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Monitoring Blood Glucose Levels in Critically Ill Patients

by

Linda C. Slater-MacLean 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Nursing

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Dedication

To my Husband, Stuart, my Daughter, Caitlin, and my Son, Ian

and

To my Mom, Carol, and in memory of my Dad, Donald

Abstract

Maintaining blood glucose within normoglycemic ranges has been shown to reduce morbidity and mortality in critically ill patients. In the clinical setting different methods with varying degrees of accuracy are used to obtain and to measure blood glucose levels. Using a repeated measures within-subjects design, capillary and arterial blood samples were collected from n=45 subjects recruited from an intensive care unit in a large tertiary care hospital. Blood glucose levels were measured using three bedside glucose meters, a Point-of-Care blood gas analyzer, and a blood glucose reference instrument. When compared to capillary samples, the measurement of blood glucose using arterial samples was more accurate. The Abbott Freestyle® blood glucose meter was the most accurate of the three blood glucose meters for measuring blood glucose using arterial sampling. The Bayer Chiron 865® blood gas analyzer was also shown to be a highly accurate instrument to measure arterial blood glucose.

Acknowledgements

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To the Critical Care Nurses and Intensivists who have chosen to care for critically ill patients and their families, none of this would have been possible without you.

Table of Contents

List of Tables

List of Figures

Chapter 1 Introduction

In healthy individuals, blood glucose (BG) is tightly regulated in the body and kept within a narrow range of 3.5 to 5.5 mmol/L (Mesotten & Van den Berghe, 2003). Key factors regulating BG include hormonal, neural and hepatic autoregulatory mechanisms (Ganong, 2001). Insulin is secreted in response to elevated BG and glucagon is secreted in response to low BG (Guyton & Hall, 2000). BG regulation is extremely important for the brain because glucose is the only nutrient that can be used by mature neurons to meet energy demands (Guyton & Hall, 2000). Acutely, low BG will cause loss of consciousness while high BG can cause dehydration and electrolyte imbalances (DiNardo, Korytkowski & Siminerio, 2004). Chronic increases of BG cause tissue damage, especially to smaller blood vessels, and lead to increased risks of heart attack, stroke, end-stage renal disease and blindness (Ganong, 2001).

In critical illness, defined as any condition requiring support of failing vital organ systems (Van den Berghe, 2003), there are alterations in BG regulation. In particular, critical illness can cause acute (stress) hyperglycemia as a result of the metabolic and hormonal changes that accompany stress responses (Preiser, Devos & Van den Berghe, 2002). Stress hyperglycemia is typically defined as BG greater than 11.10 mmol/L (Hirsch, 2002; Lewis, Kane-Gill, Bobek & Dasta, 2004; McCowen, Malhortra & Bistrian, 2001). Furthermore, insulin resistance, the existence of metabolic characteristics of insulin deficiency despite normal or increased plasma insulin concentrations (Robinson & van Soeren, 2004), is also common in critical illness (Chittock, Henderson, Dhingra & Ronco, 2003; Robinson & van Soeren, 2004). Hyperglycemia in insulin resistance may reflect problems at the receptor and postreceptor level, particularly in the

liver, skeletal muscle and the heart (Chittock, et al., 2003; Van den Berghe 2003). Glucagon and catecholamines increase hepatic glucose production and decrease peripheral glucose uptake (Robinson & van Soeren, 2004).

Insulin resistance and stress hyperglycemia are frequently observed in critically ill patients, even when BG has previously been normal (Chittock et al., 2003; Van den Berghe et al., 2003). Insulin resistance has been observed in many forms of critical illness and the degree of insulin resistance appears to be directly proportional to the severity of the stress response (Mizock, 2003).

Historically, hyperglycemia has been of little concern in critical care units and has often been overlooked or only addressed in patients with known disorders of glucose metabolism, such as diabetes mellitus (Robinson & van Soeren, 2004). Hyperglycemia is currently seen as a pathological rather than a physiological response (Hirsch, 2002; Messoteen & Van den Berghe, 2003; Mizock, 2003). Recent studies have suggested that hyperglycemia, in critically ill patients is associated with various complications including poor wound healing, increased infection rates (McCowen et al., 2001; Van den Berghe et al., 2001), increased risk of congestive heart failure, cardiogenic shock, death after myocardial infarction and ischemic stroke (Hirsch, 2002; Mizock, 2003). There is mounting evidence that tighter control of BG in critically ill patients results in a decrease in both morbidity and mortality (Chittock et al., 2003; Van den Berghe et al., 2003).

