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Abstract

Stress hyperglycemia and hypoglycemia are associated with increased morbidity and mortality in the critically ill. Intermittent, random blood glucose (BG) measurements can miss episodes of hyper- and hypoglycemia. The purpose of this study was to determine the accuracy of the Symphony® continuous glucose monitor (CGM) in critically ill cardiac surgery patients. Fifteen adult cardiac surgery patients were evaluated immediately postoperatively in the intensive care unit. Prelude® SkinPrep prepared the skin and a sensor was applied to 2 test sites on each subject to monitor interstitial fluid glucose. Reference BG was sampled at 30- to 60-minute intervals. The skin at the test sites was inspected for adverse effects. Accuracy of the retrospectively analyzed CGM data relative to reference BG values was determined using continuous glucose-error grid analysis (CG-EGA) and mean absolute relative difference (MARD). Using 570 Symphony CGM glucose readings paired with reference BG measurements, CG-EGA showed that 99.6% of the readings were within zones A and B. BG measurements ranged from 73 to 251 mg/dL. The MARD was 12.3%. No adverse device effects were reported. The Symphony CGM system is able to safely, continuously, and noninvasively monitor glucose in the transdermal interstitial fluid of cardiac surgery intensive care unit patients with accuracy similar to that reported with other CGM systems. Future versions of the system will need real-time data analysis, fast warm-up, and less frequent calibrations to be used in the clinical setting.

Keywords

biosensor, continuous glucose, diabetes, intensive care, tight glycemic, transdermal

Severe hyperglycemia has been shown convincingly to be detrimental in acutely ill patients in terms of both mortality and morbidity.^{1–5} Specifically in cardiac surgery patients, uncontrolled hyperglycemia is associated with higher rates of death and complications such as sternal wound and other nosocomial infections.^{6–9} In addition, hypoglycemia is strongly correlated with mortality in critically ill patients^{10–13} and even 1 episode of severe hypoglycemia (blood glucose [BG] < 40 mg/dL) has been independently associated with an increased risk of death.¹⁰

Intensive insulin protocols, a fundamental tool for glycemic control, have become ubiquitous in intensive care units (ICUs). In fact, greater than 90% of hospitals surveyed practiced tight glycemic control in their ICUs.¹⁴ In a survey of ICU managers, 80% listed increased time investment as the major drawback to intensive insulin therapy while patient discomfort secondary to frequent blood testing was cited by 30% of participants.¹⁴

Critically ill patients stand to benefit from implementing continuous glucose monitoring (CGM) to improve intensive

insulin therapy.^{15–16} CGM systems range from invasive (intravascular) to noninvasive (transdermal).¹⁶ Minimally invasive and noninvasive technologies exist on a spectrum and rely on measuring BG from interstitial fluid, across the skin, or via saliva and tears. Methods to capture and analyze interstitial fluid include iontophoresis, electrical current applied across the skin; sonophoresis, low-frequency ultrasound applied across the skin; skin blister technique; micro-pore technique; and microneedle technique.¹⁷ Accepted metrics to evaluate accuracy and compare CGM systems include Clarke error grid (CEG) analysis,¹⁸ continuous

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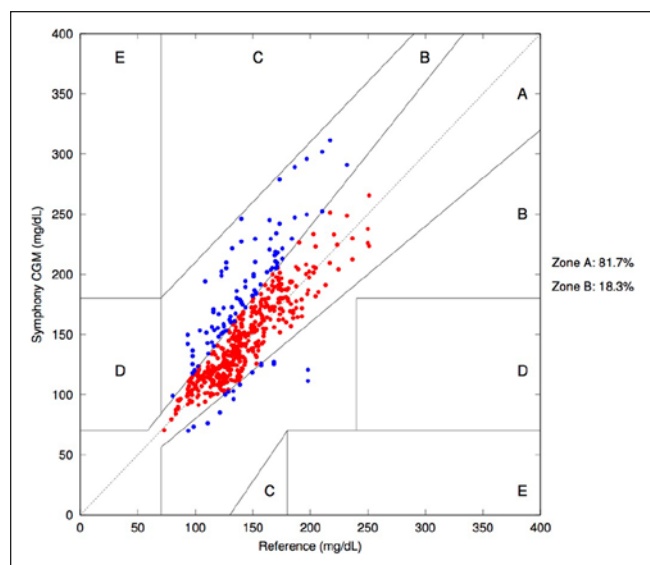


