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Heart Rate Variability as a Potential Non-Invasive Measure of Blood Glucose Levels

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Abstract

Background: Diabetes is a group of metabolic diseases that cause severe chronic complications and is approaching epidemic proportions worldwide. Ideal management of diabetes involves non-invasive glucose monitoring. Heart rate variability parameters may be viable as non-invasive, prospective markers of blood glucose.

Methods: Healthy members of the general public (n = 25; 27.56±9.26 years of age) uninhibited by regular medications or chronic illness were recruited. Blood glucose levels and heart rate variability were assessed at the start, middle, and end of a six-hour period using self-monitoring of blood glucose techniques and ten-minute electrocardiogram, respectively. Correlation analysis was performed on data collected at three time points (10:00am, 1:00pm, and 4:00pm).

Results: All correlations reported are significant ($p < 0.05$). The change in blood glucose levels from fasting (10:00am) to postprandial (1:00pm) was negatively correlated with fasting low frequency power. Postprandial glucose levels were negatively correlated with fasting low frequency power, postprandial low frequency power, and postprandial total power. The change in blood glucose levels from postprandial (1:00pm) to normal (4:00pm) was positively correlated with fasting low frequency power, fasting low frequency to high frequency ratio, as well as postprandial low frequency and postprandial total power.

Conclusion: Frequency-domain heart rate variability parameters may be useful in predicting the magnitude and direction of acute fluctuations in blood glucose levels, and thus could be developed as non-invasive markers of blood glucose.

Keywords: Autonomic nervous system; Blood glucose; Diabetes; Heart rate variability; Metabolic disorders; Hyperglycaemia; Renal failure; Blindness; Neuropathy; Cardiovascular disease; Diabetic neuropathyhealing properties

Abbreviations: BGL: Blood Glucose Level; BP: Blood Pressure; CGM: Continuous Glucose Monitoring; DM: Diabetes Mellitus; ECG: Electrocardiogram; HRV: Heart Rate Variability; HF: High Frequency; LF: Low Frequency; NSW: New South Wales; TP: Total Power

Introduction

Diabetes is considered a leading epidemic of the 21st century, affecting 422 million individuals worldwide [1]. It is a group of metabolic disorders characterised by chronically high blood glucose levels (BGLs), a condition which is also known as hyperglycaemia [2]. Despite the well-known associations between sedentary lifestyles and metabolic disorders such as diabetes, adherence to recommended exercise guidelines remains low [3]. Complications such as renal failure, blindness, and neuropathy can arise when hyperglycaemia is undetected or poorly managed [4] as certain cells in the renal nephrons, eyes, and neurons of the autonomic nervous system are susceptible to hyperglycaemic damage [5]. Consequently, the progression of diabetes is associated with a decline in autonomic modulation of the heart and an inevitable increase in the risk for cardiovascular disease [6-8]. The literature agrees the most effective means of reducing complications of diabetes is stringent control of BGLs [9,10].

Problematically, many people with diabetes are unaware of their condition – as many as 75% of diabetes populations in some regions [11]. Additionally, glycaemic control is poor even in populations of those who are aware of their condition; in a large-scale study, roughly half of a diabetes population failed to maintain their BGLs at the recommended healthy level [12]. Limitations such as the invasive nature of all commercially

successful measures of blood glucose may explain these alarming statistics [13]. Invasive procedures, such as drawing a sample of blood using a lancet device and glucometer, are commonly used for their accuracy [14,15]. However, the associated pain presents a psychological barrier to self-monitoring of blood glucose (SMBG) [16]. A non-invasive marker of BGLs may improve patient compliance with SMBG and facilitate glycaemic control in diabetes [17,18].

Heart rate variability (HRV) parameters reflect autonomic output of the nervous system and can be recorded using a non-invasive electrocardiogram (ECG) [19]. In a healthy human, the autonomic nervous system modulates control over the heart via two counterregulatory branches – the sympathetic and parasympathetic systems – though this control is reduced in diabetes [20-23]. HRV is one of the most commonly used measures of autonomic activity [24] and is studied widely as a marker for sudden cardiac death after myocardial infarction and as an indicator of diabetic neuropathy [25-27]. HRV can be extrapolated from short-term ECG recordings using advanced computational methods. Spectral techniques are used to determine the total power of frequency-domain HRV, and this in turn can be split into different HRV parameters based on predefined frequency bands, such as low frequency and high frequency. These parameters reflect the contributions of sympathetic and parasympathetic systems to autonomic modulation of the heart.

