Fully Automated Closed-Loop Insulin Delivery Versus Semiautomated Hybrid Control in Pediatric Patients With Type 1 Diabetes Using an Artificial Pancreas

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OBJECTIVE — The most promising β-cell replacement therapy for children with type 1 diabetes is a closed-loop artificial pancreas incorporating continuous glucose sensors and insulin pumps. The Medtronic MiniMed external physiological insulin delivery (ePID) system combines an external pump and sensor with a variable insulin infusion rate algorithm designed to emulate the physiological characteristics of the β-cell. However, delays in insulin absorption associated with the subcutaneous route of delivery inevitably lead to large postprandial glucose excursions.

RESEARCH DESIGN AND METHODS — We studied the feasibility of the Medtronic ePID system in youth with type 1 diabetes and hypothesized that small manual premeal "priming" boluses would reduce postprandial excursions during closed-loop control. Seventeen adolescents (aged 15.9 ± 1.6 years; A1C 7.1 ± 0.8%) underwent 34 h of closed-loop control; 8 with full closed-loop (FCL) control and 9 with hybrid closed-loop (HCL) control (premeal priming bolus).

RESULTS — Mean glucose levels were 135 ± 45 mg/dl in the HCL group versus 141 ± 55 mg/dl in the FCL group ($P = 0.09$); daytime glucose levels averaged 149 ± 47 mg/dl in the HCL group versus 159 ± 59 mg/dl in the FCL group ($P = 0.03$). Peak postprandial glucose levels averaged 194 ± 47 mg/dl in the HCL group versus 226 ± 51 mg/dl in the FCL group ($P = 0.04$). Nighttime control was similar in both groups (111 ± 27 vs. 112 ± 28 mg/dl).

CONCLUSIONS — Closed-loop glucose control using an external sensor and insulin pump provides a means to achieve near-normal glucose concentrations in youth with type 1 diabetes during the overnight period. The addition of small manual priming bolus doses of insulin, given 15 min before meals, improves postprandial glycemic excursions.

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Results of large-scale studies demonstrating that the sustained benefits of near-normal glucose control (1–4) in type 1 diabetes are obtained at the cost of more frequent severe hypoglycemia clearly underscore the need for improved treatments to achieve target A1C levels more safely. Despite the development of insulin analogs and insulin pumps, A1C levels and the risk of severe hypoglycemia remain too high in too many patients, particularly in children and adolescents (5). Biological islet cell replacement therapies are currently not justified for children, given the risks of immunosuppressive therapy (6).

An alternative approach to β-cell replacement involves the use of a mechanical system, consisting of a continuous glucose sensor, insulin pump, and control algorithm for calculating rates of insulin delivery (i.e., a closed-loop artificial pancreas). External glucose sensors and insulin pumps are commercially available and are of sufficient accuracy for consideration for use in an artificial β-cell system (7,8). In addition, controller algorithms have been developed and evaluated in several in vivo and in silico settings (9,10). Nevertheless, the delays inherent in insulin absorption and action from the subcutaneous route of delivery have led some investigators to suggest that the external route is incompatible with an effective fully closed-loop (FCL) system (11).

A recently published study of a FCL system using subcutaneous glucose sensing and insulin delivery in adults with type 1 diabetes demonstrated the short-term feasibility of an external artificial pancreas (12). However, postprandial hyperglycemic excursions were not eliminated, and late postprandial hypoglycemia was common (12). Such problems might be expected to be exaggerated in adolescents, in whom the larger premeal bolus doses frequently required to overcome the peripheral insulin resistance of puberty (13) may exacerbate the delays inherent in the subcutaneous route of insulin delivery. We hypothesized that the addition of small, manual, premeal priming bolus doses of insulin would ameliorate many of the problems caused by these delays. The goals of this study were to assess the feasibility of a closed-loop artificial pancreas device in adolescents with type 1 diabetes and to evaluate whether the use of premeal priming boluses of insulin improve performance of the closed-loop system.

