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Effect of confounding factors on blood pressure estimation using pulse arrival time

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Abstract

Two confounding factors were selected and analyzed in blood pressure estimation using pulse arrival time (PAT) for each individual. The heart rate was used as the confounding factor for the cardiac cycle, and the duration from the maximum derivative point to the dicrotic peak (TDB) in the photoplethysmogram was used as another confounding factor representing arterial stiffness. By considering these factors with PAT in multiple regression analysis, the performance of blood pressure estimation is enhanced significantly in the diastolic phase as well as in the systolic phase. The reproducibility of this method was also validated with formerly obtained regression equations from the training set. The correlation between estimated and measured blood pressure decreased a little, but the validity was still maintained (r ∼= 0.8). This shows the value of the method in non-intrusive blood pressure estimation for individual patients and may be useful for various applications.

Keywords: blood pressure, pulse arrival time, PPG, arterial stiffness, confounding factor, multiple regression

1. Introduction

With the increasing need for non-intrusive measurement of blood pressure (BP), blood pressure estimation with pulse arrival time (PAT) was recently developed (Geddes et al 1981, Sameshima et al 2003, Siﬁ et al 2003), replacing conventional constrained measurement by auscultatory and oscillometric methods using a mechanical cuff. PAT is the time delay from the ECG R-peak to the characteristic point of pulse wave in the peripheral artery and can also
be represented as the sum of pre-ejection period (PEP) and pulse transit time (PTT). It offers a simple way to monitor BP using PAT, which has a linear relationship with BP, especially with systolic blood pressure (SBP).

The method needs to be calibrated for each individual using a regression process. This was presented as inter- and intra-subject analyses in our previous study (Kim et al. 2006). PAT was obtained from ECG and photoplethysmogram (PPG) measured non-intrusively. In a series of experiments with various blood pressures, each subject showed a high correlation between PAT and SBP. However, the correlation coefficient decreased due to differences in physiological characteristics among individuals when all subjects’ data were considered together. Some studies have attempted to solve this generalization problem by considering individual characteristics such as arm length, age and weight (Langenberg et al. 2003, Lee et al. 2005). Our study, however, focused on intra-subject analysis, in which individual characteristics did not need to be considered.

Another problem with the BP estimation method with PAT is its poor performance in the diastolic phase compared to systolic. Most previous studies examined the relationship only between SBP and PAT, and even in studies in which DBP was evaluated the correlation between DBP and PAT was not significant enough. This is because DBP has a small range of variations compared with SBP. To overcome this problem, the pulse transit time (PTT), which is calculated from PAT by excluding the pre-ejection period (PEP), can be used (Pollar and Obrist 1983, Marie et al. 1984). This study showed better correlation for DBP estimation than SBP. However, the method also requires another measurement tool to determine PEP timing. Additionally, the augmentation index (AI) was found to be correlated with DBP, but not with SBP (Yasmin and Brown 1999, Wilkinson et al. 2001, Nurnberger et al. 2003). However, this reported result has been controversial (Cameron et al. 1998, Tanaka et al. 1998).

The purpose of this study is to evaluate the effect of heart rate (HR) and arterial stiffness in BP estimation with PAT. These factors were examined for suitability as performance-enhancing parameters for BP estimation. Statistical analysis was conducted using single and multiple regression methods for each individual subject. The method was verified through a reproducibility experiment.

2. Methods

2.1. Confounding factor—HR

Blood pressure is related to heart rate as well as to PAT in the cardiovascular system (Drinnan et al. 2001). Heart rate represents the cardiac cycle, which determines the heart’s preload and cardiac output. Cardiac output in turn affects BP. Even though the RR interval, which is the inverse of HR, could also represent the cardiac cycle, HR was chosen as the first confounding factor due to its wide application in previous studies and statistical appropriateness. In our experiments, HR also showed a higher correlation than the RR interval. Figure 1 shows the correlation between the HR and RR intervals and SBP or DBP for two experimental BP variation trials. HR results had a slightly higher correlation with both SBP and DBP, suggesting that it is the more appropriate confounding factor for BP.

