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ORIGINAL ARTICLE

The PILGRIM Study: In Silico Modeling of a Predictive Low Glucose Management System and Feasibility in Youth with Type 1 Diabetes During Exercise

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Abstract

Background: Predictive low glucose management (PLGM) may help prevent hypoglycemia by stopping insulin pump delivery based on predicted sensor glucose values.

Materials and Methods: Hypoglycemic challenges were simulated using the Food and Drug Administration–accepted glucose simulator with 100 virtual patients. PLGM was then tested with a system composed of a Paradigm® insulin pump (Medtronic, Northridge, CA), an Enlite™ glucose sensor (Medtronic), and a BlackBerry® (Waterloo, ON, Canada)-based controller. Subjects ($n = 22$) on continuous subcutaneous insulin infusion (five females, 17 males; median [range] age, 15 [range, 14–20] years; median [range] diabetes duration, 7 [2–14] years; median [range] glycated hemoglobin, 8.0% [6.7–10.4%]) exercised until the PLGM system suspended insulin delivery or until the reference blood glucose value (HemoCue®; HemoCue GmbH, Großostheim, Germany) reached the predictive suspension threshold setting.

Results: PLGM reduced hypoglycemia (<70 mg/dL) in silico by 26.7% compared with no insulin suspension, as opposed to a 5.3% reduction in hypoglycemia with use of low glucose suspend (LGS). The median duration of hypoglycemia (time spent <70 mg/dL) with PLGM was significantly less than with LGS (58 min vs. 101 min, respectively; $P < 0.001$). In the clinical trial the hypoglycemic threshold during exercise was reached in 73% of the patients, and hypoglycemia was prevented in 80% of the successful experiments. The mean ($\pm$SD) sensor glucose at predictive suspension was 92 ± 7 mg/dL, resulting in a postsuspension nadir (by HemoCue) of 77 ± 22 mg/dL. The suspension lasted for 90 ± 35 (range, 30–120) min, resulting in a sensor glucose level at insulin resumption of 97 ± 19 mg/dL.

Conclusions: In silico modeling and early feasibility data demonstrate that PLGM may further reduce the severity of hypoglycemia beyond that already established for algorithms that use a threshold-based suspension.

Introduction

EXERCISE IS KNOWN TO LEAD to hypoglycemia, which is particularly frequent in youth with diabetes.[1] Hypoglycemia is challenging because it may occur when the patient is distracted, unaware, or asleep.[2,3] Hypoglycemia diminishes counterregulatory responses ("hypoglycemia begets hypoglycemia"[4]), can lead to hyperglycemia, and can contribute to glucose variability because of the release of counterregulatory hormones and overtreatment with glucose. In rare cases, severe, prolonged hypoglycemia can result in cardiac arrhythmias, neurologic sequelae, or even death.[5,6] Real-time continuous glucose monitoring offers the possibility of proactively avoiding hypoglycemic episodes through adjustable alert limits.[7–9] However, patients do not always react to the alerts.[10] Suspension of insulin in continuous subcutaneous insulin infusion (CSII) at the beginning of moderate exercise has been shown to reduce the risk of exercise-induced hypoglycemia but potentially to increase the risk for ensuing hyperglycemia.[11]

The Paradigm® VEO™ (Medtronic, Northridge, CA) is equipped with a low glucose suspend (LGS) feature that

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interrupts insulin delivery for up to 120 min.[12,13] After the LGS is triggered, if the patient fails to respond by resuming insulin delivery, insulin suspension will last for 120 min, after which insulin delivery will be automatically resumed for 4 h, even if the sensor glucose (SG) value falls below the set LGS threshold again. The goal of this algorithm with insulin delivery cycling on and off is to prevent the occurrence of diabetic ketoacidosis after LGS events.[14,15] On the way to closing the loop, triggering insulin suspension when SG is predicted to reach the hypoglycemic range could be even more effective in preventing hypoglycemia,[16–18] and resuming insulin delivery when the predicted SG level is above the hypoglycemic range may be more effective in avoiding the risk of hyperglycemia. Both features characterize the ongoing development from LGS to predictive low glucose management (PLGM). Computer simulation is capable of providing information about the safety and the limitations of feedback control algorithms, guiding clinical studies, and ruling out ineffective control scenarios in a cost-effective manner. Thus computer simulation testing ("in silico") of threshold suspend algorithms is regarded as a prerequisite to clinical trials of approaches eventually leading to closed-loop control.

