Inhaled Formoterol Diminishes Insulin-Induced Hypoglycemia in Type 1 Diabetes

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OBJECTIVE

Hypoglycemia is one of the major factors limiting implementation of tight glycemic control in patients with type 1 diabetes and is associated with increased morbidity and mortality during intensive insulin treatment. β-2 Adrenergic receptor (AR) agonists have been reported to diminish nocturnal hypoglycemia; however, whether long-acting inhaled β-2 AR agonists could potentially be used to treat or prevent hypoglycemia has not been established.

RESEARCH DESIGN AND METHODS

Seven patients with type 1 diabetes and seven healthy control subjects received inhaled formoterol (48 μg), a highly specific β-2 AR agonist, or a placebo during a hyperinsulinemic-hypoglycemic clamp study to evaluate its capacity to antagonize the effect of insulin. In a second set of studies, five subjects with type 1 diabetes received inhaled formoterol to assess its effect as a preventive therapy for insulin-induced hypoglycemia.

RESULTS

During a hyperinsulinemic-hypoglycemic clamp, compared with placebo, inhaled formoterol decreased the glucose infusion rate required to maintain plasma glucose at a target level by 45–50% ($P < 0.05$). There was no significant effect on glucagon, epinephrine, cortisol, or growth hormone release (P = NS). Furthermore, in volunteers with type 1 diabetes 1 h after increasing basal insulin delivery twofold, glucose levels dropped to 58 ± 5 mg/dL, whereas hypoglycemia was prevented by inhaled formoterol ($P < 0.001$).

CONCLUSIONS

Inhalation of the β-2 AR–specific agonist formoterol may be useful in the prevention or treatment of acute hypoglycemia and thus may help patients with type 1 diabetes achieve optimal glucose control more safely.

Hypoglycemia remains the major risk factor limiting the use of and compliance with intensified insulin therapeutic regimens (1,2), which have been shown to prevent or delay complications in patients with type 1 diabetes (3). Severe hypoglycemia may occur in some patients without warning symptoms (4,5), preventing them from taking corrective action and necessitating help from other individuals. Thus, for many patients, the immediate fear of hypoglycemia exceeds the fear of long-term complications.

A fall in blood glucose in subjects without diabetes provokes a multitiered response, including suppression of endogenous insulin secretion, release of counterregulatory hormones, and symptoms of hypoglycemia, which together act to restore

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euglycemia (6,7). In type 1 diabetes, this critical defense system may be interrupted at every level (6,8,9). Loss of endogenous insulin and reliance on exogenous hormones make rapid insulin reductions impossible, and the loss of islet β-cells also leads to the loss of glucagon responses to hypoglycemia, a stimulus-specific defect seen in the vast majority of type 1 diabetes patients after several years (6,9,10). Diminished epinephrine (adrenaline) response in type 1 diabetes, however, appears to be mainly a hypothalamic metabolic adaptation to antecedent recurrent hypoglycemia that occurs in patients with type 1 diabetes (1,11,12). The impaired epinephrine response is often accompanied by hypoglycemia unawareness, which greatly magnifies the risk of hypoglycemia (6). To avoid further episodes of hypoglycemia and interrupt this vicious cycle, a reduction in insulin delivery and/or increased carbohydrate consumption are commonly recommended (13), measures that generally worsen glycemic control.

