Severe Hypoglycemia–Induced Fatal Cardiac Arrhythmias Are Augmented by Diabetes and Attenuated by Recurrent Hypoglycemia

Candace M. Reno,1 Jennifer VanderWeele,2 Justin Bayles,1 Marina Litvin,2 Allie Skinner,1 Andrew Jordan,1 Dorit Daphna-Iken,2 and Simon J. Fisher1

Diabetes 2017;66:3091–3097 | https://doi.org/10.2337/db17-0306

We previously demonstrated that insulin-mediated severe hypoglycemia induces lethal cardiac arrhythmias. However, whether chronic diabetes and insulin deficiency exacerbates, and whether recurrent antecedent hypoglycemia ameliorates, susceptibility to arrhythmias remains unknown. Thus, adult Sprague-Dawley rats were randomized into four groups: 1) nondiabetic (NONDIAB), 2) streptozotocin-induced insulin deficiency (STZ), 3) STZ with antecedent recurrent (3 days) hypoglycemia (~40–45 mg/dL, 90 min) (STZ+RH), and 4) insulin-treated STZ (STZ+Ins). Following treatment protocols, all rats underwent hyperinsulinemic (0.2 units $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$), severe hypoglycemic (10–15 mg/dL) clamps for 3 h with continuous electrocardiographic recordings. During matched nadirs of severe hypoglycemia, rats in the STZ+RH group required a 1.7-fold higher glucose infusion rate than those in the STZ group, consistent with the blunted epinephrine response. Second-degree heart block was increased 12- and 6.8-fold in the STZ and STZ+Ins groups, respectively, compared with the NONDIAB group, yet this decreased 5.4-fold in the STZ+RH group compared with the STZ group. Incidence of third-degree heart block in the STZ+RH group was 5.6%, 7.8-fold less than the incidence in the STZ group (44%). Mortality due to severe hypoglycemia was 5% in the STZ+RH group, 6.2-fold less than that in the STZ group (31%). In summary, severe hypoglycemia–induced cardiac arrhythmias were increased by insulin deficiency and diabetes and reduced by antecedent recurrent hypoglycemia. In this model, recurrent moderate hypoglycemia reduced fatal severe hypoglycemia–induced cardiac arrhythmias.

People with type 1 diabetes experience an average of two episodes of symptomatic hypoglycemia each week and at least one episode of temporarily disabling severe hypoglycemia each year (1). Symptoms of hypoglycemia range from mild to severe and can include anxiety, palpitations, tremor, hunger, sweating, cognitive dysfunction, seizures, and coma (2). When severe, hypoglycemia can cause brain damage and even death (3–6). Up to 10% of deaths among young people with type 1 diabetes are caused by hypoglycemia (7). The “dead in bed syndrome” describes the sudden, unexplained death of young people with type 1 diabetes (6,8). Case reports have confirmed hypoglycemia associated with sudden death (6,7), but how severe hypoglycemia causes sudden death is not well understood. Our previous research in a rat model suggests that cardiac arrhythmias induced by severe hypoglycemia precede sudden death (3).

The risk of severe hypoglycemia is increased in patients who experience repeated episodes of hypoglycemia. This increased risk is thought to be due to a blunted counter-regulatory response induced by recurrent hypoglycemia and lack of awareness of hypoglycemia (4,9–12). While recurrent hypoglycemia can be considered maladaptive, our laboratory and others (13) have advanced the notion that the adaptive response to recurrent hypoglycemia can be considered beneficial in that it reduces brain damage and cognitive dysfunction induced by a subsequent episode of severe hypoglycemia (4). However, whether recurrent hypoglycemia is also beneficial during severe hypoglycemia to reduce fatal cardiac arrhythmias is unknown. We therefore wished to test, using a rodent model of streptozotocin-induced insulin deficiency, the hypothesis that the adaptive response to recurrent moderate hypoglycemia could reduce the incidence of severe hypoglycemia–induced fatal cardiac arrhythmias. Mechanistically we sought to explore the possible

1Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, University of Utah, Salt Lake City, UT
2Division of Endocrinology, Metabolism, and Lipid Research, Department of Medicine, Washington University in St. Louis, St. Louis, MO
Corresponding author: Simon J. Fisher, sfisher@u2m2.utah.edu.

