Comparison of Pulse Rate Variability and Heart Rate Variability for Hypoglycemia Syndrome

Şükrü Okkesim; Gamze Çelik; Mustafa S. Yıldırım; Mahmut M. İlhan; Özcan Karaman; Ertuğrul Taşan; Sadık Kara

1. Background

Hypoglycemia is an important complication of glucose-lowering therapy in patients with diabetes mellitus (DM) [1]. Hypoglycemia causes a series of metabolic, neural and clinical responses. Insulin hormone secretion is reduced whereas glucagon, epinephrine, nor-epinephrine, cortisol and growth hormone are increased as an outcome of autonomic activation within the body [2–4]. The hemodynamic changes are related to hypoglycemia; which can be summarized as a raise in heart rate and peripheral systolic blood pressure, a decline in central blood pressure, and peripheral arterial resistance (resulting in a widening of pulse pressure), a rise in myocardial contractility, stroke volume, and cardiac output. As a result, although the cardiac workload is transitory, it is increased significantly during hypoglycemia. The severe complications of hypoglycemia contain cardiovascular events, neurologic damage, trauma and death. The ‘dead-in-bed’ syndrome is the name of the unexplained sudden deaths of healthy patients with DM who are found dead in an undisturbed bed. This situation may be formed by hypoglycemia-induced cardiac arrhythmia [5]. The rate of experiencing hypoglycemia increases at night, and it is an especially risky situation because autonomic counter-regulatory response reduce at sleep [6, 7].

In order to prevent the sudden death, early detection of hypoglycemia has a vital significance. As is present at literature, QT interval and heart rate variability (HRV) are used to get the features for early detection [8–12].

HRV has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals acquired from the electrocardiography (ECG) [13]. Sympathetic (SNS) and parasympathetic nervous systems (PNS) control the heart rate. SNS tends to increase the heart rate and its response is slow. PNS, on the other hand, tends to decrease the heart rate [14]. One of the main features computed from HRV using frequency-domain analyzing methods is calculating the power in the 0.15–0.40 Hz (high frequency – HF) and 0.04–0.15 Hz (low frequency – LF). The powers in the HF and LF bands are regulated by PNS and SNS respectively [15, 16].

Keywords
Insulin-induced hypoglycemia, finger pulse plethysmography, electrocardiography

Summary

Background: Heart rate variability (HRV) is a signal obtained from RR intervals of electrocardiography (ECG) signals to evaluate the balance between the sympathetic nervous system and the parasympathetic nervous system; not only HRV but also pulse rate variability (PRV) extracted from finger pulse plethysmography (PPG) can reflect irregularities that may occur in heart rate and control procedures.

Objectives: The purpose of this study is to compare the HRV and PRV during hypoglycemia in order to evaluate the features that computed from PRV that can be used in detection of hypoglycemia.

Methods: To this end, PRV and HRV of 10 patients who required testing with insulin-induced hypoglycemia (IIHT) in Clinics of Endocrinology and Metabolism Diseases of Bezm-i Alem University (Istanbul, Turkey), were obtained. The recordings were done at three stages: prior to IIHT, during the IIHT, and after the IIHT. We used Bland-Altman analysis for comparing the parameters and to evaluate the correlation between HRV and PRV if exists.

Results: Significant correlation (r > 0.90, p < 0.05) and close agreement were found between HRV and PRV for mean intervals, the root-mean square of the difference of successive intervals, standard deviation of successive intervals and the ratio of the low-to-high frequency power.

Conclusions: In conclusion, all the features computed from PRV and HRV have close agreement and correlation according to Bland-Altman analyses’ results and features computed from PRV can be used in detection of hypoglycemia.

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2. Objectives

HRV measures based on ECG recordings are often imperfect in early detection of hypoglycemia. Physiological processes such as respiration or non-physiological influences such as power line interference and electrodes contact shift can all add noises to the ECG signals, and therefore affect the accuracy of HRV estimates [15].

