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*ORIGINAL ARTICLE*

# Multinight "Bedside" Closed-Loop Control for Patients with Type 1 Diabetes

Sue A. Brown, MD,[1,*] Boris P. Kovatchev, PhD,[1] Marc D. Breton, PhD,[1] Stacey M. Anderson, MD,[1] Patrick Keith-Hynes, PhD,[1] Stephen D. Patek, PhD,[1] Boyi Jiang, MA,[1] Najib Ben Brahim, MS,[1] Paul Vereshchetin, MS,[1] Daniela Bruttomesso, MD,[2,*] Angelo Avogaro, MD,[2] Simone Del Favero, PhD,[2] Federico Boscari, MD,[2] Silvia Galasso, MD,[2] Roberto Visentin, MS,[2] Marco Monaro, MS,[2] and Claudio Cobelli, PhD[2]

## Abstract

***Background:*** Studies of closed-loop control (CLC) systems have improved glucose levels in patients with type 1 diabetes. In this study we test a new CLC concept aiming to "reset" the patient overnight to near-normoglycemia each morning, for several consecutive nights.

***Subjects and Methods:*** Ten insulin pump users with type 1 diabetes (mean age, 46.4 ± 8.5 years) were enrolled in a two-center (in the United States and Italy) randomized crossover trial comparing 5 consecutive nights of CLC (23:00–07:00 h) in an outpatient setting versus sensor-augmented insulin pump therapy of the same duration at home. Primary end points included time spent in 80–140 mg/dL as measured by continuous glucose monitoring overnight and fasting blood glucose distribution at 7:00 h.

***Results:*** Compared with sensor-augmented pump therapy, CLC improved significantly time spent between 80 and 140 mg/dL (54.5% vs. 32.2%; $P < 0.001$) and between 70 and 180 mg/dL (85.4% vs. 59.1%; $P < 0.001$); CLC reduced the mean glucose level at 07:00 h (119.3 vs. 152.9 mg/dL; $P < 0.001$) and overnight mean glucose level (139.0 vs. 170.3 mg/dL; $P < 0.001$) using a marginally lower amount of insulin (6.1 vs. 6.8 units; $P = 0.1$). Tighter overnight control led to improved daytime control on the next day: the overnight/next-day control correlation was $r = 0.52$, $P < 0.01$.

***Conclusions:*** Multinight CLC of insulin delivery (artificial pancreas) results in significant improvement in morning and overnight glucose levels and time in target range, with the potential to improve daytime control when glucose levels were "reset" to near-normoglycemia each morning.

## Introduction

A News Focus in the January 10, 2014 issue of *Science*[1] highlighted the topic of the "artificial pancreas"—the commonly accepted term for closed-loop control (CLC) of blood glucose (BG) in diabetes. Eighteen months earlier, a *Nature* Outlook featured the same topic.[2] These articles reflect a rapidly growing trend in the technological management of diabetes—the merger of a continuous glucose monitor (CGM), an insulin pump, and a control algorithm into a CLC system that automates insulin delivery. Between 2008 and 2012, promising results from inpatient CLC studies were reported by several groups.[3–8] A summary can be found in a 2011 review of the artificial pancreas field, pointing out the superiority of CLC over insulin pump therapy in terms of (1) increased time within target glucose range, (2) reduced incidence of hypoglycemia, and (3) better overnight control.[9] The transition of CLC to a wearable outpatient

[1]Center for Diabetes Technology, University of Virginia, Charlottesville, Virginia.
[2]University of Padova, Padova, Italy.
*These authors contributed equally to the clinical conduct of this trial.
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system began in 2012 with the introduction of the Diabetes Assistant (DiAs)—the first wearable CLC system using a smartphone as a computational platform for its control algorithm.[10,11] Other recent trials confirmed the effectiveness of overnight CLC at diabetes camps for children[12] and at patients' homes,[13,14] placing laptop computers equipped with control algorithms at their patients' bedside.

