Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas
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Chapter 9

Day and night closed loop control in adults with type 1 diabetes mellitus: a comparison of two closed loop algorithms driving continuous subcutaneous insulin infusion versus patient self management


On behalf of the AP@home consortium

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**ABSTRACT**

Objective: To compare two validated Closed Loop (CL) algorithms versus patient self-control with CSII in terms of glycemic control.

Research design and methods: This study was a multi-center, randomized, three-way crossover, open label trial in 48 patients with type 1 diabetes mellitus for at least 6 months, treated with CSII. Blood glucose was controlled for 23 h either by the algorithm of the Universities of Pavia and Padova with a Safety Supervision Module developed at the Universities of Virginia & California at Santa Barbara (iAP), or by the algorithm of University of Cambridge (CAM) or by patients themselves in Open Loop (OL), during three hospital admissions including meals and exercise. The main analysis was on an intention to treat basis. Main outcome measures included time spent in target (glucose levels between 3.9 and 8.0 mmol/L, or between 3.9 and 10.0 mmol/L after meals.

Results: Time spent in target range was similar in closed and open loop: 62.6% for OL, 59.2% for iAP and 58.3% for CAM. While mean glucose level was significantly lower in open loop, 7.19 / 8.27 / 8.26 mmol/L (overall P=0.001), percentage of time spent in hypoglycemia (<3.9 mmol/L) was almost threefold reduced during closed loop, 6.4% / 2.1% / 2.0% (overall P=0.001) with less time ≤2.8 mmol/L (overall P= 0.038). There were no significant differences in outcomes between algorithms.

Conclusion: Both CAM and iAP algorithms provide safe glycemic control.
INTRODUCTION

The burden of managing Type 1 Diabetes Mellitus (T1DM) is considerable for the patient (1). Automating glucose measurements and insulin administration may ease diabetes management. This is known as a “closed-loop system” or “artificial pancreas” (AP). A computer algorithm determines insulin infusion rates from continuously measured glucose levels, aiming to keep glucose levels within target range. AP systems have a long development history (2). One of the earliest systems was the Biostator device (Miles Laboratories, Elkhart, IN, USA) which entered the market in 1977 (3). The Biostator was a bedside device which required intravenous access to determine blood glucose and infuse insulin or glucose. The necessity of intravenous access limited usability of the device to in-hospital settings. Outpatient use became conceivable with the advent of continuous glucose monitoring (CGM) systems which measure glucose in interstitial fluid via placement of a sensor in the subcutaneous fat. Although subcutaneous CGM combined with continuous subcutaneous insulin infusion (CSII) allowed for closed loop experiments, CGM accuracy needs to be improved upon and is considered to be one of the limiting factors in development of AP systems (4,5). Closed loop (CL) algorithms should take into account the uncertainty surrounding CGM reported glucose values, as well as the delay of insulin action after its administration. Many current algorithms used to develop an AP are based on model predictive control (MPC) (6,7) while others are based on the proportional–integral–derivative (PID) approach (8-11) which may also employ insulin feedback (12). MPC can be used to take into account limited CGM accuracy, delays in insulin absorption and glucose peaks brought about by meals (4). This work aims to compare two CL algorithms; one from the University of Cambridge (CAM) and the other from collaboration between the Universities of Pavia, Padova (13) and the University of Virginia and University of California at Santa Barbara (international Artificial Pancreas, iAP)(14) against patient self-management (open loop (OL)). Both algorithms employ model predictive control (MPC) to control blood glucose levels and have shown that their use leads to diminished occurrence of hypoglycemia at night when used for CL control in small scale CRC trials (15,16). The CAM algorithm is initialized using subject’s weight, total daily insulin, and the basal 24 hour pump
profile while the iAP algorithm uses subject’s weight, basal 24 hour pump profile, iAP but not CAM algorithm also uses information about correction factors, insulin-to-carbohydrate ratios, and pump setting during exercise. Both algorithms use mealtime announcement to apply prandial insulin boluses which has been shown to lead to improved postprandial glucose excursions (17), however, while CAM algorithm uses this information to administrate the meal bolus computed with the conventional therapy, the iAP meal bolus is automatically computed by the MPC control algorithm including in the cost function the conventional therapy as references. The Cambridge algorithm uses a two-compartment model of glucose kinetics and a three-compartment model of insulin action solved analytically for computational speed and robustness. The model is adapted at each control cycle to a particular subject by modifying two model parameters representing unexplained glucose flux to accommodate the prediction error and meal carbohydrate bioavailability. In addition, several versions of the model are tested to assess the likelihood of slow/fast insulin absorption and slow/fast meal absorption. The versions are combined in a probabilistic fashion taking into account prediction accuracy of each model version. The iAP MPC algorithm uses the mean linearized model of the in-silico population of the FDA approved Virginia/Padova simulator for all the patients. Both algorithms are only aware of the CGM data monitored during the trial and do not take into account safety blood glucose values measured for safety reasons during trials. Recent results on a near full-day study showed that the iAP algorithm reduced mean glucose concentration without increasing hypoglycemia (18). This study aims to assess safety of these systems on a broader scale, i.e. in a large series of 48 patients investigated in several clinical research sites, including centers naïve to such trials, in order to increase external validity of the reported results. Secondly, we wanted to extend duration of experiments beyond night-time to encompass a near full day (23 hours). By doing this we were able to test the algorithms’ ability to cope with meals and exercise, important challenges for CL control (4,11,18,19).
METHODS

