Real-Time Hypoglycemia Prediction Suite Using Continuous Glucose Monitoring

A safety net for the artificial pancreas

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OBJECTIVE — The purpose of this study was to develop an advanced algorithm that detects pending hypoglycemia and then suspends basal insulin delivery. This approach can provide a solution to the problem of nocturnal hypoglycemia, a major concern of patients with diabetes.

RESEARCH DESIGN AND METHODS — This real-time hypoglycemia prediction algorithm (HPA) combines five individual algorithms, all based on continuous glucose monitoring 1-min data. A predictive alarm is issued by a voting algorithm when a hypoglycemic event is predicted to occur in the next 35 min. The HPA system was developed using data derived from 21 Navigator studies that assessed Navigator function over 24 h in children with type 1 diabetes. We confirmed the function of the HPA using a separate dataset from 22 admissions of type 1 diabetic subjects. During these admissions, hypoglycemia was induced by gradual increases in the basal insulin infusion rate up to 180% from the subject's own baseline infusion rate.

RESULTS — Using a prediction horizon of 35 min, a glucose threshold of 80 mg/dl, and a voting threshold of three of five algorithms to predict hypoglycemia (defined as a FreeStyle plasma glucose readings <60 mg/dl), the HPA predicted 91% of the hypoglycemic events. When four of five algorithms were required to be positive, then 82% of the events were predicted.

CONCLUSIONS — The HPA will enable automated insulin-pump suspension in response to a pending event that has been detected prior to severe immediate complications.

Diabetes Care 33:1249–1254, 2010

The Diabetes Control and Complications Trial (DCCT) proved that glucose control in the closer-to-normal range (tight glycemic control) reduced the likelihood of eye, kidney, nerve, and cardiovascular complications of diabetes (1,2). Unfortunately, the DCCT also showed that the incidence of severe hypoglycemia was three times higher in the intensively treated group compared with the standard treatment group (1). In the DCCT, 55% of the severe lows occurred during sleep hours (1). Further, in the adolescent portion of the DCCT, the risk for severe hypoglycemia was even greater, with one episode every 1.17 years (85.7 per 100 patient-years) (2). One report in children found 75% of severe lows to occur during the nighttime hours (3). The high frequency and duration of nocturnal hypoglycemia has been confirmed in clinical research center (CRC) studies, in which frequent laboratory reference glucose values were obtained. For example, in a DirecNet study of exercise-induced nocturnal hypoglycemia, children who did not exercise had a 28% incidence of nocturnal hypoglycemia (glucose <60 mg/dl), and those who exercised had a 48% incidence of nocturnal hypoglycemia (4). In a recent study (5) of bedtime snacks and nocturnal hypoglycemia, on nights when adult subjects did not have a snack, 57% became hypoglycemic (<70 mg/dl), with an average duration of hypoglycemia of over 2.5 h. In this study, the duration of hypoglycemia was as long as 8.75 h.

Real-time continuous glucose monitoring (CGM) is becoming available with the Food and Drug Administration (FDA) approval of the MiniMed Guardian, the DexCom STS, and the Abbott Navigator. One of the major perceived benefits of real-time glucose monitoring is the ability of these devices to have alarms for hypoglycemia. For a real-time alarm to be effective, it must awaken a sleeping subject. The first FDA-approved real-time glucose monitor was the GlucoWatch™. To determine whether the alarm function on the GlucoWatch was effective in awakening children while they were sleeping, an infrared camera was used to videotape them throughout the night in the CRCs. During this admission, reference glucose values were obtained every half hour to document hypoglycemia. In this study, 71% of youths wearing the watch did not respond to nighttime alarms (6), placing these patients at a risk for nocturnal hypoglycemia despite wearing a real-time continuous glucose sensor. One possible correction of this problem would be to have the sensor send a signal to the pump so that it will stop infusing insulin when pending or real hypoglycemia has been reached and the patient has not responded to alarms. This is the primary focus of the hypoglycemia prediction algorithm.

