



# Early Detection of Hypoglycemia in Type 1 Diabetes Using Heart Rate Variability Measured by a Wearable Device

Marleen Olde Bekkink,<sup>1</sup> Mats Koeneman,<sup>2</sup> Bastiaan E. de Galan,<sup>1</sup> and Sebastian J. Bredie<sup>1,2</sup>

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## OBJECTIVE

Changes in heart rate variability (HRV) occur at the initiation of hypoglycemia due to sympathetic nervous system activity. We investigated the use of HRV detection by a wearable device as an early alert for hypoglycemia.

## RESEARCH DESIGN AND METHODS

This proof-of-principle study included 23 patients with type 1 diabetes (14 women, mean age  $42 \pm 11$  years). Patients wore a VitalConnect HealthPatch for 5 days. Hypoglycemia was defined as glucose  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L) by fingerstick measurement. HRV was analyzed in standardized periods before the hypoglycemic event.

## RESULTS

Sixty-six hypoglycemic events were recorded. Hypoglycemia caused a typical HRV pattern in 36 (55%) of the hypoglycemic events. Eighteen events (27%) showed an atypical pattern. Ten events were unclassified (15%), and two did not display a change in HRV (3%).

## CONCLUSIONS

Hypoglycemia causes early changes in HRV that can be detected by a wearable device. Measuring real-time HRV seems promising for early hypoglycemia detection.

People with type 1 diabetes (T1D) are at continuous risk of hypoglycemia (1). Typical symptom generation that allows for timely detection of impending hypoglycemia is critical to avoid severe hypoglycemia. However, patients with impaired awareness of hypoglycemia (IAH) have lost the capacity to sense these typical symptoms and are at sixfold higher risk for severe events (2). Since hypoglycemia stimulates the sympathetic nervous system, measuring heart rate variability (HRV), which reflects the balance between the sympathetic and parasympathetic nervous system (3), could be useful for real-time early detection of hypoglycemia. Wearable devices are now available for continuous heart rate measurement with high accuracy and a sufficient sample rate (4) that allows for real-time HRV monitoring in an outpatient setting. This study explores whether HRV changes detected by a wearable device have the potential for early indication of hypoglycemia in people with T1D.

## RESEARCH DESIGN AND METHODS

### Setting and Study Population

Individuals with T1D aged  $\geq 18$  years were recruited from the Radboud University Medical Center outpatient clinic between June 2017 and February 2018. Exclusion

<sup>1</sup>Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

<sup>2</sup>REshape Center for Innovation, Radboud University Medical Center, Nijmegen, the Netherlands

Corresponding author: Marleen Olde Bekkink, [marleen.oldebekkink@radboudumc.nl](mailto:marleen.oldebekkink@radboudumc.nl)

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M.O.B. and M.K. contributed equally to the manuscript.

B.E.d.G. and S.J.B. share senior authorship.

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criteria were cardiac arrhythmias and use of medication affecting heart rate. The study was approved by the institutional review board, and all patients provided written informed consent.

### Procedure

Patients wore a HealthPatch (VitalConnect, San Jose, CA) on the chest for 5 consecutive days. The HealthPatch continuously measured heart rate via single-lead electrocardiogram recording, which was then transmitted via Bluetooth to an Apple, Inc. device (Cupertino, CA). Awareness state was assessed using the Dutch modified version of the Clarke questionnaire, in which a score  $\geq 3$  classified as IAH (5,6).

Patients were asked to carry out their normal daily activities during the study period (5 days), including showering and exercise. Patients already using a real-time continuous glucose monitor (CGM) were instructed to always confirm sensor-detected hypoglycemic events by fingerstick measurement. Patients not on a glucose sensor were provided with a blinded device (Dexcom G4) for the duration of the study. In total, GCM data were available from 16 patients, i.e., 11 already using real-time CGM and 5 using a blinded device.

Hypoglycemia was defined based on fingerstick glucose measurement and categorized into mild (glucose  $\leq 70$  mg/dL [ $\leq 3.9$  mmol/L]) and serious ( $< 54$  mg/dL [ $< 3.0$  mmol/L]) magnitude, corresponding with the cutoffs for hypoglycemia alert value and clinically important hypoglycemia (7). Hypoglycemic events were excluded from further analysis if they occurred  $< 2$  h after a previous event, had commenced  $> 1$  h before fingerstick measurement, or lacked recovery (glucose  $> 70$  mg/dL [ $> 3.9$  mmol/L]) for  $\geq 15$  min after a previous event).

Patients were asked to record in a diary any hypoglycemic event, including the time of day, the presence or absence of accompanying symptoms, and prior exercise (if applicable). After 5 days, the HealthPatch, diaries, and CGM readouts were collected for analysis.

