Autonomic Cardiac Regulation During Spontaneous Nocturnal Hypoglycemia in Patients With Type 1 Diabetes

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OBJECTIVE—Experimental clamp studies have suggested that hypoglycemia evokes a reduction of cardiac vagal control in patients with type 1 diabetes. However, there are limited data on the influence of spontaneous nocturnal hypoglycemia on cardiac autonomic regulation.

RESEARCH DESIGN AND METHODS—Adults with type 1 diabetes (n = 37) underwent continuous glucose monitoring via a subcutaneous sensor as well as recording of R-R interval or electrocardiogram for 3 nights. Heart rate (HR) variability was analyzed during periods of hypoglycemia (glucose <3.5 mmol/L) (minimum length of 20 min) and a control nonhypoglycemic period (glucose >3.9 mmol/L) of equal duration and at the same time of night.

RESULTS—The duration of hypoglycemic and control episodes (n = 18) ranged from 20 to 190 min (mean 71 min). HR (62 ± 7 vs. 63 ± 9 beats per min; P = 0.30) or the high-frequency component of HR power spectrum (2,002 ± 1,965 vs. 1,336 ± 1,506 ms^2; P = 0.26) did not change during hypoglycemia. Hypoglycemia resulted in a significant decrease in the low-frequency component of HR variability (2,134 ± 1,635 vs. 1,169 ± 1,029 ms^2, respectively; P = 0.006). The decline in the glucose concentration displayed a significant positive correlation with the decrease of the low-frequency component of HR variability (r = 0.48; P = 0.04). The latter was closely related to an increase in muscle sympathetic nerve activity recorded in 10 subjects during controlled sympathetic activation.

CONCLUSIONS—Spontaneous nocturnal hypoglycemia in patients with type 1 diabetes results in a reduction of the low-frequency component of HR, which is best explained by excessive sympathetic activation without a concomitant withdrawal of vagal outflow.

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Individuals with type 1 diabetes adhering to strict glycemic control are prone to suffer severe hypoglycemia. Other well-established risk factors for hypoglycemia include a history of severe hypoglycemia and impaired awareness of hypoglycemia (1–3). Despite advanced technology and new insulin analogs, the fear of hypoglycemia is still a major problem complicating the management of diabetes (4,5).

Since 1991, when Tattersall and Gill (6) introduced the term "dead in bed syndrome," the role of hypoglycemia as a factor predisposing young adults to sudden arrhythmic death has been hypothesized (7,8). According to earlier studies, ~2–4% of deaths of type 1 diabetic subjects have been attributed to hypoglycemia (9). However, more recent reports have indicated that as many as 6–10% of deaths in individuals with type 1 diabetes were the result of hypoglycemia (10–12).

Heart rate (HR) variability has been used to detect autonomic dysfunction in various clinical settings. A dysfunction of autonomic nervous system has been associated with increased mortality after myocardial infarction (13,14) in patients with diabetes (15,16) and in the general population (17). Nonetheless, very little is known about changes in the parameters of HR variability during hypoglycemia. In our previous clamp study, controlled hypoglycemia resulted in progressive reductions of the high-frequency spectral component and beat-to-beat HR variability (SD1) in patients with type 1 diabetes and their healthy counterparts—evidence of reduced cardiac vagal outflow during hypoglycemia (18). Since symptoms at the time of hypoglycemia induced by clamp technique in the awake state may contribute to autonomic responses, it was decided to assess the effects of spontaneous hypoglycemia on HR variability during sleep in type 1 diabetic subjects.

RESEARCH DESIGN AND METHODS

We recruited 37 adults (15 men and 22 women) with type 1 diabetes for studies on spontaneous nocturnal hypoglycemia. Mean ± SD age was 28 ± 6 years (range 19–41). The known duration of diabetes was 13 years (1–30), and mean HbA_{1c} was 8.0% (5.2–10.6). None of the patients with diabetes had a history of cardiovascular disease or were taking any drugs affecting the cardiovascular system, and all had normal 12-lead electrocardiograms. There were no signs of diabetes complications apart from diabetic retinopathy. The study protocol was approved by the local ethics committee of Oulu University Hospital, and all of the participants signed informed consent forms approved by the ethics committee.With the first 26 participants, R-R interval was measured continuously via two dermal electrodes with a real-time microprocessor-based QRS detection (Polar Electro, Kempele, Finland). The last 11 patients underwent electrocardiogram recording using an Oxford Medilog System (Medilog AR12; Oxford Instruments, Abingdon, U.K.). At the same time, they were attached to a continuous glucose-monitoring system (CGMS) measuring glucose level (range 2.2–22.0 mmol/L) via a subcutaneous MMT-7002 sensor (Medtronic Diabetes, Northridge, CA). The participants calibrated the CGMS

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in a standard, recommended way during monitoring. They were asked to keep a diary detailing their meal times, insulin injections, exercise, hypoglycemic symptoms, and bedtimes. The participants were provided with the recorders overnight and returned them to the laboratory on the next day. Each patient underwent this procedure three times.