A variety of therapeutic approaches have been developed to reduce the risk of hypoglycemia, including patient education, judicious use of carbohydrate intake, changes in dosing or timing of insulin delivery, and intensification of glucose monitoring (13–17). In addition, a few small pilot clinical trials have suggested that certain drugs offer potential utility in increasing defenses against hypoglycemia in patients with type 1 diabetes, including terbutaline (18), diazoxide (19), and naloxone (20). Among these drugs, terbutaline, a specific β-2 agonist, has been reported to prevent nocturnal hypoglycemia (21), although the nighttime dose of terbutaline required was associated with hyperglycemia the following morning (18). The more specific long-acting β-2 agonist, formoterol, has been shown in rodent studies to limit insulin-induced hypoglycemia by diminishing the inhibitory effect of insulin on glucose production (22). Formoterol's effect appears to be mediated in large part via a direct effect on the liver, although activation of β-2 receptors in the ventral medial hypothalamus might contribute as well (23). It is noteworthy that formoterol is approved for acute treatment of asthma when used in combination with steroids and comes in an inhaled formulation, which could provide direct access to the arterial circulation and more rapid onset of action. Its long half-life (10 h) (24) also makes it a potential therapeutic agent to prevent nocturnal hypoglycemia. The current study was therefore undertaken to assess the efficacy of inhaled formoterol during an acute bout of insulin-induced hypoglycemia in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Study subjects participated in two research protocols; their characteristics are summarized in Table 1. The first protocol involved a control group with seven healthy volunteers (3 men and 4 women; age 36 ± 3 years) without diabetes and seven subjects (2 men and 5 women; age 31 ± 4 years) with type 1 diabetes (6 on insulin pump and 1 on multiple daily insulin injections) who were matched by sex, age, and BMI. As expected, hemoglobin A_{1c} levels were higher in the individuals with type 1 diabetes. The second protocol included five subjects (1 man and 4 women; age 35 ± 6 years) with type 1 diabetes (4 on insulin pump therapy and 1 on multiple insulin injections). The protocol was approved by the Yale University Institutional Review Board (Human Investigation Center). All subjects provided written informed consent before enrolling in the study.

Study participants came to the Hospital Research Unit (HRU) of Yale New Haven Hospital for a screening visit. They were excluded if they had any major medical disorders (liver, cardiovascular, kidney disease), diabetes complications (neuropathy, nephropathy, retinopathy), hypertension, asthma, or cardiac arrhythmias. Participants who qualified for the study were invited to return to the HRU for one of the two protocols. Both protocols used a randomized, placebo-controlled, double-blinded, cross-over design, with two separate visits at least 1 week and not more than 2 months apart for administration of inhaled formoterol (Merck & Co., Inc.) or a placebo, followed by a hyperinsulinemic euglycemic-hypoglycemic clamp. All studies were performed at the same time of the day in the morning, after a 10-h overnight fast.

Participants in the control group and the participants with type 1 diabetes on insulin pump therapy were admitted on the morning of the study, whereas participants with type 1 diabetes on injectable insulin were admitted to the HRU the night before the study, where they received an overnight basal intravenous infusion of regular insulin to maintain glucose levels at a target range (100–120 mg/dL). In the morning of the study, an intravenous plastic catheter was inserted in an antecubital vein for insulin and glucose infusion. A second intravenous catheter was placed in the contralateral arm for blood draws. The metabolic protocols used are described below:

Protocol 1: Hyperinsulinemic Euglycemic-Hypoglycemic Clamp Study

In the morning of the study, baseline blood samples were obtained for glucose and glucoregulatory hormone (insulin, glucagon, epinephrine, norepinephrine, growth hormone, and cortisol) measurements (Fig. 1). Immediately before the hyperinsulinemic-hypoglycemic clamp study was started, inhaled formoterol (48 μg) or inhaled placebo was given.

Table 1—Subject characteristics

	Protocol 1		Protocol 2
	Control (n = 7)	Type 1 diabetes (n = 7)	Type 1 diabetes (n = 5)
Sex (n)			
Male	3	2	1
Female	4	5	4
Age (years)	36 ± 3	31 ± 4	35 ± 6
Weight (kg)	70.0 ± 4.9	70.2 ± 4.0	64 ± 6
BMI (kg/m^2)	23.7 ± 0.8	25.8 ± 1.1	24.2 ± 2.1
HbA_{1c} (%)	5.3 ± 0.1	6.8 ± 0.3*	7.2 ± 0.4
HbA_{1c} (mmol/mol)	34.5 ± 1.0	51.3 ± 3.2*	55.2 ± 4.5

Continuous data are expressed as the mean ± SE. *$P < 0.05$ comparing control vs. group with type 1 diabetes.

