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SYMPOSIUM

Evaluation of the VIA® Blood Chemistry Monitor for Glucose in Healthy and Diabetic Volunteers

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Abstract

Background:
Manual methods of blood glucose monitoring are labor-intensive, costly, prone to error, and expose the caregiver to blood. The VIA® blood chemistry monitor for glucose can automatically measure plasma glucose (PG) every 5 minutes for 72 hours using blood sampled from a peripheral vein/artery or a central vein.

Methods:
VIA performance was evaluated in eight normal and five type 1 diabetic (T1DM) subjects in 15 separate experiments. The VIA device was connected to a peripheral vein and reported a PG value every 5 minutes during each 510-minute experiment. Blood samples were collected manually every 10 minutes and assayed using a HemoCue® β-glucose analyzer (HC). Whole blood HC measurements were corrected to PG values. Paired HC/VIA measurements ($n = 717$) were analyzed.

Results:
Mean PG was 90 ± 14 and 96 ± 12 mg/dl in normal subjects and 194 ± 64 and 173 ± 48 mg/dl in T1DM subject as measured by the HC and VIA, respectively. Clark error grid analysis revealed 86% points in zone A, 11% points in zone B, and 2% points in zone D. Linear regression analysis yielded the following equation: $VIA = 0.732 \times HC + 30.5$ ($r^2 = 0.954$). Residual analysis revealed a glucose-dependent bias between the HC and the VIA. VIA data were transformed using the linear regression equation to correct for bias. After the correction, the mean absolute relative difference between the VIA and the HC was less than 10%, and 99.6% of data were in zones A and B. The VIA was able to sample blood automatically every 5 minutes for more than 8 hours in the laboratory setting. On average, the VIA reported glucose values for 94% of the samples it attempted to obtain.

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Abbreviations: (CEG) Clark error grid, (CVC) central venous catheter, (HC) HemoCue β-glucose analyzer, (IIT) intensive insulin therapy, (MARD) mean absolute relative difference, (PG) plasma glucose, (T1DM) type 1 diabetes mellitus, (VIA) VIA blood chemistry monitor for glucose

Keywords: continuous glucose monitoring system, CGM, glucose sensor, VIA blood chemistry monitor for glucose, VIA glucose monitoring system, V-GLU1 glucose sensor

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Abstract cont.

Conclusions:
This study demonstrated that the VIA blood chemistry monitor for glucose can reliably sample blood frequently for a prolonged period of time safely and effectively in diabetic and nondiabetic volunteers. Agreement between the two devices was the closest at normal glucose concentrations. After correcting for a glucose-dependent bias between the devices, the MARD was consistently less than 10% for all glucose ranges.

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Background

Blood glucose monitoring is performed routinely in the hospital to manage patients at risk for hyperglycemia and hypoglycemia. Frequent monitoring is required to effectively control glycemia with a low incidence of hypoglycemia.[1–6] Current manual methods are labor-intensive, costly, prone to error, and expose the caregiver to potentially infectious blood.[7–9]

Samples of blood for point-of-care glucose monitoring are commonly obtained from the fingertip using a lancet.[8,10–12] The concentration of glucose in capillary blood can be affected by finger edema, decreased tissue perfusion, increased glucose utilization, insufficient depth of lancet penetration, excessive tissue compression to acquire an able sample, and location of dermal puncture (fingertip, palm, forearm, heel).[11,13] Thus, capillary sampling is not recommended in patients with hypotension, hypo-perfusion, hypoxemia, and finger edema.[14–17] Repeated dermal puncture of adequate depth will cause pain, fingertip tenderness, and possible infection.[18]

Obtaining blood samples from a peripheral vein is a clinical challenge. Repeat venipuncture with a needle may not be possible due to a lack of suitable veins, unavailability of an experienced phlebotomist, and patient discomfort. Catheters inserted into a peripheral vein may not permit repeat blood sample acquisition because of low flow, vessel wall collapse, obstruction from a valve, vessel thrombosis and catheter occlusion due to clot, fibrous tissue, and kinking.[19–21] Sample contamination with glucose or dilution with a salt solution can occur, despite removing several milliliters of blood and fluid prior to sample acquisition.[22–24] The amount of blood removed and discarded can be excessive when samples are obtained frequently.[25,26] Nurses have developed a variety of methods to acquire a blood sample from a stopcock, often without validation. Sampling methods are not applied consistently and may lead to error in measurement.[27] Similar issues limit frequent manual blood sample acquisition from a catheter inserted into a peripheral artery or central vein.

In addition to measurement errors because of sample acquisition and handling, many point-of-care glucose meters do not achieve the degree of accuracy and precision recommended by the American Diabetes Association or the International Organization for Standardization.[28–31] Hospital-grade glucose meters and strips may be affected by changes in humidity, blood pH, temperature, hematocrit, oxygenation, drugs, and interfering substances.[32]

The prospective studies by Van den Berghe and colleagues highlight the importance of glycemic control in medical and surgical patients requiring intensive care.[4–6] Retrospective studies involving medical and surgical patients in the intensive care unit also demonstrate a strong correlation between the degree of glycemic control and morbidity, mortality, length of stay, and cost.[2,12, 33–44] Evidence suggests a correlation between blood glucose variability and increased morbidity/mortality.[45,46]