Received 10 March 2017 and accepted 31 August 2017.
© 2017 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.
contribution of insulin therapy per se, versus insulin-induced hypoglycemia, in mediating susceptibility to arrhythmias. In addition, because the effect of diabetes on severe hypoglycemia–induced cardiac arrhythmias remains unexplored, we tested the hypothesis that diabetic rats have an increased susceptibility to hypoglycemia-induced cardiac arrhythmias when compared with nondiabetic rats.

RESEARCH DESIGN AND METHODS

Animals
Adult male Sprague-Dawley rats (weight, 250–300 g; Charles River Laboratories, Malvern, PA) were housed individually in temperature- and light-controlled environments and fed ad libitum a standard chow diet and water. All studies were done in accordance with and approved by the Animal Studies Committee at Washington University School of Medicine and the University of Utah School of Medicine.

Surgery
All four groups of rats underwent surgery for carotid artery (blood glucose and hormone sampling) and jugular vein (insulin and glucose infusions) and electrocardiogram (ECG) lead placement, as previously described (3) (Fig. 1A and B).

Induction of Diabetes
Two days after cannulation, three groups of rats received intraperitoneal injections of streptozotocin (65 mg/kg; Sigma, St. Louis, MO) to induce diabetes (n = 64); a fourth group of rats received sodium citrate buffer and acted as a control (NONDIAB group; n = 28). Blood glucose was measured from the tail vein (Ascensia Contour; Bayer HealthCare, LLC, Mishawaka, IN).

Insulin Treatment
Two days after streptozotocin injection, rats in one group were implanted with subcutaneous insulin pellets (2 units/day; LinPlant; Lin Shin, Toronto, ON, Canada) (STZ+Ins group; n = 12). To avoid the possible confounding effects of recurrent hypoglycemia in these insulin-treated rats, a glycemic goal of 200–300 mg/dL was chosen. Glucose levels were checked via the tail vein twice daily.

Recurrent Hypoglycemia
Approximately 2 weeks after streptozotocin injection, insulin-deficient rats were randomized to one of two groups: 1) insulin deficiency with recurrent saline (STZ group; n = 32) or 2) insulin deficiency with recurrent hypoglycemia (STZ+RH group; n = 20). The rats with recurrent hypoglycemia underwent recurrent moderate hypoglycemia (40–45 mg/dL for 90 min) for three consecutive days, with subcutaneous insulin injections (22–25 units/kg; Humulin R; Elly Lilly, Indianapolis, IN). The STZ group was injected with saline for 3 days. Food was withheld after injections and blood glucose was measured every half hour via the tail vein. To terminate hypoglycemia, rats were subcutaneously administered 50% dextrose (Hospira, Lake Forest, IL) and allowed free access to food. Hyperinsulinemic–severe hypoglycemic clamps were performed on day 16 (i.e., after the preceding 3 days of treatment with recurrent hypoglycemia or saline).

Hyperinsulinemic–Severe Hypoglycemic Clamp
All four groups of rats, which had been fasted overnight and were awake and unrestrained, were subjected to hyperinsulinemic (0.2 units · kg$^{-1}$ · min$^{-1}$; Humulin R), severe hypoglycemic (10–15 mg/dL) clamps with continuous ECGs for 3 h, as previously described (3).

Arterial blood samples were obtained throughout the clamp in order to measure blood glucose, electrolytes, and gases (pHox Plus C arterial blood gas analyzer; Nova Biomedical, Waltham, MA). Epinephrine was measured by ELISA (Abnova, Taipei, Taiwan). Insulin was also measured by ELISA (Crystal Chem Inc., Downers Grove, IL). Respiration was determined by counting visible breaths. ECGs were recorded and arrhythmias assessed using PowerLab 26T software (LabChart; ADInstruments, Colorado Springs, CO), as previously described (3).