At time "zero," an intravenous continuous infusion of insulin was started at a rate of 2 mU/kg/min. Dextrose 20% was started concomitantly and adjusted based on plasma glucose levels to maintain glucose levels within the euglycemic range (95–100 mg/dL) for 30 min. Subsequently, plasma glucose levels were allowed to fall into the hypoglycemic range (~55–58 mg/dL) for the subsequent 60 min. Measurements of insulin and counterregulatory hormones were obtained throughout the entire study. Pulse and blood pressure were measured with an automatic vital signs monitor every 30 min throughout the clamp in all participants, except in two participants in the type 1 diabetes group whose vital signs were not recorded. During hypoglycemia, all participants were asked "how do you feel?" and any symptoms mentioned were recorded.

Protocol 2: Hypoglycemia Prevention Study

To evaluate if inhaled formoterol could prevent the development of insulin-induced hypoglycemia, five volunteers with type 1 diabetes were studied. Subjects receiving insulin pump treatment were admitted in the morning of the study and kept at their basal insulin infusion rate, whereas the subject receiving multiple daily insulin injections was admitted the night before the study and placed on an insulin drip overnight to maintain glucose levels at ~100–120 mg/dL (Fig. 2). The rate of the insulin infusion required overnight to maintain glucose levels within the target range was used as the participant's basal insulin infusion rate. In the morning of the study, baseline blood samples were obtained for glucose and glucoregulatory hormones (see above) and after that, an intravenous continuous infusion of insulin at ~80–100% of the subject's basal subcutaneous insulin infusion rate was started. To evaluate if formoterol could prevent insulin-induced hypoglycemia, subjects received inhaled formoterol (48 μg) or placebo 60 min before being exposed to a twofold increase in the basal insulin infusion rate. This higher insulin infusion rate was maintained for 60 min until the end of the study. During this time, glucose levels were monitored every 5 to 10 min and allowed to drop freely. If plasma glucose levels declined to a moderately severe hypoglycemic range (<55 mg/dL), an intravenous infusion of dextrose 20% was started and titrated as needed to avoid further decline in the plasma glucose levels. Insulin and counterregulatory hormones were measured throughout the study protocol.

