The Effects of Blood Glucose Changes on Frequency-domain Measures of HRV Signal in Type 1 Diabetes

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Abstract—The analysis of time duration between consecutive R waves of electrocardiogram (ECG) is a standard method to evaluate the variations in heart rate. The physiological literature reveals that blood glucose levels modulate the autonomic nervous system (ANS) activity and heart rate variability (HRV) is representative of the cardiovascular autonomic function. In the research described here, a pilot investigation was carried out to investigate the relationship between HRV signal measures derived from ECG and arterial blood glucose changes in a female subject with type 1 diabetes mellitus (T1DM) subject during normoglycemic and mildly hyperglycemic conditions. A CleveLabs BioCapture wireless device was used to acquire ECG signals from a 160 Kg, 59.6 year old female volunteer with type 1 diabetes. The PhysioToolkit Software was used to extract the HRV signal and the Kubios software package was deployed to perform comprehensive HRV signal analysis. This software has an easy-to-use graphical user interface that displays the HRV signal and provides three options to calculate: Time-domain, Frequency-domain and Nonlinear Dynamics parameters from raw HRV signals. In its Frequency-domain analysis section, it provides frequency bands such as VLF (Hz), LF (Hz), and HF (Hz), with LF/HF as an index that reflects the sympathovagal balance of the ANS. ECG data were acquired for 30 minutes during normoglycemic condition and for another 30 minutes during mildly hyperglycemic conditions, while blood glucose levels were measured manually by the subject using a glucometer every 5 minutes. ECG signal segments of 5 minute durations were then processed to extract HRV signals and these in turn were analyzed to provide frequency-domain measures. The results indicated that blood glucose changes were inversely related to LF/HF. For this dataset, it was observed that mean ± std of the LF/HF decreased from 6.0 ± 1.04 to 0.91 ± 0.17 when blood glucose levels increased from 156 ± 22 mg/dl to 202 ± 29 mg/dl. Further investigation is underway to recruit more diabetic subjects to acquire a large dataset and explore the relationships between different HRV signal parameters and blood glucose changes under different glycemic conditions in a comprehensive way.

Keywords: heart rate variability (HRV); frequency-domain analysis; blood glucose levels; type 1 diabetes.

I. INTRODUCTION

Heart rate variability (HRV) measures have a close relationship to sympathetic and parasympathetic nervous system. HRV is an important index to assess and monitor cardiovascular diseases or symptoms such as arrhythmia, coronary artery disease, myocardial infarction, and hypertension [1]. The time interval between consecutive beats in the ECG (tachogram) is the simplest cardiovascular signal to characterize heart rate variability in different analysis domains, and has been applied in various clinical situations [2].

Reduced variations in heart rate, which are indicative of abnormalities in ANS activity, are closely related with increased risk for cardiac events [3, 4]. HRV also gives information about the sympathetic-parasympathetic autonomic balance and about the risk of sudden cardiac death in patients suffering from heart conditions [5]. HRV measurements are easy to obtain and are reproducible, if measured under standardized conditions [6].

HRV signal analysis provides a quantitative marker of the autonomic nervous system (ANS) as the regulation mechanisms of HRV originate from the sympathetic and parasympathetic arms of the autonomic nervous system. In the last ten years, over 2000 articles have been published about HRV [1]. These articles have explored the relationships between HRV and blood pressure, myocardial infarction, nervous system, cardiac arrhythmia, diabetes, respiration, renal failure, gender, age, drugs, smoking, and alcohol consumption [7]. HRV signal analysis seems to become even more popular in quantitative patient data analysis in the future.

The frequency-domain components of the HRV signal, derived from its power spectral analysis, reflect autonomic cardiac modulation and are sensitive indicators of autonomic function in diabetic patients [1]. Spectral analysis of HRV signal can partially distinguish parasympathetic from sympathetic influence on the heart [8] and may provide important insight into the pathogenesis of autonomic neuropathy in hyperglycemia. HRV over a short time span at rest is a simple index of vagal integrity, and is widely used to evaluate the parasympathetic influence of the ANS function in diabetic patients [9].

