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Calculation and Validation of Continuous Pulse Transit Time Based on Normalized Pulse Wave Velocity

HANGSIK SHIN[1], (Member, IEEE), AND AHYOUNG CHOI[2], (Member, IEEE)
[1]Department of Biomedical Engineering, Chonnam National University, Yeosu 59626, South Korea
[2]Department of Software, Gachon University, Seongnam 13120, South Korea

Corresponding author: Ahyoung Choi (aychoi@gachon.ac.kr)

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ABSTRACT Typically, the pulse transit time (PTT) is extracted as a discrete value per heartbeat: it is calculated as the time difference between specific points of the pulse waveforms measured at two different sites. However, this is not a perfect representation because a pulse wave propagates continuously. In this study, we propose a method to determine the continuous PTT (CPTT) by calculating consecutive time delays of photoplethysmography (PPG) waveforms measured at the fingers and toes of 14 young, healthy volunteers. The proposed CPTT is calculated as the average time delay determined by moving the segmented PPGs and has a correlation of 0.744 with conventional PTT. In addition, the proposed CPTT showed a -0.712 correlation coefficient ($P < 0.001$) with the continuous pulse-wave velocity derived from the continuous blood pressure waveform. These results suggest that the proposed CPTT is a promising indicator for pulse-wave velocity estimation.

INDEX TERMS Blood pressure, photoplethysmography, pulse transit time, pulse-wave velocity.

I. INTRODUCTION

The time it takes for ventricular depolarization to induce changes in the blood volume of a specific part of the human body is defined as the pulse arrival time (PAT). Similarly, the timing difference of the change in blood volume between the measurement sites during ventricular contraction, arising from differences in distance, is defined as the pulse transit time (PTT) [1]. Although these parameters are fundamentally different, they are used interchangeably in many research studies. PAT and PTT have been calculated in various ways. In most cases, PAT is calculated as the time interval between the QRS complex and a specific point of a photoplethysmography (PPG) waveform, such as its upper or lower extreme, or its maximum slope. However, PTT can also be derived using other physiological signals, including pulsation. Impedance plethysmography (IPG), ballistocardiogram (BCG), seismocardiogram (SCG), and phonocardiogram (PCG) are representative signals that are used in PTT analysis [2]–[6]. In addition, various sites are used to PAT or PTT. Generally, PAT is measured with ECG and PPG, and chest and finger optical sensors are used. However, for PTT, there are many combinations of measurement sites and methods, such as the ECG QRS-carotid artery pressure wave, ECG QRS-femoral artery pressure wave, finger–toe PPG or ear–toe PPG, wrist–finger PPG, BCG-to-finger PPG, SCG-to-finger PPG, carotid–femoral artery pressure wave, or wrist IPG to finger PPG [1]. PTT has been studied in cardiovascular and hemodynamic analyses. Recently, PTT has been used to detect heart failure [7], mechanical alternans [8], sleep disorders [9], and cardiac output and stroke volume [10]–[12]. PTT is most widely used in cuffless blood pressure (BP) measurement [1], [3], [13]–[23]. In most BP estimation research based on PAT or PTT, PAT is calculated as the time between the ECG QRS complex and the onset or peak of finger PPG, and PTT is calculated as the time between sites in multisite PPGs, such as finger–toe PPG. Gesche used QRS-PPG_{finger} PAT to estimate the increase in blood pressure due to exercise and showed a correlation coefficient (R) of 0.84 in 63 subjects [15]. In a study by Nitzan, QRS-PPG_{toe} PAT and PPG_{toe}–PPG_{finger} PTT showed R values of 0.670 and 0.515, respectively [24]. PTT measurement presents some

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TABLE 1. Subjects' Information.

Subject No.	Age (years)	Gender (M/F)	Height (cm)	Weight (kg)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
1	29	M	185.0	103.0	30.1	125	73
2	26	M	175.0	63.2	20.6	111	65
3	24	M	171.1	67.9	23.1	135	71
4	17	M	171.4	65.4	22.2	138	68
5	22	F	159.3	47.2	18.5	101	65
6	19	F	157.2	52.3	21.1	104	69
7	22	F	162.2	65.5	24.7	113	77
8	19	F	151.7	53.1	23.0	115	82
9	19	F	153.9	51.4	21.7	99	64
10	24	M	180.4	65.3	20.0	113	63
11	23	M	174.5	65.9	21.6	110	69
12	24	M	172.2	68.1	22.9	133	71
13	21	F	159.6	56.1	22.0	107	60
14	21	F	153.2	48.7	20.7	101	67
Mean ± SD	22.1 ± 3.2	M 7, F 7	166.2 ± 10.8	62.4 ± 13.9	22.3 ± 2.7	114.5 ± 13.1	68.6 ± 5.8