As a result, the practice of how critical care physicians and registered nurses manage hyperglycemia in critically ill patients has begun to change. Elevated BG is no longer clinically acceptable. Recent studies suggest that in critically ill patients, maintaining BG levels within a "tight" range between 4.4 mmol/L and 6.1 mmol/L

(Chittock, et al., 2003; Vincent, Abraham, Annane, Bernard, Rivers & Van den Berge, 2002) in order to prevent the adverse short and long-term effects of elevated BG levels. Consequently, more frequent sampling and measurement of BG has begun to occur in critically ill patients.

In critical care units, it is imperative that the method of obtaining a blood sample to measure BG and the analytical instruments used to quantify levels be reliable and valid. Unquestionably, it is crucial to accurately monitor BG levels in critically ill patients and to identify when changes in BG levels have occurred. The registered nurse's ability to accurately determine BG, and to initiate, maintain or discontinue insulin infusions based on accurate sampling and measurement, is of tremendous importance in minimizing the overall mortality and morbidity of critically ill patients.

Purpose of the Study

The purpose of the study was to investigate the relationships between capillary and arterial blood glucose using three different blood glucose meters (BGMs); the Lifescan SureStepFlexx® (BGM #1), the Roche Accu-Chek Inform® (BGM #2) and the Abbott Freestyle® (BGM #3); and two POC BG analyzers, the YSI 2300 Stat Plus® (the reference instrument) and the Bayer Chiron 865® blood gas analyzer in a critically ill population.

Study Objectives

The specific objectives that were addressed included the following:

1. To determine if there are differences in BG values when measured by a capillary sample as compared to an arterial sample using the Lifescan SureStepFlexx® BGM.

2. To determine if there are differences in BG values measured by whole blood capillary samples using three different BGMs (BGM #1, #2, #3) compared with the YSI 2300 Stat Plus® glucose reference analyzer.
3. To determine if there are differences in BG values measured by whole blood arterial samples using three different BGMs (BGM #1, #2, #3) and the Chiron 865® blood gas analyzer as compared to the YSI® glucose reference analyzer.

Significance of the Study

Among critically ill patients, there needs to be ongoing commitment to evaluate new interventions shown to decrease mortality in randomized, controlled trials into clinical practice. Examples include limiting tidal volumes with a reduction in mortality (22%) among patients with acute lung injury and acute respiratory distress syndrome (Acute Respiratory Distress Syndrome Network, 2000), use of recombinant human activated protein C (antithrombotic/profibrinolytic/anti-inflammatory properties) among patients with severe sepsis with a reduction in mortality of 19% (Bernard et al., 2001) and, maintaining BG levels between 4.4-6.1mmol/L with a reduction in mortality of 32% (Van den Berghe et al., 2001). In order to obtain the benefit of tight glucose control among critically ill patients, it is clear that the method of obtaining a blood sample to measure BG levels and the analytical instrument used to quantify the sample be reliable and valid. Currently, there is significant variation in the types of blood sampling (capillary, arterial) as well as the specific BG analytical system used (BGM, BG reference analyzers) to determine consecutive patient BG values. This interchange of sample and analytical

techniques can lead to clinical misinterpretation and inappropriate interventions and, more importantly, place critically ill patients at risk for hypoglycemia or hyperglycemia.

Consistency across studies is important also. Comparative studies like this can help guide future analytical instrument and blood sampling protocol development. It can also support future direct comparisons across practice settings and multi-site studies. It is crucial that BG levels in critically ill patients be accurately monitored so that changes in BG be rapidly and accurately detected. In this manner, the morbidity and mortality of critically ill patients will be reduced.

