Day and Night Closed-Loop Glucose Control in Patients With Type 1 Diabetes Under Free-Living Conditions: Results of a Single-Arm 1-Month Experience Compared With a Previously Reported Feasibility Study of Evening and Night at Home

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OBJECTIVE

After testing of a wearable artificial pancreas (AP) during evening and night (E/N-AP) under free-living conditions in patients with type 1 diabetes (T1D), we investigated AP during day and night (D/N-AP) for 1 month.

RESEARCH DESIGN AND METHODS

Twenty adult patients with T1D who completed a previous randomized crossover study comparing 2-month E/N-AP versus 2-month sensor augmented pump (SAP) volunteered for 1-month D/N-AP nonrandomized extension. AP was executed by a model predictive control algorithm run by a modified smartphone wirelessly connected to a continuous glucose monitor (CGM) and insulin pump. CGM data were analyzed by intention-to-treat with percentage time-in-target (3.9–10 mmol/L) over 24 h as the primary end point.

RESULTS

Time-in-target (mean ± SD, %) was similar over 24 h with D/N-AP versus E/N-AP: 64.7 ± 7.6 vs. 63.6 ± 9.9 (P = 0.79), and both were higher than with SAP: 59.7 ± 9.6 (P = 0.01 and P = 0.06, respectively). Time below 3.9 mmol/L was similarly and significantly reduced by D/N-AP and E/N-AP versus SAP (both P < 0.001). SD of blood glucose concentration (mmol/L) was lower with D/N-AP versus E/N-AP during whole daytime: 3.2 ± 0.6 vs. 3.4 ± 0.7 (P = 0.003), morning: 2.7 ± 0.5 vs. 3.1 ± 0.5 (P = 0.02), and afternoon: 3.3 ± 0.6 vs. 3.5 ± 0.8 (P = 0.07), and was lower with D/N-AP versus SAP over 24 h: 3.1 ± 0.5 vs. 3.3 ± 0.6 (P = 0.049). Insulin delivery (IU) over 24 h was higher with D/N-AP and SAP than with E/N-AP: 40.6 ± 15.5 and 42.3 ± 15.5 vs. 36.6 ± 11.6 (P = 0.03 and P = 0.0004, respectively).

CONCLUSIONS

D/N-AP and E/N-AP both achieved better glucose control than SAP under free-living conditions. Although time in the different glycemic ranges was similar between D/N-AP and E/N-AP, D/N-AP further reduces glucose variability.

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Targeting nearly normal glucose with insulin therapy in type 1 diabetes (T1D) to prevent long-term diabetic complications remains a daily challenge for the patients. Indeed, reduction of time spent in hyperglycemia is associated with an increased occurrence of hypoglycemia, as initially reported by the Diabetes Control and Complications Trial (DCCT) (1). Insulin pump therapy in patients with T1D, combined with continuous glucose monitoring (CGM), including recent automated threshold or hypoglycemia prediction-based suspense of insulin infusion, has shown significant reductions of hypoglycemia occurrence while aiming at near-normoglycemia (2); however, adjustment of insulin delivery according to multifactorial changes in insulin need is still an unachieved goal (3).

A closed-loop control system, or artificial pancreas (AP), is designed to automate insulin infusion aiming at more time in target range while reducing both time spent in hypo- and hyperglycemia and decreasing the disease burden (4). Currently investigated AP systems include a CGM device, a wearable insulin pump, a glucagon pump, when applicable, and a control unit embedded in a smartphone or small tablet and wirelessly linked to the two other devices. Various algorithms are used to drive insulin infusion (and glucagon when applicable) (5–8). AP systems have been extensively tested for safety and efficacy in in-hospital and transitional studies (9–15). Two recent studies investigated single- versus dual-hormone closed-loop control: the first was performed in adults and adolescents for 24 h in a clinical research center and the second one in children and adolescents for 3 nights in a diabetes camp. Both studies suggested a possible reduction of hypoglycemia thanks to glucagon availability (16,17).

Moving AP trials toward a home setting under free-living conditions has been the last reported step. Several recent studies have targeted overnight closed-loop glucose control (18,19), including a randomized controlled crossover study from our research teams that included dinner in addition to overnight closed-loop control and compared 2-month AP use at home to sensor-augmented pump (SAP) therapy (20). Meanwhile, other research teams of our European Union–funded AP@home consortium reported a 12-week AP day and night experiment in free-living conditions in a randomized controlled crossover trial versus SAP (21). Although these two AP@home studies were performed in different European centers using two different closed-loop control algorithms, albeit both based on model predictive control, the average percentage of time spent in the same targeted glucose range of 3.9–10.0 mmol/L over 24 h appears rather similar: 63.7% in our 2-month study versus 67.7% in the 12-week study (20,21). This similarity is somewhat unexpected because our 2-month study used AP only for evening and night, whereas the 12-week study used AP day and night. Of note, reported control periods with SAP in these two studies also showed a similar average percentage of time spent in the target range of 59.4 vs. 56.8%, respectively, indicating that both study populations had similar nonautomated glucose control. We therefore proposed to our patients a 1-month nonrandomized study extension to assess additional improvements in glucose control that could be achieved by our AP system used over 24 h versus during the previous evening and nighttime experiment in similar free-living conditions.

RESEARCH DESIGN AND METHODS

Study Design

This was a 1-month single-arm nonrandomized extension study of a multinational initially randomized crossover open-label study in patients with T1D treated by continuous subcutaneous insulin infusion that investigated evening and night use of an AP (E/N-AP) at home versus patient-managed SAP therapy. The original study has been reported elsewhere (20). The extension study assessed the efficacy of glucose control achieved by day and night AP use (D/N-AP) for 1 month under free-living circumstances.

