Cardiac responses to insulin-induced hypoglycemia in nondiabetic and intensively treated type 1 diabetic patients

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INTENSIVE TREATMENT OF PATIENTS with type 1 diabetes slows the progression of microvascular complications but markedly increases the risk for insulin-induced hypoglycemia (11). Intensive treatment is also associated with blunted catecholamine responses to falling plasma glucose concentrations (1, 9, 20, 27), which might be expected to impair the cardiovascular response to hypoglycemia. Cardiac output normally increases with hypoglycemia (18), and diminished augmentation of cardiac output might impair the systemic delivery of glucose and other substrates.

The cardiovascular responses to hypoglycemia have been examined in healthy nondiabetic subjects after bolus intravenous administration of insulin (15, 16, 18). Severe insulin-induced hypoglycemia (1–2 mmol/l) leads to a transient increase in cardiac output, heart rate, and calculated left ventricular stroke volume, with an associated decrease in calculated systemic vascular resistance (18). Hypoglycemia also results in a significant increase in left ventricular ejection fraction (LVEF), indicating increased myocardial systolic function (15, 16). However, diabetic subjects were not included in those studies, so that the cardiac effects of insulin-induced hypoglycemia in this patient population remain unknown. In addition, these earlier studies did not assess the effects of hypoglycemia on diastolic function, which is an important component of cardiac performance (3).

Complicating the study of the cardiovascular effects of insulin-mediated hypoglycemia is the fact that cardiac function is also influenced by the effects of hyperinsulinemia per se. Even under euglycemic conditions, hyperinsulinemia increases cardiac output (4) through sympathetic activation (28, 29) and nitric oxide-mediated vasodilation in skeletal muscle (33). After an intravenous insulin bolus, LVEF increases before the onset of hypoglycemia in normal subjects (15). However, the non-steady-state conditions after bolus insu-
lin injection make it difficult to determine the contribution of hyperinsulinemia to the hypoglycemic effects observed in these earlier studies. In addition, the contribution of hyperinsulinemia per se to the cardiac response to insulin-induced hypoglycemia in patients with diabetes is unknown.

The present studies were therefore undertaken to address the following questions concerning the cardiovascular effects of insulin-induced hypoglycemia. Do intensively treated type 1 diabetic patients augment their left ventricular function during moderate sustained insulin-induced hypoglycemia (glucose concentration ~2.8 mmol/l)? Is their response comparable to that of nondiabetic subjects? Do cardiac responses to hypoglycemia involve changes in both left ventricular systolic and diastolic function? Finally, what is the contribution of hyperinsulinemia per se to the hemodynamic responses to insulin-induced hypoglycemia in both diabetic and nondiabetic subjects?

METHODS

Subjects. Patients with intensively treated type 1 diabetes were recruited to participate as subjects in this study. All had diabetes for >10 yr and had achieved good glycemic control (hemoglobin A1c: 6.2 ± 1%). Of the nine diabetic subjects, seven were receiving treatment with a continuous-infusion insulin pump. The diabetic subjects had no other medical problems and were taking no medications (other than insulin) at the time of the study. Healthy, nondiabetic volunteers on no medications were also recruited to participate as subjects in this study. All subjects refrained from vigorous exercise and caffeine for 24 h before study. The clinical characteristics of the participants are summarized in Table 1. All diabetic subjects underwent symptom-limited exercise treadmill testing with myocardial perfusion imaging with the use of a 99mTc-sestamibi flowtracer (Du Pont, N. Billerica, MA) to exclude the presence of occult myocardial ischemia. Exclusion criteria included pregnancy, the presence of significant systemic disease other than diabetes, and a history of hypoglycemic seizures. The protocol was approved by the Human Investigations Committee of the Yale University School of Medicine and the Radiation Safety Committee of Yale-New Haven Hospital. All participants gave informed, written consent before participating in the study.

