Original Article

Feasibility of Automating Insulin Delivery for the Treatment of Type 1 Diabetes

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An automated closed-loop insulin delivery system based on subcutaneous glucose sensing and subcutaneous insulin delivery was evaluated in 10 subjects with type 1 diabetes (2 men, 8 women, mean [±SD] age 43.4 ± 11.4 years, duration of diabetes 18.2 ± 13.5 years). Closed-loop control was assessed over ~30 h and compared with open-loop control assessed over 3 days. Closed-loop insulin delivery was calculated using a model of the β-cell's multiphasic insulin response to glucose. Plasma glucose was 160 ± 66 mg/dl at the start of closed loop and was thereafter reduced to 71 ± 19 by 1:00 P.M. (preprandial lunch). Fasting glucose the subsequent morning on closed loop was not different from target (124 ± 25 vs. 120 mg/dl, respectively; $P > 0.05$). Mean glucose levels were not different between the open and closed loop (133 ± 63 vs. 133 ± 52 mg/dl, respectively; $P > 0.65$). However, glucose was within the range 70–180 mg/dl 75% of the time under closed loop versus 63% for open loop. Incidence of biochemical hypoglycemia (blood glucose <60 mg/dl) was similar under the two treatments. There were no episodes of severe hypoglycemia. The data provide proof of concept that glycemic control can be achieved by a completely automated external closed-loop insulin delivery system. *Diabetes* 55:3344–3350, 2006

O ptimal treatment of type 1 diabetes should achieve normoglycemia at all times, without risk of hypoglycemia. Such a treatment should dramatically reduce or prevent diabetes complications and significantly improve patients' quality of life. This goal may be accomplished through pancreatic or islet cell transplantation, but availability of these tissues is limited, survival and function are unpredictable, and long-term immunosuppressive therapy is required (1). The potential for an automated closed-loop system, or artificial β-cell, to achieve round-the-clock glycemic control, has not been fully explored.

An artificial β-cell requires a glucose sensor, an insulin-delivery pump, and an algorithm for calculating insulin delivery. Technological and scientific advances have made sensors and pumps available, but linking the two as a "closed loop" has been challenging (2). Lingering questions remain regarding the suitability of different glucose-sensing sites (subcutaneous versus intravascular), insulin-delivery sites (subcutaneous versus intravascular versus intraperitoneal), and sensor reliability. In addition, no one algorithm has been universally accepted as optimal for insulin delivery (3).

Herein, we describe the feasibility of achieving glycemic control in patients with type 1 diabetes using a system comprised of a subcutaneous glucose sensor, an external insulin pump, and an algorithm emulating the β-cell's multiphasic glucose-induced insulin release (4–6).

RESEARCH DESIGN AND METHODS

Ten patients with previously diagnosed type 1 diabetes were studied (2 men, 8 women; mean [±SD] age 43.4 ± 11.4 years, BMI 26.5 ± 2.1 kg/m², diabetes duration 18.2 ± 13.5 years [range 4–48], HbA$_{1c}$ 7.2 ± 0.8%, daily insulin requirement [DIR] 0.54 ± 0.08 units · kg^{-1} · day^{-1}). Subjects had been treated with continuous subcutaneous insulin infusion (CSII) using Lispro insulin (Lilly, Indianapolis, IN) for at least 6 months before study enrollment and were required to have an HbA$_{1c}$ <9%. Data from a previously published study (7) characterizing insulin secretion over a 24-h period in nondiabetic subjects are included for comparison of the glucose profiles ($n = 17$) obtained with a similar diet. The study was approved by the University of California, Los Angeles Institutional Review Board, and all patients gave written informed consent.

Glycemic control under CSII therapy was characterized over a 3-day outpatient period using a continuous glucose monitoring system (CGMS) (Medtronic MiniMed, Northridge, CA). The CGMS records sensor current every 5 min and glucose profiles are obtained retrospectively (8). Patients were instructed to keep their daily routine but to take a minimum of seven fingerstick blood glucose readings per day (preprandial and 2-h postprandial and at bedtime) with their home glucose meters. Patients were also instructed to record meal carbohydrate content, physical activity, and any hypoglycemic episodes or supplemental carbohydrate in a logbook.

To evaluate the closed-loop insulin delivery system, patients were admitted to the general clinical research center at ~5:00 P.M., and their insulin pump was replaced with a Medtronic 511 Paradigm Pump capable of communicating telemetrically with a laptop computer. Two subcutaneous glucose sensors were inserted in the abdominal area and connected to radio frequency transmitters, which were also communicating with the laptop. The sensor signal (nA) was transmitted to the laptop every minute and smoothed using a weighted average of the previous seven values. The rate-of-change of the signal (derivative; nA per minute) was calculated from the slope of the previous 15 values. Sensor glucose (SG) and its rate-of-change were calculated by multiplying the smoothed sensor signal and its derivative by a calibration factor (see SENSOR CALIBRATION below for details). Calibration, smoothing, and insulin-delivery calculations were performed on the laptop computer and the insulin-delivery rate transmitted by radio frequency to the pump as a series of 0.1-unit boluses. The radio frequency communication had a range of ~10 m to allow patients to move about the room. Two sensors were used as a precaution to avoid interrupting the experiments in case of sensor malfunction or transmission failure.

