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ORIGINAL ARTICLE

Real-Time Continuous Glucose Monitoring in an Intensive Care Unit: Better Accuracy in Patients with Septic Shock

Carol Lorencio, M.D.,[1,5]* Yenny Leal, M.Sc.,[2]* Alfonso Bonet, M.D.,[1] Jorge Bondia, Ph.D.,[3] Cesar C. Palerm, Ph.D.,[4] Abdo Tache, M.D.,[1] Josep-Maria Sirvent, M.D.,[1] and Josep Vehi, Ph.D.[2]

Abstract

Objective: This study assessed the accuracy of real-time continuous glucose monitoring system (RTCGMS) devices in an intensive care unit (ICU) to determine whether the septic status of the patient has any influence on the accuracy of the RTCGMS.

Subjects and Methods: In total, 41 patients on insulin therapy were included. Patients were monitored for 72 h using RTCGMS. Arterial blood glucose (ABG) samples were obtained following the protocol established in the ICU. The results were evaluated using paired values (excluding those used for calibration) with the performance assessed using numerical accuracy. Nonparametric tests were used to determine statistically significant differences in accuracy.

Results: In total, 956 ABG/RTCGMS pairs were analyzed. The overall median relative absolute difference (RAD) was 13.5%, and the International Organization for Standardization (ISO) criteria were 68.1%. The median RADs reported for patients with septic shock, with sepsis, and without sepsis were 11.2%, 14.3%, and 16.3%, respectively ($P < 0.05$). Measurements meeting the ISO criteria were 74.5%, 65.6%, and 63.7% for patients with septic shock, with sepsis, and without sepsis, respectively ($P < 0.05$).

Conclusions: The results showed that the septic status of patients influenced the accuracy of the RTCGMS in the ICU. Accuracy was significantly better in patients with septic shock in comparison with the other patient cohorts.

Introduction

HYPERGLYCEMIA IS A COMMON phenomenon in critically ill patients, and one that has been shown to be associated with a worse prognosis.[1–4] Such effects can be explained by different phenomena.[5–9] For this reason the management of glycemia in intensive care unit (ICU) patients has been the focus of multiple studies. One aim of some of these studies has been to define the target range within which the patients' blood glucose (BG) must be maintained in order to improve their prognosis. Although some studies have claimed that the strict control of glycemia (80–110 mg/dL) significantly decreases the morbidity and mortality of critically ill patients,[10–13] such a tight target is also associated with an increase in hypoglycemia. Other studies[14–16] have indicated that a less strict range helps avoid the risk of hypoglycemia without an increase in mortality.

While it is still being debated what the target for glycemic control should be, what is not in question is the need to manage glycemia in critically ill patients. In ICUs, BG monitoring is performed intermittently using different bedside BG meters, which imposes an additional burden on the ICU staff. Continuous glucose monitoring would allow for better control of glycemia by identifying real-time (RT) fluctuations in BG and allow the staff to anticipate episodes of hyper- and hypoglycemia, potentially with fewer manual measurements.

Previous studies have evaluated the accuracy of continuous glucose monitoring system (CGMS) devices in critically ill patients.[17–27] Some of these clinical trials in the ICU have reported that the CGMS glucose values were accurate compared with BG measurements.[17,22,24,26,27] Other studies have concluded that although the CGMS could be clinically useful in the ICU, it is not sufficiently accurate and reliable at present to be used for therapeutic decisions.[18–20,21,23] In contrast, one

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[1]Department of Intensive Care, University Hospital of Girona Doctor Josep Trueta, Girona, Spain.
[2]Institute of Informatics and Applications, University of Girona, Girona, Spain.
[3]University Institute of Control Systems and Industrial Computing, Polytechnical University of Valencia, Valencia, Spain.
[4]Medtronic Diabetes, Northridge, California.
[5]Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain.
*The first two authors contributed equally to this work.

study indicated that although the CGMS gave accurate results, a high rate of underestimation of hypoglycemia made this device unreliable in the ICU.[25]