The extension study was performed in 2014–2015, recruiting 20 patients from medical centers at the universities of Amsterdam (the Netherlands), Montpellier (France), and Padua (Italy) among the 32 patients who completed the previous randomized crossover study. At the end of this study, patients were invited to participate in the extension study. The potential participants were provided with an information letter and a consent form that were specific to the extension study. The baseline characteristics of the 20 patients who enrolled in the extension study and the 12 patients who did not volunteer for this extension study are presented in Table 1. No clear difference appeared between these two groups. Among the 20 patients who entered the extension study, 8 ended the randomized crossover study by SAP and 12 by E/N-AP. The average interval between the end of the randomized crossover study and the start of the nonrandomized extension study was 65 days. During this period, the patients went back to their prestudy continuous subcutaneous insulin infusion therapy. The study extension was performed in accordance with the Declaration of Helsinki and was approved by the institutional ethics review board at each site.

Details of Procedures

After signed informed consent for the extension study, each patient spent ~2 h in the hospital. The clinical team checked that the patient was proficient in study device use, including the Accu-Chek Spirit Combo insulin pump, Aviva Combo glucose meter (Roche Diagnostics, Mannheim, Germany), and Dexcom G4 Platinum CGM (Dexcom, San Diego, CA). After the patient received an abbreviated training to use the AP platform in order to refresh his or her knowledge of the system, the connections between the pump, the CGM device, the Bluetooth Low Energy translator box (see description in the next section), and the AP platform were initiated, and the platform was turned in closed-loop mode.

A telephone number was given to the patients so that they could contact the clinical staff in case of any event. A logbook was provided for patients to note details about hypoglycemic and hyperglycemic episodes, physical activity, and noticeable events. Finally, CGM sensors and pump consumables were provided as required for at least 4-week use of the system. Approximately 1 to 3 days after the start of the extension period, a member of the clinical staff called the patient to check whether the patient had encountered any problems with the protocol or the devices. If needed, pump

Table 1—Baseline characteristics of patients who participated in the extension study (Study population) and patients who did not (Discontinued)

Variable	Study population (n = 20)	Discontinued (n = 12)
Age (years)	46.3 ± 11.0 (21–61)	49.1 ± 11.9 (24–68)
Sex		
Male	9 (45.0)	5 (42.0)
Female	11 (55.0)	7 (58.0)
BMI (kg/m^2)	24.9 ± 3.5 (20.5–33.4)	25.6 ± 3.5 (19.5–30.9)
HbA_{1c} (%)	8.2 ± 0.7 (7.5–10.0)	8.1 ± 0.6 (7.4–9.2)
HbA_{1c} (mmol/mol)	66 (58–86)	65 (57–77)
Diabetes duration (years)	28.9 ± 12.8 (10–49)	29.1 ± 7.0 (14–39)
Duration of CSII use (years)	9.7 ± 5.2 (3.2–23.0)	18.1 ± 11.7 (4.3–39.0)
Total daily insulin dose (units/kg)	0.5 ± 0.1 (0.4–0.7)	0.6 ± 0.2 (0.3–1.0)

Data are presented as n (%) for categorical variables and as mean ± SD (min–max) for continuous variables. CSII, continuous subcutaneous insulin infusion.

and AP parameters (basal rates, carbohydrate ratio, correction factor, etc.) could be revised and reconfigured in agreement with the study clinician.

The CGM glucose alarm thresholds for hypo- and hyperglycemia were initially set at 5.0 and 11.1 mmol/L but could be modified by the patients. For safety, patients were instructed to test for ketones (Freestyle Precision Xtra β-Ketone; Abbott, North Chicago, IL) if capillary glucose was >16.7 mmol/L and to measure capillary glucose before making clinical decisions concerning insulin dosing or hypo- and hyperglycemia treatment. Patients were requested to check for catheter occlusion/dislodgement and pump dysfunction in case of hyperglycemia without an obvious explanation, to calibrate their CGM twice daily, and to perform at least four capillary glucose measurements per day. Patients were free to adjust their insulin bolus. There were no limitations on diet and normal daily activities, including exercise.

Device data were read-out at the week 4 visit.

The AP Platform

In the extension phase presented here, we used the same AP system as used in the study described previously (20). The AP consisted of the Diabetes Assistant (DiAs) developed at the University of Virginia (Charlottesville, VA), a smartphone holding the control algorithm with wireless Bluetooth connections to the CGM, and the insulin pump (22). Because no direct Bluetooth access was available in the Dexcom G4 Platinum receiver, wireless connection between DiAs and CGM was granted by placing the receiver in an ad hoc developed USB-Bluetooth converter (relay box).

The DiAs system was run on a Nexus 5 smartphone (LG Group, Seoul, South Korea) running a modified Android operating system (22). The controller implemented on the DiAs was based on modular architecture as described by Patek et al. (23) using a model predictive controller (24).

In case of system dysfunction and unsuccessful troubleshooting, pump basal rate insulin delivery was automatically reset within 30 min to the patient's pre-extension basal rates.

The DiAs was preset with the patient's basal rate pattern, carbohydrate-to-insulin ratio, and correction factor. Patients received a training and troubleshoot booklet to use the AP platform.

The patients interacted with the DiAs using a graphical user interface (25) that allows real-time input, such as meal announcements, premeal capillary glucose level, or self-administered hypoglycemia treatment, and displays CGM and insulin delivery graphs. The interface also provides hypo- and hyperglycemia alerts. Patients used the DiAs built-in bolus calculator to determine mealtime boluses.