practical difficulties. The biggest obstacle involves accurate identification of specific points of the PPG waveform. To calculate PTT, two signal reference points (e.g., QRS complex of ECG or pulse onset of PPG) must be defined. In other words, PTT depends on feature detection and can be drastically inaccurate if feature detection fails. For example, the reference point of the two signals must be matched by a beat. If a detection error occurs in one of the two signals and the matching order changes, the calculated PTT will be wrong, and the error will accumulate or propagate. Moreover, a plethysmograph, which is the main instrument used for PTT calculation, has a gently curved shape; its waveform changes depending on the measurement site, and there are many ways to wear the sensor that may result in an undesirable error in the PTT calculation. Currently, one PTT value is derived per beat because it is calculated from a specific point of the PPG waveform. However, PTT actually differs according to the cardiac cycle phase: it should be shorter in the systolic phase and longer in the diastolic phase, as is easily seen by considering the dynamic pressure equation, $q = \rho u^2/2$, where q, ρ, and u are the dynamic pressure, fluid density, and flow speed, respectively. That is, PTT, as a reciprocal of flow speed, can be represented as a continuous parameter that varies with the blood pressure waveform. In our research, we call the continuous change in PTT within a pulse "continuous PTT" (CPTT). In this study, we propose a new way to measure CPTT that represents an innovative approach to PTT analysis. It is a robust PTT measurement technique that overcomes PPG waveform uncertainty by omitting preprocessing steps, such as complicated feature detection. Therefore, we calculate CPTT without feature detection by calculating average waveform delay and observe the correlation between multi-site PTT. In addition, we observe through experiments whether the proposed CPTT can be an indicator of continuous pulse wave velocity.

II. MATERIALS AND METHODS

A. SIGNAL ACQUISITION

We enrolled a total of 23 volunteers in this experiment. The data obtained from 9 subjects were excluded from the analysis due to poor PPG signal quality, such as poor perfusion or severe motion artifacts, frequent calibration of the Finometer, and recording errors. Consequently, the data from 14 subjects (7 male and 7 female) with average age 22.1 ± 3.2 years, height 166.2 ± 10.8 cm, weight 62.4 ± 13.9 kg, and systolic/diastolic blood pressure 114.5 ± 13.1/68.6 ± 5.8 mmHg, were used for the analysis. Table 1 summarizes the subjects' health information. None of the subjects had any reported cardiovascular disease, and we prohibited activities, such as drinking and smoking, that could stimulate the autonomic nervous system for 2 h before each experiment. We simultaneously recorded PPGs on the left index finger (PPG_{finger}) and the left second toe (PPG_{toe}). We used a Biopac MP150 (Biopac Systems, Inc., CA, USA), two amplifier modules (PPG100C), and two optical transducers (TSD200) to record the PPGs. We also used a Finometer (Finapres Measurement Systems, Arnhem, Netherlands), a volume clamp-based noninvasive continuous blood pressure measurement device, to measure the blood pressure waveform. The finger cuff of the Finometer was worn on the left middle finger. The signals were simultaneously recorded at a 1 kHz sampling frequency for 5 min with the subject in the supine position. We used an automatic blood pressure measurement device, HEM-907 (Omron Co., Ltd., Kyoto, Japan), to measure systolic and diastolic blood pressure. Systolic and diastolic blood pressure were measured before and after PPG

measurement, and averaged. The signals were recorded while the subjects lay comfortably in a resting position; in order to minimize motion-related noise, the subjects were asked not to move during the experiment. The experimental protocol was approved by the Ethics Committee of Wonju Christian Hospital, Wonju, Republic of Korea, and all participants signed informed consent forms before the experiments.

B. PULSE TRANSIT TIME CALCULATION

PPG-based conventional PTT can be calculated as the time difference between the maximum slopes of finger PPG (PPG_{finger}) and toe PPG (PPG_{toe}) [9], [18]. The temporal error of the characteristic point for the pulse waveform based on the maximum slope is known to be smaller than that of the systolic peak or pulse onset [9]. To detect the maximum slope point, we initially detected the systolic peaks using a modified adaptive peak detection threshold method [25] with manual correction by experienced researchers. The modified adaptive peak detection algorithm has one more stage than the conventional method: it detects the maximum or minimum amplitude within a specific range before and after the peaks detected by the conventional method. Then, we determined the maximum value of the derivative PPG in the 300 ms interval before the systolic peak.