Chapter 2 Literature Review

An extensive review of health-related databases, including CINAHL, MEDLINE, MD Consult, Web of Science and PubMed was completed to: determine current perspectives on BG monitoring; review BG sampling methods; and most importantly, determine whether or not any differences had been reported among blood sampling, analytical instruments, and BG values obtained in critically ill patients. The existence of key differences between sampling techniques and methods of BG measurement was of primary interest for this review. Key words used for this literature review included: blood glucose, blood glucose meters, blood glucose monitoring, critical care, critical care nursing, critically ill, glucose, glucometer, glucometry, intensive care unit, physiological monitoring, and point-of-care (POC).

Physiology of Blood Glucose

Circulating BG comes from dietary intake of carbohydrates, release of glucose from glycogen and the breakdown of noncarbohydrates (gluconeogenesis) (Urden, Stacy & Lough, 2002). Despite large fluctuations in the supply and demand of carbohydrates, the concentration of glucose in the blood is normally maintained within a narrow range (3.5-5.5mmol/L) by hormones that modulate glucose (Burtis & Ashwood, 2001). These hormones include insulin, which decreases BG, and the counterregulatory hormones (glucagons, epinephrine, cortisol and growth hormone) which increase BG concentrations (Burtis & Ashwood, 2001).

The pancreas, in addition to its digestive functions, secretes insulin and glucagon (Urden et al., 2002). Within the pancreas are the islets of Langerhans, which produce insulin within beta cells and glucagon within alpha cells (Marieb, 1989). Insulin is a

hypoglycemic hormone and glucagon is a hyperglycemic hormone (Marieb, 1989). Collectively these two hormones help regulate BG levels in the body (Figure 1).

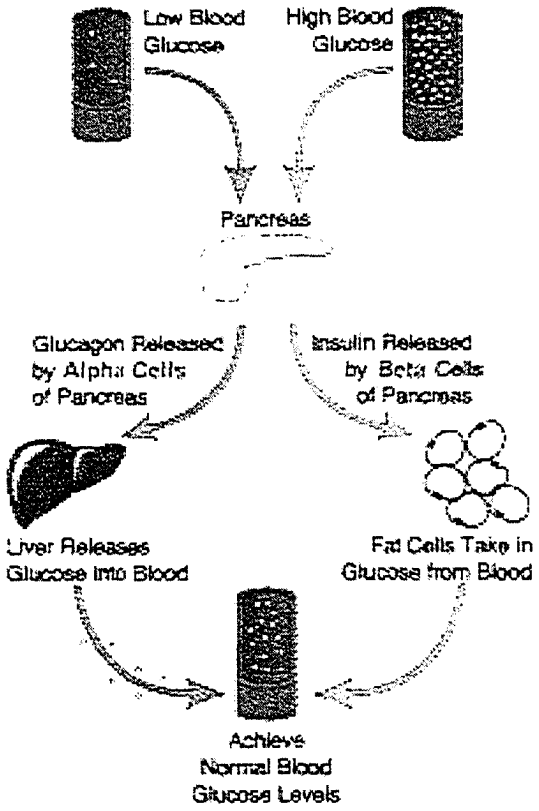


Figure 1. Physiology of Blood Glucose

Insulin is a small protein that lowers BG by enhancing membrane transport of glucose into cells (Marieb, 1989). Insulin is immediately released after a meal in response to the absorption of glucose into the blood and facilitates the storage of glucose as glycogen in the liver (Guyton & Hall, 2000). In addition, insulin is required for the storage of fats and proteins in the tissues (Guyton & Hall, 2000). When secreted into the blood, insulin circulates predominantly in an unbound form, has a plasma half-life that averages about 6 minutes, and is cleared from the circulation within ten to fifteen minutes (Guyton & Hall, 2000). Any rise in BG increases insulin secretion, which then increases

glucose transport into the liver, muscle and other cells in order to bring the BG concentration back to a normal range (Guyton & Hall, 2000).