Figure 1. Clarke error grid analysis. Zone A is defined as clinically accurate. Zone B indicates that an incorrect, but benign treatment is given. Zone C indicates that an overcorrective treatment is given. Zone D represents values where an error was not detected. Zone E corresponds to erroneous treatment being given. In this data set, 81.7% of values fell in zone A while 18.3% fell in zone B.

glucose-error grid analysis (CG-EGA),¹⁹ and mean absolute relative difference (MARD).^{20,21} The CEG plots the device values versus a reference control and is divided into 5 areas (Figure 1).¹⁸ The CG-EGA aims to show errors in rate and direction of BG change between the device and control by combining a point-error grid (P-EGA) and rate-error grid (R-EGA).¹⁹ The MARD is the measure of relative difference between device and reference BG measurements.^{20,21} A lower MARD corresponds with a more accurate device.²¹

Schierenbeck et al showed that in 30 cardiac surgery patients, glucose measured with a central venous catheter with integrated microdialysis produced a MARD of 5.6% and 100% of values within zones A and B on CEG analysis.²² Kosiborod et al reported a MARD of 12.2% for a subcutaneous system.²³ Our group reported a MARD of 12.4% with an earlier version of a transdermal system.²⁴

Subcutaneous and transdermal systems utilize interstitial fluid for glucose measurement. Glucose diffuses from the capillary endothelium to the interstitial fluid without a transporter. Thus, differences in blood flow affect the BG concentration. Moreover, the metabolic rate of adjacent cells, presence of insulin, and nerve stimulation influence interstitial fluid glucose levels.²⁵ Nevertheless, Holzinger et al showed that the accuracy of subcutaneous glucose monitors was unchanged with circulatory shock requiring treatment with norepinephrine.²⁶ The present study was designed to determine the accuracy of a transdermal CGM, the Symphony® CGM (Echo Therapeutics, Philadelphia, PA, USA), in critically ill cardiac surgery patients.

Methods

Study Population

The study was performed in the 10 bed cardiothoracic ICU at Tufts Medical Center in Boston, Massachusetts. Patients were recruited between February 15 and April 1, 2012. Adult patients scheduled for elective cardiac surgery who were expected to receive intensive insulin therapy during their stay in the ICU were eligible for inclusion unless 1 or more of the following criteria were met: currently enrolled in another trial, abnormal skin conditions on the target site (tattoo, scar, excessive hair, rash, inflammation, etc), known history of hypersensitivity to glucose oxidase or medical adhesives, and pregnancy. The insulin protocol in place in the cardiothoracic ICU called for a BG range of 100-180 mg/dL, especially geared to avoid hypoglycemic episodes. The Tufts Medical Center Institutional Review Board approved the protocol.

We chose this patient population because, throughout the procedure and afterward, there are frequent and unpredictable changes in blood sugar levels. There are also changes in core temperature that may affect perfusion to the subcutaneous elements. We wanted to demonstrate the “robust” nature of this device in a rapidly changing glucose environment. Having continuous glucose data will also aid in understanding the pharmacokinetics of IV insulin.

Study Design

Fifteen adult patients were enrolled in the study after reviewing and signing an informed consent. Subject demographics were recorded. A study investigator identified 2 test sites on the upper arm of each patient and applied a target base to each site. The Prelude® SkinPrep (Echo Therapeutics, Philadelphia, PA, USA) was used to remove dead skin cells in a 6 mm circle at the center of each target base so that interstitial fluid glucose could be accessed. A controlled microdermabrasion process was utilized to minimize any disruption or inflammation at the site. A Symphony CGM sensor was then applied at each site. The mean device lag time was 10 minutes. After a 1-hour warm-up period, sensor data recording was initiated with data points stored in the transmitters every minute for 24 hours. During this time, arterial blood samples were taken at 30- to 60-minute intervals. The reference BG values were measured with the YSI 2300 Stat+ Glucose Analyzer (YSI Inc, Yellow Springs, OH, USA), converted to plasma equivalent values using each patient’s measured hemoglobin level. At the conclusion of the study, the skin at the test sites was inspected for redness or any other effects from the sensor, abrasion, or adhesive and graded on a 4-point scale, with follow-up inspection at 1 and 7 days.

