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Determining the arterial stiffness through contour analysis of a PPG and its association with HbA1c among diabetic patients in Malaysia

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ABSTRACT. Diabetes mellitus accelerates atherosclerosis. Monitoring arterial condition promises to be an advantage in the detection of any abnormalities. In this study, the characteristics of analysis by photoplethysmogram (PPG) were investigated non-invasively among diabetic patients. An area under the curve (auc-PPG) was compared for two levels of HbA1c, namely HbA1c < 8% (Group 1) and HbA1c > 10% (Group 2). Auc-PPG was found to be significantly higher among diabetic subjects with HbA1c < 8% than among those with HbA1c > 10%. Further analysis was performed to investigate the effect of age on auc-PPG. The mean values of auc-PPG were still significantly higher among diabetic patients with HbA1c < 8% than among those with HbA1c > 10%. These results show that the auc-PPG method could be a parameter in determining the arterial stiffness in relation to the level of HbA1c.

Keywords: atherosclerosis, cardiovascular disease, diabetes mellitus, vascular endothelium, photoplethysmogram.

Determinação da rigidez arterial pela análise de contorno de PPG e sua associação com HbA1c entre pacientes diabéticos da Malásia

RESUMO. Diabetes mellitus acelera a aterosclerose. O monitoramento arterial promete ser uma vantagem na detecção de qualquer anormalidade. Investigaram-se as características de análise não invasiva por fotopletismograma (PPB) entre pacientes diabéticos. A área sob o arco (auc-PPG) foi comparada para dois níveis de HbA1c, ou seja, HbA1c < 8% (Grupo 1) e HbA1c > 10% (Grupo 2). Auc-PPG foi significativamente mais alta entre os sujeitos diabéticos com HbA1c < 8% do que entre aqueles com HbA1c > 10%. Investigou-se o efeito da idade sobre auc-PPG. Os valores médios de auc-PPG foram ainda significativamente mais altos entre pacientes diabéticos com HbA1c < 8% do que entre aqueles com HbA1c > 10%. Os resultados mostram que o método auc-PPG poderia ser um parâmetro para determinar a rigidez arterial em relação ao nível de HbA1c.

Palavras-chave: aterosclerose, doença cardiovascular, diabetes mellitus, endotélio vascular, fotopletismograma.

Introduction

Atherosclerosis is a slow disease in which arteries become clogged and hardened. Complications of atherosclerosis cause high morbidity and mortality in patients with diabetes mellitus. The global prevalence of diabetes is estimated to be 220 million (IFTIKHAR; WAQAR, 2011). Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia 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 remain undiagnosed for many years. One-third to one-half of type 2 diabetes cases are undiagnosed (ENGELGAU et al., 2000). Insulin resistance is the main characteristic in the pathogenesis of type 2 diabetes. In addition, elevated insulin levels and insulin resistance may be present for several years prior to the diagnosis of type 2 diabetes. Type 2 diabetes represents more than 90% of cases of diabetes and atherosclerosis (BECKMAN et al., 2002).

A previous study has reported that atherosclerosis is strongly associated with arterial stiffness (VAN et al., 2001). Several studies have demonstrated an increased trend in arterial stiffness for patients with type 2 diabetes (HENRY et al., 2003; TAMMINEN et al., 2002). The main contributor factor to increased arterial stiffness in type 2 diabetes is age. Other possible contributors are impaired glycemic control (SCHRAM et al., 2004; WOODMAN; WATTS, 2003) and the formation of advanced glycation end-products (AGEs) (BECKMAN et al., 2002). Another study has demonstrated the association between HbA1c and arterial stiffness in diabetic patients with hypertension. In that study, arterial stiffness was assessed using the brachial-ankle pulse wave velocity (ba-PWV) technique (CHEN et al., 2009). However, several works have applied photoplesthysmography (PPG) as an alternative method for non-invasively assessing arterial stiffness (MILLASSEAU et al., 2002, 2006; SHARIATI et al., 2008; SPIGULIS et al., 2002).

