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Continuous Measurement of Glucose

Facts and Challenges

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CLINICAL practice guidelines increasingly call for clinicians to meet benchmarks of care and use surrogate laboratory data as a marker of compliance. Blood glucose homeostasis and proper monitoring in perioperative and critically ill patients is currently an intense area of emphasis and investigation.[1] Since 2001, the target concentration for blood glucose has gone from tight control (80–110 mg/dl)[2] to a more liberal goal (<180 mg/dl).[3–5] The most recent recommendations evolved because of concerns over increased mortality in patients who developed hypoglycemia, often during intense insulin therapy.

Traditionally, glucose has been measured with highly accurate central laboratory devices (CLDs) or blood gas analyzers. Point-of-care (POC) meters, however, have migrated to the hospital bedside, although their accuracy for bedside use has come under scrutiny.[6]

Optimal ambulatory and hospital management of hyperglycemia has driven the pursuit of real-time glucose monitoring systems.[7] The difficulty of maintaining intraoperative glucose control favors improved monitoring methods.[8] In addition, critically ill patients with stress-induced dysglycemia may be at high risk and benefit from improved glucose measurement.[9] The first continuous glucose monitor (CGM) was approved for use in the United States in 2005. Compared with the CLD, CGMs have limitations. There are significant challenges to resolve before CGMs can be approved for use in the perioperative period or critical care setting. The individual glucose readings may be inaccurate in comparison with one-time measurements. Nonetheless, there is evidence that CGM use in ambulatory patients with type 1 diabetes can both decrease HbA1c and reduce the incidence of hypoglycemic episodes.[10] In addition, in a prospective randomized trial, Holzinger *et al.*[11] reported that the use of CGM reduced the incidence of hypoglycemia in critically ill patients. Because newer CGMs are likely to be used in perioperative and critically ill patients, it is important that future studies access clinical outcomes such that health care providers understand both the capabilities and limitations of these devices. This commentary addresses these points and comments on future development of CGMs.

Site of Measurement

The three Food and Drug Administration (FDA)-approved CGM systems all use the subcutaneous space and measure glucose in interstitial fluid (IF). The small glucose molecule (180 Da) is transferred from blood to the IF fairly rapidly and without a transporter. There is a noticeable lag when comparing changes in blood glucose to the measured value in IF, but the implications of this remain controversial.[12] The lag time differs depending on the sensor used.[13] Although it has been speculated that CGM in the subcutaneous space might be inaccurate during shock, Holzinger *et al.* reported no effect on CGM accuracy over a 72-h study period in a series of patients in circulatory failure requiring norepinephrine.[11]

There are no approved devices in the United States that use an intravascular sensor, but a number of companies continue to pursue this approach. A Swedish company, CMA Microdialysis (Solna, Sweden), has recently introduced a CGM system in Europe using microdialysis that works in conjunction with a central venous catheter. Although these devices lack a lag time in glucose equilibration, a number of potential problems are associated with central venous access

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including infection, clot formation, need for a dedicated vascular port, and interference from other infused substances.

Several CGMs currently under development assay glucose using whole blood obtained from a peripheral or central vein. One approach using hydrogel technology was the subject of a recent report in ANESTHESIOLOGY.[14] These sensor data were compared with arterial blood gas values measured conventionally in a series of pig experiments. Although the data seemed excellent, there are a number of potential pitfalls with this technology as it moves from the bench to the bedside. The primary problem for intravascular and subcutaneous devices is buildup of tissue deposits (so-called biofilm) on the sensor surface (see the article by Wang *et al.*[15] for a complete discussion), making them progressively inaccurate over time and requiring frequent recalibrations and sometimes, replacement. There are also several techniques that aspirate whole blood to an *ex vivo* bedside measurement device. These include the OptiScan technology that aspirates 3 ml whole blood every 15 min, centrifuges it, measures glucose in approximately 0.15 ml plasma with a mid-infrared sensor, and then returns the remaining blood to the patient.[16] Other devices test aspirated blood using enzyme-based systems similar to the popular POC devices.[6]

Sensor Technologies

Clinically available CGMs use enzyme-based technologies. Glucose from the IF reacts with an enzyme system, generating either a measured molecule such as nicotinamide adenine dinucleotide or an electrical current, which is then translated into a glucose reading (see the article by Rice *et al.*[6] for a more complete discussion). Because there is a long history of using these enzyme-based systems in POC devices, an obvious advantage is that interferences and other potential problems are well known (see interferences section below).