DiAs allowed for secured data streaming over the Internet to a remote monitoring Web site using the smartphone 3G connection (26). This allowed for assisting the patient in case of problems or to see glucose evolution.

Outcomes

All glucose control outcome measures were predefined in a statistical analysis plan. The main end point for this extension study was percentage of time spent in target range (3.9–10 mmol/L) over 24 h. Secondary end points included mean blood glucose, SD of blood glucose, percentage of time spent below 3.9 mmol/L and above 10 mmol/L, and daily insulin use. Separate analyses were performed to analyze primary and secondary end points during evening and night (2000–0800), daytime (0800–2000), morning (0800–1200), and afternoon (1200–2000). Safety was assessed by the frequency of moderately severe (>15 min, <2.8 mmol/L) and overall (>15 min, <3.9 mmol/L) hypoglycemic episodes and adverse events. Percentage time of closed-loop use was defined as the actual time spent in closed-loop compared with the considered interval.

Statistical Methods

Data analysis was based on the intention-to-treat principle. All data were analyzed from patients who completed at least 3 weeks of AP use over 24 h. Only data from patients participating in the original study and in the extension study (n = 20) were included for analysis. From each treatment period in the original study, only the last 4 weeks were considered. All glucose indices were computed from the CGM data.

We report variables as median (25th and 75th percentiles) for nonnormally distributed data and as mean ± SD otherwise. To compare the effect of the three different treatments, a multiway ANOVA was performed including patient and treatment as explanatory factors. If the residuals or the data were not normally distributed, the nonparametric Friedman test was used. If the ANOVA or the Friedman test detected a significant difference between treatments, the determination of significant differences between the treatments was performed by multiple comparisons. A paired difference (Δ) (with its CI) for each pair was computed if the ANOVA was considered. All P values are two-tailed. Analyses were performed with the Matlab Statistic toolbox (version 8.3).

RESULTS

All patients completed the 4-week extension study. None requested assistance from the investigation team for revision of AP parameters or for technical

issues during the entire extension study. No intervention from the investigation team was prompted by remote monitoring alarms. Table 2 reports the results of the primary and secondary outcomes over 24 h (D/N) and over E/N (2000–0800). Table 3 summarizes the results of the primary and secondary outcomes during daytime (0800–2000), morning (0800–1200), and afternoon (1200–2000).

CGM-Derived Outcomes

Day and Night (24 h)

The percentage of time in target range was improved with D/N-AP and E/N-AP versus SAP: 64.7 ± 7.6 and 63.6 ± 9.9 vs. 59.7 ± 9.6, significantly with D/N-AP ($P = 0.01$), and close to significance with E/N-AP ($P = 0.06$). Significant improvements came from reduced percentage of time below target range, both with D/N-AP and E/N-AP versus SAP: 1.9 ± 1.1 and 2.1 ± 1.3 vs. 3.2 ± 1.8 (both $P < 0.001$). No difference was found between D/N-AP and E/N-AP ($P = 0.74$). Mean glucose was not significantly different among the three treatments (the two AP periods and SAP): both 8.9 mmol/L vs. 9.0 mmol/L. The mean ± SD glucose profile over 24 h for D/N-AP versus SAP is shown in Fig. 1*A* and for E/N-AP versus D/N-AP is shown in Fig. 1*B*.

Evening and Night (2000–0800)

The percentages of time in target range and below target range were significantly improved during both AP periods versus SAP, whereas the percentage of time above target range was only significantly reduced during E/N-AP versus SAP: 32.6 ± 10.4 vs. 38.1 ± 11.1 ($P = 0.03$), resulting in a significantly increased percentage of time in tight target range (4.4–7.8 mmol/L) also only during E/N-AP versus SAP: 36.8 ± 10.0 vs. 31.6 ± 7.7 ($P = 0.03$). Mean blood glucose was, however, similar during the three compared treatment periods.

Daytime (0800–2000)

The percentage of time in target range and mean blood glucose levels showed no difference among the three treatments during the daytime, but a trend toward improvement of the percentage of time in target range was recorded with D/N-AP versus SAP: 64.9 ± 8.1 vs. 60.7 ± 10.3 ($P = 0.09$) and with D/N-AP vs. E/N-AP: 61.2 ± 11.7 ($P = 0.15$). Simultaneously, the percentage of time below target range with D/N-AP was significantly lower compared with SAP: 2.3 ± 1.3 vs. 3.4 ± 2.2 ($P = 0.01$), but was not significantly different between SAP and E/N-AP: 2.9 ± 1.9 ($P = 0.39$). Of note, although the percentage of time above target range was similar during AP periods and SAP, the percentage of time with glucose above 16.5 mmol/L was significantly lower with D/N-AP versus E/N-AP: 1.8 (0.4, 3.1) vs. 2.6 (0.7, 5.6) ($P = 0.004$).

Morning (0800–1200)

The morning period was characterized by significant improvements in the percentage of time in target range, above target range, and in tight target range during D/N-AP versus SAP, resulting in a lower mean blood glucose: 8.5 ± 0.8 vs. 9.1 ± 1.3 ($P = 0.03$).

Afternoon (1200–2000)

Only the percentage of time below target range was significantly improved during D/N-AP versus SAP: 2.5 (1.4, 3.0) vs. 3.2 (2.2, 4.9) ($P = 0.008$), with a trend for improvement between D/N-AP and E/N-AP: 3.0 (1.7, 4.4) ($P = 0.07$).

