Reduced Hypoglycemia and Increased Time in Target Using Closed-Loop Insulin Delivery During Nights With or Without Antecedent Afternoon Exercise in Type 1 Diabetes

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OBJECTIVE—Afternoon exercise increases the risk of nocturnal hypoglycemia (NH) in subjects with type 1 diabetes. We hypothesized that automated feedback-controlled closed-loop (CL) insulin delivery would be superior to open-loop (OL) control in preventing NH and maintaining a higher proportion of blood glucose levels within the target blood glucose range on nights with and without antecedent afternoon exercise.

RESEARCH DESIGN AND METHODS—Subjects completed two 48-h inpatient study periods in random order: usual OL control and CL control using a proportional-integrative-derivative plus insulin feedback algorithm. Each admission included a sedentary day and an exercise day, with a standardized protocol of 60 min of brisk treadmill walking to 65–70% maximum heart rate at 3:00 P.M.

RESULTS—Among 12 subjects (age 12–26 years, A1C 7.4 ± 0.6%), antecedent exercise increased the frequency of NH (reference blood glucose <60 mg/dL) during OL control from six to eight events. In contrast, there was only one NH event each on nights with and without antecedent exercise during CL control ($P = 0.04$ vs. OL nights). Overnight, the percentage of glucose values in target range was increased with CL control ($P < 0.0001$). Insulin delivery was lower between 10:00 P.M. and 2:00 A.M. on nights after exercise on CL versus OL, $P = 0.008$.

CONCLUSIONS—CL insulin delivery provides an effective means to reduce the risk of NH while increasing the percentage of time spent in target range, regardless of activity level in the mid-afternoon. These data suggest that CL control could be of benefit to patients with type 1 diabetes even if it is limited to the overnight period.

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While exercise has a myriad of benefits including improvements in cardiovascular health, body composition, and psychological well-being, it often is a double-edged sword for patients with type 1 diabetes. In patients with diabetes, the benefits of exercise are offset, in part, by the inadequacy of current methods of insulin replacement to respond to changing metabolic demands both during and after exercise, leading to an increased risk of hypoglycemia. Most severe hypoglycemic events occur during sleep, and the frequency of biochemical hypoglycemia is increased on nights after afternoon exercise. Indeed, in a study of 50 well-controlled children and adolescents with type 1 diabetes, the Diabetes Research in Children Network (DirecNet) showed that the percentage of nights during which blood glucose levels fell to ≤60 mg/dL nearly doubled (from 28 to 48%) for nights with compared with nights without antecedent afternoon exercise (1).

A number of pathophysiologic factors contribute to the increased vulnerability of youth with type 1 diabetes to nocturnal hypoglycemia (NH) after sedentary or physically active days. Using the hypoglycemic clamp technique, Jones and colleagues demonstrated that plasma epinephrine responses to hypoglycemia are markedly blunted in children and adolescents with and without diabetes during deep sleep at night (2). These findings were extended by Banarer and Cryer, who also demonstrated decreased epinephrine responses to hypoglycemia during sleep in adults with type 1 diabetes (3). Using the euglycemic clamp technique to maintain stable plasma glucose and insulin levels during the night, McMahon and colleagues have more recently shown that the rate of exogenous glucose infusion had to be sharply increased 7–11 h after afternoon exercise, even in the face of unchanged plasma insulin concentrations (4). In patients who receive fixed basal insulin doses given by insulin pump or injections of long-acting insulin analogs, the increased metabolic demands that occur on nights after afternoon exercise combined with the impaired ability of falling glucose levels to stimulate an adequate epinephrine response during sleep put patients with type 1 diabetes at increased jeopardy for NH (5).

Continuous glucose monitoring (CGM) systems provide a means to optimize overnight glucose control in patients with type 1 diabetes by more fully exploiting the variable basal infusion rate capability of insulin pumps based on

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retrospective analysis of overnight glucose profiles. However, even optimized overnight basal rates in generally sedentary children can lead to NH on nights after unexpected antecedent afternoon exercise. While the JDRF CGM randomized clinical trial demonstrated that CGM is effective in lowering A1C levels in patients with type 1 diabetes who use the devices frequently, the risk of severe hypoglycemic events was not reduced and prolonged episodes of NH were common in children and in adults (6,7). Recently, use of sensor augmented pump (SAP) therapy has been demonstrated to decrease time spent in hypoglycemia compared with pump therapy alone; yet, episodes of hypoglycemia could not be eliminated (8). Additionally, while SAP therapy may be the best possible treatment modality currently commercially available, its use by patients has been limited, with data from the Type 1 Diabetes Exchange estimating usage of CGM to 6% of study participants (9). These data support the contention that no treatment of type 1 diabetes will be optimal until there is feedback control of insulin-delivery rates based on real-time changes in sensor glucose levels.