Statistical Analyses
All data are represented as means ± SEMs. ANOVA was used to determine significance, unless otherwise indicated. Two-way repeated-measures ANOVA was used to compare glucose infusion rates. A Fisher exact test with

![Figure 1](image-url) —Experimental protocol. A: Rats were divided into four groups: 1) NONDIAB (n = 28), 2) STZ (n = 32), 3) STZ+RH (n = 20), and 4) STZ+Ins (n = 12). B: All rats underwent surgery to place catheters and ECG leads (day 0). Rats were injected 2 days later with either STZ or sodium citrate buffer. On day 4, one group of rats was treated with subcutaneous insulin pellets. On day 8, vascular lines were externalized, cleared, and replaced under the skin. On days 13–15, one group of rats underwent recurrent hypoglycemia (STZ+RH) while the other groups of rats were given saline. On day 16, all rats underwent hyperinsulinemic/severe hypoglycemic (10–15 mg/dL) clamps.
RESULTS
For 2 weeks after the initial randomization, rats had a mean glucose of $107 \pm 1$, $528 \pm 7$, $523 \pm 9$, and $308 \pm 13$ mg/dL in the NONDIAB, STZ, STZ+RH, and STZ+Ins groups, respectively (Fig. 2A). Body weight increased among rats in the NONDIAB group during the experiment, but it did not change in the insulin-deficient (STZ, STZ+RH) or insulin-treated (STZ+Ins) groups (Fig. 2B). The STZ+RH-treated rats, which underwent 90-min periods of recurrent hypoglycemia, saline-injected rats (STZ group) had glucose values of $528 \pm 17$, $517 \pm 8$, and $522 \pm 19$ mg/dL, respectively; rats in the NONDIAB group had glucose values of $108 \pm 7$, $109 \pm 3$, and $106 \pm 1$ mg/dL, respectively; and the rats in the STZ+Ins group, recurrently treated with insulin, had glucose levels of $398 \pm 47$, $233 \pm 48$, and $335 \pm 40$ mg/dL, respectively (Fig. 2C).

Severe Hypoglycemic Clamp
Glucose levels during the 3-h severe hypoglycemic clamp were evenly matched among the four groups (NONDIAB, 12 ± 0.2 mg/dL; STZ, 13 ± 0.3 mg/dL; STZ+RH, 13 ± 0.5 mg/dL; STZ+Ins, 13 ± 0.5 mg/dL; Fig. 3A). Insulin was similar among the groups during the clamp (data not shown). The mean glucose infusion rates for these four groups were 5.5 ± 0.5, 1.7 ± 0.3, 2.7 ± 0.4 and 0.3 ± 0.1 mg/kg/min, respectively (Fig. 3B). Epinephrine levels were similar among the groups during the basal period (before insulin infusion). During severe hypoglycemia, epinephrine increased in all groups; however, this response was blunted in the STZ+RH group (NONDIAB, 3,124 ± 81 pg/mL; STZ, 3,508 ± 387 pg/mL; STZ+RH, 1,856 ± 348 pg/mL; STZ+Ins, 2,695 ± 336 pg/mL; $P < 0.03$) (Fig. 3C).

Mortality due to severe hypoglycemia was not significantly different among the NONDIAB (14%), STZ (31%), or STZ+Ins (33%) groups. However, treatment with recurrent hypoglycemia decreased mortality 6.2-fold to just 5% in the STZ+RH group ($P < 0.035$, Fisher exact test; Fig. 4A).

Severe hypoglycemia–induced cardiac arrhythmias were consistently increased in rats in the STZ and STZ+Ins groups, whereas recurrent hypoglycemia reduced these arrhythmias. First-degree heart block was increased in the STZ (1.6 ± 0.8/min) and STZ+Ins (0.6 ± 0.2/min) groups compared with the NONDIAB group (0.009 ± 0.007/min; $P < 0.05$) (Fig. 4B). Second-degree heart block was similarly increased in the STZ (18 ± 2/min) and STZ+Ins (10 ± 4/min) groups compared with the NONDIAB group (1.5 ± 0.7/min; $P < 0.05$) (Fig. 4C). Antecedent recurrent hypoglycemia virtually eliminated first-degree heart block (0.004 ± 0.003/min; $P < 0.007$) and reduced second-degree heart block by 82% (3 ± 0.8/min; $P < 0.001$). As shown in Fig. 5, rats in the STZ and STZ+Ins groups had an increased frequency of second-degree heart block compared with rats in both the NONDIAB and STZ+RH groups. The incidence of third-degree heart block was 20%, 44%, and 42% in the NONDIAB, STZ, and STZ+Ins groups, respectively, but this was reduced to just 5.6% in the STZ+RH group ($P < 0.04$, Fisher exact test) (Fig. 4D). Nonsustained ventricular tachycardia (Vtach; defined as four or more premature ventricular contractions in a row) was present in 50% of the rats in the STZ+Ins group.
Severe Hypoglycemia means with values in the NONDIAB (3,124 were similar among the groups. During severe hypoglycemia, epinephrine was blunted in the STZ+RH group (1,856 a similar glucose level. *

Sensitivity, specificity, and positive predictive value to predict mortality were 100%, 90%, and 71%, respectively, for third-degree heart block, and 64%, 58%, and 26%, respectively, for second-degree heart block. First-degree heart block and nonsustained Vtach were highly specific, but not sensitive, predictors of mortality.

