Journal of Diabetes Science and Technology
Volume 2, Issue 3, May 2008

CONTROVERSIES in
Continuous Glucose Monitoring

Continuous Glucose Monitoring Awaits Its "Killer App"

Steven J. Russell, M.D., Ph.D.

Abstract

Continuous glucose monitoring (CGM) could drive a paradigm shift in diabetes care, but realization of this promise awaits a complementary shift in the way CGM data is used. The most exciting use for CGM is as the input for automated, closed-loop glucose control. Although first generation CGM devices leave much room for improvement, closed-loop control does not have to wait. Algorithms should target blood glucose levels above the normal range for safety in the setting of imperfect CGM measurements. If the mean glucose under closed-loop control is sufficiently close to the chosen target, hemoglobin A1c goals could be met while minimizing risk of hypoglycemia. CGM may also improve the care of intensive care unit patients treated with intensive insulin therapy and the large numbers of diabetic patients in general hospital wards.

J Diabetes Sci Technol 2008;2(3):490-494

CGM: An Enabling Technology In Need of a Killer App

In the jargon of computer programmers, a killer application is a piece of software so desirable that it motivates large numbers of people to buy the device that runs it. Without a killer app, the most sophisticated computer may not sell. On the other hand, the application is useless without the sophisticated device to run it. The killer app and the enabling core technology need each other to succeed. In the same way, continuous glucose monitoring is an enabling core technology awaiting an application that will make it indispensable. Automatic, closed-loop blood glucose (BG) control would be such an application. A practical, closed-loop device would make continuous glucose monitoring (CGM) technology indispensable, not only to most of the type 1 diabetic population, but also to a significant fraction of the much larger type 2 diabetic population. Without some form of near continuous glucose monitoring, closed-loop control will not be possible. Although there are many technologies in development, the only devices with immediate potential for realizing closed-loop control in outpatients are interstitial fluid (ISF) sensing CGMs. In the near term, CGM may also have utility in improving the safety of diabetic patients, who make up more than 25% of inpatients on general hospital wards, and of

Author Affiliation: Massachusetts General Hospital Diabetes Center, Boston, Massachusetts

Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (FDA) Food and Drug Administration, (HbA1c) hemoglobin A1c, (ICU) intensive care unit, (IIT) intensive insulin therapy, (ISF) interstitial fluid, (LOS) length of stay, (MARD) mean absolute relative difference

Keywords: CGM, closed-loop glucose control, continuous glucose monitoring, diabetes mellitus, intensive insulin therapy

Corresponding Author: Steven J. Russell, M.D., Ph.D., Massachusetts General Hospital Diabetes Center, 50 Staniford Street, Suite 340, Boston, MA 02114; email address sjrussell@partners.org

critically ill patients receiving intensive insulin therapy in the intensive care unit (ICU).

Modest Successes for CGM as an Adjunct to Open-Loop Diabetes Management

Currently available CGM devices or those that are in testing have been developed for the outpatient market and are targeted primarily at type 1 diabetes patients. There are data for the effectiveness of CGM in improving glycemic control, but the largest effects are in patients controlled poorly at baseline.[1-3] Patients who have already achieved fairly good glycemic control have quite modest improvements in hemoglobin A1c (HbA1c) with CGM, but may benefit from a reduction in hypoglycemia. This can be particularly valuable in the setting of hypoglycemic unawareness, but the relatively low specificity of alarms is a problem. CGM devices have been approved by the Food and Drug Administration (FDA) only as an adjunct to traditional self-monitoring of BG. Patients are not meant to take action on the basis of CGM data without confirmation by capillary BG measurement. Therefore, if used as directed, CGM actually increases the already heavy workload of diabetes management. A successful, closed-loop BG control system will achieve good control, prevent hypoglycemia, and at the same time reduce the amount of work required to manage BG. Such a system would revolutionize diabetes management and would rapidly render stand alone pumps and CGMs obsolete.

The Missing Pieces: An Effective Control Algorithm and Counter-Regulatory Capability

Why hasn't closed-loop control been achieved already? Some argue that first generation CGM devices are not sufficiently accurate to drive a closed-loop system, but the following scenario suggests that the primary difficulty lies elsewhere. Consider a CGM with the following performance characteristics: the mean absolute difference between the CGM-reported BG and a reference venous BG (the mean absolute relative difference, or MARD) is 13%, with a MARD of 11% for reference BG values above 100 mg/dl.[4] The largest and most clinically concerning deviations from the reference BG occur in rare instances (<0.1%) when the CGM temporarily reads up to 70 mg/dl higher than the reference blood glucose (e.g., CGM BG 140, reference BG 70). This can occur due to a lag in the CGM response following a steep drop in BG. More than 99% of CGM values are within 45 mg/dl of the reference value when the CGM value is >100 mg/dl.[4] Therefore, if the target BG was set at 115 mg/dl and the closed-loop system succeeded in tightly clamping the CGM BG at this value, more than 99% of the reference BG values would be between 70–160 mg/dl. In fact, the actual range would be much smaller if the clamp was efficient, since the largest differences between reference and CGM BG occur in the setting of rapid changes in blood glucose.