HRV measures may have further applications in the evaluation of glycaemia as acute changes in metabolic activity are marked by autonomic responses. Insulin, for one, plays an important role in mediating the effect of glucose fluctuations on sympathetic activity [28,29]. The long-term effects of abnormally high BGLs on autonomic function are well established in the literature, and some studies have investigated acute correlations between HRV and BGLs [30-36]. However, no study to date has successfully implemented autonomic markers alone as predictors of BGL fluctuations. Previous research conducted by our research unit [33] has identified several key correlations between HRV parameters and BGLs measured concurrently in a sample of type 1 and type 2 diabetes but found no correlations of significance within a healthy control group. This may be because healthy individuals, by nature, experience very little glycaemic change over short-term periods. As such, the present study intends to continue this research by assessing HRV and BGLs across a six-hour time period, including at 10:00am, 1:00pm, and at 4:00pm, with a focus on healthy individuals. In this paper, we aim to justify the development of HRV measures as non-invasive markers of BGLs.

Materials and Methods

Subjects

A total of 25 healthy individuals were recruited from the local Sydney metropolitan population for this study. Participants were excluded from the study if they suffered from a chronic health condition, were on regular medication, smoked > 10 cigarettes per day, consumed > 10 standard drinks per day, or were pregnant. To comply with ethics protocol, participants were also screened for high blood pressure and were removed from the study if systolic blood pressure exceeded 160 mmHg or if diastolic blood pressure exceeded 100 mmHg. No recruited individual was excluded from the study. All participants were required to sign a consent form before the experiment, as well as abstain from food, drink (except water), nicotine, and alcohol for eight hours prior to study commencement [37,38]. The study protocol was conducted in a controlled laboratory setting and was approved by the University of Technology Sydney Human Research Ethics Committee (HREC: 2014000110).

HRV and BGLs were assessed at the start (10:00am), middle (1:00pm), and end (4:00pm) of a six-hour period using 10-minute ECG recordings and blood glucose 'fingerpicks', respectively. The first assessment provided baseline measurements as participants were in a fasting state and was always conducted at roughly 10:00am. The second and third assessments always occurred three hours after one another, at approximately 1:00pm and 4:00pm. Between testing periods, participants were free to resume their daily activities and consume regular meals, as suggested by the literature [39]. Glucose peaks observed after a normal, daily meal are similar to glucose peaks after a two-hour glucose tolerance test [40]. However, differences in meal composition between individuals can confound post-prandial glucose profiles [41] and, as such, participants were required to report all food and drink consumed during the study so that kilojoule intake could be used as a covariate in the correlation analysis. Participants could be tested one-hour either side of these time points, i.e. the 10:00am assessment could be conducted anytime between 9:00am and 11:00am. HRV parameters are known to fluctuate over the day due to circadian rhythms [42], and the literature suggests restricting these 'testing windows' to no longer than two hours to standardise the time points between participants [43].

At each time point, HRV was recorded for 10 minutes using a three-lead FlexComp Infiniti (SA7550) encoder (Thought Technology Ltd., Montreal, Canada) at a sampling rate of 2048 Hz, using the Einthoven electrode placement [44]. Of the various short-term HRV recordings, 10-minute ECG recordings have the best reproducibility and provide an accurate representation of autonomic activity [45]. SMBG techniques were used to assess BGLs as their invasive nature is cause for significant noncompliance in type 2 diabetes [46], which constitutes 85-90% of all cases of diabetes [47].

The aim was to investigate whether HRV was correlated with BGLs as measured by current SMBG techniques. As such, BGLs were assessed using an ACCU-CHEK® Performa II glucometer [48] (Roche Diagnostics GmbH, Mannheim, Germany) with a finger prick test applied to the ring finger on the dominant

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hand [49]. Blood pressure (BP) was measured pre-study and post-study using an OMRON HEM-7000 automated BP monitor (OMRON, Kyoto, Japan) after each participant had been allowed to rest in a seated position for five minutes [37]. Due to the dynamic nature of BP, the mean of the three BP recordings was used to provide better accuracy, with a two-minute rest interval between each recording [37,50].

