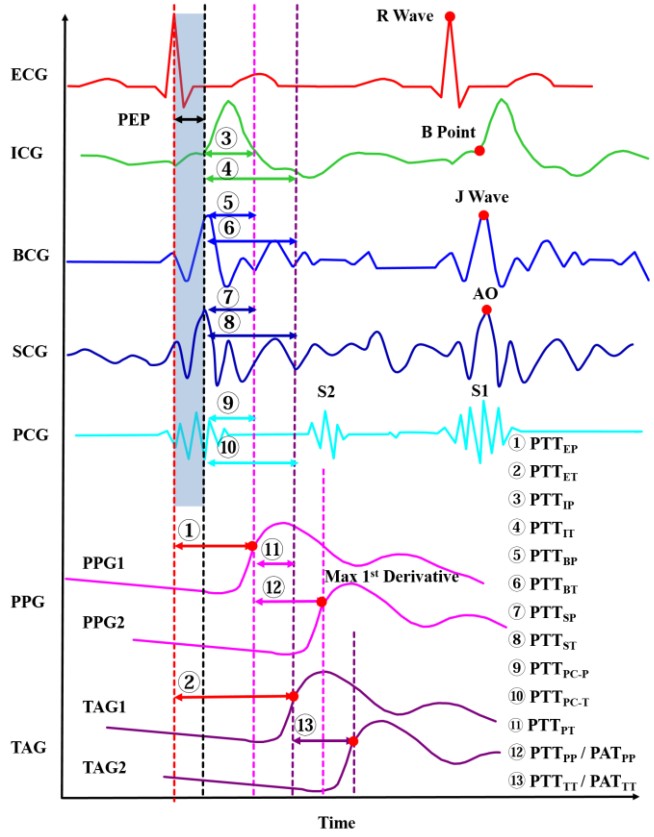


Fig. 8. Diagram of pulse transit time (PTT) calculation [41].

ECG is the most widely used technique for proximal timing reference. In addition, ICG, BCG, SCG, and PCG, which contain the information on cardiac mechanical vibrations, have been utilized to determine PTT. Recently, researchers have attempted to use BCG and SCG for unobtrusive BP monitoring [42], because they enable the derivation of some cardiovascular surrogates such as the cardiac output, stroke, and systolic time intervals. SCG, which quite similar to BCG, records mechanical oscillations caused by the heart movement and blood flow through big blood vessels in the upper part of the body. The waveform of SCG can be mathematically modeled as an instantaneous force in the vertical direction by analyzing the equilibrium of forces exerted on blood in the main artery of the body and aorta, which is described as follows [43]:

$$m \cdot y'' = -F_r + F_0 - F_{b1} - F_{bp} + F_b + F_p \tag{3}$$

where m is the mass of flowing blood; y'' is its acceleration; Fr, F_0, F_{b1}, and F_{bp} are partial impactive forces developed during a systole; and F_b and F_p are coupling forces that come across the whole cardiac cycle.

PPG is a well-developed technique for distal signal recording because of its noninvasiveness, continuous measurement ability, ease of use, and low cost. The variants of the PPG technique, such as multi-wavelength PPG [44] and contact or contact-free imaging PPG [25, 45], have demonstrated potentials for PTT-based cuffless BP measurement. In addition, bioimpedance and continuous wave radar have been employed for PTT calculation [46, 47].

PTT-BP Modeling

PTT-based BP estimation principally relies on the Moens–Korteweg (M-K) equation:

$$PWV = \sqrt{\frac{Eh}{\rho D}} \tag{4}$$

The M-K equation correlates PWV with the modulus of elasticity of the artery E, the thickness of the arterial wall h, the diameter of the artery D, and the blood density ρ. If ρ is assumed to be constant among the other three variables (i.e., E, h, and D), E is the major factor that PWV depends upon. Furthermore, according to Hughes *et al*. [48], the elastic modulus E is exponentially correlated with the mean distending pressure P, as given by (5).

$$E = E_0 \cdot e^{\gamma P} \tag{5}$$

where E_0 is the zero-pressure modulus and γ is a constant typically between 0.016 and 0.018. The combination of (4) and (5) and the relationship between PWV and PTT; that is, $PWV = L/PTT$, where L is the distance between the heart and some peripheral sites, provide the arterial pressure:

$$P = \frac{1}{\gamma}\left(-2\ln PTT + \ln\frac{\rho L^2 D}{hE_0}\right) \tag{6}$$

