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Impact of Retrospective Calibration Algorithms on Hypoglycaemia Detection in Newborn Infants Using Continuous Glucose Monitoring

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Abstract

BACKGROUND: Neonatal hypoglycaemia is common and may cause serious brain injury. Diagnosis is by blood glucose (BG) measurements, often taken several hours apart. Continuous glucose monitoring (CGM) could improve hypoglycaemia detection, while reducing the number of BG measurements. Calibration algorithms convert sensor signals into CGM output. Thus, these algorithms directly affect measures used to quantify hypoglycaemia.

AIM: Quantify the effects of recalibration and filtering of CGM data on measures of hypoglycaemia (BG < 2.6mmol/L) in neonates.

METHODS: CGM data from 50 infants were recalibrated using an algorithm that explicitly recognised the high-accuracy BG measurements available in this study. CGM data were analysed as: 1) Original CGM output; 2) re-calibrated CGM output; 3) re-calibrated CGM output with post-calibration median filtering; and, 4) re-calibrated CGM output with pre-calibration median filtering. Hypoglycaemia was classified by: number, duration, severity and hypoglycaemic index.

RESULTS: Recalibration increased the number of hypoglycaemic events (161 to 193), hypoglycaemia duration (2.2% to 2.6%) and hypoglycaemic index (4.9 to 7.1 μ mol/L). Median filtering post-recalibration reduced hypoglycaemic events from 193 to 131, with little change in duration (2.6% to 2.5%) and hypoglycaemic index (7.1 to 6.9 μ mol/L). Median filtering pre-recalibration resulted in 146 hypoglycaemic events, a total duration of hypoglycaemia of 2.6%, and a hypoglycaemic index of 6.8 μ mol/L.

CONCLUSIONS: Hypoglycaemia metrics, especially counting events, are heavily dependent on CGM calibration BG error and the calibration algorithm. CGMs tended to read high at lower levels, so when high accuracy calibration measurements are available it may be more appropriate to recalibrate the data.

1.0 Background

Neonatal hypoglycaemia is a common condition that may cause seizures and permanent brain injury in newborns [1]. There remains significant controversy regarding the definition of hypoglycaemia, and consequently, the effect it can have on the child's later development [2, 3]. Diagnosis is typically by blood glucose (BG) measurements. However, BG measurements are often taken several hours apart and hypoglycaemic events between BG measurements can go undetected [4]. Continuous Glucose Monitoring (CGM) devices provide a continuous estimate of BG concentration and have the potential to improve the detection and diagnosis of hypoglycaemia.

The first CGM device to be approved by the Food and Drug Administration (FDA) in 1999, was the MiniMed Continuous Glucose Monitoring System (CGMS) [5]. The CGMS consists of a small pager-like monitor that receives information from a sensor inserted just beneath the skin [6]. The sensor is coated with a glucose oxidase membrane which, as glucose in the interstitial fluid is oxidised, produces a small electrical current that is proportional to the glucose concentration. The monitor stores a value every 5 minutes (288 per day).

Calibration BG measurements, normally obtained using a finger-stick glucometer, are required to convert electrical current into meaningful CGM output. Point-of-care testing devices are reported to have errors in the range of 2-10% [7-10], and often perform worse in ICU patients due to varying levels of hematocrit, medication and other affects [11-13]. After initial calibration, it is recommended that CGM devices be calibrated at least 4 times daily [14]. A 10 minute time delay is incorporated into the calibration process to account for the transport of glucose from the blood to the interstitial fluid [15].

The retrospective calibration algorithm used by the CGMS Systems Solutions Software employs linear regression [5]. Linear regression with multiple calibration BG measurements may contribute to the CGMS reporting high during hypoglycaemia and reporting low during hyperglycaemia [6]. However, it may also balance the impact of errors in finger stick glucose meters. Thus, important clinical observations such as excursions from normal BG levels may be directly affected by the calibration algorithm used and the quality of calibration BG measurements.

Several previous studies have investigated CGM calibration schemes, both retrospective and real-time, in adults and children [16-18]. However, CGM devices have also been used to evaluate aspects of glucose metabolism in at-risk newborn infants [4, 19-22]. In the case of [4], laboratory determinations of BG concentrations were available for the dataset and are assumed to be a “gold-standard” assessment. Alternative calibration algorithms can be applied to the CGM readings, utilising the high accuracy BG measurements, and compared to the factory calibrated CGM readings. This study explores and quantifies the impact of calibration and non-linear filtering on metrics of hypoglycaemia in neonates using CGM devices.

