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SYMPOSIUM

Use of an Intravascular Fluorescent Continuous Glucose Sensor in Subjects with Type 1 Diabetes Mellitus

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Abstract

Background:

Stress hyperglycemia in the critically ill is associated with increased morbidity and mortality. Continuous glucose monitoring offers a solution to the difficulties of dosing intravenous insulin properly to maintain glycemic control. The purpose of this study was to evaluate an intravascular continuous glucose monitoring (IV-CGM) system with a sensing element based on the concept of quenched fluorescence.

Method:

A second-generation intravascular continuous glucose sensor was evaluated in 13 volunteer subjects with type 1 diabetes mellitus. There were 21 study sessions of up to 24 h in duration. Sensors were inserted into peripheral veins of the upper extremity, up to two sensors per subject per study session. Sensor output was compared with temporally correlated reference measurements obtained from venous samples on a laboratory glucose analyzer.

Results:

Data were obtained from 23 sensors in 13 study sessions with 942 paired reference values. Fourteen out of 23 sensors (60.9%) had a mean absolute relative difference ≤ 10%. Eighty-nine percent of paired points were in the clinically accurate A zone of the Clarke error grid and met ISO 15197 performance criteria. Adequate venous blood flow was identified as a necessary condition for accuracy when local sensor readings are compared with venous blood glucose.

Conclusions:

The IV-CGM system was capable of achieving a high level of glucose measurement accuracy. However, superficial peripheral veins may not provide adequate blood flow for reliable indwelling blood glucose monitoring.

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Abbreviations: (CGM) continuous glucose monitoring, (ISO) International Organization for Standardization, (IV-CGM) intravascular continuous glucose monitoring, (MAD) mean absolute difference, (MARD) mean absolute relative difference

Keywords: accuracy, fluorescence, glycemic control, hypoglycemia, intravascular continuous glucose monitor, sensor

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Introduction

Hyperglycemia is common in critically ill patients[1] and is associated with increased morbidity and mortality in various patient subgroups.[2–5] Intravenous insulin infusions are used to maintain glycemic control in these patients, relying upon frequent glucose measurement for proper dose titration. To date, studies on inpatient glucose control have been conducted using a variety of glucose monitoring technologies and universally with intermittent monitoring of blood glucose concentration. Intermittent monitoring gives rise to the risk of hyperglycemia and hypoglycemia developing unobserved, whereas continuous glucose monitoring (CGM) offers the potential to reduce these risks while allowing more intense blood glucose control. The success of CGM in the inpatient setting will be dependent upon fast and accurate blood glucose measurements, as well as timely response to abnormal values. The clear need for such systems is currently unmet.[6]

Fluorescence-based glucose sensors are excited by light of one wavelength and emit light at another, longer wavelength. The amount of light emitted is proportional to the level of glucose present in these sensors. It is possible to "tune" the fluorescence to be particularly sensitive in the hypoglycemic range, and due to the fundamental mechanism by which fluorescence occurs, it is intrinsically sensitive and yields low noise measurements when compared with other optical measurement methods.[7–9]

The study described here examined the 24 h accuracy and performance in volunteers with type 1 diabetes of a second-generation prototype of the GluCath® system, an intravascular continuous glucose monitoring (IV-CGM) system intended for use in hospitalized patients. A previous study similarly examined a first-generation device at 8 h durations.[10] The device is being developed by GluMetrics, Inc. (Irvine, CA) and, at the time of these studies, was limited by United States law to investigational use only.

Methods

The IV-CGM system is intended to measure blood glucose continuously in hospitalized patients and consists of a sensor, a monitor, a connecting cable between the monitor and the sensor, and a sterile calibration verification solution (**Figure 1**). The sensor consists of a 250 μm outer diameter optical fiber with the glucose-sensing chemistry immobilized in a hydrogel at the distal tip of the fiber. The sensor is surrounded by a microporous membrane of high-density polyethylene that allows for passage of plasma and small plasma constituents. Conversely, large molecules or structures, such as red blood cells, are excluded by the small pores in the membrane (approximately 0.1 μm in diameter). The sensor is coated with a heparin-based antithrombogenic coating to inhibit fibrin and thrombus formation on the sensor. The total outer diameter of the sensor is 430 μm.

