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ORIGINAL ARTICLES

Use of a Continuous Glucose Sensor in an Extracorporeal Life Support Circuit

Garry M. Steil, Ph.D.,[1] Jamin Alexander, B.A.,[1] Alexandra Papas, B.S.,[1] Monica Langer, M.D.,[2] Biren P. Modi, M.D.,[2] Hannah Piper, M.D.,[2] Tom Jaksic, M.D., Ph.D.,[2] Rebecca Gottlieb, Ph.D.,[3] and Michael S. D. Agus, M.D.[1]

Abstract

Background:

Standard care for infants on extracorporeal life support (ECLS) relies on intermittent measurement of blood glucose (BG); however, this can lead to significant changes in BG that go unrecognized for several hours. The present study was designed to assess performance and clinical applicability of a subcutaneous glucose sensor technology modified for use as a blood-contacting sensor within the ECLS circuit.

Methods:

Twelve children, aged 3 years or less, requiring ECLS support were studied. Three continuous glucose sensors (Medtronic MiniMed) were inserted into hubs placed in line with the ECLS circuit. Blood glucose was assessed with a laboratory analyzer (BG_{LAB}; Bayer Rapidlab 860) approximately every 5 h (mean 4.9 ± 3.3 h) with more frequent samples obtained with a bedside monitor (HemoCue) as needed. Sensor current (I_{SIG}) was transmitted to a laptop computer and retrospectively calibrated using BG_{LAB}. Sensor performance was assessed by mean absolute relative difference (MARD), linear regression slope and intercept, and correlation, all with BG_{LAB} as reference.

Results:

The BG_{LAB} averaged 107.6 ± 36.4 mg/dl (mean ± standard deviation) ranging from 58 to 366 mg/dl. The MARD was 11.4%, with linear regression slope (0.86 ± 0.030) and intercept (9.0 ± 3.2 mg/dl) different from 1 and 0, respectively ($p < .05$), and correlation ($r^2 = 0.76$; $p < .001$). The system was not associated with any adverse events, and placement and removal into the hubs was easily accomplished. Instances in which more frequent BG values were obtained using a bedside HemoCue (BG_{HEMO}) monitor showed the sensor to respond rapidly to changes.

Conclusions:

We conclude that continuous sensors can be adapted for use in an ECLS circuit with accuracy similar to or better than that achieved with the subcutaneous site. Continuous glucose monitoring in this population can rapidly detect changes in BG that would not otherwise be observed. Further studies will be needed to assess the benefit of continuous glucose monitoring in this population.

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Author Affiliations: [1]Department of Medicine, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts; [2]Department of Surgery, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts; and [3]Medtronic MiniMed, Northridge, California

Abbreviations: (BG) blood glucose, (CF) calibration factor, (ECLS) extracorporeal life support, (MARD) mean absolute relative difference, (OS) offset current, (SC) subcutaneous, (SG) sensor glucose

Keywords: cardiopulmonary bypass, continuous monitor, extracorporeal, extracorporeal life support, glucose

Corresponding Author: Garry M. Steil, Ph.D., Children's Hospital Boston, MCCP 11S, 300 Longwood Ave., Boston, MA 02115; email address Garry.Steil@childrens.harvard.edu

Background

Infants on extracorporeal life support (ECLS) are among the most tenuous of pediatric critically ill patients, with a mortality rate of 33–62% and significant variations in blood glucose (BG) concentration[1,2] secondary to stress, corticosteroid administration, and exogenous glucose. Hyperglycemia is the most common abnormality of glucose metabolism seen in ECLS patients, but hypoglycemia resulting from insufficient endogenous glucose production or insulin therapy can also occur and may exacerbate adverse neurologic outcomes.[3,4] Current standard care utilizes intermittent laboratory measurement of glucose concentration; however, this practice is inherently flawed, as significant changes may go unrecognized for several hours. We previously investigated the performance of a first-generation extracorporeal glucose monitoring system designed to be blood contacting[5] and adapted for the ECLS circuit in babies.[6] In the present study, a second-generation system based on subcutaneous (SC)-glucose sensor technology (Medtronic MiniMed, Northridge, CA) was evaluated. The study was designed to assess performance and clinical applicability of the system in pediatric surgical patients on ECLS.