Glucose Variability

SD of blood glucose over 24 h was significantly reduced with D/N-AP versus SAP: 3.1 ± 0.5 vs. 3.3 ± 0.6 mmol/L ($P = 0.049$). Although D/N-AP and E/N-AP both reduced SD of blood glucose during evening and night vs. SAP, SD of blood glucose was significantly reduced with D/N-AP versus E/N-AP in daytime: 3.2 ± 0.6 vs. 3.4 ± 0.7 mmol/L ($P = 0.003$), more in the morning: 2.7 ± 0.5 vs. 3.1 ± 0.5 mmol/L ($P = 0.02$), than in the afternoon: 3.3 ± 0.6 vs. 3.5 ± 0.8 mmol/L ($P = 0.07$).

Other Outcomes

Insulin Use

Mean insulin delivery over 24 h was similar with D/N-AP and SAP but lower with E/N-AP both versus D/N-AP ($P = 0.02$) and SAP ($P = 0.0005$). Although insulin delivery was similar with the three investigated treatments during evening and night, it was significantly reduced with E/N-AP versus SAP during the morning ($P = 0.009$).

Safety

The decreased time spent below target range over 24 h and during evening and night in the AP periods was confirmed by significant reductions of the mean number of hypoglycemic episodes below 3.9 mmol/L per week and low blood glucose index vs. SAP. Although the risk and occurrence of hypoglycemia was similar with all three treatment modes during the morning, D/N-AP was associated with a significantly lower low blood glucose index versus SAP in the whole daytime ($P = 0.02$) and in the afternoon ($P = 0.001$). No serious adverse events occurred, including no severe hypoglycemic episodes, as defined by DCCT (1), and no hospitalization for ketoacidosis.

CONCLUSIONS

This report is, as far as we know, the first to compare the efficacy of E/N-AP and D/N-AP glucose control to SAP during several weeks in the same group of outpatients in free-living conditions. Over 24 h, both AP options provide a similar benefit compared with SAP in the reduction of time spent with blood glucose below 3.9 mmol/L. The average time spent with blood glucose in the targeted nearly normal range over 24 h is significantly increased with D/N-AP versus SAP and marginally increased with E/N-AP versus SAP. As could be expected, improvements in time spent in target range and below target range were similar during the evening and night period with both AP options. Daytime data are of greater interest, because the D/N-AP was active in this period, but the E/N-AP was not. Direct comparison between the two AP options is not conclusive because D/N-AP use was a nonrandomized extension of the previous randomized comparison of E/N-AP versus SAP; however, we notice that although no significant difference between SAP and E/N-AP was found in the percentage of time below target range and in target range (as expected) during the daytime, D/N-AP reduces significantly the percentage of time below target range versus SAP, with a simultaneous trend toward improved percentage of time in target range. Benefits of D/N-AP vs. E/N-AP appeared in the morning through improved mean blood glucose levels and time in target range and decreased time above target range compared with SAP and in the afternoon through reduced time below target range also when compared with

Table 2—Main and secondary outcomes over 24 h and over E/N-AP

	Intention-to-treat analysis				
	24-h AP (D/N-AP) *n = 20*	E/N-AP *n = 20*	Control period (SAP) *n* = 20	Paired differences (with CI)* E/N-AP – D/N-AP SAP – D/N-AP SAP – E/N-AP *n* = 20	*P* value
D/N (24 h)					
Median glucose, mmol/L	8.9 (8.5, 9.4)	8.9 (8.6, 9.5)	9.0 (8.7, 9.5)		0.71
					0.51
					0.95
SD of glucose, mmol/L	3.1 ± 0.5	3.3 ± 0.6	3.3 ± 0.6	0.1 (−0.1, 0.3)	0.23
				0.2 (0.0, 0.4)	0.049
				0.1 (−0.1, 0.2)	0.71
Time spent at glucose concentration, %					
4.4–7.8 mmol/L	35.4 ± 5.8	35.5 ± 9.0	32.4 ± 7.5	0.1 (−3. 7, 3.9)	1.00
				−2.9 (−6.7, 0.9)	0.16
				−3.1 (−6.9, 0.7)	0.14
3.9–10 mmol/L	64.7 ± 7.6	63.6 ± 9.9	59.7 ± 9.6	−1.1 (−5.2, 3.0)	0.79
				−5.0 (−9.1, −0.9)	0.01
				−3.9 (−8.0, 0.2)	0.06
>10 mmol/L	33.3 ± 7.3	34.2 ± 10.0	37.0 ± 10.2	0.9 (−3.4, 5.1)	0.87
				3.7 (−0.6, 7.9)	0.10
				2.8 (−1.5, 7.0)	0.26
<3.9 mmol/L	1.9 ± 1.1	2.1 ± 1.3	3.2 ± 1.8	0.2 (−0.5, 0.9)	0.74
				1.33 (0.6, 2.0)	<0.001
				1.1 (0.4, 1.8)	<0.001
<2.8 mmol/L	0.2 (0.1, 0.3)	0.1 (0.0, 0.3)	0.3 (0.1, 0.5)		0.99
					0.49
					0.40
No. of hypoglycemic events per week					
<3.9 mmol/L	5.0 ± 2.4	4.9 ± 2.6	6.4 ± 3.1	−0.1 (−1.4, 1.2)	0.98
				1.4 (0.1, 2.6)	0.03
				1.4 (0.2, 2.7)	0.02
<2.8 mmol/L	1.3 (0.7, 1.9)	0.9 (0.3, 1.8)	1.7 (1.0, 3.2)		0.59
					0.59
					0.13
Blood glucose indices					
Low	0.5 ± 0.2	0.6 ± 0.3	0.8 ± 0.4	0.0 (−0.1, 0.2)	0.79
				0.3 (0.1, 0.4)	<0.001
				0.2 (0.1, 0.4)	0.001
High	7.1 (5.8, 8.7)	6.6 (6.1, 9.2)	7.7 (6.6, 8.7)		0.61
					0.33
					0.88
Insulin need, IU/24 h	40.3 ± 15.2	36.6 ± 11.6	42.3 ± 15.5	3.8 (7.1, 0.5)	0.02
				1.9 (−1.4, 5.2)	0.34
				5.7 (2.4, 9.0)	0.0005
Time in closed-loop (or glucose sensor use for SAP phase) over 24 h, %	80.4 (68.1, 87.7)	42.9 (39.6, 46.1)	92.1 (78.0, 98.1)	–	–
E/N (2000–0800)					
Mean glucose, mmol/L	9.2 ± 0.8	9.1 ± 0.9	9.3 ± 1.0	−0.1 (−0.5, 0.3)	0.91
				0.1 (−0.3, 0.5)	0.75
				0.2 (−0.2, 0.6)	0.49
SD of glucose, mmol/L	3.1 ± 0.6	3.1 ± 0.7	3.4 ± 0.6	−0.0 (−0.3, 0.2)	0.95
				0.2 (−0.0, 0.5)	0.05
				0.3 (0.0, 0.5)	0.03
Time spent at glucose concentration, %					
4.4–7.8 mmol/L	35.3 ± 8.7	36.8 ± 10.0	31.6 ± 7.7	1.5 (−3.4, 6.4)	0.73
				−3.7 (−8.7, 1.2)	0.16
				−5.3 (−10.2, −0.3)	0.03
3.9–10 mmol/L	64.7 ± 9.7	66.0 ± 10.6	58.9 ± 11.0	1.3 (−3.7, 6.4)	0.80
				−5.8 (−10.9, −0.7)	0.02
				−7.2 (−12.2, −2.0)	0.004
>10 mmol/L	33.7 ± 9.6	32.6 ± 10.4	38.1 ± 11.1	−1.1 (−6.2, 3.9)	0.85
				4.3 (−0.7, 9.4)	0.10
				5.5 (0.4, 10.5)	0.03