RESEARCH DESIGN AND METHODS

— Seventeen subjects meeting the following criteria were recruited: age 13–20 years; clinical diagnosis of type 1 diabetes for >1 year; A1C <9%; insulin pump therapy use and carbo-

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Abbreviations: FCL, fully closed loop; HCL, hybrid closed loop; PID, proportional-integrative-derivative.

hydrate counting; and no other chronic medical condition (except treated hypothyroidism or celiac disease). Written informed consent was obtained from subjects aged ≥18 years and written parental permission and subject assent for subjects aged <18 years. The study was approved by the Yale University Human Investigations Committee. Subjects were randomly assigned to either the FCL group ($n = 8$) or the hybrid closed-loop (HCL) group ($n = 9$). Subjects in the FCL and HCL groups were similar with regard to age (16.8 ± 1.6 vs. 15.1 ± 1.0 years), duration of diabetes (6.9 ± 4.6 vs. 5.7 ± 2.9 years), and A1C (6.9 ± 0.8 vs. 7.3 ± 0.9%).

Study procedures

Baseline open-loop assessment. At the initial outpatient visit, subjects underwent insertion of a Medtronic Datalogger continuous glucose monitor (Medtronic Diabetes, Northridge, CA) and were trained on its use. Subjects wore the sensor for 3 days to establish a baseline of glycemic excursions but were masked to the data. These data were downloaded when the Datalogger was returned at the time of the inpatient admission.

Closed-loop study. Subjects were admitted to the Yale Hospital Research Unit on the afternoon before the closed-loop study. Two subcutaneous glucose sensors were inserted in the abdomen, and an intravenous catheter was placed into an antecubital vein for frequent blood sampling. Subjects continued on open-loop control overnight. At 7 A.M. the pump was switched from open-loop to closed-loop control, which continued until 5 P.M. on the following day. Venous glucose levels were sampled every 30 min from 6 A.M. to 10 P.M. and every 60 min from 10 P.M. to 6 A.M. until study completion. Plasma insulin levels were obtained every 30–60 min during the last 24 h of the study. Meals were provided at 8 A.M., noon, and 5 P.M.

In the FCL group, all of the insulin was given under control of a laptop computer using a proportional-integrative-derivative (PID) controller algorithm. In the HCL group, a bolus of rapid-acting insulin, equivalent to ~25–50% of the dose that the subject would have taken for the meal, was given ~15 min before the meal. The remaining insulin was given under computer control according to the same PID algorithm.

System considerations

The closed-loop system consisted of three components: a Medtronic Paradigm 715 insulin pump, a Medtronic continuous glucose sensor, and the Medtronic external physiological insulin delivery algorithm. Algorithm calculations were based on glucose sensor signals received each minute from a radiofrequency transmitter. Specifics of the algorithm have been described extensively (12,14,15). Insulin delivery was based on a model of the multiphasic insulin response of the β-cell, consisting of three components—proportional (P), integral (I), and derivative (D)— according to the following formulas, in which (n) denotes the sampling time of the most recent 1-min glucose value and ($n - 1$) the previous sampling time:

$$P(n) = K_p \cdot [G(n) - \text{target}]$$

$$I(n) = I(n-1) + \frac{K_p}{T_I} \cdot [G(n) - \text{target}]$$

$$D(n) = K_P T_D \cdot dGdT(n)$$

$$PID(n) = P(n) + I(n) + D(n)$$

K_p was set individually, based on the daily insulin requirement (in units per kilogram per day): K_p = daily insulin requirement/135). From 6 A.M. to 10 P.M., T_D and T_I were set to 90 and 450 min, respectively, and from 10 P.M. to 6 A.M. they were adjusted to 60 and 150 min. The initial I component [$I(n - 1)$] was set to the subject's basal rate at the start of closed-loop control (7 A.M.) and thereafter constrained to be greater than 0 and less than the open-loop minimum basal rate plus 2.4 × weight × K_p. The glucose target was set at 100 mg/dl during the day and 120 mg/dl during the night.

Glucose sensors were calibrated approximately every 12 h. Plasma glucose levels were measured at the bedside by the YSI 2300 glucose analyzer (YSI Life Sciences, Yellow Springs, OH). Plasma insulin was measured by enzyme-linked immunoabsorbent assay with an intra-assay coefficient of variation (CV) of 1.43 ± 0.15% and inter-assay CV of 6.9 ± 1.9% (ALPCO Diagnostics, Windham, NH).

Statistical considerations

Venous plasma glucose concentrations were used to compare differences in glucose control between two treatment groups. The first 10 h of the 34-h study were excluded from the analysis because those subjects in the FCL group with elevated plasma glucose levels at the start of closed-loop control received the equivalent of a premeal priming dose when they were switched from open-loop to closed-loop during the hour before breakfast (i.e., from 7 A.M. to 8 A.M. on day 1). In two HCL group subjects, the priming bolus was given only for breakfast, but these subjects were included in the HCL group with the other seven subjects who received the priming bolus for every meal. Daytime was defined as 6 A.M.–10 P.M. and nighttime as 10 P.M.–6 A.M.