On admission, an intravenous line was placed for blood sampling and patients were instructed to self-administer insulin therapy for that evening's dinner and for the 10:00 P.M. snack. Blood samples were taken at ~2:00 and
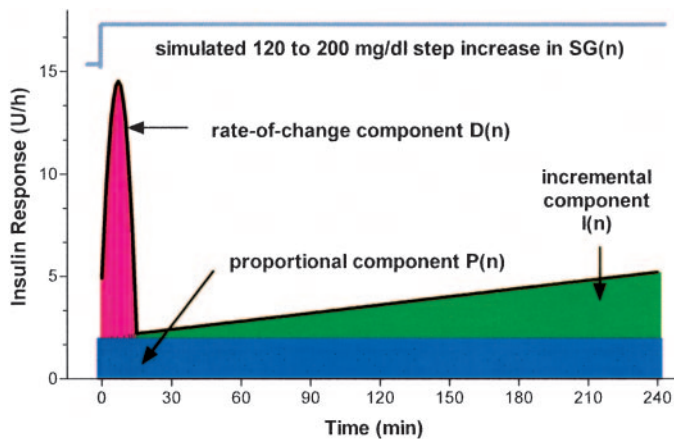
FIG. 1. Simulated response of the *PID* algorithm to a hyperglycemic clamp. Delivery is comprised of a component, *P*(n), that is proportional to the difference between SG and target; a component, *I*(n), that increments a basal rate in proportion to the difference between SG and target; and a component, *D*(n), that adjusts insulin delivery in proportion to the rate of change of SG. The response is shown for K_P = 0.025 units/h per mg/dl, T_I = 150 min, and T_D = 66 min (see text for equations).

6:00 A.M. to assess plasma glucose and correct any unexpected hypo- or hyperglycemia. At 7:00 A.M., pump basal insulin-delivery rates were set to zero and closed-loop insulin delivery started. Sensors were calibrated at this time, but insulin delivery was calculated using plasma glucose values measured every 10 min until 11:00 A.M. At 11:00 A.M., sensors were evaluated by correlating plasma glucose with sensor current, and the sensor with a higher correlation value (*r*) and signal (nA) was used to control insulin delivery. In the event of sensor malfunction or radio frequency transmission problems, control was switched to the second of the two sensors (two occurrences each).

Completely automated closed-loop insulin delivery using the sensor was continued until 11:00 A.M. the next day in subjects 1–6 and until 1:00 P.M. in subjects 7–10. From 11:00 A.M. until the end of the study, blood samples were collected every 20 min for immediate assessment of plasma glucose and later assessment of plasma insulin and free fatty acid (FFA). Meals were served at 8:00 A.M. and 1:00, 6:00, and 10:00 P.M. (snack). Carbohydrate content was based on a weight-maintaining diet (87.9 ± 11.5, 69.0 ± 8.8, 45.3 ± 7.7, and 55.1 ± 8.4 g at lunch, dinner, snack, and breakfast, respectively). If plasma glucose fell below 60 mg/dl, 15-g supplemental carbohydrate was given in juice and more frequent 5-min samples obtained for measuring glucose.

Insulin delivery. Insulin delivery was calculated based on a model of the β-cell's multiphasic insulin response (5,6). The model has three components: proportional (*P*), integral (*I*), and derivative (*D*). The *P* component delivers insulin in proportion to the difference between SG and target glucose; the *I* and *D* components produces the slow second-phase rise (*I*) and rapid first-phase rise (*D*) seen during hyperglycemic clamps (4) (Fig. 1). The model is commonly referred to as a "proportional-integral-derivative" controller in engineering applications (9) and can be expressed in an incremental form as:

$$P(n) = K_p[SG(n) - \text{target}]$$
$$I(n) = I(n - 1) + K_P/T_I \cdot [SG(n) - \text{target}]$$
$$D(n) = K_P \cdot T_D \cdot dSGdt(n)$$
$$PID(n) = P(n) + I(n) + D(n) \quad (1)$$

In Eq. 1, "*n*" denotes the most recent 1-min value and "*n* − 1" denotes the previous 1-min value.

Each component of the model can be viewed from an intuitive, or nonmathematical, perspective. Component *P* increases insulin delivery when glucose is above target and reduces insulin delivery when glucose is below target but provides no contribution when glucose is at target. Thus, it does not contribute to the underlying basal requirement typically needed to maintain fasting glucose at target. Component *I* adjusts upward when glucose is above target, downward when glucose is below target, and is unchanged when glucose is at target. It is the only component to provide insulin when glucose is at target and stable and is comparable to basal insulin secretion. Because this component is incremented up or down, it ensures that target is always achieved when the system is at steady state (any value of glucose other than target results in a change in insulin delivery, which is by definition not steady state). Component *D* increases insulin delivery when glucose is rising and

decreases delivery when glucose is falling. This stabilizes the system in that any change in plasma glucose is counteracted by a change in insulin delivery, irrespective of the prevailing glucose level (e.g., it suspends insulin delivery when glucose is falling, even if the glucose level is above target). Total insulin delivery is the sum of the three components.

