Repeated measurement analysis of the area under the curve of photoplethysmogram among diabetic patients

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Abstract: Non-invasive studies using photoplethysmography(PPG) have great potential to be used for a wide range of clinical measurements. In this study, we propose that arterial stiffness may be measured using an approach based on a pulse contour analysis of PPG. The area under the curve (auc-PPG) was compared between patients with HbA1c<8% (Group 1) and HbA1c>10% (Group 2). The auc-PPG was significantly higher in diabetic subjects with HbA1c<8% than in those with HbA1c>10%. To investigate the association between the first and repeated measurements, a paired t-test was conducted. There was no significant difference in auc-PPG between the first and repeated measurements for either group of diabetic patients. These results indicated that the arterial stiffness in patients with different levels of HbA1c can be approximated using auc-PPG.
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1. Introduction

Atherosclerosis is an inflammatory disease in which the arteries become clogged and hardened (Siogkas et al., 2011; Tomaso et al., 2011). Complications of atherosclerosis cause high morbidity and mortality in patients with diabetes mellitus. A previous study has reported that atherosclerosis is strongly associated with arterial stiffness (van Popele et al., 2001). Several studies have demonstrated a trend of increasing arterial stiffness in type 2 diabetes (Tamminen et al., 2002; Henry et al., 2003). Aging is the main factor that contributes to the development of type 2 diabetes and also to increased arterial stiffness. Other possible contributors to the increased arterial stiffness in type 2 diabetes are impaired glycaemic control (Schram et al., 2004; Woodman and Watts, 2003) and the formation of AGEs (Beckman et al., 2002). Various techniques have been used to measure arterial stiffness, including pulse pressure, pulse wave velocity (PWV), ultrasound-derived indices, magnetic resonance imaging (MRI-derived) indices and waveform analyses. However, at present, most arterial stiffness measurements are made in the context of experimental and physiological studies.

PWV is accepted as the ‘gold standard’ measurement of arterial stiffness (Laurent et al. 2006), but it is solely a measure of large artery segments (Glasser et al. 1998) and offers no insight into the status of smaller blood vessels. Assessment of smaller arteries may allow much earlier identification of cardiovascular events related to arterial stiffness (Cohn 2006), as is significant since structural changes in the aorta are probably a late manifestation of cardiovascular abnormalities. Several previous studies have applied photoplesthysmography (PPG) to assess arterial stiffness in a non-invasive manner (Millasseau et al., 2002; Millasseau et al., 2006; Shariati et al., 2008). The PPG pulse wave provides a ‘window’ into the properties of small arteries and stiffening of the small arteries alters the magnitude and timing of reflected waves (Duprez et al. 2004).

PPG is an optical, non-invasive measurement technique that can be used to detect changes in the blood volume in the peripheral vessels in different body parts (e.g., fingers, earlobes or toes) and is often used in clinical research. PPG is the most commonly employed non-invasive technique and operates at a red or near infrared wavelength (Allen, 2007). The advantages of this technique are its ease of set-up and use, low cost and operator independence. When the heart pumps, it generates a blood volume pulse that propagates through the arterial tree. This pulse is influenced by the wave reflection from the branch arteries (Rubins et al., 2008). Changes in the blood volume in the fingertips will produce a PPG pulse waveform. This waveform provides information about the original aortic rhythm, vascular system characteristics, peripheral properties and blood flow (Iketani et al., 2000). The PPG blood volume pulse is similar to the blood pressure pulse, and undergoes similar changes during vascular disease, such as damping and loss of pulsatility. The damping has been associated with a reduction in vessel compliance and increased peripheral resistance, although these changes have yet to be fully explained.

A previous study (Chen et al., 2009) demonstrated the relationship between arterial stiffness and haemoglobin A1c (HbA1c) in diabetic patients with hypertension. HbA1c is technique that is used to quantify average blood glucose levels over a 3-month period (Choi et al., 2011). Another study (Stratton et al., 2000) has reported that microvascular complications of diabetes are strongly associated with HbA1c levels and that any reduction in HbA1c is likely to reduce the risk of complications.