Heart rate was variable throughout the clamp (Fig. 6A). At baseline, rats in the STZ (301 ± 8 bpm) and STZ+RH (357 ± 8 bpm; P < 0.01) groups had lower heart rates than rats in the NONDIAB group (367 ± 4 bpm). Insulin treatment for 12 days in STZ-treated rats increased baseline heart rate (STZ+Ins, 406 ± 6 bpm) to levels greater than those in the NONDIAB group. As blood glucose levels declined with insulin infusion, heart rate decreased in all groups (NONDIAB, 294 ± 2 bpm; STZ, 246 ± 8 bpm; STZ+RH, 265 ± 6 bpm; STZ+Ins, 273 ± 6 bpm).

The corrected QT interval was increased at baseline in all STZ-treated groups (STZ, 160 ± 5 ms; STZ+RH, 167 ± 3 ms; STZ+Ins, 167 ± 3 ms) compared with that in the NONDIAB group (123 ± 5 ms; P < 0.05) (Fig. 6B). QTc increased during the clamp in all groups. The mean QTc during severe hypoglycemia was 175 ± 1, 172 ± 3, 186 ± 2, and 180 ± 3 ms in the NONDIAB, STZ, STZ+RH, and STZ+Ins groups, respectively.

Respiration (Fig. 6C), oxygen saturation, carbon dioxide, and pH levels were similar among the groups throughout the duration of the clamp (data not shown). Only after fatal cardiac arrhythmias did respiration, oxygen, and pH levels decline and carbon dioxide levels increase. Potassium levels decreased to a similar extent during severe hypoglycemia in all groups (NONDIAB, 3.4 ± 0.2 mmol/L; STZ, 3.3 ± 0.1 mmol/L; STZ+RH, 3.6 ± 0.2 mmol/L).

**DISCUSSION**

Recurrent episodes of hypoglycemia in people with type 1 diabetes are traditionally considered harmful because the adapted brain elicits a reduced counterregulatory response and has a reduced awareness of hypoglycemia, thereby increasing the risk for severe hypoglycemia (1,6,8). This study demonstrates that in rats, hypoglycemia-induced cardiac arrhythmias are exacerbated by type 1 diabetes. Consistent with our previous studies indicating that the adaptive response to recurrent hypoglycemia may be beneficial (4), recurrent hypoglycemia diminished fatal cardiac arrhythmias in this rat model.

Various types of cardiac arrhythmias were observed during severe hypoglycemia, including all forms of heart block (first, second, and third degree), which were increased in insulin-deficient rats (in the STZ groups) compared with rats in the NONDIAB group. Interestingly, insulin treatment of streptozotocin-treated rats (as a model of insulin-treated type 1 diabetes) had no effect on the severity of cardiac arrhythmias during severe hypoglycemia. However, recurrent antecedent hypoglycemia significantly reduced these fatal cardiac arrhythmias. It was noted that high-grade atrioventricular block led to sudden death during severe hypoglycemia, consistent with previous findings (3). As
indicated, second- and third-degree heart blocks were highly sensitive and specific in predicting mortality. In addition, detailed temporal analysis revealed that respiratory arrest consistently followed fatal cardiac arrhythmias, thus revealing that respiratory arrest is a consequence, not a cause, of fatal arrhythmias. These data indicate that 1) insulin deficiency and hyperglycemia increase severe hypoglycemia–induced cardiac arrhythmias; 2) insulin treatment in streptozotocin-treated rats, in order to model type 1 diabetes, has no effect on severe hypoglycemia–induced cardiac arrhythmias; and 3) antecedent recurrent hypoglycemia in the STZ model significantly reduces fatal arrhythmias during subsequent severe hypoglycemia.