C. CONTINUOUS PULSE TRANSIT TIME CALCULATION

Like a typical PTT, the CPTT can be derived from two pulse waveforms measured at different body sites. The pulse waveform, which represents the pulsatile components, could be a pressure wave or a volumetric wave. In the preprocessing stage, unnecessary signal components are removed from all signals, as the measured signals can be affected by specific modulation-independent and path-dependent pulsatile waves. Therefore, we used a bandpass filter and moving average filter to suppress the respiratory component and high-frequency noise outside the pulsatile range. Because we used PPGs to calculate CPTT, we used a bandpass filter with a 0.5 – 10 Hz passband and a moving average filter with a 100 ms averaging window. The 0.5 – 10 Hz frequency range is often used in PPG signal processing, and the 100 ms window size corresponds to 10 Hz low-pass filtering.

The CPTT calculation is based on the waveform delay in each signal. In other words, CPTT can be derived from the delays between signals measured at different sites for every sample point. To ensure that all signals have similar amplitudes, the filtered signals are normalized after being standardized as a normal distribution. Subsequently, we set a sliding window with a specific length and calculated the waveform delay between the analysis points by cross-correlating the two signals. The maximum value of the cross-correlation result indicates the time delay at which the signals are best aligned. In our research, we used PPG measured at the left index finger as $PPG_{proximal}$ and PPG measured at the left second toe as PPG_{distal}. We set the analysis window size to 500 ms and shifted it by 1 ms when calculating the signal delay, which was defined in all samples within the analysis interval and

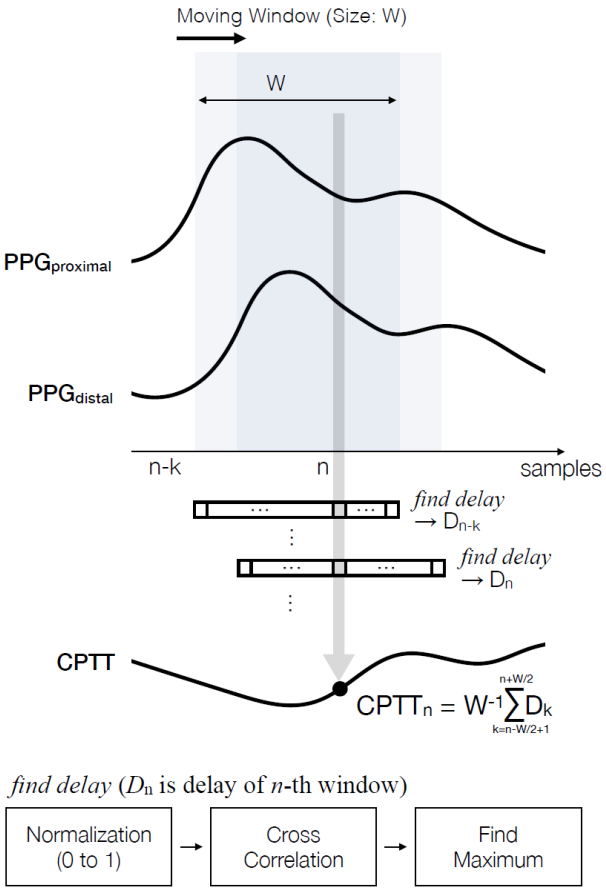

FIGURE 1. CPTT calculation procedure. In this research, the window size and sampling interval are 500 ms and 1 ms, respectively.

represented the average of all delays calculated by means of the sliding window. Figure 1 shows the CPTT calculation procedure. $PPG_{proximal}$ is the PPG at the measurement site closer to the heart, and PPG_{distal} is the PPG at the point farther from the heart. The windows represent the n^{th} analysis interval with a specific length. D_n, the delay of the n^{th} window, is calculated through normalization, cross-correlation, and identification of the maximum value. The delays of each window accumulate at each index, and are then averaged. Therefore, the n^{th} value of CPTT, $CPTT_n$, can be calculated using (1).

$$CPTT_n = \frac{1}{W}\sum_{k=n-W/2+l}^{n+W/2} D_k, \tag{1}$$

where W is the total number of windows overlapping at a sample time, which is the same as the total number of samples in a window.