Methods

Patient Enrollment

A convenience sample of children 3 years old and under who were expected to require support for more than 24 hours were recruited between March 22, 2005, and February 16, 2006. Patients with evidence of thrombus in the circuit, determined by visual inspection by the respiratory therapist monitoring the ECLS circuit, were excluded from the study. The protocol was initiated after the patient was stabilized on ECLS and informed consent obtained. The study was approved by the Children's Hospital Boston Committee on Clinical Investigation. The device was deemed nonsignificant risk in consultation with the Food and Drug Administration, with the opinion confirmed by the local committee on clinical investigation.

Continuous Glucose Monitor System

Three glucose sensors were introduced into the circuit using sterile technique. Each sensor was inserted into a hub (**Figure 1A**) placed in the venous (afferent) limb of the circuit. The sensors were given 5 minutes to hydrate before being connected to transmitters (**Figure 1B**) that wirelessly relayed the sensor signal (nA current) each minute to a laptop computer running proprietary Medtronic MiniMed software (sensor placement shown; **Figure 1C**). Each sensor signal was saved to a file for later retrospective calibration as described later, with the variability between sensors placed in the same circuit assessed by correlation. Sensors were replaced every 48 hours or removed if the ECLS circuit was changed or discontinued. During the course of the study, a modified transmitter was introduced to reduce run-in time, with the two transmitters denoted throughout the article as TX1 (unmodified) and TX2 (modified). Run-in time is defined as the time between first inserting and powering the sensor and the time the sensor is deemed sufficiently stable to report glucose values (typically 2–10 hours depending on sensor manufacturer).

Reference Glucose Measurements

Blood glucose was determined by a central laboratory (BG_{LAB}) using a Bayer Rapidlab 860 (Tarrytown, NY) analyzer approximately every 5 hours, with more frequent 5–10 minute values (BG_{HEMO}) obtained as needed using a bedside monitor (HemoCue; Ängelholm, Sweden).

Calibration Algorithm

One-point calibration was performed using the first BG_{LAB} value following 2 h of equilibration time (run in) and the first available value following 6 h intervals thereafter. At each calibration time, a calibration factor (CF) was obtained by dividing BG_{LAB} by sensor current (I_{SIG}); sensor glucose (SG) was subsequently calculated as $SG = CF \times I_{SIG}$. On occasions when frequent BG_{HEMO} values were obtained by bedside clinicians in order to assess rapid changes in BG, a second retrospective calibration was performed using linear regression to determine sensor sensitivity (CF_{LR} = 1/slope of regression; mg/dl pernA) and offset current (OS; nA; intercept of regression). Offset current is defined as the

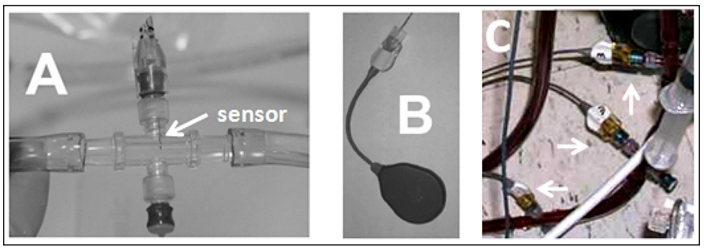

Figure 1. (A) Pre-inserted hub with glucose sensor; **(B)** transmitter; **(C)** afferent circuit showing placement of redundant sensors. Sensor signals were transmitted to a bedside laptop computer and retrospectively calibrated.

expected current as the glucose concentration approaches 0. For cases in which frequent BG_{HEMO} values were available, identified in the text as examples, SG was calculated by first subtracting the offset ($SG_{LR} = CF_{LR} \times [I_{SIG} - OS]$).