Steil and colleagues carried out the "first in man" studies of a closed-loop (CL) system using an external insulin pump, external glucose sensor, and a proportional-integrative-derivative (PID) algorithm in 10 adult patients with type 1 diabetes in a clinical research center setting (10). While delays in insulin absorption resulting from the use of the subcutaneous route of insulin administration contributed to early postprandial hyperglycemia and late postmeal hypoglycemia, overnight glucose control was outstanding. Subsequent studies have demonstrated the ability of CL systems to regulate glucose levels during the overnight period (11–17), but physical activity of study subjects was restricted in most of these inpatient investigations. In this study, we used the same exercise paradigm that doubled the rate of NH in the DirecNet study (1) to examine and compare the frequency of NH during open-loop (OL) and CL insulin delivery on nights with and without antecedent exercise in the afternoon in a group of adolescents and young adults with well-controlled type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects and enrollment

Subjects were recruited from the Yale Type 1 Diabetes Program and local advertising. Inclusion criteria included age 12–30 years, clinical diagnosis of type 1 diabetes of at least 1 year's duration, current use of insulin pump therapy, A1C <9% (<75 mmol/mol), BMI <95th percentile for age and sex, normal hematocrit and serum creatinine levels, no other chronic medical condition (except treated hypothyroidism), and no medications (other than insulin) known to affect blood glucose levels; also, female subjects could not be pregnant or lactating. After a complete explanation of the study protocol, written informed consent was obtained in subjects ≥18 years; in subjects <18 years, both an adolescent assent and parent permission were obtained. The study was approved by the Yale University Human Investigation Committee.

Study design

A randomized, crossover study design was used to compare overnight blood glucose control during OL and CL therapy on days with and without antecedent afternoon exercise. We hypothesized that CL insulin delivery would be superior to OL control in preventing NH, especially on nights after antecedent afternoon exercise, and that CL control would be able to maintain a higher proportion of blood glucose levels within the 70–180 mg/dL target range, even in the face of afternoon exercise.

Study procedures

All study subjects were admitted to the Yale Hospital Research Unit (HRU) on two occasions for 48-h assessments (study days 1 and 2) of glycemic control using either CL insulin delivery or conventional OL insulin pump therapy in random order (Fig. 1). During both CL and OL admissions, subjects underwent a treadmill exercise protocol in the afternoon on one of the 24-h periods (exercise day) and rested throughout the other 24-h period (sedentary day)—also in random order. Meals (self-selected by study subjects from a hospital menu) were identical during both admissions and on both study days were provided at 8:00 A.M., noon, and 5:00 P.M.. Carbohydrate intake averaged 93 ± 24 g/meal (90 ± 22 g breakfast, 93 ± 26 g lunch, and 96 ± 27 g dinner) and ranged between 42 and 127 g. No snacks were allowed, except for treatment of hypoglycemia.

All subjects were admitted to the HRU in the afternoon prior to study day 1. Intravenous catheters were placed for measurement of reference plasma glucose levels, which were measured at the bedside every 30 min by the YSI 2300 Glucose Analyzer (YSI Life Sciences, Yellow Springs, OH). In 10 of the 12 subjects, blood samples were obtained for determination of plasma insulin levels every 30 min between 10:00 P.M. and 6:00 A.M. Patients were treated with 15–30 g oral carbohydrates if reference blood glucose fell below 60 mg/dL. During both admissions, subjects were able to move about their rooms or the hallway, but vigorous physical activity was not permitted, except during the exercise protocol.

Subject preparation: procedures for OL studies. On the afternoon of admission to the HRU, a new infusion set was inserted for use with their home insulin pump. During this admission, subjects were advised to continue their "usual care"; therefore, subjects tested blood glucose levels on a glucose meter as desired, determined how much insulin to bolus for meals, and made their usual adjustments (if any) to basal insulin infusion rates during exercise.