Previous studies (7–9) have shown that when insulin infusion is stopped for 2 h or when an infusion set is disconnected for up to 30 min (7), there is essentially no risk of the patient developing significant ketones or acidosis. Three previous studies (8–10) have demonstrated that turning off an insulin pump for 2 h

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Received 10 August 2009 and accepted 18 January 2010. DOI: 10.2337/dc09-1487.

did not result in diabetic ketoacidosis (DKA). In all three studies, blood β-hydroxybutyrate concentrations were determined using both a meter (Precision Xtra™) and the hospital laboratory. In two of the studies (9,10), the continuous subcutaneous insulin infusion pumps were purposely turned off for periods of 4 and 5 h, with a gradual increase in β-hydroxybutyratek concentrations after 2 h to the upper normal range. No cases of DKA occurred in these studies.

RESEARCH DESIGN AND METHODS

The hypoglycemia prediction algorithm (HPA) was developed using data derived from 21 Navigator studies, which assessed Navigator function over 24 h in children with type 1 diabetes, aged 3–18 years, conducted in clinical research centers (CRCs) (11). Then the HPA functionality was confirmed using a separate dataset from 22 CRC admissions of type 1 diabetic subjects with a mean age of 20 years (range 6–38). In this study, hypoglycemia was induced by gradual increases in the basal insulin infusion rate by a mean of 180%, 18 of 22 subjects (82%) reached a glucose value of ≤60 mg/dl (12,13). Promising results were reported by Buckingham et al. (12), where when two different algorithms were used 60% of the pending hypoglycemic events were predicted and prevented.

CGM data were introduced to the HPA as if it were a real-time measurement; the different algorithms analyzed the data and an alarm was produced if a quorum was reached by the voting algorithm. Three hypoglycemia thresholds of 70, 80, and 90 mg/dl were evaluated, each with three different prediction horizons (*V*) of 35, 45, and 55 min and with three voting thresholds of 3, 4, and 5.

Hypoglycemia Prediction Algorithm

The core of the HPA is a set of individual alarms that are combined through a voting system into one combined alarm. With each new CGM datum, each individual alarm will run independently and will indicate hypoglycemia or euglycemia. Then, if the number of individual alarms that have gone off in the last 10 min is above a preset voting threshold (*V*), the voting alarm will trigger. A low voting threshold will generate more alarms, giving more warning but less accuracy. Finally, the combined alarm will trigger if either the voting alarm or the threshold alarm goes off. Figure 1 shows the flow of the combined hypoglycemic detection algorithm (14). Glucose predictions and analysis from CGM data can be performed in more than one way by applying different mathematical methods such as optimal estimation techniques (15,16), time series (17), and other methods. The HPA system consists of five prediction algorithms:

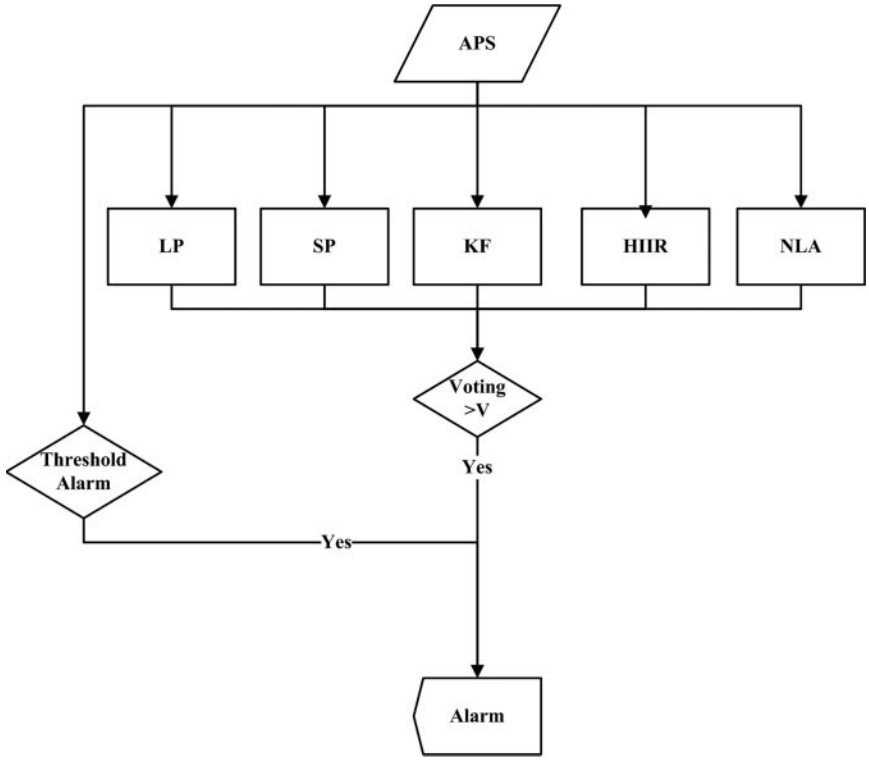

Figure 1—*Hypoglycemia alarm flowchart. The overall alarming algorithm combines multiple independent alarms into one single alarm using a voting system, where APS is the artificial Pancreas Software (24) feeding the data to the algorithms, LP is the linear prediction algorithm, SP is statistical prediction algorithm, KF is the Kalman filter algorithm, HIIR is the hybrid impulse response filter, and NLA is the numerical logical algorithm.*

1. Linear projection: This alarm uses a 15-min linear extrapolation and uncertainty threshold based on the SD of the glucose measurements in the previous 15 min.
2. Kalman filtering: A Kalman filter is used to estimate glucose and its rate of change, which are then used to make predictions about future glucose levels. The filter is tuned to trade off the probability that a measured glucose change is real versus the result of sensor noise. The approach is presented in more detail in simulation studies by Palerm et al. (16) and applied to clinical hypoglycemic clamp data in Palerm and Bequette (18) and as part of a meal detection algorithm in Dassau et al. (19).
3. Hybrid infinite impulse response filter: The infinite impulse response filter takes advantage of a linear discrete-time signal-processing method (20) that generates output predictions using previous output (measured glucose concentration) without input (insulin infusion). Predicted outputs are recursively applied to the filter coefficients for a prediction horizon. The filter coefficients are updated when prediction and parameter errors are larger than user-specified bounds. The hybrid filter prediction with a factor (α) between fixed and adaptive filter coefficients is considered for safe and accurate glucose predictions. It is flexible to tune the filter performance by adjusting the data window length (WL), prediction horizon (*p*), and error criteria (ε_1 and ε_2).
4. Statistical prediction: Multiple empirical, statistical models are used to estimate future blood glucose values and their error bounds. From these, a probability of hypoglycemia is generated and thresholded to produce an alarm. The statistical prediction algorithm is divided into three compo-

