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Impact of heart disease and calibration interval on accuracy of pulse transit time–based blood pressure estimation

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Abstract
Continuous blood pressure (BP) measurement without a cuff is advantageous for the early detection and prevention of hypertension. The pulse transit time (PTT) method has proven to be promising for continuous cuffless BP measurement. However, the problem of accuracy is one of the most challenging aspects before the large-scale clinical application of this method. Since PTT-based BP estimation relies primarily on the relationship between PTT and BP under certain assumptions, estimation accuracy will be affected by cardiovascular disorders that impair this relationship and by the calibration frequency, which may violate these assumptions. This study sought to examine the impact of heart disease and the calibration interval on the accuracy of PTT-based BP estimation. The accuracy of a PTT-BP algorithm was investigated in 37 healthy subjects and 48 patients with heart disease at different calibration intervals, namely 15 min, 2 weeks, and 1 month after initial calibration. The results showed that the overall accuracy of systolic BP estimation was significantly lower in subjects with heart disease than in healthy subjects, but diastolic BP estimation was more accurate in patients than in healthy subjects. The accuracy of systolic and diastolic BP estimation becomes less reliable with longer calibration intervals. These findings demonstrate that both heart disease and the calibration interval can influence the accuracy of PTT-based BP estimation and should be taken into consideration to improve estimation accuracy.

Keywords: heart disease, calibration interval, pulse transit time, blood pressure, estimation accuracy

(Some figures may appear in colour only in the online journal)
1. Introduction

Despite advances in modern medicine, cardiovascular disease (CVD) remains an extremely common and potentially lethal condition and is a leading cause of death worldwide. Elevated blood pressure (BP), or hypertension, is widely accepted as one of the most important risk factors for premature CVD and is the number one risk factor for early death (Forouzanfar et al. 2015). Hypertension is highly prevalent, with more than 40% of adults worldwide being afflicted, and this percentage is rising due to a rapid increase of the aging population. Worse still, hypertension is a ‘silent killer.’ People suffering from it can feel fine for years before symptoms start, such that less than 50% are aware of their diagnosis, and only around 30% of cases are under control (Chow et al. 2013). BP variability has been reported to be a valuable prognostic indicator for hypertension (Parati et al. 2013). Continuous BP measurement is therefore important for the early prevention, detection, management and treatment of hypertension and related CVD. The auscultatory and oscillometric techniques are the two methods most commonly used for BP measurement, but they are insufficient for ambulatory monitoring because of the requirement of an occluding cuff and their discontinuous properties. Although arterial tonometry and vascular unloading methods are available for noninvasive continuous BP monitoring, they still cannot avoid that the cuff may cause discomfort. Compared with cuff-based approaches, a cuffless BP technique based on pulse transit time (PTT) possesses the advantage of unobtrusiveness, freeing the user from the clumsy cuff, and enables continuous BP measurement over an extended period of time (Zheng et al. 2014). PTT is the time taken by the arterial pulse traveling from the heart to the peripheral arterial site, and it can be easily calculated from electrocardiogram (ECG) and photoplethysmogram (PPG).

PTT-based BP estimation is based on the recording of pulse wave velocity (PWV) through the following equations (Hughes et al. 1979, Nichols et al. 2011):

\[
\text{PWV} = \frac{Eh}{\sqrt{\rho d}} \tag{1}
\]

\[
E = E_0 e^{\gamma P_m} \tag{2}
\]