To evaluate the clinical efficacy of predictive automatic suspension of insulin delivery, we used a similar study design of exercise-induced hypoglycemia among adult subjects with type 1 diabetes. The ASPIRE (Automation to Simulate Pancreatic Insulin REsponse) in-clinic study[19] was a randomized crossover study where subjects used a sensor-augmented insulin pump system with the LGS feature set to stop insulin delivery for 2 h once an SG value of ≤70 mg/dL was detected. Subjects fasted overnight and exercised until their plasma glucose value reached ≤85 mg/dL on different occasions separated by washout periods lasting 3–10 days. Exercise sessions were done with the LGS feature turned on or with continued insulin delivery regardless of the SG value. This study in adults demonstrated that automatic suspension of insulin delivery significantly reduced the duration and severity of induced hypoglycemia without causing rebound hyperglycemia.[20] In several recent studies the LGS approach has been shown to be successful in pediatric patients[21] and in patients with hypoglycemia unawareness[22] and in the large ASPIRE in-home trial[23] under outpatient conditions.

In this investigation we tested the potential benefits of the predictive algorithm under in silico conditions compared with threshold suspend and CSII without suspension, followed by the PILGRIM (PredIctive Low Glucose Management in Realtime Sensing Insulin PuMp Therapy) Study looking at the feasibility in children and adolescents—a group with particular risk for hypoglycemia—with a comparable experimental design of exercise-induced hypoglycemia as in the adult LGS ASPIRE in-clinic study.

Study Design and Methods

In silico monitoring

Hypoglycemic challenges were simulated using the Food and Drug Administration–accepted University of Virginia glucose simulator with 100 virtual patients.[24] The study consisted of three arms: Arm A, control (no pump suspension); Arm B, hypoglycemia mitigation via PLGM; and Arm C, hypoglycemia mitigation via threshold suspend (i.e.,

LGS). In order to induce hypoglycemia, the virtual patients received a manual bolus after the commencement of study. The bolus amount was patient specific (based on insulin sensitivity) and was chosen such that the blood glucose nadir was between 50 and 70 mg/dL. For both algorithms, the pump suspension threshold was set at 70 mg/dL. For PLGM, the 30-min glucose prediction was performed by a time-series forecasting approach.

Exercise induction: study population

Eligible participants were 12–21 years of age (inclusive), had been on CSII for at least 3 months prior to screening, had had type 1 diabetes for more than 12 months, had a total daily insulin requirement of 0.6–1.2 U/kg/day, and had glycated hemoglobin (HbA1c) levels of >5.8% and ≤12.0% at screening. Subjects could not participate if they had experienced an episode of severe hypoglycemia within the last 3 months prior to the experiment.

Study materials

The PLGM system was composed of a Paradigm VEO insulin pump, an Enlite™ glucose sensor connected to a MiniLink™ transmitter (all from Medtronic, Inc.), and a control algorithm installed in a BlackBerry® (Waterloo, ON, Canada) phone. The algorithm was equipped with a PLGM feature that leads to an interruption in the supply of insulin for a period of up to 120 min. During this study, a 30-min predictive horizon with sensor threshold of 70 or 80 mg/dL was used. The PLGM suspended basal insulin when SG was predicted to be at or below the threshold of 70 or 80 mg/dL in 30 min. This resulted in a fixed suspension for 30 min (Zone 1, Fig. 1). After Zone 1, basal insulin remained suspended for up to a maximal time of 90 min based on SG and predicted SG values (Zone 2). Thereafter, basal insulin was resumed for a 30-min fixed basal delivery (Zone 3). Resumption of basal insulin occurred when the SG value was above 80 mg/dL *and* predicted to be at or above in 30 min and insulin had been suspended for at least 30 min.

Study design

This was a single-center trial (Kinder- und Jugendkrankenhaus Auf der Bult, Diabetes-Zentrum für Kinder und Jugendliche, Hannover, Germany). The protocol, protocol amendment, consent form, and subject information sheet were reviewed and approved by appropriate authorities according to local regulations and by an appropriately constituted review board prior to trial initiation. This study was performed in accordance with the Declaration of Helsinki and its amendments and with Good Clinical Practice, as defined by the current International Conference on Harmonisation, at trial initiation. All subjects (and their legal guardians for children and adolescents) were informed of the risks and benefits of the trial and that they could withdraw from the trial at any time, for any reason. Consent was obtained in writing before any trial-related activities, and the investigator retained the consent forms.

