What goes up must come down: glucose variability and glucose control in diabetes and critical illness
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Chapter 9

Accuracy and reliability of continuous glucose monitoring in the intensive care unit: a head-to-head comparison of two subcutaneous glucose sensors in cardiac surgery patients

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Abstract

Objective: To investigate accuracy and reliability of two different continuous glucose monitoring (CGM) devices in patients who underwent cardiac surgery.

Methods: We performed a prospective, observational, investigator-initiated study in a 20-bed intensive care unit (ICU) of a teaching hospital. We studied 60 consecutive patients who underwent cardiac surgery. Two CGM devices (Guardian Real-Time, Medtronic Minimed; FreeStyle Navigator, Abbott Diabetes Care) were placed subcutaneously in the abdominal wall before surgery. Both devices were calibrated simultaneously upon arrival at the ICU and further according to manufacturers’ instructions. An arterial reference blood glucose value was measured every two hours. Relative absolute deviation (RAD) between reference and sensor glucose was calculated in six 5-minute intervals from the reference glucose, to assess a possible delay.

Results: Of the 1,017 reference glucose values measured 77.7% could be paired with a Guardian and 91.8% with a Navigator glucose value, missing values indicating technical problems with the devices: unintentional signal loss (both systems) or an interruption of real-time representation of glucose values after delayed recalibration (Guardian). Median [IQR] RAD was significantly smaller for Navigator than for Guardian measurements at the first and second interval (11% [8-16] and 10% [8-16] compared to 14% [11-18] and 14% [11-17], P = 0.05 and 0.001). The delay was estimated to be 5-9 minutes for the Navigator and 15-19 minutes for the Guardian.

Conclusions: FreeStyle Navigator performed better regarding accuracy and reliability than the Guardian Real-Time in cardiac surgery patients at the ICU. Use of this device seems feasible in these patients.
Introduction

Occurrence of hyperglycaemia in the intensive care unit (ICU) is common, also in patients without a known history of diabetes. Severe illness causes hormonal changes resulting in hyperglycaemia through increased gluconeogenesis in the liver and increased insulin resistance. This transient so called stress-hyperglycaemia is associated with increased mortality. Several trials assessed the effect of intensive insulin therapy on outcome in this patient group with conflicting outcomes. However, glycaemic control remains a widespread practice, although the target range is unclear. Besides hyperglycaemia also hypoglycaemia, as a consequence of intensive insulin therapy or due to severe illness, and glucose variability are independently associated with mortality.

At present, intermittent manual blood sampling has to be performed to achieve glycaemic control. This method is time consuming, certainly when the patients’ glucose levels fluctuate. Moreover, no information is available for the period in-between measurements with perhaps unnoticed hypoglycaemic episodes. Continuous glucose monitoring (CGM) could therefore be of value in achieving glycaemic control, providing real-time glucose values as well as an alarm function to alert for glucose values outside a predefined range, and information on rapid increases or decreases in glucose levels.

Promising as CGM in the ICU may be, the accuracy and reliability of these devices is uncertain in critically ill patients. Different studies report “acceptable” differences between sensor and reference glucose values, but it can be debated how large an acceptable deviation in the ICU may be, also because it is known from outpatient data that accuracy is worse in the hypoglycaemic range. CGM measurements reflect interstitial rather than plasma glucose levels, so microcirculatory changes seen in the critically ill might influence CGM function. However, in patients who underwent cardiac surgery a good correlation between arterial and interstitial glucose was found using an experimental micro dialysis system, suggesting that this patient group lends itself for CGM.

In this study we investigated the accuracy and reliability of two different CGM devices, the Guardian® Real-Time (Medtronic Minimed, Northridge, CA) and FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA), postoperatively in cardiac surgery patients in an investigator-initiated trial.

Methods

Patients
We performed a prospective observational study in a 20-bed medical/surgical ICU in
the Onze Lieve Vrouwe Gasthuis (OLVG; Amsterdam, the Netherlands) to obtain glucose monitoring data from the two devices. The study was approved by the Institutional Ethical Review Board according to the declarations of Helsinki. We included subsequent patients above the age of 18 who were planned to undergo elective cardiac surgery; coronary artery bypass grafting (CABG) and/or valve surgery. We excluded patients with an abdominal condition which would prohibit sensor insertion. Eligible patients received an information letter at least one week before hospital admission. Before the planned surgery patients were asked to give written informed consent after oral explanation of the study. During ICU admittance Acute Physiology and Chronic Health Evaluation (APACHE) IV predicted mortality score was calculated for the first 24 hrs of admission and Sequential Organ Failure (SOFA) score was obtained daily. Also the European System for Cardiac Operative Risk Evaluation (euroSCORE) score, a method of calculating predicted operative mortality risk for patients undergoing cardiac surgery, was recorded for every patient.