2.0 Subjects and Methods

2.1 Subjects:

This study used CGM data from 50 babies at risk of hypoglycaemia, admitted to the Waikato Hospital Newborn Intensive Care Unit (NICU). The cohort contained 26 males and 24 females with a median gestational age of 34 weeks and a median birth weight of 2172g. The primary risk factors used to identify infants likely to become hypoglycaemic include diabetic mother, prematurity and being small or large for gestational age.

2.2 Continuous Glucose Monitoring:

All patients had interstitial glucose monitoring using the CGMS[®] System Gold™ (Medtronic, Minimed, Northridge, CA, USA). Monitoring began on admission to the NICU and finished after 7 days or when the baby was no longer considered at risk of hypoglycaemia. During the monitoring period nurses recorded all BG concentrations, feeding and medication for the management of hypoglycaemia. Nurses remained blinded to CGM measurements and all calibration BG measurements were entered per the manufacturer's recommendations. Data were downloaded to a PC using CGMS system solutions software version 3.0C, which calibrated the CGM readings retrospectively.

2.3 Calibration Measurements

Blood samples were taken by nursing staff via heel-pricking at one hour of age, then two to four hourly (before feeds) for 12 hours. In babies receiving intravenous dextrose, BG was measured 4 hourly for 12 hours, and then less frequently as clinically indicated. The median [inter-quartile range (IQR)] interval between calibration BG measurements was 4.8 [3.5 – 6.4] hours.

All BG calibration measurements were made using a blood gas analyser (Radiometer, ABL800Flex, Copenhagen). This device has a reading range of 0.0 to 60.0mmol/L and a C.V. of 1.4-2.2% [23, 24]. Furthermore, a study by Watkinson et al. showed that a device from the same family, using the same glucose electrode, had a coefficient of variation of 2.1% in ICU patients and performance was not affected by haematocrit, pH or PaO₂ [24]. Due to the location of the blood gas analyser, a short time delay (estimated < 15mins maximum) was possible between taking the blood sample and obtaining the glucose concentration.

2.4 Calibration Algorithms

The factory calibration algorithm used by the CGMS is based on linear regression [6, 25]. The linear regression algorithm is aimed primarily at ambulatory individuals with type 1 diabetes who use the CGM device to help manage BG levels. This population typically uses a finger stick glucometer for calibration which analyses capillary BG and typically has up to 10% error [7-10]. Hence, the use of linear regression implicitly balances calibration BG errors and CGMS errors, and CGM outputs do not necessarily exactly correspond to BG measurements.

The calibration measurements in this study were determined using a gold standard for BG measurement. Thus, data were recalibrated to make better use of the accurate calibration measurements by forcing the CGM output through all BG measurements. It should be noted there are many ways that the data could be recalibrated and the algorithm used in this study represents just one example based as directly as possible upon the current method [5, 14].

The factory CGM blood glucose estimation is determined using Equation 1:

$$BG_{CGM} = Slope * (Valid_{I_{sig}} - Offset) \quad (1)$$

Where:

- BG_{CGM} – Blood glucose estimate by the CGM (mmol.L⁻¹)
- $Slope$ – Calibration parameter found using linear regression (mmol.L⁻¹.nA⁻¹)
- $Valid_{I_{SIG}}$ – Electrical current detected by the monitor from the sensor (nA)
- $Offset$ – Calibration parameter that is used if the sensitivity ratio is below a threshold

To recalibrate, Equation 1 is rearranged to Equation 2:

$$Reqd_slope(i) = \frac{BG_{Cal}(i)}{(Valid_{I_{sig}}(i) - Offset(i))} \quad (2)$$

Where:

- BG_{Cal} – Blood glucose level for calibration (BG analyser measurement) (mmol.L⁻¹)
- $Reqd_slope$ – Slope that forces BG_{CGM} through calibration measurements (mmol.L⁻¹/nA)

The recalibration algorithm forces the output CGM trace to pass through the calibration BG measurements, while preserving the raw sensor current ($Valid_{I_{SIG}}$) and $Offset$ parameter. At each calibration measurement a value of slope ($Reqd_slope$) is calculated using Equation 2. Linear interpolation of $Reqd_slope$ gives the new, continuous slope function which is inserted to Equation 1 with the unmodified $Valid_{I_{SIG}}$ and $Offset$ parameters, to give the recalibrated CGM. This recalibration provides a comparator to assess the impact of calibration on outcome CGM traces.