Data are expressed as means ± SD or SEM and, where appropriate, as median with interquartile range (25th–75th percentile). Sensor accuracy was calculated as the mean and median relative absolute difference of the sensor glucose and venous glucose levels for all paired points (16). Comparisons between FCL and HCL groups were made using t tests for normal data and Mann-Whitney tests for nonparametric data. Comparisons of sensor glucose distributions between open-loop and closed-loop conditions were made by χ^2 tests. Calculations were performed using Prism 4 (GraphPad Software, San Diego, CA).

RESULTS

Sensor performance

Sensor glucose values effectively tracked venous glucose values during closed-loop control, although there was a tendency for the sensor glucose levels to underestimate venous glucose levels during postprandial peaks (Fig. 1*A*). Point accuracy of the sensor, expressed as mean ± SD and median (interquartile range) relative absolute deviation from the venous glucose value, was 13.2 ± 10.9% and 10.9% (5.0–18.6%), respectively, consistent with other published studies (7,8).

Glycemic control and insulin delivery during FCL control

Mean venous plasma glucose levels and sensor and venous glucose profiles during FCL control are shown in Table 1 and Fig. 1*A*. As shown in Fig. 1*B*, insulin delivery rates increased rapidly after each meal and returned to basal rates within 2–3 h. However, delays in insulin absorption resulted in peak plasma insulin concentrations occurring 1–2 h after maximum insulin delivery rates and sustained elevations in postprandial insulin levels. Indeed, plasma insulin concentrations after

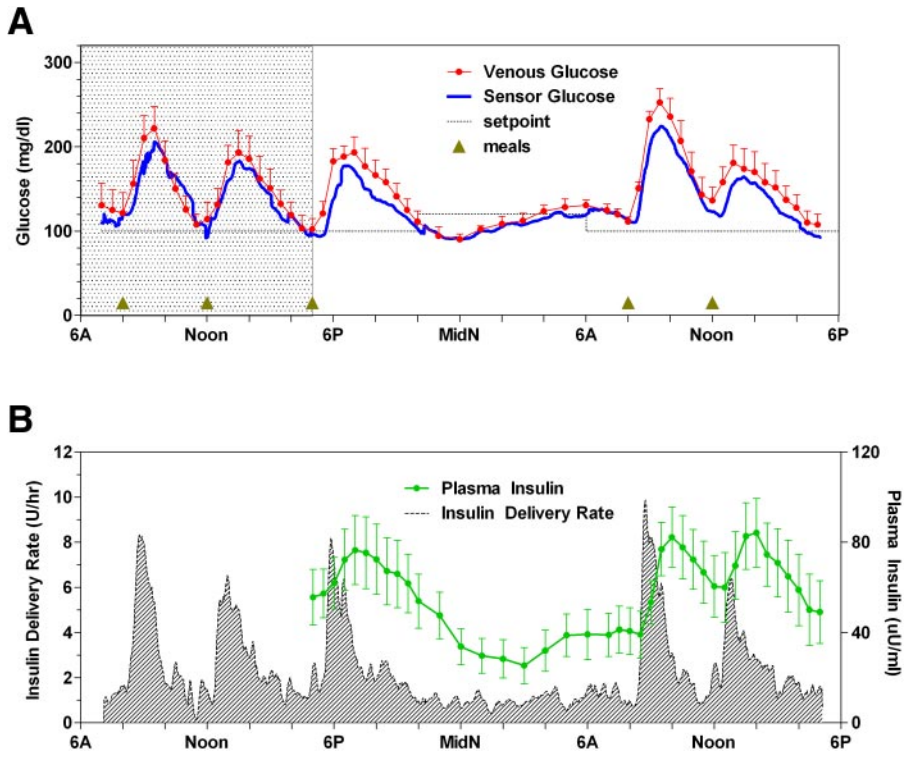

Figure 1—*Summary of closed-loop experiment in eight subjects undergoing FCL glucose control. x-axes are aligned to facilitate comparison of panels.* A*: Sensor glucose levels (blue line) closely track venous blood glucose levels (in red). The dotted area during the first day indicates period excluded from analysis. Daytime (6 A.M.–10 P.M.) and nighttime (10 P.M.–6 A.M.) target glucose levels of 100 and 120 mg/dl, respectively, are indicated by the thin black dashed line. Meals are marked by brown triangles.* B*: Insulin pump delivery rates (in units per hour) are indicated by the shaded region and left axis; plasma insulin levels sampled every 30–60 min during the last 24 h of the closed-loop period are shown in green. Note persistent late postprandial hyperinsulinemia despite decreasing insulin delivery rates. Please see http://dx.doi.org/db07-1967 for a high-quality digital representation of this figure.*

dinner did not reach nadir levels until ~3 A.M. (Fig. 1*B*).