The sensor is housed in an extension set with a telescoping mechanism allowing for deployment through a commercial catheter. The sensor is stored dry, sterilized with ethylene oxide, and rehydrated approximately 3 h prior to use.

The IV-CGM system uses a quenched chemical fluorescence sensing mechanism to optically measure glucose in blood. The sensor chemistry consists of three molecular components: a fluorophore, a quencher, and a boronic-acid-based glucose receptor, all of which are immobilized in the hydrogel matrix. In the absence of glucose, the quencher strongly interacts with the fluorophore, yielding low fluorescent emission. When glucose is introduced to the system, it binds with the receptor site of the quencher. This binding decreases the interaction between the

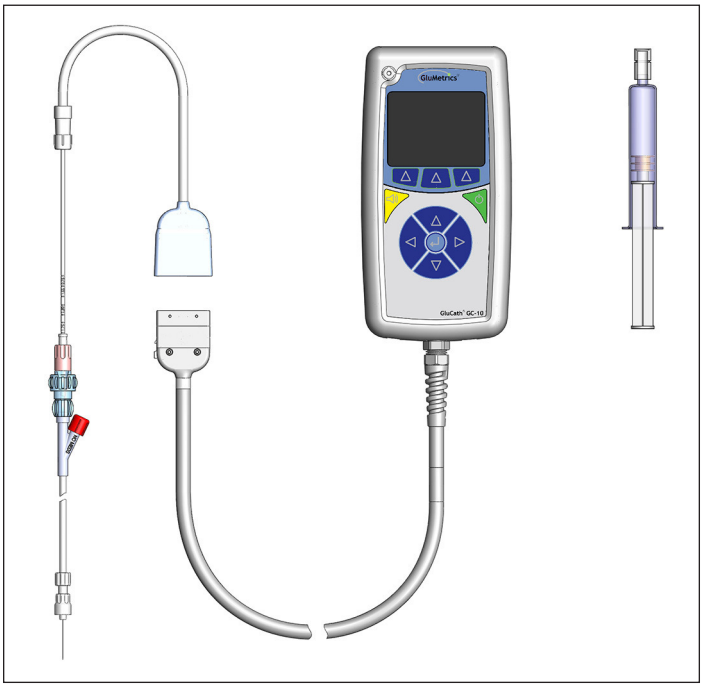


Figure 1. Components of the GluCath IV-CGM system.

quencher and the dye, resulting in an increase in fluorescence proportional to the concentration of glucose present (**Figure 2**).

Light-emitting diodes located in the monitor emit blue light, which travels down an optical fiber to the sensing chemistry at the distal tip of the sensor. The sensing chemistry fluoresces green at 530 nm in proportion to the glucose level, which is transmitted back to the monitor via the same optical fiber. The intensity of the fluorescence is measured by a detector circuit in the monitor and is converted to the reported glucose value using a proprietary algorithm. The sensor contains a temperature probe adjacent to the optical fiber to measure the temperature in the vicinity of the sensor and correct for the effect of temperature on the glucose response. Differences in the fluorescent sensor response at two distinct excitation wavelengths, 420 and 470 nm, are used to measure the pH and to correct for the effect of pH on the glucose response. The sensor is insensitive to physiological changes in ionic strength of the blood plasma.

A 24 h outpatient feasibility study was designed to evaluate the sensor. The study was Institutional Review Board approved. All subjects gave informed witnessed consent to participate in the study. The subjects were otherwise healthy volunteers with type 1 diabetes mellitus. Thirteen individual subjects were enrolled in the study: 1 subject participated three times, 6 subjects participated two times, and 6 subjects participated once, for a total of twenty-one case study sessions. Subjects ranged in age from 20 to 69 years old, with a mean age of 47 years. Duration of diabetes in the subjects ranged from 8 to 49 years, with a mean of 22 years.