Continued on p. 6

Table 2—Continued

	Intention-to-treat analysis				
	24-h AP (D/N-AP) *n = 20*	E/N-AP *n = 20*	Control period (SAP) *n* = 20	Paired differences (with CI)* E/N-AP – D/N-AP SAP – D/N-AP SAP – E/N-AP *n* = 20	*P* value
<3.9 mmol/L	1.6 ± 1.0	1.4 ± 1.0	3.1 ± 2.0	−0.21 (−1.0, 0.6)	0.79
				1.5 (0.7, 2.3)	<0.001
				1.7 (0.9, 2.5)	<0.001
<2.8 mmol/L	0.1 (0.0, 0.3)	0.0 (0.0, 0.2)	0.2 (0.1, 0.3)		0.31
					0.88
					0.13
No. of hypoglycemic events per week					
<3.9 mmol/L	1.8 (1.4, 2.2)	1.3 (1.1, 2.0)	2.5 (1.4, 4.2)		0.61
					0.01
					<0.001
<2.8 mmol/L	0.5 (0.2, 1.2)	0.2 (0.0, 0.6)	0.8 (0.3, 1.3)		0.20
					0.44
					0.009
Blood glucose indices					
Low	0.4 ± 0.2	0.4 ± 0.2	0.8 ± 0.4	−0.0 (−0.2, 0.1)	0.76
				0.3 (0.1, 0.4)	<0.001
				0.3 (0.2, 0.5)	<0.001
High	7.5 ± 2.5	7.3 ± 2.7	8.4 ± 3.0	−0.2 (−1.5, 1.0)	0.91
				0.8 (−0.4, 2.1)	0.26
				1.0 (−0.2, 2.3)	0.12
Insulin need, IU/E/N	16.5 ± 7.5	15.7 ± 6.1	17.3 ± 7.0	−0.8 (−3.4, 1.7)	0.71
				0.8 (−1.7, 3.4)	0.70
				1.7 (−0.9, 4.2)	0.26
Time spent in closed-loop over E/N, %	83.5 (67.7, 89.0)	72.2 (69.7, 80.4)	–	–	–

E/N-AP and control period data come from initial randomized clinical trial, and 24-h AP data come from nonrandomized extension in the same patients (*n* = 20). Mean variables are shown with the ± SD and median variables with 25th and 75th percentile. *95% CI of paired difference is given when data and residual are normally distributed.

SAP. Although not numerically documented for the specific morning and afternoon periods, glucose profiles shown in the 12-week D/N-AP experiment in free-living conditions in a randomized controlled crossover trial versus SAP (21) look very similar to ours presented in Fig. 1*A*.

The specific and significant improvements obtained with D/N-AP compared with E/N-AP appeared on glucose variability in the daytime, both in the morning and in the afternoon, as assessed by the SD of mean glucose. Of note, insulin use was also significantly higher over 24 h with D/N-AP than with E/N-AP. No significant discrepancy was identified between the percentage distribution of basal and bolus insulin delivery during the daytime, both in morning and afternoon periods, between the two AP modes (data not shown). However, because meal bolus management for breakfast and lunch was based on meal announcement to the control system with the D/N-AP versus pump bolus calculator with the E/N-AP, one may speculate that this difference of meal bolus computing, followed by algorithm-based tuning of later postmeal control, may have played a role in the lower variability during the morning and afternoon with D/N-AP. The effect may be stronger for the coverage of breakfast and postbreakfast insulin needs, as shown by the better performance of D/N-AP versus SAP on morning glucose control.

