Measuring Arterial Stiffness Using Photoplethysmogram

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***Abstract*— Monitoring of the arterial condition promises an advantage in detection of any abnormalities occurred among diabetic patients. In this study, the characteristic of photoplethysmogram (PPG) has been investigated non-invasively to measure the status of arterial stiffness. A total of 101 Type 2 diabetic patients, aged 50 to 70 year were participated in this study. The patients divided into two groups which Group 1 consist of patients with HbA1c<8% and those with HbA1c>10% is in Group 2. An area under curve (auc-PPG) has been investigated and chosen as PPG parameter. An independent sample t-test used to compare an auc-PPG between two levels of HbA1c which are HbA1c<8%(Group 1) and HbA1c>10%(Group 2). The result shows that auc-PPG has been found significantly higher among diabetic subjects with HbA1c<8% than those with HbA1c>10% (Group 1 (M=0.455, SD=0.068), Group 2 (M=0.403, SD=0.067), p<0.0001). Further analysis is carried out to investigate the effect of age on auc-PPG. As a result, the mean values of auc-PPG is still significantly higher among diabetic patient with HbA1c<8% than those with HbA1c>10% (Group 1 (M=0.453, SD=0.009), Group 2 (M=0.405, SD=0.009), p<0.0001). The auc-PPG could be considered as one parameter in determining the status of arterial stiffness in relation to the level of HbA1c.**

Keywords*— Atherosclerosis, Cardiovascular disease, Diabetes mellitus, Vascular endothelium, Photoplethysmogram.

I. INTRODUCTION

Complications of atherosclerosis cause high morbidity and mortality in patients with diabetes mellitus. The global prevalence of diabetes is estimated to be 220 million [1]. Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes, the most prevalent form of diabetes, is often asymptomatic in its early stages and can be remain undiagnosed for many years and one-third to one half of type 2 diabetes is undiagnosed [2]. Type 2 diabetes represents more than 90% of those with diabetes and atherosclerosis [3].

Previous study has reported that atherosclerosis is strongly associated with arterial stiffness [4]. Several studies have demonstrated an increase trend in arterial stiffness in Type 2 diabetes [5-6]. The main contributor to the increased arterial stiffness in Type 2 diabetes is age. Other possible contributors are impaired glycemic control [7-8] and the formation of advanced glycation end products(AGEs) [3]. Previous study demonstrated the association between HbA1c and arterial stiffness in diabetic patients with and without hypertension. Arterial stiffness has been assessed using noninvasively technique with brachial-ankle pulse wave velocity (ba-PWV) [9]. Several works have applied photoplesthysmograph(PPG) as the alternative method for assessing arterial stiffness noninvasively [10-13].

PPG is an optical non-invasive measuring technique that can be used to detect blood volume changes in the peripheral vessels at different body parts (fingers, earlobes, toes, etc) and often used in clinical research [14]. The blood volume pulsations, produced by the heart, propagate through the arterial tree. These pulsations are affected by reflected waves from the arterial branching sites. The fingertip PPG expresses change in the volume of blood in the fingertip as the pulse waves. This provides information on beats of aortic origin, characteristics of the vascular system, properties of peripheral vessels and the state of blood flow [15]. The blood pressure pulse is similar to the PPG blood volume pulse, with similar changes occurring in 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. PPG is the most often non-invasively employed and operates at a red or near infrared wavelength [14]. The advantages of this technique are it is simple to use, ease to set-up, low in cost and it is operator-dependant.

Haemoglobin A1c (HbA1c) is used to quantify average blood glucose levels over a 3-month period [16]. Several studies have reported that microvascular complications of diabetes are strongly associated with HbA1c and any reduction in HbA1c is likely to reduce the risk of complications [17].

Therefore, the aim of the present study is to evaluate the association of arterial stiffness with PPG-based technique with two level of HbA1c (HbA1c<8% and HbA1c>10%) among diabetic patients.

