Ajay D. Rao,[1,2] Istvan Bonyhay,[3] Joel Dankwa,[1] Maria Baimas-George,[1] Lindsay Kneen,[1] Sarah Ballatori,[3] Roy Freeman,[3] and Gail K. Adler[1]

Baroreflex Sensitivity Impairment During Hypoglycemia: Implications for Cardiovascular Control

Studies have shown associations between exposure to hypoglycemia and increased mortality, raising the possibility that hypoglycemia has adverse cardiovascular effects. In this study, we determined the acute effects of hypoglycemia on cardiovascular autonomic control. Seventeen healthy volunteers were exposed to experimental hypoglycemia (2.8 mmol/L) for 120 min. Cardiac vagal baroreflex function was assessed using the modified Oxford method before the initiation of the hypoglycemic-hyperinsulinemic clamp protocol and during the last 30 min of hypoglycemia. During hypoglycemia, compared with baseline euglycemic conditions, *1)* baroreflex sensitivity decreases significantly (19.2 ± 7.5 vs. 32.9 ± 16.6 ms/mmHg, $P < 0.005$), *2)* the systolic blood pressure threshold for baroreflex activation increases significantly (the baroreflex function shifts to the right; 120 ± 14 vs. 112 ± 12 mmHg, $P < 0.005$), and *3)* the maximum R-R interval response (1,088 ± 132 vs. 1,496 ± 194 ms, $P < 0.001$) and maximal range of the R-R interval response (414 ± 128 vs. 817 ± 183 ms, $P < 0.001$) decrease significantly. These findings indicate reduced vagal control and impaired cardiovascular homeostasis during hypoglycemia.

Rigorous glycemic control is the cornerstone of diabetes management; however, this results in increased episodes of iatrogenic hypoglycemia (1). Multiple community- and hospital-based studies have shown an association between exposure to hypoglycemia and increased mortality (2,3). Furthermore, results of several large-scale clinical trials investigating the outcome of intensive glycemic control have shown increased cardiovascular mortality or a lack of cardiovascular benefit (4–7). These results raise the possibility that exposure to hypoglycemia has adverse and unknown effects that persist after hypoglycemia resolves and may oppose cardiovascular benefits of improved glycemic control (8,9).

Prior exposure to hypoglycemia impairs the hormonal and muscle sympathetic nerve activity (MSNA) response to subsequent hypoglycemia (10), the hormonal responses to subsequent exercise (11), and autonomic control of cardiovascular function (12). After exposure to hypoglycemia, induced by the hypoglycemic-hyperinsulinemic clamp protocol, individuals exhibit decreased baroreflex sensitivity (BRS), decreased MSNA response to transient hypotension, and decreased norepinephrine response to orthostatic stress compared with prior exposure to euglycemic-hyperinsulinemic conditions. These changes in autonomic cardiovascular control are present in the euglycemic state 16 h after hypoglycemic exposure (12). The time of onset for these changes is not established.

The baroreflex plays a central role in maintaining cardiovascular homeostasis. Impaired baroreflex function is associated with increased mortality in patients with diabetes, hypertension, and cardiovascular disease (13–15). Thus, hypoglycemia-induced changes in autonomic cardiovascular control could contribute to the mortality associated with hypoglycemia (7,8,16).

The modified Oxford test is the gold standard for characterizing the baroreflex. By assessing baroreflex function across a wide range of clinically relevant blood pressures, this test defines the full hemodynamic range of baroreflex engagement. The modified Oxford method has not been used to assess BRS during hypoglycemia. The

COMPLICATIONS

[1]Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[2]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Temple University School of Medicine, Philadelphia, PA
[3]Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Corresponding author: Roy Freeman, rfreeman@bidmc.harvard.edu.

purpose of this study was to test the hypothesis that impairment in baroreflex cardiovascular control begins during hypoglycemia. We therefore assessed baroreflex function using the modified Oxford method before and during a hypoglycemic-hyperinsulinemic clamp protocol in healthy participants.