All subjects were instructed to abstain from rigorous physical activity (e.g., gym activity, swimming, or running) in the 24-h interval prior to the hypoglycemia induction. The patients were admitted on the night before and placed on an
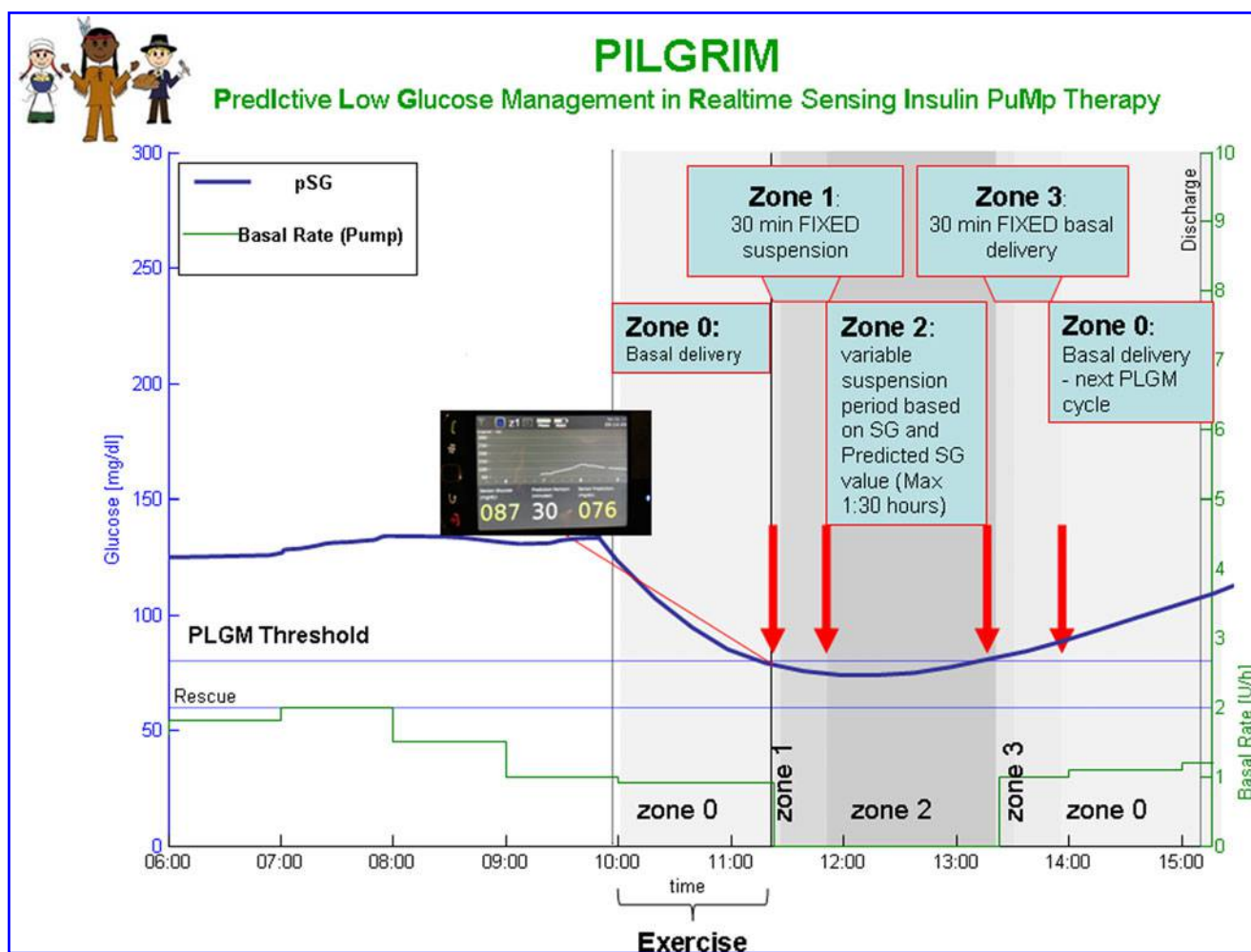
FIG. 1. Schematic overview of the experimental setup in the PILGRIM Study. PLGM, predictive low glucose management; pSG, pump sensor glucose; SG, sensor glucose. (Color graphics available online at www.liebertonline.com/dia)