2.5 Median Filtering

Median filters are used to remove unwanted and potentially un-physiological high-frequency noise from the CGM signal. They have proven to be a simple and effective method of removing this noise and smoothing CGM traces [26, 27]. A retrospective composite median filter was used in this study because it allows faster and slower glucose dynamics to be captured more effectively. The filter averages a 3 point median and a 5 point median both centred about the time point of interest. The filter was implemented both prior to recalibration (on the *Valid I_{SIG}*) and post calibration on the CGM output.

2.6 Analysis

Part 1:

Four analyses of the CGMS data from the 50 babies were performed in this study: 1) Original CGM output; 2) Recalibrated CGM output; 3) Recalibrated and median filtered CGM output; and finally, 4) Filtered *Valid I_{SIG}* then recalibrated CGM output. Each of the recalibrated variations, with and without filtering, is compared to the original CGM output to see the effect of recalibrating/filtering on clinical measures of hypoglycaemia. Hypoglycaemia was defined as one or more consecutive CGM measurement(s) below 2.6mmol/L, surrounded by CGM measurements greater than or equal to 2.6mmol/L. The metrics used to quantify hypoglycaemia were:

- **Number:** Number of independent hypoglycaemic events
- **Duration:** Percent of CGM record below 2.6mmol/L
- **Severity:** Lowest measurement of hypoglycaemic event.
- **Hypoglycaemic index:** Similar in concept to the Hyperglycaemic index presented in [28], defined as the area between the 2.6mmol/L threshold and the CGM trace (for CGM trace <

2.6mmol/L) summed over the entire length of stay, normalised by the length of data record.

Note: the units used in this study are $\mu\text{mol/L}$, not mmol/L as in [28].

Part 2:

A subset of 43 infants with at least 3 days of CGM data were analysed for hypoglycaemic index on a day-by-day basis, for recalibration and filtering. Seven patients were excluded from the analysis due to having less than 3 days of CGM data. For each day, using the original CGM output, patients were ranked by hypoglycaemic index. The ranks were preserved for the three recalibrated and filtered CGM analyses to highlight changes in hypoglycaemic index for individual patients. For example, a patient with a high hypoglycaemic index using default manufacturer calibration may show low hypoglycaemic index when recalibrated. A further integral index metric was used to represent the total hypoglycaemic index across the 43 patients on that day, quantifying this result to a single value for easy comparison.

3.0 Results

Part 1:

Figure 1 shows the distributions of CGM errors (CGM minus BG) at the time of calibrations. Sub-plot 1 shows the distribution for all CGM-BG data (1074 pairs). Sub-plot 2 shows the distribution of errors where either the CGM or BG measurement is less than or equal to 3mmol/L (145 pairs). Sub-plot 3 shows the distribution of errors where either the CGM or BG measurement is greater than 7mmol/L (62 pairs). In all 3 sub-plots the dashed vertical line represents the median, and the solid vertical lines represent the inter-quartile range (IQR).

Calibration BG measurements detected 53 hypoglycaemic events during the study, of which 16 were at a time when the CGM was also hypoglycaemic. For the other 37 hypoglycaemic calibration BG measurements, the CGM was above 2.6mmol/L.

Figure 2 shows a section of CGM trace comparing original (black dashed line), recalibrated (solid blue line), Recalibrated and filtered (green dotted line), and Filtered Valid ISIG then recalibrated variations (purple dash-dot line). In this example, overall trends in calibration parameters and CGM output are preserved. However it is clear in Figure 2 that metrics of hypoglycaemia will vary for each method of signal processing and for each patient. Figure 3 shows the CGM trace in this study that had the largest change in hypoglycaemia metrics after recalibration. The original CGM trace (black dashed line) suffered from particularly bad factory calibration for the first 12 hours of monitoring, during which time there was a significant period of hypoglycaemia. However, all four calibration BG measurements in the first 12 hours were above 2.6mmol/L, and consequently the recalibrated CGM trace (solid blue line) had no hypoglycaemia.

