Methods for Continuous Non-invasive Measurement of Blood Pressure: Pulse Transit Time a Review

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Abstract

Blood pressure (BP) measurement is regarded as one of the most important parameters in the clinical evaluation of patients. It is helpful in both acute and chronic cases. Most medical examinations include BP measurement as it is the best indicator of cardiovascular health. In some cases, it is very important to examine the status of pressure valves continuously for long time periods. To prevent premature death, it can be used for daily health-care monitoring. The main problem with BP measurement is that all existing techniques use an inflatable cuff which is a discrete technique and may cause discomfort for the patients. Recently, few alternative techniques have been developed for non-invasive continuous measurement of BP. This review focuses on brief discussion of some of the methods for BP measurement both invasive and non-invasive and due to fewer side-effects and convenience of attachment of sensors of photoplethysmogram (PPG), this review mainly focuses on the plethysmography technique using pulse transit time for BP measurement. At present, many researchers are working on this method, and it has the potential to be the most widely used technique for a long time non-invasive continuous observation of BP in the future. This review also briefly discussed some of the artifact removal techniques in the PPG waveform and inaccuracies related to sensors due to the external factors such as noise and temperature.

Key words: Blood pressure measurement, diastolic blood pressure, electrocardiogram, empirical mode decomposition, intrinsic mode function, pulse transit time, R-peak, systolic blood pressure

INTRODUCTION

The world's awareness toward health care raised in recent years due to the rise in aging population and their vulnerability toward acute diseases such as high BP.[1] BP has become a vital parameter to mark the status of cardiovascular health in human beings. The pressure exerted on the walls of the blood vessels by the circulating blood is defined as BP. BP varies from a minimum level called diastolic BP (DBP) to a maximum level called systolic BP (SBP). SBP is the measure of the maximum pressure applied to the walls of the artery due to the contraction of heart on the onset of the cardiac cycle. When the heart is in a relaxed state, the minimum pressure applied by the blood circulating inside the artery is called as DBP.

Clinically, SBP and DBP are measured in millimeter of mercury (mmHg), for example, the typical value of SBP/DBP of a healthy person is 120/80 mmHg.[2] Variation in these values may cause severe problems such as a low value of SBP (SBP <90 mmHg) may cause the poor distribution of blood in small vessels leads to lack of oxygen and nutrients in the body.[3] If the value of SBP is high (SBP >140 mmHg) then the risk of rupture of blood vessels increases which may lead to damage of organs such as liver, heart, brain, or kidney.

Due to large variations in BP values, long-term constant monitoring could be very helpful for doctors to diagnose the problems on time. Hence, it is the requirement that the techniques for measuring BP should be highly accurate and the devices used should not use regular cuff for the long

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time which causes discomfort to the patients and should not require regular supervision. Therefore, non-invasive long-term continuous BP measurement methods are highly valuable in today's life.

In this review, existing BP measurement techniques are surveyed. The aim of the review is to unite all the diverse techniques and to describe each technique briefly and discusses the pros and cons of each of them. We start by introducing conventional BP measurement techniques such as invasive and non-invasive. Then, we will discuss the PTT technique and advances in PTT analysis. This review also discusses the methods to overcome the artifacts in PTT analysis and removal techniques of those artifacts in brief.

The outline of the paper is as follows. In Section 2 BP measurement background is demonstrated, and the PTT principle is introduced. Section 3 describes PTT in detail along with the previous work that has been done on it. Section 4 discusses the artifacts occurring due to sensors, used to get electrocardiogram (ECG) and photoplethysmogram (PPG) waveforms and few of the transformations used to remove it. Section 5 concludes the review.

BACKGROUND

Invasive measurement

BP measurement is predominantly categorized into invasive and non-invasive methods.[4] The invasive technique gives the most accurate readings of BP. This method is an intra-arterial method which uses a catheter.[5] A Teflon or polyurethane based cannula is inserted into a non-end radial artery. A tubing system is attached to the cannula to provide constant saline infusion. Through the liquid, in the infusion tube, the pressure waveform is transferred to a diaphragm which is basically a pressure transducer. The electrical signals which give the BP are generated using these pressure waveform displacements.

Despite having many advantages such as accuracy and continuity, this method is not used widely because of its major disadvantages of complexity, pain, patient risks, and infection.