Fourty-eight patients with type 1 diabetes mellitus were included in this three-way randomized cross-over intervention study in six clinical centers (Academic Medical Center Amsterdam, the Netherlands; Centre Hospitalier Regional Universitaire Montpellier, France; Medical University Graz, Austria; Profil Institute for Metabolic Research GmbH, Neuss, Germany; University of Cambridge, United Kingdom; University of Padova, Italy). The trial was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by the medical ethical committees of participating centers.

Main inclusion criteria included aged 18 or above, T1DM treated with CSII with a rapid-acting insulin analog for at least 3 months. Main exclusion criteria included pregnancy and use of medications which significantly impact glucose metabolism (supplemental table S1). Patients visited the CRC for an inclusion visit and provided informed consent. The remainder of the inclusion visit included CGM training and determination or estimation of VO$_2$Max.

The main intervention comprised three 24-hour admissions (duration of intervention 23 hours) to the CRC during which patients underwent the study interventions in random order (CL with CAM or iAP and OL). Admissions were at least 1 week apart to prevent carry-over effects. Between 24 to 48 hours before admission a non-blinded Dexcom Seven Plus CGM sensor (Dexcom Inc, San Diego, CA, USA) was placed and calibrated using finger-stick glucose values. During each study visit, CGM was calibrated with plasma glucose measurements performed either with a YSI (YSI Incorporated, Yellow Springs, OH, USA)( Graz, Neuss, Padova) or a blood glucose meter (Roche Diagnostics GmbH, Mannheim, Germany)(Amsterdam, Cambridge, Montpellier). Calibration was performed four times per 24 hours: at 6.45 pm (before dinner), 11 pm (before bedtime), 7 am (before breakfast) and at 2.30 pm (before exercise). At the beginning of each admission an Omnipod Insulin Patch-Pump (Insulet Corp, Bedford, MA, USA) filled with insulin aspart (Novo Nordisk A/S, Bagsvaerd, Denmark) was placed on the abdomen. The CL algorithms ran on a
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personal computer loaded with Windows XP Professional (Microsoft Corp, Redmond, WA, USA), code was executed using MatLab 2009b (MathWorks Inc, Natick, MA, USA) in case of iAP and as a separate executable in case of CAM. The CL algorithm was fed with CGM data either automatically (Amsterdam, Montpellier, Padova) or by manual transfer of glucose data (Cambridge, Graz, Neuss), depending on regulatory requirements and availability of devices. The algorithms were unaware of plasma glucose values. The CL algorithms calculated the appropriate insulin doses, which were then automatically or manually transferred to the patch pump. The control cycle was 5 minutes for iAP and 15 minutes for CAM in automated centers, and 15 minutes for both algorithms in manual centers. In both automated and manual centers, the attending physician could override actions initiated or suggested by the CL algorithm at any time.