Glycemic control and insulin delivery during HCL control

Mean daytime and peak postprandial glucose levels were lower in the HCL group than were corresponding values in the FCL group ($P = 0.03$ and $P = 0.04$, respectively), and the difference in overall mean 24-h glucose levels approached statistical significance ($P = 0.09$) (Table 1). Mean nighttime glucose levels were nearly identical in the two groups (Table 1). A comparison of FCL and HCL glucose profiles is shown in Fig. 2.

Use of the priming dose with HCL control resulted in significantly greater incremental increases in plasma insulin concentrations over baseline in the HCL than in the FCL group in the first 30 min after a meal (9.2 ± 3.5 vs. −0.1 ± 1.6 μU/ml, $P < 0.02$) (Fig. 3). The area under the curve in the first 30 min was also greater in the HCL than in the FCL group (709 vs. 344 μU · min/ml, $P < 0.01$).

Hypoglycemia

Hypoglycemia (venous glucose <60 mg/dl) occurred once in three subjects (one FCL subject at 51 mg/dl and two HCL subjects at 57 mg/dl), all between 11 P.M. and 1 A.M. Corresponding sensor glucose levels were 41, 60, and 69 mg/dl, respectively. All three episodes were corrected with 15 g oral carbohydrate.

Comparison with open-loop control

Glycemic control during closed-loop delivery was significantly better than prestudy home open-loop control, as assessed by the Datalogger. Over the 3-day open-loop period, 58% of sensor glucose values were between 70 and 180, 33% were >180, and 9% were <70 mg/dl. Corresponding glucose values during closed-loop control were 85, 12, and 3%, respectively ($P < 0.002$). There were no significant differences in the time spent within, above, and below target between the FCL and HCL groups.

CONCLUSIONS — This study demonstrates that an FCL artificial pancreas using an external glucose sensor and insulin pump is feasible and remarkably effective in adolescents with type 1 dia-

Table 1—*Glycemic control parameters in FCL and HCL subjects*

	All subjects		FCL		HCL		*P* value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	(FCL vs. HCL)
24-h plasma glucose (mg/dl)	138 ± 50	130 (104–160)	141 ± 55	130 (103–170)	135 ± 45	129 (104–156)	0.09
Daytime plasma glucose (mg/dl)	154 ± 53	146 (115–184)	159 ± 59	150 (113–194)	149 ± 47	141 (116–173)	0.03
Nighttime plasma glucose (mg/dl)	112 ± 27	113 (91–130)	111 ± 27	117 (88–131)	112 ± 28	111 (95–130)	0.81
Peak postprandial glucose (mg/dl)							
All meals	211 ± 51	200 (170–248)	226 ± 51	229 (181–272)	194 ± 47	189 (161–225)	0.04
Breakfast	243 ± 55	248 (197–292)	262 ± 43	275 (232–292)	226 ± 62	225 (160–281)	0.19
Lunch	189 ± 45	180 (159–232)	205 ± 50	190 (172–253)	175 ± 39	170 (145–208)	0.19
Dinner	200 ± 36	198 (172–222)	211 ± 45	200 (176–241)	191 ± 23	198 (170–207)	0.26
Nocturnal glucose nadir (mg/dl)	76 ± 18	72 (63–91)	72 ± 16	70 (63–76)	79 ± 20	75 (61–97)	0.48
Time from dinner to nadir (h)	7 ± 1	6 (6–8)	7 ± 2	6 (6–9)	7 ± 1	7 (6–8)	0.67

IQR, interquartile range.

