Continuous glucose and exhaled breath analysis in the Intensive Care Unit
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INTRODUCTION

Many critically ill patients are treated with insulin for shorter or longer periods during their stay in the intensive care unit (ICU) [1]. Intensive monitoring of the blood glucose level is a prerequisite for both efficient and safe insulin titrations in these patients [2]. Presently in the ICU, glucose levels are monitored manually through intermittent measurements of the blood glucose level in central laboratories or using laboratory-based blood gas analyzers and/or glucose strips at the bedside [3]. Intermittent manual glucose monitoring, however, is impractical and expensive, time and blood consuming [4], and could even cause dangerous insulin titration errors in critically ill patients [5]. Glucose monitoring through so-called continuous glucose monitoring (CGM) could overcome some of the shortcomings and drawbacks of intermittent manual glucose monitoring. Specifically, CGM could allow for smoother insulin adjustments based on trends of the glucose level visualized on a monitor [3]. Several CGM devices for use in the ICU are being developed. These all require thorough accuracy testing in diverse cohorts of critically ill patient before they can be implemented in daily ICU practice.

This chapter provides an overview of diverse CGM techniques and CGM devices intended for use in the ICU. This chapter also deals with how point and trend accuracy of CGM systems could be studied in critically ill patients and how the accuracy results could be reported.

Search strategy

We searched MEDLINE (1966–2013) using the following search terms: (‘intensive care’[MeSH Terms] OR ‘intensive care’[tiab]) OR (‘critical care’[MeSH Terms] OR ‘critical care’[tiab]) OR (‘critical illness’[MeSH Terms] OR ‘critical illness’[tiab]) AND (‘glucose’[tiab] AND (‘continuous glucose monitoring’[tiab] OR ‘continuous glucose measurement’[tiab] OR ‘CGM’[tiab])). Retrieved articles, and cross-referenced studies from those articles, were screened for pertinent information.

Articles were selected if they evaluated a CGM device intended to use in ICU patients. Articles reporting on studies in animals were excluded, as were articles reporting on studies of CGM in other than ICU populations. Revisions and articles that did not report outcomes of interest were also excluded, and in case we found duplicate articles of the same study in abstracts and articles, we report from the most complete data set.

Next, we performed an Internet-search, using similar search terms in Google™. We visited commercial website identified by this search and looked for pertinent information. We also visited websites of medical congresses for information and abstracts of studies that were not yet published.

In August 2013, the two searches identified several CGM devices that were already available for use, as well as devices that were in a developmental phase (table
Studies concerning CGM accuracy in critically ill patients were very limited, and the results of most studies were only available on commercial websites or presented in abstracts presented on medical congresses.

**CGM devices**

Common to all CGM devices is that they measure glucose levels continuously, or intermittently but frequently, though in different body fluids (i.e., whole blood, plasma, dialysate, or interstitial fluid) using dissimilar procedures (i.e., automated blood draws, or no blood draws at all) and distinctive measurement techniques (i.e., based on a chemical reaction, or using fluorescence or spectroscopy) (table 1). While measurement in plasma is considered the ‘gold standard’ for intermittent glucose measurements in the ICU setting, of all CGM devices only one device is reported to measure glucose levels in automated bedside–prepared plasma (OptiScanner). Other devices measure glucose levels in whole blood (GlySure, GluCath, and GlucoClear), dialysate from blood (Eirus and Diramo) or interstitial body fluids (Sentrino, Symphony, and GlucoDay).

CGM devices are reported to measure the glucose level in venous blood via a sensor inserted through a peripheral venous catheter (GluCath) or a central venous catheter (GlySure). Other CGM devices automatically draw venous blood via a central venous catheter (OptiScanner) or via a peripheral venous catheter (GlucoClear). For measurements of the glucose level in subcutaneous tissue, one single sensor or a set of sensors is used (Symphony, Sentrino). Systems that measure glucose levels in dialysate, prepare dialysate in a catheter designed for this purpose and inserted into a central vein (Eirus, Diramo) or into the subcutis (GlucoDay).

CGM devices measure glucose levels by using the glucose oxidase test (Eirus, Diramo, GlucoClear, Symphony, Sentrino and GlucoDay), fluorescence (GlySure and GluCath) or spectroscopy (OptiScanner). The glucose oxidase test is based on an enzymatic reaction, which uses glucose oxidase as a catalyst to bind glucose to water and oxygen to form gluconic acid and hydrogen peroxide. When there is more glucose, more hydrogen peroxide will be released, which can subsequently be measured [6]. The fluorescence technique is based on emission of light by a substance after absorbing light. Fluorescent chemistry is sensitive to glucose. When the glucose level increases, the fluorescent signal increases, which is detected with an optical fiber [7]. The spectroscopy technique is based on the characteristic absorption of vibrational nodes of different molecules, including glucose. Mid–infrared spectroscopy can be used because the glucose spectral peaks are in the mid–infrared region [8].

