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ORIGINAL ARTICLE

Feasibility of Overnight Closed-Loop Control Based on Hourly Blood Glucose Measurements

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Abstract

Introduction:

Safe and effective closed-loop control (artificial pancreas) is the ultimate goal of insulin delivery. In this study, we examined the performance of a closed-loop control algorithm used for the overnight time period to safely achieve a narrow target range of blood glucose (BG) concentrations prior to breakfast. The primary goal was to compare the quality of algorithm control during repeated overnight experiments.

Materials and Methods:

Twenty-three subjects with type 1 diabetes performed 2 overnight experiments on each of three visits at the study site, resulting in 138 overnight experiments. On the first evening, the subject's insulin therapy was applied; on the second, the insulin was delivered by an algorithm based on subcutaneous continuous glucose measurements (including meal control) until midnight. Overnight closed-loop control was applied between midnight and 6 a.m. based on hourly venous BG measurements during the first and second nights.

Results:

The number of BG values within the target range (90–150 mg/dl) increased from 52.9% (219 out of 414 measurements) during the first nights to 72.2% (299 out of 414 measurements) during the second nights ($p < .001$, χ^2-test). The occurrence of hypoglycemia interventions was reduced from 14 oral glucose interventions, the latest occurring at 2:36 a.m. during the first nights, to 1 intervention occurring at 1:02 a.m. during the second nights ($p < .001$, χ^2-test).

Conclusions:

Overnight controller performance improved when optimized initial control was given; this was suggested by the better metabolic control during the second night. Adequate controller run-in time seems to be important for achieving good overnight control. In addition, the findings demonstrate that hourly BG data are sufficient for the closed-loop control algorithm tested to achieve appropriate glycemic control.

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Abbreviations: (APTS) automated pancreas test stand, (BG) blood glucose, (CGM) continuous glucose monitoring, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (SD) standard deviation

Keywords: artificial pancreas, closed-loop insulin delivery, continuous subcutaneous insulin infusion, overnight control

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Introduction

In order to avoid long-term complications, people with diabetes mellitus require life-long insulin treatment, which controls glucose concentrations sufficiently well.[1–3] Improvements in diabetes management have been achieved with the development of continuous subcutaneous insulin infusion (CSII),[4–7] but diabetes management is still far from optimal and requires human interaction. Continuous glucose monitoring (CGM) sensors, which are available commercially, provide more insight into glycemic behavior and further enhance glycemic control.[8–10] The research of reliable closed-loop insulin delivery systems, also called artificial pancreas, is of major interest in diabetes management. While the first artificial pancreas systems, invented independently by Albisser and colleagues[11] and by Pfeiffer and colleagues,[12] were large machines primarily used in clinical environments, technological developments provided means for miniaturization. In current closed-loop research, the closed-loop systems combine CGM systems with insulin infusion pumps, and could, in principle, work without any human interaction. In closed-loop systems, computer algorithms are used to calculate the required amount of insulin solely on the measurements from the CGM system. Insulin is then delivered via the infusion pump according to these calculations.

One of the main challenges in performing subcutaneous–subcutaneous closed-loop systems is in administering the correct amount of insulin despite the lag time caused by subcutaneous glucose measurement and the action profile of subcutaneously administered insulin.[13–17] The accuracy and reliability of the CGM devices used seem to be another limiting factor.[13] Further challenges are intrapatient and interpatient variability. The performance of a closed-loop control algorithm was examined for the overnight time period. The algorithm was used to safely achieve a narrow target range of blood glucose (BG) concentrations prior to breakfast meals. The primary goal of this study was to compare the quality of algorithm control during repeated overnight experiments. The main difference between the overnight experiments was the conditions during the evening prior to overnight control.

Materials and Methods

This single-center exploratory study was performed in compliance with Good Clinical Practice, International Organization for Standardization 14155, the Declaration of Helsinki (revised edition, Seoul 2008), and the German Medical Devices Act. The study protocol was approved by the ethics committee at the University of Ulm, Germany. The study took place at the Institut für Diabetes-Technologie GmbH in Ulm, Germany.

Twenty-four subjects provided written consent and were enrolled in this study. All subjects had to have type 1 diabetes mellitus with CSII therapy for more than 3 months. The study was performed in 2003 and 2004.