The pulse-plethysmograph (PPG) is a noninvasive, and straightforward signal for detecting blood volume fluctuations by optical means and it is commonly used to evaluate vascular compliance, blood oxygen saturation, heart rate and respiratory rate [17–20]. The pulsatile feature of the PPG waveform is synchronized with each heartbeat and its main frequency which is based on heart rate. The pulse waves come from alterations of blood volume in arterial tissues by means of each heartbeat.

Pulse-to-pulse variability (PRV), can be evaluated from peak to peak time intervals of the PPG signal [21]. Several studies have demonstrated that PRV is an accurate estimate of HRV [21–23].

Some research reported that ECG does not provide a proper signal for ambulatory situations and in bed applications to have an alarm for dead-in-bed syndrome [14, 20–22]. The reason for this is that ECG has some problems like drift, the large number of wires, adhesive electrode patches and complex morphology. On the other hand, inexpensive optical sensors, which are robust and need less maintenance, are used in the PPG system. It uses a lot less power than ECG and needs only one wire; therefore it is an ideal ambulatory device. Furthermore PPG signal can be used as an alternative physiological signal for the clinically relevant parameters like heart and respiratory rate and respiratory induced intensity variations, neurologically induced skin perfusion changes and asymmetry of brain [24].

Information with respect to the effect of hypoglycemia on HRV is available in literature; however the effect of hypoglycemia on PRV is not. Taking into account all of these, this study is to investigate the estimation of variations in heart rate using PRV from a PPG signal for hypoglycemia.

The algorithms that we suggested for PPG’s local maximum and PSD are proved to be useful. Thanks to this study PPG and features computed from it can be evaluated. These algorithms contribute to research that are concerned with the use of PRV for detection of hypoglycemia. In addition, investigation should continue in order to use PPG as a routine method in clinic to detect hypoglycemia.

3. Methods

3.1 Materials

All the medical part-related steps of this study were completed by endocrinologists in the Department of Endocrinology and Metabolic Diseases at Bezm-i Alem University. Ethics approval was obtained for the study from Bezm-i Alem University Clinical Research Ethics Committee – Decision No: 71306642/050-01-04/219

ECG and PPG signals were recorded from 10 patients. ▶ Table 1 shows the demographic information of the study participants. The use of alcohol, smoking and caffeine, use of drugs that can affect the heart rhythm and function, excessive exercising, being over the age of sixty were used as exclusion criteria.

Insulin-induced hypoglycemia test (IIHT) was applied to all patients, at Bezm-i Alem University in the Department of Endocrine and Metabolic Diseases. IIHT is a gold standard test to diagnose secondary adrenal insufficiency. It is utilized in the response to stress in the suspicion of ACTH or growth hormone deficiency.

In this test, 0.15 U/kg of insulin dose was administered to the patient. Glycemia was measured with a special device which is called a continuous glucose measurement system (CGMS) every five minutes. When glycemia reached 40 mg/dl, the test was terminated and intravenous dextrose was administered to restore the glycemia levels.

The vital importance of lowering glycemia requires full attendance of a doctor and a nurse during the IIHT. As outlined in the introduction section, the effects of hypoglycemia can lead to death. In experimental hypoglycemia studies on humans, volunteers are informed about the possible side effects of hypoglycemia with the volunteer information sheet which was given to the participants before IIHT. After the signing the information sheet volunteers become a participant in the study. When the patients read the information sheet and learned that the test may cause a serious side effect, most of them did not want to participate in the study. In fact, this issue is seen in experimental hypoglycemia studies. Therefore the number of patients has been limited in these studies [25–28].