Manual non-invasive BP measurement

Various non-invasive techniques have been developed for BP estimation that is broadly classified as manual and automated. These techniques are more secure, fast and require a little expertise. The two most common manual methods for non-invasive BP measurement are palpatory and auscultatory. These are cuff based methods in which the sphygmomanometer contains a manometer and inflatable cuff. The upper arm of the patient is placed at the level of heart, and the inflatable cuff is folded over the arm of the subject and is inflated until the artery is completely occluded. The palpatory method only estimates SBP; hence, it is used in emergency cases. Furthermore, SBP measurements have errors up to 25%.[5] Here, the expertise palpates the radial pulse of subject's wrist. SBP is the pressure level which appears when the pulse first disappears at the inflation and then appears again during the deflation. Recently, the palpatory method with DBP measurements is also introduced for BP measurement.[6]

In the auscultatory method, the Korotkoff sound is detected with the slow deflation of the cuff placed around the brachial artery along with a stethoscope. The examiner listens to these sounds to approximate SBP and DBP. The SBP is when the cuff is inflated, and the Korotkoff sound is first detected, whereas the DBP is when the Korotkoff sound is disappeared. Since trained staff is required for the implementation of this method; hence, it is still confined to the hospitals only. Moreover, for the patients with low flow states, this pressure is difficult to detect and also due to the anxiety of patients the readings become inaccurate.[7]

Room temperature, background noise, talking, exercise, muscle tension, alcohol, nicotine consumption or positioning of the arm, etc., are the factors that can affect the reading of BP taken using auscultatory method.[8] All the clothing which covers the cuff should be removed, the patient should sit straight with back supported and legs uncrossed, the cuff should be at the level of the heart, the cuff bladder should be at least 80% of the length and 40% of the circumference of the arm are the few recommendations given by the American Heart Association.[8] Both the above-mentioned methods use mercury manometer which is considered an environmental hazard. Hence in countries like North America and Europe, the mercury manometer is replaced by automated BP meters that do not use mercury.[9,10] The Figure 1 classifies all the techniques used for BP measurement broadly.

Automated non-invasive BP measurement

Many techniques have been developed as an alternative to manual BP measurement. Such techniques come under automated mode. These are broadly classified as continuous and sampling based. Beat to beat arterial BP variations can be provided by continuous recording techniques.[11] These are further classified as plethysmography,[12] tonometry,[13] and vascular unloading.[14] For short time measurement of <1 min, sampling techniques are used.[11] These techniques are further classified as automated auscultatory,[15] Doppler ultrasound sphygmomanometry,[16] and oscillometry. All above[17,18] classifications have their own advantages and disadvantages.

High accuracy and low risk are the main factors to be considered from the doctor's point of view in the measurement of continuous non-invasive BP. Comfort, less pain during long term monitoring are the factors to be considered by patient's

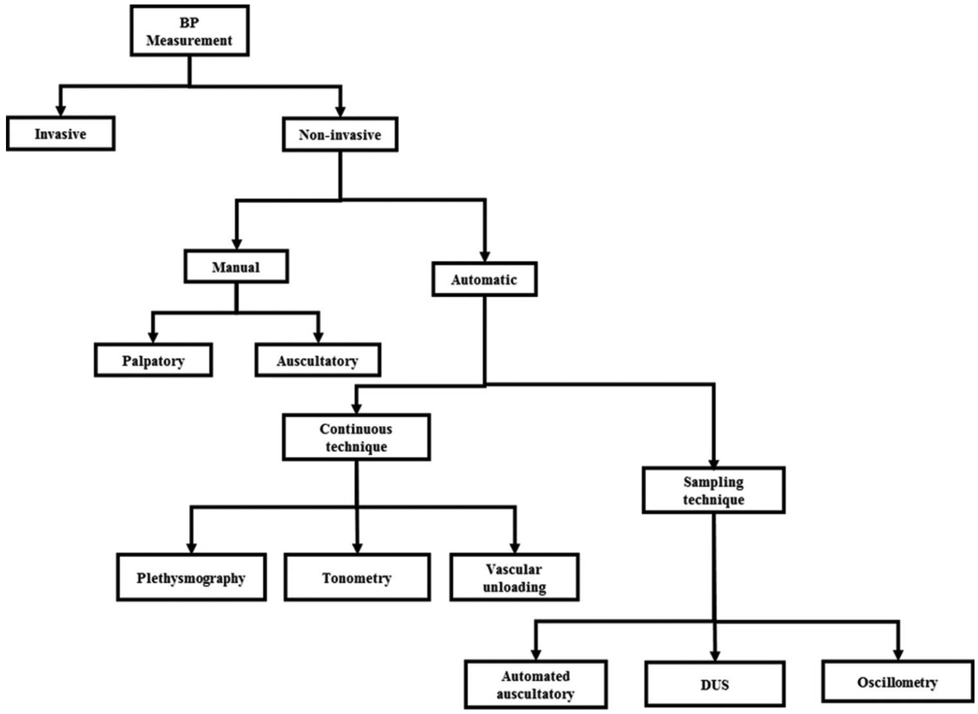

Figure 1: A broad classification of all the techniques involved in blood pressure measurement