The relative amount of insulin delivered in each component is balanced by three parameters (K_P, T_I, and T_D), which are constants. The amount of insulin delivered in component *P* is determined by parameter K_P, which was set in relation to the subject's DIR (in units per kilogram per day); DIR is calculated as the average insulin during the 3-day CGMS open-loop monitoring period. The amount of insulin delivered by component *D* was adjusted with a parameter T_D, which was set at 66 and 50 min when glucose was rising [$T_{D(RISE)}$] and falling [$T_{D(FALL)}$], respectively. Parameter K_P was related to DIR and $T_{D(FALL)}$ as:

$$K_P = \text{DIR}/factor \cdot 1{,}000/T_{D(FALL)} \quad (2)$$

Here, factor is analogous to the so-called "1,500" or "1,800" rules often used as glucose correction factors in CSII treatment (10). The factor was empirically adjusted between 1,800 and 2,100 in the first four subjects and subsequently fixed at 1,900 for the final six subjects. The rate at which component *I* adjusted up or down was set with a parameter T_I, which allowed only small changes during the day [$T_{I(DAY)}$ = 450 min; 6:00 A.M. to 10:00 P.M.] but more rapid changes during the night [$T_{I(NIGHT)}$ = 150 min]. This component was initialized to the subject's basal rate at the start of closed loop (7:00 A.M. basal rate). A maximum-allowed rate for *I* was set to three times the 7:00 A.M. basal rate when glucose was >60 mg/dl and to K_P60 if glucose was <60 mg/dl. Insulin delivery was suspended when the sum of the three components was <0. Subjects whose plasma glucose was above target at the start of closed loop received a one-time correction bolus of $K_P T_{D(FALL)}[SG(n) - \text{target}]$. Target glucose was set at 120 mg/dl.

Insulin pharmacokinetics. Delays in subcutaneous insulin absorption were assessed using a two-compartment subcutaneous-insulin kinetic model. In this model, the plasma insulin response [$I_p(t)$] to a bolus of insulin was characterized with the equation:

$$I_P(t) = A \cdot [e^{-t/\tau_1} - e^{-t/\tau_2}] \quad (3)$$

This equation is based on the assumption that insulin diffuses and is cleared from the body in proportion to its concentration. Parameters τ_1 and τ_2 are time constants defining how fast the insulin profile rises and falls [time to peak following a bolus equal $\ln(\tau_1/\tau_2)/(1/\tau_2 - 1/\tau_1)$]. Parameter *A* defines the magnitude of the response (in microunits per milliliter) and is used to calculate insulin clearance [clearance = $100/A/(\tau_2 - \tau_1)$]. Multiple boluses were assumed to add linearly, and parameters were estimated using nonlinear least squares (Mlab; Civilized Software, Bethesda, MD).

Sensor calibration. Sensors were calibrated using 7:00 A.M. reference glucose and sensor current values (one point calibration [11]), with additional calibrations as needed (median two times per subject). The calibrations yielded a calibration factor (in milligrams per deciliter per nA) that was multiplied with sensor current to obtain SG [SG(*n*); in milligrams per deciliter] and multiplied the rate of change of the sensor current to obtain dSGdt(*n*) (in milligrams per deciliter per minute).

Biochemical measurements. Plasma glucose was measured with a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin was measured with enzyme-linked immunosorbent assay (ALPCO Diagnostics, Windham, NH). Plasma FFAs were measured by enzymatic colorimetric assay with reagents supplied by Waco Chemicals (Richmond, VA).

Statistical analysis. Glucose control was assessed by histogram analysis of the open- and closed-loop SG profiles and by the frequency of intervention requiring supplemental carbohydrate. Average DIR for the two treatment periods was compared by paired *t* test. Sensor performance was evaluated by comparison of SG with the respective blood glucose reference (home glucometer for pump therapy and Beckman glucose analyzer for closed-loop insulin delivery treatment). Statistical calculations (*t* test, correlation, regression) were performed using GraphPad Prizm (version 3.02; GraphPad, San Diego, CA) or Mlab (*F* test for equal variance about the mean). Data are reported as means ± SD.

RESULTS

Glycemic control. Fasting plasma glucose was 160 ± 66 mg/dl at the start of closed-loop insulin delivery (7:00 A.M.; Fig. 2), indicating that in some subjects the overnight basal insulin rate was insufficient to maintain normoglycemia. Open-loop adjustments in insulin delivery were done at 2:00 and 6:00 A.M. but did not bring glucose to target in four
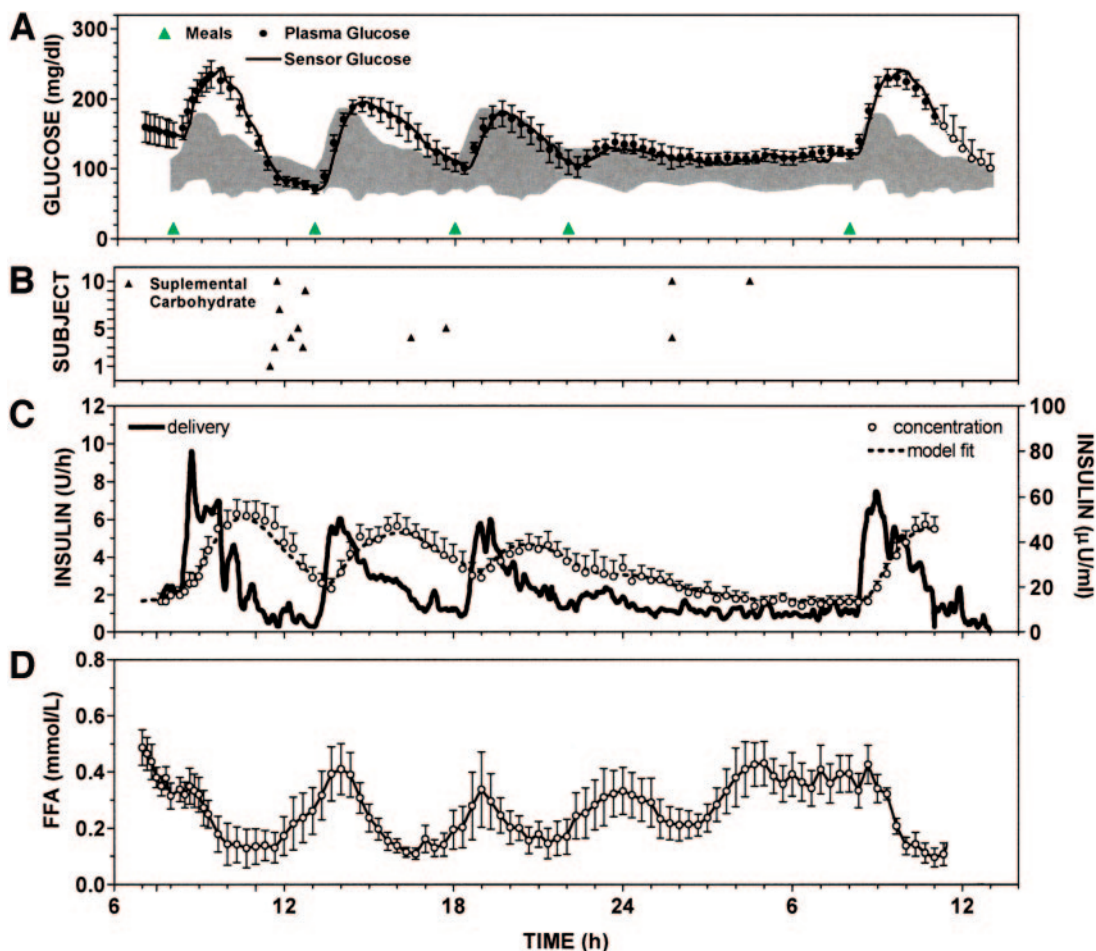
FIG. 2. *A*: Plasma and sensor glucose levels obtained during artificial β-cell treatment. Shaded area indicates means ± 3 SD of the nondiabetic control group (*n* = 17) studied with a similar diet (adapted from Steil et al. [7]). *B*: Time at which supplemental carbohydrate (15 g in juice) was given (carbohydrate was given whenever blood glucose fell below 60 mg/dl). *C*: Insulin delivery (*left axis*), plasma insulin concentration (○, *right axis*), and insulin-model fit (line). *D*: FFA levels.