Several authors have described, in general terms, the methods currently accepted to measure the accuracy of CGMS devices.[28,29] The accuracy of these devices can be determined using the mean and median relative absolute difference (RAD) values between the CGMS measurements and BG measurements,[28] as well as by the International Organization for Standardization (ISO) criteria.[30]

The aims of this study were to assess the accuracy, in a mixed ICU, of the Guardian® REAL-Time CGMS (RTCGMS) (Medtronic, Northridge, CA) and to determine whether the septic status of the patient, considering different degrees of sepsis,[31] has any influence on the accuracy of the RTCGMS. In particular, tissue perfusion is impaired in patients with septic shock, a condition that may influence the relationship between BG and interstitial glucose. The accuracy of the RTCGMS was assessed using numerical accuracy criteria.

The results of this study were presented, in part, at the 23rd European Society of Intensive Care Medicine Annual Congress[32] and the 4th International Conference on Advanced Technologies & Treatments for Diabetes.[33]

Subjects and Methods

Patients and setting

Forty-one patients (14 medical, 21 surgical, and six trauma patients) admitted to an 18-bed mixed ICU at the Doctor Josep Trueta Hospital (Girona, Spain) were included in a prospective observational study (Acute Physiology And Chronic Health Evaluation [APACHE] II score, 18.0 [range, 14.3–21.8]; SOFA score, 8.5 [6–10]). Of these 41 patients, 38 received sedation and mechanical ventilation. The characteristics of the patients are listed in Table 1.

This study included patients who presented with hyperglycemia and needed intravenous insulin therapy on admission to the ICU. According to the glycemic control protocol established in our ICU, based on the insulin infusion protocol described by Goldberg et al.,[34] a continuous infusion of intravenous insulin was started once the patient had BG values above 150 mg/dL to maintain the BG between 120 and 160 mg/dL. Short-acting insulin (Actrapid®, Novo Nordisk, Bagsværd, Denmark) diluted in 0.9% NaCl was used. Intravenous insulin therapy was stopped when the BG was below 110 mg/dL. The other selection criteria included the following: admission to the ICU, above 18 years of age, administration of artificial nutrition (parenteral, enteral, or mixed) as the only form of nutritional support, APACHE II score of >12, and having an arterial blood catheter because of their clinical condition. Patients younger than 18 years, pregnant women, and patients who had participated in another trial were excluded.

Under continuous glucose monitoring, the septic status of the patient was recorded every 24 h by the patient's medical team. Septic status was classified based on the definitions of the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Committee[31] in three groups: patients without sepsis, patients with sepsis, and patients with septic shock. Patients with septic shock were defined as those patients with poor tissue perfusion after a correct resuscitation, according to the guidelines for the

Table 1. Baseline Characteristics, Primary Conditions, and Outcomes of All Patients Included in the Study

Variable	Overall
Number (%)	41 (100)
Type of critically ill patients (medical/surgical/trauma) (%)	14/21/6 (34.2/51.2/14.6)
Age (years)	63.6 ± 11.0
Sex (female/%)	17/41.5
Body mass index (kg/m^2)	32.2 ± 6.6
Previously known diabetes (yes/%)	19/46.3
Stay in ICU (days)	24.4 ± 19.8
Stay in the hospital (days)	41.5 ± 31.9
ICU mortality (yes/%)	10/24.4
Hospital mortality (yes/%)	13/31.7
Sequential organ failure assessment[a]	8.3 ± 3.3
Acute Physiology And Chronic Health Evaluation score II[a]	18.8 ± 5.6
Sepsis (yes/%)[a]	31/75.6
Mechanical ventilation (yes/%)	38/92.7
CVVHDF (yes/%)	3/7.3
Nutrition (enteral/parenteral)	25/16

Data are expressed as mean ± SD values.
[a]These values correspond to the initial condition of the patient.
CVVHDF, continuous venovenous hemodiafiltration; ICU, intensive care unit.

management of sepsis,[35] and/or with vasoconstrictor therapy. Cardiogenic, hemorrhagic, and anaphylactic causes of shock were ruled out. The use of glucocorticoids and the fluid balance were not recorded. The protocol was approved by the Ethics Committee of the Doctor Josep Trueta Hospital. All of the patients gave informed consent, either signed by them if they were conscious and capacitated or signed by family members in cases of unconscious patients.