Therefore, with the accurate calibration of PTT to BP, beat-to-beat BP can be estimated from PTT. On the basis of the theoretical relationship between PTT and BP and their experimental or empirical relationship, various models that correlate PTT with BP have been established. BP is usually derived based on the equation:

$$BP = A * f(PTT) + B \tag{7}$$

where *f(PTT)* could be PTT [39, 49-57] or its variants, such as *1/PTT* [58, 59], $1/PTT^2$ [60, 61], *ln(PTT)* [40, 61], and e^{k*PTT} [62] [63]. Rather than only PTT, extra parameters related to cardiovascular activity can be introduced:

$$BP = A * f(PTT) + B \cdot parameter + C \tag{8}$$

where *parameter* can be the heart rate (HR) or other BP-related features extracted from the pulse signal (e.g., arterial stiffness, cardiac output, and pulse width) [64-66].

Because the vascular smooth muscle tone can affect the relationship between BP and PTT (9), Liu *et al*. [67] suggested that the vascular tone should be further considered into PTT-based BP estimation.

$$PTT = \frac{L}{PWV} = L \cdot \left(\frac{r_i}{2\rho}\left(\frac{ab}{r_o(t_d)}\exp\left(b\frac{r_o(t)}{r_o(t_d)}\right)\right.\right. \\ \left.\left. + \frac{\sigma_{\theta\theta}(r_o) - \sigma_{rr}(r_o)}{r_o}\frac{r_i}{\sqrt{r_i^2 + r_{o_{un}}^2 - r_{i_{un}}^2}} - \frac{\sigma_{\theta\theta}(r_i) - \sigma_{rr}(r_i)}{r_i}\right)\right)^{-\frac{1}{2}} \tag{9}$$

where r_{i_un} and r_{o_un} are the inner and outer radius of arterial wall, respectively, and $\sigma_{\theta\theta}$ and σ_{rr} are the radial and hoop stresses, respectively. Regarding the effect of the vascular tone,

a recent study proposed using the PPG intensity ratio (PIR) to evaluate the arterial diameter change and further the vasomotion. The results revealed that the accuracy achieved using the combination of PIR and PTT to estimate BP (10) was higher than that achieved using PTT alone [68].

$$SBP = DBP_0 \cdot \frac{PIR_0}{PIR} + PP_0 \cdot \left(\frac{PTT_0}{PTT}\right)^2; DBP = DBP_0 \cdot \frac{PIR_0}{PIR} \quad (10)$$

Fig. 9 presents a representative example of measured and estimated continuous and beat-to-beat BP. Because it was difficult to obtain the gold standard for continuous BP measurement, we measured continuous BP by using Finapres™. The snapshot BP of an individual measured using a cuff-based oscillometric device was 110/65 mmHg.

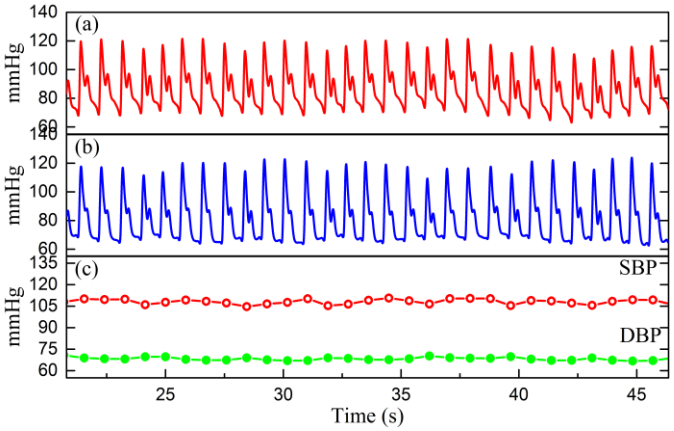


Fig. 9. (a) Continuous blood pressure (BP) of a 23-year-old healthy man: (a) continuous BP measured using Finapres™; (b) estimated continuous BP with the calibration of BP to continuous PPG; (c) estimated beat-to-beat BP derived from pulse transit time (PTT) and PPG intensity ratio (PIR) [68].

