The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 1, 55–63
doi:10.1210/clinem/dgaa562
Clinical Research Article

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Artificial Pancreas With Carbohydrate Suggestion Performance for Unannounced and Announced Exercise in Type 1 Diabetes

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Abbreviations: bpm, beats per minute; CGM, continuous glucose monitor; CLA, closed-loop with announced exercise; CLNA, closed- loop with unannounced exercise; CV, coefficient of variation; HbA_{1c}, hemoglobin A_{1c}; HR, heart rate; IOB, insulin on board; MCL, multivariable single-hormone hybrid closed-loop control system with carbohydrate recommendation; OL, open loop; T1D, type 1 diabetes; YSI, Yellow Spring Instruments.

Received: 6 May 2020; Accepted: 14 August 2020; First Published Online: 27 August 2020; Corrected and Typeset: 3 November 2020.

Abstract

Objective: To evaluate the safety and performance of a new multivariable closed-loop (MCL) glucose controller with automatic carbohydrate recommendation during and after unannounced and announced exercise in adults with type 1 diabetes (T1D).

Research Design and Methods: A randomized, 3-arm, crossover clinical trial was conducted. Participants completed a heavy aerobic exercise session including three 15-minute sets on a cycle ergometer with 5 minutes rest in between. In a randomly determined order, we compared MCL control with unannounced (CLNA) and announced (CLA) exercise to open-loop therapy (OL). Adults with T1D, insulin pump users, and those with hemoglobin (Hb)A_{1c} between 6.0% and 8.5% were eligible. We investigated glucose control during and 3 hours after exercise.

Results: Ten participants (aged 40.8 ± 7.0 years; HbA_{1c} of 7.3 ± 0.8%) participated. The use of the MCL in both closed-loop arms decreased the time spent <70 mg/dL of sensor glucose (0.0%, [0.0-16.8] and 0.0%, [0.0-19.2] vs 16.2%, [0.0-26.0], (%, [percentile 10-90]) CLNA and

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

CLA vs OL respectively; $P = 0.047$, $P = 0.063$) and the number of hypoglycemic events when compared with OL (CLNA 4 and CLA 3 vs OL 8; $P = 0.218$, $P = 0.250$). The use of the MCL system increased the proportion of time within 70 to 180 mg/dL (87.8%, [51.1-100] and 91.9%, [58.7-100] vs 81.1%, [65.4-87.0], (%, [percentile 10-90]) CLNA and CLA vs OL respectively; $P = 0.227$, $P = 0.039$). This was achieved with the administration of similar doses of insulin and a reduced amount of carbohydrates.

Conclusions: The MCL with automatic carbohydrate recommendation performed well and was safe during and after both unannounced and announced exercise, maintaining glucose mostly within the target range and reducing the risk of hypoglycemia despite a reduced amount of carbohydrate intake.

Register Clinicaltrials.gov: NCT03577158

Key Words: artificial pancreas, type 1 diabetes, exercise, closed-loop control, hypoglycemia prevention and exercise

Physical exercise has been shown to improve glycemic control and general well-being for people with type 1 diabetes (T1D). However, despite growing evidence about the health benefits of regular exercise in diabetes, exercise-associated glycemic imbalance remains a challenge in individuals with T1D (1-4). Guidelines for exercise management exist for individuals with T1D, which commonly include recommendations for carbohydrate consumption and basal insulin adjustment (1). Nonetheless, the current exercise strategies remain a burden for most patients in daily life and require high engagement and further individualization (5).

Closed-loop (CL) or artificial pancreas systems with automatic insulin infusion in response to a continuous glucose monitor (CGM) signal are safe and efficient in free-living conditions (6-8). However, physical exercise is one of the main disturbances that challenge these devices due to rapid changes in insulin sensitivity, limitations in the subcutaneous route, and the lag time and accuracy of glucose sensing in the subcutaneous space (9, 10).

Recently, Tagougui et al (11) reviewed the studies that have examined the performance of CL systems in response to exercise. Several approaches have been used to maintain optimal glycemic control during exercise such as the use of glucagon, heart rate to automate exercise detection, additional variables to improve glucose predictions, pre-exercise snacks, and a combination of these strategies. Overall, these studies have demonstrated that CL systems are able to maintain glycemic control while reducing the occurrence of hypoglycemia. However, supplemental carbohydrates consumption is still required before, during, and/or after exercise to reduce the occurrence of hypoglycemia. Despite the use of different strategies, there is no clear consensus as to which has the most effective effects on glucose control as results are difficult to compare due to the variations in CL systems, duration of use, exercise protocol, carbohydrate quantities, and outcomes reported.