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II. METHODOLOGY

A. Subject

A total of 101 Type 2 diabetic patients, aged 50 to 70 years, were recruited from the Endocrine Clinic at UKM Medical Centre from August 2010 to January 2011. These patients were confirmed diabetics by the clinical records. The study protocol has been granted approval by the Research and Ethics Committee of the National University of Malaysia Medical Centre and written informed consent of all participants was obtained.

Participants were questioned in detail using a questionnaire covering the sociodemographic factors, smoking habits and medical record review. Blood pressure (BP) was measured in a sitting position by experienced nurse. Hypertension was diagnosed for those who had been under treatment by anti-hypertension treatment medications.

The HbA1c level was measured by HPLC Ion Exchange method. Serum total cholesterol, and triglycerides were measured using an enzymatic colorimetric method, whereas HDL-cholesterol was measured using homogeneous enzymatic colorimetric. All subjects underwent laboratory test for mentioned measurements at the hematology and pathology laboratory of UKM Medical Centre, Malaysia. They were all fasting.

B. PPG Recording

PPG system consisting of sensor, software and hardware (OEM-601 from Dolphin Medical Inc.), was utilized to record PPG signal. The software was pre-installed to a personal computer for ease of data acquisition, restoration and analysis. The PPG signal was acquired using one connected finger probe which operated in transmission mode with red light emitting diodes (wavelength=660nm). At a sampling rate of 275 Hz and 16-bit resolution, data was recorded using computer and saved in ASCII format. Measurement was performed in a clinical environment at a room temperature of 25^0C. The PPG signal from the subjects was recorded in sitting position with right arm at the heart level. The finger probe was attached to index finger of the right arm. Subjects were asked to stay comfortably and breathe normally for the duration of 90 seconds.

C. Data Processing

The recorded PPG signals were pre-processed off-line using customized algorithm developed in MATLAB (The MathWorks, Inc.). Initially the signal underwent a preprocessing stage which consisted of detrending and band-pass filtering. Signal detrending was used for removing outliers, drifts, offset and motion artifacts, whereas the effects of the respiratory rhythm and higher frequency disturbances were eliminated by band-pass filtering (0.6-15Hz). Figure 1 shows an example of signal after preprocessing stage. A customized PPG valley detection algorithm was used to detect the entire valley in the data length. One pulse has been defined as two consecutive valleys. Figure 2 illustrates the example signal with valley detected.

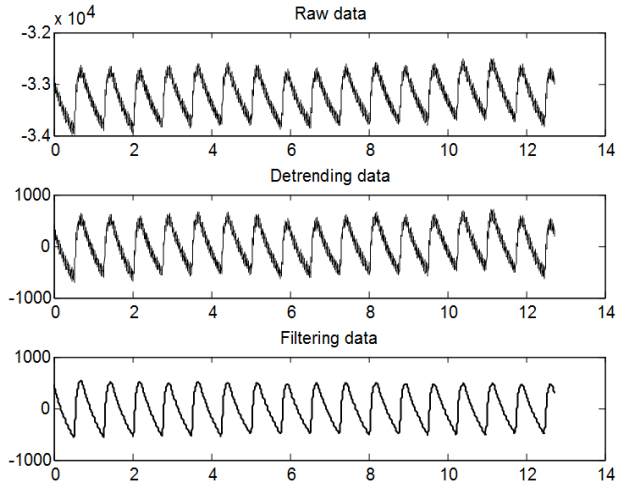


Fig. 1. Signal after preprocessing stage.