D. VALIDATION OF CPTT

To validate CPTT as a novel PTT measurement technique, we asked two questions. The first was whether CPTT is similar to conventional PTT, and the second was whether CPTT can be measured by our proposed method. To verify that CPTT is similar to conventional PTT, we measured PTT and

CPTT using PPG_{finger} and PPG_{toe}, respectively, and analyzed the correlation between the two.

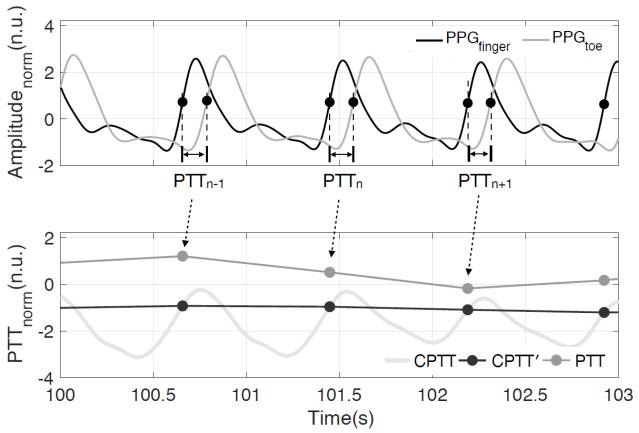

FIGURE 2. Example PPG waveforms measured at finger and toe (top). Example PTT, CPTT, and CPTT′ (bottom).

Figure 2 illustrates PPG_{finger} and PPG_{toe} waveforms, and shows that PPG_{toe} has a time delay compared to PPG_{finger}. The light gray curve in the bottom box in Figure 2 shows the CPTT waveform. This curve, calculated by the method described above, represents a continuous waveform delay. We calculated the conventional PTT in terms of the pulse transit delay by means of the time difference between pulses at a specific point (e.g., maximum slope); therefore, it has only one discrete value per beat. Thus, to compare PTT and CPTT, we obtained CPTT by sampling CPTT at every time point. We calculated PTT based on the time difference between the systolic peaks of PPG_{finger} and PPG_{toe}, and CPTT was sampled at the location of every maximum slope of PPG_{finger}. We derived the linear regression equation and calculated R to analyze the correlation between the two PTTs.

The great benefit of CPTT is that it provides a continuous PTT value at any point in a waveform. To evaluate whether the proposed CPTT actually reflects continuous wave propagation, it may be preferable to compare it to blood flow velocity measured directly. However, because we did not measure blood flow directly, we verified the validity of the proposed CPTT by comparing it to the pressure-related PWV proposed by Ma *et al.* [26]. Those authors suggest that blood pressure scales with PWV^2, and that the scaling coefficients α and β are approximately constant. Accordingly, the relationship between P and PWV can be represented by Eq. (2), which can be used to derive that PWV is proportional to the square root of blood pressure (P).

$$P = \alpha PWV^2 + \beta \tag{2}$$

$$PWV \propto \sqrt{P} \tag{3}$$

III. RESULTS

A. COMPARISON OF CPTT AND PTT

Table 2 shows the PTT, CPTT, and R values for each subject. The results intuitively show that there is no regular trend between the absolute values of PTT and CPTT′. However, normalized PTT (PTT_{norm}) and normalized CPTT ($CPTT_{norm}$) showed R = 0.744 in the 14 subjects. In Figure 3, three examples are used to illustrate the comparison between PTT_{norm} and $CPTT_{norm}$. On the top of Figure 3, the different axes show examples of PTT_{norm} and $CPTT_{norm}$ variation in subjects with the highest correlation (subject 8), median correlation (subject 6), and lowest correlation (subject 3) between PTT_{norm} and $CPTT_{norm}$. Figure 4 shows the scatterplot and linear regression curves between PTT and CPTT for all subjects. The linear regression equation was $PTT_{norm} = 0.744 \cdot CPTT_{norm}$.

TABLE 2. Values of PTT and CPTT′ and Correlation Coefficients.