Subject preparation: procedures for CL studies. On the afternoon of admission to the HRU, two continuous glucose sensors (the study sensor and a back-up sensor) were inserted in the subcutaneous space of the anterior abdominal wall and calibrated; a new insulin infusion set was placed in the hip/buttocks, and the home insulin pump was replaced by the study pump (Medtronic Paradigm 715). Insulin usage over the prior 3–7 days was used to determine algorithm parameters that were programmed into the study computer. Subjects were continued on OL control for dinner. After dinner, a run-in period of CL control was initiated at ~9:00 P.M. to achieve stable, target glucose levels at the start of the CL experiments the next morning (7:00 A.M. of study day 1).

The hybrid CL system used in this study consisted of four components: a Medtronic Paradigm 715 insulin pump, a Medtronic MiniLink REAL-Time transmitter (MMT-7703) adapted for 1-min transmission, a Medtronic Sof-Sensor (MMT-7002/7003) continuous glucose sensor, and the Medtronic external PID algorithm, which uses a PID algorithm modified to include insulin feedback (18–20). With this system, glucose sensor signals were transmitted every minute from a radiofrequency transmitter and delivered insulin commands to the pump by radiofrequency signaling. The algorithm's target glucose level was set to 120 mg/day during the day and night.

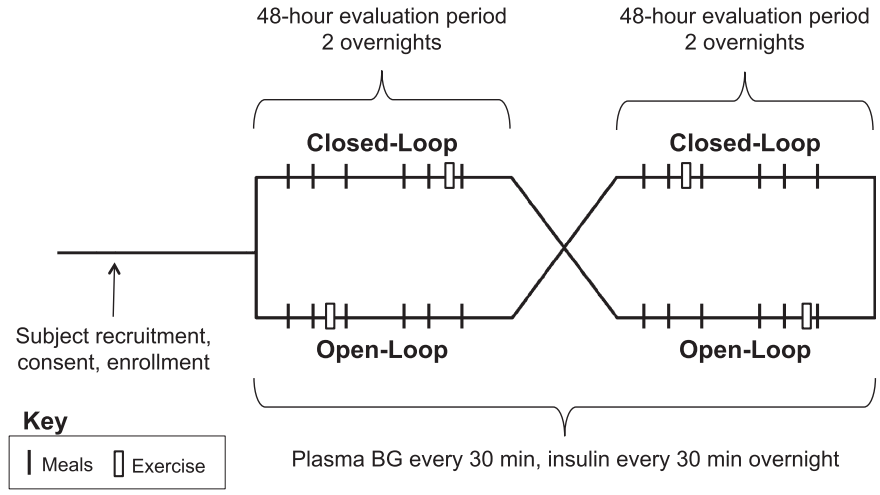

Figure 1—*Diagrammatic representation of clinical study procedures. BG, blood glucose.*

Details regarding the algorithm parameters and calibration procedures have previously been reported (21). As described previously (11), during CL control subjects also received a small manual priming bolus of 0.05 units/kg (average premeal bolus 3.1 ± 1.2 units) at the start of the meals.

Although the system operates off of one sensor, the second sensor was available in the event of a sensor malfunction. Sensors were calibrated at the start of CL control and whenever reference/sensor errors exceeded 20%. Sensor accuracy, defined as mean absolute relative deviation between sensor and reference blood glucose levels, was 10.1 ± 2.0% during the CL studies.

Exercise protocol. On the afternoon of the first admission, subjects underwent an abbreviated exercise tolerance test to determine the treadmill settings needed to obtain target heart rates. The target heart rate was calculated to approximate 50–55% maximal effort (equivalent to 65–70% maximum heart rate), where maximum heart rate was calculated as 220 − subject age (in years). As in the DirecNet study (1), exercise sessions were scheduled to begin at 3:00 P.M. to simulate typical after-school activity. The exercise session consisted of four 15-min exercise periods interspersed with three 5-min rest periods. Treadmill settings were adjusted to maintain the subject's target heart rate. Reference blood glucose levels were measured just prior to the start of exercise and at the end of each 15-min exercise period. On the day of exercise, supplemental carbohydrate was administered if starting blood glucose was <120 mg/dL. Pre-exercise per-protocol supplemental carbohydrate was needed in ~30% of subjects while on CL therapy (range of carbohydrates 15–75 g), with double the number of subjects requiring supplemental carbohydrates during the OL exercise condition (range of carbohydrates 15–120 g). During rest periods, subjects received 15–30 g carbohydrate snack if reference blood glucose was <80 mg/dL, and blood glucose levels had to be ≥80 mg/dL in order to resume exercise.