**Potential drawbacks**

Glucose levels in plasma are higher than in whole blood, demanding a conversion factor that depends on the hematocrit level [9]. Furthermore, arterial blood
glucose levels are higher compared to peripheral venous glucose levels (difference of ~ 0.2 mmol/L) and central venous glucose levels (difference of ~ 0.3 to 0.4 mmol/L) [10]. Glucose levels in dialysate tend to be slightly lower compared to glucose levels in surrounding fluids from which the dialysate is created [11]. Glucose levels in subcutaneous tissues are dependent on the speed by which glucose diffuses from the blood compartment to the interstitial spaces, as well as the rate at which glucose is taken up by cells in the subcutaneous compartment [12]. Users may take these drawbacks into account when using the GCM devices in daily practice, but researchers certainly will need to correct for this when determining GCM accuracy.

A potential disadvantage of any biosensor is the buildup of body fluid deposits on sensor surfaces, for which repeated calibrations and eventually sensor replacements are needed [13]. Need for repeated replacements of (parts of the) system is not limited to sensor–based devices, though, as all CGM devices need replacement of other parts of the system, such as cartridges, and/or dialysate–membranes. Furthermore, with the exception of CGM using a transdermal sensor (Symphony), all CGM devices must be considered ‘invasive’, and as such could cause infections and/or bleedings. Additionally, all CGM devices that measure the blood glucose level in a vein are at risk of presenting erroneous glucose levels when glucose, or other substances that interfere with the measuring technique, are infused through the same catheter or close to that catheter. Finally, the oxygen level and the pH could affect measurements by both the glucose oxidase test and the fluorescence technique [6, 7]. Drugs could interfere the glucose oxidation reaction through molecules oxidizing with hydrogen peroxide [6] and mid–infrared spectroscopy through spectrum of molecules other than glucose [8]. Users need to be aware of these drawbacks when using the GCM devices in their practice.

**Point and/or trend accuracy**

All CGM devices need accuracy testing in cohorts of patients in which they will be used. Two different types of accuracy can be tested, ‘point accuracy’, and ‘trend accuracy’. Point accuracy is the accuracy of intermittent measurements at a static point. Trend accuracy is the accuracy to detect changes in glucose levels.

Several point accuracy metrics have been used to report accuracy, including correlation coefficients, mean absolute difference (MAD) or mean absolute relative difference (MARD), and Bland–Altman plots [14, 15]. A high correlation coefficient (close to 1 or -1) means that paired glucose measurements (measurement by the device versus measurement by a reference test) lay along any straight line – but this line may not lay along the line of equality were differences between paired measurements are zero. Both MAD and MARD summarize
all paired glucose measurements in a single number, but unfortunately causes loss of important information. Another frequently used metric to demonstrate point accuracy is presenting all collected paired glucose measurements, with bias (the mean overall difference between the paired measurements) and limits of agreement (mean difference ± 1.96 \* standard deviation) in Bland–Altman plots [16].

Reports on studies testing the accuracy of home glucose meter commonly use so-called Clark–error grids (CEG) (figure 1). A CEG visualizes information by presenting all collected paired glucose measurements, ‘scoring’ clinical accuracy [17]. For this, a CEG is divided in 5 paired ‘zones’: zones A (measurement within 20% of the reference or glucose levels < 70 mg/dL); zones B (measurement more than 20% different from the reference but still clinically acceptable as they would not change the rate of insulin infusion); zones C (measurement that would lead to unnecessary changes in insulin infusion, i.e., overcorrecting acceptable glucose levels); zones D (potentially dangerous hypo- or hyperglycemic events are missed); and zones E (levels that would lead to a decision opposite to that required, i.e., treatment for hypoglycemia instead of hyperglycemia). General consensus is that 95% of the values should be in zones A and 5% in zones B [14].

It must be noted that the CEG is originally designed for testing accuracy of home glucose meters, not ICU meters. At the moment, it is uncertain whether the CEG zones are useful in the ICU setting. As an alternative to the CEG, an insulin titration–error grid has been proposed [18]. In this grid, very much alike the original CEG, accuracy zones are based on a specific guideline for insulin titration. As guidelines for insulin titration differ (extensively) between ICUs worldwide, it could be difficult to compare results of accuracy testing of CGM devices using these grids.