Hyperinsulinemic clamps. All subjects underwent two hyperinsulinemic clamp studies (13) separated by ~1 mo. The two studies consisted of 1) a hyperinsulinemic (24 pmol·kg⁻¹·min⁻¹ for 10 min followed by 12 pmol·kg⁻¹·min⁻¹ for 110 min) hypoglycemic (plasma glucose concentration ~2.8 mmol/l) clamp study and 2) a hyperinsulinemic (24 pmol·kg⁻¹·min⁻¹ for 10 min followed by 12 pmol·kg⁻¹·min⁻¹ for 110 min) euglycemic (plasma glucose concentration ~5 mmol/l) clamp study. Subjects were fasted after midnight on the day before study. The diabetic subjects were admitted to the Adult General Clinical Research Center the evening before the study and received a low-dose intravenous infusion of regular insulin (~3–12 mmol/l) to maintain a plasma glucose concentration of 5–7.8 mmol/l until the start of the experimental protocols. A retrograde catheter was inserted into a vein in the dorsum of the right hand, which was positioned in a heated box, for sampling of arterialized venous blood. A second intravenous catheter was inserted into the right antecubital vein for the infusion of insulin and glucose.

Subjects were placed under a gamma camera (Dynamo, Picker International, Cleveland, OH) to assess left ventricular function, as described in Assessment of left ventricular function. After a 30-min equilibration period, baseline blood samples and measurements of left ventricular function were obtained in triplicate. Thereafter, the primed continuous intravenous insulin infusion was initiated while a variable glucose (20% dextrose) infusion was adjusted, on the basis of plasma glucose measurements obtained at 5-min intervals, to maintain euglycemia (~5 mmol/l) for 30 min. After this 30-min period, the plasma glucose concentration was either maintained at ~5 mmol/l or allowed to decrease to ~2.8 mmol/l over a 20- to 30-min period. The plasma glucose concentration was then maintained at this level for 60 min, during which time serial assessments of left ventricular function and blood samples were obtained.

Analysis of baseline autonomic function. Baseline cardiac autonomic testing was performed at 7:30 AM before the clamp study. This included analysis of heart rate variability during deep breathing (26) and the Valsalva maneuver (23) as utilized by the Diabetes Control and Complications Trial study group (31). The standard deviation of the mean R-R interval and the circular mean resultant were calculated as indexes of parasympathetic cardiac function (17). The ratio of the longest interval after the performance of the Valsalva maneuver to the shortest interval during the maneuver was used as an index of overall autonomic function (23).

Assessment of left ventricular function. Left ventricular systolic and diastolic functions were quantified by serial equilibrium radionuclide angiography after an intravenous bolus injection of 99mTc-sestamibi (UltraTag, Mallinckrodt Medical, St. Louis, MO). Serial 5- to 7-min acquisitions were obtained in the left anterior oblique view. LVEF and peak diastolic filling rate (PFR) were computed using the Massardo count ratio method (24). Postacquisition processing of the scintigraphic data was performed in a blinded fashion. The coefficient of variation was 1.7% for the measurement of LVEF, 7.9% for PFR, and 12.8% for EDV.

Biochemical analysis. Plasma glucose concentrations were measured using an automated analyzer (Beckman Instruments, Fullerton, CA). Plasma concentrations of lactate and nonesterified fatty acids were measured by enzymatic analysis. Free plasma insulin was measured by a double-antibody

| TABLE 1. Clinical characteristics of diabetic and nondiabetic subjects |
|-----------------|-----------------|
| Diabetics       | Nondiabetics    |
| n               | 9               |
| Age, yr         | 29.8 ± 0.6      |
| Sex, M/F        | 5/4             |
| Body mass index, kg/m² | 25.3 ± 0.6     |
| Resting heart rate, beats/min | 65 ± 1         |
| Resting mean arterial blood pressure, mmHg | 94 ± 5         |
| Resting LVEF, % | 65.5 ± 0.8      |
| Resting PFR, EDV/s | 3.19 ± 0.08   |
| Resting cardiac output, l/min | 6.0 ± 0.2       |
| Standard deviation of the R-R interval, ms | 77 ± 10        |
| Variation of the R-R interval | 42 ± 6         |
| Valsalva ratio  | 1.65 ± 0.05     |

Values are means ± SE and were obtained before the hypoglycemic hyperinsulinemic clamp study. LVEF, left ventricular ejection fraction; PFR, peak filling rate; EDV, end diastolic volume. There are no significant differences for any of the parameters.