2.2. Confounding factor—arterial stiffness

Arterial stiffness is known to be related to BP (Nitzan et al. 2002). Generally, the arterial waveform of a pulse wave is thought of as a summation of incident and reflected waves. Altered timing of reflection waves due to arterial stiffness causes different shapes of the
arterial waveform. Pulse wave velocity (PWV) and augmentation index (AI) have been used in previous studies to evaluate arterial stiffness (Bramwell and Hill 1922, Eliakim et al 1971). AI is the parameter obtained from this waveform, but it requires measurement of the pressure wave using a catheter or a tonometer. The second derivative of PPG (SDPTG) has also been used to assess arterial stiffness (Takazawa et al 1998). However, this method is rather unstable due to its high sensitivity to noise and motion artifacts. So, another robust and noninvasive method for assessing arterial stiffness is needed. Figure 2 shows the 16 possible parameters of PPG for arterial stiffness assessment. Some of these parameters, such as AM/BL, have been described and used in previous studies (Babchenko et al 2001). These parameters are divided into three groups.

1. Amplitude parameters
   - AM — amplitude of maximum of PPG.
   - BL — amplitude of minimum of PPG.
   - AM/BL — AM/BL.
   - PP_t — amplitude from minimum to maximum of PPG.
   - PP_a — amplitude from minimum of dicrotic notch to maximum of PPG.
   - PP_b — amplitude from maximum of dicrotic notch to maximum of PPG.
   - PP_a/PP_t — PP_a/PP_t.
   - PP_b/PP_t — PP_b/PP_t.

2. Time parameters
   - Time_a — time from minimum to minimum of dicrotic notch in PPG.
   - Time_b — time from minimum to maximum of dicrotic notch in PPG.
   - Time_0 — time from minimum to dicrotic notch to minimum of dicrotic notch in PPG.
   - Time_0 — time from maximum of dicrotic notch to minimum of dicrotic notch in PPG.
   - Time_max_a — time from maximum to minimum of dicrotic notch in PPG.
   - Time_max_b — time from maximum to maximum of dicrotic notch in PPG.

3. Slope parameters
   - Slope_a — slope from maximum to minimum of dicrotic notch in PPG.
Slope_b—slope from maximum to maximum of dicrotic notch in PPG.
Slope_a_Norm—slope_a normalized with PP_t.
Slope_b_Norm—slope_b normalized with PP_t.

Table 1 shows the results of correlation analysis between these 16 parameters and BP for five individual subjects. Of these 16 parameters, Time_derib (TDB) shows the highest and most dominant correlation (mean value: $r = -0.689$) with both SBP and DBP for all subjects. Thus, TDB was chosen as the confounding factor for arterial stiffness.

2.3. Experiments

Experiments for parameter selection and evaluation of the results were performed using ten male subjects with an average age of 28 years (25–32 years). They were healthy and had no history of adverse cardiovascular events. They executed the Valsalva maneuver for BP increase, and data were obtained during the recovery period with 5 min from increased blood pressure.
pressure to resting state. In about 2 min, the BP reached the baseline. So, the data for 2 min were analyzed. The average data point in all subjects was about 96 beats in this period due to the intermittent calibration process. With ECG, PPG was recorded using a transmitted-type PPG sensor (NONIN finger clip 8000A, USA) on the second finger of the left hand. The PPG signal was band-pass filtered with $0.5 \sim 30 \text{ Hz}$ and digitized with a 2 kHz sampling rate and 12 bit resolution. Table 1 shows the results of correlation analysis. Also, a FINOMETER® PRO (Finapres Medical Systems) was used for beat-to-beat blood pressure measurement. A BIOPAC data acquisition system (BIOPAC, USA) was used for the acquisition of ECG, PPG and BP for comparison. Parameters were calculated with Matlab software (MathWorks, USA), and SPSS 12.0 (SPSS Inc.) was used for single and multiple regression analyses.

3. Results

3.1. Correlation of blood pressure with confounding factors

Figure 3 shows the correlation of the chosen confounding parameters with blood pressure for one study participant. SBP generally shows a higher correlation with PAT and HR than DBP, but a similar correlation with TDB, which leads us to expect higher accuracy for the estimation of DBP including this parameter.

3.2. Single and multiple regression analysis

Table 2 shows the results of single and multiple linear regression analyses. In single regression analysis, there were significant correlations with SBP for all subjects (A: 0.947, B: 0.924, C: 0.944, D: 0.725, E: 0.848). $R^2$ is the coefficient of determination. It shows how much of the variance in the dependent variable can be attributed to the independent variable. For subject A, 89.6% of SBP could be attributed to PAT. In the case of DBP, correlation coefficients were lower (A: 0.891, B: 0.809, C: 0.703, D: 0.653, E: 0.722), which agrees with the results of previous studies. In multiple regression analysis, the correlation with BP was investigated considering confounding factors. Correlation coefficients were improved for DBP as well as SBP. When both confounding parameters were considered, the average correlations were 0.867 and 0.831 for SBP and DBP, respectively. The effect of confounding factors is represented as
increased correlation especially in DBP estimation ($p = 0.005$; figure 4). Figure 5 shows the increased correlation with the inclusion of confounding factors in the estimation of DBP.
**Figure 4.** BP correlation coefficients for ten subjects according to the single and multiple regression methods. The $P$-value decreases significantly for DBP estimation ($p = 0.005$). $^*p < 0.05$, $^{**}p < 0.01$.