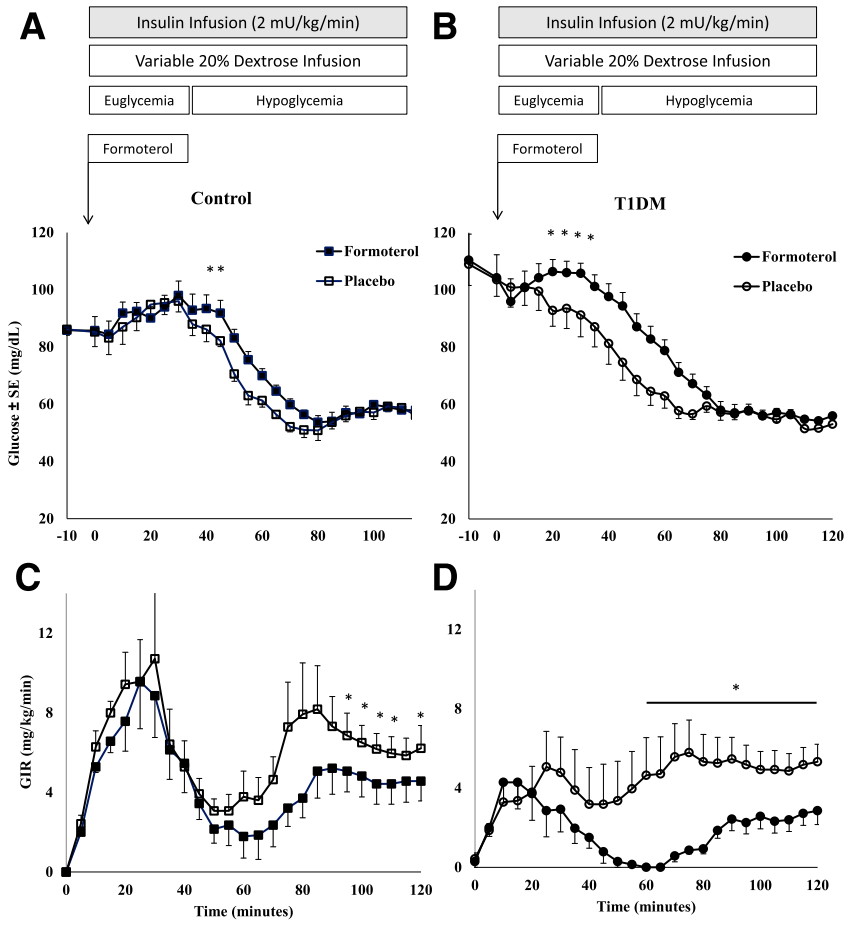

Figure 1—Protocol 1: Plasma glucose concentration and GIR during the hypoglycemia-hyperinsulinemic clamp in the control subjects and type 1 diabetes participants after receiving inhaled formoterol or placebo. *A*: Plasma glucose concentration in the control group. *B*: Plasma glucose concentration in the group with type 1 diabetes (T1DM). *C*: GIR in the control group. *D*: GIR in the group with type 1 diabetes. Data are the mean ± SE. **P* < 0.05 comparing formoterol vs. placebo treatment.

Biochemical Analysis

The plasma glucose concentration was determined by the glucose oxidase method (YSI Life Science, Yellow Springs, OH). Plasma insulin and glucagon (Millipore, St. Charles, MO), growth hormone (MP Biomedical, Irvine, CA), and cortisol (Diagnostic Products Corp., Los Angeles, CA) were measured by double-antibody radioimmunoassay, and plasma catecholamines were measured by high-performance liquid chromatography (ESA, Chelmsford, MA).

Statistical Analysis

Statistical analyses were performed using SPSS 19.0 software (IBM Corp.). All values represent the mean ± standard error (SE). A two-way repeated-measures ANOVA was performed to identify the interaction effect of treatment over time within each group. Comparisons within subjects were determined by the two-tailed Student *t* test for paired samples and between subjects by the unpaired Student *t* test for equality of means. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Protocol 1: Hyperinsulinemic Euglycemic-Hypoglycemic Clamp Study

Glucose and Hormone Levels

Baseline fasting plasma glucose levels (107 ± 6 mg/dL vs. 86 ± 1 mg/dL; $P <$ 0.01) were higher in the subjects with type 1 diabetes compared with the control group. However, within each group,

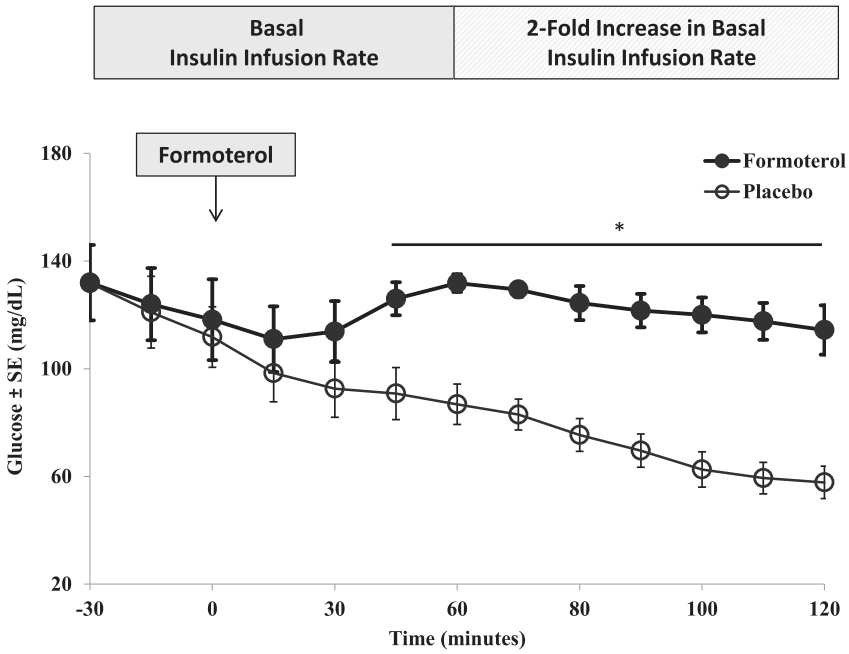

Figure 2—Protocol 2: Plasma glucose concentration during the hypoglycemia prevention study in volunteers with type 1 diabetes treated with inhaled formoterol or placebo. Data are mean ± SE. *$P < 0.05$ comparing formoterol vs. placebo treatment.