In this report we present the effectiveness of a new CLC approach—the Unified Safety System (USS Virginia)—which runs on a portable platform (DiAs) and takes over a person's glucose control in the evening with the goals to stabilize and consistently ''reset'' BG levels closer to normal glycemic levels by the morning. Such an approach follows the natural wake–sleep circadian cycle and takes advantage of overnight unperturbed (no meal or exercise) glucose homeostasis.

## Subjects and Methods

### *Study participants*

Eligible patients were 21–65 years of age, had had type 1 diabetes for at least 1 year, had a hemoglobin A1c level of $<9\%$, and were insulin pump users for at least 1 year with predefined pump parameters (basal rate, insulin to carbohydrate ratio, and correction factor). Patients were excluded for the following criteria: episodes of diabetic ketoacidosis or a severe hypoglycemic episode in the past year; pregnant or breast-feeding; uncontrolled thyroid disease; uncontrolled microvascular disease (e.g., active proliferative retinopathy); uncontrolled hypertension; significant cardiovascular disease or seizure disorders or other conditions known to increase the risk of hypoglycemia, including use of $\beta$-blockers; self-reported hypoglycemic unawareness; use of medications known to affect glucose other than insulin (e.g., metformin); and use of substances known to interfere with CGM measures such as acetaminophen. Study participants were recruited through outpatient clinics and advertisements at two sites: the University of Virginia (UVA), Charlottesville, VA, and the University of Padova, Padova, Italy. Each site received Institutional Review Board or Ethical Board approval. The studies were designed and implemented with Good Clinical Practice and the Declaration of Helsinki. The studies at UVA were conducted under Food and Drug Administration Investigational Device Exemption number 130143. All patients gave informed consent.

### *Study design*

Patient eligibility was determined during a screening visit. Training with the study CGM (Dexcom G4™ Platinum; Dexcom, San Diego, CA) and insulin pump (Accu-Chek® Spirit Combo; Roche Diagnostics, Indianapolis, IN) was offered, after which patients were randomized to experimental (CLC) and control sensor-augmented pump (SAP) sessions. All patients participated in CLC and SAP in a crossover design. For the control session, patients wore a single CGM and either their personal (UVA) or study (Padova) insulin pump. Patients were asked (1) to check a capillary glucose measurement by fingerstick at least four times a day, including at wake-up and bedtime, (2) to use the bolus calculator function in the pump to record carbohydrates consumed and all insulin boluses delivered, (3) make all insulin dosing decisions per their usual care during the control session, (4) consume their typical diet during both study sessions, and (5) exercise per their usual routine. Moderate alcohol consumption was permitted.

During the experimental sessions, patients stayed overnight in a house (UVA) or hotel (Padova) wearing the study insulin pump and two CGMs: a primary sensor driving the control algorithm and a secondary one exclusively for added safety per study protocol. In case of primary sensor failure, the secondary sensor was allowed to be used as a replacement. Patients started DiAs between 20:00 and 22:00 h in pump-only mode (in this mode DiAs administered their usual basal rate with no insulin delivery modulation). In addition, patients could bolus as usual with their home pump parameters through DiAs. Patients were asked to consume their evening meal before 20:00 h and were allowed to snack prior to initiation of CLC per their usual routine in both the SAP and CLC conditions. At 23:00 h, DiAs was switched to closed-loop mode (USS Virginia) if capillary glucose was between 80 and 249 mg/dL; CLC could be delayed up to 2 h if these conditions were not met. During CLC (23:00–07:00 h), no food was allowed except hypoglycemic treatments. Capillary glucose was assessed at fixed times: prior to meals, bedtime, and 03:00 h, or if the CGM was reading $<90$ or $>260$ mg/dL. The CGM was calibrated per the manufacturer's guidelines and prior to the evening meal if not recently calibrated; the protocol required additional calibration if the primary and secondary CGMs were more than 20% apart when checked at 03:00 and 05:00 h. Patients were treated with glucose tablets or liquid for hypoglycemia any time capillary BG was $<70$ mg/dL, regardless of symptoms. In addition, a patient could be treated if the glucose level was $<80$ mg/dL with a rapid BG decline or presence of hypoglycemic symptoms. All hypoglycemia treatments with carbohydrates were based on capillary glucose readings.