where \(E\) is the artery elastic modulus, \(E_0\) is the elastic modulus of vessel wall at zero pressure, \(\gamma\) is a coefficient depending on particular vessel (ranging from 0.016 to 0.018 mmHg\(^{-1}\)), \(P_m\) is mean BP (MBP), \(h\) is the vessel thickness, and \(d\) the arterial diameter. PWV has a reciprocal relation to PTT, i.e. \(\text{PWV} = \frac{L}{\text{PTT}}\), where \(L\) is the distance between the heart and certain peripheral site; thus BP can be derived from PTT with the performance of calibration, under the assumption that \(\gamma, \rho, \) and the ratio of \(h\) to \(d\) remain constant. Therefore, accurate BP estimation with PTT mainly relies on two aspects: the relationship between PTT and BP, and the right assumptions. PTT-based BP measurement has been well investigated over the last 15 years (Chen et al. 2000, Poon and Zhang 2005, Cattivelli and Garudadri 2009, Gesche et al. 2012, Bilo et al. 2015). Although the usage of PTT for reliable BP measurement has been disputed (Payne et al. 2006), a variety of studies have revealed that the PTT method is promising (Gesche et al. 2012, Forouzanfar et al. 2013, Vlahandonis et al. 2014, Peter et al. 2014, Mukkamala et al. 2015), and it is expected to be the most widely used method for cuffless continuous BP measurement in the future. Nevertheless, unsatisfactory accuracy and the requirement of recalibration are two most challenging problems that should be resolved before large-scale application (McCarthy et al. 2013, Peter et al. 2014). In particular, accurate measurement of BP is essential to adequately prevent, diagnose, and treat BP-related CVD. According to equations (1) and (2), the major factors that determine PWV and thus affect
the relationship between PTT and BP are arterial elasticity, arterial wall thickness, vessel diameter, and blood density. Accordingly, alterations in arterial elasticity attributable to cardiovascular disorders would distort the coupling of PTT and BP. Furthermore, the change in arterial geometry properties over time due to the control of neural regulation and other factors may violate these assumptions, although central PTT instead of peripheral PTT was suggested to alleviate the influence of neural regulation (Sola et al 2013). In other words, heart disease and calibration frequency would have a large impact on the accuracy of PTT-based BP estimation.

Previous studies (Wagner et al 2010, Spießhöfer et al 2014) have investigated the relationship between PTT and BP in patients with chronic heart failure and found that the PTT–BP relationship was impaired in patients and the impaired PTT–BP relationship further affected the accuracy of PTT-based BP estimation. In addition, several studies have demonstrated that periodical recalibration of PTT-based BP measurements might lead to improved accuracy (Chen et al 2000, Wong et al 2009). However, few studies have investigated the impact of both heart disease and the calibration interval on the accuracy of PTT-based BP estimation, especially if the calibration interval exceeds 1 month. The present study evaluated the accuracy of PTT-based BP estimation in patients with heart disease, including hypertension, congestive heart failure, atrial fibrillation, and ischemic heart disease, and compared it with that of healthy subjects. In addition, the accuracy using different calibration intervals that last for 1 month was examined.

2. Methods

2.1. Subjects and protocol

Data from our previous experiment were revisited in this study (Poon and Zhang 2005). Ninety subjects were enrolled in this study, but five subjects were excluded due to insufficient data quality. Among the 85 study subjects, 37 were healthy (aged 27.4 ± 10.0 years, 21 males) and 48 had CVD (aged 80.7 ± 12.0 years, 16 males), including hypertension, congestive heart failure, atrial fibrillation, and ischemic heart disease. The demographics of the subjects are shown in table 1. All subjects provided informed consent prior to the experiment, in accordance with the guidelines of the institutional research ethics board.

The reference BP was measured by an experienced registered nurse using an auscultatory method with mercury sphygmomanometers, and 45s ECG and PPG signals were recorded for PTT calculation right after the BP measurement, with subjects seated at rest. For each subject, one dataset was collected for calibration, and three subsequent datasets lasting for 15 min were recorded to test BP measurement. Data from the other three trials, with three datasets for each trial, were collected during the subsequent two weeks and one month after the first trial.

Table 1. Demographics of the study subjects.