Processing heart rate variability parameters

Of the studies that have investigated acute associations between HRV and BGLs, frequency-domain HRV parameters have been favoured as they reflect specific types of autonomic modulation [32,33]. These parameters were extrapolated from the ECG after the raw ECG data was processed by a band pass filter set to 5-30 Hz using the Kubios HRV software [51,52]. This reduced artefacts such as background noise present during the recordings [53]. From the ECG recording, a time-series graph was generated by plotting the R-R values which denote the distance in milliseconds between each contraction or main electrical depolarisation of the heart [54]. The time-series graph was subject to a fast Fourier transform to produce a power frequency spectrogram [38,54,55].

Within the spectrogram, three distinct frequency bands were identified: low frequency (LF) power (0.04-0.15 Hz), high frequency (HF) power (0.15-0.4 Hz), and total power (TP), which was represented by the entire spectrogram (0.00-0.4 Hz) [55,56]. LF power reflects sympathetic activity, the branch of the autonomic nervous system dedicated to the fight or flight response; HF power reflects parasympathetic activity, the opposing branch associated with the rest and digest phase; and TP reflects overall autonomic activity [56,57]. The LF: HF ratio was also calculated as an index of sympathovagal balance [58]. LF, HF, and TP parameters were all-natural logarithm transformed as their distribution was revealed to be highly skewed, though this is typical of HRV studies [37,59,60].

Statistical analysis

A one-way analysis of variance was used to determine whether the BGLs and HRV parameters changed significantly between the three assessments. Partial Pearson's correlation was employed to determine associations between HRV parameters and BGLs, adjusting for kilojoule intake as a covariate. As no kilojoule information was available for the fasting assessment (10:00am), Pearson's correlation was used instead. Significance level was set at $p < 0.05$. The HRV parameters used in the analysis included LF power, HF power, the LF: HF ratio, and TP. The blood glucose variables were defined as fasting blood glucose (BGL1), postprandial blood glucose (BGL2), normal blood glucose (BGL3), the change from fasting to postprandial (ΔBGL 1-2), the change from postprandial to normal (ΔBGL 2-3), and the change from fasting to normal (ΔBGL 1-3).

Results

Descriptive statistics

Data was collected from 25 participants at three different time points across the day and included in the statistical analysis. The mean age of the sample was 27.56 ± 9.26 years, with a sex breakdown of 44% males, and the mean body mass index was 24.18 ± 3.39 kg/m2. The results of the analysis of variance are presented in Table 1. BGLs increased significantly from fasting (10:00am) to postprandial (1:00pm) ($p < 0.01$) and fasting to normal (4:00pm) ($p = 0.02$) after all participants consumed a regular meal. Additionally, LF and HF values decreased from fasting to postprandial, though only the change in LF power was significant ($p < 0.01$). The decrease in TP from fasting to postprandial ($p < 0.01$) was expected as it reflects both LF and HF units.

Table 1: Changes in mean heart rate variability parameters and blood glucose levels between assessments.

					p	
Variable	**Test 1 (10:00am)**	**Test 2 (1:00pm)**	**Test 3 (4:00pm)**	**Test 1 vs 2**	**Test 2 vs 3**	**Test 1 vs 3**
BGL (mg/dL)	91.17±11.53	106.31±30.63	101.08±27.75	<0.01*	0.22	0.02*
LF (ms2)	6.97±0.88	6.65±1.01	6.84±0.83	<0.01*	0.17	0.34
HF (ms2)	5.93±1.20	5.64±1.26	5.93±0.96	0.08	0.08	0.98
LF: HF	1.04±1.09	1.00±0.94	0.92±1.05	0.76	0.61	0.24
TP (ms2)	7.47±0.87	7.12±0.96	7.35±0.69	<0.01*	0.07	0.32

Key: * Statistically significant ($p < 0.05$); BGL: Blood Glucose Level; HF: High Frequency; LF: Low Frequency; mg/dL = Milligrams per deciliter; ms2: Millisecond squared; TP: Total Power. Data presented as mean ± standard deviation. LF, HF, and TP values are presented as the natural logarithm.