Intensive insulin therapy (IIT) methods attempting to achieve near-normal glycemia (target range: 80–110 mg/dl) have been plagued by an unacceptably high rate of hypoglycemia.[3–6,47–58] Results from published clinical trials[4,6,59] show a higher incidence of hypoglycemia in the IIT group compared to the conventional treatment group (**Table 1**). The fear of hypoglycemia and the increased morbidity/mortality associated with hypoglycemia remain major barriers to the clinical application of IIT protocols in the hospital setting.[1,3,6,60,61]

Table 1.
Incidence (%) of Hypoglycemia (Defined as a Glucose Measurement below 40 mg/dl) among Patients Receiving either Intensive Insulin Therapy or Conventional Insulin Therapy (CIT)

IIT	CIT	Sample	Method
5.1	0.8	Arterial whole blood	Radiometer ABL700
18.7	3.1	Arterial or capillary whole blood	HemoCue β-glucose analyzer
17.0	4.1	Arterial or capillary whole blood	HemoCue glucose 201 analyzer

The average time required for a nurse to acquire a blood sample and measure the concentration of glucose using a point-of-care meter has been estimated to be 4.7 minutes.[62] Thus, 1 to 2 hours of a caregiver's day are required solely to monitor the glucose concentration of a patient managed with IIT.

Therefore, there is great clinical need for a safe, effective, and user-friendly medical device that automatically and continuously monitors the concentration of glucose in the blood of hospitalized patients at risk for hyperglycemia and hypoglycemia. Real-time glucose monitoring provides important trend information: (1) absolute concentration (mg/dl, mmol/liter), (2) direction of change (stable, increasing, or decreasing), and (3) rate of change (stable, slow, or fast). The trend information can be used by the bedside nurse to titrate the delivery of insulin and glucose to maintain glycemia in the desired range. The risk for hypoglycemia and the fear of hypoglycemia will be minimized and/or eliminated.

The VIA® blood chemistry monitor for glucose was developed by VIA Medical Corporation (San Diego, CA) in 1991 to automate the process of glucose monitoring in the hospital environment. The device received Food and Drug Administration-approved labeling to measure the concentration of glucose as frequently as every 5 minutes for 72 hours using blood sampled from a radial artery catheter, a peripheral venous catheter, or the proximal port of a central venous catheter (CVC). The system was designed to automatically deliver a sample of patient blood to an external flow-through glucose sensor using a bidirectional infusion pump (**Figure 1**).

The sensor (**Figure 2**) measures the concentration of PG in a whole blood sample using the enzyme glucose oxidase and classic electrochemistry to produce hydrogen peroxide (**Figure 3**). The device automatically returns each sample back to the patient's bloodstream, avoiding blood loss and caregiver exposure to bodily fluids. The sensor is automatically recalibrated prior to each measurement using a glucose-containing reference solution to ensure accuracy in the clinical setting. The VIA displays the PG concentration (in mg/dl or mmol/liter) approximately 60 seconds after each sample is obtained.[63–66]

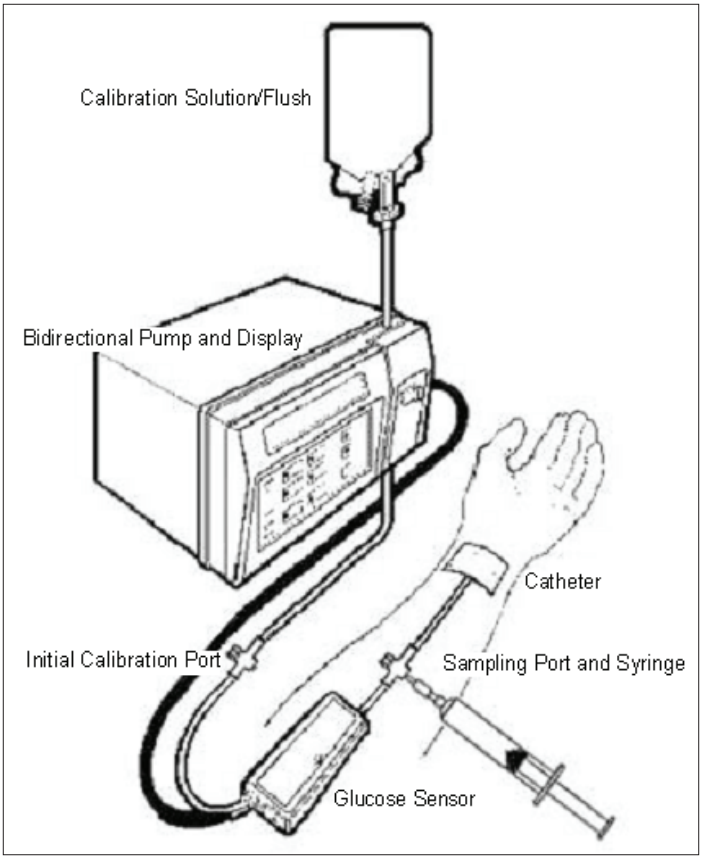

Figure 1. Diagram of VIA blood chemistry monitor for glucose. The VIA sensor requires a two-point calibration prior to use. A calibration/flush solution is produced by injecting 10% glucose solution into a 500-ml bag of Isolyte to produce a final concentration of ~82 mg/dl. The solution is flushed through the tubing and sensor into a sterile collecting bag attached to the distal end of the tubing. Ten milliliters of normal saline is then injected into the stopcock of the tubing to bath the sensor in a glucose-free solution. The monitor then infuses 10 ml of the Isolyte–glucose reference solution into the sensor and tubing. The monitor performs a two-point calibration (0 and 82 mg/dl) to correlate the output signal (mA) of the sensor to a known glucose concentration. Once calibrated, the Isolyte–glucose solution is infused continuously through the tubing and sensor at a rate of 5 ml/hour. Prior to each glucose measurement, the monitor performs a one-point calibration using the Isolyte–glucose solution (82 mg/dl) as the reference. The assembled system is illustrated attached to a catheter inserted into a peripheral vein.