Subject No.	PTT (ms)	CPTT′ (ms)	Correlation Coefficient of normalized PTTs
1	127.4 ± 11.5	108.2 ± 7.4	0.541
2	112.2 ± 6.0	91.5 ± 6.9	0.831
3	135.1 ± 14.7	121.5 ± 10.5	0.506
4	123.0 ± 9.2	90.4 ± 9.7	0.784
5	109.0 ± 7.1	66.5 ± 7.8	0.726
6	168.6 ± 14.2	152.7 ± 14.4	0.762
7	159.4 ± 7.0	148.4 ± 8.5	0.555
8	120.1 ± 13.8	97.7 ± 16.3	0.935
9	150.4 ± 11.0	123.9 ± 10.1	0.873
10	154.6 ± 8.3	138.1 ± 6.2	0.748
11	133.3 ± 34.1	89.7 ± 14.9	0.681
12	130.7 ± 11.7	107.1 ± 14.0	0.929
13	81.3 ± 9.6	69.4 ± 10.6	0.868
14	39.6 ± 4.8	20.8 ± 4.3	0.678
	Average (N = 14)		0.744

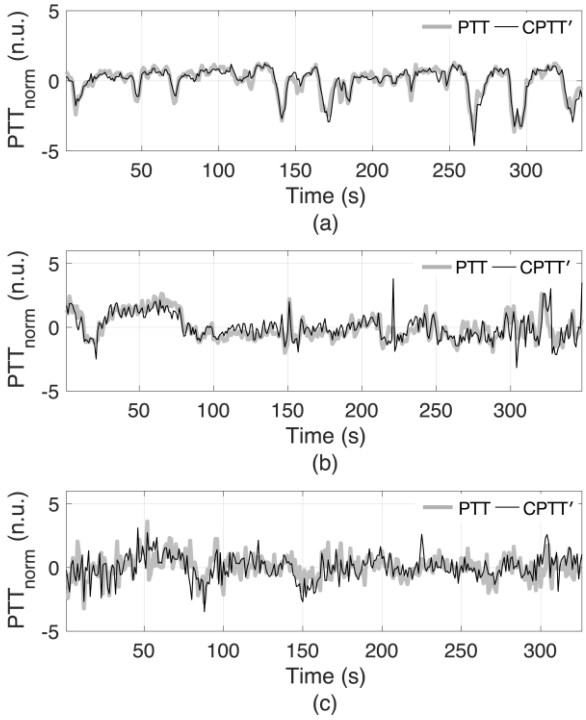

FIGURE 3. Examples of normalized PTT (PTT_{norm}) and CPTT-derived normalized PTT ($CPTT'_{norm}$) of subject 8 (R = 0.935), subject 6 (R = 0.762), and subject 3 (R = 0.506) (from top).

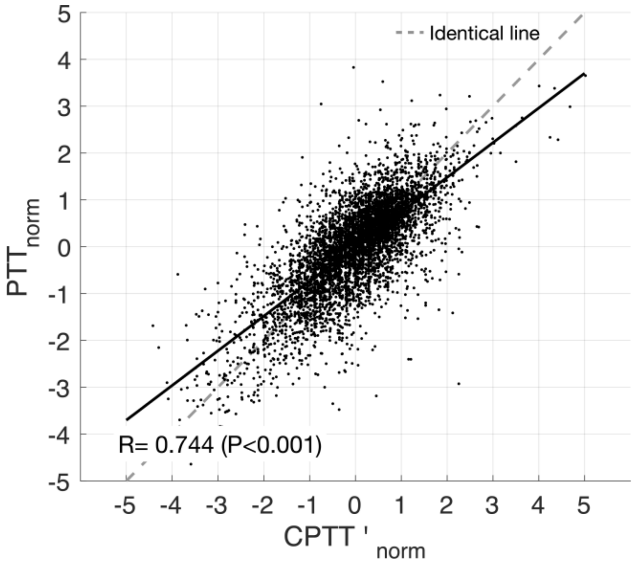

FIGURE 4. Scatterplot and regression curve of $CPTT'_{norm}$ versus PTT_{norm}. The correlation coefficient between PTT_{norm} and $CPTT'_{norm}$ is 0.744.

B. CPTT COMPARED WITH CONTINUOUS FLOW VELOCITY.

Figure 5 shows examples of the continuous variation in CPTT and derived PWV. Figure 5(a), (c), and (e) represent $CPTT_{norm}$ and PWV_{norm} for the entire duration of recording of the subjects with the highest, median, and lowest correlations of $CPTT_{norm}$ and PWV_{norm}, respectively. Figure 5(b), (d), and (f) are enlarged views of the waveform inside the black rectangle in Figure 5(a), (c), and (e), which clearly demonstrate that the long-term variation in $CPTT_{norm}$ and PWV_{norm} are inversely proportional. Moreover, in the pulse-by-pulse observation in Figure 5(a), (c), and (e), we confirmed that the changes in $CPTT_{norm}$ and PWV_{norm} due to pulsation were inversely related. However, variations in CPTT and PWV were not perfect inverses and showed individual differences.