Study Device: Automated Pancreas Test Stand

The subjects were provided with the study device, the Automated Pancreas Test Stand (APTS). The APTS consisted of two CGM sensors of the same type (SCGM1, Roche Diagnostics GmbH, Germany, investigational device). The SCGM1 sensors measured glucose based on the microdialysis method. A push–pull flow resulted in a perfusion of the microdialysis membrane with 0.3 µl/min, then glucose oxidase was mixed with the dialysate, which passed the *ex vivo* sensor. The generated current was averaged every 60 s. Nielsen and colleagues[18] showed that the system performed well with a mean absolute relative error of 10.6 (5.8–53.0) and %PRESS (predicted error sum of the squares) of 11.9 (7.1–50.6). Two conventional off-the-shelf BG meters (ACCU-CHEK® Active, Roche Diagnostics GmbH) were used for calibration of the SCGM1 device with capillary BG measurements. The signal was corrected for the time that is needed for fluid transportation from the catheter to the extracorporeal sensor (about 30 min).[19] The CGM sensors and a modified insulin infusion pump (ACCU-CHEK D-TRON, Roche Diabetes Care AG, Switzerland, formerly Disetronic Medical Systems AG) were connected to a personal digital assistant that transmitted and received the information through WLAN (wireless local area network) interface, which was connected to a laptop computer on which the control algorithm, invented by Roche Diagnostics Operations, Inc., was running.

Although the APTS was able to communicate wirelessly with the SCGM1 device, venous BG values obtained from the ACCU-CHEK Compact Meter (Roche Diagnostics GmbH) were manually entered into the control algorithm.

The algorithm, a so-called empirical algorithm, predicted a glucose value at a predetermined time in the future,

compared that predicted glucose value to a predetermined glucose value range, and determined a corrective amount of insulin to be administered when the predictive glucose value was outside of the predetermined glucose value range.

A predictive model was based on the following equation: $\Delta G = -(\text{TotalInsuRemain} - \text{BasalReq}) * \text{Sensitivity}$, wherein ΔG is the future change in glucose level at a predetermined time; TotalInsuRemain is the amount of insulin remaining in the subject's system at the current time; BasalReq is the amount of insulin that the subject is estimated to need at the predetermined time; and Sensitivity is the subject's insulin sensitivity.

Insulin recommendations were provided every 10 min. The algorithm based its calculations solely on the last BG reading (either hourly BG values or subcutaneous glucose measurements) and recent insulin deliveries.

The controller was set to a target value of 120 mg/dl (6.7 mmol/liter), with a target range of 90–150 mg/dl (5.0–8.3 mmol/liter).

A controlled closed-loop system was established, i.e., each recommended insulin delivery had to be confirmed manually by a health care professional, so interaction was needed every 10 min. Basal rate delivery was simulated by administration of small single boluses up to six times per hour with 0.1 unit increments. The actual infusion rate could be automatically reduced to 50% of the basal rate setting, in case the algorithm predicted hypoglycemia. Although a small single bolus could equal zero, the sum of all single boluses applied within an hour never was below the 50% threshold.

The algorithm was able to work in three modes. The first mode is the so-called observation mode: BG values and insulin delivery data are provided to the algorithm; however, no insulin calculation takes place. The patient uses his or her own therapy rules. The two other modes are so-called controller modes. The algorithm calculates the next required insulin dose based on the available data. In one controller mode, insulin recommendations are based on the intravenously measured BG values, and in the other modes, recommendations are based exclusively on the subcutaneously measured tissue glucose values.

The BG values obtained with the SCGM devices were displayed in real time on the laptop computer, independent from the current algorithm mode.

More details about this algorithm can be found in the U.S. patent no. 6,544,212.

Study Protocol

Each subject had to visit the study site on three occasions with at least 3 weeks between two visits. Each visit lasted 4 days.

On day 1, the subjects were connected to the study device, the APTS, around 7 p.m., and a venous catheter and a Medtronic Minimed CGMS device were placed in addition to the two SCGMs. At 10 p.m. on day 3, the subjects were disconnected from the APTS. On day 4, the subjects left the study site in the morning. The study procedures were identical during each visit and are displayed in **Figure 1**.

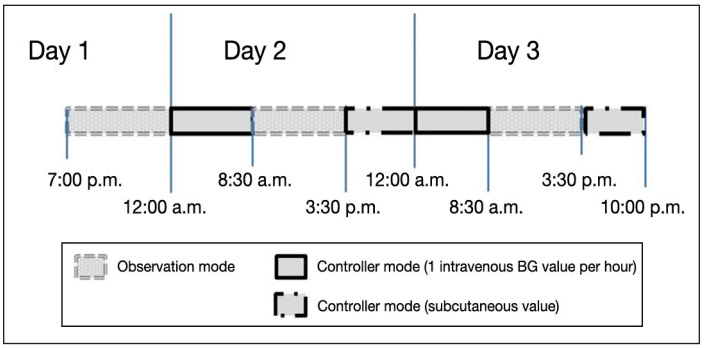

Figure 1. Study procedure.