Another study (Spigulis et al., 2002) has shown that in patients with diabetes, the PPG pulses become damped, and the dicrotic notch becomes less prominent. However, as reported in (Allen and Murray, 2003), it is difficult to locate the dicrotic notch in older subjects (>50 years) and in patients with certain other diseases, thereby increasing the uncertainty in the timing measurements related to the reflected wave. Therefore, the present study proposed the use of the area under the curve of the PPG pulse (auc-PPG) to describe the shape (contour) of the PPG pulse without the need to locate the dicrotic notch. The aim of the present study was to evaluate the relationship between auc-PPG as an indicator of vascular function and two levels of HbA1c (HbA1c<8% and HbA1c>10%) in diabetic patients.

2. Subjects and Methods

Subjects

A total of 101 Type 2 diabetic patients, aged 50 to 70 years, were recruited from the Endocrine Clinic at the Pusat Perubatan UKM (PPUKM) from August 2010 to January 2011. Only 56 patients participated in the second set of measurements, which were taken from January 2011 to September 2011. These patients were confirmed to have diabetes based on their clinical records. The study protocol was approved by the Research and Ethics Committee of the PPUKM, and written informed consent was obtained from all participants.

Participant information was gathered in a questionnaire that included items related to socio-demographic factors, smoking habits and medical history. Blood pressure (BP) was measured by an experienced nurse with the patients in a sitting position. The pulse pressure (PP) was calculated as the difference between systolic blood pressure and diastolic blood pressure. The HbA1c level was measured by ion-exchange HPLC. Serum total cholesterol and triglycerides (TG) were measured using a colorimetric method, and high-density lipoprotein (HDL) cholesterol was measured using a homogeneous enzymatic colorimetric method. All subjects were required to fast before undergoing the laboratory tests. The measurements were performed at the haematology and pathology laboratory of the UKM Medical Centre, Malaysia.

PPG Recordings

A PPG system consisting of a sensor, software and hardware (OEM-601 from Dolphin Medical Inc.), was used to record the PPG signals. The software was pre-installed on a personal computer (PC) for ease of data acquisition, restoration and analysis. The PPG signal was acquired using one connected finger probe that operated in transmission mode with red light-emitting diodes (wavelength=660 nm) at a sampling rate of 275 Hz and 16-bit resolution. The data were recorded using the PC and saved in ASCII format. Measurements were performed in a clinical environment at room temperature (25°C). The PPG signals were recorded with the subjects in a seated position with the right arm at heart level. The finger probe was attached to the index finger of the right arm. The PPG was measured over 90 seconds, during which the subjects were asked to remain comfortable and breathe normally.

Data Processing

The recorded PPG signals were pre-processed off-line using MATLAB (The MathWorks, Inc.). The pre-processing stage consisted of de-trending using the MATLAB ‘detrend’ function and band-pass filtering with an algorithm that used a hamming and Fast Fourier Transform (FFT) technique. The band-pass filter had a bandwidth of 0.6 – 15Hz and sampling frequency of 275 Hz. Outliers, drifts, offset and motion artefacts were removed by signal de-trending, whereas the effects of respiratory rhythms and higher frequency disturbances were eliminated by band-pass filtering. Figure 1 shows an example of a PPG signal after the pre-processing stage.

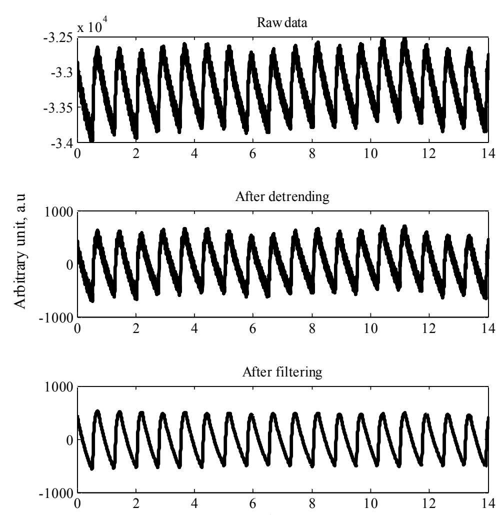

Figure 1. Representative PPG signal after the pre-processing stage

A PPG valley detection algorithm was used to detect all valleys in the data. One pulse is defined as two consecutive valleys, as shown in Figure 2.