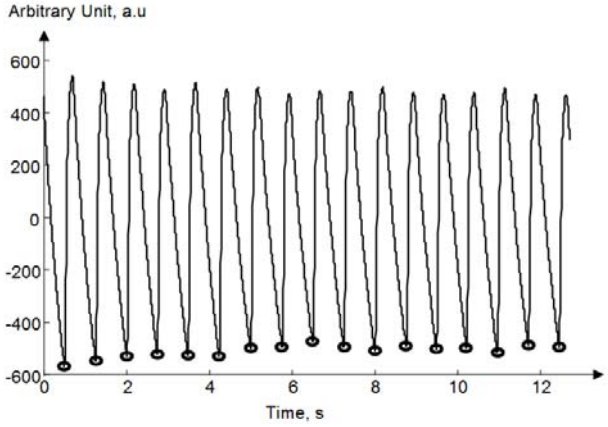
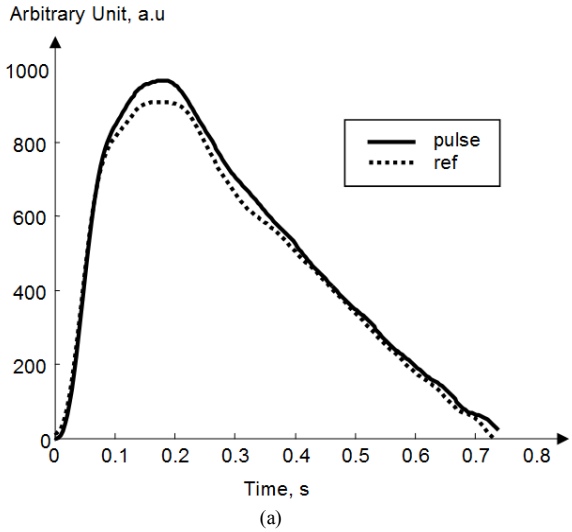
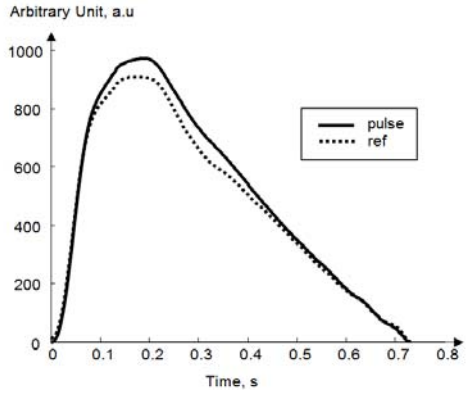


Fig. 2. Signal with valley detected.



(a)



(b)

Fig. 3. Reference pulse and some of pulse of PPG signals with error percentage: (a) 21.12%, (b) 28.34%

Some examples of reference pulse and some of pulse of PPG signals with different error percentage are shown in Figure 3. Next, the area under curve (auc-PPG) was calculated for the selected pulse PPG. Auc-PPG was calculated using trapezoid rule in MATLAB with following equation:

$$auc = \frac{1}{2}(a1 + a2 + ...a_n)\Delta t \qquad (1)$$

where a = amplitude and Δt = small change in time

The trapezoidal rule is a numerical integration method to be used to approximate the area under a curve or the integral. Using trapezoidal rule to approximate the area under a curve first involves dividing the area into a number of strips of equal width. The sum of these approximations gives the final numerical result of the area under the curve.

Figure 4 shows the amplitude (a1, a2) and small change in time (Δt) which represent of one strip used in trapezoid method. Clearly, as the number of trapezoids increases, the fit between graph and the trapezoids gets better which leading to a better area approximation. Through the calculation, auc-PPG represents the total of blood volume change in each heartbeat. Mean auc-PPG calculated for all pulse selected for each subject.

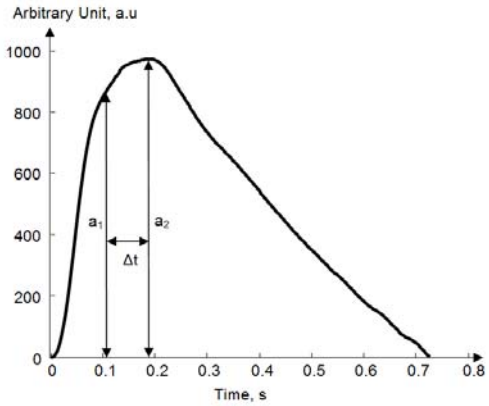


Fig. 4. Example of one strip used in trapezoid method.