The top section of Table 1 compares the number, duration and severity of hypoglycaemia events, as well as the hypoglycaemic index for each variation of the CGM calibration. The results are presented for the overall cohort (50 patients) and per-patient to show any potential skewed results from individual patients. The bottom section of Table 1 shows the effect of recalibration and/or filtering on the hypoglycaemic state of patients over the monitoring period. For example, the top left cell in bottom section of Table 1 (“24”) indicates that 24 patients who had hypoglycaemia in the original CGM data still had hypoglycaemia in the recalibrated CGM data. Conversely, the second row in column one (“1”) indicates that 1 patient who had hypoglycaemia in the original CGM data had no hypoglycaemia in the recalibrated CGM data.

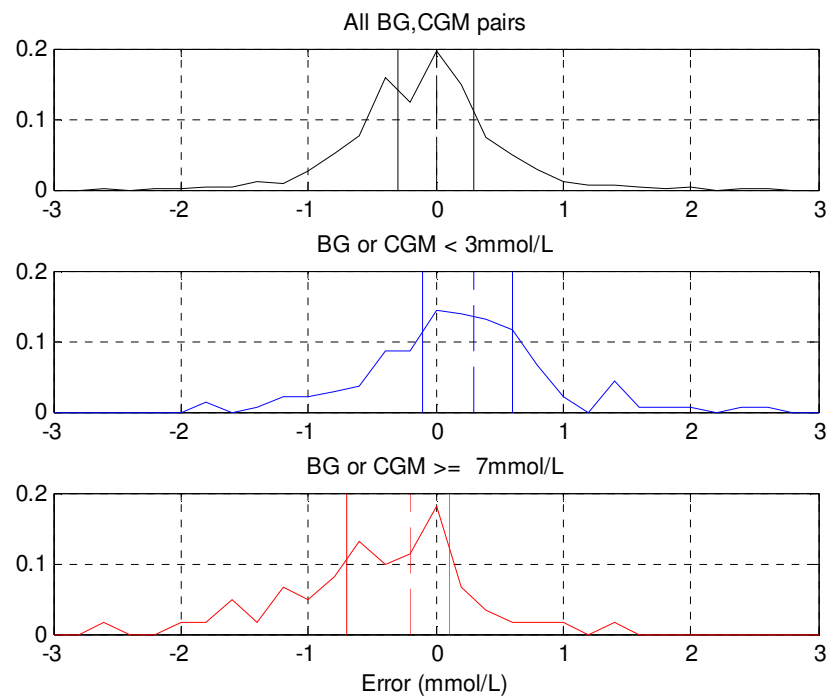


Figure 1: Distribution of errors between CGM and BG measurements with median (dashed vertical line) and inter-quartile range (solid vertical lines), for different glucose levels.