Based on previous studies related to abnormal cardiovascular autonomic function it has been observed that blood sugar levels and certain components of the HRV signal are inversely related [10]. The HRV of the diabetic patients was characterized by a decreased LF/HF ratio [11]. In this
work the authors documented that the person with type 1 diabetes had a lower LF/HF ratio compared to healthy subjects.

It is now well established that frequency-domain parameters of the HRV signal, namely: the calculated low frequency (LF), high frequency (HF), and the ratio of LF/HF parameters are useful indices of autonomic function. The LF/HF ratio is an index that relates the balance between sympathetic and parasympathetic parts of the autonomic nervous system and hence shows the level of sympathetic dominance (stress) in a subject. HRV is inversely associated with plasma glucose levels and is reduced in diabetics as well as in subjects with impaired fasting glucose levels [12]. In our preliminary observations from the data acquired from our subject with T1DM, it was observed that LF/HF component of the HRV signal reduced with an increase in blood sugar level.

The aim of this pilot investigation was to explore the correlation between frequency domain indices of HRV signal and blood sugar levels in a diabetic subject during 30 min periods of electrocardiographic monitoring.

II. METHODS AND MATERIALS

A. The Investigative Review Board at the University of Texas at El Paso approved the study, and informed consent was signed by the subject.

B. ECG data acquisition

The ECG signals provide the raw data for calculations of the RR intervals, heart rate and then the HRV signals. Wireless technology enables a wide variety of new remote monitoring applications. Wireless monitoring systems transmit data via electromagnetic waves at a defined frequency. Radio frequency (RF) transmission is typically used for this type of applications. In this investigation, the CleveMed BioRadio was used for collecting cardiac data at different blood glucose levels. A 2.4 GHz carrier signal, which transmitted the acquired ECG data to a receiver connected to a laptop or desktop personal computer (PC) was used for this purpose. The ECG signals of the subject were collected in real time during usual daily sedentary work activities.

C. Determination of inter-beat (RR) intervals and heart rate time series

RR intervals were determined from ECG recordings, using the Physio Toolkit Software available at the following website: (http://www.physionet.org/physiotools). This software uses a digitized set of ECG signals and determines the exact time of occurrence of QRS complexes (the part of the ECG waveforms immediately preceding the contraction of ventricles). The time intervals between consecutive heart beats (from the start of a QRS complex to the beginning of the next QRS complex) are then measured in the electrocardiogram. Figure 1 shows the method used to calculate RR intervals. Although custom dictates using the beginning of the QRS complex as the reference (fiducial) point, it should be noted that this point can be difficult to locate in a noisy or low amplitude ECG signal, leading to measurement errors. For determination of inter-beat intervals, it is preferable to use the R-wave peak as the reference point because this will lead into smaller errors.

The choice of the reference point used by the QRS detection algorithm is an important practical consideration in heart rate determination algorithms. PhysioToolkit uses robust integrative techniques that are not sensitive to noise spikes in their QRS detectors.

The software used in this research calls on a specific command to obtain the RR intervals, writes it to the standard output, and saves it in a text file.

D. HRV analysis tool

After extraction of RR intervals the derivation of HRV signal was performed. Once the time between the two successive R-waves in ECG signal has been recorded, the time series was built from all RR intervals, and then was shown as function of time.

The Kubios HRV Analysis software package available from the following link (http://kubios.uku.fi/) was used. This software package was used for analyzing the variability of heart beat intervals. It has an easy-to-use graphical interface that shows the HRV waveform and calculates the time-domain, frequency domain, and non-linear dynamics parameters from the raw HRV signal. Figures 2a and 2b show the RR interval time series during normoglycemic and slightly hyperglycemic conditions, respectively.
ECG signal from the subject was recorded for 5 minutes during each condition using the CleveMed BioRadio device. The raw ECG signal was processed by Physio Toolkt software to estimate RR intervals. After extraction of RR intervals and derivation of HRV signal the Kubios software was used to analyze it.