**Admission days:**

Patients arrived at the CRC at 6 pm (see figure 1). A meal of 80 grams of carbohydrates was given at 7 pm for dinner, followed by sleep from 11 pm through 7 am the next day. A 50 gram carbohydrate breakfast was given at 8 am, followed by a 60 grams carbohydrate lunch at noon. Exercise, consisting of two bouts of 15 minutes exercise at 50% VO\textsubscript{2}max, was started at 3 pm and the study ended at 6 pm. Time and carbohydrate contents of meals were announced to the system 15 minutes before eating. In case of the iAP algorithm, the mealtime insulin bolus was then calculated by the algorithm. In case of the CAM algorithm, the algorithm advised a bolus of 80% of the patient’s usually calculated mealtime bolus. In case of OL control, patients treated themselves as usual with the advice to administer mealtime boluses 15 minutes before commencement of the meal as this has been shown to significantly reduce postprandial glucose excursion (20). Size of mealtime boluses was determined by patients themselves based on carbohydrate contents of the meals, which was announced to them. During OL visits, subjects were given the option of reducing usual basal rates, one to two hours before exercise. Patients could also choose to eat a snack before exercise, while all patients were given a snack consisting of 20 g of carbohydrates if the reference plasma glucose was <7.8 mmol/L 30 minutes before exercise. This snack was announced to the iAP algorithm, but not to the
CAM algorithm. In case of hypoglycemia measured by YSI, patients were treated with a 15 g carbohydrate snack, such rescue carbohydrates were announced to both algorithms. Rescue carbohydrates were given on the basis of YSI values only at 3.3 mmol/L or lower in patients experiencing symptoms of hypoglycaemia and at 2.8 mmol/L or lower in patients not experiencing symptoms. No additional carbohydrates were provided to the patient other than those mentioned before. Throughout the admission, blood was sampled for measurement of plasma glucose and insulin levels every 30 minutes. Blood sampling frequency increased to every 15 minutes after meals and exercise and decreased to once an hour at night. Blood was sampled for plasma glucose measurement using the YSI 2300STATplus analyzer (YSI incorporated, Yellow Springs, OH, USA). Heparinised plasma was frozen for central determination of insulin aspart concentrations using an insulin chemiluminescence assay (Invitron Ltd, Monmouth, UK) (The Institute of Life Sciences, Swansea University, S. Luzio).

![Diagram of Loop, CGM, and Sampling]

**Figure 1:** Overview of the admission day. Patients underwent open loop or closed loop control and were served three meals. The admission day also included an exercise bout. Closed loop control was continuous for 23 hours.

**Data acquisition**

An electronic clinical data management system was used (OpenClinica, OpenClinica LLC, MA, USA). The closed-loop software also kept records of all CGM glucose data, YSI glucose data, administered insulin data and information concerning meals and exercise. All these files were checked and locked in a central database before data analysis.
Data analysis and outcomes

All outcome measures were predefined in a statistical analysis plan. The primary outcome was time spent in target range, defined as plasma glucose values between 3.9 and 8.0 mmol/L in the basal or late postprandial state and plasma glucose values between 3.9 and 10.0 mmol/L in the early postprandial phase (up to 3 hours after the meals). Other outcomes are listed in table 1. An intention to treat analysis (ITT) and a per protocol analysis (PP) were done. The aim of the IIT analysis was to describe overall performance of the system, accepting any failure or poor performance of any system component (e.g. insulin pump, sensor, algorithms and/or operator failure). The aim of the PP analysis was to describe performance of the CL algorithms at times that all other parts of the system were functioning adequately. For the PP analysis, timeframes were removed from the intervention session in case of poor performance of system components. This was defined by consensus of all clinical partners and according to a predefined and objective set of implementation rules (supplemental table S2). Linear interpolation was used between CGM data points to allow for 1 minute pairing of YSI and CGM data. If more than 3 hours of data were missing, no interpolation was performed. For each outcome a repeated measures analysis of variance taking into account the sequence of study interventions was fitted. When the repeated measures model detected a significant difference, pairwise testing was done between all three treatments using a two-tailed t-test. In addition, differences in outcome measures were assessed between centers using manual control and centers using fully automated control and between centers using YSI values for sensor calibrations and those who used finger stick values for sensor calibration. All statistical analyses were performed with PASW Statistics 18.0 (IBM Corporation, Armonk, NY, USA).
### Table 1: Glucose derived outcomes (Mean (SD) or median (IQR) for hypoglycemic measures): Percent Time in target, Percent Time in hypoglycemia, severe hypoglycemia and Hyperglycemia. Reported also; mean Glucose (mmol/L).