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radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX). Plasma samples from diabetic patients were subjected to polyethylene glycol (PEG) precipitation before radioimmunoassay. Plasma epinephrine and norepinephrine were measured by high-performance liquid chromatography. Plasma cortisol and glucagon were measured by radioimmunoassay.

Statistical analysis. All values are reported as means ± SE. Analyses of χ²- and t-tests were used to compare baseline data between the diabetic and nondiabetic groups. Analysis of variance for repeated measures was used to determine differences in continuous variables over the course of the experiment. After data were imported into Statistical Analysis Software (SAS, Cary, NC), PROC MIXED was used. For changes during euglycemia, three covariance structures were tested: compound symmetric, autoregressive order 1, and unstructured. Because of unevenly spaced data during hypoglycemia, spatial power law, unstructured, and compound symmetric covariance structures were run. The model with the covariance structure with the largest values of Akaike’s Information Criterion and Schwarz’ Bayesian Criterion was chosen to obtain estimates of the effects of patient group, time, and the interaction of patient group and time. A value for P < 0.05 was considered statistically significant.

RESULTS

Subject characteristics. The subjects with and without diabetes were well matched with respect to age, sex, body mass index, heart rate, blood pressure, resting LVEF, and resting PFR (Table 1). Although there was a trend toward a higher baseline cardiac output in the nondiabetic group, the difference was not statistically significant (P = 0.08). There were no significant differences in the baseline (resting) values for LVEF, PFR, or cardiac output between the hypoglycemic and euglycemic studies in either group. There were no differences in baseline autonomic function, as evidenced by similar standard deviations and variations in the R-R interval and a similar Valsalva ratio in the diabetic and nondiabetic groups (Table 1).

Responses to hyperinsulinemic hypoglycemia. During hyperinsulinemic hypoglycemia, insulin infusion (12 pmol·kg⁻¹·min⁻¹) increased the plasma insulin concentration from 76 ± 15 to 589 ± 92 pmol/l in the diabetic group and from 58 ± 8 to 947 ± 82 pmol/l in the nondiabetic group (P < 0.05 vs. diabetic group). The lower free insulin concentrations in the diabetic subjects may reflect insulin binding by insulin antibodies and the PEG plasma precipitation. The plasma glucose concentration profiles were nearly identical during the hypoglycemia protocol in both groups (Fig. 1). However, the steady-state glucose infusion rate required to maintain hypoglycemia during the last 30 min of the study was 14.8 ± 4.0 μmol·kg⁻¹·min⁻¹ in the diabetic group and only 7.7 ± 1.7 μmol·kg⁻¹·min⁻¹ in the nondiabetic group (P < 0.05, Fig. 1). Hyperinsulinemic hypoglycemia increased the plasma lactate concentration in both diabetic and nondiabetic subjects (Fig. 1), although to a lesser extent in the diabetic group (P < 0.05). Skeletal muscle glycogen is mobilized during hypoglycemia (7), and the smaller increase in the lactate concentration in the diabetic group may reflect decreased epinephrine-stimulated glycogenolysis. In addition, the plasma nonesterified fatty acid concentration decreased in both groups during hyperinsulinemic hypoglycemia (Fig. 1).

As expected, the counterregulatory response to hypoglycemia was blunted in the diabetic subjects (Fig. 2). Specifically, epinephrine concentrations increased 8-fold in the diabetic group vs. 20-fold in the nondiabetic group (P < 0.05). Similarly, norepinephrine concentrations increased only 60% in the diabetic group vs. almost threefold in the nondiabetic group (P < 0.05). In addition, the increase in plasma cortisol and glucagon concentrations during hypoglycemia was significantly greater in the nondiabetic group (P < 0.05).

During hypoglycemia, there was a small but significant increase in the heart rate in both the diabetic and nondiabetic groups (Table 2). However, there was a
The cardiac output, calculated as the product of heart rate and stroke volume, increased by almost 2 l/min in both the diabetic and nondiabetic groups (Table 2). However, once again, the increase in cardiac output was slower in the diabetic group (Fig. 3D). Although there was a trend toward a higher end diastolic volume in the nondiabetic group during the hypoglycemic study, the difference was not statistically significant (Fig. 3B).

