Received: 3 October 2020 | Revised: 10 November 2020 | Accepted: 28 November 2020

DOI: 10.1111/dom.14287

BRIEF REPORT

WILEY

Rapid glucose rise reduces heart rate variability in adults with type 1 diabetes: A prospective secondary outcome analysis

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Abstract

To investigate differences in heart rate variability (HRV) during oral glucose tolerance tests (OGTTs) in response to the rate of change in glucose and to different glycaemic ranges in individuals with type 1 diabetes. This was a single-centre, prospective, secondary outcome analysis in 17 individuals with type 1 diabetes (glycated haemoglobin 53 ± 6.3 mmol/L), who underwent two OGTTs (after 12 and 36 hours of fasting) investigating differences in HRV in response to rapid glucose increases/decreases and different glycaemic ranges during OGTT. Based on the rate of change in glucose level, the variables heart rate ($P < 0.001$), square root of the mean standard difference of successive R-R intervals ($P = 0.002$), percentage of pairs of R-R intervals with >50 ms difference ($P < 0.001$) and corrected QT interval ($P = 0.04$) were significantly altered, with HRV particularly reduced during episodes of rapid glucose rises. Glycaemic ranges during OGTT had no impact on HRV ($P < 0.05$). Individuals with type 1 diabetes showed no changes in HRV in response to different glycaemic ranges. HRV was dependent on the rate of change in glucose, especially rapid increases in glucose level.

KEYWORDS
autonomic regulation, heart rate variability, oral glucose tolerance test, type 1 diabetes

1 | INTRODUCTION

Assessment of heart rate variability (HRV) has received attention as a non-invasive subclinical method to assess autonomic regulation in individuals with type 1 diabetes.[1–3] Vinik et al[4] showed that chronically reduced HRV is associated with increased risk of arrhythmia, myocardial infarction, sudden cardiac death and cardiac autonomic neuropathy in people with type 1 and type 2 diabetes. Impaired cardiac autonomic modulation is a progressive phenomenon that is associated with hypoglycaemia and overall glycaemic control, however, the mechanisms behind the development of this alteration are not yet fully understood.[5,6]

Poor glycaemic control was also shown to be associated with increased glycaemic variability, however, whether this association also induces acute cardiac responses has still not been investigated in detail. To address this knowledge gap, we assessed HRV during oral glucose tolerance tests (OGTTs) following 12- and 36-hour fasting periods in individuals with type 1 diabetes.

2 | METHODS

2.1 | Setting and study population

This was a single-centre, prospective, secondary outcome analysis performed in adults with type 1 diabetes. The study protocol was approved the local ethics committee (30-238 ex 17/18) and registered at the German Clinical Trials Register (drks.de; DRKS00016148). The primary outcome of the study was the difference in insulin sensitivity after 12 and 36 hours of fasting. The study was performed according to Good Clinical Practice and the Declaration of Helsinki. Prior to inclusion, participants received a detailed explanation of all study procedures from a medically trained researcher and, subsequently, gave their written informed consent. Eligibility criteria included: diagnosis of type 1 diabetes for longer than 12 months; age >18 years; treatment with exogenous insulin via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII); C-peptide level ≤0.3 nmol/L; and glycated haemoglobin (HbA1c) <80 mmol/mol (<9.5%). In addition, the participants with type 1 diabetes included in this study were free of neuropathy. The participants received intermittently scanned continuous glucose monitoring with the FreeStyle Libre 1 device (Abbott Laboratories, Abbot Park, Illinois). For the course of the 4-hour OGTT, the participants underwent electrocardiography with a Holter monitor (Faros 180; Bittium, Oulu, Finland) using one channel with a 1000-Hz sampling rate. For both trial arms, 75 g glucose (Glucoral, Germania Pharmazeutika GesmbH, Vienna, Austria) was dissolved in 300 mL water and consumed together with the participant's regular individual dose of bolus insulin.

Sensor glucose data obtained from the intermittently scanned continuous glucose monitor were interpolated from 15 minute intervals to 5 minute intervals and merged with the HRV data. Glucose data were stratified for hypoglycaemia level 1 (3.0–3.8 mmol/L), euglycaemia (3.9–10.0 mmol/L), hyperglycaemia level 1 (>10.0–13.9 mmol/L) and hyperglycaemia level 2 (>13.9 mmol/L).[7] The different rates of change in glucose were calculated as follows: decrease in sensor glucose of >10 mg/dL within 5 minutes (D2), decrease in sensor glucose of 0.3 to 0.6 mmol/L mg/dL within 5 minutes (D1), stable glucose, defined as a change of <0.3 mmol/L within 5 minutes (N), increase in sensor glucose of 0.3 to 0.6 mmol/L within 5 minutes (I1) and an increase in sensor glucose of >0.6 mmol/L within 5 minutes (I2). Data derived from the OGTTs after 12 and 36 hours of fasting were combined for the analysis.