Statistical Analysis

Mean absolute relative difference (MARD) between blood and sensor glucose, linear regression of the blood value versus sensor value, and correlation were all performed using BG_{LAB}. At each calibration time point, the sensor reading prior to calibration was paired with the BG values (BG_{LAB}) when assessing accuracy to allow all possible BG_{LAB} values to be used in assessing performance metrics (MARD, SG versus BG_{LAB} slope and intercept, and correlation). Analysis was performed separately for the two transmitters used in the study (TX1 and TX2) with the data combined when no statistically significant difference was observed. Example profiles in which the more frequent BG_{HEMO} determinations were used to assess rapid changes in glucose are identified within the manuscript, with the calibration method (linear regression versus one point) and source of the BG measurement (laboratory versus HemoCue) noted. Retrospective one-point calibration was performed using MATLAB version 7.6 (MathWorks, Inc., Natick, MA). Statistical analysis (linear regression for slope and offset; Mann–Whitney for comparisons of MARD) was performed using GraphPad Prizm (version 5.00 for Windows, GraphPad Software, San Diego, CA).

Results

Twelve patients [5 male, 7 female, median age 10 days (range 1–998), and body weight 3.5 kg (range 2.8–14.7 kg)] were enrolled in the study. Six patients were diagnosed with congenital cardiac disease, 5 with congenital diaphragmatic hernias, and 1 with respiratory failure. Fifty-four sensor profiles were obtained, 36 with TX1 and 18 with TX2, totaling 2095 h of data collection and 365 paired BG_{LAB}–SG measurements. Median sensor duration was 45.5 h (range 18.3–48 h). Median time from start of ECLS to sensor insertion was 70.5 h (range 14.0–263.0). Sensors were inserted into and removed from the ECLS circuit without incident. There were no adverse outcomes from the sensor use and no discernable increase in the incidence of clot formation, air embolus, or need for circuit changes.

Average BG concentration during the study was 106 ± 36 mg/dl (mean ± standard deviation), ranging from 58 to 366 mg/dl. Regression analysis performed separately on profiles obtained with TX1 and TX2 did not indicate a difference ($p = 0.14$; **Figure 2**, regression lines not shown) and data were combined to form a single regression with slope and intercept (0.86 and 9 mg/dl, respectively) different from the unbiased $BG = SG$ line ($p < .05$; **Figure 2**, dashed line). Blood glucose and SG were significantly correlated ($r^2 = 0.76$; $p < .001$). The MARD was 10.1% and 14.1% for TX1 and TX2, respectively (p = not significant), with a combined value of 11.4%.

The regression slope less than 1 (**Figure 2**) suggests that SG was overestimated at values below where the regression line intersected the $SG = BG$ line and underestimated above this point. Closer examination in a subject treated for hypoglycemia (**Figure 3A**, treatment with exogenous glucose shown with arrows; frequent blood samples obtained with HemoCue) confirmed the one-point calibration overestimated BG_{HEMO} in the low region (time ~28 h) and underestimated it in the high region (time ~38 h). To determine if the bias was due to a difference in reference meters (laboratory values versus bedside HemoCue) the sensors were recalibrated based on the linear regression slope and offset of BG_{HEMO} versus I_{SIG}. All three sensors in the circuit were observed to be highly correlated with the HemoCue determinations (**Figure 3B**; $r^2 = 0.9942$, 0.9905, and 0.9911) but showed significant OS current (~7.8 nA). Recalibration with the OS removed showed all three sensors to track