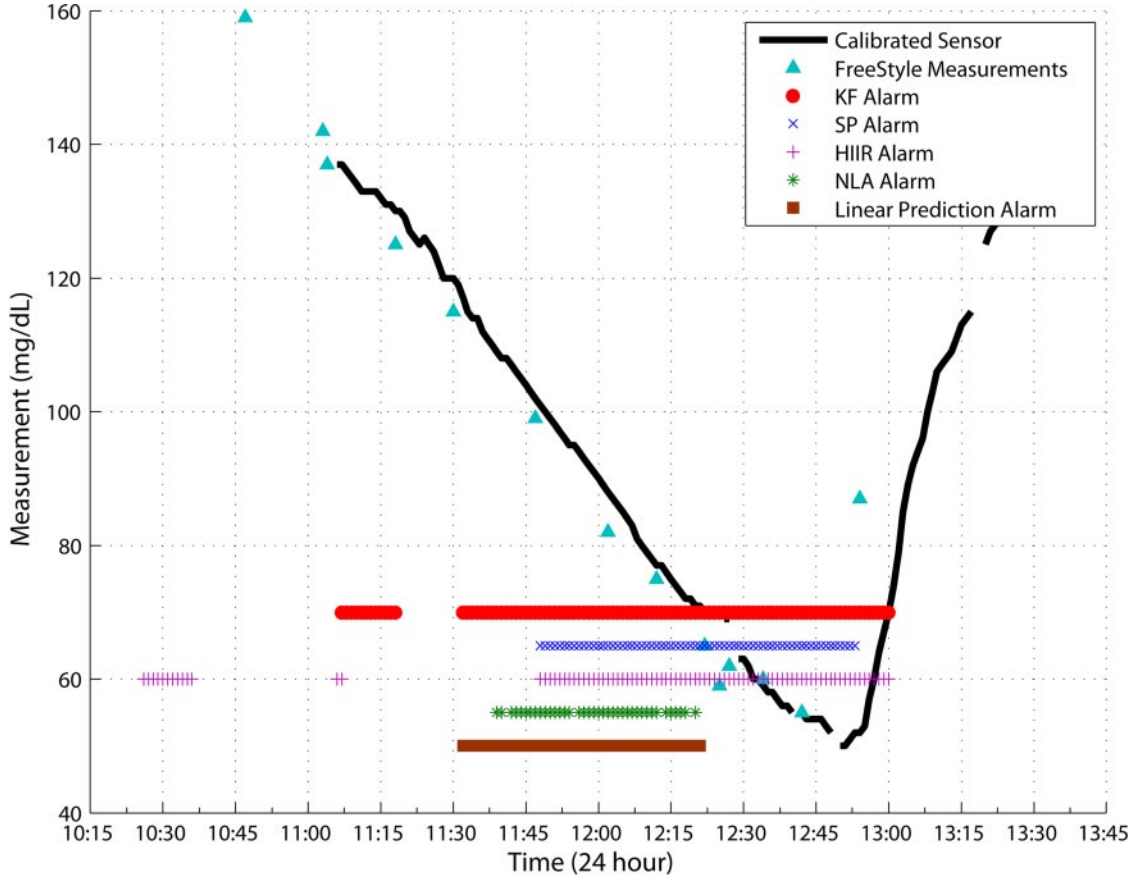

Figure 2—*An example hypoglycemic event and successful detection using an alarm threshold of 70 mg/dl and a prediction horizon of 55 min. A high-quality digital representation of this figure is available in the online issue.*

nents: *1*) calibration, which converts raw CGM and capillary blood glucose measurements into a physiologically consistent, accurate blood glucose history; *2*) prediction, which uses training data and the recent calibrated blood glucose history to generate predictions and associated accuracy estimates; and *3*) hypoglycemic alarming, which transforms the predictions and accuracy estimates into a probability of the patient becoming hypoglycemic, which is then thresholded into a binary alarm (12,21).

5. Numerical logical algorithm: Numerical logical algorithm feeds a three-point calculated rate of change using backward difference approximation and the current glucose value into logical expressions to detect impending hypoglycemia. The logical expressions verify that the rate of change is both negative and within an acceptable range as well as that the CGM glucose values are within predefined boundaries and that a pending hypoglycemic event is predicted within the threshold time window. Numerical logical algorithm provides insensitivity to sensor signal dropouts and easy tuning.

Voting system

The voting system, as described in Fig. 1, polls each algorithm to determine whether it should alarm. If the number of algorithms that predict hypoglycemia is above the voting threshold (*V*) more than twice in a time window of 10 min (first crossing will prime the alarm and the second will fire the alarm) or the sensor blood glucose is below the hypoglycemic threshold, then the alarm sounds. Therefore, an alarm sounds if one of the following is true:

- The number of individual alarms meets or exceeds the voting threshold;
- The sensor interstitial glucose value is below the hypoglycemic threshold.

RESULTS — The five hypoglycemic prediction alarms were run for all proposed parameter combinations on 18 sets of data from 18 admissions. It should be noted that the reported results are based solely on the predictive part of the method.

As can be seen from Fig. 2, hypoglycemia was reached at around noon (defined as glucose ≤70 mg/dl). This event has been predicted by the different algorithms 55, 45, and 35 min ahead of the event, and an alarm could have been issued at this time depending on the quorum threshold (e.g., 55-min warning time if two different algorithms were to issue a positive vote twice in a 10 min window). If the number of positive alarms required was three or four, a warning time would have been 40 and 35 min, respectively, sufficient time for a suspension of the pump to have prevented the event.

Table 1 shows the results from running the individual and combined algorithms against the historical pump shutoff data. The numbered columns (e.g., 1, 2, 3, 4, and 5) indicate the voting threshold for the case. The data also show that the prediction rate declines as the voting threshold increases. This can be seen in the range of prediction times obtained by varying the settings of the tuning param-

Table 1—*HPA ability to predict hypoglycemia events based on historical datasets with different voting thresholds*

Prediction horizon (min)	Alarm threshold (mg/dl)	Percent predicted hypoglycemic events for the given alarm scenario									
		1	2	3	4	5	KF	SP	HIIR	NLA	LP
35	70	91	64	55	36	18	82	55	45	91	55
45	70	100	82	73	64	36	100	64	64	91	73
55	70	100	100	100	82	36	100	100	82	91	100
35	80	100	100	91	82	45	100	100	82	91	82
45	80	100	100	100	91	64	100	100	91	91	91
55	80	100	100	100	100	82	100	100	100	91	91
35	90	100	100	82	73	55	100	100	91	64	73
45	90	100	100	82	82	55	100	100	100	64	73
55	90	100	100	82	82	55	100	100	100	64	73