### *CLC technology*

The control system was implemented on DiAs, a modular, portable artificial pancreas platform developed at UVA.[10,11] DiAs operates on a commercially available Android™ (Google, Mountain View, CA)-based phone, enabling wireless communication with the CGM and the insulin pump, as well as data transfer through the wireless telephone network or WiFi to a secure central server for remote monitoring and automated alerts about patient and system state.[15] Its modular architecture allows different modes of operation (e.g.. pump-only, CLC) to be swapped in during use for clinical trials. The DiAs graphical user interface (GUI) is designed to be operated by the patient.[16] DiAs runs the USS Virginia CLC algorithm, which is based on a mathematical model of the human glucose–insulin dynamics and uses Kalman filtering to predict hypoglycemia and hyperglycemic risks 30 min ahead. Basal rate is then modulated up or down based on the predicted glycemic risk. The USS Virginia is designed to ''slide'' its glucose target of each person from 160 mg/dL after dinner to 120 mg/dL in the morning with the goal to achieve near-normoglycemia before wakeup. A dedicated safety system triggers alarms/alerts based on two ''traffic light'' signals for hypoglycemia and hyperglycemia displayed on the DiAs GUI: green, no risk; yellow, basal rate modulation occurring to decrease risk; and red, acute risk, external intervention needed.[17] Participants were instructed to check their capillary glucose level if a red light alarm occurred.

### *Study end points*

The primary end point measure was time within target range of 80–140 mg/dL overnight (23:00–07:00 h) for 5 consecutive nights of CLC compared with SAP of the same duration with the hypothesis that CLC will improve time within target range overnight compared with SAP. The secondary end points included distribution of mean glucose upon awakening (approximately 07:00 h), time spent in range overnight 70–180 mg/dL, percentage of time <70 mg/dL or >180 mg/dL overnight, time in range during the day and night, and number of hypoglycemic events.

### *Statistical analysis*

Sample size was determined assuming an effect size of 0.5 in the paired *t* test comparison between CLC and SAP. The unit of analysis was 1 night; power of 0.95 and significance at 0.05 were assumed. The observed effect size was 0.6, which with 49 nights analyzed for each session resulted in achieved power of 0.98. Nights were only rejected from analysis if less than 4 h of CGM recording was available. All metrics were computed from CGM data using the primary sensor during CLC. Comparisons were made using paired Student's *t* test. The Wilcoxon sign rank test was used when Gaussian distribution of the outcome could not be assumed. Results are reported as mean ± SE values.

Table 1. Baseline Patient Characteristics

| *Characteristic* | *Value* |
|---|---|
| Age (years) | 46.4 ± 8.5 |
| Gender | 8 F/2 M |
| Weight (kg) | 64.2 ± 8.9 |
| Height (cm) | 167.3 ± 5.8 |
| Body mass index (kg/m$^2$) | 22.9 ± 2.9 |
| Hemoglobin A1c (%) | 7.03 ± 1.05 |
| Duration of diabetes (years) | 20.9 ± 11.4 |
| Total daily insulin dose (units) | 28.3 ± 9.6 |
| Total daily insulin per weight (units/kg) | 0.4 ± 0.1 |

Data are mean ± SD values.
F, female; M, male.

## Results

### *Patient characteristics*

Ten patients were enrolled: five at UVA and five in Padova. Their characteristics are presented in Table 1. In total, 49 out of 50 nights in CLC and 49 out of 50 nights in SAP were included in the analysis. One CLC night was excluded because of insulin pump occlusion prior to the initiation of CLC, resulting in prolonged hyperglycemia and necessitating a pump infusion site change. One SAP night was excluded from analysis because less than 4 h of CGM recording was available.