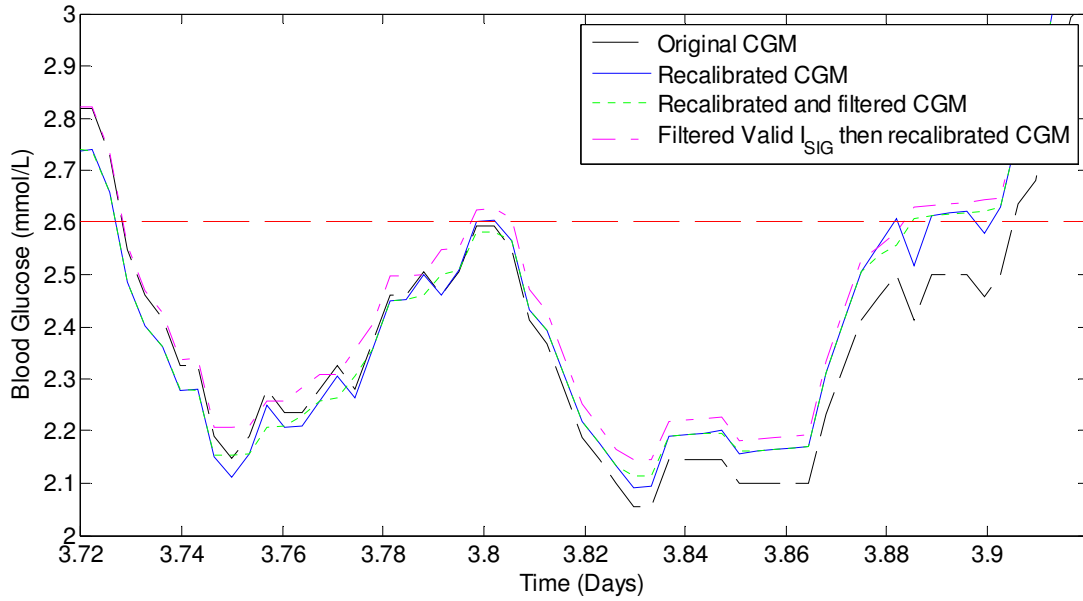


Figure 2: Comparison of a section of CGM trace containing hypoglycaemia for Original CGM, Recalibrated CGM, Recalibrated and filtered CGM, and Filtered $Valid I_{SIG}$ then recalibrated CGM. Hypoglycaemia is defined as one or more consecutive CGM measurement(s) below 2.6mmol/L, surrounded by one or more CGM measurement(s) above 2.6mmol/L. Note: recalibrating increases the number of hypoglycaemic events from 1 to 4, then filtering reduces it back to 1 in this example.

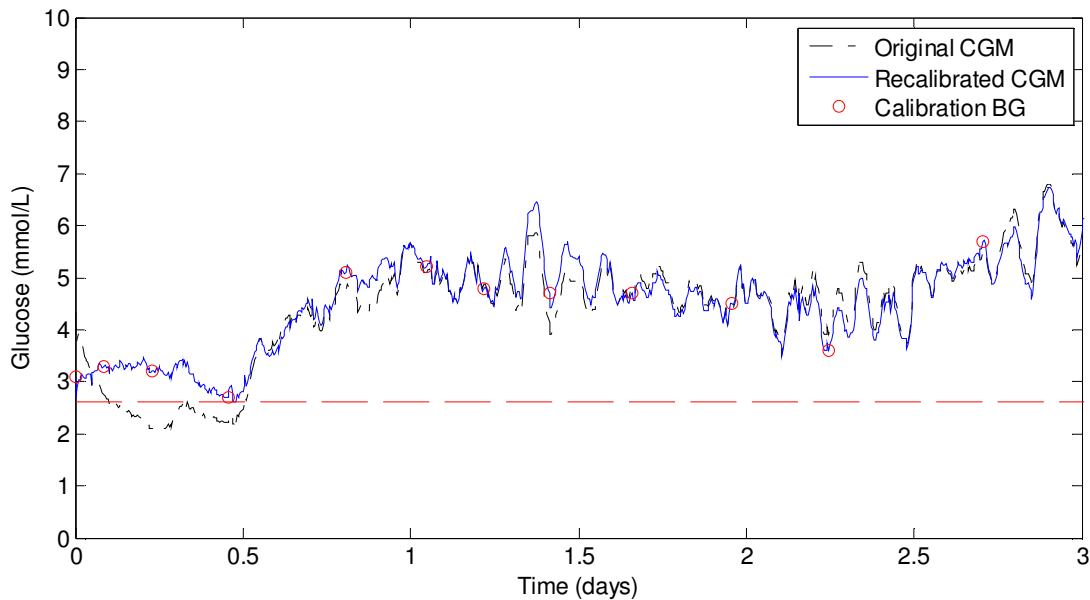


Figure 3: The CGM trace that had the largest change in hypoglycaemia metrics after recalibration. The original CGM trace (black dashed line) contains a long period of hypoglycaemia in the first 12 hours of monitoring. However, all four calibration BG measurements in this period were above 2.6mmol/L and consequently the recalibrated CGM trace (blue solid line) had no hypoglycaemia.

Table 1: Effect of recalibration and filtering on recorded CGM hypoglycaemia for the entire cohort and per-patient. Results are presented as Median [Inter-quartile range] where applicable.