R–deviation (RD) and absolute R deviation (ARD) have been proposed as rate accuracy metrics [15]. RD is defined as the difference between rates of change of measurements by the device and the reference test, divided by the time interval [15]. The ARD is the absolute value of RD [15]. Unfortunately, like in MAD and MARD, only reporting RD or ARD causes loss of important information.

More recently, the ‘continuous glucose–error grid analysis’ (CG–EGA) has been proposed for testing rate accuracy of CGM devices (figure 2) [19]. The CG–EGA combines point accuracy with rate accuracy though a rate error grid, a point error grid, and an error matrix. The rate error grid plots the rate of change of the glucose level measured by the CGM device and the reference test. A bit similar to original CEG, the rate error grid is divided in 5 paired ‘zones’: zones Ar (rate) (the accurate zone) and Br (the benign error zone), in these zones errors do not cause inaccurate adjustments; zone Cr (over- or underestimation of the
rate of change); zones Dr (reference test detects a change, which is undetected by the CGM device); and zones Er (reference test detects a change, but an opposite change is detected by the CGM device). The point error grid looks like the original CEG, but also takes glucose changes into account. Indeed, in this adjusted grid, zones are defined depending on the speed of change of glucose levels. When there is no significant glucose change, zones are similar to the original CEG, but when reference glucose levels are declining the upper limits change, and when reference glucose levels are increasing the lower limits change. Finally, results from the point and error grids are to be put into an error matrix with three regions, one for hypoglycemic range, one for normoglycemic range and one for hyperglycemic range. The CG–EGA is a complex tool. Also, the creation of a CG–EGA requires (very) frequent sampling to come to meaningful conclusions. However, one should keep in mind that the rate of sampling has an important effect on the results [20].

An alternative for the CG–EGA could be the polar plot, originally developed for testing trend accuracy of cardiac output monitors (figure 3) [21]. A polar plot shows the agreement between measurements by a device and measurements by a reference test as the angle made with the line of identity (where the difference between the measurements is zero) and the magnitude of change as the radian [21]. This way of accuracy testing, however, so far has not yet been used for testing accuracy of CGM devices.

**Reported accuracies of CGM devices**

Studies on point accuracy of CGM devices for use in the ICU are very scarce (table 2). The search in Medline identified only two point accuracy studies in ICU patients (Eirus [11] and GlucoDay [22]). The Internet-search identified several point accuracy studies presented as abstracts (Glysure [23], GluCath [24], Symphony [25] and Sentrino [26]) or on commercial website (OptiScanner [27], Diramo [28] and GlucoClear [29]). Most studies were rather small regarding the number of patients as well as the number of paired measurements. Notably, accuracy was sometimes only tested in ‘less severely ill’ patient population, i.e., patients in the ICU after (cardiac) surgery [11, 25, 26, 28, 29].

Two studies tested trend accuracy (GlucoDay [22], Symphony [25]). In the study of GlucoDay, a paired sample was obtained in 5 medical ICU patients every 15 minutes. The error matrix of the CG–EGA showed all samples in the hypoglycemic range in zone A, in the hyperglycemic range 88% in zone A and B and in the normoglycemic range 94% in zone A and B [22]. In the study of Symphony in post–cardiac surgery patients, paired samples were obtained only every 30 – 60 minutes. Although not specified for the range of glucose levels, 100% of the samples were in the A and B zone [25].
DISCUSSION

The most frequently suggested potential benefit of CGM in ICU patients is a reduction in time spent by nurses measuring glucose level [30]. Whether CGM truly reduces time spent on glucose monitoring, however, has not yet been demonstrated. CGM devices could indeed reduce the number of manual measurements. However, initiation, repeated manual calibrations and replacement of (parts of) the system could also use up nursing time. Whether time spent with using CGM weighs against the burden of intermittent manual measurement in central laboratories or using laboratory–based blood gas analyzers and/or strips at the bedside could be subject of future studies.

Intermittent manual glucose monitoring is usually seen as expensive [4]. It is questionable, however, whether use of CGM will reduce costs associated with glucose monitoring. Indeed, CGM device will come at a price, as do the disposables used with these devices. Costs for glucose monitoring should never be considered in isolation, but together with potential financial benefits and other healthcare costs (e.g., cost prevented by reducing the incidence of dysglycemia). Therefore, health–economy analyses could accompany future studies of CGM in critically ill patients.