Measurement Limitations

Accuracy

The attractiveness and advantage of CGM is obvious: real-time, frequent glucose measurements. The tradeoff is a reduction in accuracy compared with CLDs. An often-used analogy, but worth repeating, is that the single glucose measurements can be equated to a still camera and the CGM compared with a camcorder.[17] The camera gives a single, very accurate picture in time, just as the CLD provides a very accurate glucose measurement. The camcorder affords a fuzzy image, but these series of pictures, although not as clear as the images from the still camera, give real-time information and direction of change. Likewise, the CGM supplies a series of glucose values that are not as accurate as the CLD, but provides real-time direction and rate of change information. This advantage, especially in direction of change, is potentially invaluable for directing therapies and possibly predicting hypoglycemia. Each marketed device has a particular accuracy profile, but none are nearly as accurate as CLDs. For a comprehensive discussion of accuracy of each of the FDA-approved CGM systems, please see the article by Clarke and Kovatchev.[18]

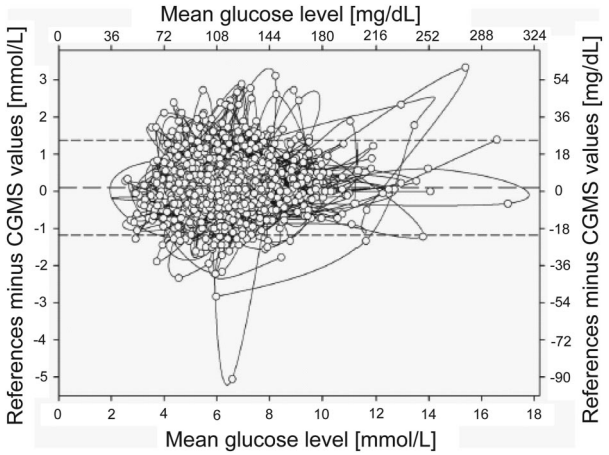

Fig. 1. A Bland-Altman plot using repeated measures to present the agreement between the continuous glucose-monitoring system and reference, with the data points of individual patients connected by a line. The limits of agreement are −21 mg/dl and 25 mg/dl. CGMS = continuous glucose-monitoring system. (Reproduced with permission from Brunner R, Kitzberger R, Miehsler W, Herkner H, Madl C, Holzinger U: Accuracy and reliability of a subcutaneous continuous glucose-monitoring system in critically ill patients. Crit Care Med 2011; 39:659–64.)

Assessing CGM accuracy as a "clinician-consumer" can be very challenging, and the following graphic example illustrates this crucial point. Brunner *et al.*[19] reported 2,045 CGM data points paired with blood gas analyzer values and calculated a Pearson correlation coefficient of 0.92, with 92.9% of the values meeting International Organization for Standardization standards (see Regulatory Issues). They concluded that the system is "… reliable for use in critically ill patients …" and showed "… strong correlation …" to reference readings. Figure 1 is a Bland-Altman plot showing that even in the hypoglycemic range (less than 75 mg/dl), there are a number of points that measured falsely high by greater than 25 mg/dl[19]; this is an error that could lead to a severe outcome if left undetected. It should be noted that when the results of the CGM were plotted against a blood gas analyzer on an insulin titration grid (showing the correct action with respect to insulin therapy), >99.1% of the values were in the clinically acceptable treatment zones.[19,20]

Sensor Drift

CGM sensors all require calibration, some several times a day, to ensure accuracy to meet the manufacturer's specifications. It would be best to calibrate CGM with a CLD or blood gas analyzer, because many of the POC meters lack FDA-required accuracy standards.[6] However, because many CGM are calibrated outside of a health care facility, the most accurate device available should be used. Many newer tech-

nologies in the developmental stages are exciting, but may be affected by significant sensor drift compared with the IF-based devices. This will be a concern moving forward for regulatory approval. One reason for drift in some CGMs in development is tissue (or biofilm) deposition on the sensor. There are efforts under way to inhibit this drift, but as of now, it remains unresolved. Because of this drift over time, the sensors need to be replaced at various intervals depending on the individual product.