Table 3 shows the correlation coefficients of PWV_{norm} and $CPTT_{norm}$. The R value across all subjects was -0.712. This value stemmed from the known correlation between PTT and PWV from pulse to pulse. Therefore, to investigate the correlation coefficient within a single pulse only, we removed the offsets of CPTT and PWV, and then calculated R. Finite-impulse response filtering with a 0.5 – 7 Hz passband and linear trend removal was applied to remove the offset. Figure 6 shows the scatterplot and regression equations of $CPTT_{norm}$ and PWV_{norm}. The results show that the proposed CPTT is inversely proportional to the estimated PWV ($R = -0.712$). Intrapulse analysis produces the same result ($R = -0.570$).

IV. DISCUSSION

As a result, we confirmed two results through this research. The first is that the newly proposed CPTT′ has a significant ($P < 0.001$) correlation with conventional PTT

TABLE 3. Correlation Coefficients of PTT_{norm} and $CPTT_{norm}$.

Subject No.	Correlation Coefficient of PTT_{norm} and $CPTT_{norm}$	
	Pulsation with offset	Pulsation only
1	-0.872	-0.783
2	-0.519	-0.570
3	-0.875	-0.595
4	-0.758	-0.781
5	-0.646	-0.616
6	-0.771	-0.587
7	-0.895	-0.611
8	-0.582	-0.425
9	-0.638	-0.535
10	-0.887	-0.771
11	-0.710	-0.323
12	-0.513	-0.658
13	-0.666	-0.565
14	-0.651	-0.570
Total ($N = 14$)	-0.712	-0.570

($R = 0.744$). However, this result was obtained by sampling CPTT at specific times of PPG_{finger}, such as the maximum slope time, to allow for an exact comparison with conventional PTT; hence, the extraction point cannot be said to perfectly match a corresponding point in the CPTT waveform. In other words, the correlation between PTT and CPTT, as calculated in this study, may depend on which point is used to extract the CPTT waveform. Here, the feature point of the CPTT waveform are defined as a specific point in the waveform, such as the maximum rising or falling slope or the maximum or minimum fiducial point. In this work, we compared CPTT′ and PTT where CPTT′ is the average value of the analytical interval. Therefore, CPTT′ sampled from CPTT does not have the same value as conventional PTT calculated at a specific point, and may be greater or less than PTT calculated at a given point. Therefore, we normalized PTT and CPTT′ before the regression formula was derived. In addition, the integrity of CPTT may be less than that of PTT because calculating CPTT involves waveform samples associated with both the systolic and diastolic regions. Therefore, further research is necessary to minimize the waveform interval required to calculate the runtime delay.

The second consequence of this study was that we determined whether CPTT could be used to continuously track the flow velocity, which represents a continuous pulse-wave velocity (CPWV). We found that CPTT showed $R = -0.712$ with estimated PWV according to the formula taken from Ma's research [25]. Additionally, $R = -0.570$ when the comparison is done within a single pulse and CPWV without offsets in order to minimize the effect of the variation between pulses. This result suggests that, although there is a slight decrease in correlation, there is a significant negative correlation in the intrapulse comparison. In addition, when comparing CPTT and estimated PWV, it is interesting to note that, although the pulse waveforms of CPTT and PWV are inversely proportional in Figure 5(e), R is negative, apparently because CPTT reflects PWV in individual pulses but does not reflect the overall change. Therefore, this implies