The SAFE-AP system is a single-hormone hybrid CL controller that includes carbohydrate recommendations as an additional control input. It is based on a proportional derivative with an insulin feedback controller that integrates a safety layer with insulin-on-board (IOB) constraints and sliding mode reference conditioning (12-15). The hybrid CL system includes a second feedback loop with a controller that triggers carbohydrate recommendations to the patient (16). Both control loops are coordinated to ensure that the counter-regulatory effect of rescue carbohydrates is not counteracted with insulin. Additionally, if physical activity is announced, the system can also take feed-forward actions to further prevent hypoglycemia (17, 18). Mitigation modules to improve safety and performance of the overall system were also used (17, 19).

The objective of this study was to evaluate the safety and performance of this new multivariable single-hormone hybrid CL control system with carbohydrate recommendation (MCL) under challenging unannounced and announced exercise in patients with T1D.

Research Design and Methods

Study design and participants

This open-label, randomized, 3-arm, in-hospital crossover clinical trial was conducted at the Hospital Clínic de Barcelona, Spain. The study was performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study was approved by the local Ethics Committee and all participants gave informed consent. The study is listed on clinicaltrials.gov under the registration number NCT03577158.

The inclusion criteria were age 18 to 65 years (inclusive), clinical diagnosis of T1D for at least 1 year, HbA_{1c} between 6.0% and 8.5%, insulin pump use for at least 6 months, body mass index within 18 to 30 kg/m^2, and no advanced chronic micro- and macrovascular complications. Individuals with prior history in the last 6 months of at least 1 episode of severe hypoglycemia, diabetes ketoacidosis requiring hospitalization with hypoglycemia

unawareness assessed using a validated questionnaire (20), or who were pregnant or breastfeeding were excluded.

Patients were instructed to wear a CGM device during a 6-day period before the first exercise test. Data from CGM were used to optimize the following parameters: insulin to carbohydrates ratio, sensitivity factor, and basal insulin needs. These parameters were used to optimize the overall home blood glucose control (21, 22), after which the controller was tuned. Initial IOB during each trial was also estimated from CGM data for the controller initialization. Participants continue to use unblinded CGM in between visits.

Randomization and masking

Participants were randomly assigned (1:1:1) to perform physical exercise on 3 different sequences: MCL with unannounced exercise (CLNA), MCL with announced exercise (CLA), and open loop (OL) with announced exercise (sensor-augmented pump therapy). There was a washout period of at least 1 week between studies. Each participant underwent an in-hospital standardized physical exercise protocol on 3 occasions. Participants and investigators analyzing this study data were not masked to treatment.

Procedures

The screening visit included informed consent acquisition, a detailed physical examination, and confirmation of the inclusion/exclusion criteria, an electrocardiogram, a safety clinical laboratory analysis, and a hemoglobin (Hb)A_{1c} measurement. In women of childbearing age, a urine test for pregnancy was also performed. Participants also answered the short version of the International Physical Activity Questionnaire (23). Participants were randomized into the 3 sequences and CGM training was given. During 3 separate in-hospital visits, participants arrived at the investigational clinical site at 8:00 AM after having a standardized breakfast of 50 g of carbohydrates at home. Although patients received instructions on breakfast protocol, compliance was not checked. At 8:30 AM, the MCL controller was initialized in the closed-loop sequences. The exercise protocol started at 12:00 AM (t = 0) and consisted of three 15-minute sets on a cycle ergometer (Wattbike Pro, Wattbike Ltd, UK) at 70% of maximum heart rate with 5 minutes of rest between sets. Participants were in MCL or OL until 3:00 PM (t = 180 minutes). Patients wore a heart rate monitor (Polar RCX3, Kempele, Finland) to ensure the desired exercise intensity, calculated as:

$$HR_{exercise} = HR_{rest} + \frac{70\,(HR_{max} - HR_{rest})}{100}$$

where heart rate $(HR)_{exercise}$ is the heart rate (beats per minute [bpm]) during the physical activity period, HR_{max} is the maximum heart rate (bpm), and HR_{rest} is the rest heart rate (bpm).