subjects. Preprandial glucose at lunch (1:00 P.M.) was lower than target (71 ± 19 mg/dl [95% CI 57–85]), but the subsequent preprandial levels at dinner, snack, and breakfast were all not different from target (109 ± 41 [80–138], 110 ± 5 [70–149], and 121 ± 21 mg/dl [106–136], respectively). Two-hour postprandial glucose levels (189 ± 41 [159–218], 172 ± 61 [128–215], and 225 ± 35 mg/dl [200–249] for lunch, dinner, and breakfast, respectively) were higher than those observed in nondiabetic subjects studied under similar conditions (Fig. 2*A*; shading indicates mean ± 3 SD of glucose, data adapted from 7).

There were 13 occurrences of biochemical hypoglycemia, symptomatic in only one case, with 8 of these occurring between 11:00 A.M. and 1:00 P.M. after initiating closed loop (Fig. 2*B*; all case subjects treated with supplemental carbohydrate). During CGMS-monitored CSII therapy, there were also 13 incidents in which SG fell below 60 mg/dl in the 24-h period between lunch on the 2nd day (11:00 A.M.) and lunch on the 3rd day (11:00 A.M.; same 24-h period the closed loop was evaluated on). There were no episodes of severe hypoglycemia during closed-loop or CSII periods. FFA levels were suppressed after all meals during closed loop (Fig. 2*D*).

Preprandial glucose fell below 60 mg/dl on three occasions (Fig. 3*A*). Two-hour postprandial glucose was above 180 mg/dl approximately one-third of the time following lunch, dinner, and snack, and in 9 of 10 subjects following breakfast (Fig. 3*A*). Mean 24-h glucose concentration (Fig. 3*B*) was similar to that obtained with CSII therapy (133 ± 52 vs. 133 ± 63 mg/dl; *P* > 0.65), but the variance about the mean was significantly reduced (*P* < 0.05, *F* test for equal variance). This resulted in plasma glucose in the range 70–180 mg/dl 75% of the time using closed-loop insulin delivery versus only 63% of the time during CSII.

Insulin delivery. Of the three components comprising the total insulin delivery, component *D* rapidly delivered insulin during postmeal increases in SG and suppressed or suspended delivery during periods where SG was falling. Component *I* adjusted upward when glucose was above target and downward when glucose was below target. Component *P* gave insulin when glucose was above target and subtracted from the net insulin delivery when glucose was below target. Figure 4 shows the three components of insulin delivery in one of the study subjects. For this subject, plasma glucose fell below 60 mg/dl one time during the closed-loop insulin delivery control (Fig. 4*A*); thus, 15 g carbohydrate were given in orange juice (∼12.8 h). At the time, glucose fell below 60 mg/dl and insulin delivery had been suspended by the algorithm for ∼40 min. Three occurrences of glucose falling below 60 mg/dl were observed during standard CSII therapy (Fig. 4*A*).