Measurement Lag

All CGM systems that measure IF in the subcutaneous space have a lag time between the blood and IF, which is approximately 7–15 min. It has been reported that the DexCom Seven® system (DexCom, Inc., San Diego, CA) has the least lag,[13] at 7 min. Recently, some postulated that this time lag may be similar to the delay in blood glucose change between the vascular space and the central nervous system, implying that the lag seen with the CGM may, in fact, parallel the central nervous system. If this theory is correct, the delay in the current CGM systems may more accurately reflect central nervous system glucose concentrations than we previously realized. These delays have neither been measured in anesthetized patients where decreased tissue perfusion may increase lag nor have they been compared with highly sensitive microdialysis measurements of brain glucose.

Interferences

CGM will all have different interferences. The enzyme-based devices, depending on which enzyme is used, have a number of drug interferences including acetaminophen, maltose (a breakdown product of icodextrin in peritoneal dialysis fluid), ascorbic acid, dopamine, and mannitol. Inaccuracy may occur in some devices due to changes in pH, hematocrit levels, blood oxygen tension, and peripheral perfusion. For an excellent discussion of enzyme interferences, see the article by Dungan *et al.*[21] The interferences of emerging technologies are mostly undetermined.

Infection Risk and Need for Anticoagulation

The placement of a foreign body in a patient with diabetes is always worrisome, but the risk of infection with subcutaneous sensors compared with intravascular probes seems low. Some of the newer technologies using peripheral intravenous catheters, or even more concerning, central venous catheters for blood sampling, certainly raise concerns. In addition, some of the intravenous technologies in development require the use of an anticoagulant (*e.g.*, heparin) to prevent blood from clotting on the sensor surface or in the device itself. With the incidence of heparin-induced thrombocytopenia on the rise, exposure of large numbers of patients to heparin may be problematic.

Statistical Accuracy *versus* Clinical Reality: FDA Labeling

Evaluating CGM

CGM is currently more of a "direction of change" than an absolute blood glucose value monitor. Currently, it cannot be relied on for exact point-to-point accuracy, and the traditional statistical treatments such as the Bland-Altman plots[22] will not suffice in substantiating accuracy. In 2004 Clarke and colleagues[17] introduced the continuous glucose-error grid analysis. This appears to be a natural extension of the original Clarke error grid,[23] which addressed device error in glucose measurement in terms of severity of an incorrect intervention (or lack of intervention). The continuous glucose-error grid analysis not only plots accuracy of the device compared with a standard, but it marks temporal characteristics of the CGM, noting the ability to predict future trending. Thus, rate and direction of change are rated by the continuous glucose-error grid analysis and give a potential yardstick with which to compare CGM systems. It is also important that CGM products be evaluated in the hypoglycemic range, because it is clinically most relevant to be accurate at levels less than 70 mg/dl. These concepts were clarified and further refined in an in-depth analysis by Clarke and Kovatchev[24] describing the statistical tools available for evaluation of CGM, which can be directly applied to the perioperative arena. Specifically, the use of risk assessment is especially useful. In addition, bias should not be a measurement tool for CGM systems. If the device is equally inaccurate above and below reference values, the bias can be very close to zero, implying an accurate tool. For example, a shotgun blast, randomly focused on a target, has a bias close to zero because the points are spread evenly around a point.[25]