We compared the VIA to the Hemocue® β-glucose analyzer (HemoCue AB, Angelholm, Sweden). The HC is a practical and reliable point-of-care glucose meter used by our institution's clinical laboratory. It was chosen as the comparison device because of its established accuracy,

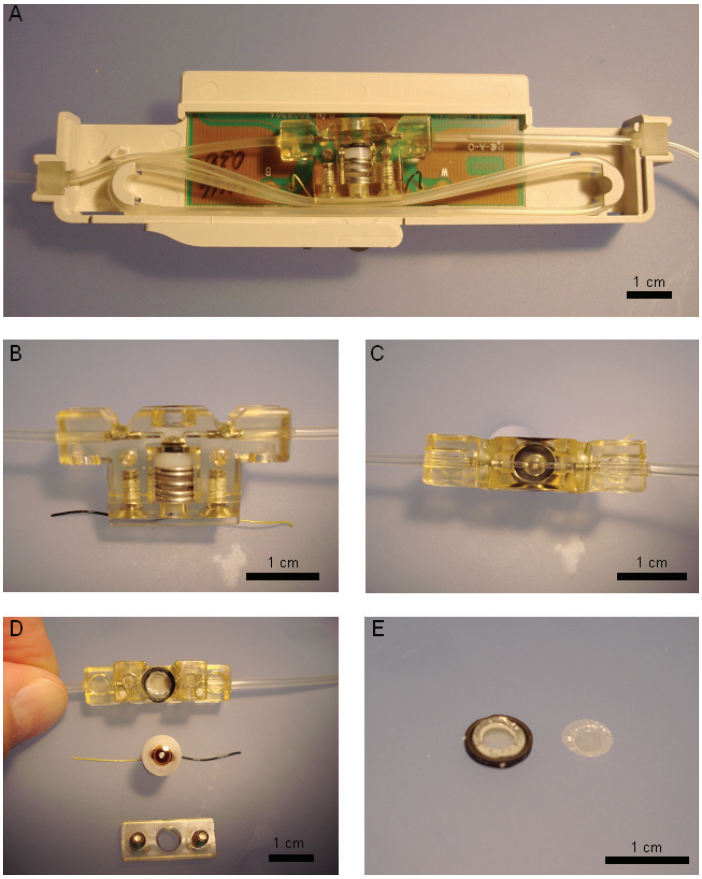

Figure 2. Sensor components for the VIA blood chemistry monitor for glucose. (**A**) Sensor and circuitry in cartridge. The blood sample travels through tubing over the flow-through sensor (right to left) to fill the loop of tubing (~1.2 ml). After the sample is analyzed, calibration solution is infused through the tubing and sensor (left to right) to return the sample back into the patient's bloodstream. (**B**) Side view of sensor with cartridge removed. The blood sample travels through the tubing (right to left) into the reservoir adjacent to the surface of the outer membrane of the glucose sensor (center of black washer). A spring pushes the electrode base (white plastic) into a washer (black silastic) and housing (clear acrylic) to produce a hermetic seal. Outer and inner membranes are located between the washer and the electrode base. (**C**) Top view of sensor. Light travels through the acrylic housing, blood reservoir, outer membrane, and inner membrane to visualize the electrodes of the sensor (center of black washer). Blood remains external to the outer membrane of the sensor. (**D**) Bottom view of sensor with the electrode base removed from the housing. Outer membrane, enzyme layer, inner membrane, and washer are seen within the housing. (**E**) The porous outer membrane of sensor attached to a black silastic washer (**left**). The inner porous membrane (**right**) is removed to visualize the glucose oxidase enzyme layer (clear liquid on inner surface of outer membrane).

precision, low blood volume requirement, ease of use, specificity for glucose, and low sensitivity to hematocrit. When calibrated appropriately, the HC provides an accurate measurement of whole blood glucose over the physiological range of glucose concentrations (40–400 mg/dl).[67–69]