Daily insulin use with closed-loop insulin delivery was well correlated with that during standard CSII therapy (r^2 = 0.87, *P* < 0.001) (Fig. 5), but the total use was higher
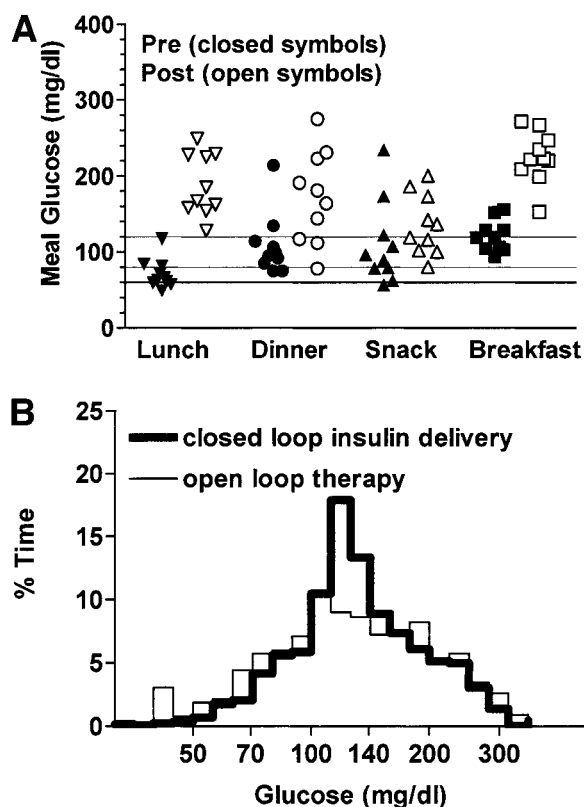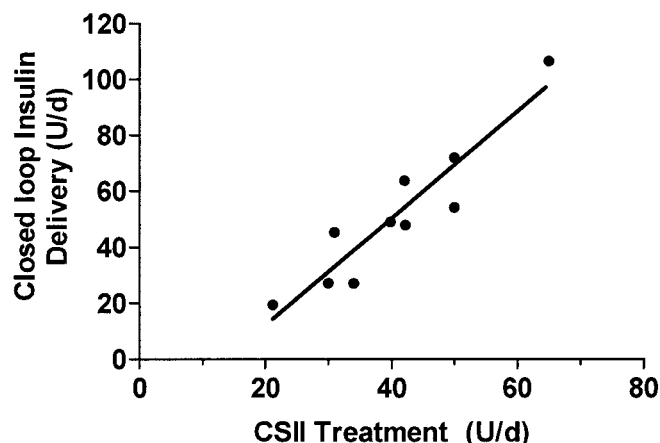
FIG. 5. DIR using standard CSII therapy versus closed-loop insulin delivery. DIR during CSII therapy was assessed as an average of 3 days; insulin use during closed-loop insulin delivery was calculated over the 24-h period, starting at 11:00 A.M.

with the closed-loop insulin delivery (51 ± 25 vs. 41 ± 13 units/day, $P < 0.05$). Regression analysis indicated that the slope (1.915 ± 0.2636 SE) and intercept (-26.34 ± 11.13 SE) were different from 1 and 0, respectively.

Changes in plasma insulin concentration were delayed with respect to insulin delivery. Model analysis (Fig. 2*C*) estimated that the peak insulin concentration occurred 60 ± 29 min after the delivery of each 0.1-unit bolus. The model accounted for >97% of the plasma insulin appearance. Insulin clearance was estimated as 15.5 ± 7.0 ml · $\text{min}^{-1} \cdot \text{kg}^{-1}$.

Sensor performance. Sensor performance was similar during the CSII treatment period (open loop) and closed-

FIG. 3. *A*: Pre- and postglucose level for the four meals taken during closed-loop insulin delivery. *B*: Percentage of time glucose was within the indicated ranges during CSII and closed-loop insulin delivery.
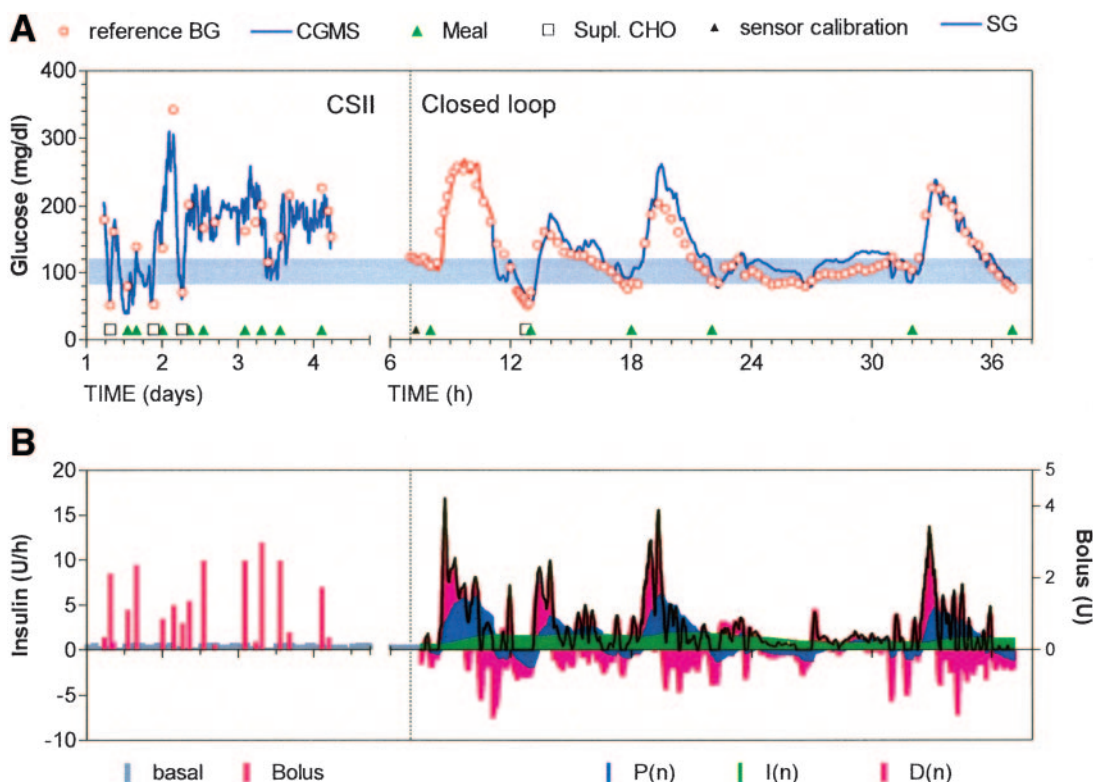