Glycogen is a polysaccharide (formed from linked glucose units) and is stored primarily in skeletal muscle and liver cells. When BG falls and the glycogen stored in the liver is broken down into glucose, the secretion of insulin rapidly decreases (Ganong, 2001). Additionally, in response to decreased BG, glucagon is secreted by pancreatic alpha cells (Marieb,1989). Glucagon is catabolic, mobilizing stored glucose, fatty acids, and amino acids into the bloodstream (Robinson & van Soeren, 2004), thus increasing BG levels. In addition, the release of catecholamines (epinephrine and norepinephrine), cortisol and growth hormone also increase BG by stimulating hepatic glycogenolysis and gluconeogenesis, and simultaneously inhibiting peripheral insulin-mediated glucose tissue uptake (Ganong, 2001).

Insulin administration has been found to improve clinical outcomes in critically ill, hyperglycemic patients (Pittas, Siegel & Lau, 2004). In addition to lowering BG, insulin promotes muscle protein synthesis, inhibits lipolysis, has anti-inflammatory properties, decreases platelet aggregation and increases fibrinolysis (Chittock et al., 2003; Lewis et al., 2004). Insulin restores normal intracellular calcium levels, limits myocardial damage following myocardial infarction and prevents arrhythmias (DiNardo et al., 2004). Maintaining normoglycemia with an insulin infusion significantly reduces the risk of mortality in intensive care units (Van den Berge et al., 2003).

Alterations in Blood Glucose in Critical Illness

Hyperglycemia is most often evident shortly after admission to the critical care unit and may resolve as the underlying illness subsides (McCowen et al., 2001). Patients

with ongoing infection or injury may demonstrate persistent metabolic deregulation and protracted hyperglycemia (McCowen et al., 2001). In addition, medications commonly administered in intensive care units may exacerbate hyperglycemia, for example, epinephrine, norepinephrine, corticosteroids and immunosuppressants (DiNardo et al., 2004; Lewis et al., 2004). Medications formulated in fat emulsion, such as the commonly used sedative agent, propofol, increase BG levels significantly (Dinardo et al., 2004). Parenteral and enteral feeding of critically ill patients with dextrose containing solutions (Krinsley, 2003; Mizock, 2003) also can contribute to hyperglycemia.

Hyperglycemia in acute and prolonged critical illness results from a combination of increased gluconeogenesis and insulin resistance (Robinson & van Soeren, 2004). In addition, excessive counter-regulatory hormones (glucagon, growth hormone, catecholamines and glucocorticoid) and high circulating or tissue levels of cytokines (tumor necrosis factor, interleukins) produce hyperglycemia in critically ill patients. Although the resulting hyperglycemia was regarded as an adaptive response to ensure an adequate supply of glucose to the brain, red blood cells and injured tissues (Chittock et al., 2003), it is now regarded as harmful. Recent studies have correlated hyperglycemia on admission to critical care with increased susceptibility to infections and poorer outcomes following myocardial and cerebral ischemic events (Preiser et al., 2002). Elevated BG levels are associated with increased morbidity and mortality after burns, surgery, stroke, myocardial infarction and head trauma (Lewis et al., 2004; Mizock, 2003; Preiser et al., 2002; Van den Berghe, 2003).

Insulin Therapy for Critically Ill Patients

Hyperglycemia among critically ill patients should no longer be considered merely a surrogate marker of the severity of critical illness, but as a condition that must be aggressively controlled (Preiser et al., 2002). Hyperglycemia is a marker of poor clinical outcomes, including increased mortality in critically ill patients (DiNardo et al., 2004). Insulin requirements in individual patients vary widely, and are dependent on insulin production reserves, insulin sensitivity before and during critical illness, caloric intake in the ICU, and the severity and nature of the illness (Van den Berghe, 2003).

Attempts to control BG concentrations in critically ill patients have traditionally used "sliding scale" insulin to obtain "acceptable" (<12 mmol/L) glucose concentrations (Brown & Dodek, 2001; Mizock 2003). "Sliding scale" insulin protocols involve measuring BG levels, and the results determines how much subcutaneous (s.c.) insulin is to be administered. However, the s.c. protocols have been associated with poor glycemic control, due to the unpredictable absorption of s.c.insulin in critically ill patients with compromised peripheral circulation. Therefore, sliding scale insulin protocols are not recommended for critically ill patients (DiNardo et al., 2004; Mizock, 2003).