In spite of the increased arrhythmias in the STZ and STZ+Ins groups, the associated trend for increased mortality in these two groups did not reach statistical significance. This study may not have been sufficiently powered to detect a mortality difference the STZ and NONDIAB groups. In a previous study with higher power, severe hypoglycemia–induced mortality was increased in diabetic rats (n = 95) and reduced in nondiabetic rats that underwent preconditioning with recurrent hypoglycemia (n = 27) (3).

The mechanisms of how antecedent recurrent hypoglycemia reduces severe hypoglycemia–induced fatal cardiac arrhythmias remains to be established. It is hypothesized that the blunting of the counterregulatory response, particularly epinephrine, may reduce arrhythmias. Our previous research showed that nonselective β-adrenergic receptor blockade prevents mortality resulting from severe hypoglycemia (3). As previously noted by our laboratory and others, 3 days of recurrent moderate hypoglycemia leads to a blunted epinephrine response during hypoglycemia on the fourth day (4,9–11) (Fig. 3). Consistent with this blunted counterregulatory response to hypoglycemia in rats that underwent antecedent recurrent hypoglycemia, the glucose infusion rate in the STZ+RH group was 1.7-fold higher than that in the STZ group. It should be noted that epinephrine levels were similar in the NONDIAB, STZ, and STZ+Ins groups, whereas arrhythmia frequencies were significantly greater in the STZ and STZ+Ins groups. Thus
hypoglycemia-induced increases in epinephrine levels alone are not likely to be the only mediators of severe hypoglycemia–induced cardiac arrhythmias. Sympathetic and parasympathetic innervation of the heart may also contribute to severe hypoglycemia–induced fatal cardiac arrhythmias. However, further studies are needed to address each of these mechanisms.

The role of hypokalemia in increasing the risk of severe hypoglycemia–induced mortality and the potential for potassium supplementation to reduce this mortality in both nondiabetic and diabetic rats have been previously reported (3,14). In a clinical study, Robinson et al. (15) demonstrated that potassium supplementation reduces QT dispersion during moderate hypoglycemia in healthy patients. However, in this study potassium levels fell to a similar level during hypoglycemia in all groups, indicating that hypokalemia is not likely to account for the observed differences in cardiac arrhythmias and mortality.

Prolongation of the QT interval is thought to be proarrhythmic (16). Interestingly, all three streptozotocin-treated groups had increased QTc at baseline compared with the nondiabetic controls. Insulin treatment for 2 weeks (STZ+Ins) and 3 days of insulin-induced recurrent hypoglycemia (STZ+RH) had no effect on baseline QTc intervals on the day of the clamp. Because the STZ+RH group had markedly reduced arrhythmias compared to the other groups despite QTc prolongation, it is suggested that QTc prolongation is a marker of severe hypoglycemia and is associated with cardiac arrhythmias, but it may not be sufficient to cause fatal arrhythmias during severe hypoglycemia.

Hypoglycemia is a known activator of the sympathetic nervous system, which might be expected to increase heart rate. In these studies, however, all groups demonstrated a decreased heart rate during hypoglycemia compared to baseline, suggesting that vagal tone is increased. Sinus bradycardia during hypoglycemia has been noted clinically.
(17,18). Therefore, the current findings indicate 1) an important role for the parasympathetic nervous system that is dependent on the depth and duration of hypoglycemia, and 2) the utility of this model to understand better the pathophysiological response to hypoglycemia. Because bradyarrhythmias preceded sudden death during severe hypoglycemia in our rat model, future studies should address to what extent increased vagal tone potentially drives severe hypoglycemia–induced cardiac arrhythmias.

Evidence indicates that both parasympathetic and sympathetic control of the heart are diminished in diabetes. Previous studies showed that rats injected with streptozotocin had a lower heart rate 10–14 days after injection, and insulin treatment in rats injected with streptozotocin slightly increased heart rate, returning it to normal (19). Similarly, in the current study, rats in our STZ and STZ+RH groups had lower basal heart rates than rats in the NODIAB group; these lower rates were restored to normal with insulin treatment in streptozotocin-injected rats (STZ+Ins group).

Thus, streptozotocin-induced insulin deficiency leads to altered autonomic control of the heart and may explain the decreased heart rate in streptozotocin-treated rats in our study.