FIG. 4. Example of CSII therapy versus artificial β-cell treatment. *A*: Sensor (blue line) and reference blood glucose (BG) values during CSII therapy versus artificial β-cell treatment using reference blood glucose (red line; 7:00 A.M. to 11:00 P.M.) and SG (blue line; hours 11–38). Supplemental carbohydrates (Supl. CHO) were given when glucose fell below 60 mg/dl. *B*: Basal (shaded background; *left* axis) and bolus (vertical markers; *right* axis) values during CSII therapy and closed-loop insulin delivery.
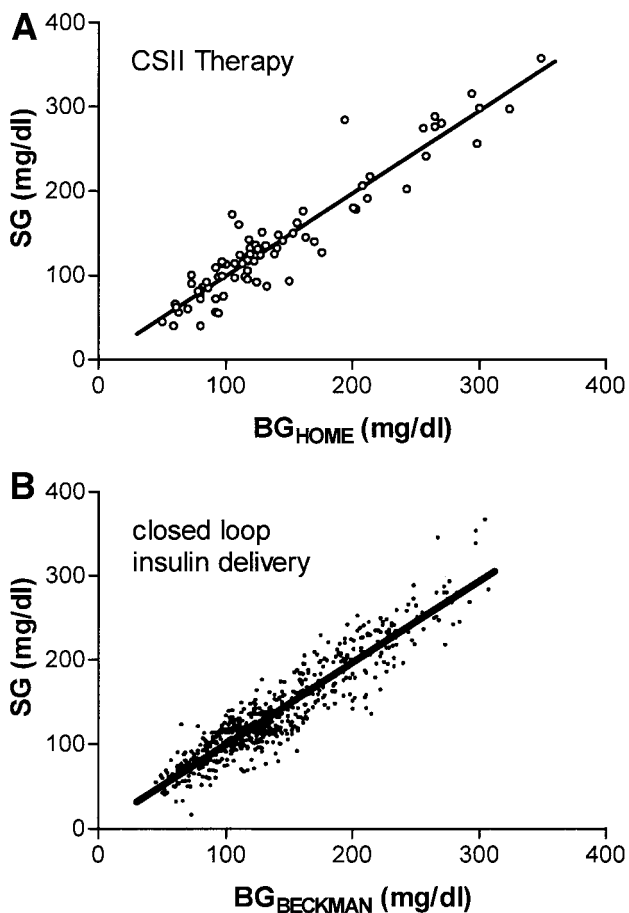
FIG. 6. *A*: **Linear regression analysis of the patient's reference glucose values (BG$_{HOME}$) with CGMS glucose values obtained during the CSII treatment period.** *B*: **Similar analysis comparing Beckman glucose analyzer values (BG$_{BECKMAN}$) with real-time SG during closed-loop insulin delivery.**

loop insulin delivery treatment period (mean absolute difference [MAD] 14.0 and 13.7%; r^2 = 0.86 and 0.89, respectively) (Fig. 6). Separate analysis of the two sensors in place during the closed-loop portion of the study indicated MADs of 17.7 and 16.9%, suggesting that the ability to switch between sensors during the study period biased the sensor MAD in the positive direction (MAD = 14.0 for the sensor used during closed loop). Retrospective calibration of the CGMS sensors used during CSII therapy indicated a small (3.1 mg/dl) but statistically significant (P = 0.0012) bias in glucose reading (Fig. 6*A*); real-time calibration during closed-loop insulin delivery treatment indicated SG was unbiased (P = 0.58; paired t test), with regression analysis indicating a slope not different from 1 and an intercept not different from 0 (Fig. 6*B*).

DISCUSSION

The present study demonstrates that a closed-loop insulin delivery system based on subcutaneous insulin delivery and subcutaneous glucose sensing is feasible. Mean glucose during closed-loop control was similar to that achieved under standard CSII therapy, but the variance about the mean was reduced (Fig. 3*B*). Biochemical hypoglycemia was infrequent, with an incidence similar to that observed during CSII (about once per patient in any 24-h period). Occurrences of biochemical hypoglycemia were detected by the glucose sensor and led to a suspension of

the insulin delivery (e.g., 12:00–1:00 P.M. glucose excursion) (Fig. 4*A*) in all instances.

Although closed-loop insulin delivery resulted in tighter glucose control than that achieved with standard CSII treatment, as assessed by variance about the mean, the control was not as good as that in the nondiabetic population consuming a similar diet. In particular, postprandial glucose was higher and postmeal nadir glucose lower than desired. The elevated postprandial levels may have partially been due to the high target glucose level chosen for this study for safety reasons (target was 120 mg/dl, whereas fasting glucose in the nondiabetic population was ~100 mg/dl) (Fig. 2). A lower target is expected to shift the glucose profile down and reduce the area under the curve of individual meal responses, the latter resulting from the higher glucose clearance expected at lower glucose levels.

