Chapter 6

Photoplethysmographic assessment of haemodynamic variations in diabetics affected by diabetic retinopathy

Abstract

The characterisation of the PPG pulses of diabetics affected by diabetic retinopathy and nondiabetics gives us an idea about how the activity of the autonomous nervous system is affected by the disease. Bilateral symmetry studies help in detecting the inadequacy of the sympathetic nervous system. The right-left baseline or amplitude correlation coefficient, being less dependent on age, provides a parameter for the assessment of diabetic retinopathy. The correlation coefficient is found to be low for diabetics compared to the normals and this has been verified using a statistical signal processing approach. Another parameter which is related to the distensibility of the arteries has been derived from the second derivative of the PPG and it has been found that diabetics have a lower value of this parameter when compared with age matched normal subjects.
6.1. Introduction

PPG provides a qualitative measure of the tissue blood volume increase during systole by measuring the light attenuation through the tissue as a function of time. The PPG signal oscillates with the heart cycle period, due to the systolic increase in the tissue blood volume resulting in a lower transmission of light (1-2). The different components of the PPG signal, such as the amplitude of the pulsatile component of the PPG signal (AM) and the baseline (BL) mainly fluctuate in the low-frequency region and these are mediated mainly by the sympathetic nervous system (3-4). The fluctuations in the finger blood volume are due to the constriction and relaxation of the tissue blood vessels which are predominantly affected by the sympathetic nervous system.

Microvascular blood flow in the human skin is subjected to rhythmic variations reflecting the influence of heartbeat, respiration, intrinsic myogenic activity, neurogenic factors and endothelial activity. The available noninvasive diagnostic methods for the evaluation of blood flow through cutaneous microcirculation are venous occlusion plethysmography (VOP) and laser doppler flowmetry (LDF) (5). Though laser Doppler flowmetry is a popular diagnostic method, vasomotion in adjacent vessels under its probe does not consist of a single rhythmic component. Hence spectral analysis has to be performed to detect periodic components within the complex signal and obtain a detailed insight into the mechanism involved in peripheral blood flow regulation (6). Hence a
simple, noninvasive, economic and less time consuming method is desired to assess microcirculation and that is where PPG has proved its worth.

Diabetes Mellitus is a chronic, systemic, life-threatening disease that can affect the eyes & nervous system, as well as the heart, kidneys and other organs. It is a major risk for vascular disorders affecting both microcirculation and macrocirculation. Diabetic retinopathy (DR) is the complication caused to retina due to diabetes and may lead to blindness if untreated. It is an ocular manifestation of systemic disease which affects up to 80% of all patients who have had diabetes for 10 years or more. Previous works on diabetics and nondiabetics available in the literature were mainly focussed on the effects of diabetic neuropathy, especially related to foot problems (6-9). Recently work has been done on the identification of diabetic retinopathy stages using the non-linear features of the higher order spectra using support vector machine classifier based on image signal processing (10). The nature of fluctuation of each PPG parameter can be determined by simultaneously measuring the PPG signal in both the hands and evaluating the synchronisation of the variability of the PPG parameter in the two hands (11). The PPG pulse becomes more dampened with almost no dichrotic notch in the case of diabetics. Measurement of the right-left correlation coefficient can detect the inadequacy of the sympathetic nervous system (12). The right-left amplitude (AM) correlation coefficient only slightly depends only slightly on age and so it is a parameter for retinopathy assessment. This parameter does not require the
use of age-adjusted normal ranges and is therefore advantageous over age-dependent parameters. In our proposed work we have compared the correlation coefficient of the amplitude of the PPG signal for the diabetics and nondiabetics for assessing the bilateral symmetry and verified the same using statistical signal processing. Correlation functions were estimated to measure the similarity of signals. The second derivative of the PPG (SDPPG) has also been used to arrive at a parameter which is closely related to the distensibility of arteries. The method employed in the present studies is simple, economical, reliable and less time consuming and could become an effective screening tool for the early diagnosis of diabetic retinopathy.

6.2 MATERIALS AND METHODS

6.2.1 Subjects

PPG examinations were performed on the index fingers of 15 healthy subjects (8 males and 7 females) aged 38-61 years (mean age 45.8 years) with no known vascular disease and of 15 diabetic patients (6 male and 9 female) aged 38-78 years (mean age 45.0 years). The duration of the diabetes was 2-25 years. The recordings were done at Ranjini eye care clinic, Vyttila under the supervision of a medical practitioner. Subjects on anti-hypertensive therapy were excluded from the study due to the potential influence of the same on the SDPPG components. Subjects with liver and renal dysfunction and gastrectomy were also excluded from the
study. The non-diabetic patients had no known neurological or cardiovascular disease. Patients treated with beta-blockers were excluded from the study, because beta-blockers pharmacologically reduce sympathetic activity. The clinical characteristics of the diabetic patients and the non-diabetic subjects are given in Table 6.1.