**Glucose monitoring**

Two needle-type sensors, Guardian® Real-Time (Guardian; Medtronic Minimed, Northridge, CA) and FreeStyle Navigator® (Navigator; Abbott Diabetes Care, Alameda, CA), were inserted in the abdominal wall on either side of the umbilicus and calibrated before surgery to allow stabilization of the signal. Upon arrival at the ICU after surgery, the device’s internal clock was matched with the bedside computer and both devices were calibrated simultaneously. Further calibrations were performed according to manufacturers’ instructions. Except from the calibrations, all sensor dealings were performed solely by the investigators. The devices were removed after 48 hrs of ICU admission or earlier when the patient was discharged.

During the study an arterial blood glucose value was measured with the AccuChek handheld glucose measurement device (Performa II, lot 320098, Roche/Hitachi®, Basel, Switzerland) as a reference value every two hours. These samples were used as calibration when needed and as reference otherwise. An in-house quality assurance study showed that the slope of the regression between this point-of-care measurement method and arterial glucose measurement by blood gas analysis was 1.0 (95% CI 1.00-1.02, n = 1393, sample range 2.9-30.0 mmol/l; Passing-Bablok regression) and 95% of the absolute differences between reference and point-of-care measurement were lower than 15%, thereby meeting the ISO 15197 guideline. All results were stored in the ICU’s clinical information system (iMD-Soft; MetaVision, Tel Aviv, Israel). Using a dynamic computerised algorithm implemented in 2001, glucose values between 5.0 and 8.0 mmol/l were targeted. The glucose protocol was started for every patient at time of arrival at the ICU. Insulin infusion was started when admission blood glucose exceeded 8.0 mmol/l. When admission glucose was lower than 8.0 mmol/l, blood glucose was measured every 2 hrs and insulin was started when blood glucose exceeded 8.0 mmol/l. The nursing staff was
instructed to adjust the insulin infusion rate depending on the current glucose value and the rate of glucose change based on the previous five measurements. The 2-hr reference glucose values were used as input in this algorithm. The nursing staff did not act upon the sensor glucose values.

Data interpretation and statistics
The Guardian device displays the average sensor glucose every five minutes and stores all these values. The Navigator device refreshes the displayed glucose every minute and stores the value of every tenth minute. The relative absolute deviation (RAD) \( \frac{|\text{sensor value} - \text{reference glucose}|}{\text{reference glucose}} \) between reference and sensor glucose values was calculated to assess the accuracy of the devices. For this purpose we linked the reference value to the first available sensor value after the reference value using the exact sampling times of both devices obtained after downloading the individual data. To assess a possible delay of the CGM devices the reference value was linked to subsequent sensor values up to 30 minutes after the reference value. We calculated the interval between each reference-sensor pair in minutes and created six five-minute intervals (0-4, 5-9, 10-14, 15-19, 20-24, 25-29 minutes) in which we could match reference with sensor glucose values. These five-minute intervals permit a fair comparison between both sensors independent from the sampling frequency, since the Navigator stores data only every tenth minute and the Guardian every five minutes. The median RAD per patient per interval was calculated for each sensor and subsequently both sensors were compared using a Wilcoxon signed ranks test for not normally distributed paired data. Assessment of the lag time on the RAD per sensor was calculated using repeated measures ANOVA. All analyses were performed using SPSS version 16.0.

For each sensor, all paired samples of reference glucose values and matching next sensor values were plotted in a Clarke error grid \(^13\). Also, the absolute differences between sensor readings and reference glucose measurements were plotted against the average of the two in a Bland-Altman plot \(^14\).

Results
We included 61 patients in the study, of whom 1 patient dropped out due to cancellation of surgery because of intercurrent febrile illness. In total we included 60 patients in the final analysis of whom 48 were males. The median (range) age was 65 (25-85) years and 26.7% of the patients were previously diagnosed with diabetes. The majority of the patients underwent only a CABG procedure (53.3%). Median (IQR) APACHE IV PM and maximum SOFA scores were 0.01 (0.003-0.02) and 6.0 (5.3-7.0). Patient characteristics are reported in Table 1.
Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients, n=60</th>
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<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>48 (80.0)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.0 (59.0-73.8)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>Procedure, n (%)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>CABG + valve surgery</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td>APACHE IV PM</td>
<td>0.01 (0.003-0.02)</td>
</tr>
<tr>
<td>SOFA max</td>
<td>6.0 (5.3-7.0)</td>
</tr>
<tr>
<td>euroSCORE</td>
<td>4.0 (2.0-5.0)</td>
</tr>
<tr>
<td>ICU stay, hours</td>
<td>23.0 (19.0-45.8)</td>
</tr>
<tr>
<td>ICU readmission, n (%)</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>Death in ICU/hospital, n</td>
<td>0</td>
</tr>
<tr>
<td>Glucose ICU, mean (SD)</td>
<td>8.2 (2.1)</td>
</tr>
</tbody>
</table>

Data are given in median (IQR) unless stated otherwise. CABG, coronary artery bypass grafting; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation score; SOFA, sequential organ failure assessment score; euroSCORE, European System for Cardiac Operative Risk Evaluation. Valve surgery includes mitral valve plasty, tricuspid valve plasty, aortic valve replacement or a combination of these.