It is possible that postprandial glucose control can be improved by increasing insulin delivery in response to the rate of change of glucose (component *D*). This component (Fig. 1) creates a response analogous to the β-cells first-phase insulin secretion (7,12–14) and has been used to aid many closed-loop intravenous insulin delivery systems (15–19), including those of the Biostator (20–22). However, the system being evaluated here relies on subcutaneous insulin delivery, which adds a substantial delay to the appearance of insulin in plasma. To adjust for this delay, the contribution of this component was increased relative to that previously reported with intravenous insulin delivery (~10 min [5]) or estimated from the β-cell response to a hyperglycemic clamp (~40 min [6]). The values used in the current study (66 and 50 min during a rise and fall in glucose, respectively) were derived from preliminary studies in diabetic canines (23,24). However, the current data suggest that the contribution of the *D* component could be increased even further and that there is no need to reduce the contribution during a fall in glucose [$T_{D(FALL)}$ does not need to be less than $T_{D(RISE)}$]. An increase in this component should result in more insulin being given in the early rising portion of the meal response and a more rapid suppression of insulin delivery once glucose begins to return toward euglycemia (D_{con}) (Fig. 4). An earlier response should lower the peak meal glucose, and a more rapid suppression should elevate the nadir, decreasing the risk of hypoglycemia.

Another approach to reduce postprandial glucose levels is to have the patient administer a bolus of insulin before the meal, augmenting early insulin delivery and subsequently reducing peak plasma glucose. Early results obtained with this approach suggest that the area under the curve of the meal response can be decreased as much as 40% (25). A patient administered meal bolus would allow insulin to appear before glucose actually increases, which is analogous to the β-cell's cephalic-phase (26) insulin response. Providing the algorithm with advanced knowledge of an impending meal may also allow algorithm parameters to be specifically adjusted for meals (23). Time information could also be added to allow a "qualitative meal announcement" (2), which could adjust the algorithm parameters to be more aggressive at breakfast than other meals. Breakfast was the most difficult meal to control in the present study (Fig. 2), and preliminary results in the pediatric population suggest that this continues to be the case (25).

Improvements in the nadir glucose level following a meal can be expected if insulin delivery is decreased as the plasma insulin level rises. This negative-feedback mecha-

nism exists in the β-cell (27) and can be effected in the artificial β-cell system by using a model to predict plasma insulin concentration (measuring insulin concentration in real time is unlikely to be an option). The model used here (Eq. 3) fit the data well ($r^2 = 0.98$) (Fig. 2C) and should allow the feedback mechanism to be implemented in future versions of the system.

In the present study, fasting glucose was not different from target (preprandial breakfast) (Fig. 3A). When glucose is at target, with no underlying trend up or down, all insulin delivery is provided by component I (Figs. 1 and 4B). We have previously shown with computer simulations of the Bergman minimal model that this component can adjust basal insulin delivery to compensate for any change in insulin sensitivity or endogenous glucose production (6), without necessitating a change in fasting glucose (e.g., for a decrease in insulin sensitivity, basal insulin delivery will increase until fasting glucose re-achieves the desired target level). It is anticipated that the incremental mechanism will ultimately allow basal insulin delivery to adjust to normal inter- and intraday variation in basal insulin requirement (28).

Aside from the algorithm, a long-standing concern in the development of the artificial β-cell has been sensor performance (2). In the present study, traditional measures of sensor performance showed a MAD of 13.7 and 14.0% and r^2 values of 0.86 and 0.89 (artificial β-cell treatment and CSII therapy periods, respectively). While sensor errors were present during the closed-loop study, these did not prevent closed-loop control from being achieved (Fig. 2). Errors in sensor calibration resulted in fasting glucose different from target in some individual cases, as the algorithm adjusts insulin delivery until the SG is at target (Fig. 4, hour 30); nonetheless, the resulting fasting glucose levels (~85–140 mg/dl) were within an acceptable range. Importantly, the sensors detected hypoglycemia without substantial delay. This resulted in the algorithm suspending insulin delivery until plasma glucose began to return to target. The ability of the sensor to follow the hypoglycemic excursions during closed-loop insulin delivery, without substantial delay, is consistent with our observations on the kinetics of interstitial fluid glucose during controlled hypoglycemia in normal subjects (29).

While there were no cases of severe hypoglycemia during closed-loop control, it is important to note that the subjects were carefully monitored. Plasma glucose was assessed every 20 min using a laboratory glucose analyzer, and supplemental carbohydrates were readily available. This level of monitoring is required in feasibility studies to ensure patient safety, and is expected to continue until the system is optimized. Once optimized, future studies will evaluate the system for longer durations and use a home-type glucometer rather than a laboratory analyzer.

In summary, a completely automated artificial β-cell therapy, utilizing the subcutaneous site for both insulin delivery and glucose sensing, is feasible. The system evaluated here provided stable overnight glucose levels with fasting levels not different from target. Although postprandial glucose levels were higher than those observed in nondiabetic subjects, and some hypoglycemia was observed when control was initiated, the data suggests several mechanisms by which the systems algorithm can be improved. These include increasing insulin delivery in response to the rate of change of glucose, adding insulin feedback to reduce hypoglycemia, and utilizing a meal bolus and/or a lower target glucose level to reduce post-prandial hyperglycemia. Although additional studies will be needed to optimize the system, the present study clearly indicates that glycemic control using an automated insulin delivery system is an achievable goal.