During the study, the subjects were in a semirecumbent position in an adjustable hospital bed, except for occasional walks to and from a bathroom. The sensor was inserted into a peripheral vein (e.g., cephalic or basilic vein) of the forearm or upper arm using one of two methods. The first method used a standard 22 G over-the-needle splittable introducer. After the sensor was inserted into the vessel through the introducer, the introducer was retracted from the vessel, split apart, and discarded, leaving only the sensor in the vessel. The sensor was held in place with surgical adhesive tape. The second method used a standard 20 G intravascular catheter, through which the sensor was fed. In this method, the catheter remained indwelling in the vein with the sensor protruding from the tip. A 3 ml/h saline drip was used to maintain patency. In a subset of subjects, a second sensor was placed in a different peripheral vessel using the same procedure as the initial sensor. A total of 42 sensors were placed during the course of the study. In all subjects, an intravenous catheter was placed in the contralateral arm for the purpose of obtaining venous blood samples for measurement on a laboratory reference analyzer.

The sensors remained indwelling during such times, and the monitors traveled with the patients either in a fanny pack or on a movable intravenous pole. Per the study protocol, the subjects administered insulin on the advice of a physician to achieve mild hypoglycemia (<70 mg/dl). Otherwise, the subjects adhered to their previous diabetes management regimens. All subjects ate lunch approximately 4 to 5 h after sensor insertion and gave themselves subcutaneous insulin by pump or injection per their preexisting diabetes treatment regimen.

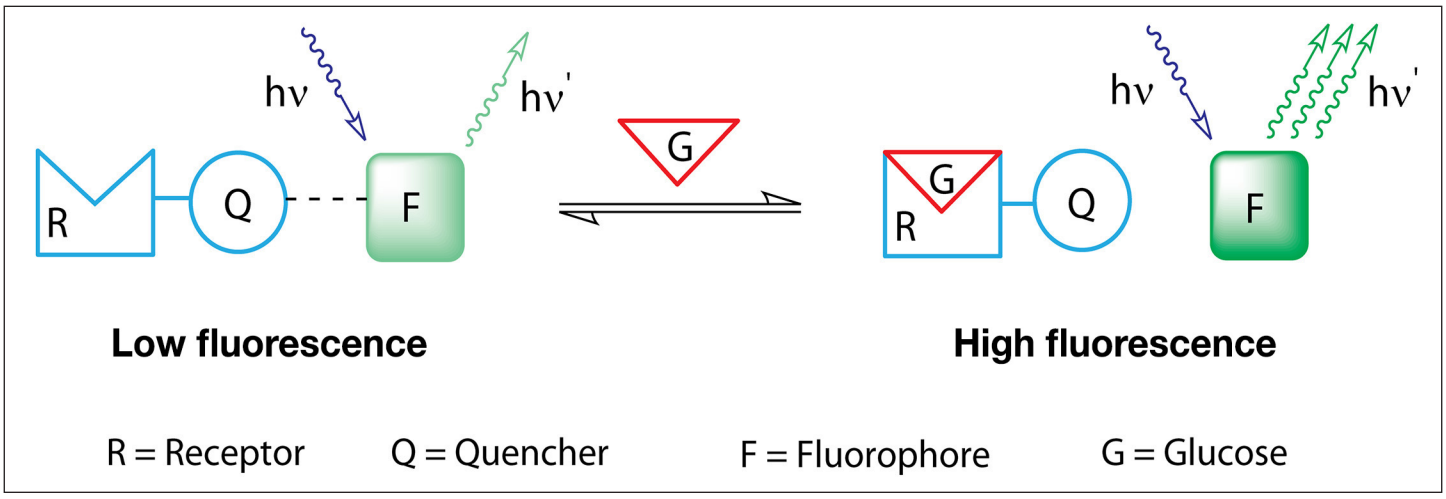


Figure 2. Three molecular components of the GluCath sensor chemistry shown in the absence of glucose (low fluorescence) and in the presence of glucose (high fluorescence).