Meal Control

At 7:30 p.m. on day 1 and day 2, patients were served a standardized dinner. It corresponded to 25% of the required daily caloric need and had the following composition: 60% carbohydrate (CHO), 20% protein, and 20% fat. At 7:30 p.m. on day 3, patients chose dinner from a buffet.

At 9:00 a.m. on day 2 and day 3, patients were served a standardized breakfast. The insulin bolus was calculated based on patients' therapy parameters.

At 4:00 p.m. on day 2 and day 3, patients had an additional meal corresponding to the caloric difference between the breakfast and dinner in order to cover the patient's daily caloric need.

The content of CHO in the meal was announced to the algorithm for insulin recommendation for the 4 p.m. meal and dinner on day 2 and day 3, as shown in **Figure 2.**

Therapy Parameters

Each subject's therapy parameters prior to the study were used as algorithm start parameters during the first visit. Based on the insulin recommendations during each visit, the therapy parameters for the following visit were adjusted. Five different parameters were used by the algorithm: basal rate in U/h, insulin sensitivity in (mg/dl)/U, and three insulin-to-carbohydrate ratios for breakfast, lunch, and dinner in U/g.

Data Preparation

The study included 24 subjects; 1 subject dropped out after the first visit. Data from this subject were excluded to provide homogeneity in the data sets. Data from 23 subjects were included in the analysis.

All 138 overnight experiments (2 experiments on each of three visits per subject) have been included in the data analysis. The hourly BG values obtained between 1 a.m. and 6 a.m. were used for evaluation. This corresponds to 828 BG values.

At midnight, the algorithm was switched from either observation mode or subcutaneous control mode to BG control mode. The BG value at midnight was excluded from the analysis, as it was too heavily affected by the infused insulin prior to this time.

Statistical Analysis

Two distinct analyses were made. The first one was about the effect of the therapy (and algorithm) parameters adjustment between the experiments. This was obtained by comparing data from the three visits. The second analysis highlighted the quality of control during the second nights in contrast to the first nights.

Statistical analysis was performed by calculating mean values and standard deviations (SDs) or medians and interquartile ranges, where appropriate. Statistical significance of continuous variables was tested with two-sided paired *t*-tests. Dichotomous variables were tested using a χ^2-test. Due to the exploratory nature of this study, *p* value adjustments were not performed.

Histograms of BG values were created to visualize the BG value distribution.

Safety Assessment

Safety was assessed by capturing hypo- and hyperglycemic episodes.

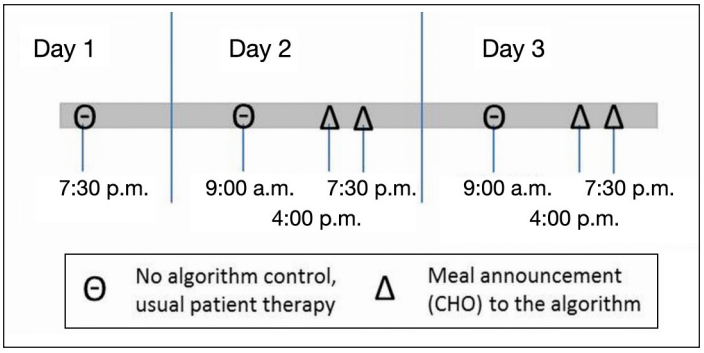

Figure 2. Meal announcement and control of the algorithm.

Hypoglycemia interventions (consumption of 18 g dextrose) were performed at whole blood glucose values below 50 mg/dl (2.8 mmol/liter), or when symptoms were reported. Hyperglycemia interventions (additional insulin delivery) were performed when glucose levels were over 250 mg/dl (13.8 mmol/liter) for more than 2 h, or in case of symptoms or a positive ketone test.

Results

Subject Disposition

Twelve patients were male, and 11 patients were female. Mean age (mean ± SD) was 40.2 ± 8.7 years, with a duration of diabetes (mean ± SD) of 20.6 ± 10.5 years. Body mass index (mean ± SD) was 24.5 ± 2.6 kg/m². Hemoglobin A1c of the patients (mean ± SD) was 7.0 ± 1.0%, and the total daily insulin need (mean ± SD) was 0.50 ± 0.12 U/kg per day.

