Correlating Heart Rate Variability to Glucose Levels

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Abstract. A study has been undertaken under the umbrella of a project focusing on noninvasive electrocardiogram (ECG) monitoring. The main goal of the study is to figure out which heart-rate variability parameter has the ability to give the most accurate information for the Glucose level of a patient. The results show that for short term continuous measurements (minimum five minutes) and without extrasystoles or noise in the ECG signal the Root Mean Square Successive Differences parameter has demonstrated better correlation capabilities with a glucose level compared to other parameters. On the other hand, for long term measurements (hourly lengths), the better indicator came to be Standard Deviation of Normal to Normal intervals however, not the combined Standard Deviation of Normal to Normal intervals but the averages of Standard Deviations of Normal to Normal intervals calculated on separate sequences.

Keywords: HRV · Glucose · Correlation · Diabetes · Time domain

1 Introduction

The abilities of the Internet coupled with the Internet of Things Devices in the past years have seen application in many fields. The most prominent being that of healthcare. The state of the art states that measuring glucose levels of patients is only made possible by taking a blood sample. On the other hand, there has been headway in the scientific community by Machine Learning methods on Heart Rate Variability (HRV) measurements to predict glucose levels in a noninvasive manner.

Diabetes is a health issue which many people are facing. The body needs to maintain its blood glucose levels, as failing to do so leads to a condition known as hyperglycemia. Over the long-term high blood glucose levels are associated with damage to the body and failure of various organs and tissues.

There have been studies presenting the ability to detect Diabetes using only ECG signals [19]. Combining both HRV and Continuous Glucose Monitoring (CGM), showed promising results in predicting and detecting Hypoglycemia [5]. Meanwhile, other studies have shown a strong correlation when it comes to the activity of the organism trying to produce insulin with the Frequency Domain indices [10][15][1].

HRV is the fluctuation in the time intervals between adjacent NN heartbeats [13], specified by duration between consecutive Normal (N) heartbeats. The goal of this paper is to further extend these studies into the Time Domain calculations and their relationship with Glucose levels. More precisely, this paper sheds some light on the implications of the standard deviation of the NN intervals (SDNN) and the root mean square of successive differences (rMSSD) in regards to the body's reaction in controlling blood glucose levels. To achieve this, an in house dataset is used, comprising of real patient ECG data with their respected Glucose levels.

HRV parameters index the neurocardiac function and are generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes. It is an emergent property of interdependent regulatory systems that operate on different time scales to help us adapt to environmental and psychological challenges. HRV reflects the regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles [9] [16].

HgA1C test can be used to diagnose diabetes and is usually used to monitor how well diabetes treatment is working overtime. This relatively simple blood test can tell a lot. The test results give a picture of the average blood sugar level over the past two to three months. The higher the levels, the greater the risk of developing diabetes complications. When it comes to the numbers, there's no one-size-fits-all target. HgA1C target levels can vary by each person's age and other factors. The goal for most adults with diabetes is an HgA1C value that is less than 7%. HgA1C test results are reported as a percentage. The higher the percentage, the higher the blood sugar levels over the past two to three months.

The motivation behind this study is to show the hidden connections between patient's HRV parameters and their HgA1C levels. In other words, to show the statistical correlation and significance of every parameter of HRV with the end goal of finding which parameters tie in with blood glucose levels [2].

The rest of the paper is organized according to the following structure. Section 2 presents the related work and findings in the specific field. Section 3 explains the mechanisms used to solve the problem and get to an answer, and Section 4 shows the results and their explanation. An extension of the result interpretation and the elaboration of limitations are discussed in Section 5. Finally, the conclusions and future work are elaborated in Section 6.

2 Related Work

This is not the first time that studies have been conducted to try and detect a correlation between HRV parameters and HgA1C levels. In fact, there are a plethora of works dating back to 2001. On the other hand, the scope of these studies varies a lot and thus a majority of them were filtered out. The scope for this study is the correlation analysis of HRV parameters and HgA1C, in a dataset comprising of patients with ECG and HgA1C measurements.

Gusev et al. [11] give a comprehensive overview of methods and techniques for using ECG and HRV in detection of glucose level in patients. We have developed a platform for reliable and accurate calculation of HRV [17].