All IV-CGM measurements were made and recorded by the monitor once every minute. Venous samples were taken once every 20 ± 5 min (or three times hourly) for approximately 16 h while awake and once every 60 ± 10 min (hourly) for approximately 8 h while asleep for measurement on an ABL 805 Flex Blood Gas Analyzer (Radiometer, Copenhagen, Denmark). Up to 54 venous samples were collected over the 24 h duration of the study. The samples were also measured with a SureStep Flexx hospital blood glucose meter (LifeScan, Milpitas, CA). All clinical decisions regarding the management of the subject's glycemic levels were made using the SureStep Flexx meter. Data from the IV-CGM system was compared with the blood gas analyzer and not the SureStep blood glucose meter.

This study marked the first attempt at calibrating the IV-CGM system prospectively. The sensors were calibrated based on a factory calibration plus a one-point *in vivo* calibration. *In vivo* calibration utilized a venous blood sample measured with the ABL Radiometer 805 blood gas analyzer. Data from the IV-CGM system was compared with the ABL Radiometer values and analyzed using accepted methods for CGM systems, such as the mean absolute relative difference (MARD), the Clarke error grid, as well as conformity with the International Organization for Standardization (ISO) 15197 standard for the clinical accuracy of glucose meters. While ISO 15197 was not designed for continuous glucose sensors, it is the relevant accuracy standard that point-of-care glucose monitoring systems must currently meet and thus provides a starting point for assessing the individual (temporally discrete) readings of a continuous glucose sensor. The prototype monitors used in the study stored the detected fluorescence emission and calculated glucose values, but did not display the calibrated data in real time.

In response to observations made over the course of the study, changes were made to the IV-CGM system to improve performance. The optical fiber was changed to resist motion artifacts. Antioxidant protection was incorporated into the sensing element to protect the sensor chemistry against oxidation by reactive oxygen species. After ultrasound observations of subclinical thrombus that partially occluded the vessel in proximity to the sensor, the heparin-based coating was modified to improve the biocompatibility of the sensor. Lastly, changes were also made to the method of device insertion to reduce the risk of sensor misplacement into the perivascular space. Ultrasound was used to evaluate the vasculature prior to device insertion, to confirm sensor deployment after insertion, and to qualitatively observe blood flow around the sensor.

Results

Twenty-three sensors from 13 study sessions and 11 individual subjects were included in the accuracy analysis. Nineteen sensors were excluded for the following reasons: low blood flow or placement in perivascular space (n = 7), device malfunctions (n = 8), and motion artifacts (n = 4). Nine of the 13 study sessions saw two sensors that were placed and included in the pooled analysis. The length of the monitoring period varied by study and subject scheduling considerations. The average monitoring time of the included sensors was 17.8 h. The maximum monitoring time was 24 h, and the minimum was 10 h. Twelve of the sensors included for analysis were monitored for over 20 h. Seven of the 23 sensors were calibrated prospectively. Due to the prototype nature of the sensor and the monitor, the remaining sensors were not calibrated prospectively. These sensors were, however, calibrated retrospectively using the raw data signals and the same calibration principles as the prospective calibration.

A total of 942 paired points between reference analyzer and sensor were obtained. Fourteen out of 23 sensors (60.9%) had a MARD ≤10% (**Table 1**). The aggregate MARD for all included sensors was 9.5%. Eighty-nine percent of paired points were in the clinically accurate A zone of the Clarke error grid, and 9.9% were in the benign error B region (**Figure 3**). Sensor performance did not markedly vary across the range of glucose concentrations when evaluated by MARD and percentage in Clarke A zone (**Table 2**). Eighty-nine percent of paired points also met the ISO 15197 criteria of ≤15 mg/dl difference for values <75 mg/dl and ≤20% difference for values ≥75 mg/dl (**Table 3**). The MARD of the seven prospectively calibrated sensors was 10.0%, and

Table 1.
Individual Intravascular Continuous Glucose Monitoring Accuracy

MARD range	Number of sensors
≤8%	8
8.1–10.0%	6
10.1–12.0%	4
12.1–14.0%	3
14.1–16.0%	2
Total	23