### Assessment of HRV

Parameters of HRV measured in the time domain analysis included standard deviation of the R-R intervals (SDNN) and square root of the mean standard

differences of successive R-R intervals (RMSSD). Frequency domain analysis was performed by power spectral analysis (fast Fourier transformation) to calculate the ratio between low and high frequency (LF:HF) changes in HRV. Both RMSSD and LF:HF are parameters of the balance between parasympathetic and sympathetic tone. The parameters were calculated with 6-min windows according to standard guidelines (4) at 90, 60, 30, and 0 min before the hypoglycemic event. Missed and premature beats were corrected. Windows with artifacts were excluded. CGM data were used to acquire peak glucose level before hypoglycemia and to calculate the slope of declining glucose (in  $\text{mmol} \cdot \text{L}^{-1} \cdot \text{min}^{-1}$ ).

### Statistical Analysis

Paired sample *t* tests were used to analyze mean changes of HRV parameters prior to hypoglycemia compared with the time of hypoglycemia. A forward stepwise linear model was used with the corrected Akaike information criterion, a method to estimate the improvement compared with the cost of adding different variables to a model (with the lowest Akaike information criterion ranked as the best model). Data are presented as means  $\pm$  SD, unless otherwise stated. Statistical analyses were performed with SPSS 25.0, and a *P* value  $\leq 0.05$  was considered as cutoff for statistical significance.

### RESULTS

Twenty-nine patients participated in the study. Four patients were excluded because of insufficient data storage and two because of absent fingerstick measurements (Supplementary Fig. 1). The remaining 23 patients were aged  $42 \pm 11$  years, with a diabetes duration of  $26 \pm 10$  years and an HbA<sub>1c</sub> of  $7.5 \pm 0.8\%$ . Nine patients (39%) had IAH (Supplementary Table 1). The HealthPatch was well tolerated and provided reliable HR measurement.

### Hypoglycemic Events

The analysis was performed on 66 hypoglycemic events (Supplementary Fig. 2). The average glucose level was 56 mg/dL (3.1 mmol/L) (range 29–70 mg/dL [1.6–3.9 mmol/L]). Twenty-two events (33%) were labeled serious. No events required third-party assistance.

### Analysis of HRV

In response to hypoglycemia, mean LF:HF increased by  $0.2 \pm 0.4$  and mean RMSSD decreased by  $4.4 \pm 18.1$  (*P* for both  $< 0.05$ ) (Supplementary Table 2), whereas SDNN did not change. Supplementary Fig. 3 shows an example of an HRV pattern at the initiation of hypoglycemia. Hypoglycemia caused a clear detectable increase in LF:HF and/or decrease in RMSSD in 36 (55%) of the events. Eighteen hypoglycemic events (27%) showed a mirrored HRV pattern, ten events (15%) were ambiguous, and two events (3%) caused no change in either parameter.

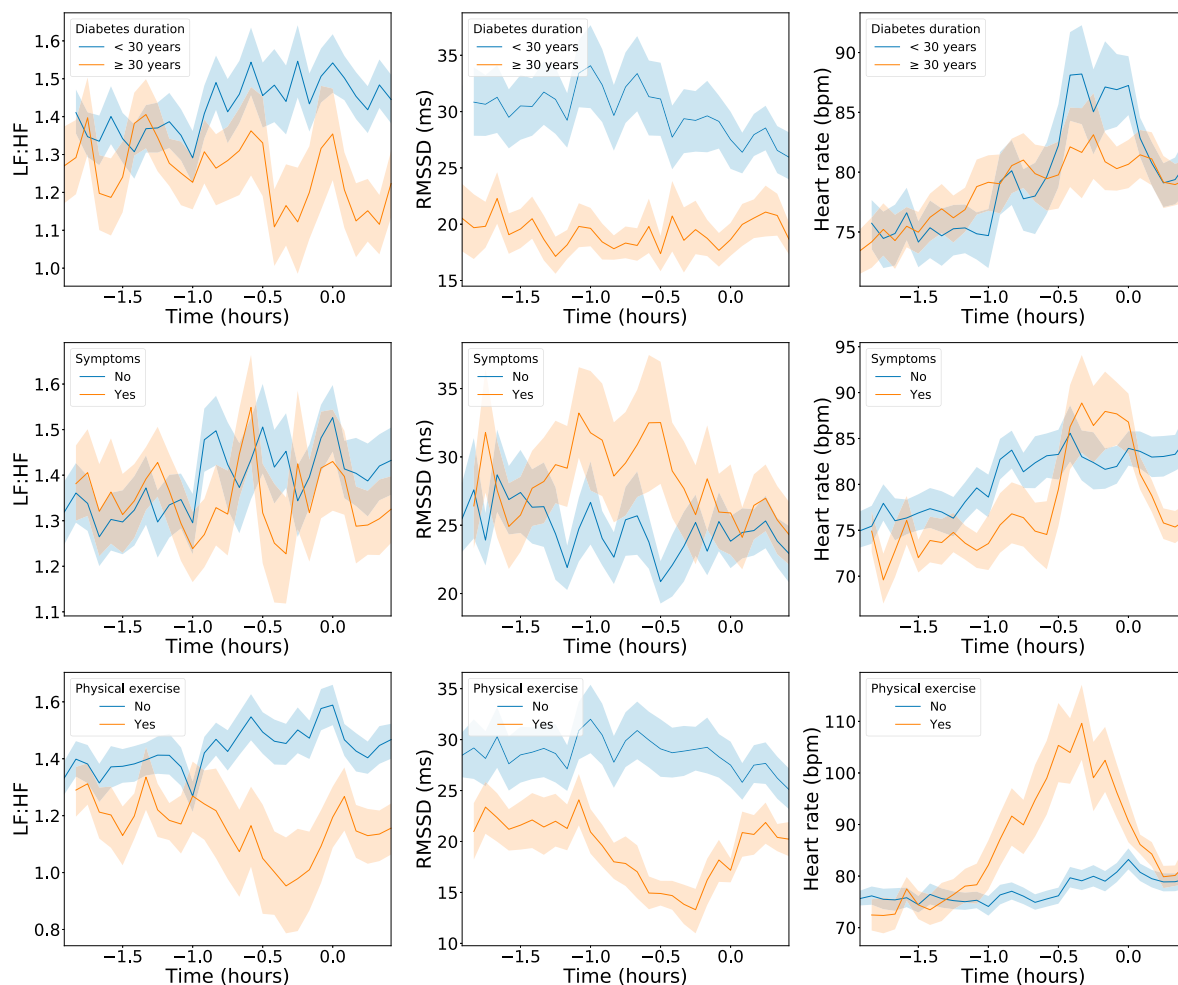
Factors associated with a more prominent change in LF:HF in linear modeling included short diabetes duration, physical activity, and rate of declining glucose (Fig. 1 and Supplementary Table 3). The glucose nadir, IAH, and occurrence of symptoms did not modify hypoglycemia-induced changes in HRV.