Blood HbA_{1c} was determined by an automatic analyzer (Advia 2400; Bayer, Tarrytown, NY). Nocturnal hypoglycemia was defined as a glucose level <3.5 mmol/L during sleep for a minimum duration of 20 min. The time (hour) and duration of hypoglycemic episodes were determined. Those periods of hypoglycemia that had a control, nonhypoglycemic (glucose >3.9 mmol/L) period of equal duration and time of night were selected for the analysis of HR variability. The spectral analysis was conducted with a special software package (Hearts7; Heart Signal, Kempele, Finland) as previously described by the Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology (19). The high-frequency (0.15–0.40 Hz), low-frequency (0.04–0.15 Hz), and very-low-frequency (0.005–0.04 Hz) components were analyzed in epochs of 5 min, and the mean of high-frequency, low-frequency, and very-low-frequency spectral power and the low frequency–to–high frequency ratio were calculated. The dynamic measures of HR variability were estimated by using a quantitative analysis of the Poincaré plot as previously described in detail (20). Two quantitative parameters were measured: beat-to-beat R-R interval variability (SD1) and long-term HR variability (SD2). The SD of N-N intervals ($SDNN_{15}$) of the Poincaré plot was used as a time domain measure of HR variability.

Muscle sympathetic nervous activation study

Since the mechanism and origin of reduction of the low-frequency spectral component without concomitant changes in the average HR or other spectral components of HR variability are not well established, we performed an additional study to determine the effect of sympathetic activation on the autonomic cardiac regulation. Ten of those 37 individuals with type 1 diabetes (5 females, age 32 ± 7 years, weight 75 ± 14 kg, height 170 ± 7 cm, and HbA_{1c} 7.1 ± 0.7%) participated in this supplemental study.

Before the start of the muscle sympathetic nervous activation (MSNA) study, the subjects were instructed to avoid hypoglycemia and keep their blood glucose >5 mmol/L. The participants lay in a supine position in a quiet room for at least 15 min prior to data collection and became accustomed to breathing at a constant metronome-guided rate of 0.25 Hz for the duration of the experiments. The cold pressor and handgrip tests were performed in a randomized order. The cold pressor test was performed by immersing the subject's hand into ice water (0–1°C) for 3 min. The handgrip test lasted 5 min at an intensity of 30% of maximal voluntary contraction. The recovery between the interventions was 15 min. Electrocardiogram was recorded by standard methods (Nihon Kohden TEC-7700). Blood pressure was recorded on a beat-by-beat basis (Nexfin; BMEYE, Amsterdam, the Netherlands). Blood pressure was also measured with an automatic blood pressure recorder at every 2 min throughout the protocol (Tango; Sun-Tech, Raleigh, NC). Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted into the peroneal nerve as previously described (21). Analog signals were recorded at a sampling frequency of 1,000 Hz using the PowerLab data-acquisition system (PowerLab/16SP; ADInstruments, Bella Vista, New South Wales, Australia). Burst frequency was analyzed as bursts per minute and as bursts/100 heart beats and the area under the curve as previously described (22,23). The power spectral analyses of R-R intervals and systolic blood pressure variability were performed by customized software (24) using an autoregressive model (Burg's algorithm). The analysis was performed during the last 2 min for both interventions.

Statistical methods

Standard statistical methods were used for the calculation of means and SDs. Because of the skewed distributions, a logarithmic transformation to the natural base was made on the measures of HR variability. The differences of logarithmic values between hypoglycemic and nonhypoglycemic periods were analyzed by paired-samples *t* test. The nonparametric Wilcoxon test was used on the absolute values of spectral analysis of HR variability. The results are presented as means ± SD and Spearman bivariate correlation coefficients (*r*).