Reliability

During the study 1,017 reference glucose values were collected. Of these 91.8% could be paired with a Navigator and 77.7% with a Guardian glucose value in the first data storage interval. Missing values indicated technical problems with the device: unintentional signal loss (Guardian: 19 patients; Navigator: 1 patient), interruption of real-time representation of glucose values after delayed recalibration (Guardian) or temporary failure of data-recording (Navigator: 4 patients). In 7 patients a new Guardian sensor had to be placed due to sensor failure. In 2 patients a new Navigator sensor was placed due to a disconnection between the actual sensor and fixation plate.

Accuracy

Median (IQR) RAD was significantly smaller for Navigator compared with Guardian glucose measurements at intervals 0-4 and 5-9 minutes after the reference glucose (11% [8-16] versus 14% [11-18], P = 0.05 and 10% [8-14] versus 14% [11-17], P = 0.001; Figure 1). The lowest RAD of the Navigator was observed 5-9 minutes after the reference glucose, but no significant effect of time was seen (P = 0.74, repeated measures ANOVA). The accuracy of the Guardian did show a delay with the lowest RAD after 15-19 minutes (11% [8-13], P = 0.01; Figure 1). The results did not differ among subgroups of patients with or without
diabetes mellitus (Mann-Whitney U Test; data not shown).

Clarke error grids of reference glucoes with corresponding next sensor values are shown in Figure 2 for each CGM device separately. For the comparisons with arterial reference glucose values 81.8% of the Navigator and 73.2% of the available Guardian glucose values fell in zone A. 17.7% of the Navigator and 25.2% of the Guardian glucose values fell in zone B. Five of the 934 Navigator values fell in zone C or D (0.5%) and none in zone E compared to 13 of the 790 Guardian values in zone C, D or E (1.3%).

To evaluate variations in accuracy over the range of measured glucose concentrations, absolute differences between sensor readings and reference glucose values were plotted (Figure 3). The variation in accuracy was larger with the Guardian looking at the range between the 5th and 95th percentile (Guardian -3.03 to 2.27 mmol/l, range 5.30 mmol/l; Navigator -1.83 to 2.53 mmol/l, range 4.36 mmol/l). There was no consistency in direction of the error. Both positive and negative differences were seen, resulting in median (IQR) differences coming close to zero (Navigator 0.10 [-0.60-0.90] mmol/l, Guardian 0.24 [-0.75-1.07] mmol/l). No trend was observed visually for more inaccuracy in the hypo- and hyperglycaemic ranges (Figure 3). We did not perform separate analyses to assess accuracy during hypoglycaemia due to too few hypoglycaemic events: no severe hypoglycaemic events (≤2.2 mmol/l) were measured and only 34 of 1,017 reference glucose values were mildly hypoglycaemic (≤4.7 mmol/l) 5.

Figure 1 Head-to-head comparison of the accuracy of both sensors
Relative Absolute Deviation (RAD) between reference and sensor glucose values at different intervals after the reference glucose measurement. RAD's are displayed in medians. *P = 0.05, **P = 0.001
Figure 2 Clarke error grids of glucose measurements
(A) Navigator. (B) Guardian. Each grid shows data pairs of reference glucose values at the x-axis with proximate sensor values (within 10 minutes for the Navigator and within 5 minutes for the Guardian) at the y-axis.

Figure 3 Bland-Altman plots of glucose measurements
(A) Navigator. (B) Guardian. The x-axis represents the average of sensor and reference glucose values in mmol/l. The y-axis represents the absolute difference between sensor and reference glucose values in mmol/l. The dashed line represents the median difference (Navigator 0.10 and Guardian 0.24 mmol/l). The dotted lines represent the 5th and 95th percentile (Navigator -1.83-2.53 and Guardian -3.03-2.27 mmol/l).

Discussion

We report that the FreeStyle Navigator CGM system performed better than the Guardian Real-Time in accuracy, defined by MAD in comparison to AccuChek arterial glucose measurements, as well as reliability, determined by the technical error rates, in postoperative cardiac surgery patients during ICU stay.