Effect of Algorithm Parameters Adjustments

Mean values of the BG concentrations [mean ± SD (range)] based on the individual subjects' mean are shown in **Table 1**.

There were no statistically significant differences between the visits: visit 1 vs visit 2: $p = .9011$; visit 2 vs visit 3: $p = .2133$; visit 1 vs visit 3: $p = .1454$.

Table 1.
Overnight Venous Blood Glucose Concentrations by Visit[a]

	Visit 1	Visit 2	Visit 3
Mean overnight BG concentration in mg/dl	104.2 ± 15.3	104.6 ± 14.9	110.4 ± 14.8
BG range in mg/dl	85.8–141.2	73.9–137.0	87.3–148.8
Number (subjects)	23	23	23

[a] For each subject, a mean value was calculated including data from two nights.

Difference between the Nights

The distribution of BG measurement values between the two nights is displayed in **Figure 3**.

The number of BG values within the target range increased from the first nights to the second nights. During night 1, 52.9% (219 out of 414) BG values were within the target range vs night 2, which had 72.2% (299 out of 414) BG values within target range ($p < .001$).

The mean BG concentrations [mean ± SD (range)] based on the individual subjects' mean over three visits increased statistically significant from the first nights to the second nights ($p = .0144$), as shown in **Table 2**.

Occurrence of Interventions

Out of 69 first nights (between midnight and 6 a.m.) as shown in **Figure 4**, hypoglycemia interventions were needed during 14 nights. Out of 69 second nights **(Figure 5)**, hypoglycemia interventions were needed only during 1 night. This decrease was statistically significant ($p < .001$).

Table 2.
Overnight Venous Blood Glucose Concentrations by Visit.[a]

	Nights 1	Nights 2
Mean overnight BG concentration in mg/dl	102.2 ± 12.8	110.5 ± 12.4
BG range in mg/dl	77.1–126.8	85.0–146.7
Number (subjects)	23	23

[a] For each subject, a mean value was calculated including data from three visits.

The last hypoglycemia intervention during night 1 was at 2:36 a.m., while the only hypoglycemia intervention during night 2 was at 1:02 a.m.

Discussion

Advancements in closing the loop are made in different directions. Most closed-loop studies, such as this one, focus on the subcutaneous–subcutaneous approach; however, there are studies incorporating subcutaneous–intraperitoneal systems.[20] Work has been done on