Regulatory Issues

Although the FDA has set certain standards (we are using the FDA regulations as a benchmark, but European Union standards are similar) for POC glucose meter accuracy,[6] the agency has not set standards for CGM.[26] There is no evidence that we know of that these POC meters are more accurate than the CGM. However, the POC devices were designed, approved, and marketed through an older regulatory process. In fairness, it is more complicated to set an accuracy target for CGM when, in addition to point accuracy, issues such as lag, direction, and magnitude of change over time must be taken into account. Recognition by the FDA and others of the continuous glucose-error grid analysis would go a long way toward setting this standard. It should be noted that POC glucose meter standards as set by the International Organization for Standardization are within 20% for values more than 75 mg/dl and within 15 mg/dl for values $\leq$75 mg/dl.[27] It is crucial to note that most POC meters, however, do not currently meet this standard.[6] CGM meters are not approved as stand-alone measurement devices for blood glucose and need to be backed up with an approved measurement device. The three CGM systems commercially

Table 1. Continuous Glucose Monitoring Systems: Today, Tomorrow, and Yesterday

Measurement Site	Technology	Manufacturer	Approved	Lag	Implant Lifespan
IF	GO/amperometric	Medtronic Minimed	FDA	7–15 min	3 days
IF	GO/amperometric	DexCom	FDA	7–15 min	7 days
IF	GO/wired enzyme	Abbott	FDA	7–15 min	5 days
IF	GO/microdialysis	GlucoDay	EU	?7–15 min	2 days
IV	Midinfrared spec	Optiscan	No	None	—
IV	Hydrogel	None	No	Unknown	—
IV	Fluorescent chemistry	Glumetrics	No	?None	—
IV	Fluorescent chemistry	GlySure	No	?None	—
Transdermal	Iontophoresis	GlucoWatch	FDA rescinded	Unknown	—
Optical	Dozens	None	No	Unknown	—
Tears	GO/fluids	None	No	Unknown	—
Anterior chamber	Polarization	None	No	Significant	—

EU = European Union; FDA = Food and Drug Administration; GO = glucose oxidase; IF = interstitial fluid; IV = intravenous.

available in the United States are shown in the upper portion of table 1.

Practical Aspects for Perioperative Medicine

What should the clinician do perioperatively with a CGM? We see no reason that these devices should be removed perioperatively, especially for cases in which the sensor does not enter the prepped field. CGM has been studied in 8 adults during abdominal surgery,[28] with the subcutaneous sensors placed in either the shoulder or the upper leg, and in 20 pediatric cardiac patients,[28] with the subcutaneous sensors placed in the abdomen or lower extremity. Although there was no adverse outcome from the sensors noted in either study, the accuracy reported was not within International Organization for Standardization guidelines for glucose measurement devices. Figure 2 is a Clarke error grid of the data from these pediatric surgical patients. Note the lack of data in the hypoglycemic range, which is the critical area to assess in evaluation of a glucose measurement tool. Interestingly, Piper *et al.*[29] reported an intraoperative alarm in 10 of the 20 patients, triggered by electrical interference, which correlated with the use of electrocautery. This contributed to unsuccessful use of the CGM during surgery in these patients. We are unaware of any recommendations regarding the use of CGM during surgery. Furthermore, except for a few studies, CGMs have not been thoroughly evaluated during surgical situations, where a number of factors, including altered peripheral tissue perfusion with resultant change in IF composition, may make the results even more suspect. Desachy *et al.*[30] reported poor correlation between a POC glucose meter and CLD measurements in critically ill patients with a low perfusion index (indicating poor peripheral perfusion). The individual readings from the CGM should not be used for therapy, but they may be used reasonably as a guide for initiating laboratory confirmation. As CGM technologies improve, however, the availability of near-continuous automated glucose values in the perioperative environment with little additional nursing work may become very advantageous.