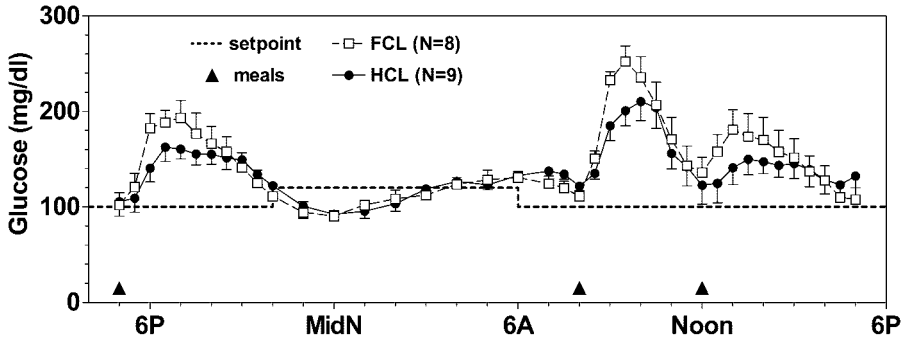

Figure 2—*Glucose control in FCL control versus HCL control. Glycemic excursions under FCL (□– – –□) versus HCL(●——●). Horizontal dashed line, target glucose level (100 mg/dl from 6 A.M. to 10 P.M. and 120 mg/dl from 10 P.M. to 6 A.M.); ▲, meal markers.*

betes. Although peak postprandial plasma glucose concentrations often exceeded 180 mg/dl with FCL control, levels >300 mg/dl were rarely seen, and glucose values promptly returned to normal by the next meal. Most importantly, 85% of all sensor glucose levels were between 70 and 180 mg/dl in the FCL group during the 24-h study period. These findings compare favorably with those for the same subjects during standard open-loop pump therapy, during which time only 58% of sensor glucose values were between 70 and 180 mg/dl. It should be noted that these subjects were already in excellent glycemic control, with mean A1C level of only 7.1%. It is important to note, however, that there were large between-subject variations in blood glucose excursions, particularly in peak postprandial glucose levels. It is unclear whether this finding is related to the algorithm itself or to variations in sensor accuracy, calibration, or lag effects, the last of which is suggested by the tendency of the sensors to underread venous glucose levels after meal-related peaks.

Because the PID algorithm is reactive, responding only to changes in glucose levels and slowed by the delays in subcutaneous insulin absorption, the FCL system should be at a disadvantage in managing postmeal glucose excursions compared with open-loop pump therapy if the premeal bolus dose requirement could be accurately determined by the patient. With optimal open-loop treatment, the patient administers the premeal bolus 15–30 min before eating, and it is infused rapidly over a few minutes. In children and adolescents with type 1 diabetes, we have recently shown that plasma insulin levels peak almost 55 min after a standard bolus of rapid-acting analog and that the peak insulin action is not observed until 40 min later (17). With FCL control, the system did not even begin to respond to the meal until 15–20 min after the subject started eating, the meal-related insulin infusion extended over 2–3 h, and peak insulin concentrations were not observed until 120 min after the meal. Nevertheless, feedback control of insulin delivery eliminated human error and resulted in outstanding control of diurnal plasma glucose concentrations overall. Furthermore, the HCL approach led to an earlier rise in plasma insulin levels and a reduction in peak postprandial glucose levels. Even better control of postprandial glucose might have been achieved if we had the opportunity to individually titrate the size and timing of the priming boluses.

This strategy of providing a priming dose of insulin before a meal and calculating the dose as 25–50% of the insulin required to cover the carbohydrate content of the meal is technically easy to accomplish with current insulin pumps and has a physiological basis in the cephalic phase of insulin secretion, which produces small increases in insulin secretion early in a meal even before systemic glucose levels begin to rise (18). In nondiabetic individuals, blockade of the cephalic phase results in impaired postprandial glucose tolerance (19). One may reasonably argue that the raison d'être of a closed-loop system is to remove human error from diabetes management altogether and that this approach actually represents a step backward. We would argue that failure by the patient to take a priming bolus merely switches the system from HCL to FCL control, either one of which will ultimately prove to be superior to open-loop therapy.