The performance of estimated continuous BP and beat-to-beat BP was evaluated in terms of root mean square error (RMSE) and mean absolute difference (MAD), respectively. They are defined as follows:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(Y_{est} - Y_{ref}\right)^2} \quad (11)$$

$$MAD = \left(\sum_{i=1}^{n}\left|Y_{est} - Y_{ref}\right|\right)/n \quad (12)$$

The performance of continuous, beat-to-beat, and snapshot BP for the representative sample is listed in Table 2. We can observe that the beat-to-beat SBP/DBP using PTT and PIR achieved comparable and even better accuracy than that measured with the Finapres when compared to the cuff-based BP.

Table 2. Accuracy of the measured continuous blood pressure (cBP), beat-to-beat BP, and snapshot BP (cuff).

Evaluation metrics (mmHg)	**RMSE**	**MAD**	
BP parameters	cBP	SBP	DBP
(b) vs. (a)	7.60	-	-
(c) vs. beat-to-beat of (a)	-	8.81	2.38
Mean of (c) vs. cuff BP	-	3.84	2.41
Mean beat-to-beat of (a) vs. cuff BP	-	4.78	0.72

Cuffless BP can be obtained through PTT by using the Bramwell and Hill equation, which is a variant of the M-K equation and is given in (13) [69]:

$$PWV = \sqrt{\frac{V}{\rho dV/dP}} \quad (13)$$

where V and P represent the blood volume and pressure, respectively, and $(dV/dP)/V$ is the relative increase in the volume of the artery per mmHg increase of pressure. Based on (13), Joseph *et al.* studied the calibration-free pulse pressure measurement by using the equation [70]:

$$\Delta P = 2\rho\left(\frac{L}{PTT}\right)^2 \frac{\Delta D}{D_d} \quad (14)$$

where PTT and D can be measured through dual magnetic and ultrasound, respectively. On the basis of this approach, researchers have calibrated the patient-dependent coefficient; that is, by using changes in hydrostatic pressure under some assumptions [21, 70, 71]:

$$\Delta BP = \frac{1}{2}\rho\frac{d^2}{PTT^2} + \rho gh \quad (15)$$

Further research using multiple parameters integrated into the model should be conducted, such as by combining the machine learning method, which is used to select optimal parameters, and physiological modeling, which represents the mechanism of dynamic BP regulation, to improve measurement reliability.

Unobtrusive System

By using PTT for BP monitoring, sensors such as ECG electrodes and PPG sensors can be integrated into clothing, accessories, and living environment through unobtrusive sensing or in the wearable form. In 2000, Hung and Zhang conceptualized BP on a wireless application protocol phone [72]. To the best of our knowledge, the earliest platform considered for unobtrusive application was integration in a T-shirt with ECG electrodes at the wrists [22]. Other unobtrusive or mobile system can be mounted on wrists as wearable watches [20], upper arms [73], or ears [74]; attached to the chest as a patch [75] or a band [47]; and implemented through mobile phones [76, 77] or weighing scales [19]. In particular, the BP watch would be one of the most popular platforms to implement the unobtrusive system. Since the development of the first prototype of BP watch in 2006 [12], there has been a growing interest in developing and researching this platform [78]. Fig. 10 presents the early implementation of unobtrusive BP systems in our lab.

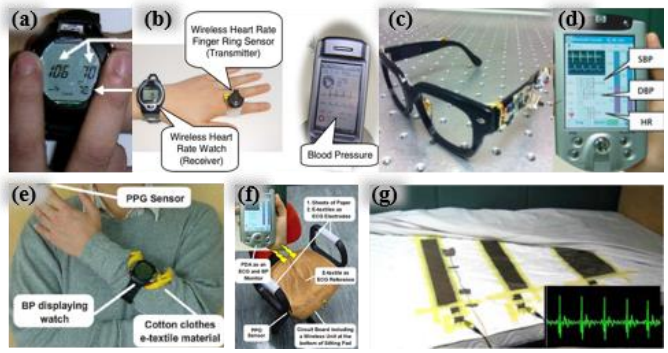


Fig. 10. Unobtrusive blood pressure (BP) measurement with realization in daily objects [79]: (a) BP watch [20]; (b) mobile phone [80]; (c) p-Eyeglasses [23]; (d) PDA [24]; (e) h-Shirt [22]; (f) u-Chair [18]; and (g) u-Bed [17].

Relevant sensors or systems can also be devised as an attachable patch or directly printed onto the human skin to enable long-term physiological and continuous BP monitoring (Fig. 11). For example, in our lab, we developed a wearable sensor patch system integrating a flexible piezoresistive sensor and epidermal ECG sensors for cuffless BP measurement. BP can be derived on the basis of the PTT method through collecting epidermal pulse by using flexible pressure sensors and ECG by using epidermal electrodes (Fig. 11a) [81]. Other examples include flexible LED and thin-film transistors, as illustrated in Fig. 11(d-f).