Table 1: Comparative study of invasive and non-invasive BP measurement methods.

Method	Advantages	Disadvantages
Invasive technique	A gold standard for BP measurement Continuous and accurate Best for long-term estimation of BP continuous technique	Uncomfortable for patients close supervision required Trained staff required The possibility of infection and pain
Non-invasive :		
Auscultatory	Gold standard Used widely	Difficult to detect Korotkoff sound if the person is not trained Cuff used Supervision required Discrete technique
Oscillometric	Automatic hence no skilled staff is required Widely used technique also used as the gold standard No supervision required	Not perfect for patients of irregular heartbeats The position of the cuff and heart should be at the same level Discrete technique Not comfortable if applied for a long time
Arterial tonometry	Beat-to-beat measurement Supervision is not required Continuous BP measurement technique	Costly compared to the sphygmomanometer With wrist movements sensitivity increases and accuracy decreases Continuous contact pressure is required More sensitive for akin abnormalities Comfort and accuracy decreases as the span of measurement increases
Pulse transit time	Long-time beat-to-beat measurement and comfort is possible No need for supervision No cuff used	Calibration required frequently Not suitable for low peripheral perfusion, low flow state or hypothermic patients A lot of work is still required in this technique

BP: Blood pressure

point of view during the investigation. The above-mentioned methods are not considered for a long time measurement due to various disadvantages [Table 1]. Fortunately, PTT analysis is one of the methods that does not involve pain or discomfort during long-term monitoring and also does not require cuff and skilled examinations.

PULSE TRANSIT TIME

A new method that goes beyond all techniques for BP measurement involves pulse transit time analysis. This method is based upon evaluating the time of travel between two familiar locations as there is a relation between travel time and BP to be measured. It can also be evaluated by the time lag between the R peak of the ECG signal and the pulse arrived at the periphery. The R wave from the PQRS pulse of the ECG is chosen because it is very easy to detect and also it occurs when the blood is pumped from heart to aorta at the onset of the heart systole and this wave further travels to the periphery. Figure 2 shows the technique for the measurement of Pulse Transit Time.

The PTT based analysis can be described using a correlation between PTT and BP,[1,19-33] where a regression model is designed using BP and PTT. And the PTT is calculated using the time traveled by the wave from R peak of ECG to any peripheral site which may include finger, toe or earlobe. Another method is employed which used as a reference for BP measurement. It may include a standard cuff based Sphygmomanometer for BP measurement. A regression model can be easily found to get the relation between BP and PTT

The major disadvantage of this technique is that a continuous calibration with the standard device is required. Furthermore, due to the discontinuous correlation between BP and PTT, the accuracy becomes low.

PTT analysis can also be described using PTT and cuff pressure dependencies. In this an inflatable cuff is used to apply variable pressures to the artery and pressure sensor is used near the cuff for the measurement of arterial pulses. The BP is then measured using PTT which is analyzed from the applied cuff pressure.

The speed of pulse wave traveling along an artery depends on the factors such as elasticity coefficient, arterial wall thickness, blood density, and vessel diameter.[34] In late 80's a mathematical equation was derived by Moens [35] for the velocity of the pulse wave that travels along the artery using the factors described above.