Correlation analysis

Correlation analysis was used to determine associations between HRV parameters and BGL variables, in which kilojoule intake was applied as a covariate (Table 2). Several correlations were observed between LF power and TP from the normal assessment and BGLs that were observed earlier in the study (ΔBGL 1-2, BGL2, ΔBGL 2-3). These findings were omitted from Table 2 as they are retroactive results, indicating that BGLs have an effect on HRV. This is not relevant to the present study, which is interested in the pursuit of prospective associations between HRV and BGLs, i.e. the capacity for HRV to predict future or concurrent glucose levels or changes.

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Table 2: Associations between heart rate variability parameters and blood glucose levels

Parameter		BGL1 (10:00am)	ΔBGL 1-2	BGL2 (1:00pm)	ΔBGL 2-3	BGL3 (4:00pm)	ΔBGL 1-3
Fasting (10:00am)	LF						
	r	-0.33	-0.53	-0.51	0.45	-0.21	-0.1
	p	0.11	<0.01*	0.01*	0.02*	0.31	0.62
	HF						
	r	-0.11	-0.17	-0.16	-0.09	-0.25	-0.28
	p	0.61	0.41	0.43	0.66	0.23	0.18
	LF: HF						
	r	-0.15	-0.24	-0.23	0.46	0.1	0.22
	p	0.48	0.25	0.28	0.02*	0.62	0.29
	TP						
	r	-0.26	-0.4	-0.38	0.22	-0.26	-0.2
	p	0.2	0.05	0.06	0.29	0.22	0.34
Postprandial (1:00pm)	LF						
	r	-	-	-0.5	0.51	-0.16	-0.05
	p	-	-	0.01*	0.01*	0.46	0.82
	HF						
	r	-	-	-0.32	0.26	-0.16	-0.12
	p	-	-	0.12	0.22	0.47	0.58
	LF: HF						
	r	-	-	-0.12	0.22	0.04	0.11
	p	-	-	0.58	0.31	0.87	0.62
	TP						
	r	-	-	-0.44	0.42	-0.17	-0.09
	p	-	-	0.03*	0.04*	0.44	0.69
Normal (4:00pm)	LF						
	r	-	-	-	-	-0.19	-0.03
	p	-	-	-	-	0.36	0.9
	HF						
	r	-	-	-	-	-0.12	-0.16
	p	-	-	-	-	0.57	0.47
	LF: HF						
	r	-	-	-	-	-0.04	0.12
	p	-	-	-	-	0.84	0.58
	TP						
	r	-	-	-	-	-0.19	-0.07
	p	-	-	-	-	0.38	0.73

Key: * Statistically significant ($p < 0.05$); BGL: Blood Glucose Level; HF: High Frequency; LF: Low Frequency; TP: Total Power; Δ = Change in. Retroactive findings were not presented in this table as this was a prospective analysis. The intention was to determine whether HRV parameters were related to concurrent or future BGLs or BGL changes. Thus, it is not relevant to this study to observe correlations between HRV parameters and BGLs that were recorded in earlier time points.

All correlations stated are significant ($p < 0.05$). Fasting LF power was negatively correlated with postprandial BGLs ($r = -0.51$, $p = 0.01$) as well as the change in BGLs from fasting to postprandial ($r = -0.53$, $p < 0.01$), and positively correlated with the change in BGLs from postprandial to normal ($r = 0.45$, $p = 0.02$). Fasting LF: HF ratio was also positively correlated with the change in BGLs from postprandial to normal ($r = 0.46$, $p = 0.02$). Postprandial LF power was negatively correlated with postprandial BGLs ($r = -0.50$, $p = 0.01$) and positively correlated with the change in BGLs from postprandial to normal ($r = 0.51$, $p = 0.01$). Additionally, postprandial TP was negatively correlated with postprandial BGLs ($r = -0.44$, $p = 0.03$) and positively correlated with the change in BGLs from postprandial to normal ($r = 0.42$, $p = 0.04$).