Enlite sensor and a Paradigm VEO Pump. The prestudy pump was removed prior to intravenous glucose administration. A variable overnight intravenous infusion of human insulin (0.5 unit/kg of body weight in 48 mL of 0.9% NaCl; Actrapid®; Novo Nordisk, Bagsværd, Denmark) by an infusion pump (Pilot A2, RS 232 DIN; Fresenius Kabi AG, Bad Homburg, Germany) was started after dinner to stabilize the fasting glucose level at 110 mg/dL (i.e., stable between 90 and 140 mg/dL for at least an hour prior to the beginning of the experiment). The overnight fluid infusion rate (half isotonic glucose solution if the blood glucose level is below 300 mg/dL; if above, normal saline [0.9% NaCl] at 60–80 mL/kg kg/24 h and an insulin dosing scheme for glucose above 200 mg/dL of 0.1 IU/kg of body weight/h, for 150–200 mg/dL of 0.05 IU/kg of body weight/h, for 100–150 mg/dL of 0.025 IU/kg of body weight/h, and below 100 mg/dL of no insulin) depended on capillary blood glucose levels.[25]

One sensor calibration was performed during the night and one calibration before exercise onset. The aggregate mean absolute relative difference for these Day 1 sensors was 15.87%. After 10 p.m. no subcutaneous insulin bolus was given until the conclusion of the study. The study pump was programmed according to preprogrammed personal settings without adjustment. Study pump insulin delivery was started

1 h prior to the planned onset of the exercise. After a stable fasting blood glucose level was reached, the intravenous glucose/insulin was stopped in the morning between 6:00 and 10:00 a.m. Patients were placed on an exercise ergometer for a maximum time of 4.5 h or until the reference blood glucose, checked at least every 15 min (HemoCue®; HemoCue GmbH, Großostheim, Germany),[26] reached 80 mg/dL. Under specific circumstances, the exercise session was continued even if the HemoCue blood glucose value reached < 80 mg/dL when the subject had no symptoms and the ''upward trend arrows'' appeared in the display of the insulin pump, indicating the glucose level was increasing. The exercise session consisted of up to six cycles of exercise, lasting between 15 to 30 min each, on a stationary bike or treadmill. Each cycle was followed by a rest period of between 5 to 15 min. Subjects were encouraged to consume fluid in order to remain hydrated. The target was to achieve a decline in HemoCue blood glucose of 0.5–1.0 mg/dL/min. This was followed by an observation period while fasting until one of the following occurred: (1) the subject required a glucose rescue (symptoms or HemoCue blood glucose level of <40 mg/dL), (2) resumption of the suspended insulin infusion occurred after successful PLGM triggering (Zone 3), or (3) the maximum observation time of 4.5 h was reached. If the subject was

unable to reach the target range of <80 mg/dL during exercise, then the subject could repeat the experiment after at least a 14-day interval or conclude the study.

Results

The results of the in silico modeling are provided in Figure 2 and Table 1. The glucose profiles and the statistics are based on the intravenous glucose values. Figure 2A shows the time-series plot of hypoglycemic challenge for the control (i.e., no suspension), PLGM, and VEO arms of the study, indicating