Statistical considerations

Reference plasma glucose concentrations were used to compare differences in glucose control between the two treatment conditions CL and OL. The overnight period was defined as 10:00 P.M. to 6:00 A.M. Hypoglycemia was defined as reference blood glucose <70 mg/dL. A treatable hypoglycemic event was defined as a reference blood glucose level <60 mg/dL. Episodes of treatable hypoglycemia needed to be separated by more than 30 min to be counted as two discrete events. The proportions of overnight blood glucose values <70, 70–180, and >180 mg/dL were also compared under OL and CL control. Descriptive statistics were calculated for reference glucose values in the CL and OL groups. Data are expressed as means ± SD or SEM as indicated. Statistical comparisons between CL and OL groups were accomplished with paired *t* tests for normally distributed data and Wilcoxon matched pairs signed rank tests for nonnormally distributed data. Comparison of reference blood glucose divided into predefined glycemic categories (<70, 70–180, and >180 mg/dL) was achieved using a χ^2 test. Calculations were performed using GraphPad Prism 5 (GraphPad Software, San Diego, CA).

RESULTS—Thirteen subjects were recruited into the study. However, one subject withdrew consent prior to any study procedures being conducted. The 12 subjects (5 females) who completed the study were aged 16.8 ± 3.6 years (range 12–26 years) and had diabetes duration of 5.7 ± 3.7 years (range 1–11.5) and an A1C level of 7.4 ± 0.6% (75 ± 17 mmol/mol).

Overall glucose control

Twenty-four hour mean blood glucose levels were modestly lower during OL compared with CL control on both sedentary (135 ± 46 vs. 140 ± 47 mg/dL, $P = 0.02$) and exercise (141 ± 63 vs. 147 ± 56 mg/dL, $P = 0.04$) days, but these differences disappeared when blood glucose levels <70 mg/dL were removed from the analyses. Baseline blood glucose levels were similar at the start of the exercise protocol on both the CL (161 ± 35 mg/dL) and OL (181 ± 80 mg/dL, $P = 0.57$) study days. The mean nadir blood glucose values during exercise were also similar on both study days, and there was no difference in the number of treatments for hypoglycemia that were needed during exercise (CL 5 vs. OL 6, $P = 0.82$). Predinner (5:00 P.M.) and 10:00 P.M. blood glucose levels during CL control were similar to corresponding values during OL control (Supplementary Table 1), and there were no significant differences in the total amount of insulin delivered between 5:00 P.M. and 10:00 P.M. on CL exercise and OL exercise days.

Overnight glucose control

During OL control on sedentary days, the mean ± SD overnight blood glucose level was 126 ± 37 mg/dL, with 87% of blood glucose levels within the 70–180 mg/dL range and 4% of values <70 mg/dL (Table 1). Nevertheless, even lower mean blood glucose levels could be achieved with overnight CL control on sedentary days, with 98% of values between 70 and 180 mg/dL and only 1.5% of values <70 mg/dL ($P < 0.0001$ vs. OL).

As expected, antecedent afternoon exercise increased the frequency of low glucose levels to 11% during the night during OL control and the frequency of hyperglycemic values also rose (Table 1). During CL treatment, excellent overnight

Table 1—*Overnight glycemic control with OL vs. CL control*

Sedentary	OL-S	CL-S	*P* value
Mean ± SD overnight (10:00 P.M.–6:00 A.M.)			
BG (mg/dL)	126 ± 37	117 ± 20	0.002*
<70 (%)	4	1.5	
70–140 (%)	60	90	<0.0001†
141–180 (%)	27	8	
>180 (%)	9	0.5	

Exercise	OL-E	CL-E	*P* value
Mean ± SD overnight (10:00 P.M.–6:00 A.M.)			
BG (mg/dL)	121 ± 50	121 ± 32	0.55*
<70 (%)	11	5	
70–140 (%)	61	75	<0.0001†
141–180 (%)	11	16	
>180 (%)	17	4	

BG, blood glucose. *Compared using a paired *t* test. †χ^2 test.

glucose control was maintained despite antecedent afternoon exercise, with 91% of glucose values in the 70–180 mg/dL range and only 5% <70 mg/dL ($P <$ 0.0001 vs. OL). As insulin doses during CL therapy are based off of sensor glucose levels, mean sensor glucose levels were also calculated for the overnight period during both CL conditions and found to be similar to that derived from reference blood glucose data, except that on the CL exercise nights only 1% of sensor glucose readings were <70 mg/dL compared with 5% of reference glucose levels.