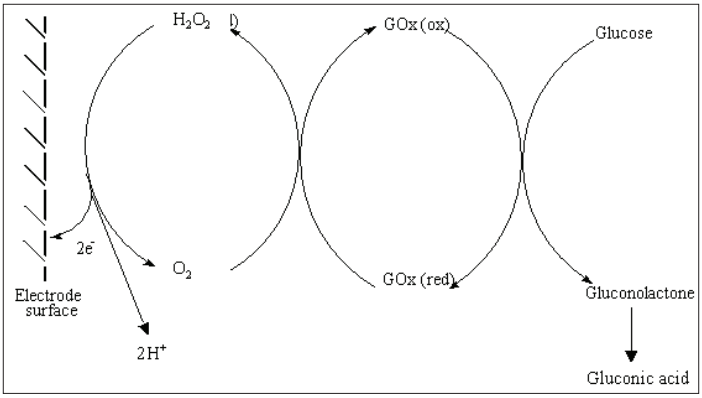

Figure 3. Electrochemistry of VIA blood chemistry monitor for glucose. Redox reactions occur within enzyme layer: (1) oxidation of ß-D-glucose by glucose oxidase to gluconolactone, (2) reduction of gluconolactone to gluconic acid, (3) reduction of glucose oxidase enzyme, and (4) reoxidation of glucose oxidase by reduction of oxygen to hydrogen peroxide, which is oxidized at the platinum electrode to produce electrons, protons, and oxygen. Two electrons are formed for each molecule of hydrogen peroxide oxidized. The output signal is converted to a glucose value by correlating the electric current of each blood sample to the current obtained using the 0- and 82-mg/dl reference solutions.

Methods

Study Subjects

Thirteen adult volunteers were recruited from the local community and consented to participate in this Institutional Review Board-approved study. Fifteen experiments were performed in eight healthy and five type 1 diabetes mellitus (T1DM) subjects (one T1DM subject was studied on three separate occasions). All experiments were performed within The Artificial Pancreas Center at Jefferson Medical College of Thomas Jefferson University in Philadelphia, Pennsylvania.

Long-standing and severe insulin deficiency was documented in all T1DM subjects by medical history. T1DM subjects did not exhibit signs or symptoms of autonomic neuropathy, gastroparesis, or hypoglycemia unawareness. Normal subjects denied a history of diabetes, impaired glucose tolerance, or symptoms suggestive of hyperglycemia.

Experimental Protocol

Study subjects were instructed to maintain their routine diets, exercise, and, if diabetic, their insulin therapy for 1 week prior to the day of experiment. T1DM subjects practicing multiple daily injection therapy were instructed to withhold intermediate-acting insulin for 18 hours and short-acting insulin for 8 hours prior to the start of the experiment. T1DM subjects practicing

continuous subcutaneous insulin therapy were instructed to discontinue therapy 2 hours prior to the start of the experiment.

All subjects were instructed to withhold food after 9 p.m. the evening prior to study. T1DM subjects were instructed to monitor glucose levels upon awakening, carry a source of carbohydrate should an episode of symptomatic hypoglycemia occur, and arrive at the laboratory in the euglycemic range. All studies began between 7 and 9 a.m.

An experienced anesthesiologist examined the subject's arms to determine an optimal location for insertion of an intravenous catheter for sample acquisition. A 22-gauge, 1.25-inch plastic catheter (Becton Dickinson, Franklin Lakes, NJ) was inserted into a forearm vein in 13 out of 15 of the experiments, whereas a 20-gauge, 1.25-inch catheter was inserted for the other two experiments. A 22-gauge catheter was inserted into a contralateral forearm vein to facilitate insulin/glucose delivery.

The VIA was connected to a computer programmed to capture and record the time, glucose measurement, error code, and recalibration data. Sensor data were also printed to paper in real time. Events such as meals, exercise, interventions, and temporary disconnection of the monitor were recorded manually in the computer database.

Immediately prior to each experiment, a VIA glucose sensor was removed from its sterile package. The blood/fluid path of the sensor and tubing was filled with the glucose solution and allowed to equilibrate to room temperature. The tubing was connected to a mechanism on the VIA that facilitated the controlled aspiration of blood and the infusion of glucose-containing flush solution. An initial two-point calibration was performed. The calibrated device was then connected to the venous catheter.

Each experiment lasted at least 510 minutes (**Figure 4**). During the experiment, each subject consumed two identical meals and exercised on a stationary bicycle (expending ~2.2 kW in 30 minutes). Each meal averaged 829 kcal with approximately 120 grams of carbohydrate. The first meal (breakfast) was started 30 minutes after the start of the experiment. The second meal (lunch) was started 210 minutes after the start of the first meal. Exogenous insulin was not delivered to normal subjects. T1DM subjects received a continuous intravenous infusion of insulin based on a simple algorithm.[70]

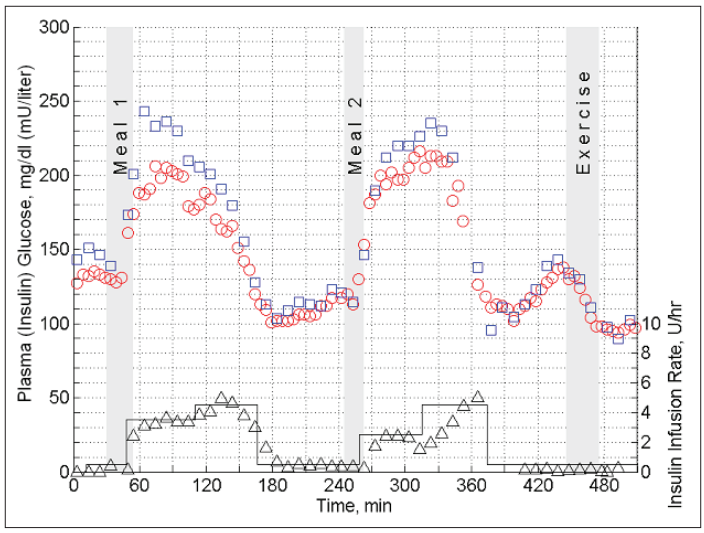

Figure 4. VIA plasma glucose data (**red circles**), HC plasma-corrected glucose data (**blue squares**) and plasma insulin (**black triangles**) for a T1DM subject displayed over the 510-minute experiment. An intravenous infusion of regular insulin (**solid black line**) was timed with the onset of meals and discontinued 2 hours after onset. The extended square wave infusion of insulin was based on a simple algorithm. Subject exercised on a stationary bicycle for 30 minutes starting at 446 minutes.

