ORIGINAL ARTICLE

Closing the Loop

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Introduction

TECHNOLOGY IS TAKING MASSIVE STRIDES and becoming a greater and greater part of daily life. The field of medicine provides a multitude of examples of the rapid progression of new technology. One prime example of this progression is the pursuit of the artificial pancreas (AP). People living with type 1 diabetes mellitus suffer from the inability to produce or adjust insulin secretions according to their metabolic needs. Technological advances such as the constant glucose monitor and continuous subcutaneous insulin infusion pumps have aided type 1 patients in controlling glucose levels. However, a great deal of patient intervention is required to prevent hyperglycemia and hypoglycemia, and this intervention can be very difficult with a busy and unpredictable lifestyle. The pursuit of the AP is the pursuit to eliminate patient involvement in blood glucose management. The hope is that in doing so human error, hypo- and hyperglycemia, and patient stress will be greatly reduced. Closed-loop AP systems now include a constant glucose monitor, constant subcutaneous insulin infusion pump, and an automated control algorithm to communicate between the two. Clinical trials have begun to show the safety and efficacy of closed-loop systems particularly in overnight inpatient settings. Research has even begun to study the ability for the closed-loop algorithms to function in outpatient environments (1). Challenges now largely revolve around controlling postprandial glucose levels, as subcutaneous insulin action is significantly slower than that of ingested glucose. Another key challenge is developing closed-loop systems that are robust enough to handle real-life scenarios in outpatient procedures. Once the technology for the AP has been established, industry may look to integrating the systems into smart phones and other socially discrete devices (2). Many promising studies are bringing the AP closer to becoming a reality. Our aim in this chapter is to present a few of the most exciting and influential studies published within the previous year on closed-loop systems.

CLINICAL STUDIES

Closed-loop insulin therapy improves glycemic control in children aged >7 years

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Diabetes Care 2013; **36**: 222–27

Background

Attempting to control hyperglycemia in patients with type 1 diabetes mellitus has led to a significant increase in episodes of hypoglycemia, resulting in a need for a completely automated AP to improve glycemic control. There has been little research in closed-loop insulin therapy for very young children. This demographic of type 1 patients is especially difficult to manage and vulnerable to episodes of hypoglycemia because of factors such as unpredictable eating patterns and erratic activity level. The goal of this study was to assess the possibility of improving nocturnal glycemic control as well as meal glycemic response using closed-loop therapy in children less than 7 years old.

Methods

In a randomized controlled crossover trial, 10 subjects aged <7 years with type 1 diabetes for 6 months treated with insulin pump therapy were studied. Closed-loop therapy and standard open-loop therapy were compared from 10:00 P.M. to 12:00 P.M. on two consecutive days. At night, control was affected with a proportional-integral component in series with a proportional-derivative component, and at 8:00 A.M., control was transferred to an algorithm using a proportional integral component in parallel with a proportional-derivative component. The primary

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outcome was plasma glucose time in range (110–200 mg/dL) during the night (10:00 P.M.–8:00 A.M.). Secondary outcomes included peak postprandial glucose levels, incidence of hypoglycemia, degree of hyperglycemia, and prelunch glucose levels.

Results

Without reaching statistical significance, closed-loop therapy did trend toward a higher mean nocturnal time within target range (5.3 vs. 3.2 hours, $p=0.12$). There was no difference in peak postprandial glucose or number of episodes of hypoglycemia. There was significant improvement in time spent >300 mg/dL overnight with closed-loop therapy (0.18 vs. 1.3 hours, $p=0.035$) and the total area under the curve of glucose >200 mg/dL ($p=0.049$). Closed-loop therapy returned prelunch blood glucose closer to target (189 vs. 273 mg/dL on open loop, $p=0.009$).

Conclusion

The closed-loop insulin therapy was able to reduce nocturnal hyperglycemia without increasing the incidence of hypoglycemia. It was also able to establish similar peak postprandial glucose concentrations and then return the concentration closer to target before the next meal.

Comment

This study evaluated a proportional-integral-derivative controller-based AP system in children aged >7 years. The authors mentioned that management of type 1 diabetes in very young children is especially difficult because of unpredictable eating patterns, erratic activity level, and increased susceptibility to severe hypoglycemia. However, with the study design performed, this challenge was not put to the test. Yet, they did test the AP system in a very insulin-sensitive age group. As noted in the article, a change to the system aggressiveness was performed in the middle of the study in order to cope better with the patient's insulin sensitivity.

In order to be able to interpret the benefit of the AP over the basal-bolus strategy, it is recommended that at least the primary endpoint will be powered. In addition, in case the study includes several secondary endpoints, it is recommended to design for these in advance to support statistical data analysis. The study results are encouraging, but it is very hard to say that this study showed any superiority of the AP system over the conventional therapy.

One other limitation is that during open-loop control, additional correction insulin boluses were allowed to be given overnight. As the authors mentioned, this should have biased the results. Future design should include a control group as well as blind the study results and measurement to the patients and in some situations to the healthcare providers (double blinded) in order to avoid changes to their treatment behavior.