RESULTS

Incidence of nocturnal hypoglycemia

Altogether, 12 of 37 patients had 18 periods of nocturnal hypoglycemia that lasted at least 20 min and for which there was an acceptable control recording. The duration of hypoglycemia-control pairs ranged from 20 to 190 min (mean 71 min). However, this may underestimate the incidence of hypoglycemia because some of the participants experienced extremely long nocturnal hypoglycemic episodes (up to 480 min), which made it difficult to find appropriate control periods.

Table 1—*Mean HR and HR variability in diabetic patients during spontaneous hypoglycemia*

	Blood glucose		
	>3.9 mmol/L	<3.5 mmol/L	*P*
HR (bpm)	62 ± 7	63 ± 9	0.30
$SDNN_{15}$ (ms)	93.4 ± 38.7	79.0 ± 41.7	0.079
HF (ms^2)	2,002 ± 1,965	1,336 ± 1,506	0.26
HFln (ms^2)	6.79 ± 1.60	6.37 ± 1.51	0.12
LF (ms^2)	2,134 ± 1,635	1,169 ± 1,029	0.006
LFln (ms^2)	7.23 ± 1.14	6.70 ± 0.91	0.011
VLF (ms^2)	2,938 ± 2,616	2,132 ± 1,964	0.088
VLFln (ms^2)	7.64 ± 0.87	7.37 ± 0.75	0.089
LF-to-HF ratio	1.8 ± 1.1	1.8 ± 1.3	0.61
LFln-to-HFln ratio	1.09 ± 0.12	1.08 ± 0.15	0.78
SD1 (ms)	45.8 ± 29.0	35.5 ± 23.6	0.090
SD1ln (ms)	3.57 ± 0.80	3.32 ± 0.76	0.093
SD2 (ms)	122.9 ± 48.9	104.6 ± 55.0	0.098
SD2ln (ms)	4.72 ± 0.47	4.53 ± 0.48	0.066

Data are means ± SD. bpm, beats per minute; HF, high-frequency power of HR variability; LF, low-frequency power of HR variability; ln, natural logarithm; SD1, SD of instantaneous beat-to-beat R-R interval variability; SD2, SD of continuous beat-to-beat R-R interval variability; $SDNN_{15}$, SD of R-R intervals.

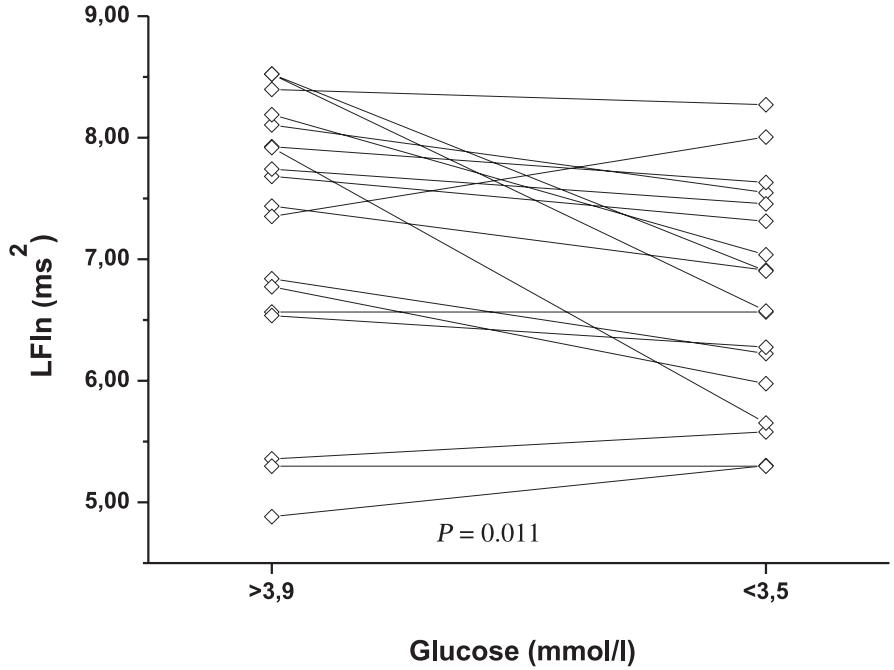

Figure 1—*Individual values of low-frequency spectral component (LFln) at different glucose levels in diabetic subjects.*

Changes in HR variability during spontaneous hypoglycemia

Spontaneous hypoglycemia did not have any effect on HR (Table1). During hypoglycemia, total HR variability ($SDNN_{15}$) showed a nonsignificant decreasing trend. The low-frequency component of HR variability decreased significantly (Fig. 1), and a nonsignificant trend toward a decrease of the very-low-frequency component was also observed (Table1). The subtle decrease of the high-frequency component of HR variability did not reach statistical significance. Nevertheless, there was no change in the low frequency–to–high frequency ratio during hypoglycemia. A nonsignificant decreasing trend was seen in SD1 and also in SD2. The decline in glucose concentration exhibited a significant, positive correlation with the decrease of the low-frequency component of HR variability ($r = 0.48$; $P = 0.04$).