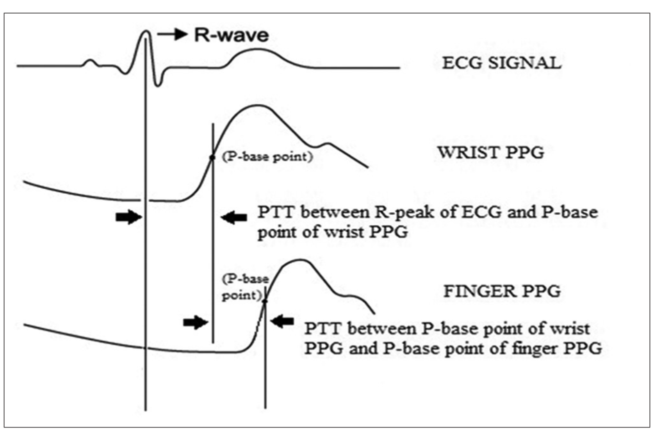

Figure 2: Measurement of pulse transit time[2]

$$WV = \frac{L}{PTT} = \sqrt{\frac{tE}{\rho d}} \tag{1}$$

Where PWV is the pulse wave velocity, E is Young's modulus of elasticity,[36] ρ is the density of blood, t is the thickness of the vessel walls, d is the diameter of the vessel, and L is the length of the vessel. After this pulse wave velocity had become the clinical index for the elasticity of artery.

In the late 90's many methods were derived to get continuous and instantaneous BP using PWV. The evaluation of PWV was done using the time elapsed between R peak of ECG and the arrival of the pulse on any marked position such as finger or toe measured with PPG. This PWV then correlated with BP measured from any standard device like sphygmomanometer.[37]

In 1981, Geddes *et al.*[38] described a linear relation between PWV and BP to measure SBP and DBP indirectly. Later, he also derived that Young's modulus E of the arterial wall had empirical exponential relation with the fluid pressure P and was not a constant.

$$E = E_0 e^{\alpha P} \tag{2}$$

Here, E_o is zero pressure modulus, is vessel parameter (e = 2.718 is Euler's number). And hence Moen and Kortweg's equation was rewritten as

$$PWV = \frac{L}{PTT} = \sqrt{\frac{tE_0 e^{\alpha P}}{\rho d}} \tag{3}$$

From 2000, PWV became a good indicator that predefines premature deaths and arterial stiffness. In 2003, Teng examined the relation between BP and PPG signal during rest, step-climbing exercise, and recovery from exercise. They also used Continuous Wavelet Transform for de-noising the PPG waveform. They showed that use of diastolic time of PPG signal to estimate BP was a better approach and can be used after adequate calibration.[39]

In 2004, Lass *et al.*[40] showed how PTT increases with the subject's age and explained the delay associated with PTT due to the pre-ejection period (PEP). The electrical signal is transformed into a mechanical pumping force which needs non-constant electromechanical delay called as PEP.[41] Many studies have been done on PEP which causes errors in BP measurements because this delay is not constant. In the same year, Fung *et al*. described BP and PTT relation ignoring PEP, elasticity factors, etc., they described the relation as.[42]

$$BP = \frac{A}{PTT^2} + B \tag{4}$$

Where A estimated from the subject's height and B is also subject dependent. Due to limitations associated with PEP as PEP increases with lower heart rates,[43] a study was performed in 2006 in which they derived pulse arrival time (PAT) as:

$$PAT=PEP+PTT \tag{5}$$

The linear approximation was described in 2013 by Xiang for a given subject as[44]:

$$BP=aPTT+b \tag{6}$$

Whereas, Proneca *et al*. described non-linear equation as: [46]

$$BP=a\ln PTT+b \tag{7}$$

Whong and Poon[56] in 2009 proposed relation between BP, PTT, and HR as

$$BP=aPTT+bHR+c \tag{8}$$

This was later used by Kumar *et al*.,[51] in their study in 2014 and derived BP using linear and non-linear regression models. They proved non-linear regression techniques as better with higher accuracies. Respiratory rate along with the HR can also be measured with the help of PPG signals using PTT technique.[43] In 2012, winokur[57] modeled a new wearable device for continuous PTT and HR measurements. They placed the device on the ear and also included ECG, ballistocardiogram (BCG), and PPG waveforms. They extracted peak time intervals between ECG, PPG, and BCG and demonstrated that BCG can be used for PEP measurements. In 2018, Huang *et al*.[55] developed an unconstrained device for daily health care and it includes a long-term cuff-less BP monitoring system. They also used ECG, PPG, and BCG waveforms for monitoring of parameters such as BP and PAT. Different approaches used by different research groups are shown in Table 2.