Although not utilized in any experiment, an infusion of 10% glucose was available as needed to treat symptomatic hypoglycemia.

The VIA automatically sampled blood from a peripheral vein and reported a PG measurement every 5 minutes. Blood samples were collected manually every 10 minutes from a stopcock within the VIA tubing (every other time the VIA acquired a blood sample). Manual samples were collected after the automatic withdrawal of blood was complete at which time the VIA glucose sensor was analyzing the blood. A syringe was attached to a stopcock between the peripheral venous catheter and the VIA glucose sensor. A small amount of blood was drawn into the syringe from the subject and discarded. A second syringe was attached to the stopcock and the blood sample was collected (**Figure 5**). Whole blood samples were mixed and inserted into the HC for analysis using the same technique described elsewhere.[68] HC measurements were made in duplicate. Each experiment yielded 41 to 52 paired data points (simultaneous measurements by the VIA and HC).

Data Analysis

The rate at which the VIA successfully withdrew a blood sample from the peripheral catheter, tested it for glucose, and reported the result was used as a performance measure. For each experiment, the number of potential VIA measurements was calculated by dividing the

duration of the experiment by the sampling period (5 minutes) and adding one additional measurement. Therefore, during a 510-minute experiment, there were 103 (510/5 + 1) potential measurements. The number of potential measurements was reduced by the number of measurements that were attempted during a deliberate disconnection between the VIA to allow the subject to use the bathroom. The number of actual VIA measurements was tabulated for each experiment, and the ratio of the actual to potential (less deliberately missed measurements) VIA measurements determined the success rate. Missed VIA measurements were further categorized as measurements performed with or without simultaneous manual sampling to investigate whether manual sampling was associated with a higher rate of missed measurements.

Plasma glucose measurements reported by the VIA were paired to the simultaneous whole blood glucose measurements made with HC. HC measurements were corrected to their plasma equivalent glucose concentrations by applying an 11% positive correction[71] in order to make an appropriate comparison of the instruments. This correction is currently used by the recently introduced HemoCue® 201 analyzer to better approximate clinical laboratory PG.[72] Data from each measurement device were divided into five glucose concentration ranges: <80 mg/dl (hypoglycemia), 80–130 mg/dl (euglycemia), 131–180 mg/dl (mild hyperglycemia), 181–240 mg/dl (moderate hyperglycemia), and >240 mg/dl (severe hyperglycemia). Inclusion of a HC/VIA pair into a range was based on the HC-corrected measurement. The relationship between the difference (VIA – HC) and the mean ([VIA + HC]/2)[73] and mean absolute relative difference (MARD) were used to compare the glucose measurement devices over each range of glucose level. Clark error grid (CEG) analysis was performed to evaluate the clinical implications of the differences between the two devices.

Data visualization and statistical analysis were performed using Matlab (The Mathworks, Inc., Natick, MA). Unless noted, data are presented as mean ± standard deviation.

Results

Study subjects ranged in age from 27 to 51 (mean: 38 years) with an average body mass index of 23 ± 3 kg/m^2 and normal hematocrit values. Seven hundred seventeen paired measurements were collected in 15 experiments. VIA measurements ranged from 69 to 145 mg/dl in normal subjects and 70 to 290 mg/dl in T1DM subjects. HC measurements (corrected to reflect PG) ranged from 63 to 150 mg/dl in normal subjects and from 61 to 377 mg/dl in T1DM subjects. PG values for the T1DM group had a higher mean and a larger variance compared to the normal group (**Figure 6**). Normal subjects had a mean PG value of 90 ± 14 mg/dl measured by the HC and 96 ± 12 mg/dl measured by the VIA. T1DM subjects had a mean PG value of 194 ± 64 mg/dl measured by the HC and 173 ± 48 mg/dl measured by the VIA.

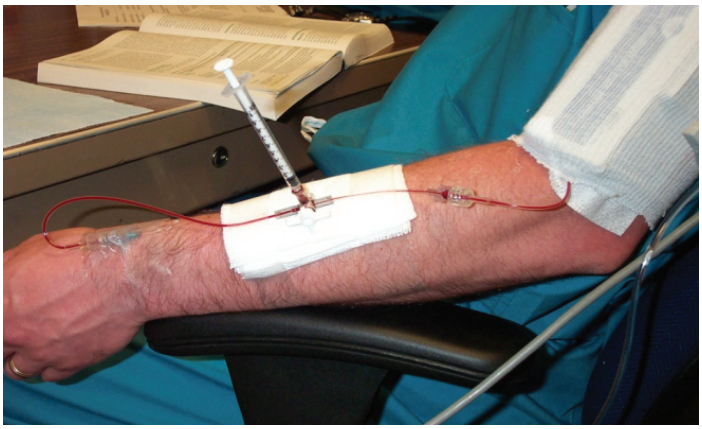

Figure 5. Study subject with a 22-gauge catheter within the peripheral vein of the left arm. A reference blood sample has been collected in a sterile 1-ml syringe attached to a stopcock during an automated sample acquisition. The sensor cartridge is attached to the upper arm with gauze.