the potential significant improvement of the PLGM over the VEO algorithm. Figure 2B represents the cumulative distributions of the duration of hypoglycemia, measured as time spent (in minutes) by the reference glucose level being <70 mg/dL. Using PLGM compared with LGS, the median duration of hypoglycemia was significantly less (58 vs. 101 min; $P < 0.001$), indicating the potential clinical benefit of the new technology. Only 13.4% of the simulations had a duration of hypoglycemia of <60 min for the VEO arm, as opposed to 44.9% of the simulations for PLGM. Table 1 shows the total reduction in hypoglycemia (intravenous glucose level
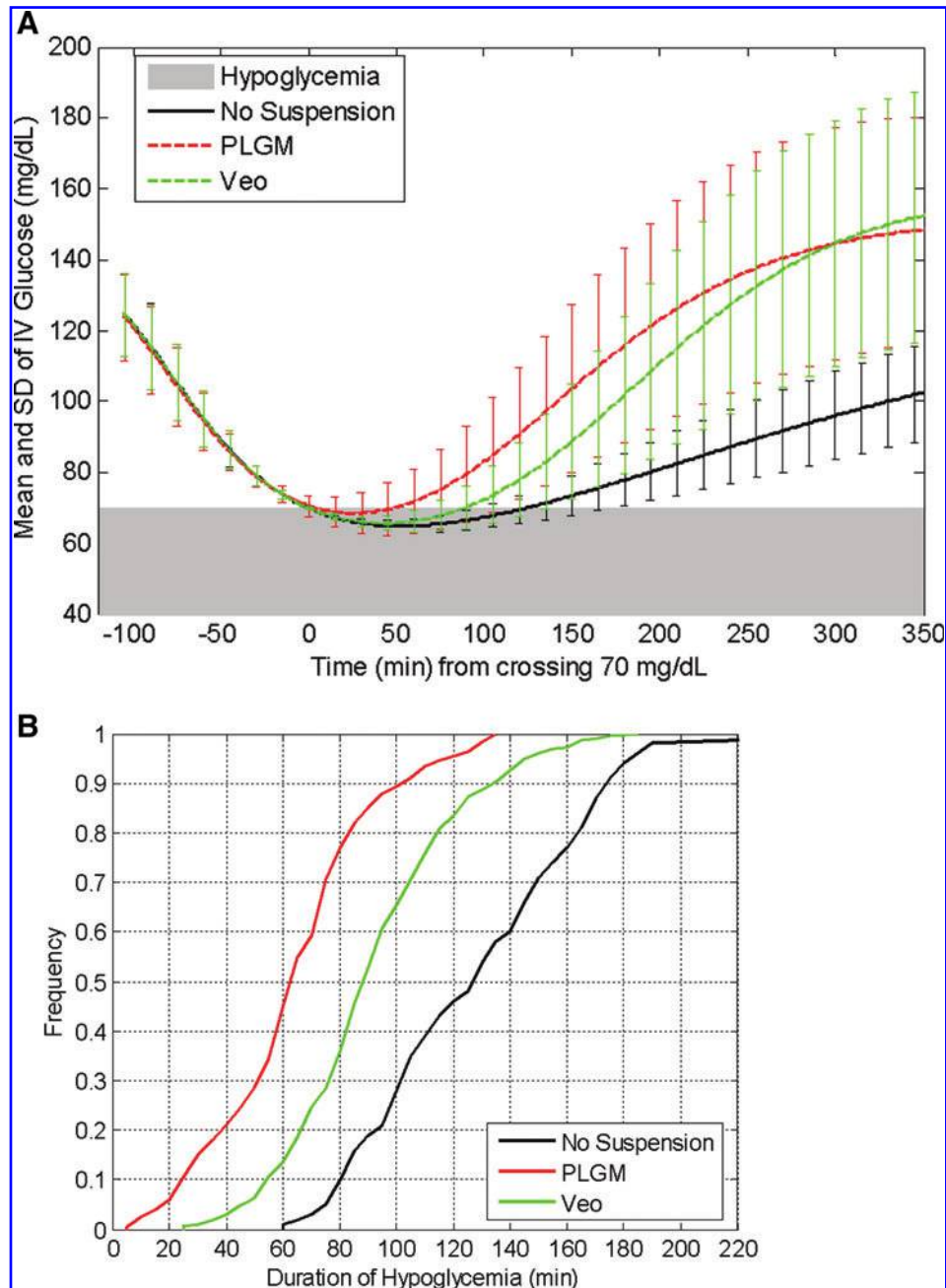
FIG. 2. The glucose profiles and the statistics are based on the intravenous (IV) glucose values in the in silico modeling. **(A)** The time-series plot of hypoglycemic challenge for the control (i.e., no suspension), predictive low glucose management (PLGM), and VEO arms of the study. The mean (continuous traces) and SDs (vertical bars) are plotted for each study arm. **(B)** The cumulative distributions of the duration of hypoglycemia, measured as time (in min) spent by the reference glucose level below 70 mg/dL. (Color graphics available online at www.liebertonline.com/dia)

TABLE 1. ALGORITHM PERFORMANCE ANALYSIS BASED ON THE RESULTS OF THE IN SILICO MONITORING

Arm	Total number of hypo events	Avg hypo duration (min)	Avg AUC <70 mg/dL (min×mg/dL)	Avg minimum glucose (mg/dL)	Avg glucose value at suspension (mg/dL)	Avg glucose value at resumption (mg/dL)	Avg suspension time (min)	Avg Max glucose after resumption (mg/dL)	Time gain in early hypo detection (min)	Number of suspensions per admission
Control	300	130.4	494.7	65						0.0
PLGM	245	65.7	189.9	68	83	80	115.1	150	45	1.1
VEO	297	93.7	338.6	65	69	86	120.0	160	0	1.0

Calculations are based on University of Virginia data analysis of 100 adult subjects, each admitted three times for 20 h.
AUC, area under the curve; Avg, average; Hypo, hypoglycemia; Max, maximum; PLGM, predictive low glucose management.

<70 mg/dL) in silico as being 18.3% less (245 vs. 300 events) by the PLGM versus the standard CSII algorithm.

In the clinical study, subjects ($n = 22$) on CSII (five females, 17 males; median [range] age, 15 [14–20] years; median [range] diabetes duration, 7 [2–14] years; median [range] HbA1c, 8.0% [6.7–10.4%]) exercised until the PLGM system suspended insulin delivery or until the reference (HemoCue) blood glucose value reached the predictive suspension threshold setting. There were in total 22 experiments. There were no device-related adverse events.