<table>
<thead>
<tr>
<th>Subjects (n = 85)</th>
<th>Health (n = 37)</th>
<th>Patients (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>57 (18–96)</td>
<td>27 (22–54)</td>
</tr>
<tr>
<td>Gender (M/F), n</td>
<td>37/48</td>
<td>21/16</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure (n)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation (n)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic heart disease (n)</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
### 2.2. PTT-based BP estimation algorithm

The PTT-based BP estimation algorithm used in this study was based on the method proposed by Poon et al (Poon and Zhang 2005). This algorithm was derived based on (1), where the elastic modulus can be defined as the stress to strain ratio and the pulse pressure (PP) is considered to be the stress within the artery. As a result, PP has an inverse relationship with PTT as follows:

\[
PP \propto \frac{1}{PTT^2}
\]  

(3)

On the other hand, MBP can be derived based on (1) and (2). With \( E \) in (1) replaced by (2), we have

\[
MBP = \frac{1}{\gamma} \left( \ln \frac{\rho d L^2}{E_0 h} - 2 \ln PTT \right)
\]

(4)

Based on the assumption that \( \rho, d, L, E_0, \) and \( h \) remain constant, MBP can be estimated with the following equation:

\[
MBP = MBP_0 + \frac{2}{\gamma} \ln \frac{PTT_0}{PTT}
\]

(5)

Therefore, the systolic BP (SBP) and diastolic BP (DBP) can be determined based on the empirical formula of MBP and PP calculation, i.e.

\[
MBP = DBP + \frac{1}{3} PP
\]

(6)

\[
PP = SBP - DBP
\]

(7)

Correspondingly, SBP and DBP can be estimated through the following model:

\[
DBP = MBP_0 + \frac{2}{\gamma} \ln \frac{PTT_0}{PTT} - \frac{1}{3} PP_0 \left( \frac{PTT_0}{PTT} \right)^2
\]

(8)

\[
SBP = DBP + PP_0 \left( \frac{PTT_0}{PTT} \right)^2
\]

(9)

where \( \gamma \) is usually taken as 0.017 mmHg\(^{-1}\); MBP\(_0\), PP\(_0\), and PTT\(_0\) are the calibrated values of MBP, PP, and PTT, respectively; and PTT is the measured value for BP estimation.

### 2.3. Data analysis

The ECG and PPG signals were recorded and sampled at 1000 Hz. The PPG signal was filtered using a wavelet transformation method with wavelet ‘coif4’ at the 4th level to reduce high-frequency noise and decomposed at the 16th level with wavelet ‘db3’ and reconstructed at the 11th level to remove the baseline drift. Beat-by-beat PTT was calculated as the time interval between the R wave peak of the ECG and the maximal PPG upslope in each cardiac cycle, as illustrated in figure 1. To distinguish it from other calculation methods, the PTT in this paper is labeled as PTT\(_{ep}\), where ‘e’ and ‘p’ indicate the first letter of the ECG and PPG. The average PTT\(_{ep}\) from all beats over 45 s of signals was calculated for each dataset.

The initial BP reading and PTT\(_{ep}\) were measured for calibration. Afterwards, BP readings were used as a reference, while PTT\(_{ep}\) was used to estimate BP with (8) and (9). The bias
and precision were evaluated in terms of the mean and standard deviation (SD) of differences between the estimated BP and the reference, respectively. The average discrepancies (mean ± SD) between healthy subjects and patients with heart disease were compared, with the boxplot of the differences plotted to check for outliers. Moreover, the differences between these two groups in terms of different calibration intervals were analyzed. A two-sample test for variance was utilized to test the variance of different groups and at different calibration intervals, with \( p < 0.05 \) regarded as statistically significant.

3. Results

3.1. Accuracy of BP estimation in healthy subjects and patients with heart disease

As shown in figure 2, for healthy subjects, the overall SBP estimation error of (0.50 ± 11.55 mmHg) was lower than that of patients with heart disease (−3.60 ± 16.02 mmHg). However, it is interesting to note that the DBP estimation error was higher in healthy subjects (1.19 ± 9.07 mmHg) than in patients (−1.06 ± 7.92 mmHg). The possible reasons for this finding will be discussed later.

To further observe the data scatter of the BP estimation error in healthy subjects and in patients with heart disease, the boxplot and data distribution of SBP and DBP differences between these two groups were drawn and are presented in figure 3. Obviously, both the SBP difference and the DBP difference were normally distributed, and more outliers of SBP and DBP difference were observed in patients than in healthy subjects (particularly SBP),
indicating the abnormalities that can occur when using PTTep to estimate BP in patients with heart disease.