There are two major sources of concern related to the risk of hypoglycemia with both FCL and HCL approaches. Because of the use of the subcutaneous route of insulin administration, plasma insulin levels remain elevated above premeal values for at least 4 h after the meal, and the glucose-lowering effects of the meal-related insulin infusion undoubtedly per-

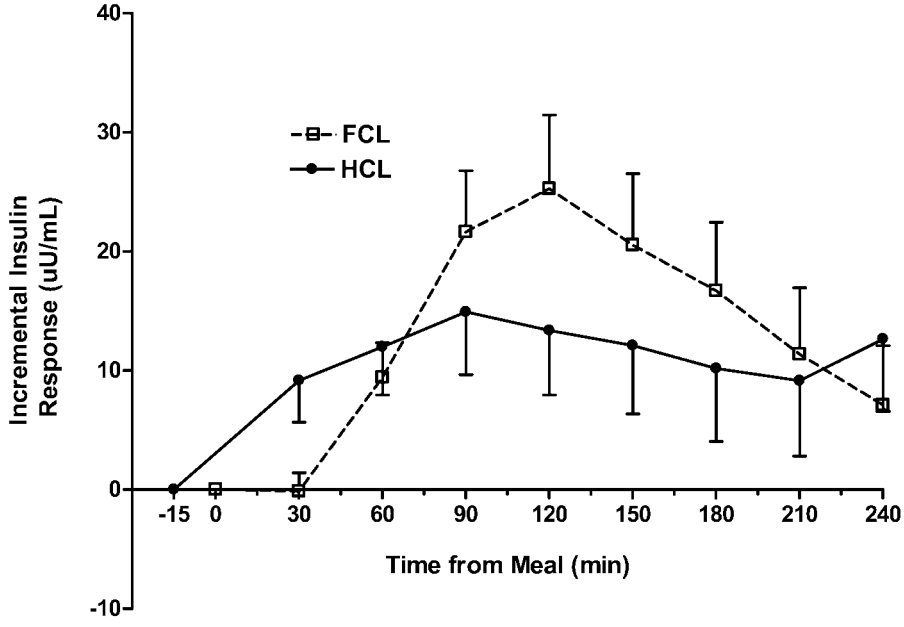

Figure 3—*Early insulin response in FCL versus HCL control. Incremental increase in plasma insulin concentrations from baseline after meals in FCL (□– – –□) and HCL (●——●) groups. Baseline insulin level was calculated from the 0-min point (time of meal) for the FCL group and from the −15 min point for the HCL group.*

sisted even longer (17). Although we did not observe any clinically important hypoglycemia during the daytime period, meals were eaten on a strict 4- to 5-h schedule, and the subjects were sedentary throughout the admission. Whether overshoot hyperinsulinemia to the extent that was observed in this study would lead to additional hypoglycemia in a more real-life setting of irregular meals and exercise remains to be determined.

It is particularly noteworthy that plasma insulin concentrations did not return to basal concentrations until 1–3 A.M., at least 8–10 h after dinner. This corresponds to the time when the nadir nighttime plasma glucose concentrations and the three hypoglycemic events were observed. We attempted to reduce the amount of insulin administered during this vulnerable period by raising the target plasma glucose level from 100 to 120 mg/dl at 10 P.M. Even if such maneuvers fail to prevent all drops in plasma glucose, clinically important hypoglycemic events would still be avoided by equipping the system with audible alarms to alert users to actual or impending hypoglycemia. In our experiment, an audible alarm set at 70 mg/dl would have alerted the wearer to all three episodes of blood glucose levels <60 mg/dl.

The other main concern for nocturnal hypoglycemia relates to use of poorly functioning sensors that substantially overread the true plasma glucose level, leading to inappropriate increases in basal insulin infusion and system-induced hypoglycemia. Sensor errors of this sort are particularly worrisome because the patient would not be alerted to impending hypoglycemia by sensor alarms. This series of experiments used nighttime target glucose of 120 mg/dl, specifically designed to minimize the risk of this kind of sensor malfunction by providing the system with a margin of error, as the following examples illustrate. The median error of the Medtronic and other current real-time continuous glucose sensors is in the 10–16% range when plasma glucose levels are between 70 and 180 mg/dl (7,8,20–23). If we assume a sensor overread error of 33%, setting the target to 120 mg/dl would drive the true glucose level to 90 mg/dl; even with an overread error of 50%, the glucose would only be driven to 80 mg/dl.

It is likely that the first generations of closed-loop systems to gain regulatory approval for clinical use will consist of a subcutaneous sensor–subcutaneous insulin pump combination and include some type of hybrid control mechanism, in which the pump can be set to closed-loop control but still accept manual inputs when desired. Such a hybrid system may be expected to provide protection from hypoglycemia overnight, as PID controllers tend to operate most effectively when not perturbed by meals, while also allowing reasonably good meal control, whether using a manual bolus or not. The present study demonstrates that such systems are not only feasible but may also be imminent because the technology is already available.

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