Exercise announcement (11:40 AM) was confirmed 20 minutes prior to the start of the activity (12:00 PM) in both the OL and CLA studies. The OL study used a temporal basal rate of 0% until the completion of the exercise protocol and followed recommended glucose management strategies considering blood glucose concentration before exercise commencement (1). The CLA system initiated the exercise mode (17) upon confirmation of exercise by the user.

Devices and assays

The MCL system was based on a glucose controller (12, 15-17, 19) built in an Android platform designed for investigational purposes (java Artificial Pancreas [jAP]). The jAP is a configurable and scalable platform in which different artificial pancreas architectures can be used (unihormonal/bihormonal, with or without additional sensors, selection of different types of controllers). The platform also includes all necessary tools for the correct monitoring and visualization of the user's data as well as different permission levels for the adjustment of the therapy.

The system was installed in a Samsung S7 (4 GB RAM, 32 GB memory) smartphone with Android 7.0 (kernel 3.18.14-12365438) including only the preinstalled and jAP applications. The smartphone was wirelessly connected to both the insulin pump and CGM using Bluetooth technology. The jAP platform retrieved glucose/insulin data from both the insulin pump and CGM and set insulin treatment according to the selected therapy of either OL or MCL. A backup Asus ZenBook (i7-7500U @ 2.70 GHz, 16 GB RAM, Windows 10 Home v18362.418) laptop was prepared for troubleshooting issues and connection errors.

All participants used the same insulin pump set (Dana Diabecare R, Sooil, Seoul, Korea), CGM (Dexcom G5, Dexcom, San Diego, CA), and glucose meter (Contour Link Meter 2.4, Ascensia Health Care, Basel, Switzerland).

The MCL, which received glucose measurements from 1 CGM device every 5 minutes, calculated 2 control actions: insulin delivery and a fast-acting carbohydrate intake recommendation. Calculated insulin was delivered automatically by changing the basal rate of the insulin pump during the next time interval. The control software had 2 main elements (1): an MCL control algorithm based on the CGM measurement that computes the insulin infusion and a recommendation of carbohydrate intake (if necessary) every 5 minutes and (2) an exercise mitigation module that triggers feed-forward actions for better glycemic control when exercise is announced. When necessary, recommendations of

carbohydrate intake by the controller are given as a predefined amount of fast-acting carbohydrates (15 g). When exercise is announced, the controller may suggest additional pre-exercise carbohydrates that were quantized in multiples of 5 g. This was a manual action performed by the patient.

The MCL system was designed, tuned, and validated using Matlab (R2017a, MathWorks, Natick, MA) (12, 15-17, 19). The CLNA and CLA version of the controller were implemented in Java 1.8 for their integration within the jAP platform. The MCL system requires insulin, meals, and glucose data from the previous 5 hours to correctly initialize its integrated components.

The time window from the computation of the current control action to the next available measurement was used, among other things, to upload data to a server used as a remote monitoring tool. A web application allowed the authorized users to remotely monitor the status of the patient in each trial. Data like CGM, infused insulin, IOB, and other useful controller parameters were presented in timed graphics in order to follow the whole trial in real time.

Safety monitoring

Arterialized reference blood glucose samples (Yellow Spring Instruments [YSI]; YSI 2300 STAT Plus, YSI Inc. Life Sciences, Yellow Springs, OH) were collected every 15 minutes before exercise and during recovery and every 10 minutes during exercise. If any glucose value reading was below 70 mg/dL and the patient showed symptoms of hypoglycemia, 15 g of glucose were provided (Diabalance gel).

Endpoints

Primary endpoints were the percentage of time spent <70 mg/dL of sensor glucose, as well as, the number of hypoglycemic events (plasma glucose <70 mg/dL) during exercise and recovery (180 minutes). Hypoglycemic events were classified as L1 events if plasma glucose was <70 mg/dL for at least 15 minutes and L2 if it was <54 mg/dL for at least 15 minutes (24).

The secondary outcomes were the following (1): percentage of time spent within 70 to 180 mg/dL and >180 mg/dL during exercise and recovery (2), coefficient of variation (CV) of CGM values during and after exercise (3), and total insulin and carbohydrates during and after exercise and on the exercise announcement event.