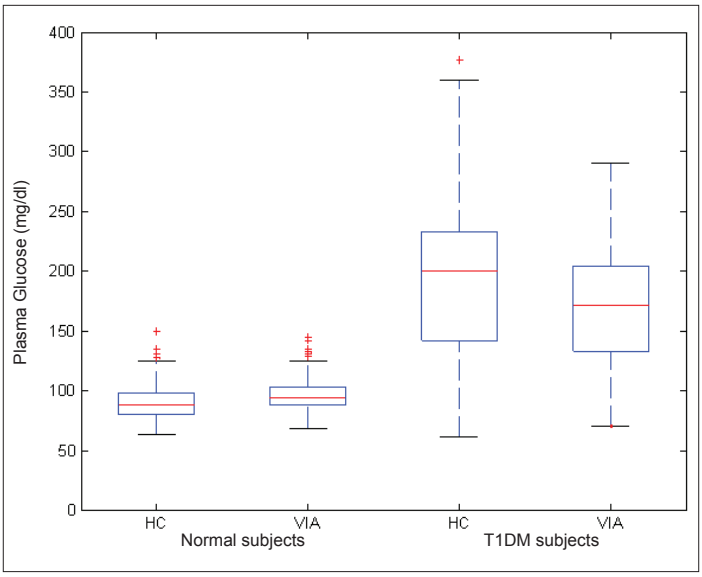

Figure 6. Box plot illustrating the range of glucose values in the dataset of 717 pairs of time-matched VIA/HC measurements where HC whole blood measurements have been corrected to represent plasma values. For each group (normal and T1DM subjects) and device (HemoCue glucose analyzer and VIA blood chemistry monitor for glucose), the red line represents the median glucose value, the boxed region spans 50% of data around the median, and the whiskers that extend above and below the boxed region represent 1.5 times the inner quartile range. Red crosses depict data outside the whiskers.

The average duration of the experiments was 515 ± 17 minutes. Combining data from all experiments, 1438 VIA measurements were performed over the span of 7724 minutes. With 1541 potential VIA measurements (1560 less 19 deliberately missed measurements during times when subjects were using the bathroom), the average success rate for the VIA was 94 ± 7%. The success rate varied between 75 and 100% (**Table 2**). With 101 failures to acquire, test, or report a PG measurement, only 14% of these missed measurements occurred when manual sampling was performed. In the experiment with the lowest success rate, poor performance was attributable to sensor instability issues as reported by the device itself. If the sensor signal was not stable, the result was not reported and an error message was generated.

Comparing simultaneous VIA and HC measurements, MARD was 17.2% in the hypoglycemia range, 7.6% in the euglycemia range, 8.1% in the mild hyperglycemia range, 13.2% in the moderate hyperglycemia range, and 15.0% in the severe hyperglycemia range. The VIA measurements were consistently higher than the HC measurements in the hypoglycemia range. The VIA measurements were consistently lower than the HC measurements in the mild, moderate, and severe hyperglycemia ranges. The paired measurements were similar in the euglycemia range. The variance in the differences between VIA and HC measurements increased as the average PG level increased (**Figure 7**). The standard deviation of these differences was lowest in the hypoglycemia range and highest in the severe hyperglycemia range (**Table 3**).

Linear regression analysis yielded a correlation coefficient, $r^2 = 0.954$, and the following regression line equation: VIA = 0.732 × HC + 30.5. CEG analysis resulted in 86% of data points in zone A, 11% in zone B, 0% in zone C, 2% in zone D, and 0% in zone E (**Figure 8**). All paired measurements that fell into zone D were from the hypoglycemic range.

Initial analysis revealed a difference (bias) that was highly dependent on the average glucose value. To remove this bias, the linear regression equation (VIA = 0.732 HC + 30.5) was used to transform the VIA measurements. Each value (VIA) was transformed into a value (tVIA) using the equation tVIA = (VIA – 30.5)/0.732. Simply, tVIA replaced HC in the linear regression equation and the equation was solved for tVIA. This process can be considered a calibration routine. Although the equation was constructed with VIA and HC data, it was used solely to transform VIA data. Because the parameters of the linear regression equation are computed by minimizing the residuals between HC and VIA, the mean difference of the data pairs (HC, tVIA) will be zero (**Figure 9**).

When the appropriate transformation was applied to VIA data, the MARD was below 10% and the mean absolute bias was less than 3 mg/dl in all glucose ranges.