PPG is an optical non-invasive technique that detects and measures blood volume changes in the peripheral vessels of different body parts (e.g., fingers, earlobes, toes, etc.) and is often used in clinical research (ALLEN, 2007). The blood volume pulsations, produced by heart, propagate through the arterial tree and are affected by reflected waves from the arterial branching sites (RUBINS et al., 2008). Fingertip PPG expresses changes in the blood volume as pulse waves, providing information on beats of aortic origin, characteristics of the vascular system, properties of the peripheral vessels and the state of blood flow (IKETANI et al., 2000). 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. 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 typically non-invasively and operates at red or near infrared wavelengths (ALLEN, 2007). The advantages of this technique are its simple usage, easy setting-up, low cost; besides, it is operator-independence.

Haemoglobin A1c (HbA1c) has been used to quantify average blood glucose levels over a 3-month period (CHOI et al., 2011). A previous study has reported that microvascular complications of diabetes are strongly associated with HbA1c and any reduction in HbA1c is likely to reduce complication risks (STRATTON et al., 2000).

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

Material and methods

Subjects

A total of 101 type 2 diabetes 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 to have diabetes from their clinical records. The study protocol was granted approval by the Research and Ethics Committee of the National University of Malaysia Medical Centre. In addition, written informed consent was obtained from all participants.

Participants were questioned in detail using a questionnaire covering socio-demographic factors, smoking habits and medical record reviews. Blood pressure (BP) was measured in a sitting position by an experienced nurse. HbA1c level was measured by the HPLC Ion Exchange method. Serum total cholesterol and triglycerides were measured using colorimetric methods, whereas high-density lipoprotein (HDL) cholesterol was measured using the homogeneous enzymatic colorimetric method. All subjects underwent laboratory tests for the mentioned measurements at the haematology and pathology laboratory at the UKM Medical Centre, Malaysia. All patients fasted for 8 hours prior to testing.

PPG Recordings

A PPG system consisting of sensor, software and hardware (OEM-601 from Dolphin Medical Inc.) was utilised to record the PPG signal. The software was pre-installed to a personal computer (PC) to facilitate 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 = 660 nm). At a sampling rate of 275 Hz and 16-bit resolution, 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 from the subjects were recorded in a sitting position with the right arm at heart level. The finger probe was attached to the index finger of the right arm. Subjects were asked to stay comfortable and breathe normally for 90 seconds.

Data processing

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

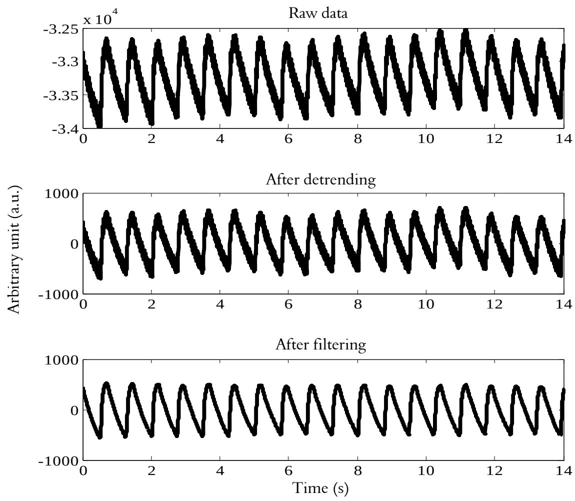

Figure 1. Representative signal after the pre-processing stage.

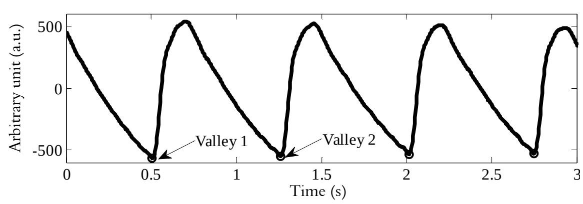

Figure 2. Representative signal with two valleys detected.

Next, the area under curve (auc-PPG) was calculated for the selected PPG pulse. Auc-PPG was calculated using the trapezoidal rule in MATLAB with the following equation:

$$auc = \frac{1}{2}\left(a_1 + a_2 + ...a_n\right)\Delta t \quad (1)$$

where a_1, a_2, ...a_n = amplitude of the n^{th} section and Δt = small change in time.

