Continuous tissue glucose monitoring correlates with measurement of intermittent capillary glucose in patients with distributive shock

D. Ballesteros*, Ó. Martínez, R. Blancas Gómez-Casero, C. Martín Parra, B. López Matamala, B. Estébanez, M. Chana

Department of Intensive Care, Hospital Universitario del Tajo, Aranjuez, Spain

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Abstract

Background: Intermittent glycemic measurements in patients admitted to the intensive care unit (ICU) can result in episodes of severe hypoglycemia or in a poor control of glycemia range. We designed a study to assess accuracy and reliability of continuous monitoring of tissue glucose for patients with distributive shock.

Methods: Consecutive patients admitted to the ICU with a diagnosis of distributive shock and the need of insulin infusion for glycemic control were included in the study. These patients were implanted a Continuous Glucose Control Monitoring System (CGMS) with the sensor inserted subcutaneously into the abdominal wall. CGMS values were recorded every 5 min. Capillary glucose (CG) was monitored for adjusting insulin perfusion according to the ICU protocol. Correlation between both methods was assessed.

Results: A total of 11,673 CGMS and 348 CG values were recorded. In five patients, CGMS failed to detect tissue glucose. A glucose value <3.33 mmol/l (<60 mg/dl) was observed in 3.6% of CGMS and in 0.29% CG values. 295 pairs of measurements were included in the statistical analysis for correlation assessment. The intraclass correlation coefficient was 0.706. The Pearson correlation coefficient was 0.71 (p < 0.0001, 95% CI 0.65–0.76). The mean of differences between both measurement methods was 0.22 mmol/l (3.98 mg/dl) (95% CI 0.66–7.31).

Conclusions: When the Continuous Glucose Control Monitoring System (CGMS) is able to obtain data (75% of the patients), there is correlation between the values obtained by this method and capillary blood glucose in patients with distributive shock. CGMS can detect more episodes of glycemic excursions outside the normal range than intermittent capillary glucose monitoring. Variables that may impair glucose metabolism and peripheral soft tissues perfusion could impair CGMS measurements.

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* Corresponding author.
E-mail address: danbalor@gmail.com (D. Ballesteros).
La monitorización continua de la glucosa de tejido se correlaciona con la medición de glucosa capilar intermitente en pacientes con shock distributivo

**Introduction**

Hyperglycemia is common in critically ill patients, appearing in 90% of them during serious illness, were diabetic or not before admission. It occurs as an adaptive response to aggression to ensure delivery of glucose to the tissues in serious situation. The most recent reports have shown that uncontrolled hyperglycemia has an adverse effect on mortality of critically ill patients. In this setting there is a resistance to insulin action of multifactorial origin, which makes difficult the control of blood glucose. For this reason, high doses of insulin can be needed, with the resultant risk of hypoglycemia.

In 2001, Van den Berghe et al. described as the strict control of blood glucose decreased morbidity and mortality in critically ill surgical and, in subsequent studies, also in medical patients. The benefits obtained with this control need to maintain blood glucose in the range of 4.44–6.1 mmol/l (80–110 mg/dl), administering insulin intravenously in most cases.

More recent studies shown that strict control of blood glucose may not be beneficial or may even get worse in the prognosis of patients, due to an increase in late mortality. The main difference in complications that appeared in the strict control group compared to the control group of less strict glycemic is the occurrence of severe hypoglycemia, which may be associated with severe morbidity and mortality.

Monitoring of capillary blood glucose has been customary in the ICU for adjustment of insulin requirements of patients, until recently. It is a simple procedure with few complications for the patient and is economical, with a good correlation with blood glucose in most patients. Studies of glycemic control in critically ill patients have been performed by measuring CG intermittently, with the risk of the existence of periods of hypoglycemia and hyperglycemia undetected between measurements. Besides the difficulty of detecting large glucose excursions, intermittent control of CG requires multiple punctures and an increase in the nurse staff workload.