To our knowledge, the only study comparing these two devices is a clamp study by Kovatchev and colleagues in type 1 diabetes patients, concluding that the numerical
accuracy was comparable during normoglycaemia. However, the Navigator performed significantly better during hypoglycaemia. It has to be noted that in our study we used a new version of the Navigator with 1-hr initiation duration instead of the older version with 10-hr initiation duration.

Regarding accuracy, our Guardian results are comparable with those from Logtenberg et al. who also performed a study in cardiac patients at the ICU, and reported a median RAD of 12.3% during the ICU period. No studies using the Navigator at the ICU have been published so far. Looking at the accuracy of both devices in our ICU population compared to data in type 1 diabetes patients, this is comparable for the Guardian and even somewhat better for the Navigator. This suggests that at least in the population of cardiac surgery patients CGM use seems feasible.

It is subject of debate whether sensor accuracy in the range that is acceptable for patients with diabetes is also accurate enough for the critically ill patient. Hypoglycaemia is to be avoided since already a single episode of low plasma glucose is independently associated with mortality and sedation makes it difficult to rely on hypoglycaemic symptoms. Potentially dangerous sensor readings are those in the higher range while the reference glucose is in the (near) hypoglycaemic range (Clark error grid zones D and E; Figure 2). For the Navigator this occurred 3 times (0.3% of all sensor readings) and for the Guardian 5 times (0.6% of all sensor readings). We think that this low percentage of potentially dangerous sensor readings is likely to be outweighed by hypoglycaemic episodes that are likely to be prevented by continuous glucose monitoring. Of note, in the present study the number of low glucose measurements is too small to draw conclusions on the accuracy of the devices during hypoglycaemia.

We found a significant time-lag of the Guardian with optimal accuracy 15-19 minutes following reference glucose. This is in accordance with Wei et al. who found a median delay of 16 minutes in their population of type 1 diabetes patients. The optimal accuracy of the Navigator was reached 5-10 minutes after the reference glucose, however no significant effect of time was found. All subcutaneous sensor measurements are accompanied by a physiological delay of 0-10 minutes required for glucose to equilibrate across the capillary endothelial barrier suggesting the Navigator has a minimal technological delay due to data processing and filtering. Our findings are different from Garg et al. who found a system time-lag of 15 minutes for the Navigator in adults with type 1 diabetes. However, they used an earlier version of the Navigator with 10-hr initiation time in their study which might explain these different findings and suggest improvement of the new system with 1-hr initiation time. The differences between the Guardian and Navigator and between different versions of the same device are intriguing; however information on data processing is proprietary. The time-lag found favours the
Navigator for clinical use, as decision making will depend on real-time sensor values.

Also regarding reliability, the Navigator performed significantly better. Moreover, the technical failure rates might be reduced when these systems attended to on a 24/24 hour basis; most of the connection problems occurred at night when no member of the study team was available. The nurses were blinded to the sensor glucose values and therefore the alarms were set off, so a connection problem at night was only noticed when there was a need for recalibration. However, the high frequency of connection problems of the Guardian system suggests some kind of interference with other ICU equipment not occurring with the Navigator system. The technical problems we experienced with the Guardian device were described earlier, although not quantified.

As a reference method we used an arterial glucose measurement performed by the AccuChek handheld device, since clinical decision rules in our and many other ICUs are based on this measurement. Mortality is decreased by targeting hyperglycaemia relying on point-of-care measurements, so we compared a new method with one proven effective. Recently it is debated however how accurate this point-of-care meter is in comparison with laboratory glucose measurements. Accuracy seems unacceptably decreased in older patients with high disease severity scores and high ICU mortality. On the other hand Meynaar et al. concluded that AccuChek measurement has acceptable accuracy for use in the ICU. As our patient group is characterised by relatively low mortality rates and severity scores, AccuChek measurements should have been sufficiently accurate. This is further substantiated by our in-house study comparing the AccuChek with a robust laboratory reference method, which showed agreement as required by the ISO guideline between the two methods. But even with the availability of a possible superior reference method, the inaccuracy of the AccuChek seems random, so that the outcome of our comparison between the two sensors would be unaffected.

In conclusion, we report that the FreeStyle Navigator CGM system performed better in accuracy as well as reliability compared to the Guardian Real-Time in cardiac surgery patients at the ICU. Remarkably, the RAD of both sensors was quite good as compared to known data for outpatients. We think that this device can be used in this group of ICU patients characterised by low disease severity scores and low mortality rates. Further studies will concentrate on patient factors influencing sensor performance and different populations of critically ill patients to allow an even better definition of the ICU population who might benefit from the now available systems. Also, whether or not the use of CGM truly improves glycaemic control and mortality has to be the subject of further research.
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References