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<tr>
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<th>Intention to treat</th>
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<tr>
<td></td>
<td>OL</td>
<td>iAP</td>
<td>CAM</td>
<td>Overall P</td>
</tr>
<tr>
<td>Perc Time in target</td>
<td>62.6 (15.8)</td>
<td>59.2 (16.3)</td>
<td>58.3 (17.6)</td>
<td>0.377</td>
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<tr>
<td>Mean glucose [mmol/L]</td>
<td>7.19 (1.40)</td>
<td>8.15 (1.27)</td>
<td>8.26 (1.38)</td>
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<tr>
<td>Perc Hypoglycemia $&lt;$3.9 mmol/L</td>
<td>6.37 (15.49)</td>
<td>2.10 (5.14)</td>
<td>2.03 (5.78)</td>
<td>0.001</td>
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<tr>
<td>Perc Severe Hypoglycemia $\leq$2.8 mmol/L</td>
<td>0.00 (1.16)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.038</td>
</tr>
<tr>
<td>Perc Hyperglycemia</td>
<td>26.7 (18.7)</td>
<td>36.8 (16.5)</td>
<td>37.9 (18.4)</td>
<td>0.001</td>
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<table>
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<th>Per protocol</th>
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<tr>
<td></td>
<td>OL</td>
<td>iAP</td>
<td>CAM</td>
<td>Overall P</td>
</tr>
<tr>
<td>Perc Time in target</td>
<td>62.8 (15.8)</td>
<td>59.3 (16.1)</td>
<td>59.6 (18.4)</td>
<td>0.519</td>
</tr>
<tr>
<td>Mean glucose [mmol/L]</td>
<td>7.19 (1.40)</td>
<td>8.27 (1.14)</td>
<td>8.15 (1.31)</td>
<td>0.001</td>
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<tr>
<td>Perc Hypoglycemia $&lt;$3.9 mmol/L</td>
<td>6.3 (16.0)</td>
<td>0.85 (4.13)</td>
<td>0.20 (5.55)</td>
<td>0.001</td>
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<tr>
<td>Perc Severe Hypoglycemia $\leq$2.8 mmol/L</td>
<td>0.00 (1.13)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.017</td>
</tr>
<tr>
<td>Perc Hyperglycemia</td>
<td>26.5 (18.7)</td>
<td>38.3 (16.6)</td>
<td>37.0 (19.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
RESULTS

**Available data**
Forty-seven patients completed the study and one patient dropped out after visit 1. The PP analysis excluded on average 10.2% of all available data (0.4% for OL, 13% for iAP and 17% for CAM), including timeframes with technical errors which could affect closed loop control or, less frequently, human factors such as operator error which could influence open loop control.

**Baseline characteristics**
Fourteen (30%) participants were female. Patients had a median (inter-quartile range (IQR)) age of 41.5 (17.0) years, HbA1c level of 7.6 (1.2) %, Body Mass Index of 25.0 (4.9) kg/m², duration of diabetes of 19.8 (19.2) years and duration of pump use of 3.6 (6.1) years.

**Glucose derived outcomes: Intention to treat analysis (table 1)**

**Time in target**
Time in target, defined as a plasma glucose level between 3.9 and 8.0 mmol/L or up to 10 mmol/L postprandially, was not significantly different between interventions: 62.6% for OL, 59.2% for iAP and 58.3% for CAM (overall P=0.377).

**Time in hypoglycemia (<3.9 mmol/L)**
There was significantly less time spent in hypoglycemia, defined as a plasma glucose level <3.9 mmol/L, during closed loop; 6.4% / 2.1% / 2.0% (P= 0.001).

**Time in hypoglycemia (≤2.8 mmol/l)**
There was significantly less hypoglycemia ≤2.8 mmol/l during CL: 0% / 0% / 0% (P= 0.038).