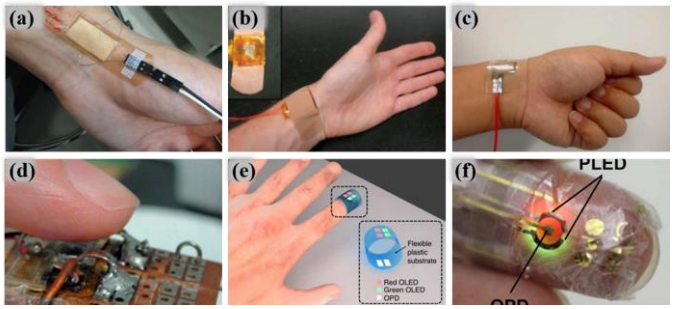


Fig. 11. Unobtrusive blood pressure (BP) measurement with flexible physiological sensors: (a-c) Flexible pressure sensor [81-83]; (d-f) flexible photoplethysmograph sensors [84-86].

The crucial aspects relevant to the unobtrusive system including the motion artifact [87], IC design [88], method repeatability [89], and security issue [90] have been studied and should be further researched for future development of unobtrusive system for BP monitoring.

B. Other Cuffless Approaches

The advancement of new-fashioned sensor materials as well as pervasive computational capability have enabled other solutions for cuffless unobtrusive BP monitoring, such as ultrasound/magnetic method, tissue character-based method, and machine learning method (Fig. 12).

Ultrasound/magnetic methods: With its ability to visualize the blood flow and the artery wall motion, ultrasound can measure the blood flow velocity, arterial vessel cross-sectional area, and flow area, which can indirectly estimate PWV. This PWV value was then used to convert the distension waveforms into pressure waveforms [70, 91, 92]. The ultrasound-based approach does not require the inflatable cuff, thus relieving the users from discomfort. This approach is also advantageous in central arterial evaluation. Nevertheless, the ultrasound device is bulky and limited to portable application and requires calibration of the arterial pressure waveform to absolute BP values. Except for ultrasound, pulsatile pressure can be obtained through magnetic resonance imaging by acquiring blood flow information [93]. Likewise, magnetic sensing (e.g., magnetic PPG transducer or magnetic Hall) can detect the pulse wave through the minute magnetic field change in the permanent magnet caused by arterial pulsation. Features are then extracted from the collected pulse wave, and BP is derived using the linear regression method [70, 94].

Tissue character-based methods: Unobtrusive BP monitoring has also been explored on the basis of the tissue character. For example, Lading *et al.* used capacitive method to detect vascular distention based on different dielectric constants between blood and the surrounding tissue and derive arterial pressure with the combination of vascular stiffness that was determined using PWV [95]. Woo *et al.* introduced a new noninvasive mechanism of tissue-informative measurement where an experimental phenomenon called subcutaneous tissue pressure equilibrium was revealed and related for application in detection of absolute BP [96]. Another reported BP meter was developed with optical sensors using the "Phase Shift Method," by which the intrinsic arterial waveform can be traced through compensating the phase difference between the phase of the incident wave and the phase of the reflected wave [97, 98].

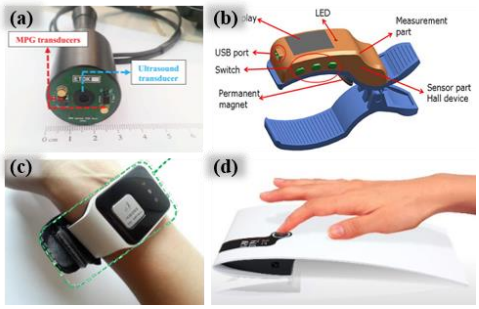


Fig. 12. Other cuffless blood pressure (BP) approaches: (a) ultrasound and pulse transducer [70]; (b) magnetic Hall for BP monitoring [94]; (c) tissue informative mechanism for wearable BP monitoring [96]; and (d) phase shift method [98].