The earliest study on HRV correlation with HgA1C dates back to 2001 [7]. This initial study was comprised of 252 patients, and the finding was that there was a negative correlation of the low frequency (LF) parameter with HgA1C. Furthermore, in 2005 Faulkner et al [8] conduct another study this time focusing on Type 1 and Type 2 diabetic patients. The study showed that Type 2 diabetic patients had lower values of Time Domain and Frequency Domain parameters when compared to Type 1 diabetic patients. Also, in 2007 a study was conducted to see how HRV changed in a group of 79 children diagnosed with Type 1 diabetes regarding glycemic control and exercise [4]. The study showed that in this group of patients the logarithm of LF, high frequency (HF), and total power (TP) was negatively correlated with HgA1C.

In more recent years there have been attempts to show a correlation between HgA1C and HRV. The Nagahama Study [20] included 8289 patients with or without diabetes. This study shows consistent results with the previously mentioned study of Type 1 diabetic children [4]. Similarly, the results describe a negative correlation between HgA1C and the logarithmic values of LF and HF. Additionally, it describes a negative correlation of the ration between LF and HF alongside remarks that the correlations were stronger in female subjects compared to their male counterparts.

The Maastricht study [6] that included 2107 patients, describes the Time Domain and Frequency Domain indices to deteriorate between diabetic and non-diabetic patients. In other words, almost all Time Domain and Frequency Domain indices showed a negative correlation with HgA1C. Furthermore, another study in 2019 [3] showed that HRV parameters tended to decline. On the other hand, the study showed a strong negative correlation of SDNN with HgA1C. Additionally, a study in 2020 [21] shows that SDDN, SDANN, VLF, LF, and HF are all negatively correlated with HgA1C. This is an interesting fact since the study comprised of only 200 patients, compared to the 8289 and 2107 patients in the other studies, and was still able to get consistent results.

There have also been attempts at predicting blood glucose levels from HRV in non-invasive monitoring systems [14]. The study shows the possibility of predicting blood glucose levels by analyzing a person's HRV parameters. The paper shows that age is an important factor in the prediction process and that SDNN alongside LF was the most prominent at predicting glucose levels. The method used to predict the variable was the implementation of a Decision Tree where

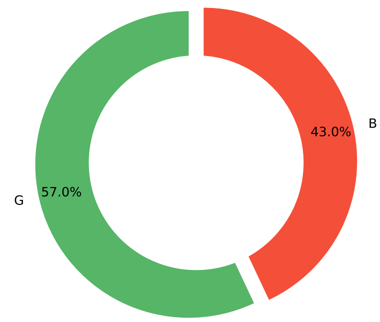

Fig. 1. In-house dataset patient distribution (Data source: Innovation DOOEL)

the before mentioned parameters Age, SDNN, and LF had the most weight in the prediction process.

In a nutshell, the aforementioned papers and studies have indicated that analysis of HRV parameters can predict HgA1C values. From these parameters, we can see that SDNN is consistent in the studies when it comes to Time Domain indices. Furthermore, Frequency Domain indices show a consistent negative correlation with HgA1C levels. Another important information is that the number of participants in the studies varied between 79 and 8289 patients, even though the difference in the population is so great the correlations between HRV and HgA1C showed consistency throughout.

3 Methods

In this study, the HgA1C test values classify the patient for the ability to control the glucose level based on the following guidelines:

- *good regulation (G)*, if the HgA1C level is less than 6.5%.
- *bad regulation (B)*, if the HgA1C level is 6.5% or higher.

An interesting finding was that the latter group (G, B) proved to be a much better distinguishing class when compared to the rest. Other classifications were taken into consideration, for example, the classification according to the diabetes type or classification by changing the "limit" of HgA1C that determines the long term glucose regulation. However, none proved to be a proper discriminator. The results are described further down in the results section.

The study was conducted on 155 patients, out of which 54 are Female and 111 are Male patients. A visual representation of the distribution of glucose regulation classification of these patients is provided in Fig. 1.

The simplest variable to calculate is the SDNN as a square root of variance. Since variance is mathematically equal to the total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. In many studies, SDNN is calculated over a 24-hour period and thus encompasses both short-term HF variations, as well as the lowest frequency components seen in a 24-hour period [12].

RMSSD is the square root of the averaged sum of squared differences in length between all adjacent N-N cycles. These variables are virtually independent of long-term trends and predominantly reflect the vagal tone [18].