ECG and PPG signals were sampled at 1000 Hz and digitized (A/D converted) at a resolution of 24 bits per sample by the MP150 units (Biopac Systems, Goleta, CA, USA). The amplifier module of the MP150 unit was used to amplify and filter with the following settings: 35 Hz low-pass, 0.05 Hz high-pass filter, and 500 gains. In order to reduce electrode impedance, skin surface was abraded and electrode gel was applied before electrode placement. The PPG signals were recorded using PPG 100C amplifier and TSD200 transducer modules of the MP150 unit. The probe of the TSD200 module, which operates on 860 ± 60 nm wavelength, was placed on the ring finger.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic informations of the subjects</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
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</tr>
<tr>
<td>Age (mean standard deviation)</td>
<td>49.2 ± 9.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 ± 2.7</td>
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<tr>
<td>Gender (male/female)</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Detailed explanations related to IIHT stages</th>
</tr>
</thead>
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<tr>
<td>Stages</td>
<td>Recording duration</td>
</tr>
<tr>
<td>Prior to IIHT</td>
<td>50</td>
</tr>
<tr>
<td>During the IIHT</td>
<td>80–120 (82.5 ± 37.2)</td>
</tr>
<tr>
<td>After the IIHT</td>
<td>50</td>
</tr>
</tbody>
</table>
The module filter settings were 3 Hz LP filter and 0.5 Hz HP filter.

The ECG and PPG recordings were completed during three stages as “prior” to IIHT, “during” and “after” the IIHT. ECG and PPG recordings were done in the supine position. The duration of recording for “prior” stage was 50 minutes. Then there was a gap for 10 minutes. After that recording for “during the IIHT” stage was done. The duration of recording for “during the IIHT” stage was in the 80–120 range. The duration of recording for “during the IIHT” stage means a range that is from a normal glucose level drops until it reaches below 40 mg/dl, thereby the recordings of signals were on-going until the glycemia reached 40 mg/dl. When the lowest glycemia level was obtained, the IIHT stage was terminated. There was no gap “after” the IIHT stage was started and the duration of recording was 50 minutes. Detailed explanations related to IIHT stages are given in Table 2.

Each patient’s metabolism represents a different counter-regulatory autonomic response to the different levels of severity of hypoglycemia. For example, counter-regulatory autonomic responses to different levels of severity of hypoglycemia changes over time, in patients with diabetes mellitus. Therefore, each patient should be evaluated for their own glycemia level. For that reason, “prior to IIHT” and “after the IIHT” stages were used as a control for “during the IIHT” stage. If a control group was created as a healthy group, different counter-regulatory autonomic responses to hypoglycemia would affect our findings.

### 3.2 Data Analysis and Processing

#### 3.2.1 Heart Rate Variability

ECG signals were recorded through lead II for obtaining HRV. So to detect R peaks for HRV we used the algorithm recommended by Manriquez and Zhang [29, 30] as seen in Figure 1 [29, 30]. The durations among successive peak were estimated to obtain RR intervals and the algorithm checks an interval of 0.33 s and accepts the point with largest value as a real R peak. So the rest of wrong peaks are naturally rejected in this stage. RR interval series were not uniformly sampled. Therefore, the cubic interpolation frequency was applied as 4 Hz to obtain a uniformly sampled HRV time series (Figure 2a).

Then, power spectral density (PSD) analysis was implemented using Welch’s method with Hann window. The Welch method calculates an average over the modified periodograms. Periodogram is defined as a classical nonparametric method to obtain PSD. The main drawback of the periodogram method is the effect of offside lobe leakage due to finite data sets. In order to minimize the effect of the offside lobe leakage, time series of the signal is divided into overlapping sequences then each data sequence is windowed in order to smooth the edges of the signals [17]. Due to this improvement, the Welch method is used to estimate the power spectral density of the interpolated HRV. Detailed formulizations for the Welch method were given in the following equations [14, 31].

\[
n = 0, 1, \ldots, (L - 1),
\]

\[
i = 0, 1, \ldots, (K - 1),
\]

\[
x_i(n) = x(n + i \times S)
\]

S is the size of the sequences and S ≠ L, (1)