Machine learning methods: With the ever-increasing computational power and development of big data technology, big data analysis using the machine learning method for cuffless BP measurement has gained increasing attention [99-103]. The general idea with this technique is to initially extract surrogate cardiovascular indexes from physiological signals, then use machine learning to train this data to adapt to the system, and finally predict BP using the trained model. A typical block diagram for predicting BP using machine learning methods is presented in Fig. 13. Multiple features were first extracted from the time domain or frequency domain of physiological signals such as ECG and PPG. A feature selection method was then employed to eliminate irrelevant and redundant features to avoid over fitting. For instance, A genetic algorithm-based feature selection method was proposed [104] to find the optimal feature set before model development for BP

estimation and thus achieved good accuracy. Machine learning methods such as linear regression, neural network, Bayesian network, and support vector machine can be used to develop the BP model. Table 3 presents the state-of-art machine learning techniques for cuffless BP measurement. Xing *et al.* proposed to extract the amplitude and frequency features by a fast Fourier transform of only the PPG signal and then use that signal to train an artificial neural network to estimate BP [103]. Kachuee *et al.* reported the extraction of many physiological parameters from ECG and PPG signals along with multiple regression [99]. Overall, existing BP models using machine learning methods demonstrate promising estimation accuracy [105]; however, the potential mechanism behind the patterns should be further studied.

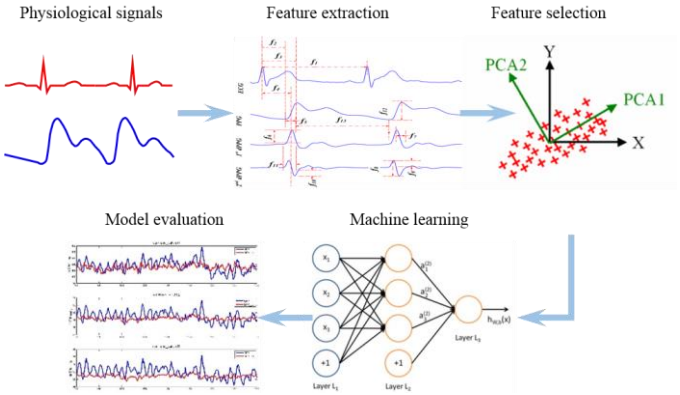


Fig. 13. Block diagram of machine learning method for cuffless blood pressure (BP) measurement.

Table 3. Machine learning methods for cuffless BP measurement.

Ref.	Key features	Methods	Subjects	Estimation Error (mean (SD) mmHg)	
				SBP	DBP
[99]	PTT, HR, AI, LASI, IPA	MLR/ ANN/ SVM	4254/ICU	14.7 (18.1)	12.4 (16.1)
[100]	PTT, time span (ratio), area (ratio)	MLR	9/Exercise	MAD: 4.73	MAD: 3.54
[103]	Amplitude and frequency	ANN	65/ICU	0.06 (7.08)	0.01 (4.66)
[104]	PTT, HR, PIR, PPG_K, time span, SDFH	MLR/ SVM	73/ natural variability	-0.00 (3.10) (short-term) -1.15 (5.79) (long-term)	0.00 (2.20) (short-term) -1.19 (5.29) (long-term)
[105]	PTT, HR, time span	RF/ MLR	285/ICU	8.29 (5.84)	4.44 (3.72)

AI: Augmentation Index; LASI: Large Artery Stiffness Index; IPA: Inflection Point Area Ratio; PIR: Ratio of PPG peak intensity to PPG bottom intensity; SDFH: Foot intensity of the second derivate PPG waveform; MLR: multiple linear regression; ANN: artificial neural network; SVM: support vector machine; RF: random forest.

Most of these methods are still in the research stage. The few commercially available devices include Sotera ViSi Mobile continuous, noninvasive BP (cNIBP) monitoring and SOMNOtouch^{TM}-NIBP, which are based on the PTT method [106]. The ViSi's cNIBP is determined on a beat-to-beat basis employing PTT and calibration with automatic noninvasive BP method. It has been cleared by FDA with its clinical performance being validated following the requirement of ISO 81060-2. Nevertheless, the ISO 81060-2 targets for cuff-based noninvasive sphygmomanometers. Thus, the standardized characterization of these new BP measurement approaches are required with an increase in market interest. This has been addressed by IEEE 1708, the standard for wearable cuffless BP measurement devices, which has highlighted the performance evaluation and calibration issue for cuffless devices [107, 108].