The initial view on the data showed a lot of readings where the noise corrupted the ECG, including when the sensor had lost the signal, bad contact of electrodes, or muscle tremor. In these cases, the recordings become not useful. Some patients had many corrupted signals within an hour or even within 5 minutes.

To analyze the patients properly and get relevant results, an algorithm was developed to post process the data and further "clean" the data of corrupted parts. With that said, the results proved promising. However, it was noticed that the algorithm would leave a lot of small parts of a signal in the final result. These small parts consisted of NN intervals shorter than 3 seconds, some went on for 3 minutes while the majority kept below 10 seconds.

This results in two methods, identified as continuous uninterrupted measurements or combined measurements. Since our experience showed that the length of continuous uninterrupted measurements is very small to determine an overall conclusion about a longer behavior of the organism to regulate the glucose level, such as the three-months average of glycated hemoglobin (HgA1C), in this paper we will analyze only methods of combined measurements.

A combination of these "clean" parts is possible through two methods: by constructing a longer measurement connecting the clean parts, or by calculating the HRV parameters on separate clean parts and then combining the statistical results. These methods we introduce are defined as:

- *Averages* - this method takes into account all the segments (minimum five minutes) of clear signal and calculates the SDNN and rMSSD of "clean" parts. Then, it calculates the average value for the analyzed measurement period.
- *Combined* - calculates the SDNN and rMSSD after connecting all "clean" parts into one measurement.

The analysis includes the visualization of the distribution of each, charting a simple line-area plot. Additionally, a Kernel Density Estimator displays the density of each group's concentration. Finally, a box and whiskers plot is used to present a different perspective on the data.

4 Results

4.1 Combined Calculation Method

Figure 2 and Fig. 3 show the HRV distribution in both classes correspondingly for SDNN and RMSSD for long-term measurements. They show that SDNN and RMSSD in long term recordings with the *combined method* do not make a good parameter for distinguishing between G and B classes of patients.

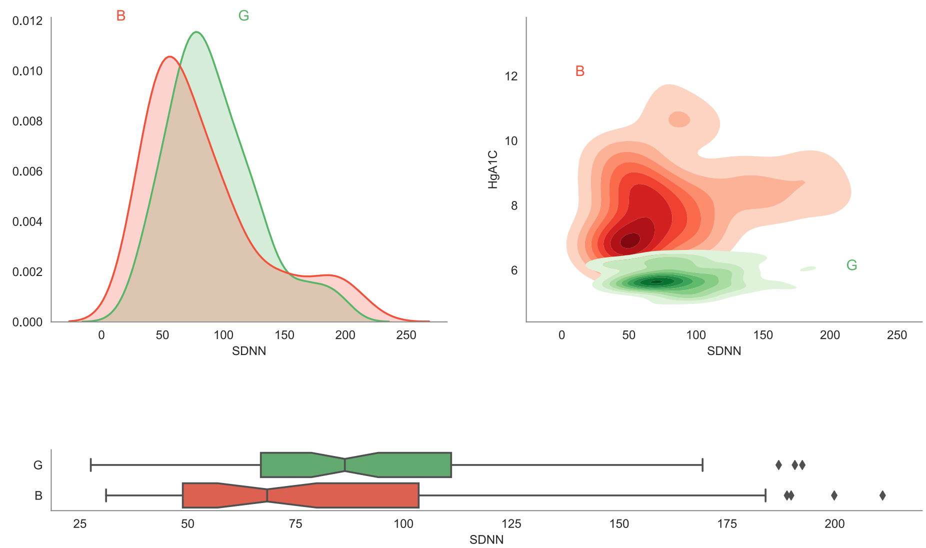

Fig. 2. Combined SDNN in long-term recordings (Data source: Innovation DOOEL)