It has been suggested that CGM could prevent dangerous insulin titration errors in critically ill patients [5]. One trial of glucose control confirmed that CGM prevents hypoglycemia, but overall glucose control did not improve [31]. One trial of closed–loop CGM–insulin titration showed improved glucose control, though [32]. Of note, these two trials used a home CGM device and still, frequent intermittent manual glucose measurements were necessary.

As yet, the number of studies assessing accuracy of CGM devices is surprisingly small. In addition, numbers of patients studied in each investigation are low and most studies are performed only in a highly selected ICU population (i.e., patients after cardiac surgery). It could be questioned if accuracy is also good in the ‘more severely ill’ patients, such as patients with severe sepsis or septic shock.

Point accuracy of some CGM devices is low. The question is whether such CGM devices are useless in the ICU setting. One advantage of CGM is that there will be many more glucose readings than with manual intermittent glucose monitoring. Thereby the user could detect trends, and trend accuracy could be more important than point accuracy. An analogy that supports use of CGM devices with poor point accuracy is the comparison between camcorders versus still cameras, as previously pointed out by Kovatchev et al. [19]: ‘Still cameras produce highly accurate snapshots at random sparse points in time, and camcorders generally offer lower resolution of each separate image but capture the dynamics of the action. Thus, it would be inappropriate to gauge the accuracy of still cameras and camcorders using the same static measure of the number of glucose readings per day.”
of pixels in a single image. Similarly, it is inappropriate to gauge the precision of [...] devices using the same measures and to ignore the temporal characteristics of the observed process.'

CONCLUSION

Implementation of CGM devices in daily ICU practice is at hand. Several CGM devices, using different body fluids and diverse sample and measuring techniques have been or are currently developed. These all need accuracy testing. The number of studies assessing accuracy of CGM devices is still limited, and most studies so far only included low numbers of highly selective ICU patient population.

References

Preliminary ICU experience of a novel intravascular blood glucose sensor. Critical Care 16: P175 (abst)


27. Optiscan, (2013) OptiScan Biomedical Presents Study Results Demonstrating OptiScanner’s Excellent Glucose Monitoring Accuracy in Critically Ill ICU Patients. Press Release 21 March


Figure 1. The Clarke Error Grid – paired measurements are plotted; measurements are most accurate in zones A and least accurate in zone E, where measurements are erroneous. See text for more details.
Figure 2.