On the nights after exercise, there were 23 episodes of biochemical hypoglycemia (reference blood glucose <70 mg/dL) for OL control compared with only 11 episodes for CL control ($P = 0.03$). Similarly, there were more than twice as many episodes of biochemical hypoglycemia detected on sedentary nights with OL control (8 episodes) compared with CL control (3 episodes). As shown in Fig. 2, there was a total of 14 episodes of treatable NH (reference blood glucose <60 mg/dL) during OL control versus a total of only 2 episodes of treatable hypoglycemia on nights with CL control ($P = 0.04$). On nights after antecedent afternoon exercise, there were eight episodes of treatable hypoglycemia in four subjects during OL control versus one episode during CL control.

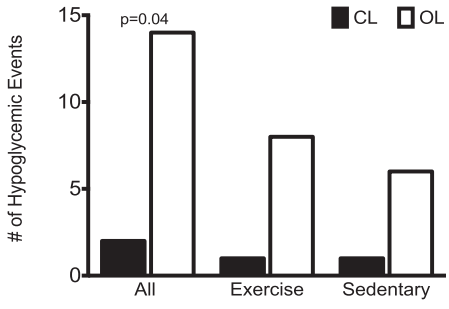

Figure 2—*Episodes of overnight treatable hypoglycemia (reference blood glucose <60 mg/dL) during OL and CL.*

On exercise days, six of the eight episodes of treatable hypoglycemia during OL therapy and the only episode of treatable hypoglycemia during CL control occurred between 10:00 P.M. and 2:00 A.M., 7–11 h after starting afternoon exercise. While insulin delivery was fixed during this period of time during OL therapy, CL insulin delivery allowed for minute-to-minute alterations in the amount of insulin received. As demonstrated in Fig. 3*A*, CL therapy was associated with lower insulin delivery between 10:00 P.M. and 2:00 A.M. compared with OL on nights after antecedent exercise (mean ± SEM, CL exercise 0.8 ± 1.09 units/h vs. OL exercise 0.98 ± 0.33 units/h; $P = 0.008$). Plasma insulin levels also tended to be lower on CL compared with OL control (mean ± SEM, CL exercise 15.57 ± 7.3 μU/mL vs. OL exercise 17.06 ± 6.76 μU/mL; $P =$ 0.06) (Fig. 3*B*) during this time period.

CONCLUSIONS—In this study, we used the same rigorous 75-min treadmill exercise protocol that was developed by DirecNet to test whether feedback-controlled insulin delivery could respond to the delayed glucose-lowering effects of afternoon exercise and lower the risks of NH. As in the DirecNet study, the exercise protocol was started at 3:00 P.M., since this is the time of the day when many youth with type 1 diabetes participate in sports and other physical activities. Moreover, as shown in the study by McMahon et al. (4) and confirmed in our patients during OL control, the delayed glucose-lowering effects of afternoon exercise would be expected to peak 7–11 h after exercise or between 10:00 P.M. and 2:00 A.M. in this study.

As seen in our recent study with the Medtronic CL system using the PID plus insulin feedback algorithm and the same 120 mg/dL target sensor glucose level (21), overnight glucose control during CL insulin delivery was outstanding on sedentary days. Indeed, 90% of reference blood glucose values were between 70 and 140 mg/dL, 98% were in the 70–180 mg/dL, and only 1.5% were <70 mg/dL—a precision that could not be achieved during the overnight period on sedentary days during OL therapy. Even more important, the CL system

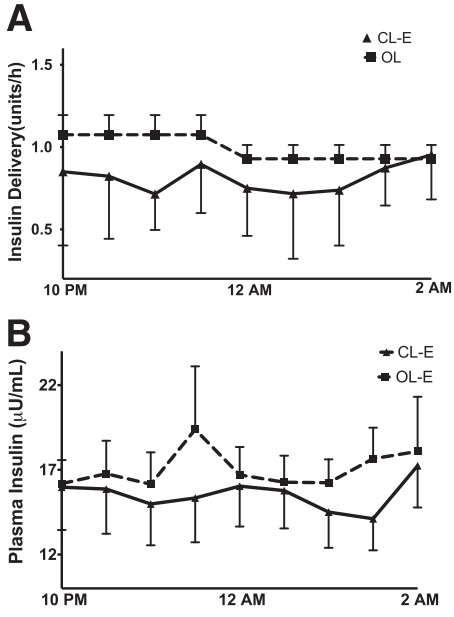

Figure 3—A*: Overnight insulin delivery in units/h 7–11 h postexercise (10:00 P.M. to 2:00 A.M.), with CL associated with lower insulin delivery (*P *= 0.008).* B*: Plasma insulin levels between 10:00 P.M. and 2:00 A.M., with trend toward significance for lower plasma insulin levels on CL nights vs. OL nights (*P *= 0.06). CL-E, CL exercise (solid line); OL-E, OL exercise (dashed line).*