Table 2. Primary and Secondary End Points

| *Variable* | *Closed-loop control* | *Sensor-augmented pump* | P *value* |
|---|---|---|---|
| Primary end point | | | |
| Time (%) in range 80–140 mg/dL overnight | 54.5 (36.5–74.7) | 32.2 (7.8–54.7) | <0.001 |
| Secondary end points | | | |
| Mean glucose (mg/dL) | | | |
| 07:00 h (wake-up) | 119.3 (103.0–130.5) | 152.9 (104.8–191.5) | <0.001 |
| 23:00–07:00 h (overnight) | 139.0 (123.0–158.1) | 170.3 (133.3–200.6) | <0.001 |
| 23:00 h (bedtime) | 148.1 (114.2–180.4) | 151.1 (116.9–173.5) | NS |
| Time (%) in range | | | |
| 70–180 mg/dL overnight | 85.4 (71.6–100) | 59.1 (30.2–100) | <0.001 |
| <70 mg/dL overnight | 0.55 (0–0) | 1.56 (0–0) | NS |
| >180 mg/dL overnight | 14.1 (0–28.4) | 39.4 (0–69.8) | <0.001 |
| >250 mg/dL overnight | 0.9 (0–0) | 10.1 (0–11.5) | 0.002 |
| 80–140 mg/dL 23:00 to 03:00 h | 38.2 (0–71.4) | 31.6 (0–63.5) | NS |
| 80–140 mg/dL 03:00–07:00 h | 70.8 (54.7–100) | 32.4 (0–61.5) | <0.001 |
| 70–180 mg/dL 24 h | 77.6 (66.5–89.7) | 67.3 (55.9–81.4) | <0.001 |
| Number of hypoglycemic episodes per night | 0.12 | 0.12 | NS |
| Glucose variability | | | |
| SD glucose overnight (mg/dL) | 28.0 (17.3–37.8) | 29.9 (16.6–40.5) | NS |
| CV glucose overnight (%) | 19.7 (13.3–25.4) | 17.9 (11.5–25.7) | NS |
| LBGI overnight | 0.65 (0.02–0.84) | 1.05 (0–0.96) | NS |
| HBGI overnight | 4.33 (1.78–6.5) | 9.92 (2.5–14.8) | <0.001 |
| Insulin administered overnight | | | |
| Overnight total (U) | 6.1 (3.6–8.1) | 6.8 (3.8–8.4) | NS |
| 23:00–3:00 h total (U) | 3.4 (2.0–4.4) | 3.4 (2.0–4.0) | NS |
| 3:00–7:00 h total (U) | 2.8 (1.7–3.0) | 3.4 (1.7–4.2) | 0.01 |
| Overnight relative to basal (%) | 122 (96–150) | 134 (100–151) | NS |
| 23:00–3:00 h relative to basal total (%) | 146 (106–190) | 145 (100–181) | NS |
| 3:00–7:00 h relative to basal (%) | 102 (76–119) | 124 (100–153) | 0.019 |

Data are mean (quartiles) values unless defined otherwise. Overnight was defined as 23:00 to 07:00 h.
CV, coefficient of variation; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; NS, not significant.