**Mean Glucose level**
Average glucose level were lower in OL than with CL: 7.19 / 8.15 / 8.26 mmol/L (overall P=0.001). Figure 2 depicts glucose levels over the time course of the experiments.
Time in hyperglycemia
Time in hyperglycemia defined as a blood glucose level >8.0 mmol/L or >10 mmol/L postprandially was lower in OL than with CL: 26.7% / 36.8% / 37.9% (P=0.001).

Glycemic Variability
Glycemic variability as expressed by Mean Absolute Glucose (MAG) and standard deviation of blood glucose levels (SD) was not significantly different: MAG of 1.802 (0.445) mmol/L/h for OL, 1.969 (0.422) for iAP and 1.833 (0.431) for CAM (overall P=0.080). The SD was 2.568 (0.821) for OL, 2.514 (0.767) for iAP and 2.592 (0.799) for CAM (overall P=0.872).

Inter-CL algorithm differences
There were no significant differences in any of these outcomes in a head-to-head comparison of the two CL algorithms (data not shown).

Figure 2: Mean glucose profiles over time for OL, CAM and iAP. Meals were given at 19:00, 08:00 and 12:00. Exercise was performed at 15:00. The dashed lines mark the target range.
Glucose derived outcomes: Per Protocol Analysis (table 1)

Time in target
Time in target, defined as a blood glucose level between 3.9 and 8.0 mmol/L or up to 10 mmol/L postprandially, was not different between interventions: 62.8% / 59.3% / 59.6% (P=0.519).

Time in hypoglycemia (<3.9 mmol/L)
There was significantly less time spent in hypoglycemia, defined as a blood glucose level <3.9 mmol/L, during CL: 6.3% / 0.85 / 0.2% (P=0.001).

Time in hypoglycemia (≤2.8 mmol/L)
There was significantly less hypoglycemia (≤2.8 mmol/L) with CL: 0% / 0% / 0% (P=0.017).

Mean Glucose Level
Mean glucose level was significantly lower in OL than with CL: 7.19 / 8.27 / 8.15 mmol/L (P=0.001).

Time in hyperglycemia
Time in hyperglycemia defined as a blood glucose level >8.0 mmol/L or >10 mmol/L postprandially was lower in OL than with CL: 26.5% / 38.3% / 37.0% (P=0.001).

Glycemic Variability
Glycemic variability as expressed by Mean Absolute Glucose (MAG) and standard deviation of blood glucose levels (SD) was not significantly different: MAG of 1.798 (0.438) mmol/L/h for OL, 1.982 (0.505) for iAP and 1.816 (0.484) for CAM (overall P=0.051). The SD was 2.569 (0.821) for OL, 2.337 (0.766) for iAP and 2.392 (0.681) for CAM (overall P=0.257).

Inter-algorithm differences
There were no significant differences in any of these outcomes between the two CL algorithms.
Additional Analyses

CGM performance
The Mean Absolute Relative Difference (MARD) of the CGM data compared to reference values was 15.1% (9.2) in the ITT analysis versus 14.1% (6.0) in the PP analysis. MARD was calculated per subject and then averaged.

Manual versus Automated centers
There were no differences in outcome measures between centers which used manual control versus those who used fully automated control (data not shown, ITT analysis), except in the case of time in target for the CAM algorithm which showed a higher time in target in the manual centers (64.7% (14.4) versus 51.7% (18.4) in automated centers P=0.010) and for time spent in hyperglycemia which was lower in manual centers (31.6% (15.0) versus 44.4% (19.6) in automated centers P=0.016).

Blood glucose meter versus YSI calibration
There were no differences in any of the glucose outcome measures between those centers calibrating the CGM devices with YSI values and those calibrating with blood glucose meter measurements (data not shown, ITT analysis).

Insulin parameters
The total number of infused insulin units per hour (median (IQR), ITT analysis) was lower in CL than with OL: 1.80 (1.0) / 1.70 (0.70) / 1.60 (0.60) IU/h (P=0.001). The difference between CL algorithms, with CAM infusing less IU/h than with iAP was also significant (P=0.001). Subsequently, the mean plasma insulin concentrations were higher in OL than with CL: 160.2 (109.7) / 156.2 (114.2) / 138.7 (107.0) pmol/L (P=0.001). This difference was also significant between iAP and CAM algorithms (P=0.009). Mean postprandial insulin infusion profiles per algorithm are depicted in supplemental figure S1.
**Safety parameters**

The manual override function of the system was never utilized in any of the experiments.