Clinical evaluation of a personalized artificial pancreas

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Diabetes Care 2013; 36: 801–9

Background

An automated AP system that is able to control blood glucose concentrations would prevent complications from hyper- and hypoglycemia as well as improve the quality of life of those living with type 1 diabetes mellitus. The objective of this study was to demonstrate the feasibility of a fully automated system that would require no user input.

Methods

Two pilot prospective trials were conducted using a multiparametric formulation of a model predictive control and an insulin-on-board algorithm. Patient data were collected for 3 consecutive days before initiating the closed-loop trial in order to develop individual models for the controller. The protocol evaluated the control algorithm for three main challenges: (a) normalizing glycemia from various initial glucose levels, (b) maintaining euglycemia, and (c) overcoming an unannounced meal of 30 g carbohydrates.

Results

Initial glucose values ranged from 84 to 251 mg/dL. Blood glucose was kept in the near-normal range (80–180 mg/dL) for an average of 70% of the trial time. The low and high blood glucose indices were 0.34 and 5.1, respectively. Two subjects repeated the study multiple times with minimal intrasubject variability.

Conclusion

This short-term study demonstrates the feasibility of controlling glycemia by delivering insulin through a fully automated AP device based on personalized model predictive control with safety components. The controller demonstrated the ability to overcome unannounced meal challenges and hyperglycemia without overdosing insulin because of the insulin-on-board system.

Comment

This study is unique in that it represents one of the first fully automated multiparametric model predictive control algorithm with insulin-on-board that does not rely on user intervention to regulate blood glucose. It provides promising results in regulating glycemia levels by tailoring the control algorithm to the individual. The key advantage of the presented AP system relies on the fact that the control laws were evaluated off-line, thus minimizing online computing power.

One of the main debates over the past years is focused on whether we can use continuous glucose monitoring (CGM) results to evaluate the closed-loop system performance or use only reference gold-standard technique. In

this study, the authors reviewed and analyzed both methods. Yet, not both methods can be used to accurately estimate the study endpoints and it may be that these should complement each other. As we move toward ambulatory studies, more emphasis should be made on how data are reported and what are the means to accurately report the clinical results. Unmodified CGM data should be considered as the primary source for data analysis at home. A number of modifications and new directions may be pursued in future studies. Extending the duration of the trials, particularly after meals, would better prove the controller's ability to avoid overdelivering insulin. As the insulin-on-board safety constraint was tuned using the subject's correction factor, future controllers may be tuned on the basis of the correction factor alone.

Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial

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CMAJ 2013; 185: 297–305

Background

Hypoglycemia remains the greatest barrier to intensifying insulin therapy in type 1 diabetic patients. Closed-loop systems that connect constant glucose monitors and insulin pumps may help control glucose levels, but cases of hypoglycemia are still reported with these systems. Dual-hormone therapy systems using both insulin and glucagon have been proposed, but their potential benefits to promoting glycemic control are unknown. The objective of this study is to determine whether dual-hormone closed-loop therapy can improve glycemic control and reduce cases of hypoglycemia in adults with type 1 diabetes mellitus in comparison to conventional insulin pump therapy.

Methods

An open-label, randomized crossover design was used to compare dual-hormone closed-loop therapy with continuous subcutaneous insulin delivery in 15 participants. Patients were admitted to a clinical research facility and received, in random order, both treatments. Each participant was challenged with a 30-minute exercise, an evening meal, a bedtime snack, and an overnight stay.

Results

Closed-loop dual-hormone therapy increased time spent in the target glucose range (median 70.7% [interquartile range (IQR) 46.1%–88.4%] for closed-loop delivery versus median

57.3% [IQR 25.2%–71.8%] for control, $p=0.003$) and reduced the number of hypoglycemic events. Eight participants (53%) had at least one hypoglycemic event (plasma glucose <3.0 mmol/L) during standard treatment, compared with just one participant (7%) during closed-loop treatment ($p=0.02$).

Conclusion

Dual-hormone closed-loop delivery improved glucose control and reduced the risk of hypoglycemia in 15 participants, as compared with continuous subcutaneous insulin infusion. The promising results of the study show that such therapy may prove useful in controlling hypoglycemia, particularly during the night.

Comment

The use of glucagon within an AP system has been debated in recent years. This is the first randomized controlled study that compares the dual-hormone AP to standard of care. The presented system relied on glucagon just for a rescue and not as part of the treatment. This is evident from the fact that insulin dosing was similar between arms and the system suspended insulin for about 40 minutes before advising glucagon, which occurred on a glucose level of 4.9 mmol/L (4.2–6.0). These results are of interest—mainly that patients maintained tight glucose control with almost no hypoglycemia during closed-loop compared to the control arm. Additional studies with more patients at different age groups as well as additional challenges are needed before the full benefit of the bi-hormonal system could be appreciated. Current obstacles in the development of a bi-hormonal AP are the need for a dual-chamber pump/delivery system and a stable formulation of glucagon. Recent developments and publications on the latter show promising results that may encourage pump manufacturers to produce a dual-chamber pump or delivery system. Yet, this study shows great potential for the use of glucagon for safety mitigation in future AP devices.