Table 2.
Aggregate Intravascular Continuous Glucose Monitoring Accuracy Stratified by Glucose Level

Glucose (mg/dl)	Number of samples	Clarke A zone	MARD	MAD (mg/dl)
40–80	107	91/107 (85.0%)	13.0%	8.7
81–120	196	160/196 (81.6%)	11.2%	11.3
121–240	557	516/557 (92.6%)	8.3%	14.3
≥241	82	74/82 (90.2%)	9.0%	23.8
All results	942	841/942 (89.3%)	9.5%	13.9

Table 3.
Aggregate Intravascular Continuous Glucose Monitoring Accuracy Stratified per ISO 15197

<75 mg/dl		≥75 mg/dl	
Absolute difference	Number of samples	Relative difference	Number of samples
≤±5 mg/dl	38/80 (47.5%)	≤±5%	326/862 (37.8%)
≤±10 mg/dl	59/80 (73.8%)	≤±10%	533/862 (61.8%)
≤±15 mg/dl	69/80 (86.3%)	≤±15%	664/862 (77.0%)
—		≤±20%	760/862 (88.2%)

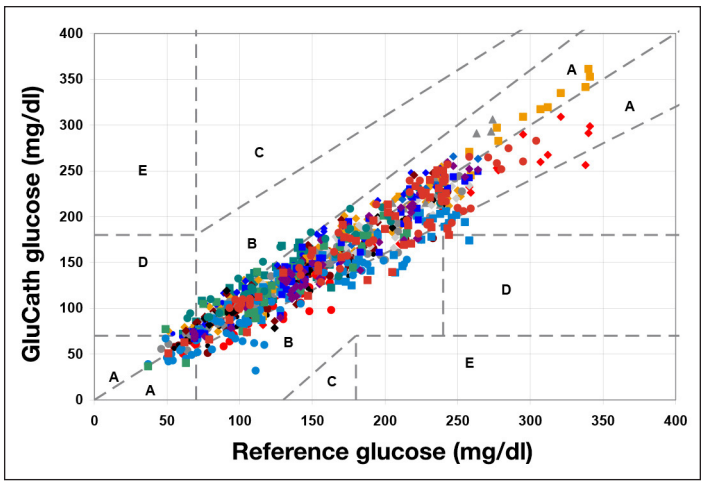


Figure 3. Composite Clarke error grid for 13 study sessions and 23 IV-CGM sensors. A total of 89.3% and 9.9% of points are in the A and B regions of the Clarke error grid, respectively, and 0.8% of the points were in the D region of the Clarke error grid.

the MARD of the 15 retrospectively calibrated sensors was 9.2%.

Individual sensor performance was qualitatively evaluated by plotting a temporal trace of the IV-CGM system compared with laboratory samples. An example of excellent performance is shown in which the sensor was calibrated once approximately 30 min after insertion and ran for 23 h with a MARD of 8.9% (**Figure 4**).

The real-time response of the IV-CGM system in response to a rapid change in glucose was evaluated for a different sensor (**Figure 5**). While at a blood glucose of 70 mg/dl, the subject drank approximately 23 g of glucose from a box of juice. The IV-CGM system displayed an initial response after a 4 min physiological lag, demonstrating a real-time response to treatment of hypoglycemia. A sensor lag time of only 6–7 min was observed when blood glucose was rapidly changing at the rate of 3 mg/dl/min.

Discussion

The IV-CGM system demonstrated the potential for improved CGM accuracy through intravascular deployment of a fluorescent sensor. All sensors provided valuable real-time trending data, and several sensors performed at an accuracy level that may be sufficient for insulin dosing. However, this study identified adequate peripheral blood flow as a necessary condition for IV-CGM accuracy. While easily accessible, peripheral veins typically have a small diameter, are easily compressible, and have numerous collateral flow alternatives, all of which can lead to pooling of blood and result in changes to local glucose concentration, such that it differs from systemic glucose levels.