Recently, continuous intravenous (IV) insulin infusion has been recommended for the regulation of BG in critically ill patients (Mesotten & Van den Berghe, 2003; Mizock, 2003; Robinson & van Soeren, 2004). The critical care registered nurse measures BG levels every two to four hours and titrates the insulin infusion, by experience or with an insulin nomogram (Brown & Dodek, 2001; Goldberg et al., 2004; Mizock, 2003; Van den Berghe, 2003) to maintain the patients's BG within the specified range. Because of the quick onset of action and short half-life (approximately 6 minutes), IV insulin

infusions can be easily adjusted (DiNardo et al., 2004). The use of insulin infusions may be simplified with standardized protocols (insulin nomograms) for IV insulin infusion. However insulin nomograms do not take into account individual variation nor underlying pathology in critically ill patients. Sometimes, standardized dosages of insulin for a range of BG levels can cause unpredictable physiological responses due to the variation in the individual responses to insulin administration. Additionally, nomograms can be described as "cook-book" approaches and limit independent decision making.

The risk of hypoglycemia is a major concern whenever insulin is administered. Hypoglycemia has been defined as BG concentration of less than 3.5mmol/L (Brown & Dodek, 2001; Mizock, 2003). Consistent, accurate monitoring of BG in critical care is required to prevent hypoglycemia. The clinical symptoms of hypoglycemia, such as sweating, tachycardia, tremors, dizziness, blurred vision, and altered mental acuity, are often masked in critically ill patients, due to the underlying condition and therapeutic interventions, such as sedation and mechanical ventilation (Mesotten & Van den Berghe, 2003). The complications of hypoglycemia can be very severe, including cardiac arrhythmias and irreversible brain damage (Mesotten & Van den Berghe, 2003). Prevention of these complications is possible by careful, accurate monitoring of BG levels.

In a study of BG regulation in critically ill patients, Van den Berghe et al. (2001) renewed interest and rekindled debate by hypothesizing that hyperglycemia or relative insulin deficiency (or both) during critical illness may directly or indirectly confer a predisposition to complications such as severe infections, polyneuropathy,

multiple organ failure and death. A prospective, randomized, controlled trial was undertaken to determine whether normalization of BG with intensive insulin therapy reduced mortality and morbidity among critically ill patients. The study sample consisted of (n=1548) adult patients admitted to an ICU over a one year period who required mechanical ventilation. Of these patients, 63% (n=970) were patients admitted post cardiac surgery.

On admission to the critical care unit, subjects were randomly assigned to receive either conventional (n=783) or intensive insulin therapy. The conventional treatment group was given a continuous intravenous infusion of insulin [50 International Units (IU) of insulin in 50 mls of 0.9% normal saline] by an infusion pump, with insulin administered only if BG exceeded 11.9 mmol/L. Infusions were adjusted to maintain BG between 10.0 and 11.1 mmol/L. In the intensive treatment group, insulin infusion was started if BG exceeded 6.1mmol/L, and infusions were adjusted to maintain normoglycemia (between 4.4 to 6.1 mmol/L). Adjustments of the insulin infusions were based on measurements of whole-blood glucose in arterial blood, performed at one to four hour intervals with the use of a glucose analyzer (ABL700®, Radiometer Medical, Copenhagen). Insulin infusions were adjusted by critical care registered nurses and supervised by a physician who was involved in the study, but not with the clinical care of the patients.

Thirty-five patients (4.6%) in the intensive treatment group died, while in intensive care, as compared with sixty-three (8%) in the conventional treatment group. The median unbiased estimate of the reduction in mortality was 32% (adjusted 95% confidence interval 2% to 55%; $p<0.04$). The study was stopped early because of a

significantly increased death rate among those assigned to the conventional treatment group.

Van den Berge et al. (2001) reported that for the intensive treatment group, reductions in the number of red blood cell transfusions (50%), bloodstream infections (46%), episodes of acute renal failure requiring dialysis or hemofiltration (41%), critical illness polyneuropathies (44%) and overall in-hospital mortality (34%) had occurred. These results suggest that intensive insulin therapy provided to mechanically ventilated, critically ill adults improved their outcome.