All the subjects were instructed to refrain from coffee consumption for 3 hours before the examination. The PPG examination was performed with the subjects in the sitting position, with their forearm resting on a table and the finger at heart level. All the subjects were asked to relax for 5 minutes before the recording to allow for cardiovascular stabilization. Subjects were asked to breathe regularly, to relax and to stay still during the measurement period.

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Diabetic (Retinopathy)</th>
<th>Non-diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Total Number</td>
<td>15</td>
</tr>
<tr>
<td>2.</td>
<td>Sex (M/F)</td>
<td>6/9</td>
</tr>
<tr>
<td>3.</td>
<td>Age, Years</td>
<td>45.8±6.2</td>
</tr>
<tr>
<td>4.</td>
<td>Systolic Blood Pressure, mm Hg</td>
<td>124.3±7.5</td>
</tr>
<tr>
<td>5.</td>
<td>Diastolic Blood Pressure, mm Hg</td>
<td>77.8±9.8</td>
</tr>
</tbody>
</table>

Table 6.1: Demographic data of diabetic and non-diabetic subjects
### 6.2.2 PPG Measurement System

The PPG acquisition unit is a self designed portable unit which consists of two amplifiers which are matched in pair, each with a bandwidth of 0.5-15 Hz. The system was designed such that the PPG pulses from the right and left index fingers could be collected simultaneously. Both the PPG probes were of the reflection type with an LED in the infrared region as the source and a matched photodiode as the photodetector. The PPG signals were sampled at a rate of 500 samples/s. A dedicated digital storage oscilloscope (Tektronix TDS 5104B, 1GHz, 5Gs/s) was used for data capture and for further offline analysis of the captured data. Care was taken to see that the effects of phase differences due to mismatching of the electronic measurement system were small relative to the right–left differences for the physiological data. Atmost care was also taken to apply similar right–left side pressure with the Velcro straps and also to have symmetrical positioning of the probes relative to the measurement sites. The gains of the two PPG amplifiers were set individually to utilize the dynamic range of the recording system. Subjects were asked to breathe regularly, to relax and to stay still for the 5 minute pulse measurement period. The block level diagram of the PPG measurement system is shown in figure 6.1.
6.2.3 System Validation

Electronic matching of the right-left PPG pulse channels is indispensable for bilateral symmetry assessment. A 1 Hz signal derived from a stable signal generator was used to externally drive the current simultaneously in the infrared LEDs of the two PPG probes causing reflected signals to arrive at each photodiode. The simulated pulse waveforms were captured by the digital storage oscilloscope at 500 Hz.
6.2.4 Pulse wave analysis

6.2.4a Bilateral symmetry measurement

Similarity in pulse waveform shape at the two index fingers for the diabetics and nondiabetics was assessed using two types of analyses:
(i). Right-left correlation coefficient for the very low frequency fluctuation of the amplitude of the PPG pulse which provides a measure of the degree of similarity and (ii) Determination of autocorrelation and crosscorrelation functions using statistical signal processing approach.

The pulse was analysed off-line using MATLAB based utilities. The obtained pulses were suitably filtered and digitally analysed for the detection of the maximum and minimum of each PPG pulse. The first 25 sec of recording free from movement artefacts was divided into ten 2.5 sec epoch and the peak to peak amplitude for each of them was normalized to unity. This was further used to determine the right-left correlation coefficient for the amplitude in both the classes of subjects. Using the statistical signal processing approach the Autocorrelation Function (ACF) and the Crosscorrelation function (CCF) were determined from which an inference regarding the degree of similarity between the PPG pulses recorded from the right and left index fingers could be obtained. Autocorrelation was used to measure the self-
similarity of each signal and CCF was employed to show the correlation between the right and left side PPG signals.

6.2.4b Analysis of Second derivative of the photoplethysmogram

Diabetes is associated with endothelial dysfunction and increased arterial stiffness, both of which may contribute to excess cardiovascular mortality in such patients. Arterial stiffening increases pulse wave velocity and wave reflection, which augments central systolic pressure and stress (13). Increased arterial stiffness is a characteristic feature of both type 1 and type 2 diabetes and can be detected using a variety of techniques (14). Current methods of assessing arterial stiffness, such as measurement of pulse wave velocity (PWV) or the use of ultrasound-derived indices, only provide information about compliance within a specific artery or arterial segment, and hence tend to be time-consuming or operator dependent. The technique of pulse wave analysis provides information about systemic arterial stiffness.

Using PPG the wave contour itself is not usually analysed because of the difficulty in detecting minute changes in the phase of the inflections. The delicate changes in the PPG waves can be easily quantified by quadratically differentiating the original PPG signal with respect to time. Several epidemiological studies have demonstrated that the information extracted from the SDPPG waveform is closely associated
with age and other risk factors for atherosclerotic vascular disease (15-17). Although the clinical significance of SDPPG measurement has been thoroughly discussed, there is still lack of sufficient studies focussing on the SDPPG waveform pattern in diabetes afflicted with retinopathy. The PPG signals recorded were double differentiated using Microcal Origin software. The SDPPG waveform consists of a, b, c and d waves in systole and an e wave in diastole as mentioned in Chapter 3. Since the b/a ratio is also dependent on age, it was calculated for the diabetics and the age matched normal subjects and there was found to be a significant difference between them.