Currently, continuous glucose monitoring is performed in diabetic outpatients by sensors positioned in the subcutaneous tissue, but these devices have not been incorporated into the routine monitoring in the ICU. The development of these devices of subcutaneous continuous glucose monitoring system emerged as a need for close monitoring of blood glucose concentrations in patients with metabolic instability or insulin pumps carriers, thereby reducing the risk of complications. These devices were first developed in the 1980s and its operation is based on subcutaneous implantation of a sensor carrying an enzyme electrode measuring interstitial glucose concentration. The device security is
very high, as it requires no more than a small subcutaneous
implant, whose placement is almost painless, the measure-
ment effectiveness in an outpatient being 100%, although
there are certain problems that can reduce their effective-
ness, as are the limited lifetime of the sensor (96 h), the
need for calibration (at least 1 time every 12 h), need for
change of anatomical site of implantation and the risk of
infection from the puncture site. The validity of its val-
ues assumes a constant relationship between plasma and
interstitial fluid glucose across the range of plasma glucose
values. A limited number of reports on its use in critically
ill patients have been published, yielding different results,
although most show a good correlation between the values
obtained with the CGMS and intermittent capillary con-
trol.4-7

Our CGMS study was performed in patients with dis-
tributive shock, patients with multiple factors that hinder
glycemic control. Our aim was to assess the reliability of
measurements obtained by a subcutaneous enzyme sensor,
in such patients whose peripheral perfusion and metabolism
may be greatly affected by hypoperfusion, mediators of
inflammation and drugs administered, altering the intracel-
lular uptake of glucose.

In our study we proceeded to assess the correlation
between tissue and capillary blood glucose continuous glu-
cose obtained intermittently in patients with distributive
shock who required intravenous insulin infusion to control
capillary blood glucose in the presence of distributive shock.

Materials and methods

Patients 18 years or older admitted to the intensive care unit
(ICU) between September 2010 and September 2011 were
considered for the study. To be included, they had to be
diagnosed of a cause of distributive shock and to require
intravenous insulin infusion for glycemic control. The diag-
osis of distributive shock was made excluding other causes
of shock (hypovolemia, haemorrhagia, cardiogenic shock,
neurogenic shock), in the presence of systolic blood pres-
sure less than 90 mmHg or at least 30 mmHg lower than their
usual systolic pressure, after an initial crystalloids load of a

In addition to treating the disease that caused the ICU
admission, in the selected patients we placed them a sensor
for continuous measurement of subcutaneous tissue glucose
level model Medtronic MiniMed Soft-Sensor™ glucose sensor
(Medtronic MiniMed, California, USA), holding up to 120 h,
to perform a CGMS. The sensor makes up to 288 glucose
measurements for 24 h (1 measurement every 5 min). The
CGMS sensors were placed in the lateral abdominal wall, in
an area with absence of skin lesions and the greatest possi-
ble distance from surgical incisions or soft tissue infections
if any. The subcutaneous sensor carries a membrane which
is coupled to the enzyme glucose oxidase and is placed on
an amperometric sensor which is able to respond linearly
to glucose in the range of 2.22–38.9 mmol/l (40–700 mg/dl).
The data are then sent through a radio receiver and down-
loaded to a computer for analysis. The data obtained by
the CGMS were processed using the CareLink Software-
pro™ (Medtronic MiniMed, California, USA) for Windows™
(Microsoft Corp. One Microsoft Way, Washington, USA). Data
were then incorporated into a database for analysis. The
 calibration of the CGMS was performed every 8 h, using the
result of CG measurement. Pairs of values corresponding to
calibration of the CGMS were not taken into account for
statistical analysis.

The CG monitor used during the study was the Optium
Xceed™ system (Abbott Diabetes Care Ltd., Witney, UK).
According to the features provided by the manufacturer,
it has an accuracy of 3–3.6% and a reliability of 98% com-
pared to capillary samples, 99% versus venous samples and
of 97% versus arterial samples. The monitor complies with
ISO 15197 rules. Its range of monitor readings is between 1.1
and 27.8 mmol/l (20 mg/dl and 500 mg/dl) for a hematocrit
between 20% and 60%. The reference samples are capillaries
obtained by finger prick. Glucose in the sample reacts with
nicotinamide adenine dinucleotide (NAD) requiring glucose
dehydrogenase (NAD-GDH) on the test strip. The minimum
volume required is 2.5 μl of blood and the time to obtain the
result is 20 s.