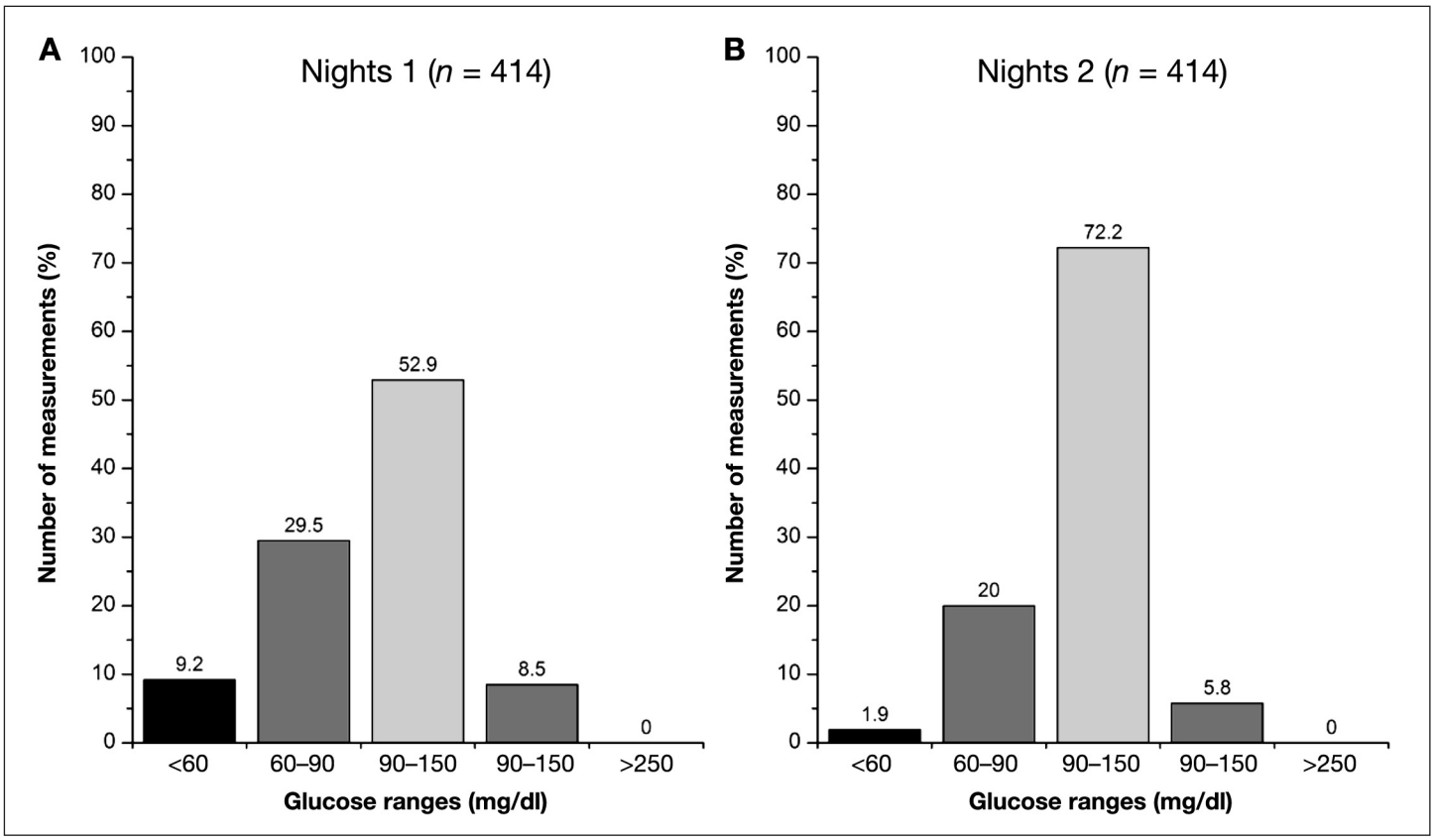

Figure 3. Distribution of BG measurement values during **(A)** 69 first nights and **(B)** 69 second nights. The algorithm's target range (90–150 mg/dl) is displayed in light grey.

different controller types, such as proportional-integral-derivative controllers,[20] hybrid closed-loop systems with meal priming boluses,[21] and most notably, model predictive controllers.[22–24] This study incorporates an empirical algorithm based on subjects' therapy data and shows that the algorithm did accomplish good overnight glucose control. A major advantage of the empirical algorithm is the use of therapy parameters, which are common to CSII and which are also used for automated bolus calculators. The algorithm optimization improved the glycemic control only slightly and had no statistically significant effect on the subjects' mean BG values. Between the first and the last visit, the mean BG increased slightly (closer to the target), while the number of hypoglycemia was significantly reduced.

Heinemann and colleagues[25] showed that significant changes in basal infusion rates can destabilize steady-state glycemia for several hours, so the action time of the previous insulin deliveries is an issue for overnight control, whether they are part of regular therapy or part of algorithm control.

The subjects used their own therapy during the first evenings, including mealtime insulin doses. Inappropriate dosing and stress caused by study procedures, such as connecting to the APTS, provided less optimal initial conditions for algorithm control after midnight during the first nights than during the second nights. Blood glucose concentrations were shifted towards the target range, and hypoglycemia was significantly reduced. Hypoglycemia interventions during the first night were necessary within a few hours after midnight, and the subjects' own therapy likely affected glycemic control at that time. This reduction of hypoglycemia seems to be achieved by better initial conditions with smaller BG variations at midnight during the second nights. This may be attributed to the previous algorithm control based on CGM during the evening, using the algorithm's features to reduce the infusion rate below the preset basal rate and to calculate boluses based on meal information. This is a main feature to support the prevention of hypoglycemia as supported by recently published studies.[26–28] If the controller recognizes impending hypoglycemia early enough, this could provide a method to achieve good glycemic control without the need for bihormonal infusion.[29]

A possible limitation of this study is the lack of a control arm. Thus the algorithm may not be the only source for the improvements seen during the second nights.