there were no differences in basal glucose levels between treatment visits (Fig. 1*A* and *B*). During the euglycemic-hypoglycemic clamp, there was a significant difference in glucose levels after formoterol treatment compared with placebo for either group studied (two-way repeated-measures ANOVA, interaction treatment by time: control, $F_{(24,120)} = 1.637$, $P < 0.05$; type 1 diabetes, $F_{(2,3,312)} = 405.81$, $P < 0.0001$). At the end of the euglycemic phase of the insulin-clamp study, formoterol or placebo treatment did not affect glucose levels in the control group (98 ± 3 mg/dL vs. 96 ± 5 mg/dL; *P* = NS). In contrast, in subjects with type 1 diabetes, formoterol treatment induced an increase in plasma glucose levels compared with the placebo treatment (106 ± 5 mg/dL vs. 91 ± 5 mg/dL; *P* = 0.02). Subsequently, to reach the hypoglycemic target range, the dextrose infusion was reduced, and glucose levels were allowed to fall. In both groups, formoterol, compared with placebo, delayed the time needed to attain hypoglycemia by 10–15 min. Target plasma glucose levels (~55–58 mg/dL) were, however, achieved during the last 30 min of the hypoglycemic phase of the insulin clamp in both groups during either treatment (*P* = NS). Insulin levels increased similarly during the hypoglycemic clamp study in both groups and were not affected by the administration of formoterol (control placebo: 158 ± 14 μU/mL, formoterol: 132 ± 11 μU/mL; type 1 diabetes placebo: 147 ± 16 μU/mL, formoterol: 141 ± 16 μU/mL; *P* = NS). However, the glucose infusion rate (GIR) during the last 60 min of the insulin clamp was significantly reduced by formoterol treatment in both control and type 1 diabetes groups (GIR: control: 6.2 ± 1.2 mg/kg/min vs. 3.9 ± 1.0 mg/kg/min, *P* = 0.05; type 1 diabetes: 5.2 ± 1.2 mg/kg/min vs. 1.7 ± 0.4 mg/kg/min, $P < 0.02$; placebo compared with formoterol, respectively) (Fig. 1*C* and *D*). The GIR required to maintain hypoglycemia after formoterol delivery was lower in the patients with type 1 diabetes than in the control group (*P* = 0.05) but not with placebo administration (*P* = NS).

As reported in Table 2, basal levels of the counterregulatory hormones before the study were comparable in the control group in both the formoterol and placebo experiments. In the group with type 1 diabetes, glucagon and epinephrine levels were comparable at baseline, whereas basal norepinephrine levels were lower on the formoterol treatment day. Evaluation of the effect of treatment with formoterol on counterregulatory hormonal response to hypoglycemia showed no treatment-by-time interaction effect in the control or the type 1 diabetes group (two-way repeated-measures ANOVA, *P* = NS). However, when the groups were evaluated separately, small changes in some of the counterregulatory hormones occurred during the euglycemic and hypoglycemic phase of the hyperinsulinemic clamp (Table 2).

Cardiovascular Response

Formoterol treatment did not affect blood pressure in the group with type 1 diabetes or the control group (data not shown). During euglycemia, however, inhaled formoterol increased the pulse rate by 6 ± 3 bpm ($P < 0.05$) in the control group, but the increase in the pulse rate in the control group in response to hypoglycemia was not significantly affected by formoterol treatment (placebo: 6 ± 2 bpm, formoterol: 7 ± 3; *P* = NS). In the subjects with type 1 diabetes, the pulse rate increased after formoterol treatment, but the small number of participants in this group (*n* = 5) limited our interpretation of these results. None of the volunteers complained of palpitations, but one participant after placebo and four participants after formoterol treatment reported feeling tremulousness during hypoglycemia.