Practically speaking, a true closed-loop system utilizing subcutaneous sensing and insulin administration cannot be completely efficient, because no feed-forward information is provided about meal timing. Insulin will be administered subcutaneously in response to a rise in blood glucose, but it will take an hour to reach peak effect. Therefore, there will always be a delay in response and at least some hyperglycemic excursion in response to a meal. In light of these constraints, what kind of performance is possible from a closed-loop system? In streptozoticin-treated, diabetic, ambulatory pigs, the closed-loop algorithm of El-Khatib *et al*. achieved a mean venous BG of 140–150 mg/dl over a period of 24 hours with no BG values <60 mg/dl.[5] The set point BG for the algorithm was 100 mg/dl. Therefore, the achieved average BG was <50 mg/dl above the set point with no values >40 mg/dl below the set point. Extrapolating to a set point of 135 mg/dl, we might anticipate an average CGM BG of 185 (corresponding to a HbA1c of ~7.4%), no CGM BG values below 95, and no reference BG values below 50 mg/dl. Therefore, this system may be capable of approaching the American Diabetes Association goal of an HbA1c less than 7% without any input from the patient and no anticipation of meals, despite the current limitations of CGM technology. Because the diabetic pigs ate meals consisting of a much higher ratio of carbohydrate to body mass than humans would ever eat (200–300 g of carbohydrate over ~20 minutes for a 50 kg pig, for example), hyperglycemic excursion after meals in humans could be smaller. Excursions could be further limited by providing some rapid-acting insulin in anticipation of the meal ("assisted closed-loop").

The CGM performance described in this scenario is that of the Abbott Diabetes Care Freestyle Navigator®.[4] The performance of the MiniMed Guardian® RT is similar in the normoglycemic range that is relevant in this scenario.[6] Therefore, this degree of performance is realistic and achievable with technology that is commercially available today. The achievement of adequate glycemic control in this scenario is critically dependent on maintaining a relatively small differential between the target BG for the algorithm and the achieved mean BG, without causing hypoglycemia. The two issues are closely connected because the ability to counteract hypoglycemia allows

more aggressive response to hyperglycemia while limiting the risk. The only published, closed-loop data in humans comes from Steil *et al.*[7] and Weinzimer *et al.*[8] using the Medtronic MiniMed CGMS® and insulin pump linked by a PID controller. The Steil *et al.* study involved 30-hour, closed-loop experiments in 10 subjects with type 1 diabetes. In addition to requiring an initial ~12-hour settling period, the closed-loop control system performance necessitated interventions with oral glucose (e.g., orange juice) to reverse episodic hypoglycemia on 13 different occasions.[7] This is clearly undesirable, especially since hypoglycemia may occur at night when the person with diabetes is asleep. Potential remedies include modifying the controller to include an inhibitory effect of insulin on subsequent insulin administration, or having the controller keep track and act in light of insulin on board. As an additional safeguard measure, El-Khatib and colleagues enabled their control system to prevent impending hypoglycemia by administering small, subcutaneous doses of glucagon in increments of 0.5 µg using an insulin pump and a standard insulin infusion set.[9] They have shown that the effect is extremely rapid, peaking in ~15 minutes. The biologic activity of reconstituted glucagon is stable for at least 1 week when kept near body temperature, so it may be used practically in an ambulatory, closed-loop device.[10] The use of glucagon allows the closed-loop controller to be more aggressive in the administration of insulin, because excessive insulin effect can be countered to prevent hypoglycemia. The threshold for glucagon administration can be set independently from the target blood glucose, so that the degree of hypoglycemia allowed by the controller is tunable. The use of glucagon is unique to El-Khatib *et al.*'s system and may provide an important advantage over systems that do not have counter-regulatory capability. This system is nearing human trials. Other closed-loop systems utilizing distinct control algorithms are also moving toward human trials. The potential of CGM to drive closed-loop control should become clearer over the next year as the results of these trials are reported.

CGM to Improve the Safety of Intensive Insulin Therapy in Critical Illness

Since the groundbreaking report by Van den Berghe *et al.* in 2001 that intensive insulin therapy (IIT) can reduce mortality and morbidity in hyperglycemic ICU patients,[11] IIT has become the *de facto* standard of care. The primary known risk of this therapy is hypoglycemia.[11,12] Most ICU protocols specify point of care testing every 1–2 hours, which takes tremendous nursing resources. Therefore, there is a pressing need for automated BG monitoring in the critical care setting. There is an FDA-approved device, the Via Blood Glucose Monitor (a.k.a. Glucoscout, International Biomedical), available for frequent sampling of arterial or venous BG. This device measures BG *ex vivo* with traditional enzyme-based chemistry and reinfuses the blood through a sterile circuit so there is no net blood loss. This device and others being developed that also sample blood directly are appealing because they avoid any physiologic lag between blood and interstitial fluid glucose. On the other hand, this approach raises distinct safety concerns. If a central venous catheter is used for glucose monitoring, it should be dedicated solely to this purpose. Otherwise, there is a risk that the sampled blood will be contaminated by glucose-containing solutions infused through another lumen of the same catheter. The resulting overestimation of BG could lead to inappropriate insulin treatment and dangerous, cryptic hypoglycemia. Likewise, if peripheral venous access is used, the catheter for glucose measurements must be the one placed most distally in that limb to avoid spurious results from glucose infused peripherally. If radial arterial access is used, reinfusion of blood and flush could cause significant edema in the hand. Sufficient access for multiple infusions is often a problem in critically ill patients, and the need for additional access could make these devices impractical in some cases. Finally, even if additional access could be obtained easily, every piece of intravascular hardware increases the risk for bloodstream infection.