This seminal study demonstrated the importance of maintaining "tight" BG control for critically ill patients, using frequent BG sampling and BG measurement. However, the majority of study subjects were admitted post-cardiac surgery. These patients had variable hematocrit readings due to their fluid requirements. Secondly, the average Acute Physiology and Chronic Health Evaluation (APACHE ll) score (a composite measurement of illness) was 9. In Canada, most critically ill patients have an average APACHE ll score of twenty or higher (Chittock et al., 2003), indicating a greater severity of illness. Thirdly, in this study, BG levels were not determined by a portable blood glucose meter (BGM), but by a more accurate blood gas analyzer based glucose meter. Most critical care units use portable BGMs for routine measurement of BG (Chaisson, 1995; Maser, Butler & DeCherney, 1994; Ray, Hamielec & Mastracci, 2001). Therefore, adjustments to the insulin infusions were based on BG values obtained from a nonstandard glucose device. Routinely, portable BGMs are kept at the patient's bedside to obtain BG values. Given that adoption of intensive insulin therapy to maintain BG levels between 4.4 and 6.1mmol/L may soon become the standard of care for critically ill

patients, this study has led to questions about existing methods for monitoring and management of BG. Most importantly, as part of the development and refinement of this new standard of care, differences in BG sampling techniques and analytical instruments must be addressed.

Blood Glucose Sampling Techniques and Analytical Instruments

Difficulty in obtaining accurate BG values in critically ill patients lies in part with the existence of many different practices and measurement systems. The different methods used to obtain the blood samples for BG monitoring from critically ill patients include obtaining blood from a capillary stick (capillary sample), from a venous puncture (venous sample), or from a catheter placed in an artery (arterial sample). Occasionally, a venous sample is sent to the hospital laboratory to obtain serum glucose, but this technique of glucose measurement has largely been replaced by the use of arterial blood sampling in critical care units. It is not practical or feasible to obtain venous samples to measure BG from critically ill patients, as the majority of these patients have indwelling arterial catheters.

Furthermore, there are several BG analysis instruments currently utilized within critical care units. The analytical instruments most frequently employed today include BGMs, "Point-of-Care" (POC) testing using blood gas analyzers, and finally serum glucose analyzers used in hospital central laboratories. While critical care registered nurses most often utilize bedside BGMs, studies among critically ill patients have often measured BG levels utilizing POC testing (Van den Berghe et al., 2001; Krinsley, 2004), and some studies have not identified how BG values were obtained (Van den Berghe, 2003; DiNardo, et al., 2004).

Bedside Glucose Meters

BGMs are small, portable devices developed for home monitoring of BG for diabetes care. Using a BGM, a drop of blood is placed on a test strip and then inserted into and analyzed by the meter (ECRI, Health Devices, 2004). An enzyme on the test strip, such as glucose oxidase or glucose dehydrogenase, reacts with the glucose present in the sample to determine the patient's BG value and the glucose result appears on a digital display screen 20-45 seconds later (ECRI, Health Devices, 2004). The use of BGMs has been shown to be an acceptable method in determining BG levels among ambulatory and hospital ward patients (Correll, Cehelsky, Mingora, Weber & Torio, 2000; Rheney & Kirk, 2000). Some BGMs have memories that permit the meter to store up to several hundred glucose readings that may be downloaded into a computer to facilitate quality control within hospitals (Burtis & Ashwood, 2001).

Critical care units have been among the first areas within hospitals to convert to using BGMs because of the need for immediate results on critically ill patients (Maser et al., 1994). To prevent large fluctuations in BG levels, frequent monitoring using bedside glucose testing (Carlson, 2001) is required.

However, a number of problems can affect BGM accuracy, including technical faults, user errors and variations in patient physiology (ECRI, Health Devices, 2004). Anecdotal evidence suggests that hypoxia among critically ill adults may interfere with accurate reading on BGMs, particularly those meters that rely on the glucose oxidase enzyme (Louie, Tang, Sutton, Lee & Kost, 2000). Low hematocrit levels (<25%) and high hematocrit levels (>50%) may cause overestimated or underestimated glucose measurements (Louie et al., 2000). BGMs are also sensitive to blood viscosity and water

content (Chen, Nichols, Duh & Hortin, 2003). Glucose in plasma is higher than glucose within red blood cells as water concentration is greater in plasma than in red blood cells (Fogh-Anderson & D'Orazio, 1998).