REFERENCES

1. Rother KI, Harlan DM: Challenges facing islet transplantation for the treatment of type 1 diabetes mellitus. *J Clin Invest* 114:877–883, 2004
2. Hovorka R: Continuous glucose monitoring and closed-loop systems. *Diabet Med* 23:1–12, 2006
3. Bequette BW: A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technol Ther* 7:28–47, 2005
4. Elahi D: In praise of the hyperglycemic clamp: a method for assessment of β-cell sensitivity and insulin resistance. *Diabetes Care* 19:278–286, 1996
5. Steil GM, Panteleon AE, Rebrin K: Closed-loop insulin delivery: the path to physiological glucose control. *Adv Drug Deliv Rev* 56:125–144, 2004
6. Steil GM, Rebrin K, Janowski R, Darwin C, Saad MF: Modeling beta-cell insulin secretion: implications for closed-loop glucose homeostasis. *Diabetes Technol Ther* 5:953–964, 2003
7. Steil GM, Hwu CM, Janowski R, Hariri F, Jinagouda S, Darwin C, Tadros S, Rebrin K, Saad MF: Evaluation of insulin sensitivity and β-cell function indexes obtained from minimal model analysis of a meal tolerance test. *Diabetes* 53:1201–1207, 2004
8. Chia CW, Saudek CD: Glucose sensors: toward closed-loop insulin delivery. *Endocrinol Metab Clin North Am* 33:175–195, 2004
9. Ogata K: *Modern Control Engineering*. Upper Saddle River, NJ, Prentice-Hall, 1997
10. Davidson PC, Hebblewhite HR, Bode B, Richardson PL, Steed DR, Welch S, Poulos E, Ybanez P: An empirical basis for modifying the "1500 rule" (Abstract). *Diabetes* 51 (Suppl. 2):A128, 2002
11. Choleau C, Klein JC, Reach G, Aussedat B, Demaria-Pesce V, Wilson GS, Gifford R, Ward WK: Calibration of a subcutaneous amperometric glucose sensor implanted for 7 days in diabetic patients: part 2. Superiority of the one-point calibration method. *Biosens Bioelectron* 17:647–654, 2002
12. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity. *Diabetes* 50:150–158, 2001
13. Breda E, Toffolo G, Polonsky KS, Cobelli C: Insulin release in impaired glucose tolerance: oral minimal model predicts normal sensitivity to glucose but defective response times. *Diabetes* 51 (Suppl. 1):S227–S233, 2002
14. Ehrmann DA, Breda E, Cavaghan MK, Bajramovic S, Imperial J, Toffolo G, Cobelli C, Polonsky KS: Insulin secretory responses to rising and falling glucose concentrations are delayed in subjects with impaired glucose tolerance. *Diabetologia* 45:509–517, 2002
15. Albisser AM, Leibel BS, Zinman B, Murray FT, Zingg W, Botz CK, Denoga A, Marliss EB: Studies with an artificial endocrine pancreas. *Arch Intern Med* 137:639–649, 1977
16. Kraegen EW, Campbell LV, Chia YO, Meler H, Lazarus L: Control of blood glucose in diabetics using an artificial pancreas. *Aust N Z J Med* 7:280–286, 1977
17. Kraegen EW, Chisholm DJ: Closure of the loop by glucose sensing: physiological and practical considerations. *Horm Metab Res Suppl* 20:1–4, 1988
18. Fischer U, Jutzi E, Bombor H, Freyse EJ, Salzsieder E, Albrecht G, Besch W, Bruns W: Assessment of an algorithm for the artificial B-cell using the normal insulin-glucose relationship in diabetic dogs and men. *Diabetologia* 18:97–107, 1980
19. Sekigami T, Shimoda S, Nishida K, Matsuo Y, Ichimori S, Ichinose K, Shichiri M, Sakakida M, Araki E: Comparison between closed-loop portal

and peripheral venous insulin delivery systems for an artificial endocrine pancreas. *J Artif Organs* 7:91–100, 2004

20. Calabrese G, Bueti A, Zega G, Giombolini A, Bellomo G, Antonella MA, Massi-Benedetti M, Brunetti P: Improvement of artificial endocrine pancreas (biostator; GCHS) performance combining feedback controlled insulin administration with a pre-programmed insulin infusion. *Horm Metab Res* 14:505–507, 1982

21. Clemens AH, Chang PH, Myers RW: The development of BIOSTATOR, a glucose controlled insulin infusion system (GCIIS). *Horm Metab Res* 7 (Suppl.):23–33, 1977

22. Fogt E, Dodd LM, Jenning EM, Clemens AH: Development and evaluation of a glucose analyzer for a glucose controlled insulin infusion system (Biostator). *Clin Chem* 24:1366–1372, 1978

23. Panteleon AE, Loutseiko M, Steil GM, Rebrin K: A novel approach for closed-loop control of meal induced carbohydrate intake (Abstract). *Diabetes Technol Ther* 6:265, 2004

24. Panteleon AE, Loutseiko M, Steil GM, Rebrin K: Evaluation of the effect of gain on the meal response of an automated closed-loop insulin delivery system. *Diabetes* 55:1995–2000, 2006

25. Weinzimer SA, Steil GM, Kurtz N, Swan KL, Tamborlane WV: Automated feedback-controlled insulin delivery in children with type 1 diabetes (T1D): a preliminary report (Abstract). *Diabetes* 55 (Suppl. 1): A102, 2006

26. Ahren B, Holst JJ: The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. *Diabetes* 50:1030–1038, 2001

27. Argoud GM, Schade DS, Eaton RP: Insulin suppresses its own secretion in vivo. *Diabetes* 36:959–962, 1987

28. Dimeglio LA, Pottorff TM, Boyd SR, France L, Fineberg N, Eugster EA: A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr* 145:380–384, 2004

29. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF: Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. *Diabetologia* 48:1833–1840, 2005