We compared the results obtained with both methods of
glucose measurement obtained in the first 72 h after the
placement of the CGMS sensor. At the time of the study, the
manufacturer recommended not to extend their use beyond
this period; following the completion of the study, up to
120 h use has been accepted.

Regardless of device implantation, patients followed the
approved protocol for glycemic control in the ICU. The mea-
urements of CG, insulin infusion and artificial nutrition
were administered according to this protocol compliance.
The glycemic control protocol aims to maintain the range
of blood glucose of patients between 5.56 and 7.78 mmol/l
(100–140 mg/dl). The patient’s blood glucose level indi-
cates the frequency of monitoring, performing every 30 min
in patients with hypoglycemia, to be held every 4 h in
patients with maintained stability of target glyemia. Intra-
venous insulin infusion was started to all patients not taking
oral diet alone (in this setting, insulin was administered
by subcutaneous injection), who presented two consecu-
tive blood glucose measurements greater than 7.78 mmol/l
(140 mg/dl), separated by 4–6 h. Patients leave the insulin
infusion protocol when they do not need insulin infusion to
maintain blood glucose <140 mg/dl or when starting oral
diet. Medical and nursing staff remained unaware of CGMS
data records; therefore, these data were not used to make
changes in insulin treatment.

In addition to CGMS and CG measurements, demographic
data (age, gender, weight, height, body mass index, previous
diagnosis of diabetes), cause of distributive shock, APACHE
II score of the first 24 h, SAPS III score, daily insulin needs,
nutritional daily caloric intake, doses of vasopressors drugs,
and the use of corticosteroids were recorded.

Statistical analysis

Results are presented using absolute frequencies and per-
centages when categorical variables are shown as mean,
median, maximum, minimum and standard deviation (SD)
in the case of quantitative variables. A descriptive analysis
was performed on the data set so as to calculate the absolu-
test difference and the relative difference to each reference
pair (difference between CGMS measurements and CG
measurements) and among means of glucose values obtained by both methods. To quantify the correlation and variability we used the Pearson correlation coefficient and the intra-
class correlation coefficient (ICC) for the whole group. The results 
were interpreted according to the criteria of Lan-
dis and Koch.\textsuperscript{29} Agreement between values was assessed 
using the Bland–Altman method, modified by Krouwer.\textsuperscript{30,31}

To assess the correlation between the two analytical meth-
ods, the nonparametric regression of Passing–Bablok was 
employed.\textsuperscript{32}

Statistical analysis was performed using the SPSS 15 soft-
ware for Windows\textsuperscript{TM} (SPSS Inc., Chicago, USA) and MedCalc 
for Windows\textsuperscript{TM} Version 12.4.0 (MedCalc Software, Ostend,
Belgium).

The present study was approved by the Committee 
on Clinical Trials and Research of our institution. Written 
informed consent for study inclusion was obtained from 
patients or from their legal representatives. The study has 
been performed in accordance with the ethical standards 
from the 1964 Declaration of Helsinki and its later amend-
ments, as well as with local laws.

**Results**

Twenty-three patients admitted consecutively to the ICU, 
fulfilling the inclusion criteria, were included in the study. 
Five of them were subsequently excluded due to the inability 
to obtain measurements of CGMS. Demographic characteris-
tics and other variables from the 18 patients who eventually 
formed part of the study are shown in Table 1.

The cause of distributive shock was sepsis in 17 patients 
(94%) and pancreatitis in 1 patient. Seven patients (38.9%) 
received parenteral nutrition alone, 7 patients (38.9%) 
enteral and 4 patients (22.2%) received both simultaneously. 
Seventeen patients (94%) required the use of vasopres-
sor drugs, mostly noradrenaline (17 patients, 94.4%), with 
administration of dopamine and dobutamine in only two 
patients. One patient required three types of vasopressor 
drugs. The hematocrit remained in all patients between 20% 
and 60% along the study period.