Glucose monitoring system

The patients were monitored for 72 h using the RTCGMS (MiniMed reference CSS72). Gold standard data were obtained through arterial BG (ABG) samples following the glycemic control protocol established in the ICU. When a patient showed high glycemic instability (hyper- and hypoglycemia), ABG samples were taken every 30 min. Then, if glycemic values were stabilized, ABG measurements were spaced to every 1, 2, 3, and until every 4 h. If the patient's nutritional intake was stopped for any reason, the glycemic control testing was performed more frequently, even during normoglycemia. ABG was measured using the whole BG concentration reported by the HemoCue® 201 DM system (HemoCue AB, Ängelholm, Sweden). Quality control checks were performed using liquid controls recommended in HemoCue's instructions. Additional ABG measurements were used for RTCGMS calibration.

The RTCGMS consists of a disposable subcutaneous needle-type sensor and an external monitor. The sensor is an amperometric system that uses glucose oxidase, which generates an electric current proportional to the glucose concentration in the interstitial fluid.[36] The sensor measures interstitial glucose every 10 s and records the mean values at 5-min intervals. The RTCGMS was placed in the subcutaneous tissue of the upper leg of each patient. This sensor location

was used because of the difficulty of placement in other locations. It was not feasible to locate the sensor on either chest, the abdomen, or the buttocks because critically ill patients were usually subject to chest X-ray and laparatomies, and most of them were in the supine position. After electrode insertion, the sensor was directly connected to the MiniLink™ REAL-Time transmitter (Medtronic). Following a 2-h initialization period, the first ABG measurement was used for RTCGMS calibration. These calibrations were performed according to the RTCGMS manufacturer's instructions (three to four per day).[37]

ABG values were used by the nurses to administer insulin therapy, according to the protocol established by the hospital. RTCGMS readings were not used to modify insulin therapy. After the third day, the RTCGMS and ABG data were downloaded to a computer using Medtronic Carelink Pro version 2.0B and HemoCue 201 DM version 3.1 software, respectively.

The accuracy of the RTCGMS in this study was evaluated using paired values (ABG/RTCGMS), excluding those used for calibration. Because the ABG and RTCGMS readings were obtained at different times, the RTCGMS readings were matched to the reference ABG within ±2.5 min.[38]

Accuracy metrics and statistical analysis methods

Descriptive statistics of demographic and clinical variables included the mean and SD values for quantitative variables and percentages for qualitative variables. Furthermore, descriptive statistics (mean [SD] and median [interquartile range]) were calculated by all RTCGMS and ABG measurements (including those used for calibration), respectively.

The accuracy criteria currently accepted by the U.S. Food and Drug Administration for CGMS statistics are the Pearson correlation coefficient (r), the mean and median RADs, and the ISO criteria. To describe the accuracy of the measurements, numerical point accuracy was evaluated using the median RAD (interquartile range) and the ISO criteria. The RAD was computed as the absolute value of the difference between the glucose levels estimated by the RTCGMS and ABG values, expressed as a percentage of the ABG values (Eq. 1):

$$RAD = \left| \left(\frac{ABG_i - RTCGMS_i}{ABG_i} \right) \right| \times 100 \qquad (1)$$

The ISO criteria included the percentage of RTCGMS readings within 15 mg/dL of the ABG readings when the ABG reading is ≤75 mg/dL or within 20.0% of the ABG readings when the ABC reading is >75 mg/dL.[30]

All of the data were reviewed for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Analysis of variance was used to determine differences between the numbers of reference measurements performed per hour in each of the groups. For data that did not follow a normal distribution, nonparametric contrast techniques were used. The Wilcoxon signed-rank test was used to compare median RADs and to determine whether there were any statistically significant differences in accuracy. The Kruskal–Wallis test was used to determine significant differences between the glycemic ranges in each of the groups. Two-sided tests were used, and $\alpha = 0.05$ was considered to be the threshold of significance. Analyses were performed using SPSS for Windows (SPSS Institute, Chicago, IL).