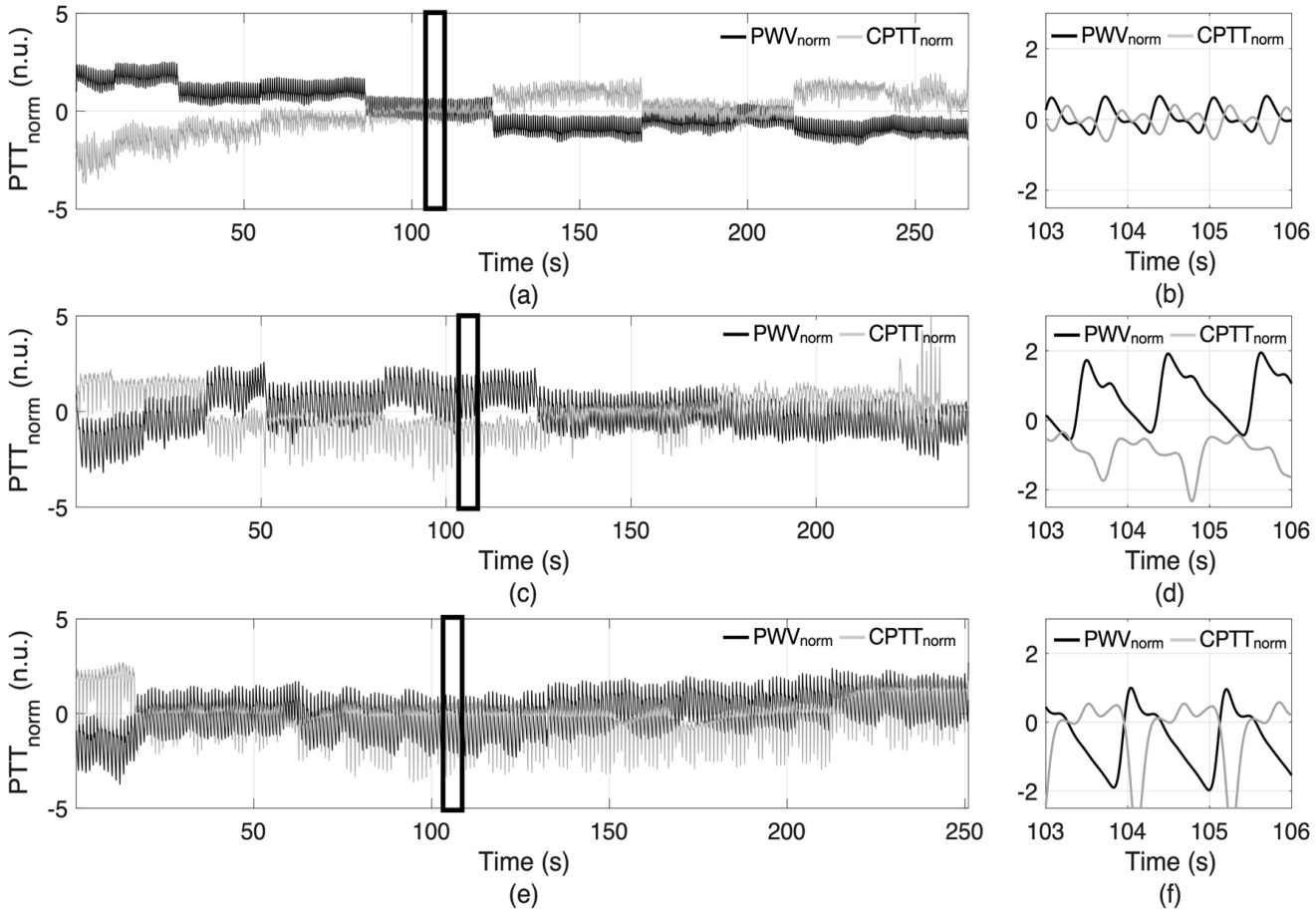

FIGURE 5. Examples of the relationship between normalized CPTT ($CPTT_{norm}$) and normalized PWV (PWV_{norm}) when the (a) highest, (c) median, and (e) lowest correlation coefficients (of subjects 8, 6, and 3, respectively) were observed between $CPTT_{norm}$ and PWV_{norm}. (b), (d), and (e) are enlarged views of the waveforms inside the black rectangles in (a), (c), and (e), respectively.

that a correction between PTT and hemodynamic parameters may be necessary to track natural changes in arterial characteristics, as they are similar to those of conventional PTT. Therefore, in order to use the proposed CPTT in a clinical setting in the future, a calibration that can reflect natural changes is required.

This research is an early step towards broader use of CPTT and has the following limitations. First, because we only used data obtained when subjects were at rest, it is difficult to generalize the findings to changes in dynamic conditions during daily life. Second, our results used data from healthy young people and did not consider factors such as age, sex, or illness. Moreover, the number of subjects was small ($N = 14$), so it is difficult to ensure sufficient statistical significance. Finally, because a comparison criterion was flow velocities that were derived indirectly, rather than those measured using the gold-standard method, there may be errors due to parameter differences. In particular, it is known that some feature points, such as the systolic peak, can vary with the reflected wave shape, which is affected by aging and vascular disease [27]. This study is based on young normotensive subjects, so the influence of this feature point type may not be significant. However, when extending the experiment to a wider range of subjects, we should consider feature point detection using tangent intersection, which is reportedly less influenced by external factors [27]. Therefore, further research is required to generalize the CPTT proposed in this study. First, verification with an intervention that causes a change in PTT, such as a forced change in blood pressure, is necessary. In addition, evaluation of more diverse subjects, such as those in various age groups and with various diseases, is necessary, and the number of subjects needs to be increased. Moreover, the derived CPTT was indirectly validated via the estimated PWV using a continuous blood pressure waveform measured by a volume-clamp device (Finometer). The Finometer waveform, unlike the direct measurement, may differ from the actual velocity of the arterial path between the two PPG measurement sites. Thus, a comparative study with a standard flow-velocity measurement device for more accurate verification will also be a meaningful follow-up. Finally, we plan to study how the accuracy improved by comparing the results of continuously predicting blood pressure using CPTT proposed in a future study.