Overall, the lack of a significant difference on major glucose control outcomes with D/N-AP and E/N-AP supports the strategy of promoting E/N-AP as a first commercial option for AP. Larger studies could be envisioned to further investigate the differences between the two control strategies. Indeed, connection issues between devices that may occur with the currently available AP systems could further challenge the limited expected benefits of AP on glucose control during the daytime. More integrated "all-in-one" devices may tackle the connectivity problems, whereas the availability of faster-acting insulin analogs could increase the benefits of AP-assisted meal bolus.

The major limitation of our study is the extension design, which does not have the demonstration strength of a randomized controlled study design. Hence the slight benefits obtained with D/N-AP may result from the previous patient experience with E/N-AP or another time effect. Alternatively, the shorter duration of D/N-AP use may have reduced its glucose control outcomes. According to this hypothesis, AP systems in development that adopt a run-to-run control strategy could further enhance the benefits of D/N-AP, to be shown in studies with a longer duration.

In conclusion, the reported present experience of D/N-AP compared with E/N-AP points to the remaining improvements needed to achieve an AP system providing optimal nearly normal glucose control at all times. Nevertheless, the sustainability of improved glucose control in the evening and overnight with AP supports its

Table 3—Main and secondary outcomes during day-time (0800–2000), morning (0800–1200), and afternoon (1200–2000)

	Intention-to-treat analysis				
	24-h AP (D/N-AP) *n = 20*	E/N-AP *n = 20*	Control period (SAP) *n* = 20	Paired differences (with CI)* E/N-AP – D/N-AP SAP – D/N-AP SAP – E/N-AP *n* = 20	*P* value
Daytime (0800–2000)					
Mean glucose, mmol/L	9.0 ± 0.5	9.2 ± 1.2	9.1 ± 1.0	0.3 (−0.2, 0.7)	0.38
				0.1 (−0.4, 0.6)	0.83
				−0.1 (−0.6, 0.3)	0.73
SD of glucose, mmol/L	3.2 ± 0.6	3.4 ± 0.7	3.3 ± 0.6	0.3 (0.1, 0.5)	0.003
				0.2 (−0.0, 0.4)	0.15
				−0.2 (−0.3, 0.1)	0.25
Time spent at glucose concentration, %					
4.4–7.8 mmol/L	35.6 ± 6.5	34.1 ± 9.3	33.4 ± 8.8	−1.4 (−5.8, 3.0)	0.72
				−2.2 (−6.6, 2.3)	0.46
				−0.75 (−5.2, 3.7)	0.91
3.9–10 mmol/L	64.9 ± 8.1	61.2 ± 11.7	60.7 ± 10.3	−3.7 (−8.4, 1.0)	0.15
				−4.2 (−8.9, 0.6)	0.09
				−0.5 (−5.2, 4.3)	1.00
>10 mmol/L	32.8 ± 7.8	35.9 ± 12.1	35.8 ± 11.4	3.1 (−2.1, 8.2)	0.32
				3.0 (−2.1, 8.2)	0.34
				−0.1 (−5.2, 5.1)	1.00
<3.9 mmol/L	2.3 ± 1.3	2.9 ± 1.9	3.4 ± 2.2	0.6 (−0.3, 1.6)	0.25
				1.2 (0.2, 2.1)	0.01
				0.5 (−0.4, 1.4)	0.39
<2.8 mmol/L	0.2 (0.1, 0.3)	0.1 (0.0, 0.3)	0.4 (0.2, 0.6)		0.79
					0.27
					0.64
No. of hypoglycemic events per week					
<3.9 mmol/L	3.3 ± 1.8	3.4 ± 1.9	3.9 ± 2.3	0.1 (−0.9, 1.2)	0.94
				0.6 (−0.4, 1.7)	0.34
				0.5 (−0.6, 1.5)	0.54
<2.8 mmol/L	0.9 (0.4, 1.1)	0.5 (0.3, 1.2)	0.9 (0.6, 1.7)		0.99
					0.35
					0.27
Blood glucose indices					
Low	0.6 ± 0.3	0.7 ± 0.4	0.8 ± 0.4	0.1 (−0.1, 0.3)	0.31
				0.2 (0.0, 0.4)	0.02
				0.1 (−0.1, 0.3)	0.37
High	7.2 (6.1, 8.8)	7.5 (5.9, 10.1)	7.4 (6.7, 8.8)		0.51
					0.71
					0.95
Insulin need, IU/day	19.3 (16.1, 31.8)	18.5 (15.5, 24.9)	22.9 (18.2, 27.5)		0.74
					0.71
					0.28
Time in closed-loop over day-time, %	73.9 ± 14.3	10.4 ± 6.1	–	–	–
Morning (0800–1200)					
Mean glucose, mmol/L	8.5 ± 0.8	8.7 ± 1.0	9.1 ± 1.3	0.2 (−0.3, 0.7)	0.60
				0.6 (0.1, 1.1)	0.03
				0.4 (−0.2, 0.9)	0.22
SD of glucose, mmol/L	2.7 ± 0.5	3.1 ± 0.5	2.9 ± 0.5	0.3 (0.1, 0.6)	0.02
				0.2 (−0.1, 0.4)	0.30
				−0.2 (−0.4, 0.1)	0.36
Time spent at glucose concentration, %					
4.4–7.8 mmol/L	42.4 ± 12.4	40.6 ± 12.9	34.5 ± 12.5	−1.8 (−8.0, 4.5)	0.77
				−7.9 (−14.1,-1.6)	0.01
				−6.1 (−12.3, 0.1)	0.06
3.9–10 mmol/L	72.3 ± 10.6	68.6 ± 9.6	62.7 ± 15.4	−3.7 (−10.3, 2.9)	0.36
				−9.6 (−16.2, −3.0)	0.003
				−5.9 (−12.5, 0.7)	0.09
>10 mmol/L	25.6 ± 10.7	29.1 ± 10.2	35.1 ± 16.4	3.5 (−3.4, 10.3)	0.44
				9.5 (2.6, 16.3)	0.005
				6.0 (−0.9, 12.8)	0.10
<3.9 mmol/L	1.5 (0.3, 3.0)	1.4 (0.8, 3.2)	1.7 (0.9, 3.1)		0.88
					0.88
					1.00