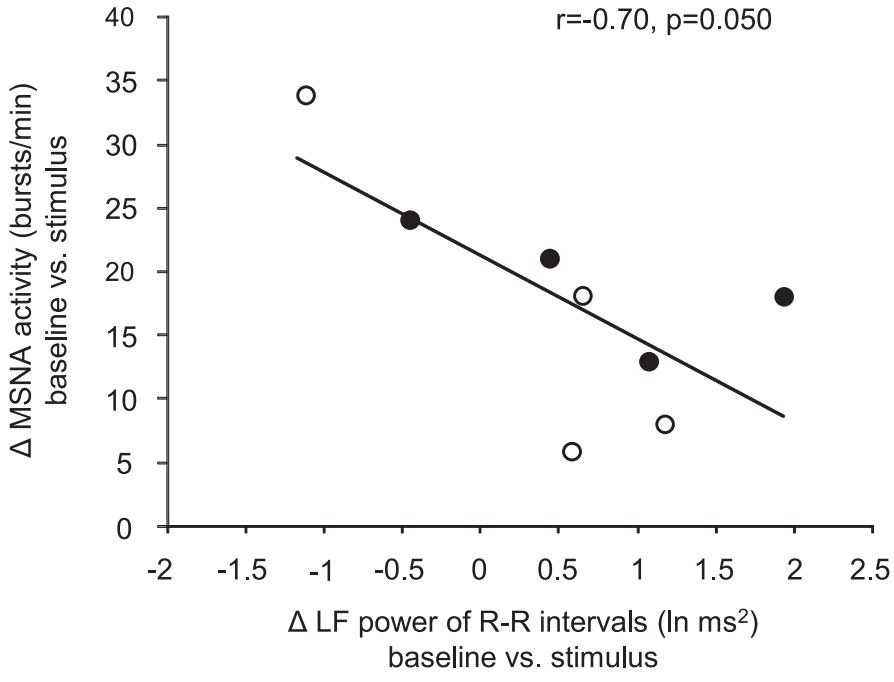

Figure 2—*Correlation between the change in low-frequency power of R-R intervals and the change in MSNA from baseline to sympathetic stimulation. Open circles are during the cold pressor test and closed circles during the handgrip test.*

Results of the MSNA study

HR increased during the handgrip test ($P < 0.001$) but did not change significantly during the cold pressor test. Low- or high-frequency powers of R-R intervals did not change significantly during the handgrip or during the cold pressor test. MSNA increased in all cases during both interventions, e.g., from 9 ± 3 to 26 ± 16 bursts per min ($P = 0.082$) during the handgrip and from 9 ± 5 to 28 ± 6 bursts per min ($P = 0.004$) during the cold pressor test, but this did not reach statistical significance during the handgrip test because of the low number of cases.

The correlation between the change in low-frequency power of the R-R intervals and the change in the other variables was further studied across both stimulations. The change in low-frequency power of R-R interval was negatively correlated with the change in MSNA ($r = -0.70$; $P = 0.050$), i.e., high sympathetic activity as documented by the increase in MSNA bursts was associated with decreased low-frequency power of R-R intervals (Fig. 2). For example, those two subjects who showed a decrease of low-frequency power spectral components during sympathetic intervention had the highest increase of MSNA bursts. A typical change in the sympathovagal outflow is seen in Fig. 3, where extreme sympathetic activation (cold hand immersion) resulted in a saturation and a decrease in low-frequency power and a paradoxical vagal activation as indicated by the lower HR and the higher high-frequency power compared with baseline.