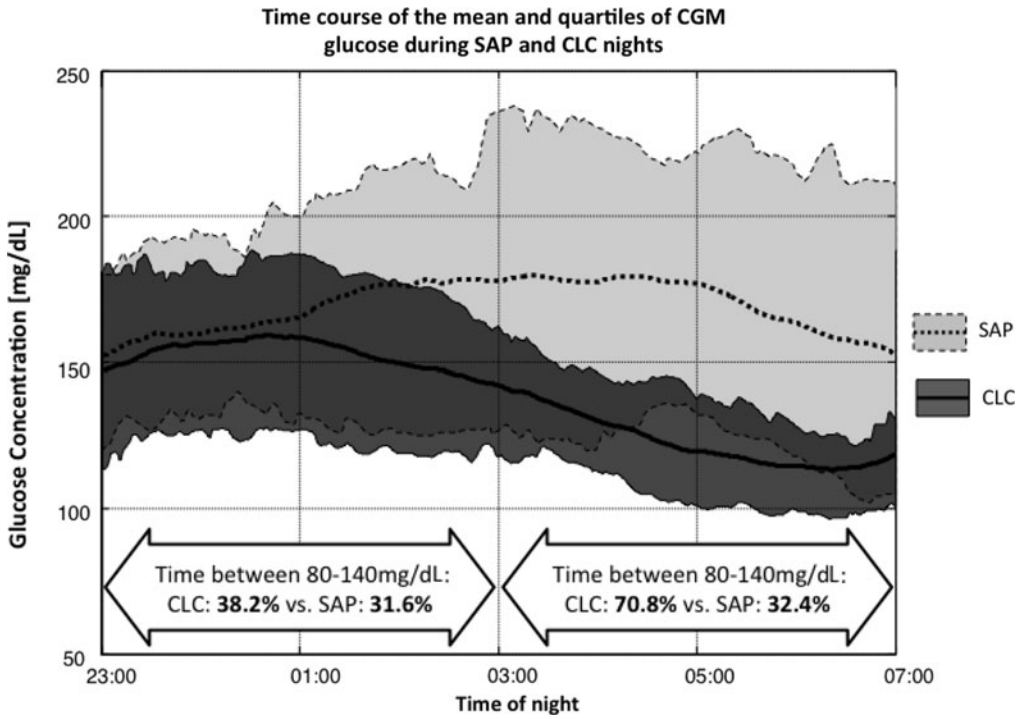


**FIG. 1.** Glycemic excursions (mean and quartiles) measured with the continuous glucose monitor overnight. CLC, closed-loop control (black region, solid line); SAP, sensor-augmented pump (gray region, dotted line).

### *Primary end point*

Although the initial glucose levels at 23:00 h were comparable between the two sessions (Table 2), CLC improved significantly the percentage time in range between 80 and 140 mg/dL overnight when compared with SAP (54.5 ± 3.7% vs. 32.2 ± 4.7%; $P < 0.001$). As presented in Figure 1, most of this improvement came from the second half of the night (70.8 ± 4.4% vs. 32.4 ± 5.6%; $P < 0.001$).

### *Secondary end points*

Figure 2 presents the glucose distributions upon awakening at approximately 07:00 h, indicating much ''tighter''