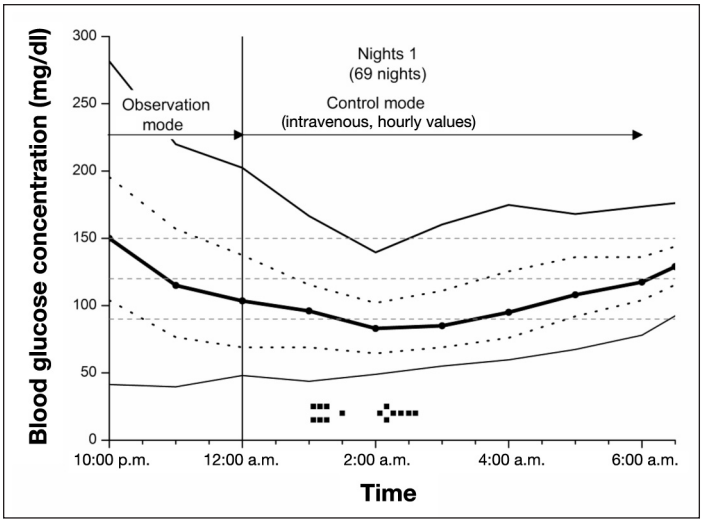

Figure 4. Median BG between 10 p.m. and 6:30 a.m. of nights 1. Displayed are medians (circles with bold line), 25/75% quantiles (dotted lines), 2.5/97.5% quantiles (thin line), the algorithm's point target and target range (grey dashed lines), and occurrence of hypoglycemia interventions (squares, below BG traces).

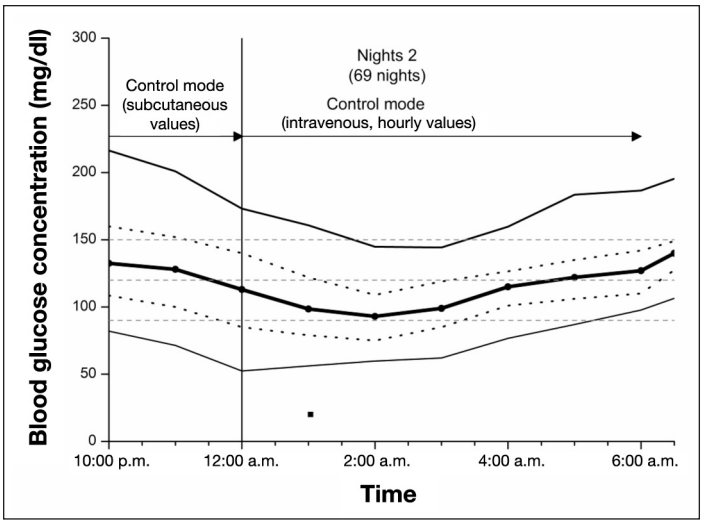

Figure 5. Median BG between 10 p.m. and 6:30 a.m. of nights 2. Displayed are medians (circles with bold line), 25/75% quantiles (dotted lines), 2.5/97.5% quantiles (thin line), the algorithm's point target and target range (grey dashed lines), and occurrence of hypoglycemia interventions (squares, below BG traces).

Another source might be the fact that the patients were in a hospital-like environment and that the patients acclimatized to this environment. This study intended to show the effect of different initial conditions on overnight control but did not discriminate between sources of this effect.

Hovorka and colleagues[22,30] showed similar results for children and adolescents and for adults: closed-loop control kept the BG within target range longer and

reduced the risk of hypoglycemia in comparison to CSII therapy, even without application of hypo- or hyperglycemia interventions.

The increasing BG values in the morning were probably caused by the algorithm adapting too slowly to the dawn phenomenon. This may be compensated for by customizing the algorithm in the early morning or by increasing the frequency at which BG measurements and algorithm actions occur.

While this study shows that good glycemic control is achievable overnight, it did not aim at major glucose variations, namely meals and exercise. Improving algorithm control during these variations, e.g., with automated meal detection,[31–33] may provide the necessary tools for user-independent closed-loop control. The venous BG measurements pose another limitation of this study. Venous BG measurements were used in this study in order to have reliable and accurate glucose data during the overnight period. Continuous glucose monitoring measurements or another method for which the subject is not required to be awake could improve the usability of the APTS.

Conclusions

This study shows that during all nights, good glycemic control was established using an empirical algorithm with BG value frequency of one per hour.

Closed-loop control allowed achievement of a narrow range of BG concentrations in the study population. Overnight controller performance improved when optimized initial control was given; this was suggested by the trend towards better metabolic control during the second nights. This means that an adequate glycemic control during the previous evening is an important prerequisite for good overnight control. This has also been confirmed by the statistical significant reduction of hypoglycemia interventions.

Considering the findings of this study, it seems necessary to grant the controller a few hours of run-in time in order to achieve adequate overnight control.

Funding:

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