Six experiments were not evaluated because the hypoglycemic threshold during exercise was not reached (i.e., the HemoCue blood glucose did not reach 70–80 mg/dL). Thus, results below are provided for the 16 experiments when PLGM was triggered or the hypoglycemic threshold was reached (Table 2). The PLGM threshold was set at 70 mg/dL for two of 16 experiments when hypoglycemia occurred because of rapidly falling glucose levels during exercise. Subsequently, the PLGM threshold was set at 80 mg/dL for the remaining experiments (14 of the 16 experiments with successful hypoglycemia induction). Of the 15 successful experiments where PLGM was triggered, hypoglycemia was prevented in 12 experiments. The mean (±SD) SG level at predictive suspension was 92 ± 7 mg/dL, resulting in a postsuspension nadir (by HemoCue) of 77 ± 22 mg/dL. The suspension lasted for 90 ± 35 (range, 30–120) min, resulting in an SG level at insulin resumption of 97 ± 19 mg/dL. The average reference glucose, actual SG, and predicted SG curves are shown in Figure 3.

Discussion

The effect of PLGM in young patients of the PILGRIM study confirms the estimations in virtual patients done by in silico modeling. It provides evidence for reducing the risk for hypoglycemia with PLGM using a novel portable platform (BlackBerry) without compromising the safety of CSII therapy in youth with type 1 diabetes. The PLGM system prevented hypoglycemia by suspending insulin approximately 30 min before a predicted hypoglycemic event. As predicted by the in silico modeling, the PLGM suspended 12 mg/dL above the preset threshold, compared with the full 2-h suspension of the current LGS system with a threshold setting at an SG value of 70 mg/dL.[21] Also, the PLGM prevented low glucose values with an average suspension time of 30 min less than the VEO, without manual intervention. Overall, the SG level at pump resumption was 5 mg/dL higher than at the time when insulin infusion was suspended. Moreover, hypoglycemia was prevented in all but three cases under the demanding conditions of vigorous exercise. (Two cases were under suboptimal experimental conditions.) Hence, PLGM is likely to represent the next widely available step in the development of the artificial pancreas. Automated insulin delivery is currently moving from the regulated research setting to the outpatient environment for overnight closed-loop control.[27,28] Breton et al.[29] reported on an in-clinic randomized crossover trial in adults and adolescents preventing hypoglycemia during and after exercise with closed-loop control. However, unannounced exercise and excessive prandial boluses still pose challenges to full 24-h closed-loop insulin delivery.[30,31] Thus the currently available LGS strategy[23] may soon be replaced by a predictive low suspend system during the day and an overnight closed loop for the night. This may be

TABLE 2. GLYCEMIC PARAMETERS USING THE INSULIN PUMP WITH PREDICTIVE LOW GLUCOSE MANAGEMENT DURING HYPOGLYCEMIA INDUCTION WITH EXERCISE

Number	Suspension threshold (mg/dL)	Did pump suspend?	Was hypo (<63 mg/dL) prevented?	Glucose at suspend SG (mg/dL)	Glucose nadir postsuspension. (HemoCue) (mg/dL)	Suspension time (min)	Glucose at insulin resumption SG (mg/dL)	Carbs/food during pump suspension	AUC based on HemoCue (min×mg/dL)		Time spent in hypo based on HemoCue (min)	
									<63 mg/dL	<70 mg/dL	<63 mg/dL	<70 mg/dL
1	70	Yes	No	102	59	30	115	12 g of glucose	28.8	128.8	11	18
2	80	Yes	Yes	89	106	45	119	—	0	0	0	0
3	70	No	NA	NA	NA	NA	NA	NA	N/A	NA	NA	NA
4	80	Yes	Yes	90	71	120	96	—	0	0	0	0
5	80	Yes	No	86	56	110	73	"1 carbunit"	114.6	336.2	21	44
6	80	Yes	Yes	92	71	120	93	—	0	0	0	0
7	80	Yes	Yes	99	134	30	115	—	0	0	0	0
8	80	Yes	Yes	88	64	120	92	—	0	129.3	0	47
9	80	Yes	Yes	83	63	65	103	—	0	158.1	0	29
10	80	Yes	Yes	85	91	80	117	—	0	0	0	0
11	80	Yes	Yes	98	65	120	90	—	0	195	0	85
12	80	Yes	Yes	95	87	80	107	—	0	0	0	0
13	80	Yes	Yes	92	92	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]
14	80	No	No	95	58[b]	120	89	—	133.6	592	56	76
15	80	Yes	Yes	84	73	105	103	—	0	0	0	0
16	80	Yes	Yes	106	63	120	52	—	0	171	0	32