In our rat model, the level of hypoglycemia necessary to observe cardiac arrhythmias was <15 mg/dL glucose. Although profoundly low, such glucose levels have been associated clinically with sudden death (6,7). Our rat model is therefore useful to study the mechanisms linking hypoglycemia to sudden death and, importantly, how we can prevent these potentially life-threatening arrhythmias.

In summary, severe hypoglycemia–induced fatal cardiac arrhythmias are 1) increased by type 1 diabetes and, conversely, 2) reduced by antecedent recurrent hypoglycemia. Because people with insulin-treated diabetes often experience hypoglycemia, understanding the mechanisms of how recurrent hypoglycemia reduces severe hypoglycemia–induced cardiac arrhythmias and mortality is important and could lead to better treatment strategies to reduce overall mortality in people at risk for severe hypoglycemia.

Prior Presentation. Parts of the manuscript were presented at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, IL, 21–25 June 2013, and at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

References
1. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169–3176
2. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26:1902–1912
3. Reno CM, Daphna-Iken D, Chen YS, VanderWeele J, Jethi K, Fisher SJ. Severe hypoglycemia–induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. Diabetes 2013;62:3570–3581
4. Puente EC, Silverstein J, Bree AJ, et al. Recurrent moderate hypoglycemia ameliorates brain damage and cognitive dysfunction induced by severe hypoglycemia. Diabetes 2010;59:1055–1062
5. Reno CM, Tanoli T, Bree A, et al. Antecedent glycemic control reduces severe hypoglycemia–induced neural damage in diabetic rats. Am J Physiol Endocrinol Metab 2013;304:E1331–E1337
6. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the “dead-in-bed” syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244–248
7. Skriverhaug T, Bangstad HJ, Stene LC, Sandvik L, Hansen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:293–305
8. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. Diabet Med 1991;8:49–58
9. McNay EC, Sherwin RS. Effect of recurrent hypoglycemia on spatial cognition and cognitive metabolism in normal and diabetic rats. Diabetes 2004;53:418–425
10. Powell AM, Sherwin RS, Shulman GL. Impaired hormonal responses to hypoglycemia in spontaneously diabetic and recurrently hypoglycemic rats. Reversibility and stimulus specificity of the deficits. J Clin Invest 1993;92:2667–2674
11. Chan O, Cheng H, Herzog R, et al. Increased GABAergic tone in the ventromedial hypothalamus contributes to suppression of counterregulatory responses after antecedent hypoglycemia. Diabetes 2008;57:1363–1370
12. Reno CM, Litvin M, Clark AL, Fisher SJ. Defective counterregulation and hypoglycemia unawaresness in diabetes: mechanisms and emerging treatments. Endocrinol Metab Clin North Am 2013;42:15–38
13. McNay EC, Cotero VE. Mini-review: impact of recurrent hypoglycemia on cognitive and brain function. Physiol Behav 2010;100:234–238
14. Heller SR, Robinson RT. Hypoglycemia and associated hypokalemia in diabetes: mechanisms, clinical implications and prevention. Diabetes Obes Metab 2000;2:75–82
15. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes 2003;52:1469–1474
16. Gruden G, Giunti S, Barutta F, et al. QTc interval prolongation is independently associated with severe hypoglycemic attacks in type 1 diabetes from the EURODIAB IDDM complications study. Diabetes Care 2012;35:125–127
17. Pollock G, Brady WJ Jr, Hargarten S, DeSilvey D, Camer CT. Hypoglycemia manifested by sinus bradycardia: a report of three cases. Acad Emerg Med 1996;3:700–707
18. Chou E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747
19. Hicks KK, Seifert E, Stimers JR, Kennedy RH. Effects of streptozotocin-induced diabetes on heart rate, blood pressure and cardiac autonomic nervous control. J Auton Nerv Syst 1998;69:21–30

Funding. C.M.R. received funding from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (grant 5T32DK091317) and JDRF (grant 3-APF-2017-407-A-N). S.J.F. received funding from the University of Utah’s Diabetes and Metabolism Research Center and the National Institute of Diabetes and Digestive and Kidney Diseases (NS070239).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.M.R. designed and conducted the experiments and wrote the manuscript. J.V. and J.B. conducted the experiments and wrote the manuscript. M.L. designed and conducted the experiments. A.S., A.J., and D.D.-I. conducted the experiments. S.J.F. designed the experiments and edited the manuscript. S.J.F. 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.