### 3.2. Accuracy of BP estimation for different calibration intervals

If only three trials of one subject right after calibration were tested (i.e. total 255 trials), the overall error of SBP and DBP estimations for the 85 subjects was $-1.44 \pm 10.69$ mmHg and $-1.21 \pm 5.07$ mmHg, respectively, which significantly increased to $-2.09 \pm 12.98$ mmHg and $-0.64 \pm 7.72$ mmHg two weeks after the initial calibration and to $-1.87 \pm 14.42$ mmHg and $-0.11 \pm 8.51$ mmHg approximately one month after the initial calibration. The change trend of SBP and DBP estimation error is shown in figure 4.

In addition, the estimation error of healthy subjects and patients with heart disease was compared at different calibration intervals, as depicted in figure 5. For SBP, the SD was significantly higher in patients than in healthy subjects at 15 min, two weeks, and one month after the initial calibration. Moreover, the precision of estimates in healthy subjects significantly decreased two weeks after the initial calibration, but there was no significant change from two weeks to one month, whereas for patients with heart disease, no significant change was observed two weeks after the calibration, but the precision of estimates decreased significantly from two weeks to one month. Those of DBP had a similar variation pattern; however, the
estimation precision for patients, on the contrary, was better than that of healthy subjects two weeks after the calibration.

4. Discussion

The purpose of this study was to examine the impact of heart disease and calibration interval on the accuracy of PTT-based cuffless BP estimation. It is noteworthy that the PTTep used in this study included a pre-ejection period (PEP), considering PEP has a positive effect on BP estimation (Muehlsteff et al. 2005, Wong et al. 2011). The results provide evidence of the following: (1) the accuracy of SBP estimation is lower in patients with heart disease than in healthy subjects, suggesting that abnormal heart conditions influence the effectiveness of using PTTep to estimate SBP, but DBP estimation was more accurate in patients than in healthy subjects; and (2) BP estimations at different calibration intervals demonstrated that the longer the calibration interval, the lower the accuracy.

4.1. Influence of heart disease on PTT-based BP estimation

A previous study (Spießhöfer et al. 2014) of PTT-based BP estimation in patients with heart failure found that its accuracy was comparable with that of the cuff-based method, but it was only reliable for a short period of time. This might have been due to a damaged PTT – BP relationship, which was probably caused by impaired ventricular – arterial coupling in patients with heart failure (Wagner et al. 2010). However, some studies have intentionally excluded subjects with heart disease (particularly arrhythmia) when using PTT to estimate BP (Gesche et al. 2012, Ruiz-Rodriguez et al. 2013), which may cause bias for certain groups. This issue also exists for the cuff-based method. For example, the oscillometric technique has been reported to be susceptible to error in elderly patients with stiff arteries because of atherosclerosis (Jones et al. 2003) and in patients with arrhythmia, such as atrial fibrillation (Cleland et al. 1998, Beevers et al. 2001). Arterial stiffness was considered as the underlying mechanism of disagreement between an oscillometric BP monitor and a sphygmomanometer (van Popele et al. 2000).
The results of the comparison between healthy subjects and patients with heart disease in this study indicated that estimating BP using PTTep can be affected by the state of the cardiovascular system and the existence of pathology. This suggests that the level of covariation of PTTep and BP is significantly attenuated in subjects with heart disease. As a result of the impaired relationship between PTTep and BP, the PTTep method seems to be more susceptible to error, as evidenced by the number of failed measurements and the outliers (Bartsch et al 2010). However, it is interesting to note that DBP estimation seemed to be more accurate in patients than in healthy subjects, as shown in figure 2(b). Physiologically, DBP has a slower variability than SBP. Since the SBP variability of the patient group (134.03 ± 17.28 mmHg) is significantly larger than that of the healthy group (105.65 ± 10.70 mmHg), while the DBP variability in the patient group (63.00 ± 9.55 mmHg) is comparable to that of the healthy group (62.50 ± 7.50 mmHg), it seems intuitively reasonable to assume that BP variability would affect the PTT-based BP estimation.