Nocturnal glucose control with an artificial pancreas at a diabetes camp

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N Engl J Med 2013; 368: 824–33

Background

Intensive insulin therapy is considered to be the standard treatment for patients with type 1 diabetes mellitus. Closed-

loop systems have been shown to improve glucose control and reduce nocturnal hypoglycemia in hospital settings. It is unclear if these results can be replicated outside of the hospital setting. The objective of this study is to assess the ability of the MD-Logic AP system to control nocturnal glucose in adolescent patients in a youth camp setting.

Methods

The 56 participants were between 10 and 18 years of age with at least a 1-year history of type 1 diabetes. During two consecutive nights, patients were placed on either an AP or a sensor-augmented insulin pump for one night in random order. The AP utilized the MD-Logic system, whose algorithm is based upon fuzzy logic theory, a learning algorithm, an alerts module, and a personalized system setting. The primary endpoints were the number of hypoglycemic events (defined as a sensor glucose value of <63 mg/dL [3.5 mmol/L] for at least 10 consecutive minutes), the time spent with glucose levels below 60 mg/dL (3.3 mmol/L), and the mean overnight glucose level for individual patients.

Results

Nights when the AP was used yielded significantly fewer episodes of nocturnal hypoglycemia (7 vs. 22) and significantly shorter periods when glucose levels were below 60 mg/dL ($p=0.003$ and $p=0.02$, respectively) in comparison to nights using the sensor-augmented insulin pump. There was no significant difference in the median overnight glucose level between patients. Median values for the individual mean overnight glucose levels were 126.4 mg/dL (IQR, 115.7 to 139.1) with the AP and 140.4 mg/dL (IQR, 105.7 to 167.4) with the sensor-augmented pump. No serious adverse events were reported, and at no time did the research team need to override the decisions of the AP.

Conclusion

The results of the study reveal the efficacy of the MD-Logic system as well as the reduced risk of hypoglycemia associated with its use. The improvement in the timing and amount of insulin provided, together with the presence of an alarm module, appears to be related to the improvement of glucose control and reduction in hypoglycemia.

only a single night, and the need to perform frequent sensor recalibration during the study. Future studies may look to improve the alerts module in order to reduce the number of hypoglycemia alerts and increase their specificity, increase the duration of study, broaden patient diversity, and utilize outpatient procedures to further demonstrate efficacy in daily life.

Multivariable adaptive closed-loop control of an artificial pancreas without meal and activity announcement

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Diabetes Technol Ther 2013; **15**: 386–400

Background

Numerous modeling strategies have been attempted in developing closed-loop control for an AP. Popular control algorithms tend to rely upon meal and activity announcements from the user. Adaptive control techniques provide a powerful alternative that do not necessitate any meal or activity announcements.

Methods

Adaptive control systems based on the generalized predictive control framework are developed by extending the recursive modeling techniques. Physiological signals such as energy expenditure and galvanic skin response are used along with glucose measurements to generate a multiple-input-single-output model for predicting future glucose concentrations used by the controller. Insulin-on-board (IOB) is also estimated and used in control decisions. The controllers were tested with clinical studies that include seven cases with three different patients with type 1 diabetes for 32 or 60 hours without any meal or activity announcements. During the study, subjects walked on a treadmill using a ramped up protocol and were given eight meals and snacks.

Results

The adaptive control system kept glucose concentration in the normal preprandial and postprandial range (70–180 mg/dL) without any meal or activity announcements during the test period. After IOB estimation was added to the control system, mild hypoglycemic episodes were observed only in one of the four experiments. The gradual improvement of the results across the seven experiments is largely because of improvements to the algorithm and equipment malfunction.

Conclusion

The multivariable adaptive closed-loop controller was able to operate without meal or activity announcement to yield an easier to use AP. Better blood glucose regulation is obtained by using adaptive system identification and a controller that

Comment

This research provides excellent follow-up to studies done as part of the DREAM project (3). Phillip *et al.* tested the same MD-Logic AP system on a large cohort under more realistic conditions as a step toward home use of the AP. By completing the research in the setting of a diabetes camp, the study utilizes a transitional phase between Clinical Research Center (CRC) studies and home evaluation. The challenge to the AP system in this study was even bigger as it was compared with sensor-augmented pump treatment and not to just conventional pump therapy. These studies advanced the AP research and the awareness of the public, industry, and regulatory bodies to the benefits of an AP. Limitations of the study include the high number of hypoglycemia alerts, narrow range of the patients' ages, the evaluation of each treatment over

leverages physiological information. This controller was able to regulate blood glucose in three patients.