Overall cohort results	Original CGM	Recalibrated CGM	Recalibrated and Filtered CGM	Filtered Valid ISIG then Recalibrated CGM
Number of Hypoglycaemic events	161	193	131	146
Duration (% of CGM record < 2.6mmol/L)	2.2	2.6	2.5	2.6
Hypoglycaemic index ($\mu\text{mol/L}$)	4.9	7.1	6.9	6.8
Hypoglycaemia events between 2.4-2.6mmol/L	87	87	51	61
Hypoglycaemia events between 2.2-2.4mmol/L	35	40	35	34
Hypoglycaemia events between 2.0-2.2mmol/L	18	38	23	30
Hypoglycaemia events less than 2.0mmol/L	21	28	22	21
Number of patients with no hypoglycaemia	25	19	21	19
Per-patient results				
Number of Hypoglycaemic events	1 [0 - 3]	1 [0 - 4]	1 [0 - 3]	1 [0 - 3]
Duration (% of data hypoglycaemic)	0.1 [0.0 - 1.0]	0.5 [0.0 - 2.4]	0.5 [0.0 - 2.3]	0.6 [0.0 - 2.4]
Hypoglycaemic index ($\mu\text{mol/L}$)	2.1 [0.7 - 6.8]	0.8 [0.0 - 7.1]	0.5 [0.0 - 6.0]	3.9 [0.7 - 9.5]
Hypoglycaemic State				
Original hypoglycaemia --> Hypoglycaemia (# patients)	24	22	23	23
Original hypoglycaemia --> No hypoglycaemia (# patients)	1	3	2	2
Originally no hypoglycaemia --> Hypoglycaemia (# patients)	7	7	8	8
Originally no hypoglycaemia --> No hypoglycaemia (# patients)	18	18	17	17

Part 2:

Figure 4 shows the effect of recalibration and filtering on the hypoglycaemic index of individual patients on a day-by-day basis. The top row of Figure 4 shows the hypoglycaemic index for each patient over the first 24 hours of monitoring. The second row of Figure 4 shows the second 24 hour period and the third row shows the third 24 hours. From left to right in each row, the change in hypoglycaemic index for each patient due to calibration and/or filtering can be seen (the patient order is preserved across these plots). For example, the infant with most hypoglycaemia by original CGM calibration on day 1 (shown in Figure 3) had no hypoglycaemia with any of the recalibration methods. Finally, the integral index is also indicated on each panel of Figure 4.