The \(i\)th modified periodogram is:

\[
\hat{P}_i(f) = \frac{1}{U \times L} \left| \sum_{n=0}^{L-1} x_i(n) \times W(n) \times e^{-j2\pi f \times n} \right|^2
\]

where \(U\) is the normalizing constant.

\[
U = \frac{1}{L} \times \sum_{n=0}^{L-1} W^2(n)
\]

The power spectral density is:

\[
\hat{P}_e(f) = \frac{1}{K} \times \sum_{i=0}^{K-1} \hat{P}_i(f)
\]

\(L\) is the length of the interpolated HRV \(x(n)\) and \(W(n)\) is the Hann function [32].

In Figure 3, one of the patient’s PSD graph during the IIHT stage was shown. In our study, the window size of 256 samples and 50% overlap were used so that 0.0156 Hz spectral resolution was obtained. The power in the LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) band were calculated for each patient.

### Figure 1
Flow chart for R-wave detection algorithm
3.2.2 Pulse Rate Analysis

Firstly, maximum points of the PPG signal (P\text{max}) were detected due to the P\text{max} marks of the peak of ventricular depolarization. Consequently, PP intervals of the length in time domain from one P\text{max} to the next one were determined as shown in Figure 3. So to enable detection of the P\text{max}, an algorithm was created. As seen in the following explanation of the algorithm, our algorithm will ignore the smaller one of the two possible local maximums those that are closer than min_p. Also, it is particularly impossible to not find a local maximum in the range of max_p \[33\]. The explanation of the algorithm for P waves is as follows:

1. Minimum possible pulse length (min_p) is assigned as 0.33 seconds. Maximum possible length (max_p) is assigned as 1.5 seconds.
2. First maximum between max_p and 2max_p is assigned as first peak.
3. Assign search point “n” to be max_p later from first peak. Do this until the signal is finished.
4. Search for maximum point from n-min_p to n+min_p (which is a 0.66 seconds range).
5. This local maximum is a peak candidate. Take it as a new peak
6. If it is different than the last found peak, and it is larger than points from min_p/3 before the candidate to min_p/3 after candidate.
7. Else, change searching point “n” to min_p/3 later.

As these processes are applied to the RR interval, a cubic interpolation was applied to get uniformly sampled PRV (Figure 2b) and the power of the PRV in the LF and HF band was obtained using the algorithm which is based on the Welch method.

The explanation of the algorithm for power of the PRV and LF/HF ratio is as follows:

1. Sampling frequency is defined as 1000 Hz.
2. Window length is defined as 10 minutes.
3. Sample number (win) of window is defined as:
   a. win = (10 min). (60 sec/min). (1000 sample/sec) = 600,000 samples.
4. Do this for each window:
   a. Take the corresponding window of signal,
   b. Find peaks using the function prv_peak (refer to algorithm for P waves),
   c. Calculate times of peaks, calculate time intervals of peaks (RR\text{int}), interpolate RR\text{int}, calculate power spectral density of RR\text{int} using Welch’s method,
   d. Save total power in the range [0.04–0.15 Hz] as low frequency (LF),
   e. Save total power in the range [0.15–0.4 Hz] as high frequency (HF),
   f. Calculate mean of RR\text{int}, calculate standard deviation of RR\text{int}, calculate root mean square (RMS) of RR\text{int},
5. Calculate the low frequency to high frequency ratio (LF/HF) for each window.

In the time domain, for each RR and PP intervals, the mean RR and PP (mean NN), the standard deviation of all RR and PP (SDNN) and the root mean square of the difference of successive RR and PP (RMSSD) were calculated. As a frequency domain feature, the ratio of the low-to-high frequency power (LF/HF) was calculated.

All the data processing was carried out using MATLAB’s own library developed under MATLAB R20011b Software (MathWorks Inc., Natick MA, USA).