CONCLUSIONS—As far as we are aware, this is the first study to evaluate the effects of spontaneous hypoglycemia on HR variability in diabetic individuals. The current study showed that during spontaneous hypoglycemia, the low-frequency component of HR variability decreased significantly and that this change correlated positively with the change in the glucose concentration. In addition, total HR variability, other measured components of spectral analysis, and

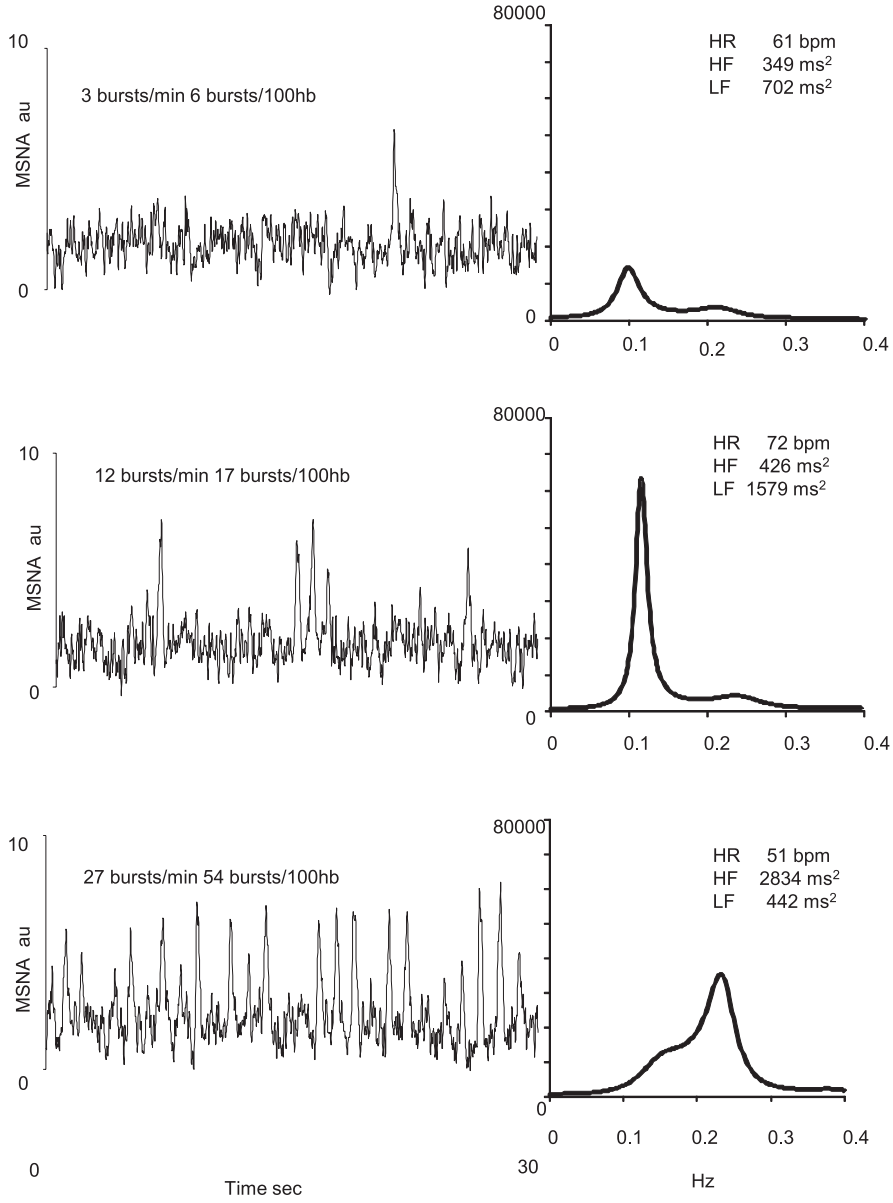

Figure 3—*Raw MSNA signal (30-s recording for all) and corresponding spectral analysis of R-R interval (2 min recording for all) at baseline* (upper panel)*, during the handgrip* (middle panel)*, and during the cold pressor tests* (lower panel)*. au, arbitrary units.*

the parameters of Poincaré plot displayed a decreasing but statistically nonsignificant trend. Since abrupt changes in HR are more closely related to cardiac vagal outflow and the average HR did not increase during hypoglycemia, we hypothesized that the reduction in the low-frequency spectral component of HR variability might result mainly from pure sympathetic activation without any concomitant vagal withdrawal. This was confirmed in our MSNA experiment, where a negative correlation was observed between sympathetic activation and the low-frequency component of HR variability. Accordingly, an increase in sympathetic activation without a concomitant vagal withdrawal leads to a decrease in low-frequency power. Hence, the reduction in low-frequency power during spontaneous hypoglycemia may reflect the hypoglycemia-induced activation of sympathetic nervous system.