ARTIFACT REMOVAL IN PTT ANALYSIS

The number of patients diagnosed with BP and hypertension may get doubled or halved just due to a change in 5 mmHg BP.[58] Factors responsible for the change in BP includes sensor aging, environmental factors such as humidity, change in ambient temperature, and factors such as external noise due to fluctuating power supply and some motion artifacts such as transients and vibrations.[59] Out of all the above-mentioned factors, the change in temperature and drift over time due to aging are considered as most important.[60] All other factors are considered to be negligible and are not considered as major ones.[61,62] Many different approaches have been implemented by various researchers to completely eliminate the above-mentioned errors and to reach up to the acceptable stage of precision.[60,63] According to the international standard ISO810602 for non-invasive BP measurement, the mean absolute error should be <5 mmHg[64] and according to ANSI/AAMI SP10:2002, the standard deviation of error should be <8 mmHg.[65] Furthermore, the ideal operating temperature is typically 10–40°C. Hence, a great level of accuracy is required in medical devices.

Zhang *et al*. in 2009 used Hilbert Huang transform (HHT) to de-noise ECG signals and decomposed the signal into Intrinsic Mode Functions (IMF's) using empirical mode decomposition (EMD) and found this transform best for non-steady signals like brain electrical signals.[66] In 2010 research was done again on the HHT method for de-noising to find an alternative for the wavelet transform. They showed after simulation that the method was easier than wavelet de-noising.[67] Afterward, extensive work was done on de-noising. In 2014, Joseph *et al*.[68]used discrete wavelet transform for de-noising of Additive White Gaussian Noise from PPG waveform. They compared 3 wavelets, namely haar, db4, and Sym3. They evaluate that Daubechies (db3) wavelet function gives the accurate result among all. Beside one dimensional signal, there are two-dimensional signals scan also which can be used to diagnose many ailments.[69-74] In 2016, an adaptive technique has been developed to overcome the errors and difficulties aroused due to ambient temperature changes and sensor aging. The inaccuracies are minimized using the EMD algorithm. The above step adjusts the erroneous readings before delivering them to the end user. A signal can be defined in the terms of (a) the trend, (b) the error, and (c) the short-term changes.

$$y(t)=T(t)+SD(t)+e(t) \tag{9}$$

Where, y(t) is general time series, T(t) is the trend, e(t) is the error, and SD(t) is short time changes. The decomposed signal into IMFs can be described as

$$f = \sum_{n=1}^{m}\left(IMFn\right) + T\left(t\right) \tag{10}$$

The used algorithm is responsible for the removal of undesired noise due to change in temperature and sensor aging without any change in the phase and frequency distribution of the measured signal.[75] Table 3 compares the various techniques for the detection of trends. The root mean square error between the evaluated and reference SBP is calculated <0.1 mmHg which shows a high similarity between them.[59]

DISCUSSION

PTT based techniques are currently regarded as the most promising methods for BP measurement. Hence, BP can be evaluated from biosignals such as PPG, ECG, and BCG in a more convenient way with fewer disturbances to the patient.