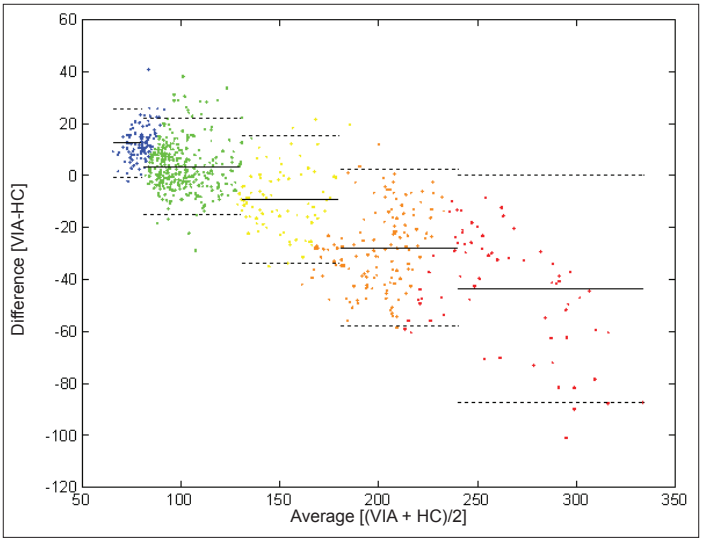

Figure 7. Bland and Altman analysis using 717 paired VIA/HC measurements where HC measurements have been corrected to represent plasma values. The color of each point corresponds to one of the five HC glucose ranges (**blue**: <80 mg/dl, **green**: 80–130 mg/dl, **yellow**: 131–180 mg/dl, **orange**: 181–240 mg/dl, **red**: >240 mg/dl). The solid black line and dashed black lines represent the mean difference ± 2 SD for each glucose range.

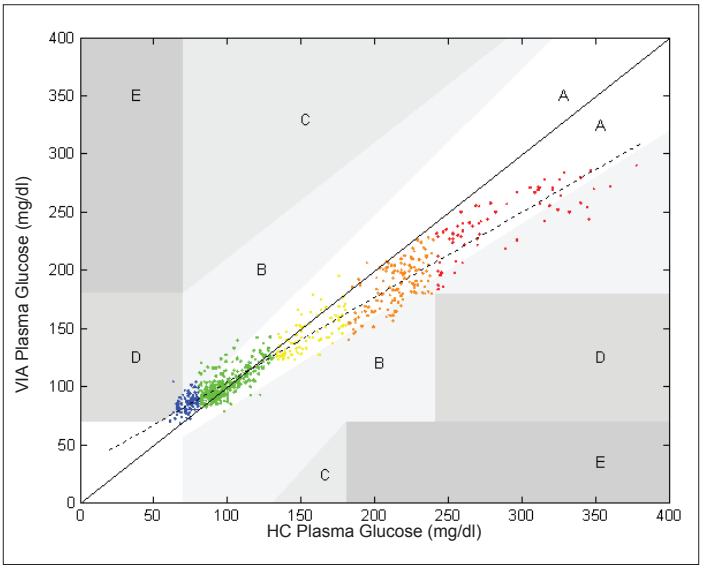

Figure 8. Clark error grid/regression analysis using 717 paired VIA/HC measurements where HC measurements have been corrected to represent plasma values. The color of each point corresponds to one of five glucose ranges (**blue**: <80 mg/dl, **green**: 80–130 mg/dl, **yellow**: 131–180 mg/dl, **orange** 181–240 mg/dl, **red**: >240 mg/dl). The **dashed black line** represents the linear regression equation.

Table 2.
Success Rate of VIA to Acquire and Test Blood from a Peripheral Venous Catheter Every 5 Minutes [a]

Experiment	Number of potential VIA measurements	Number of actual VIA measurements	Number of missed measurements			Success rate (%)
			*N*1	*N*2	*N*3	
1	102	100	1	0	1	98
2	108	105	1	0	2	97
3	101	99	2	0	0	98
4	107	106	0	0	1	99
5	104	85	1	3	15	82
6	102	100	2	0	0	98
7	102	101	0	1	0	99
8	109	101	0	1	7	93
9	105	91	3	5	6	87
10	103	94	3	1	5	91
11	103	92	2	0	10	89
12	103	96	3	0	4	93
13	110	101	0	0	9	91
14	102	76	1	1	24	75
15	97	92	0	2	3	95
	104 ± 3	96 ± 8				94 ± 7

[a] The sum of *N*1, *N*2, and *N*3 is the difference between potential and actual numbers of VIA glucose measurements performed for each experiment (i.e., the number of missed measurements). *N*1 represents the number of measurements attempted during the deliberate disconnection of VIA from the subject to allow the subject to use the bathroom. *N*2 and *N*3 are numbers of missed measurement attempts with or without simultaneous manual sampling.

Table 3.
Mean (± SD) Plasma Glucose Values, MARD, and Mean Bias for Each of the Five Glucose Ranges Based on Corrected HC Glucose Measurements

HC glucose range (mg/dl)	*N*	Mean HC glucose (mg/dl)	Mean VIA glucose (mg/dl)	MARD (%)	Mean bias [VIA–HC] (mg/dl)
<80	104	73.3 ± 4.7	85.7 ± 7.1	17.2	12.4
80–130	337	98.2 ± 12.6	101.6 ± 12.3	7.6	3.5
131–180	78	155.3 ± 15.1	145.9 ± 16.2	8.1	-9.4
181–240	130	214.2 ± 15.6	186.2 ± 19.7	13.2	-28
>240	68	284.4 ± 36.6	240.7 ± 26.8	15	-43.7

As indicated by the ± 2 SD lines in the plot, 95% of the differences between the two devices are expected to be less than 20 mg/dl in the hypoglycemic and euglycemic ranges, and these differences tended to increase as average PG value increased (**Table 4**). The transformation also reduced the number of points in zone D with less than one-half of a percent of points in zone D and 99.6% of points in zones A and B (data not shown).