This phenomenon was observed in one case with an otherwise excellent MARD of 7.4% (**Figure 6A**). Overnight, the subject rolled over onto the arm containing the sensor shortly after the 4:00 AM blood sample. Immediately subsequent to the subject rolling over, a transient low reading of glucose was observed. The observed glucose reading rebounded when the subject rolled off of the arm, presumably restoring flow to the vessel containing the sensor. This case displays the speed and accuracy of the IV-CGM system as a CGM device, while simultaneously demonstrating that caution must be taken before assuming that the blood glucose in superficial veins is representative of systemic glucose.

A second case exhibited this phenomenon more frequently, resulting in a MARD of 15.0% (**Figure 6B**). While the sensor trends glucose throughout the case, there are frequent periods where the IV-CGM system reads low compared with the reference analyzer. These periods are punctuated by events where IV-CGM performance appears to rebound (e.g., 14:50, 15:50, 20:10, 20:30, and 21:15). Three of these rebounds were temporally associated with the subject getting up from a recumbent position. As muscular activity promotes blood flow, one probable cause of the rebounds is inter-mittent blood

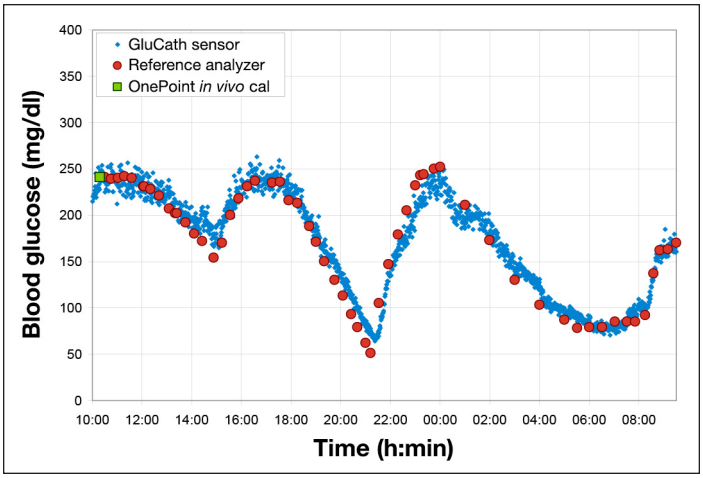


Figure 4. Temporal trace of the calibrated GluCath IV-CGM sensor for one subject with type 1 diabetes compared with ABL Radiometer 805 Blood Gas Analyzer.