Protocol 2: Hypoglycemia Prevention Study

As shown in Fig. 2, inhaled formoterol protected against the development of hypoglycemia ($P < 0.005$) in subjects with type 1 diabetes compared with the inhaled placebo. Plasma glucose significantly increased 45 min after administration of inhaled formoterol and protected against hypoglycemia ($P < 0.005$) when the basal insulin infusion rate was increased twofold at 1 h after formoterol inhalation. In the placebo treatment group, doubling the basal insulin infusion caused plasma glucose to fall to 58 ± 5 mg/dL at 1 h. In contrast, plasma glucose levels in the formoterol treatment group remained stable and were twofold higher than the levels in the placebo group at the end of the study ($P < 0.05$). Moreover, no patients required dextrose 20% infusion during the formoterol treatment study visit, whereas after placebo, three

Table 2—Counterregulatory hormone concentration during the hyperinsulinemic euglycemic-hypoglycemic clamp

	Control		Type 1 diabetes	
	Placebo	Formoterol	Placebo	Formoterol
Glucagon (pg/mL)				
Basal	76 ± 13	74 ± 11	53 ± 8	56 ± 10
Euglycemia	59 ± 11*	58 ± 13*	55 ± 10	54 ± 9
Hypoglycemia	66 ± 16	73 ± 18†	43 ± 8*†	46 ± 9*
Epinephrine (pg/mL)				
Basal	15 ± 4	16 ± 5	18 ± 4	17 ± 5
Euglycemia	12 ± 3	12 ± 4*	21 ± 5	13 ± 2
Hypoglycemia	46 ± 15†	55 ± 22	44 ± 15	19 ± 4
Norepinephrine (pg/mL)				
Basal	185 ± 37	192 ± 24	180 ± 28	133 ± 13
Euglycemia	216 ± 31	273 ± 22	226 ± 31*	211 ± 30*
Hypoglycemia	156 ± 21	181 ± 14†	241 ± 30*	190 ± 32*

Data are mean ± SE. Euglycemia represents the hormone levels at the end of the euglycemia phase (30 min) and hypoglycemia represents the average of the hormone levels at the end of the hypoglycemic-hyperinsulinemic clamp (105–120 min). *$P < 0.05$ vs. basal levels; †$P < 0.05$ hypoglycemia vs. euglycemia.

participants required intravenous infusion of dextrose 20% to avoid glucose levels falling below 50 mg/dL. Notably, the amount of insulin given during this protocol was comparable in both groups (placebo: 3.6 ± 0.4 units vs. formoterol: 3.4 ± 0.6 units; P = NS), as were free insulin levels (placebo: 15.8 ± 1.6 mU/mL vs. formoterol 15.6 ± 3.0 mU/mL; P = NS).

Immediately before the increase in the basal insulin infusion, there were no differences in the measured hormone levels (glucagon, cortisol, growth hormone, epinephrine, and norepinephrine) (P = NS) in the formoterol or placebo treatment groups at 60 min. At the end of the study, when glucose levels were markedly higher in the formoterol group, epinephrine levels were significantly lower compared with those in the control groups (placebo: 63 ± 21 pg/mL vs. formoterol: 14 ± 2 pg/mL; P = 0.05). No significant differences were seen in norepinephrine or glucagon levels.

CONCLUSIONS

Use of intensive insulin therapy in patients with type 1 diabetes is limited by higher rates of severe hypoglycemia (2), which for many patients limits their ability and motivation to achieve glycemic target goals (1). The therapeutic options for treating or preventing hypoglycemia are currently limited and generally rely on adjusting the dose of insulin or increasing carbohydrate consumption (13). Although these therapeutic modifications reduce hypoglycemia frequency and/or severity, they commonly lead to increased glucose levels. Thus, there remains a need for novel therapies that allow carrying out tight glycemic control more safely.

Previous small clinical trials showed that terbutaline diminished the risk of nocturnal hypoglycemia (18,21). In those studies, however, there was an increase in fasting glucose levels the next morning. In this study we tested whether formoterol, a more selective and long-acting β-2 agonist, could be used to counteract the effect of insulin and prevent hypoglycemia in patients with type 1 diabetes. This compound has been shown to promote glucose production in rodents and is commercially available in a more rapidly acting inhaled formulation (24).