RESEARCH DESIGN AND METHODS

Study Population
Healthy men and women, aged 18 to 40 years, were recruited from the greater Boston area. Exclusion criteria included evidence of any medical illness on history or physical examination, BMI >30 kg/m^2, tobacco use, substance abuse, pregnancy, lactation, menopause, abnormalities on electrocardiogram, or abnormal blood electrolyte, liver function test, complete blood count, or urinalysis values. The study protocol (NCT01394627) was approved by the Partners Institutional Review Board, and all subjects provided written informed consent.

Diet and Activity
Participants stopped over-the-counter medications 2 weeks before admission and refrained from vigorous exercise from 1 week before admission to the Center for Clinical Investigation at Brigham and Women's Hospital. Participants consumed an isocaloric diet (125 mmol/day Na$^+$, 125 mmol/day K$^+$, 20 mmol/day Ca^{2+}) lacking foods high in monoamines beginning 4 days before and continuing throughout the admission. A hypoglycemic-hyperinsulinemic clamp procedure was performed in the morning, with participants having been supine and fasting since midnight.

Hypoglycemic-Hyperinsulinemic Clamp Protocol
As previously described, participants received a primed continuous intravenous infusion of regular insulin at 80 mU/m^2 body surface area/min for ~150 min (all participants received Humulin R [Eli Lilly, Indianapolis, IN], except one who received Novolin R [Novo Nordisk, Princeton, NJ]). Twenty percent dextrose was infused intravenously to achieve blood glucose of 2.8 mmol/L (50 mg/dL) for 120 min (17). Blood samples were withdrawn through an indwelling intravenous catheter placed in a retrograde fashion in the participant's wrist/hand that rested in a warm box (150°F) throughout the procedure. Plasma glucose was assessed every 5 min using a bedside glucose analyzer (YSI 2300 STAT Plus Glucose & Lactate Analyzer; YSI, Yellow Springs, OH). Blood was collected for analysis of insulin at baseline and during the insulin infusion.

Baroreflex Assessment
Cardiac vagal baroreflex function was assessed using the modified Oxford method (18) at baseline and during the last 30 min of the hypoglycemic clamp (Fig. 1). After a baseline measurement of blood pressure and heart rate using an automated oscillometric blood pressure monitor (Dinamap; Critikon, Inc., Tampa, FL), participants received intravenous bolus injections of 100 μg sodium nitroprusside, followed 60 s later by 150 μg phenylephrine hydrochloride as previously described (12). This procedure causes a decrease in systolic blood pressure (SBP) of ~15 mmHg below baseline SBP, followed by an increase of ~15 mmHg above baseline. R-R interval and beat-to-beat blood pressure were measured using the Finometer (FMS, Amsterdam, the Netherlands). Baroreflex assessments were performed in duplicate. The
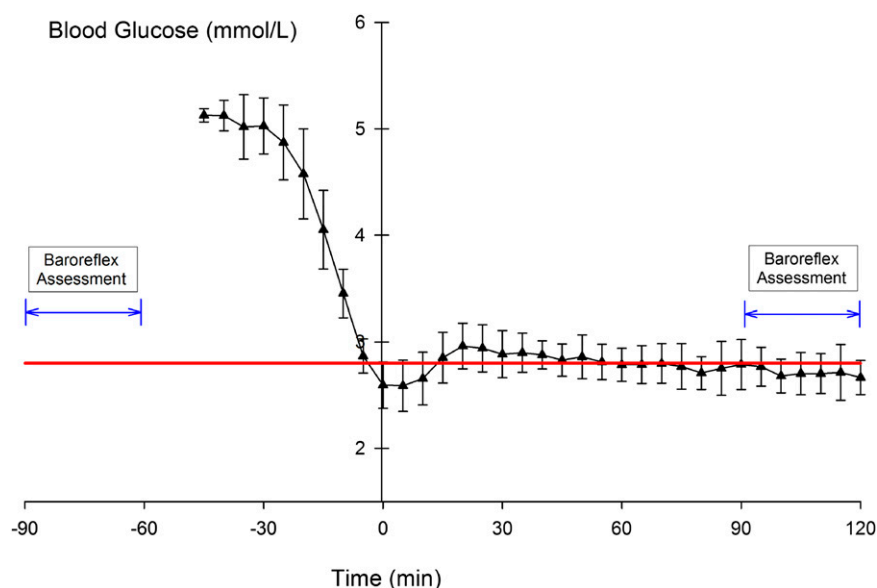