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Table 3: Regression analysis for postprandial blood glucose levels, and the significantly correlated heart rate variability parameters

Regression Summary for Dependant Variable: Postprandial BGL						
$R = 0.524$; $R^2 = 0.275$; AR = 0.171; F (3,21) = 2.652						
p < 0.075, SE of Estimate = 1.548						
Variable	β	SE of β	B	SE of B	t	p
Intercept			11.607	2.934	3.956	<0.001
Fasting LF	-0.31	0.459	-0.6	0.888	-0.676	0.506
Postprandial LF	-0.548	0.737	-0.926	1.244	-0.744	0.465
Postprandial TP	0.366	0.547	0.651	0.974	0.669	0.511

Key: BGL: Blood Glucose Level; LF: Low Frequency; SE: Standard Error; TP: Total power

As there were multiple significant correlations between BGLs at time point two and HRV variables, a multiple regression analysis was performed to determine which HRV parameter was the strongest predictor of BGLs (Table 3). The regression retained all three of the originally entered variables (fasting LF, postprandial LF, postprandial TP), though it was found to be non-significant overall ($p < 0.075$). Similarly, multiple HRV variables were significantly correlated to the change in BGLs between postprandial and normal; and, as such, a multiple regression analysis was performed to determine which HRV parameter was the strongest predictor (Table 4). The regression retained all four of the originally entered variables (fasting LF, fasting LF: HF ratio, postprandial LF, and postprandial TP), and had an overall significance of $p < 0.023$ ($p < 0.075$).

Table 4: Regression analysis for change in blood glucose between postprandial and normal, and significantly correlated heart rate variability parameters.

Regression Summary for Dependant Variable: ΔBGL 2-3						
$R = 0.648$; $R^2 = 0.420$; AR2 = 0.304; F (4,20) = 3.615						
p < 0.023, SE of Estimate = 0.977						
Variable	β	SE of β	B	SE of B	t	p
Intercept			-4.311	1.975	-2.183	0.041
Fasting LF	-0.248	0.423	-0.331	0.563	-0.587	0.564
Fasting LF: HF	0.573	0.291	0.613	0.311	1.972	0.063
Postprandial LF	-0.004	0.927	-0.005	1.077	-0.004	0.997
Postprandial TP	0.655	0.82	0.802	1.004	0.799	0.434

Key: BGL: Blood Glucose Level; LF: Low Frequency; SE: Standard Error; TP: Total Power; Δ: Change in

Together, these four variables explained 42.0% of the variance in the change in BGLs postprandial and normal ($F = 3.615$; $DF = 4, 20$; $p < 0.023$; $R = 0.648$; $R2 = 0.420$; $AR2 = 0.304$). Furthermore, the retained variables did not present as independently significant predictors, although fasting LF: HF approached statistical significance ($p = 0.063$).

Discussion

The present study assessed various HRV parameters and indices of blood glucose in healthy participants. The observed values for LF power, HF power, LF: HF ratio and TP in this sample were all similar to those reported in the literature of healthy samples, including those recorded in a fasting state [32-34]. Additionally, the mean BGLs in the sample were within the healthy range, as expected [2]. The rise in blood glucose from the fasting to the postprandial assessment was difficult to anticipate, given that participants were free to eat at any point after the fasting assessment. Peak BGLs are achieved 40-60 minutes post-meal [61,62]. Therefore, participants' BGLs may have returned to normal by the second assessment, depending on when they ate.

LF power decreased significantly from the fasting assessment to the postprandial assessment, though no significant change was seen in HF power. These are consistent with patterns seen in LF and HF power when comparing morning fasting HRV with afternoon postprandial HRV [31]. The study conducted by Armstrong and colleagues [63] on young, healthy adults is also in agreement with these findings as they reported no change in HF from the morning to the afternoon. Given that TP reflects LF and HF power, the decrease in TP was consistent with expectations.

Previous literature on the short-term associations between HRV parameters and BGLs present somewhat conflicting findings. Rothberg and colleagues concluded there are no associations between postprandial HRV and postprandial BGLs in healthy adults [33]. This conflicts with the present study which identified several correlations in the postprandial assessment. One explanation for this is that Rothberg and colleagues standardised the time in which measurements were taken to 40-60 minutes after eating, whilst the present study allowed

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participants to eat at any point between assessments. As such, participants' BGLs may have returned to normal levels in the present study. Our study agrees with Rothberg and colleagues in that there are no significant correlations between fasting BGLs and HRV. However, Lutfi & Elhakeem [32] contend that fasting BGLs are positively correlated with fasting HF power ($r = 0.33$, $P = 0.031$) and negatively correlated with fasting LF: HF ratio ($r = -0.33$, $P = 0.035$). Inconsistencies such as this highlight the need for further investigation into the acute correlations between HRV parameters and BGLs.