Associated with the increase in cardiac output was a significant increase in the LVEF during hypoglycemia in both the diabetic and nondiabetic groups (Table 2; Fig. 3E). However, there was also a slower increase in LVEF in the diabetic group, with a significant interaction between time and the presence of diabetes in the analysis of variance (Fig. 3E). In addition, there was an augmentation of diastolic function during hypoglycemia as evidenced by an increase in the PFR in both groups (Table 2; Fig. 3F). As with the changes in LVEF, the changes in PFR over time were different between the two groups, with the PFR increasing earlier in the nondiabetic group (Fig. 3F).

**Responses to hyperinsulinemic euglycemia.** To determine the contribution of hyperinsulinemia per se to the increases in systolic and diastolic cardiac function observed during hypoglycemia, left ventricular function was also examined during a hyperinsulinemic euglycemic clamp in the same subjects. As in the hypoglycemic clamps, despite identical insulin infusions, the plasma free insulin concentration increased less in the diabetic group (from 64 ± 7 to 504 ± 93 pmol/l) than in the nondiabetic group (from 56 ± 5 to 905 ± 65 pmol/l) (P < 0.05 vs. diabetic group). The steady-state glucose infusion rate at the end of the study was 34.4 ± 3.5 μmol·kg⁻¹·min⁻¹ in the diabetic group and 43.8 ± 3.5 μmol·kg⁻¹·min⁻¹ in the nondiabetic group (P < 0.05, Fig. 1). The lower requirement for exogenous glucose in the diabetic group primarily reflected the relative insulin resistance observed in type 1 diabetic subjects (12). Hyperinsulinemia in the setting of euglycemia did not significantly affect the plasma concentrations of epinephrine, norepinephrine, cortisol, or glucagon in either group (Fig. 2).

The heart rate increased in both groups during euglycemic hyperinsulinemia (Table 2; Fig. 4A). There was a trend toward an increased stroke volume in the

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**Table 2. Changes in hemodynamic parameters in diabetic and nondiabetic subjects during hyperinsulinemic hypoglycemia and hyperinsulinemic euglycemia**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diabetic Hypoglycemia</th>
<th>Diabetic Euglycemia</th>
<th>Nondiabetic Hypoglycemia</th>
<th>Nondiabetic Euglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHeart rate, beats/min</td>
<td>11 ± 2*</td>
<td>9 ± 2*</td>
<td>7 ± 3†</td>
<td>5 ± 2†</td>
</tr>
<tr>
<td>ΔStroke volume, ml</td>
<td>9 ± 3†</td>
<td>6 ± 4</td>
<td>15 ± 5‡</td>
<td>-2 ± 3</td>
</tr>
<tr>
<td>ΔCardiac output, l/min</td>
<td>1.8 ± 0.3*</td>
<td>1.2 ± 0.3*</td>
<td>2.0 ± 0.5‡</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>ΔLVEF, %</td>
<td>11 ± 2†</td>
<td>7 ± 1†</td>
<td>13 ± 2†‡</td>
<td>4 ± 2†</td>
</tr>
<tr>
<td>ΔPFR, EDV/s</td>
<td>0.88 ± 0.18*</td>
<td>0.38 ± 0.13†</td>
<td>0.79 ± 0.17†</td>
<td>0.14 ± 0.16</td>
</tr>
</tbody>
</table>

Values reported are means ± SE. Changes in hemodynamic parameters are defined as the difference between the mean values for the final 30 min of the study and the baseline measurements. *P < 0.001 compared with no change (Δ = 0); †P < 0.05 compared with no change; ‡P < 0.05 compared with the value during euglycemia.
diabetic group, but there was no change in the nondiabetic group (Table 2; Fig. 4C). Furthermore, there were no differences in the end diastolic volumes in the two groups during hyperinsulinemic euglycemia (Fig. 4B). Cardiac output increased in the diabetic group (P < 0.05) but did not increase significantly in the nondiabetic group (Table 2; Fig. 4D). The LVEF increased in the diabetic group (ΔLVEF = 7 ± 1%) and increased modestly in the nondiabetic group (ΔLVEF = 3 ± 1%).
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4 ± 2%) (Fig. 4E). In contrast to the slower increase in LVEF during hypoglycemia in the diabetic group, the time course for changes in LVEF during euglycemia was similar in the diabetic and nondiabetic groups. In diabetic subjects, hyperinsulinemia caused an increase in the PFR during euglycemia, whereas the PFR in the nondiabetic group was not affected by insulin infusion (Table 2; Fig. 4F).