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

Figure 3 shows the amplitudes (a_1, a_2) and small change in time (Δt) for one strip used in the trapezoidal approximation method. Clearly, as the number of trapezoids increases, the fit between the graph and the trapezoids improves, leading to a better area approximation. Through this calculation, auc-PPG represents the total blood volume change in each heartbeat. The mean auc-PPG was calculated for all pulses selected for each subject.

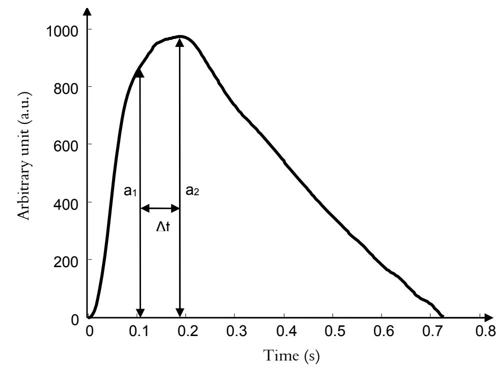

Figure 3. Example of one strip used in the trapezoidal approximation method.

Results

Comparison analysis

All analyses were conducted using SPSS software program (SPSS 16). Data were presented as either frequencies, expressed as percentages, or means (M) with standard deviation (SD). An independent sample t-test was used to compare age, lipid profile, systolic blood pressure, diastolic blood pressure and auc-PPG. Gender was compared between study groups using a chi-square test. A 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:

(i) groups were approximately the same size
(ii) the variances of the two populations were equal
(iii) observations were independent
(iv) dependent variable was an approximate normal distribution.

Table 1 shows the clinical characteristics of the two groups of patients:

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, with $t(99) = 3.868$, $p < 0.001$ and effect size (η^2) = 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 1. Characteristics of the studied subjects.

Characteristics	Group 1	Group 2	Stats
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
Systolic blood pressure (mm Hg)	140.60 (17.83)	146.73 (20.44)	p = 0.111
Diastolic blood pressure (mm Hg)	74.91 (9.13)	79.33 (11.90)	p = 0.037
Triglycerides (mmol L^{-1})	1.54 (0.86)	2.09 (1.15)	p = 0.007
HDL (mmol L^{-1})	1.23 (0.33)	1.20 (0.35)	p = 0.613
LDL (mmol L^{-1})	2.66 (1.04)	3.35 (1.45)	p = 0.009
Total cholesterol (mmol L^{-1})	4.57 (1.08)	5.49 (1.50)	p = 0.001
Auc-PPG (a.u)	0.455 (0.068)	0.403 (0.067)	p < 0.001

Data are given as means (SD). *Gender is given as n (%).

Effect of age on auc-PPG

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

(i) independence of observations
(ii) normal distribution of the dependent variable
(iii) homogeneity of variances
(iv) linear relationships between the covariates and the dependent variable
(v) homogeneity of regression slopes.

Results from Table 2 indicate that after controlling for age group, there is still a significant difference in auc-PPG between Group 1 and Group 2, with $F(1,98) = 13.88$, $p < 0.001$ and partial $\eta^2 = 0.124$. 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 for age. It shows that the mean value of auc-PPG with and without controlling for age group is similar.

Table 2. Analysis of covariance for auc-PPG.

Source	df	MS	F	p	η^2
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 3. 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

Discussion

A previous study has shown that diabetes causes the PPG pulse to become damped (SPIGULIS et al., 2002). In addition, the dicrotic notch is difficult to measure, which increases the uncertainty in the measurements related to the reflected wave. The present study describes an auc-PPG, which is calculated using the trapezoid rule for each pulse selected without identification of the dicrotic notch.

Considering similarities in contour ensures the reliability of the auc-PPG measurements from pulse to pulse because contours play an important role in calculating the area under the curve of PPG. Pulses were selected with percentage errors equal to or less than 40%. A large difference in contour was found for larger percentages after manually comparing the shape of a reference pulse to all pulses in the PPG signal. Figure 4 shows the example of a pulse contour with different error percentages.