Finally, 11,673 CGMS and 348 CG values were obtained, 
with 295 paired. Mean CGMS value was 7.45 mmol/l 
(134.07 mg/dl) (SD 39.62) and mean CG value was 
7.82 mmol/l (140.70 mg/dl) (SD 40.12). Among values 
of CGMS, 1934 (16.57%) were consistent with mea-
surements <5.56 mmol/l, 162 (46.55%) were 
>7.78 mmol/l, corresponding with the target blood glucose 
ranges <5.56 mmol/l, and 4619 (39.57%) with values 
>7.78 mmol/l and 139 (39.94%) were within the target range 
of protocol.

Glucose values <3.33 mmol/l (<60 mg/dl) were obtained 
in 42 measurements (3.6%) recorded by CGMS, without any 
severe hypoglycemia (<2.22 mmol/l; <40 mg/dl); CG values 
showed a single episode of glucose <3.33 mmol/l (0.29%), 
2.28 mmol/l being the lowest recorded value.

After comparing the values of CGMS and CG, the ICC was 
0.70, showing a substantial degree of agreement on the 
range proposed by Landis and Koch.\textsuperscript{29} Of the total variability, 
29.4% was due to the method used for glucose measurement.
The Pearson correlation coefficient was 0.71 ($p < 0.0001$, 95% 
CI 0.65–0.76). Fig. 1 shows the positive linear correlation 
between CGMS and CG values using the regression method 
of Passing–Bablok.

Mean difference between the 295 paired measurements 
is shown in a Bland–Altman analysis (Fig. 2). There is a tendency of the CGMT with respect to CG to overestimate blood 
glucose in the high blood glucose ranges and underestimate 
in the low range, with normalization in the range of normo-
glycemia. In 95% of the measurements the difference from 
the GC is ±1.61 mmol/l (29 mg/dl), which is lower difference 
in the 5.55–8.33 mmol/l (100–150 mg/dl).

In our study, no complications related to the insertion 
of the subcutaneous device is presented, showing its safety 
when it is inserted following the deployment instructions 
and with appropriate aseptic precautions.

**Discussion**

Tight control of blood glucose levels in the critically ill 
patients, its impact on morbidity and mortality and the 
blood glucose range established as beneficial and safe have 
been the subject of numerous studies in the last decade.

Leuven studies 1 and 2 compared a strict protocol 
of glycemic control in critically ill patients, defined as
The results from both Our results show that CGMS 10,11
The study of Krinsley showed a 11.11 mmol/l (180- - -200 mg/dl).
In fact, the results 5.56
The most important concern about a strict control of blood glucose is hypoglycemic episodes, especially most severe (blood glucose level below 2.22 mmol/l) which can be related to increased mortality.13 In fact, the results from the recently published NICE-SUGAR study showed that 82% of moderate hypoglycemia and 93% of those severe appeared in the strict blood glucose control group. There was an increased mortality rate in patients with moderate (OR 1.41, 95% CI 1.21–1.62, p < 0.001) and severe hypoglycemia (OR 2.10, 95% CI 1.59–2.77, p < 0.001). Mortality increased in patients with repeated hypoglycemia (more than one episode of hypoglycemia per day), in patients with distributive shock and in those with severe hypoglycemia in the absence of insulin.14,30 Our results show that CGMS can detect blood glucose <3.33 mmol/l at a rate 12.4 times greater than CG (glucose values <3.33 mmol/l recorded by CGMS and by CG, 3.6% and 0.29% respectively), although these data could be altered by the greatest number of values obtained by the CGMS, being part of the recorded data pertaining at the same episode. Therefore, continuous monitoring of glucose is an attractive method to prevent hypoglycemic episodes, while maintaining a desirable blood glucose range in critically ill patients, who are subjected to multiple causes of significant variability in glycemia. The increase in this variability has also been associated with mortality and may be modified by a continuous monitoring system.37
In addition, one of the main advantages of the CGMS is the ability to recognize trends in the patient’s blood glucose under insulin treatment, allowing an early reaction, even before the disturbance occurs (hypoglycemia or hyperglycemia), and decreasing the onset of serious complications associated with consequences of morbidity and mortality.
CGMS, used initially in diabetic outpatients, has been proven to be safe and reliable in critically ill patients with different admission diagnoses, when compared with plasma glucose measurements.18,22,23,25-27 We have compared CGMS values obtained by a device to the patient’s bedside, with CG values. Systems measuring capillary whole blood glucose have an acceptable reliability and accuracy, with a good correlation, when compared to plasma glucose, allowing fast results and avoiding high blood volume samples.19 Therefore, we believe that it is appropriate to make the comparison of values obtained by CGMS with commonly employed glucose determination systems. Our study showed a positive linear correlation between the two measurement methods (Fig. 1), with a proportional error in the extreme values, without clinical relevance since the mean of the differences of values reached 0.22 mmol/l (3.98 mg/dl) (Fig. 2).
Figure 1 Scatterplot of paired data. The solid line represents the regression line; the dotted lines represent the confidence interval of 95%. Correlation coefficient = 0.71 (p < 0.0001), 95% CI 0.65–0.76. The figure shows the existence of a positive linear correlation between the two methods of measurement.
Figure 2 Bland–Altman plot modified by Krouwer. In this case the differences between the two methods of measurements are plotted against the CG, considered as the reference method in this study. The black line represents the bias between both methods of measurement, and the black dotted lines represent ±1.96 SD. The mean difference (bias) is 3.98 ± 29.04 mg/dL. The dashed pink line represents the correlation between the two methods. The orange dotted line shows 95% CI.
For our study, we selected patients with distributive shock because these patients have a very difficult glycemic control as a result of the inflammatory response, insulin resistance and erratic caloric intake.