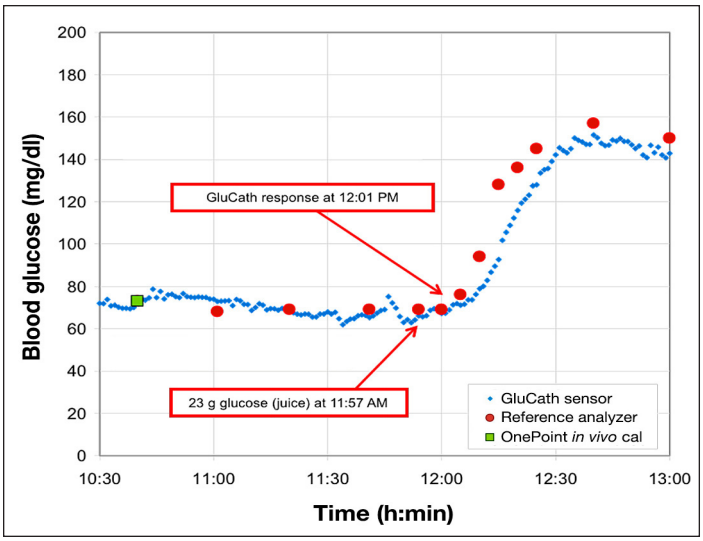
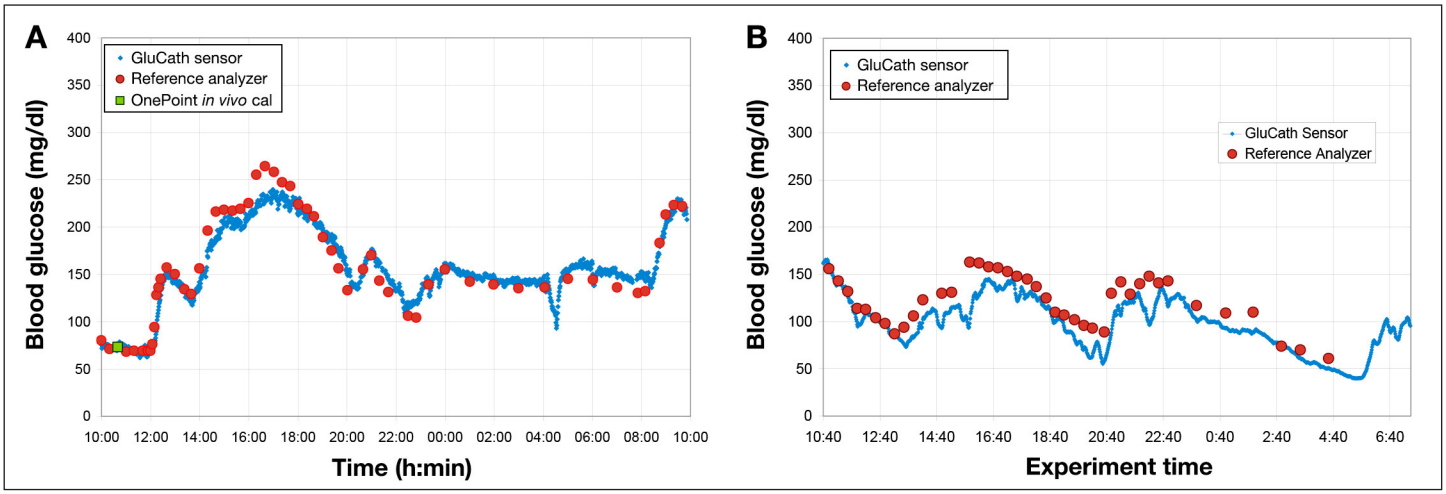


Figure 5. Response of the IV-CGM system to a 3 mg/dl/min rapid change in blood glucose caused by consumption of 23 g of glucose from a box of juice.

flow surrounding the sensor. Note that, in this case, the venous sampling port lost patency approximately 2 h before the end of the study; capillary finger sticks measured by the SureStep Flexx were used to monitor safety during this period. The sensor subsequently responded to a glucose rise caused by a light breakfast between 5:00 and 6:40 AM. In this case, relevant clinical information on the trending of blood glucose was collected, albeit compromised by variance in glucose levels observed between peripheral venous and capillary blood. While low glucose readings in the euglycemic and hypoglycemic ranges represent a relatively benign clinical error, they contribute to the existing CGM limitation of frequent false hypoglycemia alarms.

Conclusions

This study extended the use of the second-generation GluCath IV-CGM system to 24 h in humans. Twenty-three of the 42 sensors were successfully deployed intravascularly and recorded blood glucose measurements for performance analysis. The IV-CGM system demonstrated a high level of accuracy in these sensors, with all sensors in aggregate having a MARD of 9.5%. Fourteen out of 23 individual sensors had a MARD of ≤ 10%. The variability of blood flow in superficial veins of the periphery contributed to reduced accuracy in some sensors and episodes of reduced glucose readings in numerous sensors. Adequate blood flow is thus a necessary condition for systemically relevant indwelling intravascular blood glucose monitoring. Enhanced ultrasound measurements capable of quantifying blood flow velocity could be incorporated in future research examining the relationship of vessel size, blood flow, and the presence of indwelling catheters on thrombus formation and intravascular sensor performance.



Figures 6. Temporal traces of the calibrated GluCath IV-CGM system for two subjects, displaying evidence of low flow.

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Disclosures:

Howard Zisser, Lois Jovanovič, Kateryna Markova, and Wendy Bevier are employees of Sansum Diabetes Research Institute, which was paid by GluMetrics Inc., to conduct the clinical study. They do not own stock in GluMetrics nor did they receive any additional compensation. Matt Romey and Paul Strasma are full-time employees of GluMetrics Inc.

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