The CGM values were blinded to all study and clinical personnel. After the sensors were removed, the data were downloaded to a PC for replay through a monitor simulator to retrospectively apply the prospective calibration algorithm,

Table 1. Patient Characteristics.

Gender	
Female	27% (4/15)
Male	73% (11/15)
Age (years)	
Mean/SD	63.5/12.6
Min/median/max	39/61/87
BMI (kg/m ²)	
Mean/SD	28.4/7.0
Min/median/max	16.8/28.9/45
History of diabetes	
None	80% (12/15)
Type 1	6.7% (1/15)
Type 2	13.3% (2/15)

Max, maximum; Min, minimum; SD, standard deviation.

using reference BG values. Calibration was performed every 4 hours, at 1, 5, 9, 13, 17, and 21 hours after sensor application.

Analysis

Device performance was evaluated for clinical, point and rate accuracy using a variety of methods, including CG-EGA (The Epsilon Group, Charlottesville, VA, USA),¹⁹ MARD,^{20,21} mean absolute difference (MAD),²⁰ ISO 15197:2003 guidelines.²⁷ Analysis was completed using Matlab (MathWorks, Natick, MA, USA) and Excel (Microsoft, Redmond, WA, USA).

Results

Patient characteristics for the 15 study patients are included in Table 1. BG measurements ranged from 73 to 251 mg/dL. Using 570 Symphony CGM glucose readings retrospectively analyzed and paired with reference BG measurements, CG-EGA showed that 99.6% of the readings were within zones A and B. The MARD was 12.3%. On CEG Analysis, 81.7% of values fell within zone A and 18.3% of values fell within zone B (Figures 1 & 2). A modified Bland-Altman plot comparing the difference between the paired CGM and reference BG value to the reference BG for all measurements showed a standard deviation of difference (CGM—reference) of 20.09 and mean of difference (bias) of 7.83 (Figure 3). No adverse device effects were reported for the Prelude skin permeation or the Symphony CGM at 1 and 7 days.

Discussion

The chief finding of this study is that the Symphony CGM was safe and relatively accurate in continuously measuring BG in critically ill patients after cardiac surgery. The Symphony CGM is noninvasive, avoiding needle insertion and the potential for intravascular contamination, and the

MARD was 12.3%. The ideal CGM system should have a low lag time, be accurate, be free of interferences from medications or changes in physiologic states, be adaptable to changing ICU environments, have minimal interaction with skin or surrounding tissues, be minimally invasive, and be cost effective.¹⁶ Limitations of the current Symphony device are lag time, calibration frequency and sensor life, as the dermabrasion site and sensor must be changed after 24 hours of use. Because of the conservative insulin protocol used, severe hypoglycemia was not observed, and the device was not challenged in this range. Device improvements will require real-time BG display, shorter warm-up and lag times, and less frequent required calibrations. Further study in a broader patient population experiencing greater swings in BG is needed.

CGM devices can measure BG in the blood, plasma, or interstitial fluid. The measurement interval varies from every 1 minute to every 15 minutes. CGM reports the BG concentration, BG change, and rate of BG change.²⁸ Potential benefits of CGM include closed-loop BG measurement, which include insulin-dosing devices, the possibility to evaluate minute-to-minute responses to interventions, such as early detection of trends toward hyperglycemia and hypoglycemia, and the ability to treat and stabilize BG to target levels.¹⁴