Comment

An effective adaptive control model for the AP would be incredibly useful in simplifying the lives of patients with type 1 diabetes mellitus. The utilization of other physiologic variables within an AP system seems logical and interesting, as it allows the system to be closer to the way the body decides on insulin delivery and similar to the way patients reach their conclusion on a day-to-day basis. Although the idea behind the new design could have great potential, the clinical results of this study are very preliminary. A fully automated closed-loop system based on subcutaneous glucose measurements and insulin delivery as presented here may be too much to wish for without faster insulin or upper bound on the size of meals. Late postprandial hypoglycemia and large glucose swings were still a challenge as noted by the authors. As this control system is studied further, it would be beneficial to obtain greater sample sizes and address the tendency of hyperglycemia in patients.

Inpatient studies of a Kalman-filter-based predictive pump shutoff algorithm

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J Diabetes Sci Technol 2012; 6: 1142–47

Background

Insulin pump shutoff is an important safety feature in avoiding nocturnal hypoglycemia. Earlier shutoff systems used a voting algorithm to process the predictions of several different algorithms and proved capable of preventing 80% of induced hypoglycemic events. The pump shutoff algorithm presented in the article replaced the voting algorithm with a single Kalman filter prediction algorithm, reducing complexity without sacrificing performance. The new algorithm handles variable sampling intervals, sensor signal dropouts, and safety constraints on allowable pump shutoff time.

Methods

The Kalman filter algorithm was first tested retrospectively on nocturnal data sets from previous studies. Outcome measurements included time-to-pump suspension in hypoglycemic cases and number of suspensions in hyperglycemic cases. Sixteen patients were tested in overnight inpatient trials. Basal insulin was manually increased to induce a decrease in blood glucose and corresponding pump suspension response.

Results

Retrospective testing of the new algorithm on previous clinical data sets indicated that, for the four cases where the previous algorithm failed, the mean suspension start time was 30 minutes earlier when using the proposed algorithm compared to the earlier algorithm. In the inpatient studies, the algorithm prevented hypoglycemia in 73% of subjects. Three failures were attributed to a positive sensor bias. Suspension-induced hyperglycemia was not assessed, because hypoglycemia was artificially induced by increasing basal insulin.

Conclusions

The new algorithm functioned well and is flexible enough to handle variable sensor sample times and sensor dropouts. It also provides a framework for handling sensor signal attenuations, which can be challenging, particularly when they occur overnight. Tests in outpatient settings are a focus for future work.

Comment

The unmet need for prevention of hypoglycemia, especially during the nighttime, led to the development of closed-loop systems and pump shutoff algorithms. Evidence from previous studies, including this one, shows us that we may need to change our goals into more realistic ones. As long as the patient is responsible for insulin delivery of the meals, or can intervene during closed-loop control (as in hybrid system setup), we should aim for minimizing hypoglycemia rather than preventing it. Even with glucagon, hypoglycemia cannot be fully prevented. Therefore, we should look at other benefits the new technologies can provide us in addition to minimizing hypoglycemia. In contrast to AP systems, which also aim at improving the overall glycemic control, pump shutoff algorithms focus only on hypoglycemia. Furthermore, these systems still need to prove that they do not cause rebound hyperglycemia. The main limitation of this study lies in its design, specifically in the way hypoglycemia was induced, and that there was neither a control group nor assessment of potential rebound hyperglycemia.

The Kalman-filter-based predictive pump shutoff algorithm, which was used in this study, is based on glucose data only. Introducing insulin data into the algorithm may improve its performance and will allow suspension of the pump even in cases where glucose is not decreasing.

Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes

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Diabetes Care 2012; 35: 1994–99

Background

Closed-loop systems release insulin based on sensor output, which picks up on glucose only as it begins to rise. Insulin

action is delayed by the slow absorption rate associated with subcutaneous infusion. The mismatch between insulin and glucose availability results in hypoglycemia and postprandial hyperglycemia. Pramlintide, an analog of human amylin, slows gastric emptying and may be able to match the rates of glucose and insulin uptake.

Methods

Eight subjects (4 female, age 15–28 years, A1C $7.5\% \pm 0.7\%$) were studied for 48 hours on a closed loop (CL) insulin-delivery system with insulin feedback: 24 hours on CL control alone (CL) and 24 hours on CL control plus 30 mg premeal injections of pramlintide (CLP). Target glucose was set at 120 mg/dL. No premeal manual boluses were given. Differences in reference blood glucose excursions, defined as the incremental glucose rise from premeal to peak, were compared between conditions for each meal.

Results

In the CLP condition, peak blood glucose was delayed by ~1 hour and reduced by an average of 25 mg/dL compared to CL. Pramlintide effects varied by meal type, with significant reductions at lunch and dinner in association with higher premeal insulin concentrations. Insulin excursions in CLP were lower in spite of elevated insulin levels, and no hypoglycemic events occurred under either condition.

Conclusions

Pramlintide delayed the time to peak postprandial BG and reduced the magnitude of prandial BG excursions. Beneficial effects of pramlintide on CL may in part be related to higher premeal insulin levels at lunch and dinner compared with breakfast. The delay introduced by pramlintide influences the closed-loop system to slow insulin release as well, resulting in elevated insulin and possibly the reduction in glucose peak magnitude observed.