All study endpoints used are in line with the up-to-date recommended outcome measures (24, 25). CGM sensor values and control action variables analysis during the exercise and recovery periods were also recorded.

Statistical analysis

Due to the exploratory nature of this study, sample size calculations were not formally performed. Comparisons between MCL arms (CLNA and CLA) versus OL were performed using the paired nonparametric Wilcoxon signed rank test (MATLAB R2019a, MathWorks, Natick, MA). Descriptive statistics, including the mean, standard deviation, median, 10th to 90th percentile range, CV, and interquartile range were also computed to describe the sample characteristics. Missing values from the original CGM signal were linearly interpolated for the computation of secondary outcomes.

Results

The baseline characteristics of the cohort are reported in Table 1. All 10 patients completed the study. During the exercise protocol, CGM data were available 93.33% of the time. One patient had an available CGM time below 60% during the OL trial due to constant disconnection of the CGM sensor and therefore, the patient was excluded from the CGM outcomes and from the CLNA versus OL and CLA versus OL comparisons.

The glycemic outcomes were calculated using the glucose readings from the YSI and CGM during the exercise and recovery periods, which resulted in a total of 180 minutes of data for each trial (Tables 2 and 3). The heavy aerobic physical activity generally provoked large and rapid glucose drops as shown in Figure 1.

During this study, a total of 15 hypoglycemic events were recorded by the YSI (4 for the CLNA arm, 3 for the CLA arm, and 8 for the OL arm) as reported in Table 2. Participants received supplemental carbohydrates, either as a feed-forward action or as recommendation by the controller on the CLNA/CLA arms and also following recommended glucose management strategies in the OL arm

Table 1. Baseline characteristics of the cohort

Characteristic	All (n = 10)	Male (n = 7)	Female (n = 3)
Age (years)	40.8 ± 7.0	41.7 ± 6.9	38.7 ± 8.4
Diabetes onset (years)	24.9 ± 11.6	27.0 ± 10.7	20.0 ± 14.5
Duration using pump (years)	8.1 ± 4.1	7.6 ± 2.4	9.3 ± 7.4
HbA_{1c} (%)	7.3 ± 0.8	7.2 ± 0.9	7.4 ± 0.4
Weight (kg)	76.5 ± 10.7	80.6 ± 9.7	67.0 ± 6.3
Height (cm)	172.9 ± 7.7	176.0 ± 5.9	165.7 ± 6.8
Total daily infusion (U)	37.5 ± 5.9	39.1 ± 5.8	33.6 ± 4.7

Data presented as mean ± standard deviation.
Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

Table 2. Primary endpoints of the study. Number of hypoglycemic events and the percentage of time <70 mg/dL and <54 mg/dL of sensor glucose

		CLNA	CLA	OL	P^a	P^b
Plasma glucose (mg/dL)	54-70	2	2	4	0.500	0.688
	<54	2	1	4	0.625	0.250
	<70	4	3	8	0.218	0.250
Sensor glucose (mg/dL)	% <70	0.0[a] (0.0-16.8)	0.0 (0.0-19.2)	16.2 (0.0-26.0)	0.047	0.063
	% <54	0.0 (0.0-0.0)	0.0 (0.0-8.4)	0.0 (0.0-6.0)	0.500	1.000

Data expressed as number or median (10^{th}-90th percentile ranges).
Abbreviations: CLA, closed-loop with announced exercise; CLNA, closed-loop with unannounced exercise; OL, open loop.
[a]*P* value between CLNA-OL.
[b]*P* value between CLA-OL.

Table 3. Secondary outcome measures, sensor glucose values, and control action variables during exercise and recovery periods