Figure 1—Timing of the baroreflex assessment (modified Oxford) relative to the plasma glucose levels (mean ± SD) during the hypoglycemic-hyperinsulinemic clamp protocol. The straight line represents the target glucose level (2.8 mmol/L).
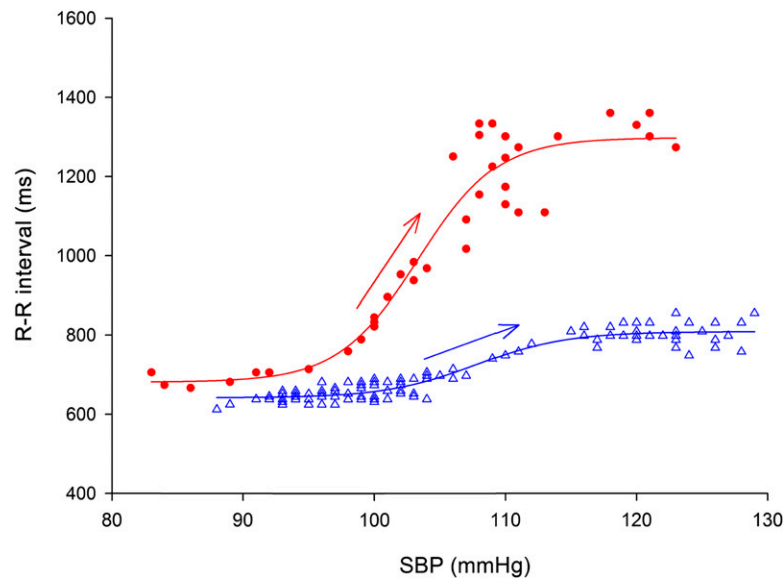
Figure 2—Baroreflex function from a representative subject measured by the modified Oxford method during baseline euglycemia (circles) and hypoglycemia (triangles). Data points represent the corresponding values of SBP and cardiac interval (R-R) during the pharmacologically induced blood pressure change. For baroreflex assessment, R-R is plotted as a function of SBP between the lowest and the highest SBP values. The linear portion (arrows) of the sigmoid function describes BRS (see RESEARCH DESIGN AND METHODS). During hypoglycemia, BRS is decreased, maximal R-R interval is decreased, and the sigmoidal baroreflex function curve shifts to the right.

minimum and maximum R-R intervals were used to define the range of heart rate response during the baroreflex function assessment. BRS was determined by the slope of the relation between the R-R interval and SBP. The threshold of baroreflex function was defined as the SBP at which the R-R interval started to increase after reaching its minimum value during the modified Oxford test. The saturation point of baroreflex function was defined as the SBP at which the R-R interval reached its maximum value (Figs. 2 and 3).

Statistical Analysis

Data were analyzed using the Student two-tailed t test and ANOVA with repeated measures (general linear model, SPSS). Categorical variables were compared using the Fisher exact test. Data are expressed as mean $\pm$ SD unless specified otherwise. A P value <0.05 was considered statistically significant. Statistical analysis was performed with SAS 9.3 (SAS Institute, Inc., Cary, NC), JMP Pro 10.0 (SAS Institute, Inc.), or SPSS software (IBM Corp., Armonk, NY).

RESULTS

Subject Demographics and Clamp Data

The analysis included 17 participants (age 26 $\pm$ 6 years, 76% male, 59% Caucasian, BMI 23.2 $\pm$ 3.6 kg/m^2). Four additional participants were excluded due to incomplete autonomic testing data (n = 3) or average blood glucose >3.0 mmol/L during the final 120 min of the clamp protocol (n = 1).