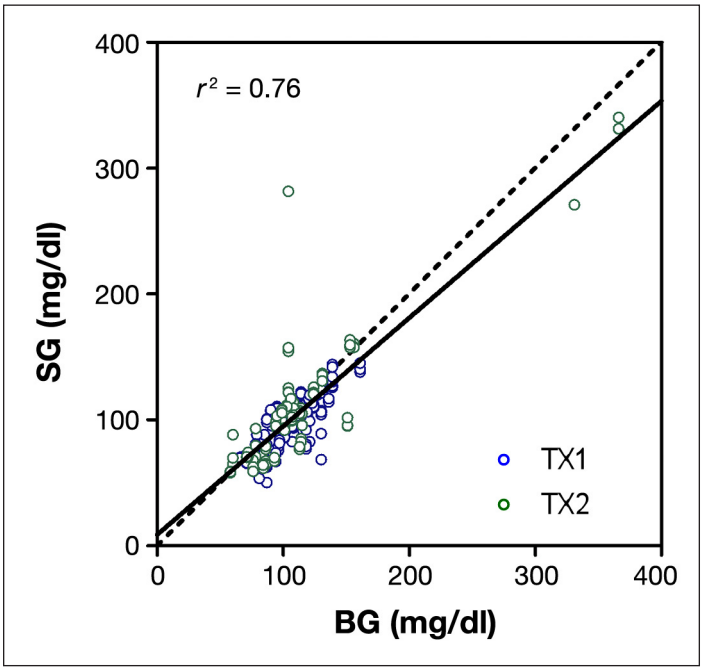

Figure 2. Regression showing paired sensor (SG) and reference glucose (BG) values. Regression slopes were not different using TX1 and TX2 (not shown), and the data were combined to form a single regression line (solid line), which was determined to have slope and offset different from the unbiased $BG = SG$ line (dashed line).

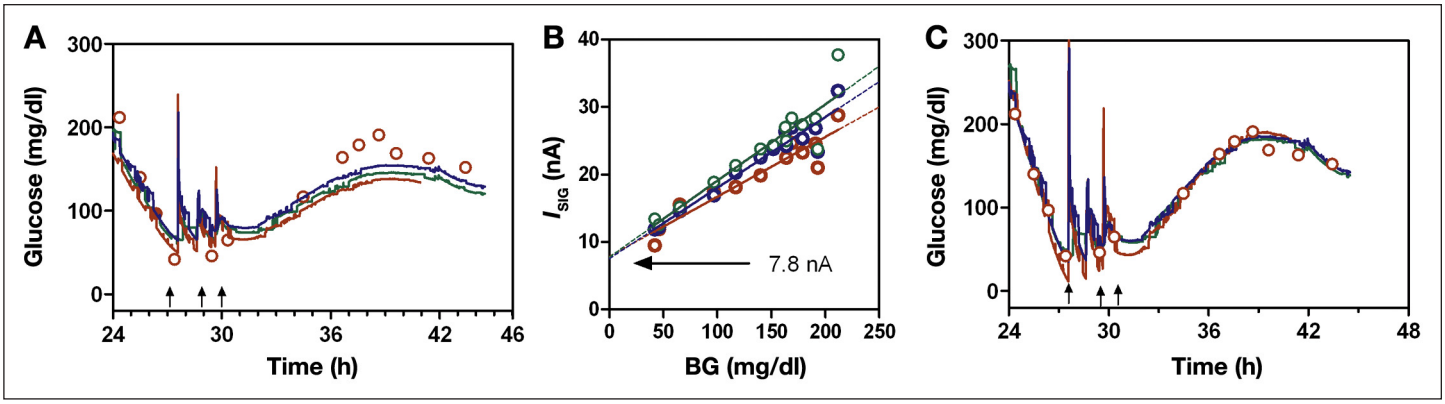

Figure 3. (A) Triplicate SG profiles obtained in one subject requiring repeat glucose boluses (marked as upward-pointing arrows) to maintain euglycemia. Sensors were calibrated using laboratory glucose values and the one-point calibration algorithm but are shown here with the more frequent bedside BG_{HEMO} measurements. **(B)** Recalibration using linear regression of BG_{HEMO} and sensor current, with sensor OS current identified as ~7.8 nA for all 3 sensors. **(C)** Recalibrated *SG* signals with OS removed.

both the low and high glucose values (**Figure 3C**, with BG_{HEMO} versus *SG* regression slope and intercept not different from 1 and 0, respectively, regressions not shown) and to respond to exogenous glucose boluses (arrows) with no discernable delay.