### CONCLUSIONS

This study reveals that spontaneous hypoglycemic events in people with T1D cause changes in HRV that can be detected by a wearable device. These changes included an increase in LF:HF and a decrease in RMSSD, but opposing effects were also seen. Hypoglycemia-induced changes in HRV were particularly prominent in patients with short diabetes duration and further influenced by sex, physical activity, and glucose peak level before and decline toward a hypoglycemic event.

We extend previously reported data on HRV responses to hypoglycemia (8–10) by showing that continuously derived HRV can be monitored by a wearable device in real-life situations. We also show that both patient-specific and situational factors modulate the effect of hypoglycemia on HRV profiles, which expands previous data on the impact of age and diabetes (duration) on HRV in general (11,12).

In the current study, nine patients had IAH. Since IAH reflects decreased sympathetic nervous system activation during hypoglycemia, we anticipated reduced diagnostic power of HRV for the detection of hypoglycemia in this group. However, specific changes in HRV during hypoglycemia were not different between patients with IAH as compared with those with intact awareness.



**Figure 1**—Response of heart rate and parameters of HRV according to diabetes duration (top), presence of accompanying hypoglycemic symptoms (middle), and physical exercise (bottom).

Our study is only a first step toward the creation of a meaningful hypoglycemia early alert device. Next steps would include adding person- and circumstance-specific data and incorporation of movement and temperature sensor data. User feedback on HRV responses to other physical and mental stressors need to be further assessed to reduce the number of false-positive alerts. Machine-learning technology could then be applied to develop individualized algorithms to further improve the sensitivity and specificity of such a hypoglycemia-alerting device. Parenthetically, given hypoglycemia’s potential role in cardiac arrhythmias and the dead-in-bed syndrome (13), a fully developed system may not only prevent such cardiac complications of hypoglycemia but also teach us who is at greatest risk.

This study’s limited scale and short duration restrict generalizability. However, the broad inclusion criteria assured

that the cohort was largely representative of the T1D population. Also, there were too few nocturnal events to analyze, which requires a larger study of longer duration. Finally, there were storage and connectivity issues. Technical improvements with the newer VitalPatch are expected to solve this problem.

In conclusion, this study shows that HRV changes at the initiation of hypoglycemia can be detected by a wearable device. Various person- and “circumstance-specific” factors modulate the association between hypoglycemia and HRV. Considering developments in wearables and data analytics, measuring real-time HRV seems promising for early detection of hypoglycemia in people with diabetes.

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**Author Contributions.** M.O.B. wrote the first draft of the paper. M.O.B. and M.K. performed data collection and analysis. B.E.d.G. and S.J.B. designed the study. All authors contributed to interpretation of the results and revision of the manuscript and read and approved the final manuscript. M.O.B. and M.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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