Continued on p. 8

Table 3—Continued

	Intention-to-treat analysis				
	24-h AP (D/N-AP) *n = 20*	E/N-AP *n = 20*	Control period (SAP) *n* = 20	Paired differences (with CI)* E/N-AP – D/N-AP SAP – D/N-AP SAP – E/N-AP *n* = 20	*P* value
<2.8 mmol/L	0.0 (0.0, 0.3)	0.0 (0.0, 0.1)	0.0 (0.0, 0.3)		0.78
					0.88
					1.00
No. of hypoglycemic events per week					
<3.9 mmol/L	0.9 ± 0.8	1.0 ± 0.8)	1.0 ± 0.7	0.1 (−0.4, 0.5)	0.93
				0.0 (−0.4, 0.5)	0.98
				−0.0 (−0.5, 0.4)	0.99
<2.8 mmol/L	0.1 (0.0, 0.5)	0.0 (0.0, 0.3)	0.1 (0.0, 0.3)		0.72
					0.60
					0.98
Blood glucose indices					
Low	0.6 ± 0.4	0.6 ± 0.5)	0.6 ± 0.4	0.1 (−0.1, 0.3)	0.74
				0.0 (−0.2, 0.2)	0.94
				−0.0 (−0.2, 0.2)	0.91
High	5.4 (3.9, 6.2)	6.8 (4.4, 8.2)	7.0 (5.8, 8.9)		0.51
					0.19
					0.80
Insulin need, IU/morning	6.0 ± 2.4	5.2 ± 2.5	6.9 ± 3.5	−0.8 (−2.1, 0.5)	0.32
				0.9 (−0.4, 2.3)	0.23
				1.7 (0.4, 3.1)	0.009
Time in closed-loop over morning, %	70.7 ± 15.0	8.2 ± 8.1	–	–	–
Afternoon (1200–2000)					
Mean glucose, mmol/L	9.2 ± 0.7	9.5 ± 1.4	9.1 ± 1.0	0.3 (−0.3, 0.8)	0.40
				−0.1 (−0.7, 0.4)	0.88
				−0.4 (−1.0, 0.1)	0.19
SD of glucose, mmol/L	3.3 ± 0.6	3.5 ± 0.8	3.4 ± 0.6		0.07
					0.25
					0.80
Time spent at glucose concentration, %					
4.4–7.8 mmol/L	32.2 ± 7.0	31.0 ± 9.1	32.8 ± 9.0	−1.3 (−6.3, 3.8)	0.81
				0.6 (−4.4, 5.6)	0.95
				1.9 (−3.1, 6.9)	0.64
3.9–10 mmol/L	61.2 ± 9.7	57.5 ± 13.7	59.6 ± 10.1	−3.8 (−8.9, 1.4)	0.19
				−1.6 (−6.8, 3.6)	0.73
				2.1 (−3.0, 7.3)	0.57
>10 mmol/L	36.3 ± 9.4	39.3 ± 14.1	36.3 ± 11.0	3.0 (−2.6, 8.5)	0.41
				−0.0 (−5.6, 5.5)	1.00
				−3.0 (−8.5, 2.6)	0.40
<3.9 mmol/L	2.5 (1.4, 3.0)	3.0 (1.7, 4.4)	3.2 (2.2, 4.9)		0.07
					0.008
					0.71
<2.8 mmol/L	0.2 (0.0, 0.4)	0.2 (0.0, 0.4)	0.5 (0.2, 0.8)		0.59
					0.07
					0.44
No. of hypoglycemic events per week					
<3.9 mmol/L	1.8 (1.5, 3.9)	2.4 (1.5, 3.2)	2.4 (1.5, 4.0)		0.88
					0.61
					0.88
<2.8 mmol/L	0.5 (0.1, 0.8)	0.5 (0.2, 0.8)	0.9 (0.4, 1.4)		0.94
					0.047
					0.10
Blood glucose indices					
Low	0.6 (0.4, 0.8)	0.7 (0.4, 1.0)	0.8 (0.7, 1.1)		0.07
					0.001
					0.42
High	7.7 (6.3, 10.5)	8.5 (6.3, 10.5)	7.7 (6.5, 8.9)		0.51
					0.80
					0.19
Insulin need, IU/afternoon	15.6 (11.5, 22.6)	14.0 (12.0, 16.8)	17.3 (13.8, 18.5)		0.73
					0.73
					0.28
Time spent in closed-loop over afternoon, %	75.5 ± 14.3	11.7 ± 7.6	–	–	–

E/N-AP and control period data come from initial randomized clinical trial, and 24-h AP data come from nonrandomized extension in the same patients (*n* = 20). Mean variables are shown with ± SD and median variables with 25th, 75th percentile. *95% CI of paired difference is given when data and residual are normally distributed.