Some profiles obtained with TX1 (example shown in **Figure 4A**) were observed to decrease for almost 24 h despite a relatively stable BG profile. Thereafter, the current was observed to be well correlated with the subsequent glucose excursion (r^2 = 0.78 and 0.81 for t > 24 h). During the excursion, both sensors had substantial *OS* current (13.5 and 13.1 nA; BG_{HEMO} versus I_{SIG} regressions not shown). In contrast, profiles obtained with TX2 (**Figure 4B**) began tracking BG_{LAB} almost immediately (r^2 = 0.92 and 0.85 for t > 2 h), albeit many still had significant *OS* current (3.8 and 2.4 nA; BG_{HEMO} versus I_{SIG} regressions not shown).

Discussion

The present study demonstrated that continuous glucose sensor technology similar to that used in earlier ambulatory studies[7–10] can be safely modified for placement into a heart–lung bypass circuit. Accuracy, expressed as MARD (11.4%), was similar to or better than that observed when similar sensors are placed subcutaneously (16–18%[10,11]). We observed a slope less than 1 in the regression of *BG* and *SG* (**Figure 2**), which would limit the ability to detect hypoglycemia[12] (**Figure 3A**); however, this was easily corrected (**Figure 3C**) by identifying a nonspecific background current (**Figure 3B**). A more surprising observation within this study was that some sensor signals showed long run-in times (**Figure 4A**) that were corrected (**Figure 4B**) with a transmitter designed to reduce the run in observed

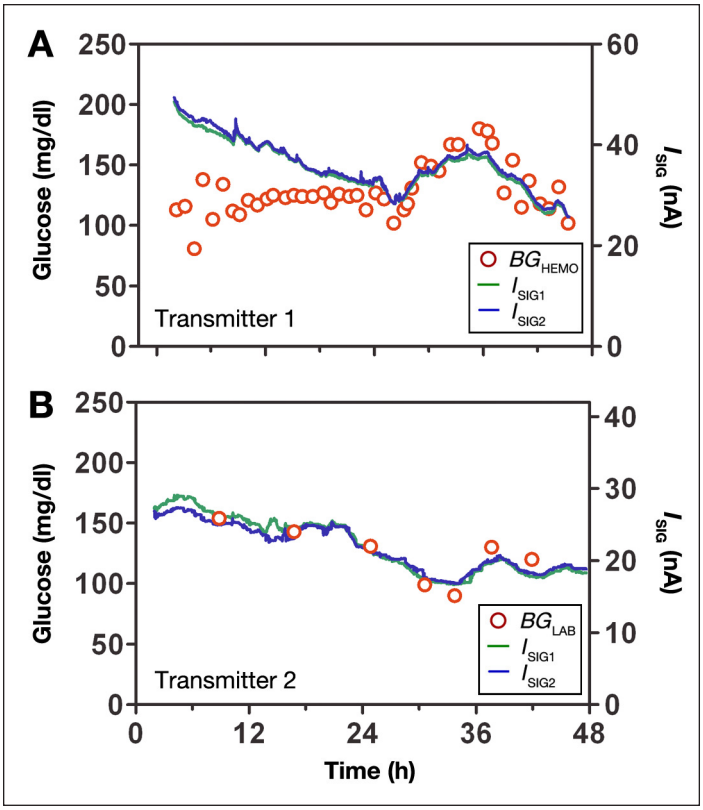

Figure 4. (A) Current in two sensors recorded with transmitter 1 (unmodified) compared to BG assessed with a HemoCue. **(B)** Sensor current obtained in two sensors connected to transmitter 2 (modified for rapid run in) compared with BG assessed with a laboratory analyzer.