Variable	CLNA	CLA	OL	P^a	P^b
Mean glucose (mg/dL)	120.5 (92.7-181.6)	127.1 (84.7-189.4)	119.6 (91.9-168.5)	1.000	0.910
Median glucose (mg/dL)	106.5 (92.5-180.5)	119.0 (86.5-194.0)	130.0 (85.6 -170.4)	0.733	0.441
IQR, glucose (mg/dL)	26.4 (22.1-46.9)	21.5[b] (13.1-55.8)	49.1 (16.4-79.4)	0.055	0.020
CV (%)	17.8[a] (9.4-31.2)	17.3[b] (10.7-25.3)	30.8 (8.5-37.4)	0.027	0.020
% of time					
Glucose >250 mg/dL	0.0 (0.0-0.74)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	1.000
Glucose >180 mg/dL	0.0 (0.0-48.9)	0.0 (0.0-41.4)	0.0 (0.0-15.1)	0.625	0.375
Glucose 70-180 mg/dL	87.8 (51.1-100.0)	91.9[b] (58.7-100.0)	81.1 (65.4-87.0)	0.227	0.039
Glucose (mg/dL) at					
Exercise announcement	136.0 (115.8-200.5)	118.0 (98.4-146.4)	118.0 (67.4-209.4)	0.426	1.000
Exercise start	121.0 (98.4-190.4)	114.0 (95.5-141.0)	116.0 (71.0-169.8)	0.734	0.910
Estimated IOB (U) at					
Exercise announcement	2.9 (2.0-4.7)	2.6 (1.8-4.2)	2.6 (1.9-4.2)	0.922	0.770
Exercise start	2.4 (1.8-4.2)	2.2 (1.5-3.6)	2.3 (1.6-3.6)	0.922	0.557
Insulin (U) during					
Exercise	0.0 (0.0-0.2)	0.0 (0.0-0.3)	0.0 (0.0-0.1)	1.000	0.813
Recovery	1.9[a] (0.8-2.7)	1.3 (0.3-2.5)	1.2 (0.5-2.3)	0.020	0.625
Exercise + recovery	2.0[a] (0.8-2.7)	1.3 (0.3-3.1)	1.3 (0.6-2.3)	0.049	0.695
Carbohydrates (g) during exercise and recovery	15.0 (0.0-31.5)	22.5 (15.0-40.5)	32.5 (0.0-40.0)	0.219	0.880

[a]*P* value between CLNA-OL.
[b]*P* value between CLA-OL.
Values expressed as median (10th-90th percentile ranges).
Abbreviations: CLA, closed-loop with announced exercise; CLNA, closed-loop with unannounced exercise; CV, coefficient of variation; IOB, insulin on board; IQR, interquartile range; OL, open loop.

(1). The CLNA and CLA systems decreased the proportion of time spent in the hypoglycemic ranges (<70 mg/dL) with values of 0.0% (0.0%-16.8%) and 0.0% (0.0%-19.2%) compared with 16.2% (0.0%-26.0%) for the OL system (Table 2).

The median (10th-90th percentile ranges) proportion of time spent in range (70-180 mg/dL) for the exercise and recovery period based on CGM sensor was 87.8% (51.1%-100%) for CLNA, 91.9% (58.7%-100%) for CLA, and 81.1% (65.4%-87.0%) for OL. The overall descriptive statistics were more favorable for the CLNA and CLA arms compared with the OL arm. Mainly the system achieved tighter control in terms of glucose variability during and after exercise (CV 26.4 mg/dL (22.1-46.9), 21.5 mg/dL (13.1-55.8), and 49.1 (16.4-79.4) for CLNA, CLA, and OL, respectively). CGM values and estimated IOB at the beginning of the physical activity were comparable in all 3 arms (Table 3).

The improvement of the overall glucose during both CL arms was nominally achieved with a trend to a lower amount of carbohydrates when compared with OL: 15.0 g (0.0-31.5) for CLNA, 22.5 g (15.0-40.5) for CLA, and 32.5 g (0.0-40.0) for OL, while infusing similar amounts of insulin in all 3 arms, see Table 3.

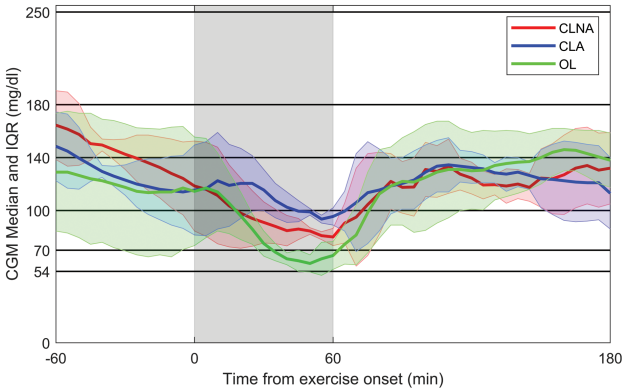

Figure 1. CGM sensor values in median (IQR) during closed-loop arms (blue, red) and open-loop arm (green). Exercise started at 12:00 PM (t = 0 on the x-axis) and finished 60 minutes later. CGM, continuous glucose monitoring; CLA, closed-loop with announced exercise; CLNA, closed-loop with unannounced exercise; IQR, interquartile range; min, minutes; OL, open loop.