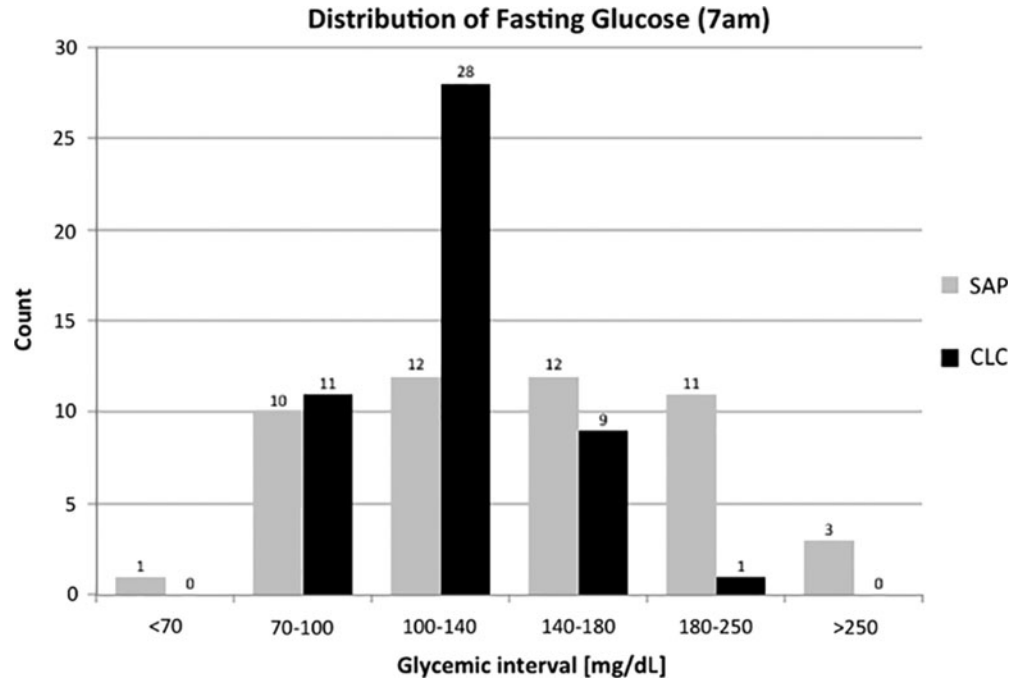


**FIG. 2.** Distribution of fasting glucose levels measured by the continuous glucose monitor at 07:00 h. CLC, closed-loop control (black columns); SAP, sensor-augmented pump (gray columns).

dispersion of BG levels across study nights and subjects during CLC compared with SAP.

As presented in Table 2, virtually all metrics of glucose control improved significantly on CLC, without increased rate of hypoglycemia. In this regard, no significant improvement in the percentage of time below 70 mg/dL was recorded, but it should be noted that the baseline level of this study population was already very low.

Figure 3 superimposes the progressively lower average glucose levels achieved overnight (lower panel) and the progressively lower insulin delivery rates during the same time periods (upper panel). This observation indicates that, although the total administered insulin was similar between CLC and SAP (6.1 vs. 6.8 units; $P = 0.1$), the timing of insulin administration was different: CLC ''preloaded'' insulin between 1:00 and 3:00 h and administered progressively lower doses thereafter.

Overnight glucose control during CLC as measured by the percentage of time between 80 and 140 mg/dL was correlated with following daytime glucose control: percentage 80–140 mg/dL, $r = 0.35$, $P < 0.05$; percentage 70–180 mg/dL, $r = 0.52$, $P < 0.01$; and mean daytime glucose, $r = -0.463$, $P < 0.01$. Overnight control during CLC was also correlated with the following daytime maximum