The HRV measures evaluated in the time domain analysis included standard deviation of R-R intervals (SDNN), square root of the mean standard difference of successive R-R intervals (RMSSD) and percentage of pairs of R-R intervals with >50 ms difference (pNN50%). Power spectral analysis for the analysis of the frequency domain was conducted via Fast-Fourier Transformation in Cardiscope (Hasiba Medical GmbH, Graz, Austria). Low frequency/high frequency (LF/HF) and RMSSD are measures of the balance between parasympathetic and sympathetic activity. Total power describes the total physiological load, while corrected QT (QTc) interval was recorded for safety measures. HRV values were assessed according to the guidelines published by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology for the assessment of HRV.[8]

2.2 | Statistical analysis

Data were assessed for distribution using the Shapiro–Wilk test. Within-group parameters of HRV during the OGTT were analysed using the Friedman test and Dunn's post hoc test ($P < 0.05$).

3 | RESULTS

Twenty-one adults with type 1 diabetes were screened for inclusion in the study, of whom one did not meet the inclusion criteria, hence a

TABLE 1 Rates of change in glucose and heart rate variability responses

	I2 (decrease in sensor glucose by >0.6 mmol/L within 5 min)	D1 (decrease in sensor glucose by 0.3 - 0.6 mmol/L within 5 min)	N (stable sensor glucose: ± <0.3 mmol/L within 5 min)	I1 (increase in sensor glucose by 0.3 - 0.6 mmol/L within 5 min)	I2 (increase in sensor glucose by >0.6 mmol/L within 5 min)	*P*
Heart rate, bpm	72 ± 9	70 ± 8	73 ± 9	75 ± 11	76 ± 10*	<0.001
SDNN, ms	78 ± 19	79 ± 24	76 ± 22	70 ± 26	70 ± 29	0.07
RMSSD, ms	42 ± 19	41 ± 16	38 ± 15	35 ± 16	33 ± 17*	0.002
pNN50%	20 ± 15	19 ± 13	17 ± 12	14 ± 12	13 ± 12*	<0.001
QTc (ms)	407 ± 19	403 ± 17	406 ± 18	408 ± 18	411 ± 21	0.04
LF/HF	0.53 ± 0.26	0.54 ± 0.23	0.58 ± 0.25	0.57 ± 0.26	0.57 ± 0.21	0.88

*Indicates statistical significance compared to I2, D1 and N ($P < 0.05$). Abbreviations: LF/HF, low frequency/high frequency; pNN50%, percentage of pairs of R-R intervals with >50 ms difference; QTc, corrected QT interval; RMSSD, square root of the mean standard difference of successive R-R intervals; SDNN, standard deviation of R-R intervals.

TABLE 2 Glycaemic ranges and heart rate variability responses

	3.0–3.8 mmol/L	3.9–10.0 mmol/L	>10.0–13.9 mmol/L	>13.9 mmol/L	*P*
Heart rate, bpm	67 ± 13	73 ± 9	74 ± 9	73 ± 8	.15
SDNN, ms	80 ± 42	76 ± 23	75 ± 28	74 ± 24	.37
RMSSD, ms	40 ± 13	41 ± 17	38 ± 16	40 ± 18	.18
pNN50%	24 ± 19	17 ± 14	15 ± 12	17 ± 12	.10
QTc, ms	396 ± 22*	412 ± 23	408 ± 18*	405 ± 18*	.08
LF/HF	0.68 ± 0.27	0.58 ± 0.27	0.55 ± 0.24	0.54 ± 0.23	.24

*Indicates statistical significance compared to euglycaemia ($P < 0.05$). Abbreviations: LF/HF, low frequency/high frequency; pNN50%, percentage of pairs of R-R intervals with >50 ms difference; QTc, corrected QT interval; RMSSD, square root of the mean standard difference of successive R-R intervals; SDNN, standard deviation of R-R intervals.

total of 20 participants were enrolled in the study. Three of these had to be excluded from the analysis because of failure of the glucose sensor. The data of 17 people with type 1 diabetes were therefore analysed (five women; age 37 ± 11 years, body mass index [BMI] 24.7 ± 2.8 kg/m^2, HbA1c 53 ± 6.3 mmol/L (7.0 ± 0.6%), diabetes duration 20.2 ± 10.8 years, eight participants on MDI/nine participants on CSII, total daily insulin dose 41 ± 15 IU). Participants injected a mean ± SD bolus insulin dose of 6 ± 2 IU prior to the start of each OGTT.

3.1 | Heart rate variability

The HRV measures, heart rate ($P = 0.15$), SDNN ($P = 0.37$), RMSSD (0.18), pNN50% ($P = 0.10$) and LF/HF ($P = 0.24$), were not significantly different among the various glycaemic ranges during the OGTT. QTc was also not significantly different ($P = 0.08$), but did demonstrate differences when compared to euglycaemia after post hoc testing ($P < 0.05$; Table 2). Total power, SDNN and LF/HF remained unchanged independent of different rates of change in glucose ($P > 0.05$). The HRV results in response to rate of change in glucose are shown in Tables 1 and 2.