Analysis of HR variability is regarded as a valid way to assess in a noninvasive manner the sympathovagal balance in the heart. The interpretation of the genesis of the low-frequency component of HR variability is somewhat controversial. It can be considered a marker of sympathetic modulation or a parameter including both sympathetic and vagal influences.

Previously, a paradoxal decrease of the low-frequency component of HR variability and a reduction in the total power of spectral analysis have been observed in patients with advanced cardiac failure (25). This condition is characterized by marked sympathetic activation during which the sinus node seems to exhibit diminished responsiveness to neural inputs. A subgroup of patients with high sympathetic activation and advanced cardiac failure has been reported to be at major risk of suffering adverse events (25–28). Observational follow-up studies have shown that reduced low-frequency spectral component after myocardial infarction is associated with worse outcome (14), such as fatal or near-fatal arrhythmic events (29), but reduced high-frequency spectral component has not been shown to be a risk marker of mortality. In this respect, reduced low-frequency spectral component observed here during spontaneous hypoglycemia may also indicate an increased risk, while reduced high-frequency spectral component observed previously during controlled hypoglycemia may not be a marker of untoward events. A similar reduction in low-frequency power has also been detected during high-intensity exercise at the time of sympathoexcitation (30). Recently, Tulppo et al. (31) have reported significantly reduced low-frequency power and a lower low frequency–to–high frequency ratio after exercise during sympathetic activation compared with baseline values in healthy subjects. In our MSNA experiment, we demonstrated a negative correlation between sympathetic activity and low-frequency power of HR variability. Additionally, we observed a decrease in low-frequency power during spontaneous hypoglycemia pointing to the emergence of sympathetic activity. In addition, during extreme sympathetic activation, a paradoxal increase in vagal outflow was seen in our example with the MSNA experiment.

Previous clamp studies provide conflicting results regarding the effect of hypoglycemia on HR variability in diabetic and healthy subjects. Laitinen et al. (32) did not observe any responses in cardiac autonomic regulation during a hyperinsulinemic-hypoglycemic clamp in healthy, nondiabetic subjects. In the study of Schächinger et al. (33), a small increase in the high-frequency spectral component was observed in healthy humans. In our previous study, cardiac vagal

activity, as assessed by the high-frequency component and SD1, decreased progressively during hypoglycemia (18). The changes were similar in both diabetic patients and nondiabetic subjects and were not observed during euglycemic clamp. There were some methodological differences between the clamp studies, which may explain the divergent results. In our study, we targeted lower glucose values (2.0–2.5 mmol/L) and selected longer time periods (15 min) for the HR variability analysis. However, the measurements in these studies were performed when there was a supraphysiological insulin concentration under experimental conditions, which may have had some influence on the results. This means that these previous results could not be directly extrapolated to real-life and studies during spontaneous hypoglycemia were needed.

Clearly, this present study has some limitations. The patient number and the number of hypoglycemic episodes were relatively small. Though we detected extensive individual differences in cardiac autonomic regulation during hypoglycemia, no subgroup analysis was possible because of the small size of the study population. Continuous MSNA measurements cannot be performed during long-term spontaneous conditions, and for these practical reasons, the MSNA measurements were done under controlled conditions. In addition, there may be some inaccuracies in measuring glucose by CGMS compared with direct plasma measurements, though the system has been validated at low glucose levels (34).

During spontaneous hypoglycemia, a marked decrease was detected in the low-frequency component of HR variability, and the other parameters of HR variability also showed a decreasing but nonsignificant trend. These results are similar to the findings encountered in severe heart failure. In all these conditions, there is an excessive sympathetic activation during which there is a change in the responsiveness of the sinus node to neural inputs. These abnormalities of cardiac autonomic regulation have been associated with cardiac adverse events and poor prognosis and during spontaneous hypoglycemia may make some contribution to the occurrence of dead in bed syndrome. Clearly, more studies involving spontaneous hypoglycemia are needed to define the role of autonomic regulation during hypoglycemia.

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M.L.K. researched data and wrote the manuscript. M.P.T., A.M.K., and M.A.K. researched data and reviewed and edited the manuscript. J.S.P., K.E.J.A., and H.V.H. reviewed and edited the manuscript. P.I.S. reviewed the manuscript. M.L.K. 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.

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