Figures 6.2(a) and 6.2(b) show the normalized mean pulse function for a diabetic and a nondiabetic of the same age respectively. The lack of dicrotic notch in the case of a diabetic as already mentioned in literature is clearly evident.

Figure 6.2(a): Normalized mean pulse of a diabetic aged 38 years

Figure 6.2(b): Normalized mean pulse of a nondiabetic aged 38 years
6.3 RESULTS & DISCUSSION

The plot of right-left correlation coefficient for the PPG amplitude vs age for both diabetics and nondiabetics is shown in Figure 6.3. It is clear from the graph that diabetics owing to the lack of bilateral symmetry have low values of right left correlation coefficient when compared to nondiabetics. The amplitude of very low frequency fluctuations showed high right-left correlation (0.93±0.05) for nondiabetic subjects and significantly lower correlation (0.38±0.16) for the diabetic patients.

Figure 6.3: Right left correlation coefficient vs age graph for diabetics and nondiabetics
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The PPG signal is known to vary from patient to patient and even from measuring site to site (18). The average and correlation of signal are not independent of time, which means that the signal is not stationary and ergodic. Hence to apply the statistical signal processing tool it was assumed that the measured time series data were locally stationary in a wide sense. The post processing of the PPG signals were done using MATLAB tool. The autocorrelation function for the left and right hand signals for a normal subject showed high correlation as shown in Figures 6.4 & 6.5, while in the case of diabetics there was less correlation which is clearly evident from Figure 6.6 & 6.7. The superposition of the autocorrelation functions of the two PPG signals recorded simultaneously from the left and right hands gives a clear illustration of this.

![Figure 6.4: Auto correlation function corresponding to the left and right hand signal of a healthy person](image-url)

Figure 6.4: Auto correlation function corresponding to the left and right hand signal of a healthy person
Figure 6.5: Superposed autocorrelation functions of plots shown in Figure 6.4

Figure 6.6: Auto correlation function corresponding to the left and right hand signals of a diabetic subject
Similarly cross correlation functions of simultaneously recorded left and right fingers were plotted and its correlation coefficient was calculated. Figures 6.8 and 6.9 show the cross correlation function of normal and diabetic subjects.

Figure 6.7: Superposed autocorrelation functions of plots shown in Fig 6.6

Figure 6.8: Cross correlation function of signals recorded from left and right index fingers of a normal subject

Figure 6.9: Cross correlation function of signals recorded from left and right index fingers of a diabetic patient
Using the SDPPG the b:a ratio for age matched controls and diabetics was determined. Since the b:a ratio of only 8 matched controls and diabetics could be obtained this study is only a pilot study. The range of age for the study was from 38-60. The average b:a ratio for subjects with diabetic retinopathy was found to be -0.773±0.2 and that for normals -0.477±0.1. The differences in mean values between the two groups were analysed by a one-tailed student t-test. p < 0.05 was considered to be statistically significant.

The similarity of pulse timing, amplitude and shape of the high frequency pulses between the right and left sides of the body were expected in normal subjects since the anatomical structures are similar (19), the peripheral vascular beds are innervated symmetrically by the autonomic nervous system (20) and the blood vessels will have incurred the same levels of age-related reduction in arterial compliance (21). The similarity in peripheral pressure at each level influences the pulse arrival times and therefore relative pulse wave velocities. Any differences in vessel properties can affect the times and shapes of the rising edge (anacrotic phase) and falling edge (catacrotic phase) of the PPG pulses. By having studied the pulses obtained simultaneously, the right-left characteristics allows important information about the peripheral circulation to be extracted. Simultaneous measurements are also likely to be better than sequential measurements in detecting right–left differences with confidence, especially if there are changes in key cardiovascular
parameters such as heart rate, body temperature, peripheral resistance or systemic blood pressure.

6.4 CONCLUSIONS

The present study shows that PPG can provide a potential tool for evaluating the role of the sympathetic nerves in the regulation of the microcirculation. The high right-left correlation coefficient for amplitude shows that the spontaneous fluctuations in the tissue volume and the systolic blood volume increase are of central origin. The lower values of the right – left correlation coefficient for diabetic patients indicates the deterioration of the sympathetic nervous system which results in asynchronous sympathetic activity in the two hands inspite of its central origin. So the PPG signal variability shows promise for the objective assessment of autonomic retinopathy. Though Photoplethysmography is not appropriate for quantitative measurement of tissue blood flow or the systolic blood volume pulse in absolute terms it can still be used as a simple and convenient means to assess the fluctuations of tissue blood volume, the systolic blood volume pulse, and the temporal relationship between them. The simplicity of the PPG measurement technique, the speed with which peripheral PPG assessments can be made and the valuable cardiovascular information contained within it could make this a useful clinical investigation tool.
References

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