When the cardiac responses to hypoglycemia and euglycemia were compared, the differences between the two studies were much more apparent in the nondiabetic group. When the euglycemic changes in LVEF and PFR were compared with those observed during hypoglycemia, the increase in both LVEF and PFR was significantly greater during hypoglycemia only in the nondiabetic group (Table 2; Fig. 5). Similarly, with respect to stroke volume and cardiac output (Table 2), significant differences between the euglycemic and hypoglycemic studies were observed only in the nondiabetic group. These results suggest that hyperinsulinemia per se accounted for most of the cardiac changes observed during hyperinsulinemic hypoglycemia in diabetic, but not in nondiabetic, subjects. They also indicate that the cardiac response to hypoglycemia per se was blunted in the diabetic subjects.

DISCUSSION

The present study is the first to assess the cardiovascular responses to insulin-induced hypoglycemia in type 1 diabetic subjects and contains several novel observations. The diabetic subjects had a significant augmentation of systolic and diastolic left ventricular function during hyperinsulinemic hypoglycemia, which together with an increase in heart rate resulted in a substantial increase in cardiac output. Overall, the changes in cardiac function during hypoglycemia were similar in magnitude but were delayed compared with those observed in nondiabetic subjects. However, in the case of the diabetic subjects, the response to insulin-induced hypoglycemia largely reflected the effects of hyperinsulinemia per se on cardiac function. In contrast, in the nondiabetic subjects, although hyperinsulinemic euglycemia modestly increased LVEF, there was significant further augmentation of LVEF and other cardiac parameters during hyperinsulinemic hypoglycemia. Thus these results suggest that the cardiac responses to hypoglycemia per se are diminished in intensively treated patients with type 1 diabetes.

The current studies examined the effects of steady-state moderate hypoglycemia during continuous infusions of insulin and glucose in both diabetic and nondiabetic subjects. In contrast, previous studies have analyzed the cardiovascular responses following the bolus administration of insulin and did so only in nondiabetic subjects (15, 16, 18). Coincident with the nadir of the blood glucose concentration in the earlier studies was a transient 25% increase in the LVEF (15, 16), which is twofold greater than that seen in the present study but occurred at a much more extreme degree of hypoglycemia (~1 mmol/l).

Recent studies have also documented an increase in LVEF during euglycemic insulin administration in nondiabetic subjects (25). In the current study, there were statistically significant increases in LVEF in the diabetic and nondiabetic groups during euglycemic hyperinsulinemia. Interestingly, the insulin-induced change in LVEF tended to be lower in the nondiabetic subjects, despite higher plasma insulin concentrations in that group. It is possible that the differences in the hemodynamic response to insulin between the diabetic and nondiabetic subjects might have been even more pronounced if the insulin concentrations had been identical during the infusions.

Diastolic performance was not assessed during hypoglycemia in previous studies. The PFR is an index of left ventricular filling during diastole and is an important determinant of cardiac performance (3). The PFR reflects not only the rate of active myocardial relaxation, which is increased by adrenergic stimulation, but is also influenced by preload, heart rate, afterload,
and the intrinsic compliance of the left ventricle (5, 6). Although patients with diabetes mellitus may have diastolic dysfunction (10, 14, 19), the subjects included in the present study had normal baseline values for PFR and were able to increase their PFR during hypoglycemia, although the increase was somewhat delayed in the diabetic group. This augmentation in diastolic filling enhances the ability of the left ventricle to fill more rapidly at higher heart rates, thereby maintaining left ventricular end diastolic volume and enabling the heart to increase the stroke volume and cardiac output during hyperinsulinemic hypoglycemia. In contrast to the augmentation of PFR during hypoglycemia, euglycemic hyperinsulinemia caused a significant increase in PFR only in the diabetic group.