In critical care units, a BGM must be accurate and reliable when compared with the POC glucose instruments and the central laboratory BG instruments. An erroneous reading can lead to inappropriate adjustment of continuous insulin infusions, which may lead to hypoglycemia or hyperglycemia. The increasing demand for tighter control of BG in critically ill patients has led to many proposals for accuracy criteria for BGMs (Chen, et al., 2003).

Point-Of-Care Testing

It is essential to provide very rapid results when monitoring BG levels among critically ill patients. POC was developed to provide information much more rapidly than is currently available from central laboratories (St-Louis, 2000). POC provides analysis not only closer to the critically ill patient, but also facilitates a shorter time to result and enables a faster management response with improved clinical outcomes (St-Louis, 2000). The goal of POC is to provide rapid (<5 minutes) test results that are valid, reliable and precise (Burtis & Ashwood, 2001). An indispensable element of everyday clinical routine (Jahn & Van Aken, 2003), POC is widely available in the critical care setting (Lewis et al., 2004). The advantage of using POC depends upon acceptable performance of the analytical instruments in comparison with standard BG reference instruments.

Direct-Reading Glucose Biosensors

Direct biosensors measure BG levels without prior dilution of the sample and these glucose biosensors are used in modern blood gas/electrolyte/metabolite analyzers

(Fogh-Anderson & D'Orazio, 1998). These direct reading biosensors in blood gas analyzers measure BG levels without prior dilution of the sample. Direct reading glucose biosensors measure the molality of glucose (the amount of glucose per kilogram of water), and do not produce different results for blood and corresponding plasma levels (Fogh-Anderson & D'Orazio, 1998). As a result, whole BG results are provided as opposed to glucose levels in plasma. Two examples of direct-reading glucose biosensors are the YSI 2300 Stat Plus® (Yellow Springs Instrument) BG reference instrument and the Bayer Chiron 865® blood gas analyzer. These devices have been reported to provide reliability, precision and accuracy for clinical use (Burtis & Aswood, 2001).

In 1987, the American Diabetes Association recommended that BG values using POC analytical instruments should fall within ±15% of laboratory reference values (Yuoh, Elghetany, Peterson, Mohammad & Okorodudu, 2001). It was also suggested that future POC analytical instruments should achieve a total variability of less than 10% as compared to standard BG analytical instruments (Voss, Bina, McNeil, Johnson & Cembrowski, 1996). In 1996, the American Diabetes Association recommended a goal for future glucose meters to be within ±5% of laboratory values. To date, these guidelines have not been met (Yuoh et al., 2001).

Within critical care, the various types of instruments detect and report fundamentally different glucose quantities. Although whole blood results from direct reading glucose biosensors can be reported as the equivalent concentration of glucose in plasma (by multiplying the whole blood result by 1.12 to approximate the plasma glucose) (Carol Shalapay, personal communication, September 7, 2004), few studies take the necessary time to convey this information. Moreover, the terms BG and plasma

glucose are frequently used interchangeably in the literature (Fogh-Anderson & D'Orazio, 1998), creating unnecessary confusion in the interpretation of study results. As a result, only a few, fragmented pieces of literature exist, and they do not completely address BG sampling and measurement in critically ill patients.

Newman (1988) identified two problems that needed to be addressed with the use of BGMs in critically ill patients. These included: (1) finding a monitoring system that has a minimum of technique variations; and (2) establishing the reliability and accuracy of a BGM in relation to the hospital's own laboratory BG system. The first part of the study compared three BGMs: (1) the Accu-Chek® glucometer (Boehringer Mannheim, Indianapolis); (2) the Glucometer® (Miles Inc., Diagnostics Division, Elkhart, Ind.); and (3) the Glucoscan 2000® (Lifescan, Inc., Mountain View, California) to the hospital laboratory. For the first part of the study, blood samples were obtained from fifty hospital staff members and analyzed by each BGM. Results from all three BGMs were highly correlated with the results from the hospital laboratory ($r=0.98$; $r=0.94$; $r=0.96$; $p<0.01$). There were no significant differences ($F=0.02$; $df=3,196$; $p>0.99$) in BG tested using the three BGMs and the hospital laboratory.