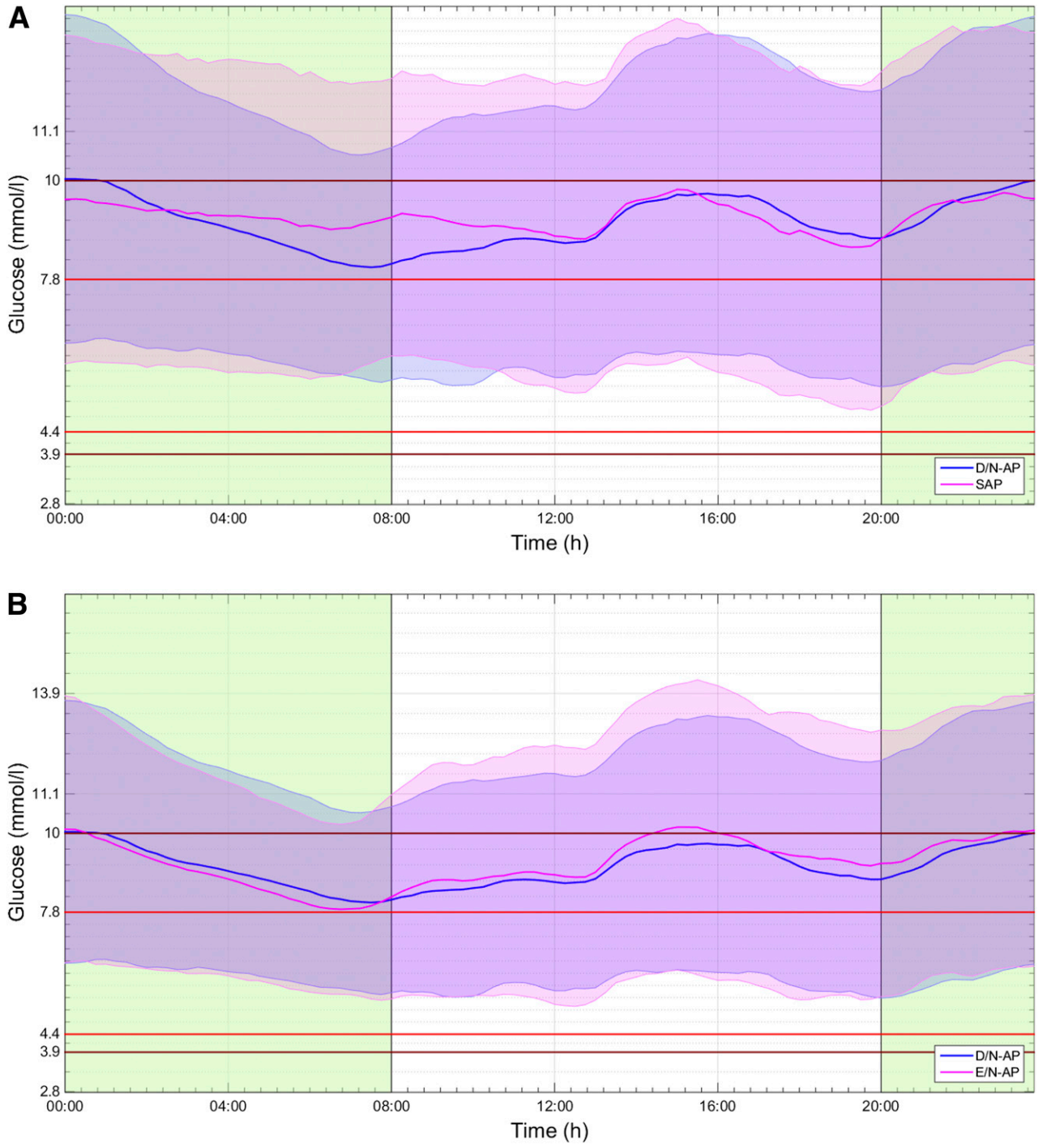

Figure 1—Glucose profile (mean ± SD) over 24 h for SAP and D/N-AP periods (*A*) and for E/N-AP and D/N-AP periods (*B*).

commercialization as a valuable additional feature of SAP therapy for patients with T1D.

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stock ownership in TypeZero Technologies. P.K.-H. holds patent applications related to the study technology, serves as chief technology officer of TypeZero Technologies, and has stock ownership in TypeZero Technologies. C.C. has received research support from Sanofi and Adocia. J.H.D. is a consultant/advisor on the speakers bureau for Dexcom, Johnson & Johnson (Animas, LifeScan), and Roche Diagnostics. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors reviewed and provided edits and comments on manuscript drafts. E.R. was the principal investigator of Montpellier and drafted the protocol and manuscript. A.F. was the main study physician responsible for the trial in Montpellier. J.K. was the main study physician responsible for the trial in Amsterdam. D.B. was the main study physician in Padua and drafted the manuscript. M.M. and C.T. developed the algorithm and analyzed data. J.P. was the senior engineer responsible for the trial in Montpellier. R.V. was the engineer providing technical support during the trial in Padua. R.C. was the engineer providing technical support during the trial in Padua and assisted the trial in Amsterdam. F.D.P. was the control engineering responsible for control algorithm implementation on the DiAs. G.L. was the computer scientist responsible for the design and implementation of the remote monitoring system used during the trial. F.B. and S.G. were clinicians providing medical support to the patients during the trial in Padua. P.M. advised on statistical analyses methods. A.A. was the coordinating physician for the performance of the trial in Padua. P.K.-H. was chief engineer of the DiAs smartphone-based system and user interface. B.K. was the principal investigator at the University of Virginia and developed the DiAs system. S.D.F. was the senior engineer responsible for the trial in Padua and assisted the trial in Amsterdam. C.C. was the principal investigator in Padua, designed the protocol, analyzed data, and drafted the manuscript. L.M. was the principal investigator of Pavia Unit, developed the algorithm, analyzed data, and drafted the manuscript. J.H.D. was the principal investigator in Amsterdam, designed the protocol, and drafted the manuscript. J.K., J.P., C.T., M.M., R.V., S.D.F., and L.M. had access to the raw data. E.R. had full access to all of the data and the final responsibility to submit for publication. E.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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