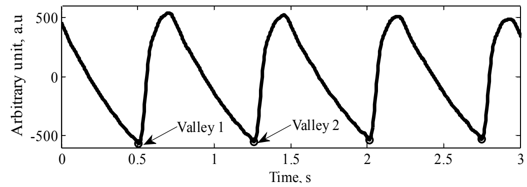

Figure 2. Representative one pulse recognition

A reference pulse was determined for each PPG signal recording such that each subject had his or her own reference pulse. The following procedure was used to determine each reference pulse:

1) Each pulse in the signal (x_1, x_2, x_3, ... x_n, where n = total number of pulses) was identified.

2) Each pulse in the signal was appointed as a reference pulse; x_{ref1},x_{ref2},x_{ref3},...x_{refn}, where n = total number of pulses.

3) Each 'appointed' reference pulse (i.e. x_{ref1}) was compared with all other pulses (i.e., x_1, x_2, x_3, ... x_n). The total error between each pulse (i.e., x_1) and reference pulse (i.e., x_{ref1}), Err, was calculated as

$$Err = \sqrt{\frac{1}{N}\sum_{i=1}^{N} error_i^2} \qquad (1)$$

where "error" is the difference between the pulse and reference pulse and N is the total number of samples (at sampling rate 275 Hz). Referring to Figure 3, double arrow indicates the 'error' and total number of double arrow indicates the total number of samples. The data produced at the end of step (3) are tabulated in Table 1 (first row).

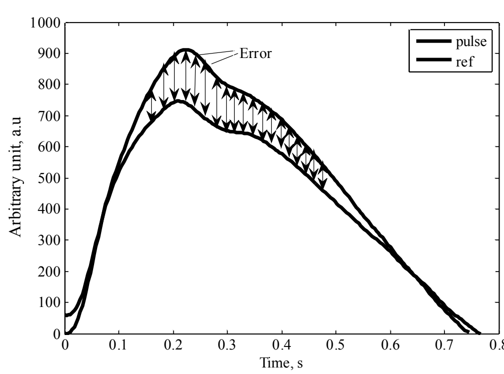

Figure 3. Representative error determination

4) The percent error was calculated as shown in (2) and sample tabulated data are shown in Table 1 (second row). Any pulse with error percentage >40% was discarded from the list of selected pulses to ensure that the selected pulse has a minimum % error with the reference pulse.

$$\%\ Error = \left(\frac{Err_i - Err_{min}}{Err_{max} - Err_{min}}\right) \times 100 \qquad (2)$$

Table 1. Example of tabulated data after the completion of Step 3 and Step 4

	x_1	x_2	x_3	x_n
x_{ref1}	Err_1	Err_2	Err_3	Err_n
x_{ref1}	$\%Error_1$	$\%Error_2$	$\%Error_3$	$\%Error_n$

5) Steps (3) and (4) were repeated for each 'appointed' reference pulse.

6) The number of selected pulses was calculated, and the 'actual' reference pulse was then determined based on the highest number of selected pulses. Table 2 shows an example of how to determine the highest number of selected pulse and x_{ref3} will be selected as a reference pulse. This is because 70 other pulses were similar to x_{ref3}.