4 | DISCUSSION

This is the first study describing how interstitial glucose variability, assessed according to rate of glucose change, affects HRV in adults with type 1 diabetes. Our analysis showed that rapid increases in glucose lead to a decrease in RMSSD and pNN50% and an increase in heart rate, suggestive of an increased stress response.

Bekkink et al[6] have shown that incoming hypoglycaemia reduces HRV, while studies with larger sample sizes that relied solely on HbA1c as a marker of glycaemia showed significantly reduced HRV values in individuals with suboptimal HbA1c (> 58 mmol/mol). This clearly indicates that hyperglycaemia deteriorates HRV and might be a first precursor to cardiac autonomic neuropathy.[5]

In contrast to other studies, we showed that different glycaemic ranges had an impact on HRV measures, with the exception of QTc (Table 2), while rapid glucose decreases were associated with greater HRV and rapid rises in glucose levels led to a higher stress response, as shown by reduced HRV. Interestingly, a rapid drop in blood glucose led to greater HRV, which is contrary to results observed previously.[6] One limitation of our study is the clinical setting, which could have influenced autonomic tone. However, baseline measurements taken in clinic prior to the OGTT were similar to those in previously published studies.[9] Because of the limited sample size and the set-up of the study, merging glycaemic ranges and rates of glucose changes and also comparing both fasting periods individually according to the different glycaemic ranges and rates of glucose change was not possible. However, the present study demonstrates the impact of rapid glucose rises on HRV in people with type 1 diabetes. The availability of CGM technology in a large number of clinical trials will help to elucidate the role of glycaemic ranges and glycaemic variability on cardiovascular health.

ACKNOWLEDGMENTS

The authors wish to thank the participants for their commitment.

CONFLICT OF INTEREST

M.L.E. has received a KESS2/European Social Fund scholarship and travel grants from Novo Nordisk A/S and Sanofi-Aventis, research grants form Sanofi-Aventis and Dexcom. O.M. has received lecture fees from Medtronic, travel grants from Novo Nordisk A/S, Novo Nordisk AT, Novo Nordisk UK, Medtronic AT, Sanofi-Aventis, research grants from Sêr Cymru II COFUND fellowship/European Union, Novo Nordisk A/S, Dexcom, Sanofi-Aventis and Novo Nordisk AT as well as material funding from Abbott Diabetes Care. H.S. has received honoraria, travel support or unrestricted research grants by Amgen, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi-Aventis. The remaining authors have nothing to declare.

AUTHOR CONTRIBUTIONS

M.L.E. and O.M. wrote the manuscript. N.J.T., P.N.P., A.A.M.O., H.K., A.M., F.A., C.S. and H.S. reviewed/edited the manuscript, contributed to the discussion and conducted/collected data. M.L.E. and O.M. researched the data. M.L.E. and F.A. performed the statistical analysis. O.M., H.S. and M.L.E. designed the study. H.S. is the

guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Paes T, Rolim LC, Filho CS, de Sa JR, Dib SA. Awareness of hypoglycemia and spectral analysis of heart rate variability in type 1 diabetes. *J Diabetes Complications*. 2020;34(8):107617.
2. Kristiansen E, Wanby P, Åkesson K, Blomstrand P, Brudin L, Thegerström J. Assessing heart rate variability in type 1 diabetes mellitus—psychosocial stress a possible confounder. *Ann Noninvasive Electrocardiol*. 2020;25(5):e12760. https://doi.org/10.1111/anec.12760.
3. da Silva AKF, Christofaro DGD, Bernardo AFB, Vanderlei FM, Vanderlei LCM. Sensitivity, specificity and predictive value of heart rate variability indices in type 1 diabetes mellitus. *Arq Bras Cardiol*. 2017;108(3):255-262.
4. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care*. 2003;26(5):1553-1579.
5. Jaiswal M, Urbina EM, Wadwa RP, et al. Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care*. 2013;36(1):157-162.
6. Bekkink MO, Koeneman M, De Galan BE, Bredie SJ. Early detection of hypoglycemia in type 1 diabetes using heart rate variability measured by a wearable device. *Diabetes Care*. 2019;42(4):689-692.
7. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603.
8. Electrophysiology TF of the ES. Heart rate variability. *Circulation*. 1996;93(5):1043-1065. https://doi.org/10.1161/01.CIR.93.5.1043.
9. Röhling M, Strom A, Bönhof G, et al. Differential patterns of impaired cardiorespiratory fitness and cardiac autonomic dysfunction in recently diagnosed type 1 and type 2 diabetes. *Diabetes Care*. 2017;40(2):246-252.

How to cite this article: Eckstein ML, Moser O, Tripolt NJ, et al. Rapid glucose rise reduces heart rate variability in adults with type 1 diabetes: A prospective secondary outcome analysis. *Diabetes Obes Metab*. 2021;23:1681–1684. https://doi.org/10.1111/dom.14287