There were no serious adverse events. The full CL period was completed for all participants, and in no instances were the stopping criteria met. For the entire study period, there were zero hyperglycemic events involving postprandial > 250 mg/dL. Due to signs and symptoms of hypoglycemia, there were 2 instances that due to medical criteria that the investigational team gave carbohydrate rescues to the participants before the carbohydrates were suggested by the controller.

Discussion

The results of this study show that the use of the new multivariable single-hormone hybrid CL control system with carbohydrate recommendation is effective and safe in maintaining blood glucose within target values during and after unannounced and announced heavy physical activity. To our knowledge, this is one of the few randomized controlled trials that has compared the performance of a CL controller for unannounced and announced exercise and sensor-augmented pump therapy.

Other studies have incorporated bihormonal control strategies with glucagon to cope with exercise (26-29). In our case, the glucagon counter-regulatory action is substituted by the recommendation of carbohydrate consumption given by the controller. There are other approaches using an artificial pancreas system and carbohydrates to compensate the exercise effect (30, 31). These strategies mostly consist of ad hoc modules that recommend carbohydrates in case a hypoglycemic event is predicted. Most common strategies in artificial pancreas clinical trials involving exercise only use rescue carbohydrates as a reactive action when glucose is below a given threshold for safety (eg, <70 mg/dL, such as in 29 and 32). A key difference from other artificial pancreas systems is that the investigated algorithm, MCL, incorporates a specific CL control strategy not only for insulin delivery but also for recommending carbohydrates as an additional control action. By incorporating the carbohydrates as a new control action, this multivariable algorithm intends to optimize the carbohydrate intake required to improve performance and guaranteeing safety. It is a fully multivariable controller with coordination between insulin and carbohydrate intake recommendation. Moreover, the CL controller used a static glucose set point of 100 mg/dL to assess the ability of the controller to maintain tight glucose control during and after heavy aerobic exercise.

The number of hypoglycemic events in the MCL studies (4 in CLNA, 3 in CLA) is about half that of the OL studies (8 instances). The small sample size of this exploratory study and meticulous adherence to the in-hospital procedures for preventing hypoglycemia implemented by trained investigators prevented the demonstration of statistical significance. Additionally, the trial revealed that the CL strategies decreased the proportion of time spent in the hypoglycemic range (<70 mg/dL), especially in the CLNA arm. The use of the MCL system maintained or increased the proportion of time spent within target glucose range, with a significant improvement in glucose variability in both CLNA and CLA arms. The improvement in glucose variability is far from negligible because it is associated to a higher risk of hypoglycemia in the upcoming hours (33).

At the same time, the controllers have reduced the control action efforts in terms of carbohydrate recommendations when compared with standard exercise recommendations in the OL arm (1). Particularly, the OL arm required twice the carbohydrates as the CLNA arm. In addition, the CL system was safe with a fixed set point of 100 mg/dL, while other similar studies used increased set points during exercise (24, 34). Our results are in line with the study performed by Patel et al (35) that showed in a CL study that using a snacking strategy could help with decreasing the exercise-induced hypoglycemia. Additionally, our approach required a lower quantity of carbohydrates to reduce hypoglycemia.

In this study, 15-g and 5-g glucose gels were used, which were the only source of carbohydrates provided to the participants. One limitation of this study is that the carbohydrates taken as feed-forward actions 20 minutes before exercise may not have had a full impact on the exercise period due to the high glycemic index and rapid rate of absorption of the gels used. Additional research is required to study the impact of different carbohydrate sources as counteractive measures to physical activity in CL strategies.