Comment

The ultimate goal of diabetes caregivers and patients is to find a solution that could release them from the day-to-day burden such as carbohydrate counting and meal-related insulin estimations. Until now, several prototypes of fully automated AP systems were proposed. However, because of the limitations imposed by subcutaneous insulin delivery, most of them experienced postprandial hyperglycemia.

Weinzimer and colleagues approach the insulin delay issue from a physiological point of view, as opposed to an engineering perspective. The initial results are encouraging and suggest that the use of adjacent therapy may be one way to overcome large unannounced meals. The use of pramlintide as part of the closed-loop system as an agent that will help to minimize postprandial hyperglycemia for unannounced meals is a novel one; however, more studies are needed with different meal compositions to better understand the effect on closed-loop systems. The control algorithm would benefit from a modification that could account for the delayed meal

effect. Second, since pramlintide was administered to patients via manual injection in this study, to preserve the nature of closed-loop systems, an automated delivery system for pramlintide should be explored as well. This may result in a dual hormone system that has its own complications.

The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes

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Diabetes Care 2012; 35: 2182–87

Background

A constant risk of intensive insulin therapy in patients with type 1 diabetes mellitus is hypoglycemia. The pursuit of an AP is not novel, yet many studies have required manual input of constant glucose monitor data or manual adjustment of insulin by physicians, or control algorithms have been housed on cumbersome devices. The goal of this study is to develop a safe, efficacious, closed-loop AP that is portable and allows for remote monitoring.

Methods

This study was designed to determine the safety and efficacy of the Medtronic Portable Glucose Control System (PGCS). This system consists of two constant glucose monitors, a control algorithm based upon proportional-integral-derivative, a Blackberry Storm smartphone, a Bluetooth radiofrequency translator, and a Medtronic Paradigm Veo insulin pump. The primary endpoint was euglycemia during overnight closed-loop control. Eight participants were between 12 and 25 years of age, diagnosed with type 1 diabetes mellitus for over a year, with an HbA1c less than 8.5%, and on insulin pump therapy for more than 6 months. Subjects underwent a week of baseline open-loop assessment before participating in an overnight closed-loop study. During the course of two consecutive nights, the PGCS was used for nocturnal closed-loop control, while open-loop control was used from 0700 to 2100 hours.

Results

Mean plasma glucose during overnight closed-loop control was 6 ± 1.7 mmol/L. Time spent below 3.9 mmol/L, between 3.9 and 8 mmol/L, and above 8 mmol/L was 7%, 78%, and 15%, respectively. Time spent in the target glucose range was significantly higher after midnight, and cases of hypoglycemia were significantly higher during the first 3 hours of

closed-loop operation. Investigator intervention was required on 7 of 16 nights of study.

Conclusion

This study represents the feasibility and safety features of a portable, automated, closed-loop system for overnight glucose control in adolescents and young adults with type 1 diabetes mellitus. Monitoring of system operations remotely via wireless network allows for an additional safety feature through physician-supervised home studies.

Comment

Miniaturization and the move toward a portable and wearable AP is a natural step in the development of the AP as demonstrated in this article and by other groups (1). This article presents, for the first time, results from a feasibility study that involved an AP on a mobile phone, allowing patients to carry the system during their everyday routine. In the future this new technology will better facilitate home studies with minimal to no interference in their daily activities. The authors also present an automatic fault detection mechanism as a safety layer that can send an alert in cases of sensor or insulin delivery failures. The ability of the system to automatically detect faults in the sensor and in the insulin pump is an important safety mechanism in a future product. Two sensors in two different insertion sites were used before and may be useful but is not practical in real life. In addition, the choice of the authors to suspend insulin dosing for 2 hours postdetection of a fault is questionable and needs to be further investigated as this may result in hyperglycemia and even positive ketones. Since it is a feasibility study, the readers should be cautioned regarding the comparison of closed-loop performed over 2 nights at a research center to open-loop data collected over 6 nights at home.

Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial

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Diabetes Care 2013; **36**: 838–44

Background

Previous trials of closed-loop systems have demonstrated their ability to improve glycemic control, particularly during sleep. The objective of this study was to assess the response of closed-loop systems to a 36-hour period with both sleep and common waking activities.

Methods

Twelve adolescents with type 1 diabetes (5 male, mean age 15.0 [SD 1.4] years, HbA1c 7.9% [0.7%], body-mass index 21.4 [2.6] kg/m²) participated in a randomized controlled crossover study. They stayed at a clinical research facility on two occasions and received, in random order, closed-loop basal insulin delivery or conventional pump therapy for 36 hours. Prandial insulin boluses were given before meals but not snacks. Patients undertook unannounced exercise at a moderate intensity, once in the morning and once in the afternoon. Primary outcome was percent time during which plasma glucose was in the target range (71–180 mg/dL).