Table 2. Example of tabulated data after completion of Step 6

Appointed reference pulse	x_{ref1}	x_{ref2}	$\mathbf{x_{ref3}}$	x_{refn}
No. of selected pulse	50	30	**70**	40

From the procedure, it is found that the running time to determine the reference pulse is proportional to the square of the total number of pulses. Once the reference pulse was identified, the MATLAB function 'trapz' was used to calculate the area under the curve of the PPG (auc-PPG) for the selected pulse (as shown in Figure 4). The trapezoidal rule is a numerical integration method used to approximate the area under a curve or to calculate a definite integral. Using the trapezoidal rule to approximate the area under a curve involves first dividing the area into equal segments. In this study, width of each segment represents a change in time, Δt (at sampling rate of 275 Hz). The sum of these approximations gives the final numerical result of the area under the curve. The mean auc-PPG was calculated for all pulses selected for each subject.

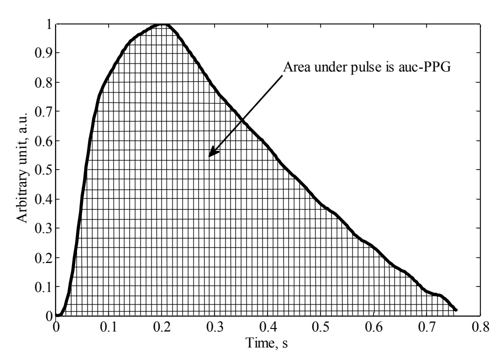

Figure 4. Normalized area under the curve of PPG pulse.

3. Results

Determination of threshold error percentage

Auc-PPG for error percentage < 20% and error percentage > 40% was compared. The result from Table 3 shows that there was a statistically significant difference in auc-PPG between error percentage ≤ 20% and error percentage ≥ 40% for 8 subjects. These results show that error percentage ≤ 40% was acceptable for consideration of similar pulses.

Comparison analysis

An independent sample t-test was used to compare age, lipid profile, systolic pressure, diastolic pressure and auc-PPG values between groups and the data were presented as means (M) with standard deviation (SD) as shown in Table 4. Table 4 shows the baseline clinical characteristics of diabetic patients with HbA1c<8% and HbA1c>10%. Gender distribution was compared between study groups using a chi-square test and data was presented as frequency (percentage). A p-value <0.05 was considered to be statistically significant. The study cohort comprised 53 diabetic patients with HbA1c<8% (24 male and 29 female) and 48 diabetic patients with HbA1c>10% (26 male and 22 female). The diabetic patients with HbA1c>10%, diabetic patients with HbA1c<8% had significantly lower TG, lower low-density lipoprotein (LDL), lower body mass index (BMI) and lower total cholesterol than did the diabetic patients with HbA1c>10%. The two groups had similar disease duration, systolic blood pressure, PP and HDL values.

Table 3. Auc-PPG for 15 patients

Subjects	Auc-PPG with		p-value
	error ≤20%	error ≥40%	
1	0.298	0.368	0.001
2	0.389	0.396	0.002
3	0.227	0.329	0.001
4	0.336	0.334	0.603
5	0.422	0.437	0.001
6	0.362	0.356	0.032
7	0.452	0.432	0.001
8	0.407	0.393	0.074
9	0.330	0.334	0.059
10	0.343	0.332	0.001
11	0.478	0.477	0.870
12	0.422	0.418	0.005
13	0.363	0.371	0.062
14	0.516	0.509	0.549
15	0.453	0.442	0.092

Table 4. Characteristics of the studied subjects

Characteristics	Group 1 (HbA1c <8%)	Group 2 (HbA1c >10%)	p-value
Sample size, n	53	48	
Male n(%)*	24(45.3)	26(54.2)	p=0.489
Age (years)	59.28 (4.729)	58.17(5.365)	p=0.269
Duration of type 2 diabetes(years)	7.43(3.073)	6.48(3.142)	p=0.126
BMI (kg/m^2)	27.93 (3.86)	30.17 (6.23)	p=0.031
Systolic blood pressure (mmHg)	140.60 (17.834)	146.73 (20.441)	p=0.111
Diastolic blood pressure (mmHg)	74.91 (9.132)	79.33 (11.897)	p=0.037
PP (mmHg)	65.7 (13.90)	67.4 (14.19)	p=0.545
Triglycerides (mmol/L)	1.537 (0.861)	2.094 (1.151)	p=0.007
HDL-cholesterol (mmol/L)	1.233 (0.330)	1.199 (0.353)	p=0.613
LDL-cholesterol (mmol/L)	2.658 (1.040)	3.350 (1.449)	p=0.009
Total cholesterol (mmol/L)	4.574 (1.079)	5.485 (1.499)	p=0.001
Auc-PPG(a.u)	0.455(0.068)	0.403(0.067)	p<0.001

Data are given as the mean (SD).