Our study has two fundamental limitations which are the small sample size of patients included in the study, although partly offset by the large number of measurements obtained from CGMS, higher than in previous studies, and the other the loss of patients due to incapacity sensing device CGMS. Five patients had to be excluded due to inability to obtain measurements, despite changing the sensor insertion site. The study was not designed to give an explanation for this finding, neither is it an analysis of subgroups. The absence of sensing could be motivated by the presence of one or more alterations in subcutaneous tissue, such as impaired microcirculation, temperature variability or subcutaneous tissue edema.22

To our knowledge, ours is the first report comparing the accuracy and reliability CGMS values with CG values in patients with distributive shock, and the first to report the inability to obtain CGMS measurements in some patients. A paper published recently by Holzinger et al., comparing the measurements obtained with the same CGMS that we used in our study with arterial blood glucose, in patients with and without shock (some of them requiring norepinephrine), did not detect any influence of these variables on the accuracy and reliability of the measurements obtained with this subcutaneous sensor.23 In another study, the same authors reported that CGMS reduced the absolute risk of severe hypoglycemia by 9.9% in critically ill patients with very different diagnosis, including septic shock.30 In addition, CGMS values have shown a better accuracy in patients with septic shock than in patients with other serious illnesses, when compared with arterial blood glucose.20

Conclusions

With the data obtained we observe that when the CGMS is able to collect data, there is a correlation between the values obtained by this and capillary blood glucose in patients with distributive shock.

The use of continuous glucose sensors tissue in ICU may benefit patients with distributive shock, because a more precise monitoring is obtained, enabling early diagnosis of the presence of glucose excursions (hypoglycemic and hyperglycemic) facilitating compliance with protocols of insulin infusion, alerting us of changes in the metabolic state of the patient, obtaining possibly decreased morbidity associated with the strict glycemic control.

There remains the problem of the lack of sensing in patients in shock, which could be overcome with the development of intravascular glucose sensors continuously.

All this should be confirmed in further studies with larger numbers of patients, preferably using as a control blood glucose levels.

Until then, the use of CGMS in patients with distributive shock can be assessed, because there is a high percentage of patients who may benefit from their use, without complications arising from their use. Also, the costs do not rise significantly because they are economic devices that work for a long time (up to 5 days), reducing the workload of nurses, although this has not been evaluated.

Competing interests

This study has received the financial support of a Cohesion Fund grant from the Health Ministry of Spain, in the year 2009.

The authors declare neither to have received any grant or financial support from the manufacturer of the device assessed in the study, nor to have any conflict of interest regarding this study.

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