Technologies on the Horizon

In addition to the currently approved CGM systems, there are a number of private and academic efforts to develop, manufacture, and market improved CGM devices. The obvious goals are increased accuracy, reduced cost, and perhaps less invasive approaches. In addition to clinical uses, CGM may become a valuable research tool. Because many of these companies operate in a "stealth" mode and academic groups

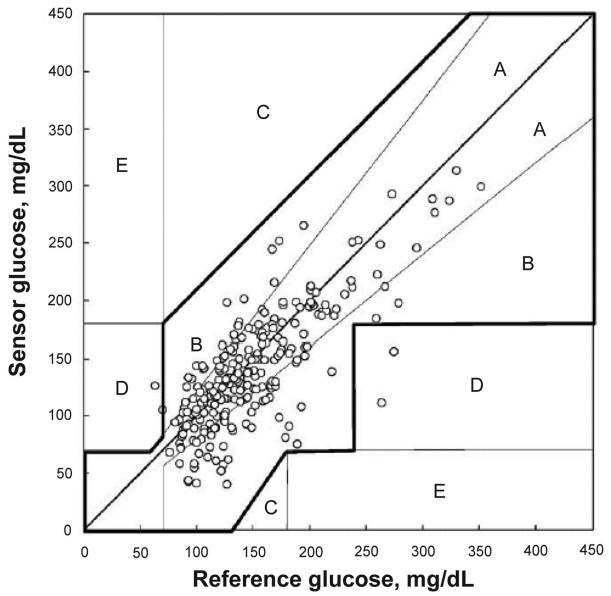

Fig. 2. A Clarke error grid for comparison points between continuous glucose-monitoring system and reference. Zone A: values differ from each other by no more than 20%. Zone B: values differ by more than 20% but do not result in an adverse treatment. Zone C: may result in overcorrection of an acceptable glucose value. Zone D: would not result in correction when, in truth, treatment should be administered. Zone E: would prompt inverse treatment. (Reproduced with permission from Piper HG, Alexander JL, Shukla A, Pigula F, Costello JM, Laussen PC, Jaksic T, Agus MS: Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. Pediatrics 2006; 118:1176–84.)

are sometimes hesitant to publish results for fear of having their technology copied, it is impossible to know all of the current efforts. Table 1 contains a partial list of CGM development efforts under way.

The Ideal CGM

The perfect CGM system would be:

- Rapid: there should be very little lag between blood glucose and the measured value.
- Accurate: each measurement should be within FDA accuracy guidelines.
- Free of interferences: there should be very few, if any, important interferences such as drugs or physiologic perturbations.
- Inert: the sensor should not react with the tissue or form a coating rendering the device inaccurate over time.
- Robust: the system must be able to perform within the dynamic and busy intensive care unit and operative setting.
- Lack of invasiveness: the system should be minimally to noninvasive to eliminate risk of infection, thrombosis, *etc*.
- Cost effective: the system should not be expensive in comparison with frequent laboratory glucose measurements.

Closing the Loop: The Artificial Pancreas

If CGM reaches a point of acceptable accuracy (as yet to be defined), the hope is to combine this technology with an insulin pump, thus creating an artificial pancreas. Early ambulatory efforts in combining CGM with modern insulin pump technology has been very encouraging, with reduction in HgbA1c and fewer episodes of hypoglycemia.[31] Newer insulin pump technology is becoming mainstream therapy for many with type 1 diabetes. See the article by Cook *et al.*[32] for proposed insulin pump inpatient guidelines that are likely to expand.

Conclusion

CGM systems are increasingly used in the management of individuals with type 1 diabetes, as well as select individuals with type 2 diabetes. These devices are likely to migrate to the perioperative environment, and anesthesiologists need to be familiar with them and know their limitations. Although CGMs may facilitate glucose control and insulin administration, there are data to support the safe application of bedside paper or computer-based algorithms guided by intermittent glucose measurements to achieve therapeutic goals.[33] These protocols vary in approach and application and appear to be most effective when applied in an individual institution in a coordinated manner.[5]

The commercial glucose measurement market is in the billions of dollars and CGM is rapidly tapping into this arena. Inevitably, with any quest for a piece of such a large market comes exciting technologies that all too often fall short of promises and expectations. As clinicians caring for these patients, we have the obligation to critically analyze new technologies to assure ourselves that we are targeting precious resources for maximum patient benefit.

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