III. RESULTS

A. Comparison Analysis

All analyses were conducted using the SPSS software program (SPSS 16). Data were presented as either frequency (percentage) or mean (standard deviation). An independent sample t-test was used to compare age, lipid profile, systole, diastole and auc-PPG. Gender was compared between study groups using a Chi-square test. P-value <0.05 was considered to be statistically significant.

An independent sample t-test was employed to investigate whether Group 1 and Group 2 differed in auc-PPG. The following assumptions were tested and met:

1. groups were approximately the same size
2. the variances of the two populations were equal
3. observations were independent
4. the dependent variable was an approximate normal distribution

Group 1: diabetic patients with HbA1c < 8%. There were 53 patients in Group 1 (24 male and 29 female).

Group 2: diabetic patients with HbA1c>10%. There were 48 patients in Group 2 (26 male and 22 female).

There was a statistically significant difference on auc-PPG between Group 1 and Group 2, t(99) =3.868, p<0.001, effect size(eta2)=0.111. Auc-PPG for Group 1 (M=0.455, SD=0.068) was statistically higher than Group 2 (M=0.403, SD=0.067) and the effect size ranged from medium to large.

TABLE I: CHARACTERISTICS OF THE STUDIED SUBJECT

Characteristics	Group 1	Group 2	Stats
Sample size, n	53	48	
Male (%)*	24(45.3)	26(54.2)	P=0.489
Age (years) †	54.91 (50-70)	53.96 (50-70)	P=0.344
Systole (mm Hg)	139.82 (17.14)	146.26 (20.32)	P=0.108
Diastole (mm Hg)	74.62 (9.19)	79.16 (11.91)	P=0.028
Triglycerides (mmol/L)	1.45 (0.71)	1.93 (0.81)	P=0.001
Hdl (mmol/L)	1.24 (0.32)	1.22 (0.35)	P=0.598
Ldl (mmol/L)	2.67 (1.05)	3.35 (1.45)	P=0.002
Total cholesterol (mmol/L)	4.57 (1.11)	5.50 (1.56)	P<0.001
Auc-PPG (a.u)	0.455 (0.068)	0.403 (0.067)	P<0.001

Data are given as mean (SD).
* Gender is given as n(%),
† Age is given as mean(range)

B. Effect of Age on Auc-PPG

The research further made an analysis to investigate the effect of age on auc-PPG. Table 2 presents the analysis of covariance for auc-PPG as a function of two groups of HbA1c, using an age group as a covariate. An analysis of covariance was used to assess whether Group 1 has higher auc-PPG than Group 2 after controlling the groups' age factor. The following assumptions were checked and all assumptions were met:

1. independence of observations
2. normal distribution of the dependent variable
3. homogeneity of variances
4. linear relationships between the covariates and the dependent variable
5. homogeneity of regression slopes.

Results from Table 2 indicate that after controlling for the age group, there is still a significant difference of auc-PPG between Group 1 and Group 2, $F(1,98) = 13.88$, $p < 0.001$, partial eta2 = 0.124. It has a medium to large effect. Table 3 presents the means and standard deviations of auc-PPG for Group 1 and Group 2, before and after controlling the age factor. It shows that mean value of auc-PPG with and without controlling of age group is similar.