[a]The translator was not functioning properly, and the experiment was stopped after the insulin suspension.
[b]In error the pump basal rate was manually resumed.
AUC, area under the curve; Carbs, carbohydrates; hypo, hypoglycemia; NA, not available; SG, sensor glucose.
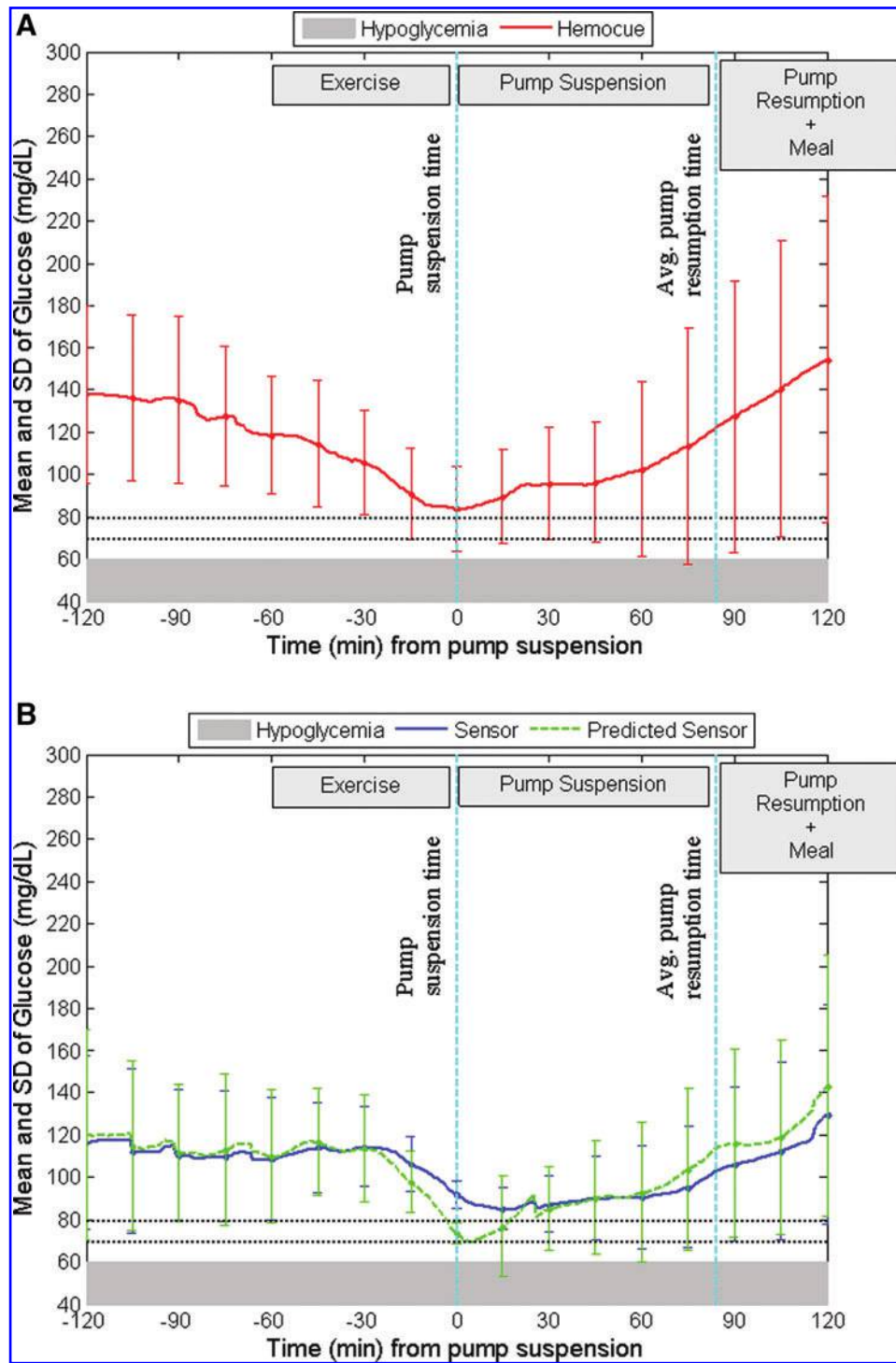
FIG. 3. **(A)** Average (Avg.) (±SD) reference glucose curves for the successful experiments as determined with the HemoCue and **(B)** average sensor (solid line) and predicted sensor (dashed line) curves. After pump resumption patients were allowed to eat. Thus, the blood glucose level rise after reflects carbohydrate intake and does not reflect any effect of insulin resumption. PLGM, predictive low glucose management. (Color graphics available online at www.liebertonline.com/dia)

the beginning of the paradigm shift when minute-to-minute insulin delivery transfers the variability from glucose to insulin until a fully closed-loop artificial pancreas is feasible.