An independent sample t-test was employed to investigate whether diabetic patients with HbA1c<8% and those with HbA1c>10% had different auc-PPG values. The mean auc-PPG of diabetic patients with HbA1c<8% was significantly higher than that of patients with HbA1c>10% ($t(99) = 3.868$, $p<0.001$). The magnitude of the differences in the means was medium ($\eta^2 = 0.111$). The difference persisted after adjusting for age ($F(1,98) = 13.88$, $p<0.001$, partial $\eta^2 = 0.124$), with a medium to large effect. These results suggested that auc-PPG approximately reflected the diabetic control status. A Pearson's correlation analysis revealed that LDL (r=–0.210, p=0.043) and diastolic blood pressure (r=–0.388, p<0.001) were all negatively and significantly associated with auc-PPG. We did not observe any relationship between auc-PPG and disease duration.

Repeated measurement

Table 5 shows the clinical characteristics of the 56 diabetic patients who underwent both measurements. The cohort included 30 diabetic patients with HbA1c<8% (15 male and 15 female) and 26 diabetic patients with

HbA1c>10% (15 male and 11 female). Diabetic patients with HbA1c<8% had lower LDL and lower total cholesterol than diabetic patients with HbA1c>10%. These two groups of diabetic patients had similar BMI, disease duration, systolic and diastolic blood pressure, PP, TG and HDL values.

Table 5. Characteristics of the studied repeat subjects

Characteristics	Group 1 (HbA1c <8%)	Group 2 (HbA1c >10%)	p-value
Sample size, n	30	26	
Male n(%)	15 (50)	15 (57.7)	p=0.565
Age (years)	59.6 (4.79)	58.5 (5.43)	p=0.440
Duration (years)	7.43 (3.00)	6.08 (3.07)	p=0.101
BMI (kg/m^2)	28.2 (3.54)	29.8 (5.55)	p=0.196
Systolic blood pressure (mmHg)	140.37 (13.39)	145.65 (18.06)	p=0.215
Diastolic blood pressure (mmHg)	75.57 (8.62)	77.58 (10.37)	p=0.432
PP (mmHg)	64.8 (10.0)	68.08 (12.90)	p=0.290
Triglycerides (mmol/L)	1.62 (0.93)	2.13 (1.37)	p=0.109
HDL-cholesterol (mmol/L)	1.20 (0.33)	1.20 (0.40)	p=0.937
LDL-cholesterol (mmol/L)	2.51 (0.67)	3.39 (1.25)	p=0.004
Total cholesterol (mmol/L)	4.42 (0.68)	5.42 (1.44)	p=0.002
Auc-PPG(a.u)	0.45 (0.06)	0.39 (0.07)	p=0.002

Data are given as the mean (SD).

For first measurement, an independent sample t-test was employed to investigate whether diabetic patients with HbA1c<8% and those with HbA1c>10% had different auc-PPG values. The auc-PPG for diabetic patients with HbA1c<8% was significantly higher than that in diabetic patients with HbA1c>10% (t (54) = 3.286, p = 0.002). The magnitude of the difference in the means was medium ($\eta^2 = 0.111$).

Furthermore, a paired t-test was employed to evaluate the relationship of auc-PPG for both measurements (as shown in Table 6). There was no significant difference between the mean auc-PPG of the first measurement and of the repeated measurement in either patient group. The first measurement of auc-PPG for diabetic patients with HbA1c<8% was similar to the repeated measurement (t (29) =0.206, p=0.838), and the magnitude of the difference in the means was very small ($\eta^2 = 0.002$). For those with HbA1c>10%, the first and second measurement were not significantly different (t (25) = −1.78, p = 0.087), and the magnitude of the differences in the mean was medium ($\eta^2 = 0.112$).