Physical exercise has a profound impact on blood glucose control. Depending on the type and duration of the activity as well as the patient's state, blood glucose levels may be difficult to maintain within the target range (1). Numerous factors can alter the performance of hybrid CL controllers, such

as overbolusing of previous meals, which is an event that can lead to high IOB levels at the beginning of physical exercise. We observed a steady decline in blood glucose and a comparable amount of active IOB across all arms during exercise periods. CLNA had a steeper decrease in blood glucose during exercise when compared with the OL. The patient's IOB was postprandial (following the morning breakfast), and glucose was largely in the target range at the start of exercise, regardless of the treatment arm.

CL control could benefit from additional sources of information (eg, HR or energy expenditure) and/or additional control actions such as the use of glucagon. Studies have shown that the use of glucagon may mitigate the risk of hypoglycemia (26-30, 32, 36). Regardless of the controller used, we observed that proper coordination with the different available control actions is mandatory. The controller must be aware of control actions performed by the patient, that is, the act of eating recommended carbohydrates should not be counteracted by the insulin control.

Our study has several limitations. First of all, it was a proof-of-concept study including a small sample size, and it was conducted in a well-controlled in-hospital environment. Accordingly, the conclusions regarding the performance of the new MCL have to account for this, and no conclusions in long-term safety and efficacy can be drawn. Free-living studies including more types and durations of physical activities are required in order to fully assess the performance and safety of the CL systems tested. The majority of the controller parameters were kept the same across all patients to generalize the tuning and make it as simple as possible. In free-living conditions, the control parameters should be further individualized to each specific participant and adapted to optimize performance and enhance safety. Due to the small duration and the exploratory nature of this study, it was not possible to address this issue. Since this study protocol ended at 3:00 PM, the study did not include the assessment of blood glucose levels during the night following exercise. Further investigation is needed to assess the ability of the CL therapy to deal with common exercise complications like overnight hyperglycemia rebound (37-39) or hypoglycemia due to increased insulin sensitivity in a longer postexercise period. When we designed the study, we decided to use a sensor-augmented pump without advanced features (predictive low-glucose suspend) as standard therapy in the OL arm because it was the most common advanced therapy used in our population. The effectiveness of predictive low-glucose suspend in the prevention of exercise-induced hypoglycemia under in-hospital conditions has been tested (40). It has been shown to reduce the need for hypoglycemia treatment (30%) after moderate-intensity exercise. From our point of view, the major impact of this sort of advanced therapy in our study has been seen during the recovery phase after exercise as insulin infusion was stopped per protocol during exercise.

In conclusion, the present study shows that both the CLA and CLNA control systems performed well and were safe during and after exercise in adults with T1D performing heavy aerobic exercise compared with the OL insulin delivery. The system was able to maintain tight glucose control reducing the risk of hypoglycemia despite the reduced amount of carbohydrate intake. Finally, longer term outpatient studies are still required to further assess the efficacy and safety of the SAFE-AP system in free-living conditions in a larger group of patients.

Acknowledgments

Financial Support: This work has been partially funded by the Spanish Government under grants DPI2016-78831-C2-1-R, DPI2016-78831-C2-2-R, and FPU0244 2015; by the EU through FEDER funds; by the National Counsel of Technological and Scientific Development, CNPq—Brazil 207688/2014-1; and by the Government of Catalonia under 2017SGR1551. C.V. is the recipient of a grant from the Hospital Clínic i Universitari of Barcelona ("Premi Fi de Residència 2018–2019").

Author Contributions: C.V. performed and supervised all the experimental studies, analyzed and interpreted data, and wrote the manuscript. A. Beneyto conceived, designed, implemented, tested, and validated all control strategies; performed the statistical analysis; analyzed and interpreted the data; and wrote the manuscript. J.F.M.S.J developed and validated the jAP platform, the remote monitoring site, the communication between devices, and revised the manuscript. C.F.N. collaborated with the development of the CGM communication and graphical user interface, implemented a hardware-in-the-loop validation system, and revised the manuscript. A. Bertachi contributed to the development of the announced control strategy and revised the manuscript. J.B. conceived and designed the study, designed and supervised implementation of the jAP system, contributed to the development of control strategies, interpreted data, obtained funding, and critically revised the manuscript. J.V. conceived and designed the control strategies, conceived and designed the study, interpreted data, obtained funding, and critically revised the manuscript. I.C. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding, and critically revised the manuscript. M.G. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding, and critically revised the manuscript. All authors contributed to the review of the report and approved the final version for submission. I.C. and M.G are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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