Results

Closed-loop delivery increased percentage time in target (median 84% [IQR 78–88%] vs. 49% [26–79%], $p=0.02$) and reduced mean plasma glucose levels (128 [19] vs. 165 [55] mg/dL, $p=0.02$) while also tightening the range (107–161 vs. 85–258 mg/dL). Time in target was 100% on 17 of 24 nights with closed-loop delivery. Hypoglycemia occurred 10 and 9 times in conventional and closed-loop conditions, respectively. All closed-loop subjects spent $\geq 70\%$ time in target, while only one-third of conventional therapy subjects had similar results.

Conclusions

Twenty-four-hour closed-loop insulin delivery can improve glycemic control in adolescents, but its abilities are challenged by unannounced exercise and excessive prandial boluses. Work is in progress to target these issues via small prandial insulin boluses, accounting for insulin levels when calculating delivery, and adding glucagon rescue infusions.

Comment

While overnight hypoglycemia has been an important consideration in the development of closed-loop systems, this article explores its applications in daily activities as well. The results of the closed-loop system during nighttime are repeated compared with other studies conducted with the same system. This article aims to show that it can also improve daytime control during scenarios of meals with preprandial insulin and physical activities. While closed loop did reach superior glycemic control during the day, it did not minimize hypoglycemia. It could be that we should aim for different objectives for the AP during daytime when patients are awake and nighttime when they are asleep. Daytime success criteria may focus more on hyperglycemia with tolerable levels in the range 50–70 mg/dL, while during nighttime we should focus on hypoglycemia minimization without worsening other glycemic control parameters. Future discussions in this field are necessary. Increasing automation of the process would be helpful, especially for populations like adolescents who may have lower compliance and more variability in their daily activities. In general, it offers an improved quality of life during the day and night, and the results of this work show that this is entirely possible.

AP INFRASTRUCTURE AND SYSTEM ENHANCEMENTS

Design of the health monitoring system for the artificial pancreas: low-glucose prediction module

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J Diabetes Sci Technol 2012; 6: 1345–54

Background

Management of type 1 diabetes mellitus through insulin administration can be dangerous as insulin is toxic at high doses. The AP device system design requires that multiple safety layers be built around the control algorithm to ensure the health of the user and the proper condition of the device. The purpose of this study was to design and evaluate the health monitoring system (HMS), a safety system for the AP device system.

Methods

The HMS evaluates the trend of glucose in a mathematically different way from the controller, and thus provides an extra layer of protection for the user. The HMS was designed as a modular using a large set of ambulatory data. It was evaluated *in silico* by inducing hypoglycemia with a missed meal [bolus for a 65 g carbohydrate (CHO) meal] and administering rescue CHO per HMS alerting. The HMS was validated in-clinic with a real-life challenge of a subject who overdosed insulin before admission.

Results

The HMS was evaluated for clinical use with a 15-minute prediction horizon. About 393 days of CGM data from seven patients was used in a retrospective study. About 93.5% of episodes were detected with 2.9 false alarms per day. During *in silico* evaluation, the HMS reduced the time spent <70 mg/dL from 15% to 3%. When the HMS was first tested in-clinic, the subject overdosed ~3 U of insulin before her arrival to a closed-loop session (against protocol). The controller reduced insulin delivery, and the HMS gave four alerts that were successfully received via clinical software and text and multimedia messages. Even with insulin reduction and CHO supplements, hypoglycemia was unavoidable but manageable because of the HMS, confirming that a safety system to detect adverse events is an essential part of the Artificial Pancreas Device System (APDS).

Conclusion

The HMS has been evaluated using respective clinical data and prospective *in silico* and human clinical trials. Despite the reduction in insulin delivery from the controller, hypoglycemia was unavoidable. This confirms that a safety system to detect adverse events is essential in closed-loop systems.

Comment

As greater trust is given to technology, the safety of that technology becomes increasingly essential. Multiple layers of safety systems are key in high-risk devices such as the AP. The evaluation of the HMS appears promising in providing such a layer. From previous studies that examined the glucose sensor's alarms, it is evident that most patients do not respond to alarms mainly because of their low reliability. Therefore, we must provide an alarm system that will have higher specificity and sensitivity than the CGM alarms. This article shows a promising algorithm but is still susceptible to erroneous CGM errors. Additional data such as insulin delivery may help in improving alert specificity. The use of alternative mathematical evaluation in the HMS system is important in supplementing the safety features built into the control algorithm. Future evaluations of the HMS in larger cohorts, in a study design that allows estimation of the system's true positive and false-positive rates as well as with different settings, will improve the design of the suggested safety layer of the AP.

Real-time improvement of continuous glucose monitoring accuracy

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Diabetes Care 2013; 36: 793–800

Background

CGM offers a potentially more effective alternative to traditional blood glucose measuring systems by keeping patients better informed of their blood glucose levels. As the primary source of data for patients and/or closed-loop systems, CGM must accurately detect hyper- and hypoglycemia. Three major confounding factors are noise from sensor measurements, inaccuracy caused by delayed absorption and processing time, and the need for prealerts to avoid glycemic excursions. The study proposes and tests a smart CGM (sCGM) system that includes software modules for denoising, enhancement, and prediction.