Given the safety and practical concerns associated with sampling blood for glucose measurements, ISF CGM may have a role in glucose monitoring of critically ill patients. There are several studies that have investigated this use of CGM.[13-18] In general, the agreement between reference BG measurements and CGM measurements has been good. Concerns about discordance between ISF glucose and BG in critically patients have largely not been realized. All of these studies have been relatively small (144 subjects studied in total), but the most significant weakness in this literature is very few paired reference and CGM glucose measurements in the hypoglycemic range. Studies that are adequately powered to draw conclusions about the accuracy of CGM devices in the hypoglycemic range are needed to determine the potential of CGM in this setting.

If the accuracy of ISF-sensing, CGM devices is adequate, the next question will be whether providing this data to ICU caregivers will improve time in range and reduce the number, duration, and severity of hypoglycemic excursion. Alarm criteria will have to be optimized to maximize

sensitivity for severe hypoglycemia while also reducing the number of false alarms. Insulin infusion algorithms will have to be modified to anticipate very frequent measurements and the availability of trend information. The availability of these tools may make it easier both to implement intensive insulin therapy, but also to perform studies that can resolve remaining controversies about its efficacy. The VISEP and GLUCONTROL trials of IIT were halted for safety concerns due to excessive, severe hypoglycemia, demonstrating that implementation of IIT remains a challenge.[19]

If CGM can prove its value in the ICU, there may be less resistance to implementation from the standpoint of costs than in the outpatient setting. In addition to improvement in morbidity and mortality, studies of IIT have also reported reduction in length of stay (LOS) in the ICU. The 2001 Van den Berghe *et al*. study reported a reduction of 3 days in the average stay of patients who were in a surgical ICU for more than 5 days.[11] Because the expense associated with ICU care is so high, the cost of a disposable sensor sufficient for 5–7 days of monitoring ($30–40 for outpatient devices) could be paid for by a reduction in the length of stay measured in minutes.

CGM to Improve Glycemic Management of Hospitalized Diabetic Patients Without Critical Illness

CGM could also have a role in improving glycemic management in the much larger population of noncritically ill inpatients with diabetes. More than 25% of inpatients in U.S. hospitals have diabetes, and both hyperglycemia and hypoglycemia are common.[20,21] CGM may help to improve the glycemic control of noncritically ill inpatients by several mechanisms. First, review of CGM data from the previous day at rounds would encourage adjustment of the insulin regimen, and provide the data required to do this intelligently. Second, the availability of alarms, ideally transmitted to the nurses' station by telemetry, would reduce the perceived risk associated with aggressive BG control. It seems likely that CGM monitoring would not replace standard, point-of-care testing, but would supplement it by rapidly drawing attention to patients with poor control or hypoglycemia, and by providing additional data for insulin regimen adjustment. The primary challenge in designing trials to investigate the utility of this approach is choosing which outcomes to measure. Initially, trials could be designed to measure improvements in glycemic control and reduction in hypoglycemia. Eventually, however, endpoints such as LOS and morbidity will likely be required to justify the expense of widely implementing CGM in hospitalized diabetes patients.

Finally, it is possible that closed-loop BG control devices, originally intended for use in type 1 diabetes patients in the outpatient setting, may come to be used for both type 1 and type 2 diabetes patients in the inpatient ward setting as well. While the devices designed for outpatient use would probably be adapted easily for ward inpatient use, automated closed-loop BG control in the ICU will be qualitatively different. ICU closed-loop devices will use intravenous insulin and glucose rather than subcutaneous insulin and glucagons, and will likely sample blood directly rather than relying on ISF sensing in most cases.

Conclusions

Closed-loop control is likely the critical technology that will drive adoption of ISF CGM in the outpatient setting, at least until something less invasive or more accurate replaces it. Monitoring for safety in a hospital setting may also contribute to wider adoption of this technology, especially in the non-ICU setting where frequent blood sampling is impractical but where improved glucose control is still desirable.

Disclosures:

Dr. Russell has received grant support for an investigator-initiated study from Abbott Diabetes Care. He is the principal investigator of a clinical trial of the closed-loop glucose control system developed by Firas El-Khatib, Ph.D. and Edward Damiano, Ph.D.

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