In this study, we utilized a moderate insulin dose (12 pmol·kg\(^{-1}\)·min\(^{-1}\)) to ensure that hypoglycemia would be sustained during the study, particularly in the young, healthy nondiabetic subjects, who have a more pronounced counterregulatory response to hypoglycemia. However, because this dose of insulin augmented cardiac function, the specific effect of hypoglycemia per se could only be defined by comparing the results of the hypoglycemic and euglycemic hyperinsulinemic studies performed in the same individual. When the results of these studies are compared (Table 2; Fig. 5), it is evident that the specific responses to hypoglycemia are different in the diabetic and nondiabetic groups. In the diabetic subjects, the effects of insulin-induced hypoglycemia can be attributed largely to the effects of hyperinsulinemia per se, because there was no significantly greater augmentation of function during the hypoglycemic clamp compared with the euglycemic clamp. In contrast, in the nondiabetic group, there were significantly greater increases in LVEF, PFR, stroke volume, and cardiac output in the hypoglycemic compared with the euglycemic study. Thus the augmentation of cardiac function in response to hypoglycemia per se appears to be blunted in diabetic subjects.

Previous studies have demonstrated that adrenal catecholamine release is blunted specifically during recurrent hypoglycemia (1, 8, 9, 20, 27). As expected, the intensively treated diabetic subjects in the present study had impaired counterregulatory responses to hypoglycemia, as reflected by the blunted rise in the plasma epinephrine, norepinephrine, cortisol, and glucagon concentrations. This impaired counterregulatory response accounts for the greater amount of exogenous glucose required during hyperinsulinemic hypoglycemia in the diabetic group and most likely results from decreased stimulation of hepatic gluconeogenesis and muscle glycogenolysis. On the basis of our findings, a diminished adrenomedullary response also delayed and attenuated the augmentation of cardiac function during hypoglycemia in the diabetic group.

The increase in cardiac function observed during euglycemic hyperinsulinemia likely reflects both insulin-mediated sympathetic activation (2, 28) and peripheral vasodilation (2, 21). The former mechanism increases cardiac contractility and heart rate, whereas the latter decreases left ventricular afterload, and both increase ejection phase indexes and cardiac output. Sympathetic activation leads to adrenomedullary epinephrine release and increased local cardiac sympathetic activity. However, as in previous studies, there was no change in the epinephrine concentration during euglycemic insulin infusions (28), suggesting that the increase in left ventricular contractile function during hyperinsulinemic euglycemia was not due to adrenomedullary release of epinephrine. Although the norepinephrine concentration tended to increase during euglycemic hyperinsulinemia in the present study, as in previous studies (28), changes in the plasma norepinephrine concentration provide only an indirect marker for cardiac sympathetic activation. Although direct measurement of neurosympathetic cardiac activity is not possible, it is likely that the increase in cardiac function during euglycemic hyperinsulinemia also reflects neurocardiac sympathetic activation.

The subjects in the present study had no evidence of coronary artery disease, hypertension, or autonomic neuropathy, all of which can affect left ventricular function and cardiac sympathetic function. Previous studies have demonstrated that type 1 diabetic patients have scintigraphic evidence of cardiac sympathetic dysinnervation based on altered \(^{123}\)I-labeled metaiodobenzylguanidine or \(^{11}\)C-hydroxyephedrine uptake, even in the absence of changes in standard autonomic testing (30, 32, 34). Although there was no evidence of cardiac autonomic neuropathy in the diabetic group on the basis of heart rate variability and standard autonomic testing, we cannot exclude the possibility that the diabetic patients in this study may have had early cardiac sympathetic dysinnervation. If present, dysinnervation might be responsible, in part, for the trend toward lower baseline hemodynamic parameters observed in the diabetic group. It is also possible that some degree of regional hyperinnervation (34) or denervation hypersensitivity might amplify the cardiac sympathetic response to hyperinsulinemia, contributing the more dramatic cardiac effects of hyperinsulinemic euglycemia observed in the diabetic group.

In clinical practice, diabetic patients may experience hypoglycemia at plasma concentrations of insulin that are lower than those used in the present study and have less cardiovascular effect than the dose utilized in our study. However, it is difficult experimentally to mimic the development of hypoglycemia seen in clinical practice, which is often unpredictable and involves a complex combination of excessive insulin administration (for the amount of food intake) and exercise. Nonetheless, the current study indicates that the response to hypoglycemia per se is diminished in intensively treated subjects with diabetes, and it is likely that the cardiac response of patients with diabetes to hypoglycemia would also be considerably less in the clinical setting.

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