**Figure 5.** Performance enhancement including confounding factors for the estimation of DBP.

Moreover, adjusted $R^2$, which is a modification of $R^2$ that adjusts for the number of explanatory terms in a model, was calculated for each case (table 2). Unlike $R^2$, the adjusted $R^2$ increases only if the new term improves the model performance more than would be expected by chance. The increased values of adjusted $R^2$ in multiple regression analysis verify the effectiveness of HR and TDB as additional parameters for BP estimation.

### 3.3. Reproducibility

We repeated the experiment after a week using the estimated equations and the same participants. Estimation of BP from PAT and confounding factors was obtained from the
Figure 6. Reproducibility of multiple regression analysis for BP estimation. The test was conducted for a week. The estimated BP from the regression equation of the training set was compared with the measured BP. The correlation coefficients decreased a little with 0.7714 and 0.8432 for SBP and DBP. However, such a level of correlation should still be enough for the estimation of BP.

4. Discussion and conclusion

4.1. Correlation with blood pressure

SBP estimation has been well evaluated with PAT with respect to intra-subject analysis (Kim et al 2006). Thereafter, it could be developed using two approaches. A generalization approach would focus on inter-subject analysis. This attempts to enhance the correlation with BP for all people by adding physical parameters such as height, weight and arm length. A second approach is to enhance the correlation with DBP. Additionally, parameters such as augmentation index and pre-ejection period were introduced in previous studies. Because this method requires supplementary measurement and lacks stability, its effectiveness is still controversial. In this study, we illustrated and demonstrated with experimental results why HR and TDB parameters for arterial stiffness should be considered in BP estimation. The correlation with BP is improved, especially for DBP, when these two confounding factors are considered in multiple regression analysis. The increase in adjusted $R^2$ when confounding factors were included verifies that the parameter introduction was more effective than chance alone. The repeated experiment supported the reliability of this study when used for young, healthy male subjects. Further studies with various populations in pathology such as hypertension are required to support the proposed method.

4.2. Waveform analysis of PPG

In TDB parameter determination for arterial stiffness, waveform analysis of PPG was made. Because the PPG signal was sensitive to noise such as motion artifact, the robustness of parameter selection is important. The robustness of PPG parameters was examined by
managing the motion artifacts during the measurement of PPG signals (Hayes and Smith 2001). This study showed that TDB is a robust and stable parameter representing arterial stiffness from PPG measurement. Statistical parameters can also be used for estimating the augmentation index from the PPG signal (Tsui et al 2007). However, it is not real-time processing and therefore is not suitable for continuous real-time blood pressure monitoring.

4.3. Limitation of the study

It is acknowledged that there are some limitations to this study. First, only a small number of healthy male subjects participated. Although the study shows the potential of the methodology for enhancing blood pressure estimation, it is necessary to conduct the method on a wider population including groups with different age, gender and cardiovascular diseases. It was anticipated that clinical data in anesthesia might be investigated in future works. Second, the heart rate could affect blood pressure differently. HR increases as BP increases in some situations, but it decreases as BP increases in other situations such as the Valsalva maneuver intervention of this study. In the former situation, the sympathetic pathway affects BP and HR. Therefore, there is no delay between BP and HR, or HR changes lead BP changes. In the latter situation, BP changes lead HR changes. This showed BP regulation via baroreflex (Baldridge et al 2002). However, with the delay between HR and BP obtained by cross-correlation analysis, it could be determined whether HR should be used positively or negatively for BP estimation.

4.4. Application to home health care

Non-intrusive blood pressure monitoring is important for patient management in the home environment. A simple method for monitoring blood pressure with ECG and PPG only and without a cuff would be widely accepted in many places as a part of home healthcare such as on a toilet seat, chair, sofa, bed, among others. By enhancing the performance of blood pressure estimation, non-intrusive blood pressure monitoring can be applied appropriately to patient care in more healthcare settings.

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