**Rescue carbohydrates**

The number of events in which a carbohydrate snack was given to the patient as a safety precaution when the patient was in hypoglycemia was significantly lower in closed loop (ITT analysis). This occurred a median (IQR) of 0 (1.0) times per patient for CAM, 0 (1.0) times for iAP and 1.0 (2.0) times for OL (total number of events 20, 30 and 78 for CAM, iAP and OL respectively, overall P=0.001) with no statistical difference between the closed loop algorithms P=0.598). In the PP Analysis, a median (IQR) of 0 (0.0) times per patient for CAM, 0 (0.0) times for iAP and 1.0 (2.0) times for OL (total number of events 11, 10 and 76 for CAM, iAP and OL respectively, overall P=0.001 with no statistical difference between the closed loop algorithms P=0.861).

**DISCUSSION**

In the largest multi-center closed loop trial performed so far with overnight and daytime control, which incorporated both meal and exercise challenges, we showed that either two closed loop systems can keep glucose in the target range comparable to patient’s self management of CSII, with the benefit of significantly less time spent in hypoglycemia. Reduction of time spent in hypoglycemia is important in view of future home use of such algorithm driven insulin infusion systems. This however, came at expense of higher mean glucose values and more time spent in hyperglycemia. We think that the latter was due to intentional detuning of both algorithms before commencement of this trial, with respect to previous studies (15,18), to enhance safety. Lower insulin levels during closed loop in both algorithms support this hypothesis, especially in the CAM algorithm where earlier overnight experiments showed similar mean insulin and similar mean glucose levels during open and closed loop control (15). Similarly, in previous 18 hour experiments the iAP algorithm reduced mean glucose (18) Detuning was primarily done to negate challenges with accuracy and functionality of the Dexcom Seven plus sensor. Because
of the possibility of occasional but substantial over-read, detuning of algorithms was necessary. Secondly, the algorithms had not been designed to accommodate an exercise bout. Now that the trial is completed and the next generation of CGM becomes available there is room for retuning the algorithms to enhance efficacy. In addition to detuning, there is of course a well known inverse relation between mean glucose achieved and hypoglycemia in T1DM (21). This trial was conducted in patients with fairly good glycemic control (median HbA1c 7.6%) and although mean glucose in closed loop was higher than in open loop, time in target range during closed loop was acceptable.

Another limitation was in the assessment of the post-exercise period which was relatively short, there is no data available regarding the occurrence of hypoglycemia beyond 3 hours post-exercise. Also, this study was limited in the fact that in 3 centers fully automated control was not allowed due to regulatory reasons. Because all required manual actions could not be completed within 5 minutes, the control cycle in manual centers was once every 15 minutes. However, this only affected the iAP algorithm as the CAM algorithm had a 15 minute control cycle both in automated and manual control centers. In this study manual mealtime announcements where used, which has as an important advantage that more rapid rises in insulinemia appear than with a fully closed loop approach. However, mealtime announcement including its content is severely dependent on carbohydrate counting by patients, which could limit its usefulness in real life settings.

This trial also showed that closed-loop experiments can be performed in relatively inexperienced centers, extending the external validity of the results beyond the centers which have been doing such experiments for years and where close collaboration between algorithm developers and clinical researchers is present.

To move forward in terms of miniaturization of the system, many of the supporting software layers will be removed and software will be embedded, which most likely will decrease the amount of software failures significantly. With results of the current trial and further miniaturization, we feel experiments outside the clinical research center are now needed to move the field forward. In particular trials with an extended period of closed loop control are needed to assess long-term effects on HbA1c levels.
In conclusion, we show that a full day of closed loop glucose control is possible, even when systems are challenged with meals and exercise, and that the level of glycemic control is comparable to open loop control. Closed loop control resulted in less time spent in hypoglycemia at the expense of higher mean glucose with intentionally detuned algorithms according to the ‘safety first’ principle. Closed loop control may be achieved with currently available insulin pumps and sensors and artificial pancreas experiments can be brought into the homes of patients with type 1 diabetes.

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