Table 6. Analysis of paired t-test

Diabetic patients with HbAc level	Measurement of auc-PPG			Measurement of HbA1c		
	First	Repeated	p-value	First	Repeated	p-value
<8%	0.447 (0.06)	0.444 (0.08)	0.838	7.13 (0.49)	7.70 (1.37)	0.011
>10%	0.39 (0.07)	0.41 (0.06)	0.087	11.51 (1.56)	10.75 (2.16)	0.079

Data are given as the mean (SD).

A paired t-test was also used to evaluate the relationship of both HbA1c measurements (Table 6). There was no significant difference in mean HbA1c between the first measurement and repeated measurement for diabetic patients with HbA1c>10 (t (25) = 1.833, p = 0.079) and the magnitude of difference in the means was medium ($\eta^2 = 0.12$). In contrast, there was a significant difference in mean HbA1c between the first and repeated measurements in diabetic patients with HbA1c<8% (t (29) = −2.729, p = 0.011). The magnitude of the differences in the means was large (η^2=0.2).

Comparison with other studies

Table 7 summaries the results of several studies related to arterial stiffness index and the level of HbA1c. In general, these studies also reported that arterial stiffness is greater in patients with higher level of HbA1c. The result from this present study was consistent with listed studies, which level of HbA1c has some effect to the arteries.

Table 7. Comparison of several arterial stiffness studies

Investigators	Subjects	Methods	Comments
Chen et al., 2009	Type 2 diabetes: with hypertension (n = 562) without hypertension (n = 438)	Brachial-ankle pulse wave velocity (ba-PWV) was used to assess arterial stiffness	ba-PWV is associated with HbA1c in diabetic patients with hypertension only
Choi et al., 2011	Type 2 diabetes (n = 370)	Brachial-ankle pulse wave velocity (ba-PWV) was used to assess arterial stiffness	ba-PWV is not associated with HbA1c, maybe because the subjects involved in this study are very old people (average age is 68.7 years with standard deviation, 8.6)
Wu et al., 2011	Type 2 diabetes : well-controlled (HbA1c<8%) (n = 21) poorly controlled (HbA1c>8%) (n = 21) Controls (n=26)	Air pressure sensing system (APSS) was used to determine the stiffness index (SI)	Patients with well-controlled type 2 diabetes had a significantly lower SI than controls Patients with poorly controlled diabetes had a significantly lower SI than those with well-controlled diabetes
Brooks et al., 2001	Type 2 diabetic patients (n = 88) Controls (n = 85)	Applanation tonometry was used to determine the aortic augmentation index (AIx)	Patients with type 2 diabetes had a significantly higher AIx than controls
Present study	Type 2 diabetes : patient with HbA1c<8% (n = 53) patient with HbA1c>10% (n = 48)	PPG was used with area under the curve of PPG (auc-PPG) is as a parameter to indicate the status of arterial stiffness	There is a significant difference in the auc-PPG between patients with HbA1c<8% and those with HbA1c>10%. Patients with HbA1c<8% had a significantly higher auc-PPG than those with HbA1c>10%

4. Discussions

The accuracy of the auc-PPG measurement in each subject depends on pulse contour of each selected pulse. This is because PPG pulse contours play an important role in calculating the area under the curve for PPG. A large difference in contour was found for larger error percentages. Pulses with an error percentage equal to or less than 40% were selected to reduce the dissimilarity between the pulses selected. Figure 5(a)-(c) show examples of pulse contours with different error percentages.