In the frequency-domain results section of the software, the calculated low frequency (LF), high frequency (HF), and the ratio of LF to HF parameters could be found. The LF/HF is an index that relates the balance between sympathetic and parasympathetic parts of the autonomic nervous system. In this paper the correlation of this parameter with blood glucose levels was explored.

III. DISCUSSION

Heart rate variations can be analyzed not only as a function of time, but also as a function of frequency and amplitude as well as others. Time-domain analysis of HRV signals is based on statistical analysis of the intervals between successive normal QRS complexes. In this research the frequency domain analysis of HRV signals was used to identify the parameters that vary with changes in blood glucose levels in a diabetic subject.

Frequency-domain analysis of HRV signals allows us to distinguish many components of the autonomic nervous system (sympathetic and parasympathetic) as well as the respiratory activity [2]. Once the frequency-domain analysis of the HRV signal is performed, standard HRV signal power spectral parameters are calculated using established FFT-based methods or parametric spectral estimation methods based on autoregressive time series modeling. To determine if the HRV signal is influenced more by the sympathetic or parasympathetic arm of the autonomic nervous system (ANS), its power spectrum density (PSD) was calculated and analyzed. The Kubios software used an autoregressive (AR) method to estimate the PSD. Figures 3a and 3b show the frequency-domain (AR spectrum) of a normal and high blood glucose level in the subject acquired from 15 minutes of HRV data during normoglycemic and slightly hyperglycemic conditions, respectively.

As discussed above, the HRV signal is a popular quantitative marker of the autonomic nervous system, which can be used as a predictor of risk for patients with diabetes. Specifically, HRV signal provides important data in regards to the parasympathetic part of the autonomic nervous system in persons with diabetes. It has been shown by researchers that HRV signal analysis plays an important role in prediction of cardiovascular disease. Some of these findings reveal that the autoregressive moving average modeling technique seems to give better resolution and would be more promising for clinical diagnosis [13]. In previous studies it was shown that HRV level decreases in patients with diabetes [14, 15]. Bellavere and his team showed in their research that the LF and HF components of HRV signal were reduced in patients with diabetes [15].

Tables 1a and 1b show the results of HRV signal analysis performed on 15 minutes of data acquired from our volunteer subject with type 1 diabetes. There is a clear indication that the LF/HF was drastically (more than 6 fold) reduced as the blood glucose level increased from a normoglycemic range to a mildly hyperglycemic value.
This research we used power spectral analysis of HRV signals to explore whether or not any correlation exists between arterial blood glucose levels and frequency-domain parameters of these informative signals. The results confirmed that indeed a relationship exists between the two. Our preliminary findings illustrate that some HRV signal features may be closely associated with blood glucose levels in a subject with T1DM. Here, we observed that LF/HF and blood glucose levels are inversely related to each other. Fijimoto have found that the most remarkable change in HRV as a result of diabetic neuropathy was a decrease in the LF/HF ratio [11]. Previous studies have shown that beat-to-beat variations of the heart rate significantly reduced in persons with diabetes [17-19]. It was reported that a decrease in the LF/HF ratio, i.e., a decline in sympathetic function, is marked in patients with diabetes [11]. In this research, we examined the LF/HF and its relation to changes in blood glucose levels in a diabetic subject. This pilot study on one subject enabled us to explore the general relationship between HRV spectral parameters and sugar levels during normoglycemic and mildly hyperglycemic conditions and helped us gain some initial insights into this approach. In the future research we plan to recruit more subjects with diabetes to refine our approach and improve our results.

The ECG is extensively used as a low cost diagnostic tool to provide significant physiological information. The measurement of ECG signal is convenient and reflects reliably on cardiac health. As such the results of this study may help to extend the use of ECG signal processing in clinical applications.

### REFERENCES