All 17 participants were insulin sensitive, with an average homeostatic model assessment of 1.05 $\pm$ 0.42 and fasting glucose of 5.0 $\pm$ 0.3 mmol/L. Insulin infusion

increased serum insulin from baseline levels of 29 $\pm$ 11 pmol/L to 731 $\pm$ 290 pmol/L. Figure 1 shows plasma glucose levels during the clamp procedure and timing of the modified Oxford test. The average plasma glucose during the 120 min of hypoglycemia was 2.8 $\pm$ 0.1 mmol/L.

Baroreflex Assessment Before and During Hypoglycemia

Blood pressure and heart rate were assessed before the modified Oxford procedures at baseline, when subjects were euglycemic, and during the hypoglycemic clamp (Fig. 1). SBPs were similar, whereas diastolic blood pressure (DBP) was significantly lower, under hypoglycemic compared with baseline euglycemic conditions (SBP$_{baseline}$ 116 $\pm$ 11 mmHg vs. SBP$_{hypoglycemia}$ 119 $\pm$ 14 mmHg, P = NS; DBP$_{baseline}$ 67 $\pm$ 7 mmHg vs. DBP$_{hypoglycemia}$ 61 $\pm$ 7 mmHg, P < 0.001). Heart rate increased significantly during hypoglycemia compared with baseline euglycemia (baseline heart rate 60 $\pm$ 8 bpm vs. 71 $\pm$ 8 bpm; P < 0.001).

The minimum and maximum (peak and trough) SBPs during the modified Oxford procedure were similar under hypoglycemic and baseline euglycemic conditions (Table 1). Analysis of baroreflex function revealed significant differences between baseline and hypoglycemic conditions (see Fig. 2 for a representative subject and Fig. 3 and Table 1 for group data). BRS decreased during hypoglycemia compared with baseline as shown by the decrease in the slope of the linear portion of the sigmoidal baroreflex function plot (19.2 $\pm$ 7.5 ms/mmHg during hypoglycemia vs. 32.9 $\pm$ 16.6 ms/mmHg at baseline, P < 0.005).
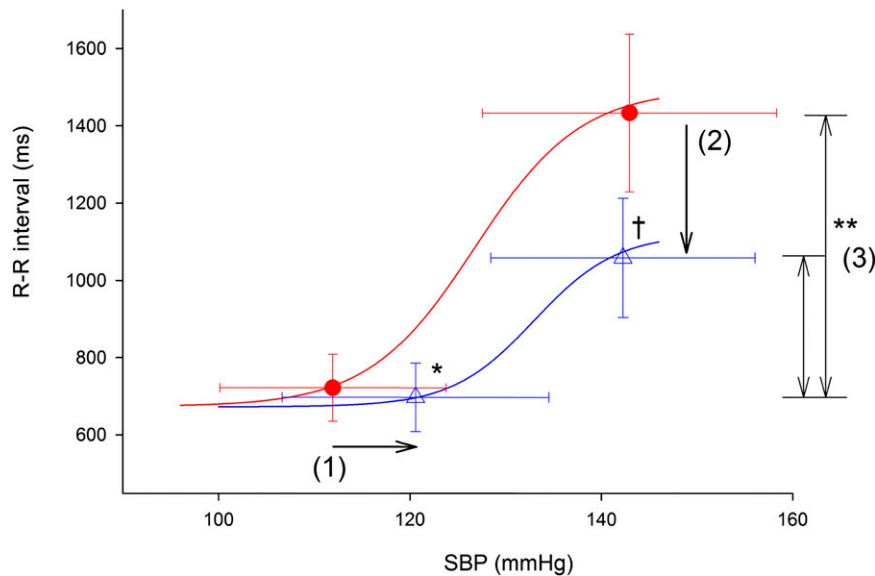
Figure 3—Baroreflex function measured by the modified Oxford method during baseline euglycemia (circles) and hypoglycemia (triangles). Group average values for the threshold and saturation blood pressures and corresponding cardiac intervals (R-R) are displayed for each glycemic condition. A sigmoidal curve is fitted to these group data for both glycemic conditions. Horizontal error bars denote the SD of blood pressure, and the vertical error bars denote the SD of the R-R interval. During hypoglycemia, the baroreflex threshold shifts to higher blood pressures (arrow 1), the R-R interval at the blood pressure saturation point decreases (arrow 2), and the R-R interval range is lower (double-headed arrows 3). Data for BRS (the slope of the linear portion of the baroreflex sigmoid curve) showing a significant decrease with hypoglycemia are reported in Table 1. *P < 0.005 for the difference in the baroreflex blood pressure threshold, hypoglycemia vs. baseline. †P < 0.001 for the difference in maximum R-R interval at the blood pressure saturation point, hypoglycemia vs. baseline. **P < 0.001 for the difference in R-R interval ranges, hypoglycemia vs. baseline.