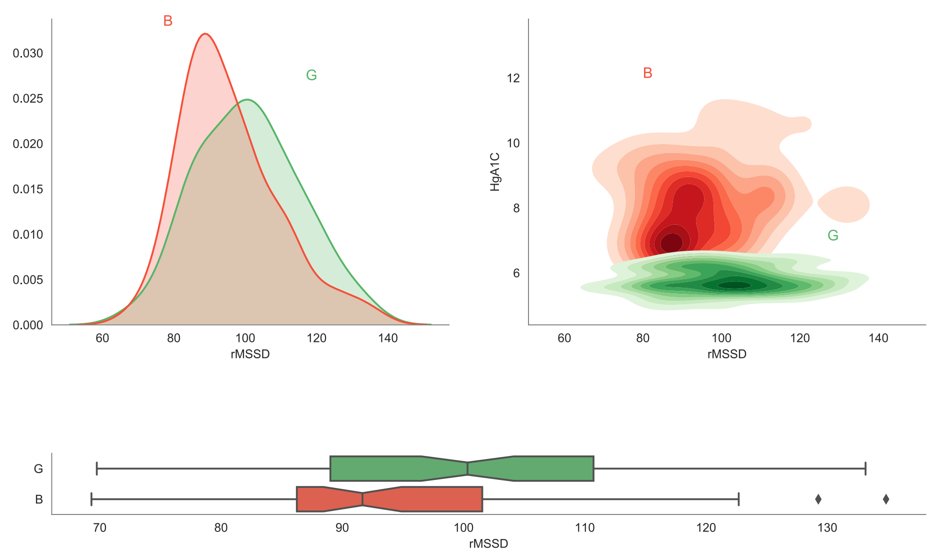

Fig. 3. Combined RMSSD in long-term recordings (Data source: Innovation DOOEL)

4.2 Averages Calculation Method

Figure 4 and Fig. 5 display the Line-Area distribution curves and HRV distribution in both classes correspondingly for SDNN and RMSSD for long-term measurements. Figure 4 shows that SDNN in long term recordings with the *aver-*

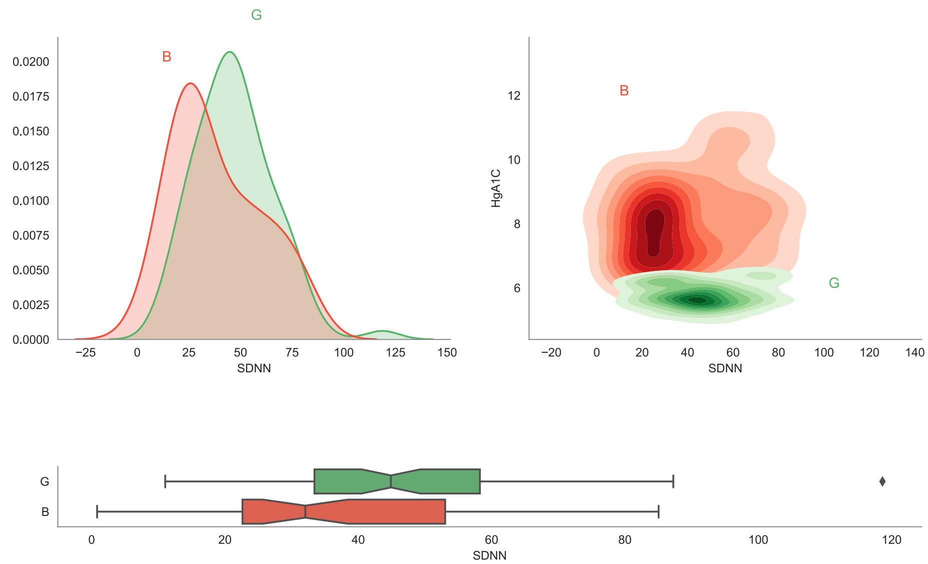

Fig. 4. Average SDNN in long-term recordings (Data source: Innovation DOOEL)