IV. Challenges and Future Directions

A. Challenges

Although current unobtrusive techniques for cuffless BP monitoring have demonstrated significant advances, there are still many issues and challenges before its wider clinical adoption. In particular, the cuffless continuous technique does not yet have adequate accuracy to replace direct invasive measurement of arterial BP. Calibration issue is another crucial problem to be addressed. The major challenges in unobtrusive continuous BP measurement, especially for PTT-based methods, are summarized in the following points.

First, most of the studies use only PTT with simple linear or nonlinear regression methods to correlate PTT with BP. Only PTT cannot fully represent dynamic BP because PTT is determined by factors other than just the arterial BP and vice versa. Furthermore, the velocity of the pulse wave is a function of the elasticity of the vessel, which would vary among individuals and within the same individual. It follows that changes in the velocity of the pulse wave for a given segment of an artery should be determined almost entirely by changes in the local BP and/or the activity of the smooth musculature of the segment.

Second, because the physiology coefficients employed for BP estimation are subject dependent, calibration is crucial to ensure the accuracy of cuffless devices. A major challenge is to find a simple and accurate way to calibrate BP individually or estimate BP directly without a calibration procedure. For most current methods, frequent calibration is required for most of the studies to ensure the acceptable accuracy within a certain period of time. This is radically due to the assumption and simplification of the M-K equation as the simplification may become unreliable under circumstances when the actual physiological state deviates too much from the assumed state. Although calibration methods using adaptive algorithms (e.g., adaptive Karman filter algorithm and recursive least square algorithm) have been explored to improve the calibration issue, the essential problem has not yet been resolved.

Additional studies addressing the issues of accuracy and calibration should be conducted. Considering the major limitations of current studies, it will be helpful to explore new indicators that can provide different information of BP changes complementary to PTT to establish appropriate models for evaluating the relationship between the indicators and arterial BP and to verify cuffless methods following the international standard.

B. Future Directions

In this paper, we have presented an overview of the techniques for continuous BP monitoring either in an invasive and intrusive or in a noninvasive and unobtrusive way.

Although significant progress has been made in developing unobtrusive continuous BP monitoring techniques in the past two decades, most of them are still in their prototype stages. Issues such as accuracy, calibration interval, and effect of heart disease remain to be addressed to enhance the reliability and robustness of these techniques for clinical use. Because of the multidisciplinary nature of this research topic, future development will greatly rely on advances in different areas such as novel sensing, physiological modeling, and data analytics. We have put forward some promising directions on the development of unobtrusive and continuous BP monitoring techniques for future research and product implementation.

Multi-modality, multi-parameter integration for improving the accuracy of indirect continuous BP monitoring: ECG and PPG signals are currently the most widely used signals for cuffless BP estimation. However, features extracted from these signals are quite limited to reflect the insightful information on dynamic BP because BP varies with time under intrinsic and extrinsic factors. Therefore, it would be valuable to integrate more comprehensive information collected from multi-modality signals such as optical, electrical, mechanical, and magnetic and extract alternative parameters that represent the cardiovascular system and relates to BP to further improve the performance of cuffless BP estimation.

Combination of machine learning and mathematical modeling: With growing interest in subject-specific modeling and machine learning, it would also be possible to use this technology to select optimal features that can best contribute to dynamic BP changes and then combine the physiological and mathematical modeling to predict continuous BP noninvasively and continuously. Considering the complexity of the cardiovascular system, selection of multiple indicators and an appropriate model is critical and require full-system integration to ensure the accuracy of indirect measurements.

Further accuracy improvement of BP estimation in patients: Because BP measurement can be affected by the state of the cardiovascular system and pre-existing pathologies, techniques such as the volume clamp method and PTT method would be affected by diseases of arteries such as arteriosclerosis, which affects the transit of arterial pressure or pulse wave throughout the arterial tree. This should be resolved particularly for a diseased population because they have high risk and require frequent BP monitoring.

Cuff-free calibration with acceptable accuracy: Unobtrusive continuous BP measurement targets the monitoring of the health status without disturbing the users during daily activities. However, the use of the cuff-based method cannot be avoided in the calibration method. As one of the biggest issues for cuffless BP measurement, calibration can be further promoted with the aim of prolonging the calibration interval and avoiding the cuff-based calibration technique. It would be interesting to introduce new physiological indices and establish new models to integrate these elements for tracking long-term BP accurately and thus reduce the calibration frequency. With these future developments, there will be some breakthrough in unobtrusive and continuous BP monitoring systems that can help in the early prevention and treatment of hypertension and reduce its burden on the society.

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