The literature proposes that insulin may play a key role in the physiology of acute correlations between HRV and BGLs. Following the consumption of a meal, the absorption of nutrients into the blood via the gastrointestinal tract is associated with a small increase in plasma insulin, even before there is a rise in blood glucose [64]. This is part of the pre-absorptive, or cephalic phase. Research has shown that activation of the autonomic nervous system during both the pre-absorptive and absorptive phases of insulin are important in determining post-prandial insulin activity [65]. As such, changes in HRV may precede the release of insulin [65]. This is relevant because insulin enacts a stimulatory effect on the sympathetic nervous system [66,67], which can be measured by LF power. This may support why LF is inversely proportional to BGLs in healthy subjects with normal autonomic function [30,34,35]. In general terms, as insulin levels increase, sympathetic activity increases and BGLs decrease. In the present study, this was only observed in the postprandial assessment, where LF power was significantly and inversely associated with BGLs at that time point.

Significant correlations were observed between fasting LF power and the postprandial BGLs, as well as the change in blood glucose from fasting to postprandial levels. Additionally, fasting LF power and fasting LF: HF ratio were associated with the change in blood glucose from postprandial to normal levels. The finding that LF power is correlated with BGLs observed in subsequent assessments is novel and indicates the potential for LF power to predict changes in BGLs, specifically after digestion has concluded and BGLs are returning to normal levels. Moreover, postprandial LF power was negatively correlated with postprandial BGLs, and positively correlated with the change in blood glucose from postprandial to normal levels. As a reflection of LF power, TP showed similar correlations. The correlations between HRV parameters and the magnitude and direction of glucose fluctuations were not previously evident in the literature and may indicate the potential for HRV to be developed into a marker of BGLs.

The present study made certain improvements on the previous study design [33]. Recording kilojoule intake and applying it as a covariate in the analysis was an important method of controlling for the different diets of the participants, which can impact glucose profiles; future studies should also compensate for this. Another strength of the study design was standardising the time points in which participants were assessed to two-hour time windows.

Improvements could be made by sampling a broader range of ages, and age should also be controlled as a covariate due to its influence on HRV parameters [68,69]. Larger-scale studies have had more success in detecting the small effect size seen between fasting HRV parameters and BGLs; therefore, the present study could have benefited from a larger sample size [34]. One of the concerns raised in this study was the limited ability of glucose meters to track changes in glucose profiles over time. If HRV were developed as a suitable replacement for current invasive SMBG techniques, it could also provide continuous glucose data and glucose fluctuations if recorded using a wearable ECG, such as a Holter monitor.

Conclusion

Current standards in the management of diabetes and monitoring of abnormal BGLs are inadequate considering the scope of diabetes and hyperglycaemia. As a leading epidemic of the 21st century, more rigorous technologies need to be developed for people with diabetes to improve patient compliance with stringent glycaemic control. There is a growing interest in the development of non-invasive, continuous markers of BGLs that may aid in diabetes management. Generally, the aim of non-invasive glucose markers is to combine data derived from biosensors with continuous glucose monitoring data to increase the precision of the glucose level prediction [70].

For example, a novel algorithm presented by Cichosz and colleagues has shown promising results by combining information from a Holter monitor with concurrent values from a continuous glucose monitoring system. The algorithm detected 16/16 hypoglycaemic events in type 1 diabetes patients with a sensitivity of 79% and a specificity of 99% [71]. This study represents an appealing line of research, as it aims to overcome some of the current problems people with diabetes face. Current SMBG is costly [16], though a portable ECG, such as a Holter monitor, may present a reduced financial burden and, at the very least, would provide a non-invasive option. The R-waves from an ECG, used in the determination of HRV parameters, have distinct profiles that make them suitable for detection by computer algorithms [72]. Consequently, the commercialization of an inexpensive portable ECG may be expanded.

This study concludes that HRV parameters measured at different time points may be useful in predicting the magnitude and direction of changes in BGLs. The development of HRV parameters as non-invasive markers of BGLs represents an optimistic line of research and could be critical in managing the diabetes epidemic. Such research could lead to the development of an algorithm capable of predicting BGLs in real time using purely non-invasive recordings from an ECG.

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