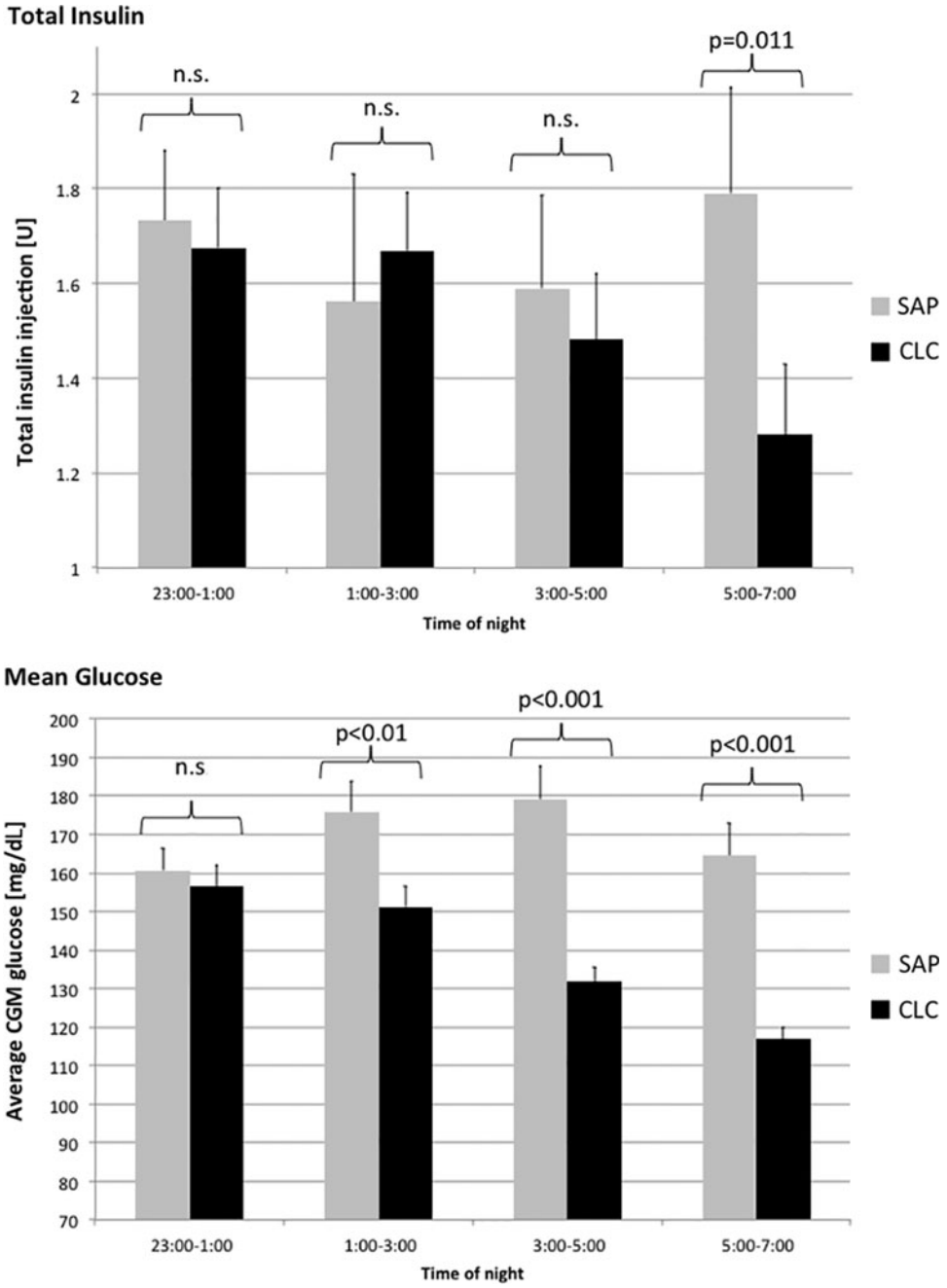


**FIG. 3.** **(Lower panel)** Average glucose and **(upper panel)** corresponding total injected insulin for closed-loop control (CLC) (black columns) and sensor-augmented pump (SAP) (gray panels), by 2-h increments at night.

glucose ($r = -0.55$, $P < 0.001$) and glycemic variability as measured by SD ($r = -0.54$, $P < 0.001$). During SAP, there were correlations between overnight glucose control of 80–140 mg/dL and percentage 80–140 mg/dL ($r = 0.31$, $P < 0.05$), and other correlations evaluated were not significant.

### *CLC system events*

The system functioned 98.3% of time without significant interruptions. There were rare incidences of pump miscommunication, with 54/3,119 (1.7%) requested microboluses not being injected by the pump, which was typically because of temporary loss of communication (<10 min) with DiAs when participants left the DiAs at the bedside while being in another room. There were no instances of the CLC being overridden or stopped by the study team because of safety concerns. CLC start was delayed in 5 nights (mean delay of 53 min). In one case, the failure of the primary CGM due to lack of adhesion to skin at the time of initiation of CLC required CGM replacement and delayed CLC by 2 h 15 min. One participant had CGM readings confirmed by fingerstick of >250 mg/dL that delayed CLC initiation by 34 min.

### *CGM accuracy*

The mean absolute relative deviation of sensor readings from capillary BG was 10.2%, based on an average of 4.15 capillary readings per night. Sensor errors did not trigger algorithm failure or adverse events.

### *Safety/adverse events*

There were no serious adverse events. Specifically, there were no instances of diabetic ketoacidosis or severe hypoglycemia requiring third-party assistance. All hypoglycemic episodes were detected by the system (hypoglycemia red light, see above) within 30 min of fingerstick measurement.