when sensors are placed subcutaneously. The run-in phenomenon is widely believed to be due to a local tissue response[13,14] to wound healing and would not be expected to occur in the extracorporeal circuit. Generally, sensor performance in an extracorporeal blood contacting loop should be expected to be better than that observed when sensors are placed subcutaneously, as

putative delays in SC interstitial fluid glucose[15–17] do not exist. Also noteworthy in the present study is the high correlation between sensor signals placed in the same circuit (**Figures 3** and **4**). Although a high correlation is desirable, it can generate instances in which an artifact observed in one sensor is also observed in multiple sensors of the same type.

The present study was not designed to look at sensor-related differences in infection or mortality or the ability of continuous glucose monitoring to aid in managing BG levels. Nonetheless, it is apparent that if a real-time calibration algorithm were used, the sensors would have allowed recognition of critically high and low BG concentrations faster than standard intermittent monitoring. Of the two calibration algorithms used here, one-point and linear regression, only the one-point can be applied in real time. The linear regression calibration used all the data points to estimated sensor sensitivity and offset, a process that can only be applied retrospectively. A real-time linear regression calibration using all available glucose points up to the time of calibration can be performed but often results in poor estimates of the OS current when the available reference BG values do not span a wide range of glucose values.[12] It is also possible to perform a one-point calibration with an arbitrary OS,[18] but this requires the OS to be similar in different sensors. In the present study, OS was similar in sensors placed in the same circuit but varied between circuits (e.g., ~7.6 nA in all the sensors shown in **Figure 3** and ~14 nA in both sensors shown in **Figure 4**). Underestimation of the true OS results in an inability of the monitor to detect hypoglycemia (**Figure 3A**).[12]

Once the OS issue is resolved, the ability to see changes in glucose in real time should allow clinicians to identify when the glucose concentration becomes abnormal and identify trends toward hyperglycemia or hypoglycemia that could generate an appropriate clinical response before severe abnormalities develop (analogous to the use of portable oxygen saturation monitoring). This ability to watch and preemptively treat evolving metabolic derangements is critical if these patients are to be maintained in a euglycemic state while minimizing risk of hypoglycemia. Continuous glucose monitoring may also allow insulin to be more effectively utilized in managing glucose levels.[19,20]

Although ECLS patients represent an important group for targeting advances in treatment, they account for only a small percentage of critically ill children. Broader benefits may be achieved in adapting the technology for patients on short-term cardiopulmonary bypass or those receiving hemodialysis or continuous hemofiltration. Tight glycemic control has been widely adopted in the treatment of adult critically ill cardiac surgical patients, and studies suggest that further benefit may be gained through maintenance of euglycemia during cardiopulmonary bypass for open heart surgery.[21–24] Success in achieving intraoperative tight glycemic control is variable, in part, due to difficulties in monitoring and responding to rapid changes in BG during cardiopulmonary bypass.[25–27] The risk of hypoglycemia has led some centers to abandon attempts at intraoperative control.[26,28] Dialysis patients, many of whom also suffer from diabetes mellitus, may also be a particularly important group of patients to target therapies that improve glycemic control.

Conclusions

We show here that continuous sensors can be adapted for use in an ECLS circuit. This technology may be useful in improving the safety of tight glycemic control in patient populations that have similar vascular access, including short-term cardiopulmonary bypass and dialysis. Changes in the sensor design, or calibration algorithm, may still be required to address problems associated with offset current. Further research will also be needed to ensure the monitor can be used in systems in which clots may be present (excluded from the present study). Nonetheless, while the blood contacting sensor evaluated here remains a work in progress, it is clear that continuous glucose monitoring can be introduced into the ECLS circuit and that doing so will allow critically high or low BG concentration to be determined more rapidly than standard intermittent monitoring.

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Disclosures:

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