In addition, a Bland–Altman analysis with limits of agreement was used to assess the accord between the measurements.[39] The Bland–Altman analysis plotted the differences between the ABG and RTCGMS (y-axis) against the means of the ABG and RTCGMS (x-axis).

Results

In total, 956 paired ABG/RTCGMS data points were obtained from all the patients who participated in the study. The Pearson correlation coefficient between the RTCGMS and ABG values was 0.7 ($P < 0.05$). The median RTCGMS was 128 (108–154) mg/dL, and the median ABG was 136 (120–156) mg/dL. Table 2 shows the overall median RAD and the measurements that fulfilled the ISO criteria for all data points.

Assessment using numerical point accuracy of the RTCGMS according to the septic status of the patient (patients with septic shock, with sepsis, and without sepsis) was also calculated (Table 2). In patients with septic shock, the median RTCGMS was 130 (110–158) mg/dL, whereas the median ABG was 136 (118–154) mg/dL. For patients with sepsis, the median RTCGMS was 124 (103–152) mg/dL, and the median ABG was 135 (120–155) mg/dL. For patients without sepsis, the median RTCGMS was 130 (108–154) mg/dL, and the median ABG was 138 (121–158) mg/dL. According to a Kruskal–Wallis test, the glycemic ranges of ABG measurements for each of the three groups were similar ($P > 0.05$), without significant differences among them. The median RAD values in patients with septic shock were significantly more accurate than the median RAD values in patients with sepsis ($P = 0.003$). When comparing patients with septic shock and patients without sepsis, significant differences in the median RAD values between the two cohorts were detected ($P = 0.001$). Moreover, the Bland–Altman plot also showed the accuracy of the RTCGMS in relation to ABG values (Fig. 1).

TABLE 2. NUMERICAL POINT ACCURACY

	RTCGMS (mg/dL)	ABG (mg/dL)	ABG calibration (mg/dL)	RAD (%)	ISO criteria (%)	Total reference readings	Number of measurements per hour
Overall	128 (108–154)	136 (120–156)	130 (116–147)	13.5 (6.0–24.1)	68.1	956	—
With septic shock	130 (110–158)	136 (118–154)	132 (117–147)	11.2 (5.4–20.5)	74.5	326	0.43 (0.36–0.60)
With sepsis	124 (103–152)	135 (120–155)	128 (113–144)	14.3 (6.7–26.9)	65.6	360	0.40 (0.30–0.55)
Without sepsis	130 (108–154)	138 (121–158)	138 (114–156)	16.3 (6.3–25.6)	63.7	270	0.50 (0.35–0.60)