To resolve this issue, more physiological parameters that are relevant to arterial properties rather than PTT should be introduced to estimate BP in individuals with heart disease. For instance, useful features of the second derivative of PPG (SDPPG) could be potent candidates (Baek et al 2010), because the indices of SDPPG denote stiffness of large arteries, peripheral vascular resistance and vascular aging (Kohijitan et al 2014). Figure 6 shows the representative PPG waveform of one healthy subject and a patient diagnosed with congestive heart failure, in which the ratios of the absolute of the height of the ‘b’ wave and that of the ‘d’ wave to that of ‘a’ wave, namely the b:a and d:a ratios, could evaluate the arterial properties (Hashimoto et al 2002). Further, the d:b ratio is obviously different between the healthy subject and the subject with heart failure, suggesting that features of SDPPG might be used to improve

\[ \text{PPG (a.u.)} \]
\[ \text{1st PPG (a.u.)} \]
\[ \text{2nd PPG (a.u.)} \]
\[ \text{Time (sec)} \]

\[ \text{Healthy subject} \]
\[ \text{Patient with congestive HF} \]

**Figure 6.** PPG, first PPG, and second PPG waveform in an exemplary healthy subject (left panel) and a patient with congestive heart failure (HF) (right panel).
PTT-based BP estimation in different populations. In addition, a recent study has proposed the combination of PPG intensity ratio and PTT to improve the accuracy (Ding et al 2015).

4.2. Influence of calibration intervals on PTT-based BP estimation

The PTT-based BP technique requires individual-specific calibration by a secondary method of device before use. Thus, the accuracy depends not only on the accuracy of the calibration method or device but also on the accuracy of the method used to track intraindividual BP changes from the calibration level, after a specific calibration (Ng 2011). The present study of different calibration intervals implies that the accuracy of BP estimation decreases as the calibration interval increases, which is consistent with findings of previous studies (Cattivelli and Garudadri 2009, McCarthy et al 2013) and our earlier work (Poon et al 2008); the calibration interval in this study lasted for approximately one month, which was far longer than similar studies (Choi et al 2013). The probable reason for this might be the change of arterial geometry properties with time, such as vessel thickness, arterial diameter, and blood density, which may violate the assumption of the PTT-based BP measurement principle, i.e. the ratio of blood vessel thickness to arterial diameter is assumed to be constant within a short period. Nevertheless, arterial BP is dynamic, and its long-term regulation is mainly attributed to neural control and fluid volume regulation (Cowley 1992). Therefore, any change in blood vessel dimensions (especially arterial diameter) over time would greatly influence the relationship between PTTep and BP, thereby creating a longer calibration interval, leading to lower estimation accuracy. Long-term accurate cuffless BP estimation using PTTep may combine other physiological indicators that can track the low-frequency variations in BP. For example, the PPG intensity ratio (Ding and Zhang 2015), which can reflect smooth muscle tone and further low-frequency arterial BP variations, can potentially track BP variations accurately over a longer period with the combination of PTT.

4.3. Limitations

There are several methodological issues and limitations in this study. First, from the perspective of experimental subjects, the ages of subjects in the healthy group and patient group were not matched. Since BP and blood vessel properties vary with age, the nonmatch may have cause discrepancies in BP estimation among groups. Another possible limitation is that the types of heart disease are not diverse enough, because this study only included each of the three main types of heart disease, i.e. congestive heart failure, bad arrhythmia, and coronary artery disease. Currently, we are working on a new method with the aim to improve the accuracy of PTT-based BP estimation and organizing a clinical experiment to further validate this method.

5. Conclusion

In summary, we have investigated the impact of heart disease and the calibration interval on PTT-based BP estimation accuracy. Analysis of the subjects, including healthy subjects and patients with heart disease, indicates that the estimation accuracy decreases significantly in subjects with abnormal cardiovascular states when compared to healthy subjects. By calibrating BP with different intervals, we found that BP can be reliably estimated after an initial calibration, but the accuracy decreases with an increase in the calibration interval. This study therefore demonstrates that both heart disease and the calibration interval should be taken in
account for BP estimation when using the PTT method. Future work should include exploring potent parameters other than PTT, exploring novel calibration methods, and establishing a new PTT-BP model to make the PTT-based method more reliable for cuffless BP measurement.

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