Methods

Two studies with 12 type 1 diabetic patients each were conducted to evaluate the performance of the sCGM. In the first, patients were fitted with two CGM sensors, one normal and one smart, and observed over the course of 7 days. In the second, patients under observation were randomly assigned to open-loop or closed-loop treatments on the third day for a 24-hour observation period. The outcome metrics used were smoothness of denoised data, level of clinical danger of inaccurate CGM, time to detect serious glycemic excursion, and false-positive rate.

Results

The denoising module reduced noise by 57% in both studies. Enhancement of the denoised data deviated less from the plasma glucose than CGM data (10.3% vs. 15.1%), boosting accuracy (87.7% vs. 75.1%). With the addition of the prediction module, sCGM was able to predict glycemic excursions 14 minutes earlier and reduce false alerts (20% vs. 42%).

Conclusions

Real-time processing using the modules enhanced CGM performance significantly. The modular nature of the proposed sCGM opens up opportunities for collaboration and provides a standardized platform for future modules. The results demonstrated a promising improvement in CGM safety, encouraging future patient studies and research into integrating the sCGM with commercial CGM systems.

An online failure detection method of the glucose–insulin pump system: improved overnight safety of type 1 diabetes subjects

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IEEE Trans Biomed Eng. 2012; 60: 406–16

Background

While closed-loop systems are a promising technology for smarter insulin therapy, failure of either the continuous subcutaneous insulin infusion (CSII) or CGM systems could result in serious risks for diabetic patients. Facchinetti *et al.* propose a method of detecting failure in real time by simultaneously using CGM and CSII data streams and a black-box model of the glucose–insulin system.

Methods

Based on previously collected CGM and CSII data, an individualized model for the glucose–insulin system is created and used to generate predictions of future glucose concentrations using CGM and CSII data-streams online. If measured CGM values are inconsistent with model predictions, a failure alert is generated. The method was tested on 100 virtual patients generated by the UVA/Padova type 1 metabolic simulator and under three different failure conditions: spike in the CGM profile, loss of sensor sensitivity, and failure of the insulin delivery pump. A second test was done on the datasets of three type 1 diabetes mellitus patients drawn from a larger database of previous closed- and open-loop trials.

Results

The method successfully generated alerts in all three failure conditions, with a small number of false-negatives and false-positives. A false-negative rate of 40% was achieved at small spikes (7 mg/dL), falling to 3% with spikes of 20–25 mg/dL. False-positives were reduced by over 66% with increasing spike size. In the sensitivity loss scenario, an average fall of 15 mg/dL elicited the correct alert 98% of the time, with 2% misclassified as spikes. Pump failure was identified within 2 hours at a rate of 86% with an average delay of 63 ± 41 min. The method correctly

identified all three types of failures in the type 1 diabetes mellitus patient datasets, with one spike false-positive.

Conclusion

The method is able to identify system failure with reasonable accuracy in both simulated and real patients. It clearly demonstrates its potential in improving the safety of type 1 diabetic patients, particularly overnight.

Comment

For the past several years, most of the research efforts were invested in the development of the core control algorithm of the AP. Now that we are close to conducting home studies, the dream of commercial AP seems closer than ever. As noted in these two publications by Facchinetti and colleagues, several improvements to the CGM algorithms and additional safety layers will benefit the clinical use of the AP and will provide a safer and more reliable device. Facchinetti *et al.* combined three modular stand-alone applications demonstrating the potential of the sCGM to provide improved signal for both the AP controller and the standard care. Their success supports their proposed approach, which is a useful plan that merits further exploration in the future.

Our ability to trust machines to provide the necessary care is a major concern as technology integrates more and more within the medical field. Use of safety systems and online/real time monitoring is widely acceptable and should be part of the AP design. The ability to provide real-time failure detection and diagnosis as demonstrated by Facchinetti *et al.* is important to the field. These two developments should be further investigated and evaluated under prospective clinical studies.

Assessing performance of closed-loop insulin delivery systems by continuous glucose monitoring: drawbacks and way forward

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Diabetes Technol Ther 2013; 15: 4–12

Background

Closed-loop systems have been tested in inpatient settings, where reference plasma glucose can be taken to ensure patient safety and provide data for evaluation. This is not possible in outpatient studies. CGM offers an alternative method for data collection, but its reliability is uncertain. Three CGM methods were tested to determine which, if any, methods are appropriate for outpatient studies.

Methods

The study was a retrospective analysis of three open-label randomized controlled crossover studies comparing conventional and closed-loop insulin therapies. Thirty-three type 1 diabetes patients, aged 12–65 with at least 1 year since

diagnosis and 3 months of pump use, were tested in two overnight sessions. Patients aged 12–18 were tested under an early evening exercise scenario, while adults (18–65) were tested under eating-in versus eating-out conditions. Glycemic control was evaluated by reference plasma glucose and contrasted against unmodified, stochastic, and recalibrated CGM data. CGM accuracy was defined as the mean absolute relative difference between sensor and plasma glucose levels.