Data are median values. Numbers in parentheses indicated the interquartile range (Q1–Q3, respectively).
ABG, arterial blood glucose; ISO, International Organization for Standardization; RAD, relative absolute difference; RTCGMS, real-time continuous glucose monitoring system.
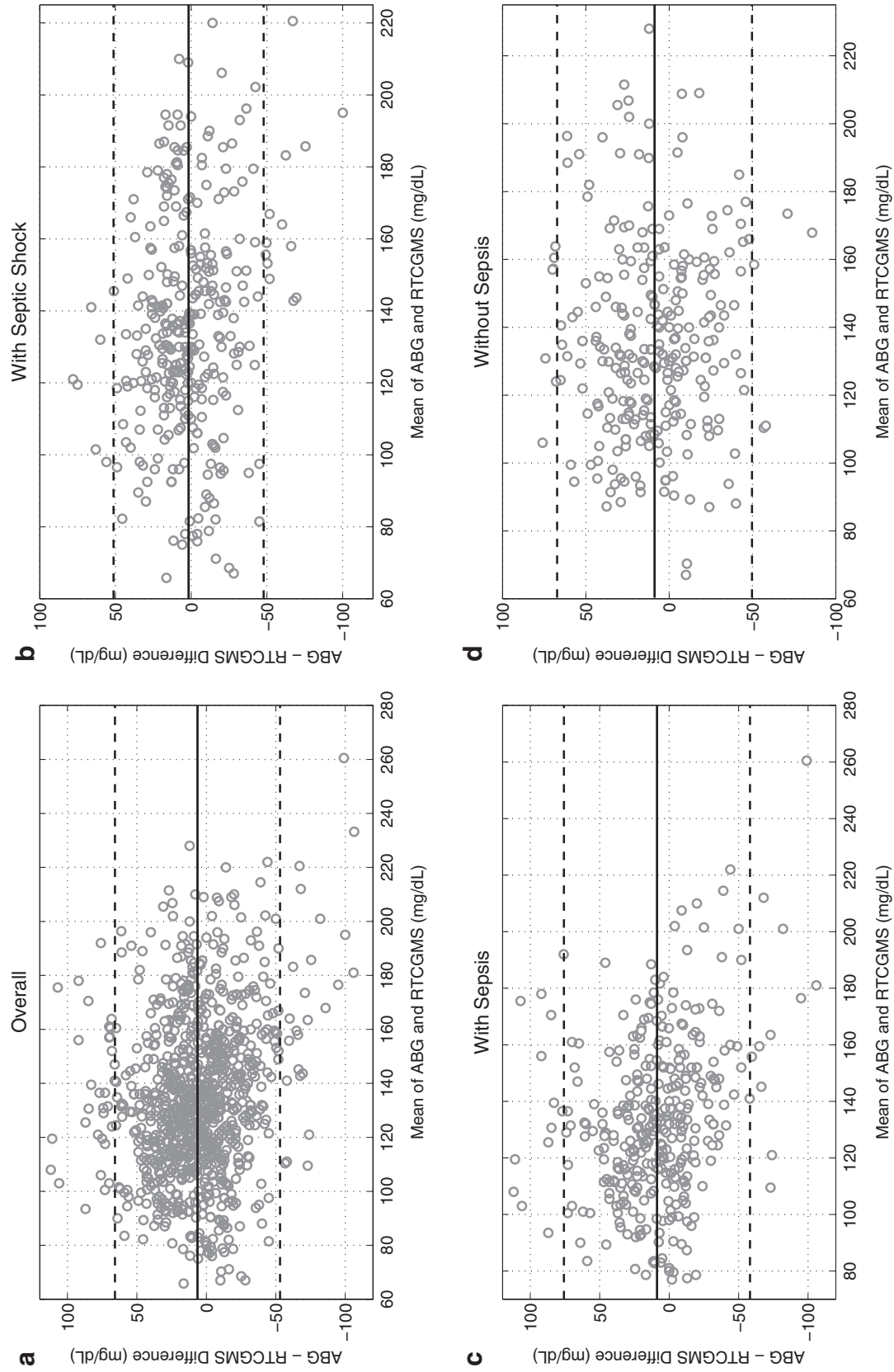
FIG. 1. Bland–Altman plot. The solid black line represents the bias, and the dashed black lines represent ±1.96 SD. **(a)** Overall data, with a mean difference (bias) of +6.4±30.3 mg/dL with limits of agreement of +65.8 and −53.1 mg/dL. **(b)** Patients with septic shock. The bias between the two measurement methods was +1.7±25.3 mg/dL, with limits of agreement of +51.3 and −47.8 mg/dL. **(c)** Patients with sepsis. In this case, the bias was +8.8±34.2 mg/dL, and the limits of agreement were +75.8 and −58.3 mg/dL. **(d)** Patients without sepsis. The bias between the two measurements was +8.8±29.8 mg/dL, and the limits of agreement were +67.2 and −49.7 mg/dL. ABG, arterial blood glucose; RTCGMS, real-time continuous glucose monitoring system.

Furthermore, 493 ABG measurements were used for RTCGMS calibration, resulting in 12 samples per patient on average. Median glucose measured during calibration was 132 (117–147) mg/dL for patients with septic shock, 128 (113–144) mg/dL for patients with sepsis, and 138 (114–156) mg/dL for patients without sepsis. So, the glycemic range of calibration measurements for each of the three groups was similar ($P > 0.05$), without significant differences among them (according to a Kruskal–Wallis test). ABG measurements used for calibration were within the range considered correct according to our protocol (Table 2).