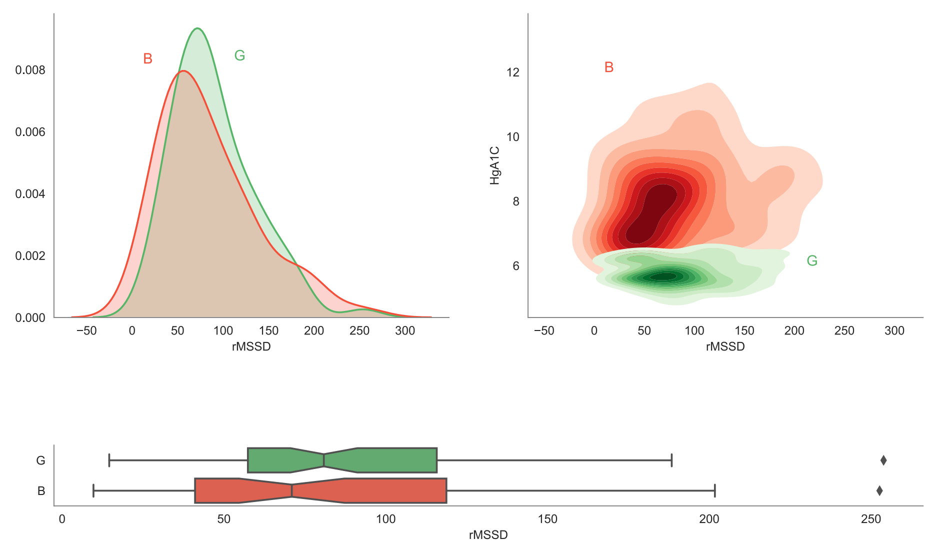

Fig. 5. Average RMSSD in long-term recordings (Data source: Innovation DOOEL)

ages method makes a good parameter for distinguishing between G and B classes of patients, while Figure 5 shows that the RMSSD in long term recordings with the *averages method* does not make a good parameter for distinguishing between G and B classes of patients.

5 Discussion

In retrospect, the Standard Deviation of Normal-to-Normal intervals has proven to be closely correlated with other biological processes. Bahremand et al. in their research [3] utilize a similar method to distinguish between diabetic and nondiabetic patients. This study compares two groups of patients divided by HgA1 C value, with the cut-off point at 7%. Their findings include a clear negative correlation between HgA1C and SDNN. In addition to SDNN, this paper shows that rMSSD is also negatively correlated with HgA1C.

Furthermore, there is evidence that the deteriorating ability of the body is related to lower Heart Rate Variability indices. In the Maastricht Study [6], including 2107 patients, it was shown that Time Domain indices had a negative tendency with the worsening glucose control of the body. Faulkner et al. [8] display the same consistent result even though the number of patients was significantly lower totaling to 132 patients. Consistent results are also demonstrated in the study conducted by Yu et al. [21]. Similarly, this study indicates that generally HRV does deteriorate among diabetic patients. However, the paper does distinguish SDNN from being strongly correlated with HgA1C. The current results fit these findings and also indicates that the HRV parameters subject to the study: SDNN and rMSSD; display a negative tendency moving from none diabetic to diabetic patients.

There is also a study performed by Novikov et al. [14] indicating the importance of SDNN and LF in devising a mechanism for detecting high blood glucose levels in non-invasive glycemic monitoring systems. The study describes how SDNN is negatively correlated with blood glucose levels, this is consistent with the current study where SDNN and rMSSD decline between the two groups of patients.

As mentioned before, the study deals with a group of 155 patients. Connecting to the previous related works one can see that the number of subjects satisfies the statistical needs. To narrow it down, the study takes SDNN and rMSSD in exploring their relationships with HgA1C levels in the patients' blood. To understand the statistical significance, these parameters posses a logistic regression was run. In both short and long term recordings, SDNN and rMSSD showed a p-value below 5% making them statistically significant in predicting HgA1C.

6 Conclusion

Taking into consideration the aforementioned analysis coupled with the visual explanation and backed up by other works, we can see an emerging pattern. When it comes to differentiating between none diabetic and diabetic patients, the cut-off value of HgA1C being 7%, SDNN and rMSSD show a negative correlation with the bodies deteriorating ability for long term glucoregulation.

Firstly, the data displays a sort of bias when it comes to the length of the recordings. The analysis of the short recordings tends to gravitate more towards rMSSD being a bigger factor in distinguishing between the two patient groups.

Secondly, patient data on longer recording times revealed that in contrast with the short term recordings, SDNN was better at distinguishing between the two patient groups. This is best seen by the distribution of the data, where the Kernel Density Plots (KDE) clearly portray a shift in the data. However, this is only true for the method of calculation on the average over all the SDNNs of each segment.

Thirdly, when it came to statistically measuring the level of impact for each parameter towards HgA1C the logarithmic scaled correlations and base correlations showed to vary at some points. The short term recording logarithmic rMSSD possessed a stronger correlation compared to its base correlation. Similarly, converting SDNN to its logarithmic form increased the power of the correlation for Long Term recordings.

To conclude, the in house dataset has proven to display consistent readings with other related work in the field. The number of patients taken into consideration is between both extremes of all the current studies. It was discovered that rMSSD in short term recordings is better at distinguishing between none diabetic and diabetic patients, while SDNN for longer recording times. Additionally, the logarithmic values of rMSSD in short term recordings had stronger correlations and the same goes for SDNN during longer recordings sessions.

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