LP, linear prediction algorithm; KF, Kalman filter algorithm; HIIR, hybrid impulse response filter; NLA, numerical logical algorithm; SP, statistical prediction algorithm.

eters, namely, hypoglycemia prediction time, hypoglycemia threshold value, and the voting threshold. As an example, 91% of the events were predicted 35 min prior to the event using a voting threshold of three, where voting of four of five predicted 82% of the events 35–55 min ahead with glucose threshold of 80 mg/dl. However, in theory, a higher success rate could be obtained by allowing any one of five to issue an alarm. This balance between aggressiveness of the HPA and effectiveness is an important factor since too many false alarms are a detriment to safety systems will result in disconnecting of the system by the user, rendering the system useless. HPA tuning knobs (prediction horizon, alarm threshold, and voting threshold, as seen in Table 1) allows the algorithm to be adjusted to meet the subject preferences as far as defining the hypoglycemia threshold, time to alarm prior to the event, and aggressiveness of the algorithm. These settings could vary between day and night and be tuned to meet individual insulin sensitivity, allowing the user to enhance specificity that would prevent false alarms resulting in pump suspension, where during the day a more aggressive tuning can be set that can alert the user to take corrective action prior to the need to suspend the pump. The use of a CGM in clinical decision making is the first step toward the artificial pancreas. The prevention of nocturnal hypoglycemia based on glucose predictions as well as missed-meal alarms will reduce glucose variability and clinical complications resulting from extreme blood glucose concentrations. CGM technology, together with telemedicine applications such as E911 (22), can provide remote glucose monitoring and triangulation as well as pump suspension. This technology will help in improving the well-being of people with diabetes and peace of mind to families of children with diabetes.

When a safety algorithm is suggested, the false-positive rate is equally as important as the true-positive rate. The evaluation of the true positive has been addressed based on retrospective analysis of clinical data. The specificity of the algorithm was further evaluated