Table 2: Research group methodologies on BP measurement using pulse transit time

Author/year	Developed model	Obtained estimates	Methodology		Description
			Type	Sensor used	
Teng and Zhang	The relation between arterial BP and certain features of PPG	SBP DBP	PWA	PPG (finger)	Proposed two parameters for the approximation of SBP and DBP using single PPG.[39]
Fung *et al.*	PTT-BP model	PEP BP	PTT	ECG+PPG	Noise filtering using stationary wavelet transforms (2 levels SWT with db3).[41]
Soo-young *et al.* (2010)	BP estimation algorithm	SBP DBP	PTT	ECG+PPG+ pressure pulse	Proposed algorithm for estimation of BP using PTT between ECG and PPG.[45]
Proença *et al.*	PTT-BP relation	SBP PTT DPTT*	PTT	ECG+PPG (finger) PPG (finger)+PPG (ear)	Shown no significant correlation between PTT and BP for young professionals after short-term exercise and pointed to less accuracy of parameters as a major cause.[46] DPTT*: Differential pulse transit time
Chen *et al.*	BP-PWV model	SBP DBP PWV	PWA	PPG (ear)+ PPG (toe)	Six different timing points were examined on PPG signal to detect the most appropriate points for the calculation of SP and DBP.[47]
Gesche *et al.* (2011)	BP-PWV relation	BP PWV	PTT	ECG (chest)+PPG (finger)	A relationship established between SBP and PWV, significant calibration between BP acquired from PWV and sphygmomanometer SBP was produced.[26]
Puke *et al.*	A prototype of the wearable sensing system	PWTT*	PWTT	ECG+PPG	Alternative for ABPM sphygmomanometer was designed. The designed system could sense time-dependent changes in BP.[48] PWTT*: Pulse wave transit time
Wibmer *et al.*	The relationship between PTT and BP using non-linear and linear models	PTT SBP DBP	PTT	ECG+PPG (finger)	Showed PTT as a good measure of SBP during exercise and could be implemented in CPET tests and showed non-linear regression gives a better result than the linear model.[49]
Myint *et al.*	Non-invasive BP monitoring system	---	PTT	PPG (wrist)+PPG (finger)	No results were published, only stated that calculating PTT using two PPG's was more feasible.[50]
Kumar *et al.*	Developed a portable, non-invasive, biomedical signal acquisition system	SBP DBP	PTT	ECG+PPG (finger)	The device can monitor, store and communicate ECG and PPG signals and can also measure BP.[51]
Goli and Jayanthi	PWV-BP function developed	PTT PWV	PTT	ECG+PPG	A non-invasive method was used PTT and PWV for BP measurement.[52]
Gholamhosseini *et al.*	Employed a tablet-based system with a triggering mechanism	SBP DBP	PTT	ECG+PPG (ear)	Tablet-based system collected data of patients, triggering mechanism for start of the process and IEEE 802.15.4 for data sharing.[53]
Kaur *et al.*	Correlation between BP and PTT	SBP DBP PTT	PTT	ECG+PPG (finger)+ PPG (wrist)	De-noising using wavelet and showed that PTT from finger and wrist gives better results as compared to that taken from ECG and PPG.[2]
Noche *et al.* (2017)	Developed a mathematical model for estimation of BP	HR BP	PTT	PPG (neck)+ PPG (finger)	Measured HR and BP using PPG and compared with a standard sphygmomanometer.[54]
Huang *et al.*	Developed a long-term dynamic BP monitoring system	SBP DBP	PTT	PPG+BCG+ ECG	Acquired ECG, PPG, and BCG to calculate BP.[55]

DBP: Diastolic blood pressure, ECG: Electrocardiogram, EMD: Empirical mode decomposition, IMF: Intrinsic mode function, PTT: Pulse transit time, SBP: Systolic blood pressure, CPET: Cardiopulmonary exercise, BCG: Ballistocardiography, ABPM: Ambulatory BP monitoring

Table 3. Different techniques for trend detection.[75,76]

Techniques	Description	Why EMD approach over other approaches??
MBA	A stochastic time series model is generated either as an ARIMA or as a state space model.	While tracking the dips in the signal, sharp edges are generated
Hodrick‑Prescott filters	No prior model specifications are required before applying them	Sharp edges are generated while tracking the dips in the signal
SSA	Post‑calibration is required	Advance calibration is required to define window length
Wavelet‑based approach	Post‑calibration is required	This type of trend detection is also not strong around edges. Therefore, resulting in distorted outputs at the sharp edges also have boundary effects.
EMD	Decomposes signal into various finite functions called as IMFs	Signals are dealt at the level of its Intrinsic mode functions which is easy and flexible.

ARIMA: Autoregressive integrated moving average, MBA: Model‑based approach, SSA: Singular spectrum analysis, IMFs: Intrinsic mode functions, EMD: Empirical mode decomposition

PTT analysis is compared with other methods, and this method shows the highest corelation between BP and PTT.

Motion artifacts are the main sources of noise among the huge spectrum of noise sources. Various transforms are being used from very long time to remove the noise from these corrupted biosignals and to reduce the errors caused due to sensors, but still, a significant amount of work has to be done in this area to increase the accuracy. All the signals used for these measurements are having very small delays in millimeters. Hence, great synchronization is required between each device. No literature has discussed any synchronization procedures. Variations in the position of sensors may lead to the change in BP values.

Usually, the steepest slope of PPG is taken as a time marker for the measurement of PTT. There are many other positions also on the PPG waveform from which the measurement of PTT can be done. No work has been done to show the best point for the PTT measurement.

CONCLUSIONS AND FUTURE WORK

From Table 1, it can be concluded that non‑invasive continuous BP measurement is a reliable technique. Due to the various advantages associated with PTT based techniques, these can be considered as the most promising methods in today's scenario for the measurement or detection of chronic diseases like BP. Due to accuracy‑related issues work is required in the field of denoising of biosignals. Hence, a lot of work has to be done in this field because until now every method possesses some disadvantages and not a single method can be considered as the reliable one.

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