The number of reference measurements performed per hour was not statistically different among the three groups ($P > 0.05$). A median of 0.43 (0.36–0.60) ABG samples per hour was performed in the septic shock group, whereas medians of 0.40 (0.30–0.55) and 0.50 (0.35–0.60) ABG samples per hour were found in the sepsis and without sepsis groups, respectively.

Numerical point accuracy of the overall data was also calculated by glucose ranges (27 data pairs were below 80 mg/dL, 727 were between 80 to 160 mg/dL and 202 were above 160 mg/dL). The results showed that the RTCGMS was equally accurate for patients with normoglycemia and hyperglycemia (median RAD of 13.9% [6.0–23.7%] and ISO criteria of 68.8%; median RAD of 12.0% [6.0–24.1%] and ISO criteria of 67.8%, respectively). The RTCGMS was less accurate in the hypoglycemic range (median RAD of 15.0% [4.2–27.3%] and ISO criteria of 51.9%).

Finally, numerical point accuracy metrics were also calculated according to the cause of the patient's critically ill status (370 medical data pairs, 433 surgical data pairs, and 153 trauma data pairs were analyzed). In agreement with the expected results, there were no significant differences in accuracy between the medical and surgical patients ($P > 0.05$). When comparing the medical cohort (median RAD of 14.5% [6.6–25.0%] with ISO criteria of 67.0%) and the surgical cohort (median RAD of 11.7% [5.4–22.4%] with ISO criteria of 71.1%), similar numerical accuracy metrics were obtained. The trauma patients were not compared because of the insufficient size of this cohort (median RAD of 15.5% [7.0–28.3%] with ISO criteria of 62.1%).

Discussion

The numerical and clinical accuracy results obtained in this study are similar to those of previously reported studies on critically ill patients.[18–23] These results also demonstrate that the type of critically ill patient (i.e., medical, surgical, or trauma) does not have a significant influence on the accuracy of the CGMS. Furthermore, the accuracy of the CGMS in the ICU was similar to that seen in patients with type 1 diabetes mellitus.[40–42] Consistent with these studies,[18–21,23] we also conclude that although the CGMS could be clinically useful in the ICU, it is not sufficiently accurate and reliable at present to be used for therapeutic decisions.

The determination of interstitial glucose showed greater accuracy in patients with septic shock. Patients with sepsis or septic shock are the most frequently admitted to the ICU. In this type of ICU patient, the BG values are usually in the hyperglycemic range, and glycemic control is often more difficult than in patients without sepsis.[5–9] For this reason, international guidelines for the management of

sepsis and septic shock recommend the practice of glycemic control.[35]

Previously, other authors have observed similar phenomena and reported better accuracy using CGMS devices in patients with septic shock,[21] in pediatric patients with inotropic support,[22] and in pediatric patients with support measures (such as mechanical ventilation or vasopressor use),[26] although their data did not achieve statistical significance. This phenomenon could be caused by the increase in capillary permeability seen in patients with septic shock. This increase in capillary permeability would result in an increase in the diffusion of the intravascular glucose to the interstitial space. Consequently, the lag time to reach the equilibrium between ABG and interstitial glucose may be smaller, which would improvement the accuracy of the RTCGMS.

In contrast, a recent study did not discover any differences in the accuracy of the CGMS in patients with inotropic support[27]; however, the average dose of norepinephrine administered in this study was quite low (0.04 μg/kg/min), and the indication for administering norepinephrine was not clear.

Calibrations over a different range would potentially yield different sensor readings and thus potentially different accuracies. In our study similar calibration ranges between groups have been used, and therefore outcomes have not been influenced by this fact.

Furthermore, no local complications (e.g., local infection, inflammation, or bleeding) resulted from the placement of the subcutaneous sensors.

The CGMS is a potential tool to provide detailed information about glucose levels. The potential benefits of the use of the CGMS would be avoiding multiple blood draws from the patient. In addition, the patient would avoid the frequent, uncomfortable, and painful punctures on the digital pad or earlobe associated with capillary BG. Other benefits of using the CGMS would be a reduction in the workload of nurses and a reduction in the risk of accidental puncture. However, there are other aspects that could hinder the routine use of CGMS in the ICU. It is necessary to provide specific training to the nursing and other ICU staff on the effective use of such systems. Finally, the high cost to implement this technology in the ICU must be taken into account.