## Discussion

Three recent trials demonstrated the superior performance of nighttime CLC over SAP insulin therapy in an outpatient setting.[12–14] This new study confirms the previous findings and adds two unique features: (1) a portable platform using a consumer electronics device (smartphone) to run the CLC system and all CGM, pump, and remote communications and (2) a control algorithm specifically designed to ''slide'' the patients' glucose levels to a target of 120 mg/dL at wakeup, thereby resetting their metabolic state overnight to near-normoglycemic morning BG levels, on consecutive nights. As a result, this study demonstrated not only significant improvement in overnight glucose control on CLC, but also significant improvement of patients' control on the next day. Such a ''carryover'' effect is not unexpected, but its magnitude has not been evaluated before and appears to be significant with correlations between overnight and next-day metrics of approximately 0.5.

The USS Virginia algorithm performed according to its design specifications, achieving an average glucose level of 119.3 mg/dL at wakeup—only 0.7 mg/dL away from its target and 33 mg/dL lower than the morning glucose levels achieved by patients on SAP. The lower average was accompanied by much narrower dispersion of morning BG levels. Time within the target range of 70–180 mg/dL was improved by 26%, and this improvement was primarily due to the second half of the night—a design feature of the USS Virginia algorithm as it attempts to achieve tighter control as the night progresses. Furthermore, tight glucose control was achieved without an increase in hypoglycemia: the few instances of hypoglycemia during the trial were detected early, and the USS Virginia system reacted with insulin attenuation and alerts.

Although CLC delivered only marginally lower total insulin amounts compared with SAP, there was a substantial difference in the timing of insulin delivery: CLC preloaded insulin earlier in the night, which resulted in progressively lower insulin doses toward the morning. Given that glucose levels were also progressively (and significantly) lower on CLC during the same time period, it may be concluded that insulin distribution on CLC was better optimized than the preset basal rates of patients' usual therapy.

This study had several limitations: (1) This was a pilot trial with a small number of patients—but each patient was studied on several consecutive nights, and the results were clearly significant with $P$ levels accommodating any statistical correction that may be desired for multiple observations on the same patient. (2) On average, the patients were in very good control (mean hemoglobin A1c level of 7%)—thus the results may not be generalizable to patients with poor control. (3) Although patients were instructed to maintain similar lifestyles in each study session, the possibility of differences in activity levels or diet may exist between the study sessions—an effect partially mitigated by the crossover design of the trial. (4) All patients had the same technology during the experimental session, but patients at UVA wore their own insulin pump during the control sessions at home—thus subtle differences in calculation of insulin on board could have introduced some, likely inconsequential, bias in the control sessions.

In general, this study attempted to approximate real-life conditions as closely as possible. The transitional nature of CLC studies necessitates that initial trials be performed in a monitored setting rather than at the patient's home. The UVA trials were done in a house, the Padova trials were done in a hotel, and during the day the patients were allowed to leave the study site and engage in their usual activities such as work, exercise, or errands or return home as long as their destination was within a reasonable distance from the study site (e.g., 30 miles). Arguably, the restricted overnight location of the CLC sessions had little influence on the performance of the CLC because (1) the patients had their own bedrooms and were taught to turn on and operate the CLC system by themselves, (2) dinner was typically at a restaurant or delivered to the house, and alcohol was permitted if desired, meaning that the evening meal challenge was comparable to a real-life setting, and (3) patients' glycemic control was improved during the day as well, even if they were not at the study location.

In conclusion, in this multinight study of adults with type 1 diabetes in an outpatient setting, CLC clearly outperformed SAP therapy, achieving significantly tighter glycemic overnight control without increased hypoglycemia. This effect was carried over to the next day, indicating that resetting patients' metabolism to near-normoglycemia every morning could have beneficial consequences on overall glucose control. The concept of an overnight artificial pancreas is therefore viable and should be investigated further as a first step toward clinically acceptable CLC.

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Address correspondence to:
*Sue A. Brown, MD*
*Division of Endocrinology*
*Center for Diabetes Technology*
*P.O. Box 400888*
*Charlottesville, VA 22908*

*E-mail:* sab2f@virginia.edu