Results

Glucose mean and variability were estimated by unmodified CGM levels with acceptable clinical accuracy. CGM overestimated time spent in target range (70–145 mg/dL) during closed-loop nights (CGM vs. plasma glucose median [interquartile range], 86% [65–97%] vs. 75% [59–91%]; $p=0.04$) but not during conventional pump therapy (57% [32–72%] vs. 51% [29–68%]; $p=0.82$) providing comparable treatment effect (mean [SD], 28% [29%] vs. 23% [21%]; $p=0.11$). Stochastic CGM gave an unbiased estimate of time in target during both closed-loop (79% [62–86%] vs. 75% [59–91%]; $p=0.24$) and conventional pump therapy (54% [33–66%] vs. 51% [29–68%]; $p=0.44$), as well as treatment effect (23% [24%] vs. 23% [21%]; $p=0.96$) and time below target. Recalibrated CGM was not superior to stochastic CGM.

Conclusions

CGM is acceptable to estimate glucose mean and variability, but without adjustment it may overestimate the benefits of closed loop. Stochastic CGM provided an unbiased estimate of time when glucose is in or below target and may be acceptable for assessment of closed loop in the outpatient setting. Recalibrated CGM has limited applications in the outpatient setting; though it performed well in closed loop, it overestimated time in target in conventional therapy, despite the use of highly accurate glucose measurements for calibration.

Comment

One of the biggest arguments the scientific community and regulatory bodies has is whether it is acceptable to use continuous glucose sensor to evaluate the safety and efficacy of the AP system. This is mainly because of the lack of accuracy of CGM compared with the gold-standard reference measurement. Thus, the motto of most groups was to evaluate the efficacy and safety of the AP using plasma gold-standard measurements. Eventually, this will not be available during home studies in which blood glucose is measured less frequently with a device that has its own error (sometimes even a higher error than the CGM itself).

On the basis of the above, Hovorka *et al.* considered various approaches, looking for the best modification to the measured CGM data as per the endpoint being assessed. The idea of introducing the measurement error into data analysis for time-in-range parameters, as proposed by the stochastic transformation, seems logical. Interestingly, this method was used by Phillip *et al.* and did not show any difference in the treatment effect of the AP (compared with control) as was estimated with unmodified CGM data and after stochastic transformation. More research is required in order to reach the

proper evaluation method of the AP system during home studies. Perhaps one can define limits on sensor accuracy in order to mark a data set as valid for analysis instead of modifying the measured CGM values.

Summary

This year brings us ever closer to a fully automated closed-loop system. Studies that were conducted at controlled research centers and at diabetic camps this year paved the way for the ongoing clinical studies conducted at patients' homes. Work on control algorithms has improved simplicity, robustness, and accuracy, and recently proposed approaches incorporate alternative data sources and architecture. Much progress has been made in patient safety, particularly in addressing overnight and pump-induced hypoglycemia and system failure, two major sources of concern when using automated systems. These developments are augmented by new systems for alerting users and third-party monitors to emergencies and the addition of dual-hormone therapies to glycemic control strategies. Some researchers are already looking beyond to outpatient research and the advancements in monitoring and data collection technology required for such endeavors (4). Combined, these efforts shift the AP from an idea tested *in silico* and in feasibility studies toward predominantly prospective controlled trials in which the efficacy and safety of the system is being evaluated against state-of-the-art treatment.

Yet, some of the challenges that were already presented last year still need to be addressed. The movement toward human studies at patients' homes makes it increasingly important to find an accurate, day-to-day measure of glucose levels to protect subjects and accurately evaluate the efficacy of tested treatments. Addressing these concerns, Kowalski and Dutta propose a standardization of glucose measurement metrics for future consideration (5). However, setting the right measures is not enough. Work should also be done to define the expected accuracy from the glucose sensor and the suitable statistical measures to be used in these studies. Furthermore, discussion on the different success criteria for the AP—when patients are awake and nighttime when they are asleep—should also be performed. In addition, other algorithms related to automatic fault detection still need to be developed and tested. This should be a joint effort of academy and insulin pump/CGM industry.

In the meantime, progress is being made on future technologies involving the AP. This includes the development of a dual-chamber insulin pump to be used with a bi-hormonal system (with glucagon or with pramlintide). Another such work is the combined AP and technosphere therapy, which has made the transition from *in silico* to inpatient trials to be discussed in the following years (6).

With existing systems improving and novel approaches being explored, we are making steady progress toward a reality in which patients can use a fully automated system in their daily lives.

Author Disclosure Statement

E.A, A.T., K.L., and E.D. have no competing financial interests. M.P. is a member of advisory boards for AstraZeneca,

Sanofi, Medtronic, and Eli Lilly. He is a consultant to Bristol Myers-Squibb, AstraZeneca, and Andromeda. He is on the speaker's bureau of Johnson and Johnson, Sanofi, Medtronic, Novo Nordisk, and Roche. He is a shareholder of CGM-3.

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