Severe hypoglycemia has been labeled as the rate-limiting step in achieving optimal metabolic control. Children with type 1 diabetes are particularly prone to hypoglycemia,[32] which leads to significant parental anxiety adding complexity to this issue.[33] Thus, sensor-augmented pump therapy with PLGM may offer a new therapeutic option with potential long-lasting consequences for youth with diabetes who are

known to have unplanned physical exercise with varying intensity from one day to another. In-depth analysis of the ASPIRE in-home trial has shown that threshold suspend is particularly successful in preventing the ''second hypoglycemia'' following an initial low glucose value (see in particular the author response).[34] This lead to an overall reduction of the mean area under the curve for nocturnal hypoglycemic events of 38%. The period following vigorous exercise is typically high risk for hypoglycemia because of the heightened insulin sensitivity, even if it does not occur during the exercise (e.g., because of a counterregulatory response). This was not observed in our study as the PILGRIM participants had large meals after the prolonged fasting during the study period. Nevertheless, the real power of PLGM could be in the prevention of hypoglycemia overnight following vigorous physical activity.

The study has apparent limitations, particularly regarding the lack of a control group in the clinical study. Also, the study did not successfully induce hypoglycemia in all subjects. Similar results were reported in the adult ASPIRE in-clinic study[20] with a comparable experimental design: 50 subjects attempted 134 sessions, 98 of which were successful. This failure in inducing hypoglycemia with exercise in a little more than a quarter of cases was exactly what was observed in the present pediatric study. In contrast to the adults, all but one pediatric subject was willing to repeat this very demanding experimental design. Additionally, it was not feasible to do control experiments with the LGS algorithm only or in CSII without any preventive hypoglycemia management. However, this lack of a control condition may be offset as the clinical PILGRIM results agree nicely with the expected results from the in silico modeling. Another limitation in both the PILGRIM and the ASPIRE in-clinic studies is the lack of any follow-up regarding late hypoglycemia following the vigorous exercise. Based on the modeling data, PLGM may lead to significant reductions in hypoglycemia events compared with standard CSII (18.3% fewer hypoglycemia events) or current threshold suspend (17.5% fewer hypoglycemia events). Thus, our findings are in agreement with the accumulating evidence[15,21,29] that such sensor-based predictive insulin adaptation is feasible and represents a clear improvement over current sensor-augmented approaches.

The mean end-observation reference glucose in the PILGRIM trial of 77 ± 22 mg/dL compared favorably with the value in the adult ASPIRE in-clinic trial.[20] Because of the fixed length of the 120-min suspension during LGS-On compared with LGS-Off sessions in the ASPIRE in-clinic study, the mean end-observation reference glucose was considerably higher (91.4 ± 41.84 vs. 66.2 ± 13.48 mg/dL) than with PLGM. Thus, with the new algorithm incorporating flexible insulin resumption, rebound hyperglycemia is less likely to be a consequence of PLGM in everyday use.

The advantages of an earlier and potentially shorter insulin suspension will now have to be tested under routine outpatient conditions. In our previous outpatient trial with the LGS system,[21] the LGS-On threshold was set at 70 mg/dL, allowing for a reduction in time spent and number of episodes of <70 mg/dL without a concomitant rise in hyperglycemia. In the present study, we changed to a higher PLGM threshold of 80 mg/dL (4.4 mmol/L) after the first set of experiments because the vigorous exercise starting from a normoglycemic range in a fasting state early in the morning led to rapidly

falling glucose values with insulin suspension happening too late. As changes in insulin sensitivity are known to differ widely both between individuals as well as within an individual on different occasions,[35] the setting of the PLGM threshold may have to be individualized. Nevertheless, the time lag between interstitial and blood glucose is known to be influenced by rapid changes of blood glucose[36,37]; thus the safety level should be a little higher when exercise is planned. The PLGM setting at 80 mg/dL with a 30-min predictive horizon resulted in successful hypoglycemia prevention in nearly all of the successful experiments. The fact that no reactive negative effects on glycemia occurred at the end of suspension emphasizes the safety and feasibility of this approach.

Acknowledgments

Author Disclosure Statement

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