The SBP threshold for activation of the baroreflex increased significantly (a shift to the right of the baroreflex plot) during hypoglycemia compared with baseline euglycemia (Fig. 2, Fig. 3, and Table 1), indicating higher blood pressures were required for baroreflex activation. The saturation point of the baroreflex curve (the point at which blood pressure increases elicited no further increases in the R-R interval) was similar during baseline euglycemia compared with hypoglycemia (Fig. 2, Fig. 3, and Table 1).

The maximum R-R interval response elicited by the increase in blood pressure during the modified Oxford procedure decreased significantly (a downward shift of the baroreflex plot) during hypoglycemia compared with baseline (Fig. 2, Fig. 3, and Table 1). Further, the range between the maximum and minimum R-R intervals was significantly decreased during hypoglycemia versus baseline, indicating a blunted heart rate response to pharmacologically induced changes in blood pressure (Fig. 2, Fig. 3, and Table 1).

DISCUSSION

Our data demonstrate that during insulin-induced hypoglycemia 1) BRS is decreased, 2) the blood pressure threshold for baroreflex activation is increased, and 3) the maximum R-R interval response and maximal range of the R-R interval responses are decreased. These findings indicate an inability to maintain optimal vagal control during hypoglycemia. Impaired cardiovascular homeostasis during hypoglycemia could contribute to the adverse cardiac outcomes associated with hypoglycemia. These results extend our previous findings, which showed a decrease in BRS 16 h after exposure to hypoglycemia (12). Taken together, these two studies suggest that hypoglycemia-mediated attenuation of cardiac vagal baroreflex function begins during hypoglycemia and persists for at least 16 h after hypoglycemia has ended.

Table 1—Characteristic points of the modified Oxford baroreflex function for all subjects during baseline euglycemia and hypoglycemia

	Baseline	Hypoglycemia
SBP (mmHg)		
Minimum	98 ± 13	102 ± 15
Threshold	112 ± 12	120 ± 14*
Saturation	143 ± 15	142 ± 14
Maximum	146 ± 1 4	145 ± 13
R-R interval (ms)		
Minimum	721 ± 86	697 ± 88
Maximum	1,496 ± 194	1,088 ± 132**
Range	817 ± 183	414 ± 128**
BRS (ms/mmHg)	32.9 ± 16.6	19.2 ± 7.5*

Data are mean ± SD. *P < 0.005 hypoglycemia vs. baseline. **P < 0.001 hypoglycemia vs. baseline.

Patients with diabetes are often exposed to asymptomatic episodes of hypoglycemia. The incidence of severe hypoglycemic episodes (those that require medical assistance) may be as high as 3.2 episodes per patient per year in individuals with type 1 diabetes and 0.1 to 0.7 episodes per patient per year in individuals with type 2 diabetes (19,20). These episodes can last up to 10% of a 24-h period (21). There is an increased interest in the potential adverse effects of hypoglycemia prompted by studies showing associations between severe hypoglycemia and cardiovascular disease and microvascular disease in individuals with type 2 diabetes (9) and by large-scale clinical studies showing an association between intensive glycemic control and adverse cardiovascular events (4–6). Multiple processes associated with cardiovascular injury or dysfunction are induced during hypoglycemia. These include increased activation of the renin-angiotensin-aldosterone system (22); increases in inflammatory cytokines, including interleukin-6, interleukin-8, tumor necrosis factor-α, and endothelin-1 (17,23,24); endothelial dysfunction (25); QT interval prolongation (26); cardiac arrhythmias (16); decrease in the spontaneous baroreflex (27); and increased sympathetic nerve activity (28). All of these factors could have a role in the adverse clinical outcomes associated with hypoglycemia.