In this study, we found that there was no significant difference in mean auc-PPG between the first and repeated measurements in either group of diabetic patients (HbA1c<8% and HbA1c>10%). The auc-PPG was not much affected, although diabetic patients with HbA1c<8% exhibited increased HbA1c in the repeated measurement and those with HbA1c>10% exhibited decreased HbA1c in the repeated measurement. The effects of hyperglycaemia are often irreversible and can lead to progressive dysfunction (Aronson and Rayfield, 2002). The mechanism underlying these phenomena is unclear, but it is suggested that cellular perturbations may persist despite the return of normoglycaemia (the so-called memory effect) (Aronson and Rayfield, 2002). The observation of persistent rather than transient changes in auc-PPG is consistent with these findings.

Our results show that there is a significant difference in auc-PPG between diabetic patients with different levels of HbA1c. These results further indicate that changes in arterial properties can be non-invasively detected by analysing pulse shape characteristics. In addition, it also show that the auc-PPG has the potential to be further developed as a promising technique for the analysis of PPG pulse shapes with a less prominent dicrotic notch. Further to that, the uncertainty of the PPG measurement and analysis related to the reflected wave can be reduced, or even can be avoided.

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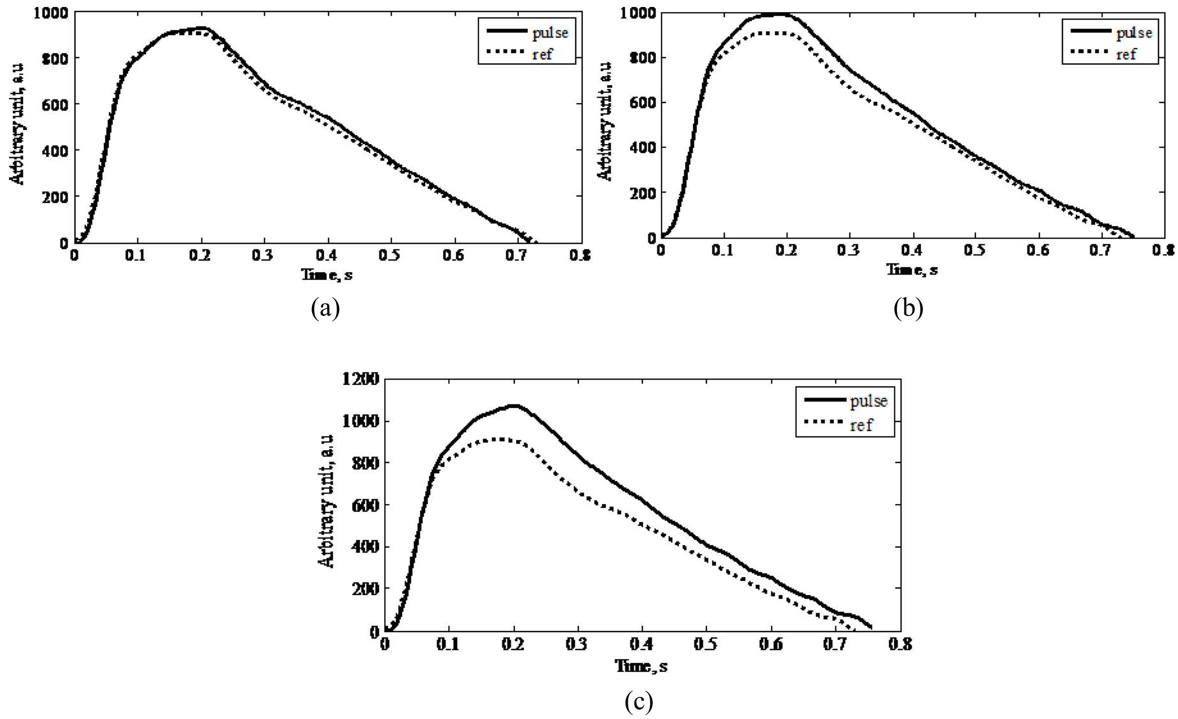

Figure 5. Comparison of a reference pulse to a pulse with: (a) 9.18% error percentage, (b) 20.88% error percentage, and (c) 43.65% error percentage.

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