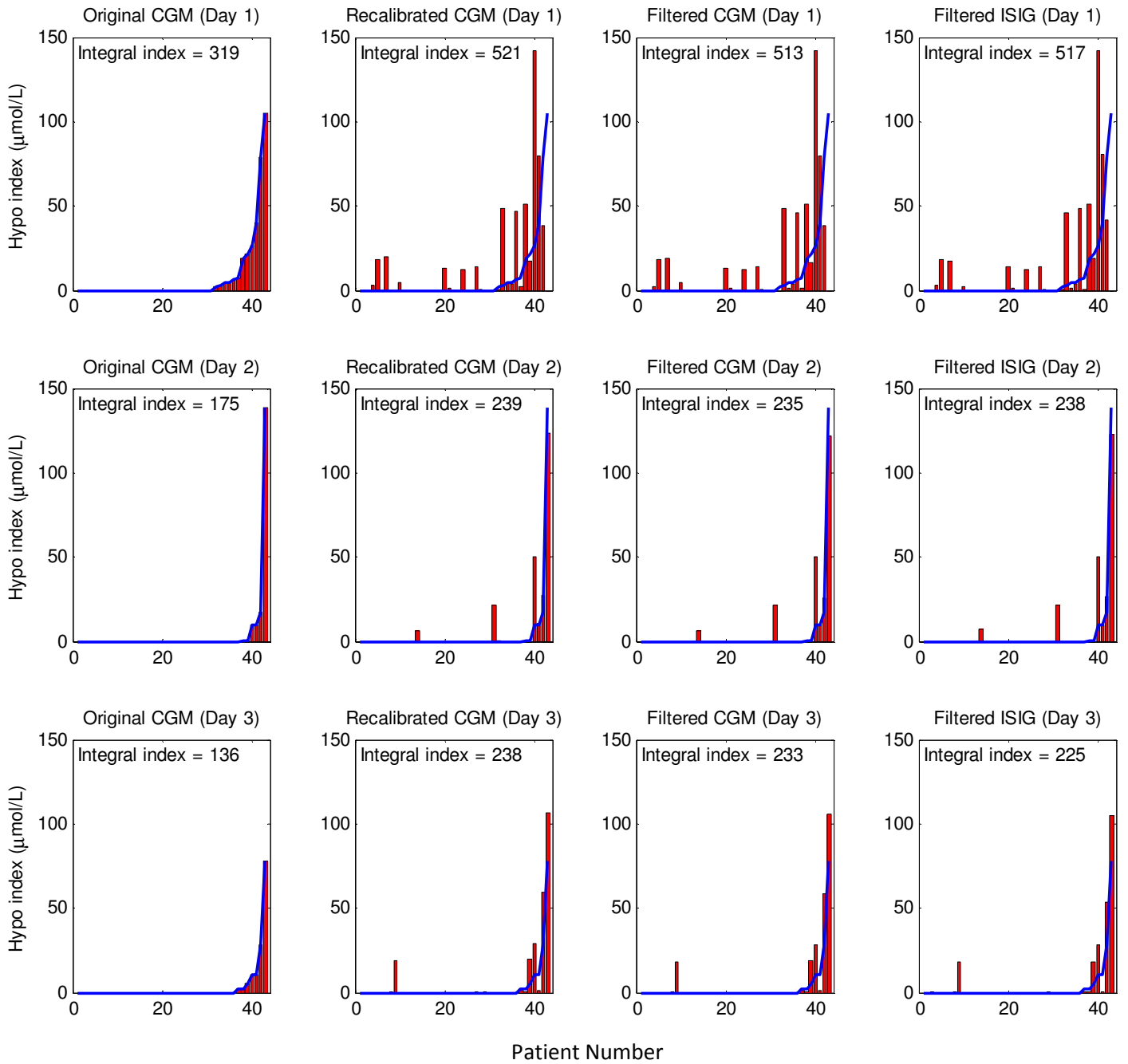


Figure 4: Comparison of ranked Hypoglycaemic Index for 43 patients (3 days) for Original CGM, Recalibrated CGM, Recalibrated and Filtered CGM, and Filtered I_{SIG} then Recalibrated. The curved solid line repeats the ranked distribution as determined by original CGM data. The integral index captures the overall area of each panel for a single comparator value.

4.0 Discussion

The aim of this study was to investigate how recalibration and nonlinear filtering of CGM data affect metrics of hypoglycaemia in at risk preterm babies. This knowledge is important for accurately relating hypoglycaemia to long term outcomes.

Part 1:

The top section of Table 1 shows all metrics of hypoglycaemia increased after recalibration compared to original CGM results, which can potentially be explained by skew in the distribution of BG vs. CGM readings at low BG concentrations. Figure 1 shows the distribution of errors between the CGM-BG paired measurements. The data set contains 1074 paired BG-CGM measurements of which 51% have a BG measurement higher than the CGM and 49% have a BG measurement lower than the CGM, and this is overall relatively centred, as expected from the regression aspect of the calibration algorithm.

More importantly, the second plot in Figure 1 shows a definite positive shift in the median when only considering low glycaemic levels. Of the 145 pairs containing either a CGM or BG measurement below 3mmol/L, 63% have a BG measurement lower than the CGM. These lower measurements pull the CGM trace down to the more accurate BG analyser value when recalibrating and cause the hypoglycaemia metrics to increase. Additionally, the bottom plot in Figure 1 shows the opposite is also true for high BG concentrations. At least for our dataset, CGM readings have a greater tendency to be lower than their BG counterparts when the concentrations are above 7mmol/L.

Furthermore, of the 53 calibration BG measurements that were hypoglycaemic, only 16 occurred at a time when the CGM was below 2.6mmol/L. The remaining 37 hypoglycaemic BG measurements were at a time when the CGM was reporting above 2.6mmol/L. Thus, recalibrating the CGM data to capture the 'missed' events is further justified, especially when using the CGM data to classify hypoglycaemia.

When comparing recalibrated CGM data to recalibrated and filtered CGM data, the large reduction in the number of hypoglycaemic events in Table 1 (193 to 131) with little change in hypoglycaemic duration (2.6% to 2.5%) can be explained with reference to Figure 2. Two different phenomena occur that reduce the number of events from 4 to 1 in this exemplar case. First, at 3.8 days the peak in the CGM trace is trimmed by the filter (filter after recalibration) stopping it crossing the normoglycaemic threshold and reducing the number of hypoglycaemic events. The opposite can also occur, where a hypoglycaemic event observed in the recalibrated CGM trace is removed by filtering (in this case a trough would be trimmed).

The second phenomenon is seen at ~3.88 to 3.9 days, where high frequency fluctuations in CGM measurements are smoothed by the filter. Smoothing these fluctuations around the threshold is likely to be the major influence on the reduced number of hypoglycaemic events observed. The variations in the number of hypoglycaemic events observed over the 4 analyses suggests that this metric alone (number of events) may not be reliable when classifying hypoglycaemia.