The present finding that autonomic control of cardiovascular function is altered during hypoglycemia extends our understanding of the potential adverse cardiovascular effects of hypoglycemia. We used pharmacological provocations to fully characterize the baroreflex across a range of physiologically relevant blood pressures, allowing us to determine the specific changes in baroreflex control induced by hypoglycemia. Our observation that BRS is reduced during hypoglycemia over a wide range of blood pressures extends and supports a prior study of spontaneous cardiac BRS during hypoglycemia (27). In addition, we show directly, for the first time, that the increase in the blood pressure threshold for activation of the baroreflex and the decrease in the range of heart rate responses to blood pressure changes during hypoglycemia both contribute to the altered autonomic heart rate control during hypoglycemia. These mechanisms indicate an inability to maintain optimal vagal control leading to a higher probability of impaired cardiovascular homeostasis and adverse cardiac events during hypoglycemia. The observation that alteration of baroreflex function is present within 90–120 min of exposure to hypoglycemia and with exposure to a relatively moderate degree of hypoglycemia (2.8 mmol/L) increases the relevancy to clinical care.

The baroreflex plays a pivotal role in cardiovascular homeostasis. Decreases in BRS lead to an impaired homeostatic response to hemodynamic stress. Baroreflex dysfunction is also associated with an increased risk of cardiac arrhythmias (29) and is a predictor of mortality in the period after a myocardial infarction

(15) and in individuals with type 2 diabetes (13). Thus, hypoglycemia-induced changes in baroreflex function could have significant clinical implications that may be particularly relevant in individuals with diabetes who experience hypoglycemia or have underlying autonomic dysfunction. Although the current studies were performed in healthy subjects, our results are consistent with published studies in individuals with diabetes. In individuals with type 1 diabetes, acute hypoglycemia reduces measures of autonomic and cardiovascular function (30). Further, indices of hypoglycemia derived from continuous glucose monitoring were associated with reduced heart rate variability in individuals with type 1 diabetes (31).

Several studies suggest that activation of carotid body chemoreceptors by hypoxia reduces BRS (32) or shifts the baroreflex stimulus response curves to higher blood pressures and heart rates (33,34). When studied in individuals with type 1 diabetes, acute hypoxia further deteriorates hypoglycemia-evoked decreases in the spontaneous cardiac baroreflex and measures of heart rate variability (35). This may be relevant in patients with sleep apnea, a common condition in individuals with diabetes (36).

Our study has some limitations. We cannot identify the exact mechanisms that underlie the decreased BRS, the increased blood pressure threshold, and the decreased maximum R-R interval response. This requires further studies. However, the changes in the baroreflex are not due to differences in the blood pressure provocation because the blood pressure range and blood pressure saturation point were similar during baseline euglycemia and hypoglycemia. In addition, the current study cannot determine the relative roles played by hyperinsulinemia and hypoglycemia in the observed impairments in the cardiovagal baroreflex. Insulin induces vasodilation and increases sympathetic activity in the presence of euglycemia (37) and, when administered centrally to anesthetized rats, increases baroreflex gain of heart rate and MSNA (38,39). In contrast, in a study in humans, hyperinsulinemia increased the MSNA baroreflex gain (i.e., the MSNA response to spontaneous changes in blood pressure) in the presence of euglycemia but did not modify cardiovagal baroreflex gain (i.e., the heart rate response to spontaneous changes in blood pressure) (40). These findings contrast with our observation that insulin-induced hypoglycemia blunts the cardiovagal baroreflex and support the hypothesis that blunting of the cardiovagal baroreflex is due to hypoglycemia, not hyperinsulinemia. Further studies are necessary to prove this point.

In summary, these data suggest that cardiac vagal baroreflex is impaired in healthy nonobese individuals during acute insulin-induced hypoglycemia. Further studies are needed to determine whether these changes occur in individuals with diabetes (41) and to determine the relevance of hypoglycemia-induced alterations

in autonomic control of cardiovascular function to clinical outcomes.

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