In the current study, inhaled formoterol significantly decreased the amount of glucose required to keep circulating glucose at a standardized hypoglycemic level during a hyperinsulinemic clamp study in healthy control subjects and in subjects with type 1 diabetes. These findings are consistent with the established insulin antagonistic effects of formoterol in humans (25) as well as rodent data showing that peripheral administration of formoterol mainly acts to directly increase hepatic glucose production with no significant effect on counterregulatory hormones (22). These results imply that the metabolic effects of inhaled formoterol are most likely due to a direct effect of formoterol on β-2 receptors in the peripheral tissues (i.e., hepatic glucose production and/or insulin-stimulated peripheral glucose uptake). However, it is possible that formoterol may affect peripheral metabolism indirectly by activating β-2 receptors in the hypothalamus (23).

To examine if inhaled formoterol could be used to prevent hypoglycemia in patients with type 1 diabetes, we gave formoterol 60 min before doubling the participants' basal insulin infusion rate. The study was designed to simulate episodes of iatrogenic insulin-induced hypoglycemia that result from an imbalance between the basal insulin dose needed and the dose of insulin given by the patient, something that particularly occurs during the first third of the nighttime sleep cycle, a time when such patients have reduced insulin requirements as well as diminished capacity to release catecholamines, making them more vulnerable to severe hypoglycemia (26). Under these conditions, we show that formoterol effectively prevented an acute hypoglycemic episode. These findings suggest that inhaled formoterol may have potential value as a preventive therapy for iatrogenic hypoglycemia, particularly in patients with type 1 diabetes with hypoglycemia-associated autonomic failure and frequent episodes of nocturnal hypoglycemia. Of note, this was accomplished without a major increase in glucose levels. However, more studies will be needed to define the optimal dose and time for it to be delivered as well as its long-term effect on glycemic control in patients with type 1 diabetes.

The study has some limitations. The short duration of the studies did not allow us to determine the effect of formoterol during the subsequent hours after completion of the study. Even though the study participants were asked to report major problems in the hours after the study and no major side effects were described, glucose levels were not monitored in a standardized fashion. In addition, the study was limited by the small number of subjects tested, and thus further studies will be necessary to confirm the efficacy of formoterol in the treatment of iatrogenic hypoglycemia.

Another limitation of this study is that the hyperglycemic effect of formoterol is not restricted to hypoglycemia, as demonstrated by an increase in plasma glucose levels in the group with type 1

diabetes at the end of the first step (euglycemic phase). Formoterol treatment may increase glucose levels, and long-term studies will be necessary to evaluate its effect on glycemic control. However, due to the limited options for prevention of hypoglycemia, formoterol treatment may be useful for a subgroup of patients with type 1 diabetes at high risk for severe and frequent episodes of hypoglycemia.

With regard to the possible adverse cardiovascular effects of formoterol, we measured vital signs during the hypoglycemia-clamp study. Neither blood pressure changes nor palpitations occurred after formoterol treatment in healthy subjects or in patients with type 1 diabetes, although small increases in pulse rate were observed.

In summary, our results from this pilot study suggest that specific β-2 agonists delivered via inhalation may prove useful during intensive insulin therapy in patients with type 1 diabetes who have hypoglycemia-associated autonomic failure and thus are at high risk for hypoglycemia. Its effects occur rapidly and appear to be a direct effect of formoterol on peripheral glucose metabolism, particularly in the liver (22), because counterregulatory hormone responses were not significantly altered in subjects with and without diabetes. Although, as our data suggest, formoterol acts to directly offset the effects of insulin and most likely can cause mild hyperglycemia (similar to the studies using terbutaline for hypoglycemia [18]), we believe that due to the limited options for prevention of hypoglycemia, a more specific β-agonist might benefit a particular group of patients unable to generate a counterregulatory hormone response, resulting in a history of severe and frequent hypoglycemia.

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Duality of Interest. R.S.S. serves on a Merck & Co., Inc. Data Safety Monitoring Board for a type 2 diabetes medication that is unrelated to formoterol. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.D.B.-D. researched data and wrote the manuscript. S.N. and R.S.S. researched data, contributed to discussion, and reviewed and edited the manuscript. J.H. researched data and reviewed and edited the manuscript. B.S. contributed to discussion and reviewed and edited the manuscript. R.S.S. 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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