TABLE II: ANALYSIS OF COVARIANCE FOR AUC-PPG

Source	df	MS	F	p	eta2
Age	1	0.047	11.32	0.001	0.104
HbA1c group	1	0.058	13.88	<0.001	0.124
Error	98	0.004			

TABLE III: MEANS AND STANDARD DEVIATIONS OF AUC-PPG FOR GROUP 1 AND GROUP 2

Diabetic patients	Unadjusted			Adjusted	
	n	M	SD	M	SE
Group 1	53	0.455	0.068	0.453	0.009
Group 2	48	0.403	0.067	0.405	0.009

IV. DISCUSSION

Several previous studies show that diabetes causes the PPG pulse to become damped [10]. The dicrotic notch is difficult to measure, in which this increases the uncertainty in measurements related to the reflected wave. The present study describes an auc-PPG, which is calculated using trapezoid rule for each pulse selected without determination of dicrotic notch.

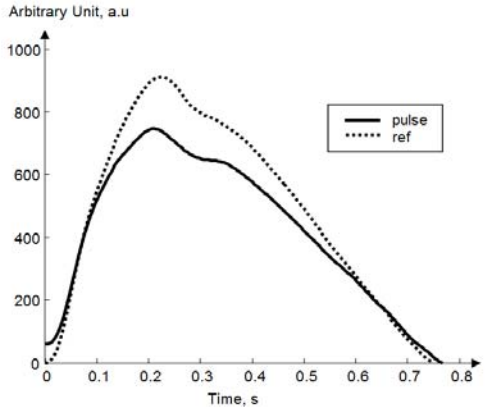


Fig. 5. Reference pulse and pulse of PPG signals with 45.33% error percentage

Consideration of the similar contour of the selected pulse ensures the reliability of the auc-PPG measurement since contour play an important role in calculation of area under curve. We have decided then, to select pulse with percentage error equal or less than 40% after manually comparing the shape of reference pulse and all pulses in the PPG signal. We have found a large difference in contour for the larger percentage as shown in Figure 5.

In the present study, we observed that diabetic patients with HbA1c<8% (Group 1) had significantly higher auc-PPG than those with HbA1c>10% (Group 2). Group 1 (M=0.455, SD=0.068), Group 2 (M=0.403, SD=0.067), $p<0.0001$), suggesting that total blood volume change for each heartbeat decreased with higher level of HbA1c. Hyperglycemia in diabetes stimulates the formation of advanced glycation end products (AGEs). AGEs directly block nitric oxide (NO) activity and produce reactive oxygen species (ROS) in vascular endothelium [1]. The AGE crosslinks within the vascular wall further, worsen vascular stiffness and enlarge artery atherosclerosis [9] due to prolonged exposure to elevated glucose level [17]. Increased viscosity occurs due to osmotic changes with fluctuation in the blood sugar and episode of dehydration. Both impaired release of NO and viscosity had influenced the blood flow in the microvessels [1]. This result shows that increased level of HbA1c possibly affected the arterial stiffness which is the smaller auc-PPG is, the stiffer the arteries are.

To investigate whether auc-PPG is affected by age, we examined the effects of age group on auc-PPG. As a result, HbA1c remains as the main factor on determining the auc-PPG with partial eta2=0.124, it is medium to large effect. As is evident from Table 3, the difference of auc-PPG between Group 1 and Group 2 remains after age group is controlled. The difference persisted after adjusted for age Group 1 (M=0.453, SE=0.009), Group 2 (M=0.405, SE=0.009), $p<0.0001$). This is probably caused by the small range of the patients' age which is between 50 years to 70 years.

The above finding is consistent with a previous study conducted by Chen et al. [9]. They have found that there is a positive association between arterial stiffness (ba-PWV) and HbA1c among the diabetic patients. Until present, the association between the response of PPG-based technique and level of HbA1c has never been discovered.

V. CONCLUSIONS

Our results have shown that there is a significant difference in auc-PPG for the different level of HbA1c. These results have explained that changes in arterial properties can be non-invasively detected by analyzing pulse shape characteristics. An auc-PPG promises a potential technique for analyzing shape with diminish dicrotic notch. Therefore, the uncertainty of the measurement that is related to the reflected wave can be reduced. These results have suggested that glycemic control is important in the prevention of arterial stiffness and vascular complications among diabetic patients.

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