outperformed OL pump therapy in this group of very well-controlled adolescents and young adults on nights after afternoon exercise: the proportion of hypo- and hyperglycemic values was significantly lower during CL control, and the number of episodes of hypoglycemia that required treatment because of blood glucose levels <60 mg/dL fell from eight during OL therapy to only one during CL control.

Episodes of biochemical and treatable episodes of NH were reduced on exercise nights because feedback control of insulin delivery rates allowed the system to automatically reduce basal insulin delivery during the vulnerable 10:00 P.M. to 2:00 A.M. period. It is also noteworthy that mean reference blood glucose levels during the overnight period with CL control during both sedentary and exercise days were nearly identical to the PID algorithm's 120 mg/dL target setting (Table 1). Additionally, regardless of prior daytime activity level, the CL system achieved a similar proportion of time spent within a targeted range of 70–180 mg/dL (CL exercise vs. CL exercise: $P = 0.23$). Thus, CL therapy was both safe and effective in allowing optimization of glycemic control under both sedentary and exercise conditions.

As per the DirecNet protocol, during OL control in this study patients remained on the same overnight basal rates on both sedentary and exercise days. While many clinicians may recommend temporary reductions in overnight basal rates in pump-treated patients to reduce the risk of hypoglycemia on nights after afternoon exercise, there are no clear guidelines for the duration and extent of reduction in basal rates, which is likely to vary from patient to patient and depends on the type of exercise. It is not surprising that previous reports have shown that use of this strategy often results in nocturnal hyperglycemia (22,23).

The current study was conducted as a proof-of-concept assessment of the effects of exercise on CL performance, and our data provide compelling evidence regarding the effectiveness of CL insulin delivery in reducing the risk of NH regardless of prior daytime activity. Recently, the first outpatient testing of an artificial pancreas in a transitional setting of a camp demonstrated that use of such insulin delivery modalities can decrease NH while providing tighter glycemic control than could be achieved with SAP therapy (24). Nevertheless, a number of obstacles remain before this technology can be safely used in the outpatient home setting. The major obstacle that needs to be overcome is to minimize the risk of patient injury due to overdelivery of insulin because of a system malfunction. As CL insulin delivery is determined by sensor glucose values, it is critical to have uninterrupted sensor data; thus, in the current study, two sensors were placed so that should a sensor fail, the alternate sensor signal could be used and thus prevent placement of a new sensor. Development of orthogonal sensors or systems that have more than one electrochemical sensor may provide redundancy to the system without necessitating the placement of two sensors. Better sensor accuracy, greater integrity of radiofrequency transmissions, and enhanced ease of patient use are among the improvements that are needed to translate this technology into outpatient treatment. In the meantime, reducing the risk of hypoglycemia by automatically reducing or temporarily suspending pump basal insulin infusion rates based on projected low glucose levels is an area of intense research interest.

Our findings extend the findings of previous studies that sought to assess the effectiveness of CL systems on overnight glucose control in patients with type 1 diabetes. In those investigations, studies were carried out on sedentary days (10–17) or days with shorter periods of physical activity (17,25,26). While the system could not decrease the rate of hypoglycemia that occurred during exercise, our data indicate that compared with OL therapy, CL insulin delivery is an effective means to ensure adequate glycemic control and reduce the risk of hypoglycemia in the overnight period, even on nights after vigorous and prolonged afternoon exercise. It should also be noted that CL control markedly reduced but did not fully eliminate the incidence of NH during exercise and sedentary days. Thus, other approaches including improved algorithms or a bihormonal system that includes small rescue doses of glucagon (26) may still be needed to completely eliminate the problem of NH.

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J.L.S. researched data and wrote the manuscript. E.C. researched data, contributed to the discussion, and reviewed and edited the manuscript. C.C.P., B.C., N.K., A.R., L.C., and M.C. researched data. W.V.T. and S.A.W. researched data, contributed to the discussion, and reviewed and edited the manuscript. J.L.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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