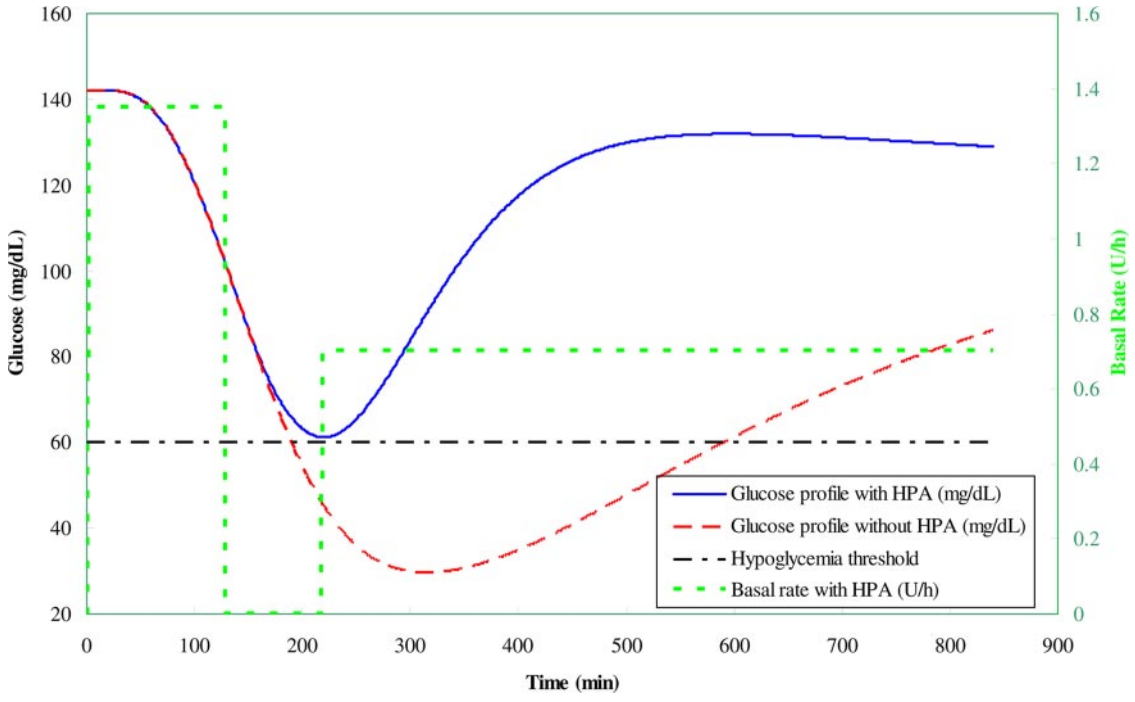

Figure 3—*HPA evaluation using the UVa/Padova Metabolic Simulator following a clinical scenario in which an erroneous basal delivery, twice the usual one, was set by the user. As can be seen in the plot, without the use of HPA the subject experienced severe hypoglycemia (red dashed line) and with the algorithm this event was prevented (blue line) by suspending the basal rate for 90 min and restoring the correct basal (green dotted line). The black dashed-dotted line denotes the hypoglycemia threshold as defined by blood glucose. A high-quality digital representation of this figure is available in the online issue.*

prospectively using the UVa/Padova FDA-accepted (23) Metabolic Simulator and is currently under clinical evaluation that will be reported in a subsequent publication. The frequency of false-positive alarms of the HPA has been assessed by running the simulator under standard conditions with a meal at 5:00 P.M., starting the hypoglycemia prediction algorithms at 9:00 P.M. and running it until 7:00 A.M. the following morning before a breakfast meal. Furthermore, the HPA was evaluated overnight using twice the usual basal insulin in order to induce hypoglycemia. The prospective analysis of the algorithm with tuning of 80 mg/dl, 45 min, and two for hypoglycemia threshold, prediction horizon and voting threshold, respectively, is provided below. This simulation supported the clinical results with only four in silico subjects crossing the 60 mg/dl blood glucose threshold out of 100 in silico adult subjects, where the glucose nadir is marginally <60 mg/dl. As can be seen from Fig. 3, the HPA predicted a pending hypoglycemic event when glucose concentration was ~104 mg/dl and suspended the pump for 90 min. This resulted in prevention of the event where, in successive simulation without the use of the algorithm, the glucose dropped to extremely low values. The false-positive rate of the algorithm with the same tuning was 9% based on a population of 100 different in silico subjects and noisy sensor. However, only three out of the nine cases where a false alarm was issued resulted in a glucose elevation of >20 mg/dl from the baseline that resulted in hyperglycemic event. It should be noted that this needs to be further evaluated by extensive clinical trials to better assess the algorithm.

The use of a sophisticated voting algorithm allows an extra degree of safety prior to issuing an alarm. In addition, voting enables the use of five different individual algorithms to predict pending hypoglycemia and not to rely on one algorithm that may or may not be the most suitable to address the variability among type 1 diabetic subjects. Furthermore, the use of a suite of algorithms allows a more robust system that can cope with glucose variability and the different glucose drop patterns that may affect rate of change and the ability to detect a pending event by a single algorithm.

CONCLUSIONS — The use of the HPA would allow for triggering of a warning alarm and/or suspension of an insulin pump, which should decrease the risk of severe hypoglycemia. Based on clinical evaluation, insulin delivery will most likely need to be suspended 30–50 min before a projected hypoglycemic event in order to prevent most hypoglycemic events (12). On one hand, longer prediction time may provide greater ability to prevent hypoglycemia events; on the other hand, it may be impractical to suspend a pump too far from an event that may not happen due to human factors (e.g., a planned meal). The Hypoglycemia Prediction Algorithm (HPA) tuning allows flexibility in the aggressiveness of the alarm and can be set to meet user preferences. Furthermore, this technology can be easily implemented in current CGM systems and as a safety net to further artificial pancreas development.

Acknowledgments — We acknowledge the Juvenile Diabetes Research Foundation (grants 22-2006-1115, 22-2006-1108, and 22-2007-479) and the Otis Williams Fund at the Santa Barbara Foundation for their financial support.

H.P.C. has received supplies/devices for research purposes from Abbott Diabetes Care. B.A.B. was given honorarium from Abbott Diabetes Care for a lecture in February 2009. No other potential conflicts of interest relevant to this article were reported.