Continuous transdermal glucose monitoring has been shown to be accurate (values falling in zones A and B for CEG analysis) for healthy controls, cardiac surgery patients, and patients with diabetes.²⁴ Ellmerer et al established that subcutaneous adipose tissue monitoring is effective in post-operative cardiac surgery patients and can be used to guide intensive insulin dosing.²⁹ Holzinger et al showed the incidence of hypoglycemia was lower in their study population when CGM was available to the clinical staff. However, CGM did not affect the degree of hyperglycemia when compared to intermittent BG testing, which could possibly be explained by having already achieved tight glycemic control in the intermittent BG testing group.³⁰ In other reports, Jacobs et al showed that their subcutaneous CGM was not sufficiently accurate outside of the euglycemic spectrum³¹ and Brunner et al did not appreciate a difference in the control of glycemic variability in their retrospective study of 63 patients.³²

The clinical accuracy of different continuous monitors in various clinical settings is still being explored. However, it is clear that there is need for a more efficient way of measuring BG in the ICU. Aragon et al showed that more than \$150 000 for nurses' salaries and over \$50 000 for supplies were spent on tight glycemic control in 1 year. Importantly, they showed that over 2 hours per day were spent measuring BG and calculating insulin doses based on paper protocols for each patient.⁶ Aside from the clinical advantage of knowing BG levels and trends in real time and the opportunity to treat proactively, there are economic and logistical needs for more efficient monitoring of BG in the ICU. The unmeasurable