3.2.3 Statistical Analysis

Since three different stages exist as "prior IIHT", “during IIHT”, and "after IIHT", we

![Heart Rate and Interpolation for HRV](http://example.com/figure2a.png)

![Heart Rate and Interpolation for PRV](http://example.com/figure2b.png)
carried out statistical comparisons of features computed from PRV and HRV. We used paired t-test with a 95% confidence limit and a p-value of less than 0.05 was considered as statistically significant. Results were expressed as means and standard deviations (SD).

Correlation between PRV and HRV features was assessed with the Pearson correlation, and their agreement and bias were compared using a Bland-Altman analysis [34]. Bias value is really useful to prove if there is a difference or not between the features. If its value is close to zero it means that parameters are almost the same. And bias should be given with a confidence interval showing the range likely to contain the true bias. The bias is expressed as a SD or a CV, depending on the plot option. Limits of agreement can be calculated and plotted on the different plots to show the likely range of differences between the methods. Large limits of agreement imply poor precision in one or both methods [35].

4. Results

In this study, in order to evaluate the effect of the counter regulatory responses on PPG that are caused by hypoglycemia PPG signals were recorded and featured as LF/HF, mean NN, SDNN, RMSD. In order to evaluate the capability of the PPG for detection of hypoglycemia, the ECG signals were recorded at three different stages and computed features were compared with ECG based features.

As shown in Table 3, mean NN intervals (mean RR and PP intervals), RMSSD and SDNN and LF/HF demonstrated a strong correlation (p < 0.05) for three
stages. The Bland-Altman analysis of all features computed from HRV and PRV represent a close agreement for three stages.

When we look in detail to at the results of the mean NN in Figure 4a, for the prior IIHT stage the bias is estimated as 0.0040 seconds and for the 95% confidence limit, upper and lower limits of agreement were significantly narrow (–0.0315 and 0.0395 seconds). For the stage “during” the bias was 0.0005 seconds and for the 95% confidence limit, upper and lower limits of agreement were –0.0011 and 0.0021 seconds (Figure 4b). For the stage “after” the bias was 0.0003 seconds and for the 95% confidence limit, upper and lower limits of agreement were –0.0036 and 0.0042 seconds (Figure 4c). Results displayed indicate a significant correlation (p < 0.05) and good agreement for SDNN, RMSSD and LF/HF ratio parameters for the three stages of IIHT.

Another notable result is related to the LF/HF ratio. An increase in the LF/HF ratio corresponds to the increase of activity in the SNS. As seen from Table 3, LF/HF ratio has a slightly bigger value for “during the IIHT” stage than other stages. As shown in Figure 5, the LF/HF from computed PRV and HRV is relatively higher at the “during the IIHT” stage, which confirms that there is an increased SNS activity during the hypoglycemia. These results are consistent with literature. Because both stages for “prior to IIHT” and “after the IIHT” glycemia have normal levels and “during the IIHT” has a greater difference in regard to glycemia level (40 mg/dl). Therefore SNS is more activated for “during the IIHT”. If the outliers are taken into account, distributions of the LF/HF ratios are coherent.

When we refer to recent literature in order to check the effect of hypoglycemia on PRV, no study has explored the time and frequency domain measures of PRV yet, as specified in this paper. Therefore, we observe that PRV is a good feature as an alternative of HRV to evaluate the counter regulatory responses to hypoglycemia.

5. Conclusion

We investigated the accuracy of PRV as an alternative of HRV for patients with and without hypoglycemia and we proved that PRV is a good feature to evaluate the counter regulatory responses to hypoglycemia. HRV and PRV methods really produce equivalent HRV estimates, without much additional information.

PPG can be used for early diagnosis of hypoglycemia but, motion artifacts issue of PPG should be solved to produce a wearable device for hypoglycemia-induced dead-in-bed syndrome. While there are successful results in the literature on the elimination of these motion artifacts in different settings [36–38], the elimination of artifacts during sleeping has to be addressed yet. Therefore, using PRV as a gold standard for evaluation of hypoglycemia requires more investigation on this subject.