References

1. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353:2643–2653
2. The Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450–459
3. The Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994; 125:177–188
4. Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzimer SA, Buckingham BA, Kollman C, Xing D, Ruedy KJ. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. J Pediatr 2005;147:528–534
5. Raju B, Arbelaez AM, Breckenridge SM, Cryer PE. Nocturnal hypoglycemia in type 1 diabetes: an assessment of preventive bedtime treatments. J Clin Endocrinol Metab 2006;91:2087–2092
6. Buckingham B, Block J, Burdick J, Kalajian A, Kollman C, Choy M, Wilson DM, Chase P. Response to nocturnal alarms using a real-time glucose sensor. Diabetes Technol Ther 2005;7:440–447
7. Zisser H. Quantifying the impact of a short-interval interruption of insulin-pump infusion sets on glycemic excursions. Diabetes Care 2008;31:238–239
8. Gandrud LM, Xing D, Kollman C, Block JM, Kunselman B, Wilson DM, Buckingham BA. The Medtronic Minimed Gold continuous glucose monitoring system: an effective means to discover hypo- and hyperglycemia in children under 7 years of age. Diabetes Technol Ther 2007; 9:307–316
9. Guerci B, Benichou M, Floriot M, Bohme P, Fougnot S, Franck P, Drouin P. Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. Diabetes Care 2003;26: 1137–1141
10. Orsini-Federici M, Akwi JA, Canonico V, Celleno R, Ferolla P, Pippi R, Tassi C, Timi A, Benedetti MM. Early detection of insulin deprivation in continuous subcutaneous insulin infusion-treated patients with type 1 diabetes. Diabetes Technol Ther 2006;8:67–75
11. Wilson DM, Beck RW, Tamborlane WV, Dontchev MJ, Kollman C, Chase P, Fox LA, Ruedy KJ, Tsalikian E, Weinzimer SA. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. Diabetes Care 2007;30:59–64
12. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, Cameron F, Chase HP. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Technol Ther 2009;11:93–97
13. Chase HP, Buckingham BA. Pump shut off to prevent nocturnal hypoglycemia. In *2nd Conference on Advanced Technologies & Treatments for Diabetes*. Athens, Greece, 2009
14. Dassau E, Cameron FM, Lee H, Bequette BW, Doyle III FJ, Niemeyer G, Chase P, Buckingham B: Real-time hypoglycemia prediction using continuous glucose monitoring (CGM): a safety net to the artificial pancreas. Diabetes 2008; 57(Suppl. 1): A13
15. Palerm CC, Bequette BW. Hypoglycemia detection and prediction using continuous glucose monitoring: a study on hypoglycemic clamp data. J Diabetes Sci Technol 2007;1:624–629
16. Palerm CC, Willis JP, Desemone J, Bequette BW. Hypoglycemia prediction and detection using optimal estimation. Diabetes Technol Ther 2005;7:3–14

17. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. IEEE Trans Biomed Eng 2007;54:931–937
18. Palerm CC, Bequette BW. Hypoglycemia detection and prediction using continuous glucose monitoring: a study on hypoglycemic clamp data. J Diabetes Sci Technol 2007;1:624–629
19. Dassau E, Bequette BW, Buckingham BA, Doyle III FJ. Detection of a meal using continuous glucose monitoring (CGM): implications for an artificial β-cell. Diabetes Care 2008;31:295–300
20. Oppenheim AV, Schafer RW, Buck JR. *Discrete-Time Signal Processing*. Upper Saddle River, NJ, Prentice-Hall, 1998
21. Cameron F, Niemeyer G, Gundy-Burlet K, Buckingham B. Statistical hypoglycemia prediction. J Diabetes Sci Technol 2008;2:612–621
22. Dassau E, Jovanovič L, Doyle III FJ, Zisser H. Enhanced 911/GPS Wizard: a telemedicine application for the prevention of severe hypoglycemia: monitor, alert and locate. J Diabetes Sci Technol 2009; 3:1501–1506
23. Kovatchev BP, Breton M, Dalla Man C, Cobelli C. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol 2009;3:44–55
24. Dassau E, Zisser H, Palerm CC, Buckingham BA, Jovanovič L, Doyle III FJ. Modular artificial β-cell system: a prototype for clinical research. J Diabetes Sci Technol 2008;2:863–872