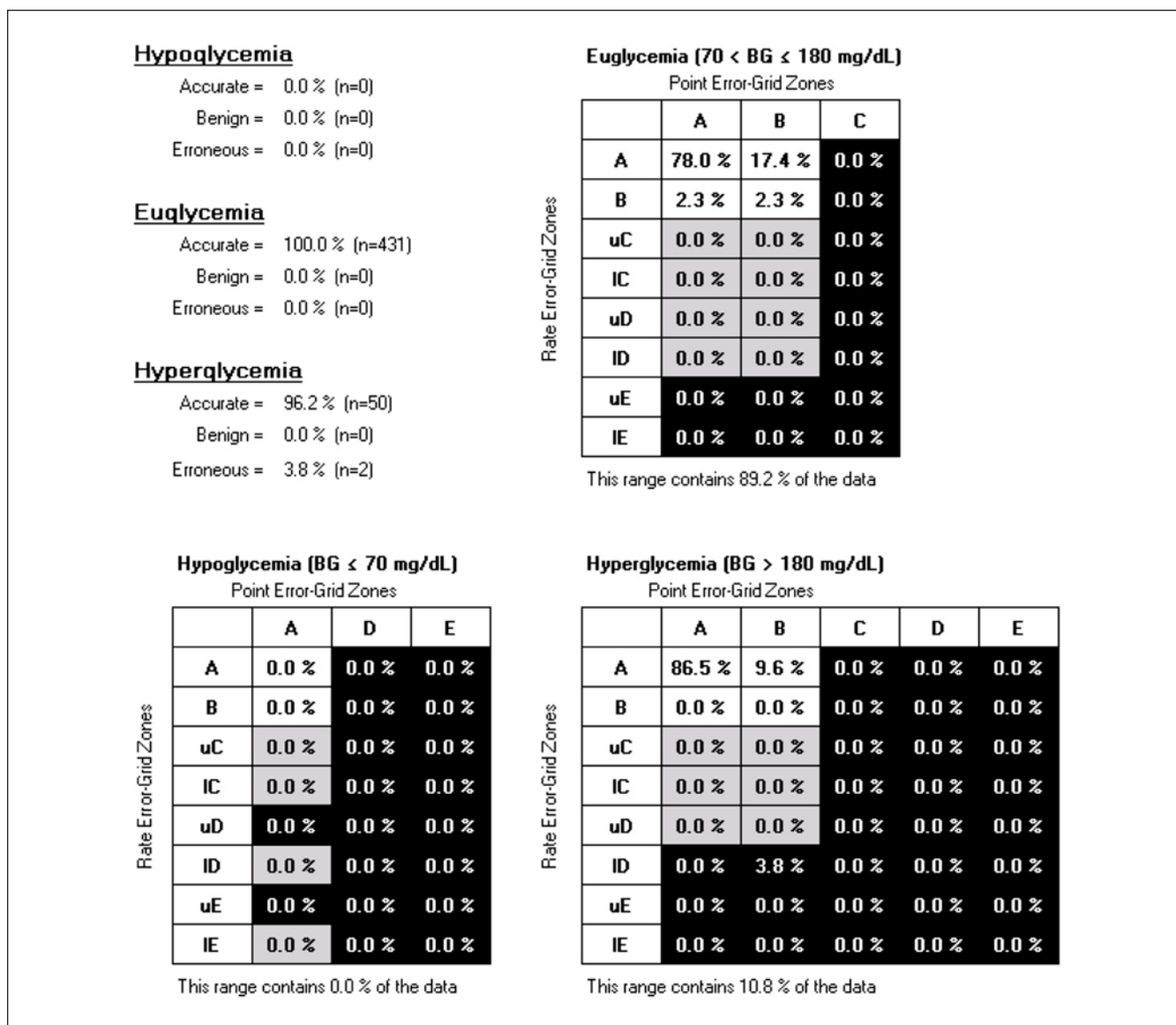


Figure 2. Continuous glucose-error grid analysis (CG-EGA). CG-EGA analysis is included for all measurement and broken down into hypoglycemia (≤ 70 mg/dL), euglycemia (70-180 mg/dL), and hyperglycemia (> 180 mg/dL) categories. Zone A is defined as clinically accurate. Zone B indicates that an incorrect, but benign treatment is given. Zone C indicates that an overcorrective treatment is given. Zone D represents values where an error was not detected. Zone E corresponds to erroneous treatment being given. The boxes shaded white are accurate readings, the boxes shaded gray are benign errors, and the boxes shaded black are erroneous readings. Overall, 99.6% (481/483) of readings were clinically accurate. All of the measurements in the euglycemic spectrum were clinically accurate and 96.2% of measurements in the hyperglycemic spectrum were clinically accurate. There were no measurements of blood glucose < 70 mg/dL in this study.

benefit to recapturing 2 hours of nursing time per patient per day resides in the other duties a skilled nurse can perform in the way of monitoring and caring for the patient.

Conclusions

The Symphony CGM was safe and accurate in measuring and retrospectively analyzing BG in postoperative cardiac surgery ICU patients. A real-time glucose monitor with a

shorter lag time and less frequent calibrations is needed for clinical applicability of the device. Further study in a broader ICU population is needed to verify the applicability to all critically ill patients.

Abbreviations

BG, blood glucose; CEG, Clarke error grid; CG-EGA, continuous glucose-error grid analysis; CGM, continuous glucose monitor; ICU, intensive care unit; MARD, mean absolute relative difference.

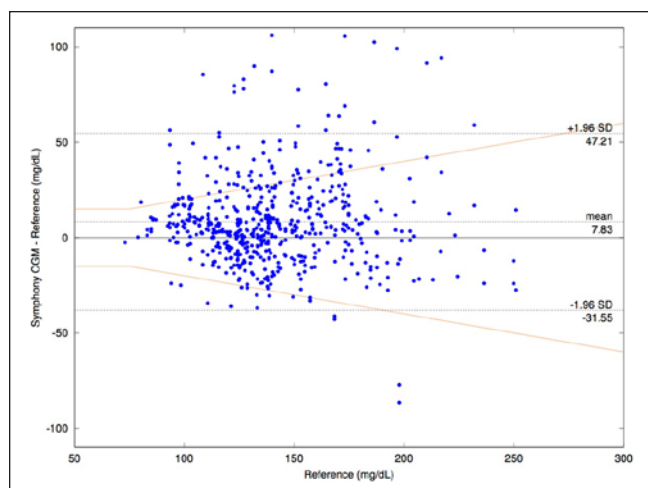


Figure 3. Modified Bland-Altman plot with superimposed ISO 15197:2003 guidelines. A modified Bland-Altman plot comparing the difference between the paired CGM and reference BG value to the reference BG for all measurements. In addition, the limits of the ISO 15197:2003 standard for blood glucose monitoring systems are superimposed for comparison. Standard deviation of difference (CGM—reference) was 20.09. Mean of difference (bias) was 7.83.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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