The bottom section of Table 1 shows the number of patients that gained, lost or stayed with/without hypoglycaemia when recalibrated and filtered, compared to original CGM data. Of the 25 babies who had hypoglycaemia in the original data set 22 to 24 had hypoglycaemia in the modified data

sets, and, 17 to 18 out of 25 of babies who had no hypoglycaemia in the original data set still had no hypoglycaemia. These results suggest that over the duration of monitoring, the CGM should be consistent ~80% of the time about which patients had experienced hypoglycaemia, independent of calibration method.

Part 2:

Figure 4 shows three important trends. First, the hypoglycaemic index, a measure of duration and severity, for a patient on any given day can change significantly after recalibration. For example, the highest ranked patient on day one using the original CGM output had a hypoglycaemic index of ~105 μ mol/L, which was reduced to 0 μ mol/L after recalibration. Conversely, several patients have no hypoglycaemic events on day 1 (original CGM), but, after recalibration all have a hypoglycaemic index greater than 0 μ mol/L. For days 2 and 3 there is far more agreement in which patients had hypoglycaemia, although in some cases the index still changes with recalibration. This outcome suggests that after day one, regardless of calibration method, patients who experienced hypoglycaemia could be identified with a higher level of confidence.

The next trend shown by Figure 4 is that hypoglycaemia is most prevalent during day 1. Comparing the plots in row 1 and 2 of Figure 4 shows the decrease in integral index from day 1 to 2 is in the range of 45% - 54%, suggesting hypoglycaemia is more prevalent in the overall cohort on day one, by any calibration method. Interestingly, further decreases were not observed from day two to three in either the original CGM data or the recalibrated/filtered CGM data of Figure 4. This result reinforces the importance of capturing the first 24 hours of CGM data and thus of proper placement and initial device calibration.

These first two trends suggest day 1 is most affected by the calibration scheme. This could be due to two reasons: First, the error between calibration BG measurements and CGM measurements tends to be larger on day 1, so recalibrating has more affect. Second, these infants are at-risk by definition and hypoglycaemia can be more prevalent on this first day of life [29, 30]. Neither effect can be ruled out in this analysis.

The third trend is an increase in integral index with recalibration, regardless of the day, which can potentially be explained by the previously mentioned tendency of the CGM device to read high low glucose levels. Conversely, there is a reduction in integral index with the addition of filtering which is likely explained by the 'rounding' or clipping of troughs, in this analysis.

5.0 Limitations

The main limitation of this study is the limited number of BG measurements available. Due to the pain and discomfort of blood sampling in neonates (typically by heel prick), it is unethical to measure BG more frequently than ~4 hourly. Ideally, a reference measurement would be sampled for nearly every CGM measurement, in addition to the ~4 calibration measurements per day. The reference measurements would allow the impact of calibration on a 'true' level of hypoglycaemia to be assessed more thoroughly and conclusively.

The limited number of BG measurements also restricts the recalibration and filtering strategies. For example, the estimated physiological delay between blood glucose and interstitial glucose was left constant at 10 minutes (manufacturers default value). Studies in the literature report delays typically in the range of 5-15minutes [27, 31-34]. However, without sufficient reference BG measurements the delay cannot be determined in this study, for this group of patients. Finally, the filter implemented in this study is effective, but represents one of a wide variety of available filters. Other more advanced filtering options are available, but without several reference BG measurements it is not possible to determine the optimal filtering strategy.

6.0 Conclusions

The aim of this study was to investigate how recalibrating and filtering CGM data affects metrics of hypoglycaemia in preterm infants. The results suggest that conventional hypoglycaemia metrics are heavily dependent on both the error in calibration BG measurements and the calibration algorithm used. All metrics of hypoglycaemia for our cohort increased after recalibration, confirming that the original, unmodified CGM output tended to report high at lower levels. If highly accurate calibration measurements are available it may be more appropriate to recalibrate the data, especially when trying to accurately classify hypoglycaemia or other specific extreme events.

More importantly and generally, calibration BG measurement error and thus calibration algorithms play a significant role in quantifying hypoglycaemia using CGM data. In particular, metrics such as number of hypoglycaemic events are particularly sensitive to recalibration effects. While this conclusion may be expected, its potential impact is quantified here, in this case for at-risk neonates for whom hypoglycaemia may carry long-term negative consequences.

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