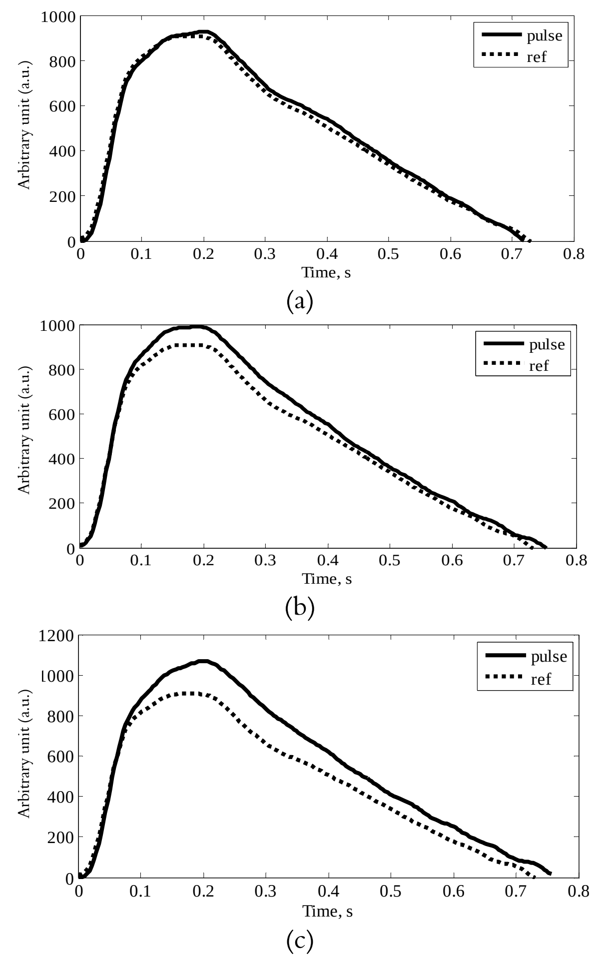

Figure 4. Comparison of a reference pulse to a pulse with: (a) 9.18% error percentage, (b) 20.88% error percentage, and (c) 43.65% error percentage.

In current study, we observed that diabetic patients with HbA1c < 8% (Group 1) had significantly higher auc-PPG than those with HbA1c > 10% (Group 2). The mean for Group 1 was M = 0.455, with SD = 0.068, while the mean for Group 2 was M = 0.403, with SD = 0.067. This was statistically significant with $p < 0.0001$. This result suggests that the total blood volume change for each heartbeat decreased in the group with the higher level of HbA1c. Hyperglycaemia in diabetes stimulates the formation of AGEs. AGEs directly block nitric oxide (NO) activity and produce reactive oxygen species (ROS) in vascular endothelia (IFTIKHAR; WAQAR, 2011). Furthermore, AGE crosslinks within the vascular wall increasing vascular stiffness and arterial atherosclerosis (CHEN et al., 2009) due to the prolonged exposure to elevated glucose levels (STRATTON et al., 2000). Increased viscosity occurs due to osmotic changes with fluctuation in the blood sugar and episodes of dehydration. Both impaired release of NO and increased viscosity influence the blood flow in the microvessels (IFTIKHAR; WAQAR, 2011).

To investigate whether auc-PPG was affected by age, we examined the effects of age on auc-PPG. HbA1c remained the main factor in determining the auc-PPG with apartial $\eta^2 = 0.124$, a medium to large effect. As evident from Table 3, the difference in auc-PPG between Group 1 and Group 2 remained after age group was controlled. The difference persisted after adjusting for age, with Group 1 having mean of 0.453 (SE = 0.009), and Group 2 having a mean of 0.405 (SE = 0.009), with $p < 0.0001$. This is most likely caused by the narrow age range of patients studied between 50 years to 70 years.

The above finding is consistent with a previous study conducted by Chen et al. (2009). In that study, a positive association between arterial stiffness (ba-PWV) and HbA1c among diabetic patients was found. Up to the present time, the association between the response of a PPG-based technique and the level of HbA1c had not been observed.

Conclusion

Our results have shown that there is a significant difference in auc-PPG for two different levels of HbA1c. These results demonstrate that changes in arterial properties may be non-invasively detected by analysing pulse shape characteristics. The auc-PPG promises to be a potential technique for analysing pulses with diminished dicrotic notch. Therefore, the uncertainty of the measurements related to the reflected wave may be reduced. These results suggest that glycaemic control is important for the prevention of arterial stiffness and vascular complications among diabetic patients.

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