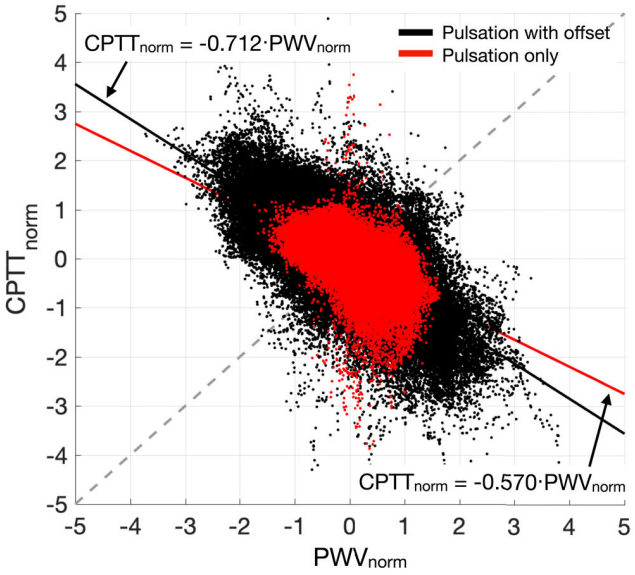

FIGURE 6. Scatterplot and regression equation of $CPTT_{norm}$ and PWV_{norm}. The black dots and line indicate the scatterplot and regression line of PWV_{norm} and $CPTT_{norm}$ with pulsation and offset, and the red dots and line indicate the scatterplot and regression line of PWV_{norm} and $CPTT_{norm}$ with pulsation only.

V. CONCLUSION

In this work, we introduce a novel concept and approach to CPTT calculation for blood pressure estimation. The CPTT is determined by calculating the correlation between multi-site PPGs consecutively and can be used to estimate conventional pulse transit time without a complex peak-detection procedure. We have confirmed that the proposed CPTT is similar to conventional PTT and can be used as an index to estimate the continuous pulse wave. Because the subjects who participated in this study were all young and healthy, our results cannot be generalized. Therefore, verification with a group of subjects of various ages, including those with hypotension and hypertension, should be performed in future studies. We believe that this study is important as it is the first to propose CPTT, the future of PTT, as a useful indicator for hemodynamic analysis and continuous blood pressure estimation.

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HANGSIK SHIN (Member, IEEE) received the B.S., M.S., and Ph.D. degrees in electrical and electronic engineering from the Department of Electrical and Electronics Engineering, Yonsei University, Seoul, South Korea, in 2003, 2005, and 2010, respectively. In 2010, he joined the Digital Media and Communication Research and Development Center, Samsung Electronics, Company, Ltd., South Korea. Since August 2013, he has been with the Department of Biomedical Engineering, Chonnam National University, Yeosu, South Korea, where he is currently an Associate Professor. His research interests include biomedical signal processing, physiological modeling and computer simulation, u-Healthcare, and mobile healthcare technologies.

AHYOUNG CHOI (Member, IEEE) received the B.S. degree from the Department of Electronic and Electrical Engineering, Ewha Womans University, Seoul, South Korea, in 2004, and the M.S. and Ph.D. degrees from the Gwangju Institute of Science and Technology, Gwangju, South Korea, in 2005 and 2011, respectively. In 2011, she researched at the Institute of Creative Technology, University of Southern California, CA, USA. In 2012, she joined the Digital Media and Communication Research and Development Center, Samsung Electronics, Company, Ltd., South Korea. Since 2016, she has been an Assistant Professor with the Department of Software, Gachon University, Seongnam, South Korea. Her research interest includes physiological signal processing, its analysis based on deep learning and mobile healthcare.