During the IIHT stage, the mean NN interval increased when compared to other stages, which means a decreased heart rate during the IIHT. SDNN which is mathematically similar to the total power of the spectrum was found to be an order of magnitude higher during and after the IIHT in comparison with prior to IIHT. As a measure derived from interval differences, RMSSD was calculated. RMSSD which is an accepted measure of parasympathetic activity and correlates very well with HF of frequency domain analysis was found to be an order of magnitude higher during the IIHT in comparison with other stages. These time domain features averaged values for “during” stages were slightly bigger than “prior” and “after”, but averages of the mean NN, SDNN and RMSSD features should be decreased during IIHT because sympathetic activity increased during IIHT. One of the reasons for this could be the slightly longer recording duration during these stages compared to other stages. Another reasons could be the impact of some noisy sources like power line on sig-

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
<th>HRV</th>
<th>PRV</th>
<th>Correlation coefficient</th>
<th>Bias</th>
<th>Lower limits of agreement</th>
<th>Upper limits of agreement</th>
<th>Standard error</th>
<th>P value</th>
</tr>
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<tbody>
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<td>Before</td>
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<td>0,72</td>
<td>0,99</td>
<td>0,0040</td>
<td>-0,0315</td>
<td>0,0395</td>
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<td>0,05</td>
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<td>0,0022</td>
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<td>-0,0069</td>
<td>0,0146</td>
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<tr>
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<td>LF/HF Ratio</td>
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<td>1,04</td>
<td>0,97</td>
<td>0,0065</td>
<td>-0,0319</td>
<td>0,0188</td>
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<td>-0,0011</td>
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<td>0,07</td>
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<td>0,0083</td>
<td>-0,0173</td>
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<td>0,76</td>
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<td>1</td>
<td>0,0003</td>
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<td>0,0042</td>
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<td>-0,0540</td>
<td>0,0343</td>
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nal (ECG and PPG) and in contrast to frequency domain, the time domain-features are easily able to effect from noisy. Therefore features computed in frequency domain are more useful than time domain. For during the IIHT, magnitude of the LF/HF ratio increased. This increase rejects more sympathetic activity during IIHT.

Recording electrophysiological signals from hypoglycemia patients is difficult and dangerous for patients. All medical doctors and other staff have to be more careful especially in the “during” stage. In experimental hypoglycemia studies on humans, volunteers are informed about the possible side effects of hypoglycemia with the volunteer information sheet which were given them before the test. When the patients read the information sheet and learned that the test may cause a serious side effect, most of them did not attend the study. For this reason, the number of patients was limited. Actually this issue exists in almost all research on the evaluation of the effect of the hypoglycemia with physiological signals [14].

We would like to underline the following biomedical engineering contributions in our study:

1. ECG and PPG signals during three stages of IIHT (before, during, and after) were recorded and analyzed. Information with respect to the effect of hypoglycemia on HRV is available in literature; however the effect of hypoglycemia on PRV information is not available. Thanks to this study PPG and features computed from it can be evaluated.

2. Early detection of hypoglycemia has a vital importance in order to prevent the harmful effects of hypoglycemia on any organ, especially the brain. Our results showed that features computed from PRV are good enough as an alternative of HRV to evaluate the counter regulatory responses to hypoglycemia.

3. Signal analyzing method for HRV from the ECG signal is relatively typical [22];
however analysis methods that we suggested for PPG signals to get its local maximum and PSD have proven to be useful. These algorithms contribute to research that are concerned with the use of PRV for detection of hypoglycemia. In addition, investigation should go on in order to use PPG as a routine method in clinic to detect hypoglycemia.

In conclusion, we have determined that PRV provides an accurate estimate of HRV in patients with and without hypoglycemia and it is very sensitive to hypoglycemia. However to produce a system for early diagnoses of hypoglycemia some other signals like galvanic skin response and body temperature should be recorded.

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