The Continuous Glucose Error Grid with the ‘Rate Error Grid’ (panel A), the ‘Point Error Grid’ (panel B) and the ‘Error Matrix’ (panel C) – the Rate Error Grid is divided in zone Ar – Er, with Ar being the most accurate zone and Er being the least accurate (erroneous) zone; the Point Error Grid has similar zones as the Clark Error Grid (figure 1), but the limits dependent on rates of change: when there is no significant glucose change, zones are similar to the original CEG; with declining reference glucose levels upper limits change; with increasing reference glucose levels the lower limits change (see arrows in panel B); the results of the point error grid and rate error grid are put into an error matrix (Panel C) with 3 zones; accurate readings , benign errors (/ / /) and erroneous readings (=). See text for details.
Figure 3.
A Polar plot. The 4 panels indicate how a polar plot is constructed. Panel A shows 4 paired glucose measurements. Panel B visualizes the same measurements with CGM measurements on the Y–axis and reference test measurements on the X–axis (note that the solid dots and squares in panel A represent the same measurements as solid triangles in panel B); a line is drawn between the consecutive measurements. In panel C, the difference between two consecutive readings (or the rate of change) by the CGM device is plotted on the Y–axis against the difference (or the rate of change) between two readings by the reference test on the X–axis (note how the rates of change make a particular angle with the line of identity, which is the line where the rate of change detected by the CGM device and by the reference test is the same). The radius is calculated as the mean of the rates measured by the CGM device and the reference test (dots in panel C). The angle with the line of identity is one coordinate in the polar plot with the radius being the other coordinate. The transformation to the polar plot is made in panel D, with the black dot representing the same black dot in panel C. Measurements with a large angle, i.e., a large difference between the rate of change measured with CGM and the reference test, are less accurate. Criteria for defining good and poor trend accuracy for the polar plot are uncertain.
<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>glucose is measured in:</th>
<th>sampling technique</th>
<th>measurement technique</th>
<th>frequency of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>OptiScanner</td>
<td>OptiScan Biomedical Corporation</td>
<td>plasma created from central venous whole blood</td>
<td>blood</td>
<td>mid-infrared</td>
<td>15 minutes</td>
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<td></td>
<td></td>
<td></td>
<td>drawn via</td>
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<td></td>
<td></td>
<td></td>
<td>a central venous</td>
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<td></td>
<td></td>
<td></td>
<td>catheter</td>
<td></td>
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<tr>
<td>GlySure</td>
<td>GlySure Limited</td>
<td>central venous whole blood</td>
<td>blood</td>
<td>fluorescence</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sensor-based</td>
<td></td>
<td></td>
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<tr>
<td>Eirus</td>
<td>Maquet</td>
<td>central venous whole blood</td>
<td>dialysate</td>
<td>glucose oxidase</td>
<td>1 minute</td>
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<td></td>
<td></td>
<td>or peripheral arterial whole blood</td>
<td></td>
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<tr>
<td>Diramo</td>
<td>Flowision AS</td>
<td>central venous or peripheral arterial whole blood</td>
<td>dialysate</td>
<td>glucose oxidase</td>
<td>1 second</td>
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<td>GluCath</td>
<td>GluMetrics Incorporated</td>
<td>peripheral venous or arterial whole blood</td>
<td>blood</td>
<td>fluorescence</td>
<td>10 seconds</td>
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<td>GlucoClear</td>
<td>Edwards Lifesciences</td>
<td>peripheral venous whole blood</td>
<td>blood</td>
<td>glucose oxidase</td>
<td>5 minutes</td>
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<td></td>
<td></td>
<td>sensor-based</td>
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<tr>
<td>Symphony</td>
<td>Echo Therapeutics</td>
<td>interstitial fluid</td>
<td>transdermal</td>
<td>glucose oxidase</td>
<td>1 minute</td>
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<td></td>
<td></td>
<td></td>
<td>biosensor</td>
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<tr>
<td>Sentrino</td>
<td>Medtronic Incorporated</td>
<td>interstitial fluid</td>
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<td>GlucoDay</td>
<td>A. Menarini Diagnostics</td>
<td>interstitial fluid</td>
<td>dialysate</td>
<td>glucose oxidase</td>
<td>3 minutes</td>
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Table 1
Overview of CGM–devices intended for use in ICU patients
<table>
<thead>
<tr>
<th>Device</th>
<th>Patients studied</th>
<th>Number of paired samples</th>
<th>Point accuracy</th>
<th>Trend accuracy</th>
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<tr>
<td>OptiScanner</td>
<td>63 medical or surgical ICU patients</td>
<td>Not reported</td>
<td>CEG analysis: 100% in zones A+B</td>
<td>–</td>
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<td>GlySure</td>
<td>16 medical or surgical ICU patients</td>
<td>296</td>
<td>CEG analysis: 99.6% in zones A+B</td>
<td>–</td>
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<tr>
<td>Eirus</td>
<td>30 peri–operative cardiac surgery patients</td>
<td>607</td>
<td>CEG analysis: 100% in zones A+B; MARD 5.6%</td>
<td>–</td>
</tr>
<tr>
<td>Diramo</td>
<td>10 post–operative cardiac surgery patients</td>
<td>359</td>
<td>CEG analysis: 100% in zones A+B; MARD 4.1%</td>
<td>–</td>
</tr>
<tr>
<td>GluCath</td>
<td>5 post–operative cardiac surgery</td>
<td>202</td>
<td>MARD 5.5%</td>
<td>–</td>
</tr>
<tr>
<td>GlucoClear</td>
<td>10 post–operative surgical ICU patients</td>
<td>1393</td>
<td>CEG analysis: 100% in zones A+B; MARD 5.0%</td>
<td>–</td>
</tr>
<tr>
<td>Symphony</td>
<td>15 peri–operative cardiac surgery</td>
<td>&gt; 600</td>
<td>MARD 12.3%</td>
<td>–</td>
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<tr>
<td>Sentrino</td>
<td>21 post–operative cardiac surgery patients</td>
<td>864</td>
<td>MARD 12.2</td>
<td>–</td>
</tr>
<tr>
<td>GlucoDay</td>
<td>50 medical ICU patients (5 patients were included for trend accuracy)</td>
<td>N = 820 (for 2-point calibration) N = 555 (for 6-point calibration)</td>
<td>CEG analysis: 95% in zones A+B for 2 point calibration 97% in zones A+B for 6 point calibration;</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2.
Overview of studies of CGM–devices in ICU patients. Abbreviations: ICU, intensive care unit; CEG, Clark error grid; MARD, mean absolute relative difference, CG–EGA, continuous glucose error grid; –, no data.