Conclusions

There is great clinical need for an accurate, robust, and user-friendly medical device able to automatically and continuously monitor the concentration of blood glucose. In this study, the VIA was able to reliably sample blood from a peripheral vein every 5 minutes for 8.5 hours. Issues related to sample acquisition were relatively

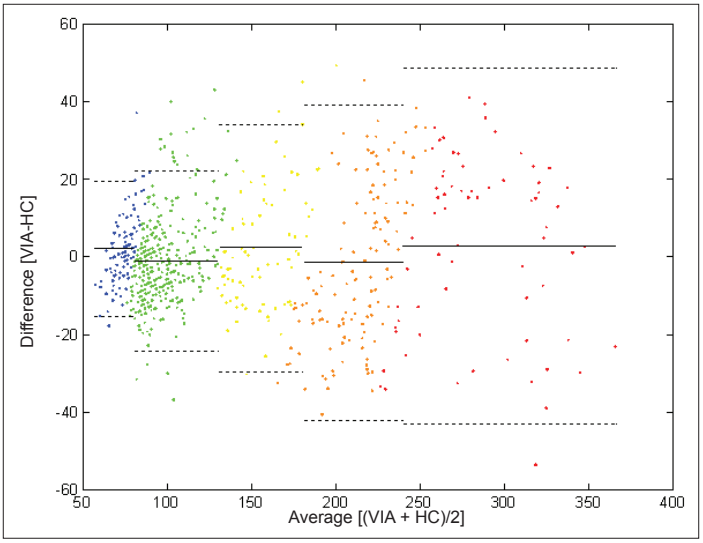

Figure 9. Blank and Altman Analysis using 717 paired tVIA/HC measurements where HC measurements have been corrected to represent plasma values. VIA measurements have been transformed by the linear regression equation: tVIA = (VIA – 30.5)/0.732. The color of each point corresponds to one of the five HC blood glucose ranges (**blue**: <80 mg/dl, **green**: 80–130 mg/dl, **yellow**: 131–180 mg/dl, **orange** 181–240 mg/dl, **red**: >240 mg/dl). The solid black line and dashed black lines represent the mean difference and ± 2 SD for each glucose range.

Table 4.
MARD and Mean Bias When VIA Measurements Are Transformed by the Linear Regression Equation: tVIA = (VIA – 30.5)/0.732

HC glucose range (mg/dl)	MARD (%)	Mean bias [VIA–HC] (mg/dl)
< 80	9.0	2.0
80–130	9.0	-1.1
131–180	7.9	2.3
181–240	8.3	-1.6
>240	7.2	2.7

uncommon using a small-gauge catheter inserted into a peripheral arm vein. The majority of failed sample acquisition attempts were resolved automatically by the VIA. Other laboratory studies and pilot clinical trials using the VIA found similar clinical performance.[63–65,74] A study of the VIA in children with diabetic ketoacidosis concluded that a cannula size greater than 24 gauge was required for the device to acquire samples reliably.[75] We anticipate, however, that repeated sample acquisition from the peripheral vein of a patient in an intensive care unit will be problematic because of low flow, vessel wall collapse, obstruction from a valve, vessel thrombosis, and catheter occlusion due to clot, fibrous tissue, and kinking.[19–21]

Attaching the VIA to a radial artery catheter should increase the likelihood for successful blood sample acquisition over time. Mechanical issues remain problematic in the clinical setting due to vessel thrombosis and clot formation within the catheter lumen. In addition, frequent monitoring has the potential to cause hand edema due to the 6-ml infusion of calibration solution at a high rate and pressure.[76–78]

Although the VIA has been approved for attachment to the proximal port of a central venous catheter, the ability to frequently sample blood from a CVC over time has not been validated. The lumen of the CVC will be exposed to static blood for 60 minutes per day when sampling with the VIA once every 20 minutes, possibly leading to catheter obstruction (50 seconds per test × three tests per hour × 24 hours per day = 3600 seconds per day). The sample can be contaminated with glucose-free or glucose-containing solutions being infused through the tubing.[15,22-24,79,80] The sample can also be contaminated with fluids infused into an adjacent CVC port.[26,81] Nursing protocols are required to ensure that the VIA blood sample is acquired without contamination from adjacent intravenous infusions.

Overall, the VIA compared favorably to the HC, although a glucose-dependent bias existed between the two devices. Compared to the HC, the VIA overestimated the glucose concentration in the hypoglycemia range (<80 mg/dl) and underestimated the glucose concentration in the mild (131–180 mg/dl), moderate (181–240 mg/dl), and severe (>240 mg/dl) hyperglycemia ranges. The closest agreement was noted in the euglycemia range (80–130 mg/dl). In a previous study by this group, the HC was found to underestimate the glucose concentration compared to laboratory measurements over a wide range of glucose values.[68] Other investigations either support[82] or refute[83–89] this relationship. These conflicting data highlight the importance of evaluating the bias and correlation of a new glucose monitoring device in the environment in which it will be used clinically. A research study should precisely control the methods of sample acquisition, handling, and reference glucose measurement. Preferably, the level of glucose should be measured in duplicate or triplicate, using an accepted glucose reference method.

In conclusion, this study demonstrated that the VIA blood chemistry monitor for glucose can reliably sample blood frequently for a prolonged period of time safely and effectively in diabetic and nondiabetic volunteers. Agreement between the two devices was the closest at normal glucose concentrations. After correcting for a

glucose-dependent bias between the devices, the MARD was consistently less than 10% for all glucose ranges.

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