In conclusion, the accuracy of the RTCGMS was similar to that reported in other studies in critically ill patients. Equally important is that the results showed that the septic status of the patient influenced the accuracy of the RTCGMS in the ICU. However, it is important to highlight that the study only focused on one specific CGMS, one based on a subcutaneous sensor in order to measure interstitial glucose concentration. Therefore, it is not possible to extrapolate the results for other glucose sensor technologies, especially for intravenous methods.

Accuracy was significantly better in the patients with septic shock compared with other patient cohorts. Therefore, the accuracy of the RTCGMS was not worse in patients with septic shock, who have the worst state of interstitial tissue perfusion. Further research is needed to confirm the predicted benefits of continuous glucose monitoring compared with standard monitoring in this type of critically ill patient.

Study limitations

Our study has some technical limitations. First, although statistically significant differences have been achieved in our

samples, future studies with a larger sample size are required. These analyses should focus on the use of the CGMS according to the septic status of the patient. Moreover, hypoglycemic events were very infrequent. For this reason, it was difficult to draw conclusions on the performance of the RTCGMS in the hypoglycemic range. In our ICU, hypoglycemic events are very infrequent because of the glycemic control protocol, not designed for tight glycemic control but to avoid hypoglycemia.

Second, in our study we observed a better accuracy of the RTCGMS in septic shock. The use of norepinephrine was recorded qualitatively but not the dose of inotropes needed in each case and the time that the patients needed them. In future studies, it would be interesting to assess if the accuracy of the RTCGMS varies depending on the dose of vasopressors. Other factors that could be interesting in assessing the accuracy of the RTCGMS, such as the use of glucocorticoids or the fluid balance, were not recorded.

Third, we did not consider other factors that could influence significantly the accuracy of the RTCGMS in critically ill patients, such as the degree of edema or the level of tissue perfusion (assessed by measuring the lactate concentration).

Fourth, although the results of the RTCGMS were not compared with the reference values obtained in a laboratory test or with a blood gas analyzer, they were compared against the device used in the ICU. ABG samples were determined with the HemoCue in whole blood. The selection of the HemoCue was based partly on that we required more frequent measurements of blood glucose, according to our protocol. The HemoCue is suitable given its minimum requirements of whole blood volume, simple calibration procedure, rapid response, lower cost, and durability in the clinical environment. Furthermore, HemoCue gives reliable results over a wide range of hematocrit values.[43]

However, there are concerns about its accuracy.[44] Whereas previous studies had found a good correlation between the HemoCue system and the laboratory plasma reference,[45,46] another study does not recommend use of the HemoCue because its lack of accuracy compared with laboratory glucose results.[47] Moreover, this device has been also used as a reference in other important studies to analyze the glycemic control.[11,15,16] So, to avoid these concerns in future studies it may be necessary to compare with laboratory measurements.

Fifth, we did not evaluate the accuracy of RTCGMS depending on its location, because of the complexity of critically ill patients. The placement of these sensors in other anatomical sites, such as the abdomen, is difficult in surgical patients. Its location in the chest is precluded because it is not recommended to expose the sensor transmitter to X-rays.[37] Furthermore, critically ill patients are usually in the supine position, and they are sedated for a long time, so it is impossible to locate the RTCGMS in the buttocks.

Finally, an important problem of our study has been the long learning interval required by the nursing and other ICU staff, to acquire the knowledge necessary for the proper use of the sensor.

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Author Disclosure Statement

C.C.P. is an employee and shareholder of Medtronic, Inc. C.L., Y.L., A.B., J.B., A.T., J.-M.S., and J.V. declare no competing financial interests.

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Address correspondence to:
Yenny Leal, M.Sc.
Institute of Informatics and Applications
University of Girona
Av. Lluís Santaló s/n, Building P-IV
17071, Girona, Spain

E-mail: yennyteresa.leal@udg.edu

or

Carol Lorencio, M.D.
Department of Intensive Care
Hospital Universitari de Girona Doctor Josep Trueta
Av. de França s/n
17001, Girona, Spain

E-mail: carol_lorencio@hotmail.com