In the second part of the study, one BGM (Glucoscan 2000®) was compared to the results obtained from hospital laboratory testing. The Glucoscan 2000® was chosen because it had a slightly higher correlation with the hospital laboratory and this BGM and its reagent strips were less expensive. Over a three months period, venous BG samples ($n=110$) were taken from patients with multisystem failure admitted to a general ICU ($n=41$). The mean age of the male ($n=30$) and female ($n=11$) patients was 68 years. BG values ranged from 1.83 mmol/L to 21.43 mmol/L. The laboratory mean value for all BG

was 9.22 mmol/L (SD=3.73 mmol/L). The Glucoscan 2000® mean was 9.23 mmol/L (SD=3.43 mmol/L). There was no significant difference found in the venous BG measured by BGM or hospital laboratory. An analysis of completion time with the first 50 BG tests revealed Glucoscan 2000® had a mean completion time of 2.4 minutes, while the laboratory had a mean time of 2.6 hours routinely and 0.5 hours in "stat" conditions. The author concluded that the high correlation (r=0.93) was evidence of that the Glucoscan provided the nursing staff with an accurate BG monitoring system. Newman (1988) emphasized the importance of quality control for BGMs to ensure both accuracy and reliability of these instruments.

Newman (1988) did not include information how the hospital staff were selected, the type of blood sampling done, or pertinent health conditions within the staff that may have affected test results. In the second part of this study, the use of venous blood for sampling among critically ill patients, the small numbers of patients included, and the fact that all the patients were on TPN with varying concentrations of dextrose can be identified as limitations of this study. In addition, indwelling arterial catheters are commonly used to obtain blood samples and for continuous blood pressure measurements among critically ill patients. Thus, venous blood sampling is rarely done in critical care units.

Maser, Butler and DeCherney (1994) examined the accuracy of BGMs using arterial blood samples to measure BG levels. Fifty consecutive patients admitted to the cardiovascular ICU after open-heart surgery were included in their study. On admission, BG samples (arterial and capillary) were analyzed by a BGM (Accu-Chek 11®, Boehringer-Mannheim, Indianapolis, IN). An additional arterial sample was sent to

hospital laboratory in a tube designed to separate the serum (in an effort to reduce possible metabolism of glucose by the cellular content of the sample). After centrifugation, the sample was evaluated by the Astra® or Synchron CX7® (Beckman Instruments, Brea, CA), using an oxygen electrode oxidation method. Sample means were analyzed to examine potential differences in arterial BG values from whole blood versus serum samples, and differences between capillary whole blood and arterial serum. In addition, the researchers used regression techniques to determine if external factors (body temperature, systemic vascular resistance, coronary bypass times) influenced the results.

These investigators found that arterial whole BG samples that were analyzed by the Accu-Chek ll® BGM were significantly higher (mean difference was 1.7 mmol/L; SEM±0.67) when compared to arterial serum glucose samples that were analyzed in the hospital laboratory ($p<0.001$). This mean difference was reduced to 0.6 mmol/L (SEM±0.60) when the arterial whole BG values >11.1mmol/L were reduced by 10% for a hematocrit of <35%. Mean capillary glucose analyzed by the BGM was significantly lower (0.5 mmol/L; SEM±0.67) than mean arterial serum values analyzed by the hospital laboratory ($p<0.05$). When capillary glucose values were corrected for a low hematocrit, the mean difference between mean arterial serum values and capillary corrected whole blood values increased to1.2 mmol/L (SEM±0.60). Therefore a single patient arterial and capillary BG sample could provide different results depending upon the glucose analyzer. Arterial whole blood samples analyzed by the bedside BGM yielded the highest glucose result as compared to those analyzed as arterial serum in the hospital laboratory. Capillary samples tested using the BGM yielded the lowest BG values as compared to

arterial serum samples analyzed in the hospital laboratory. Potentially, interventions to maintain normal BG would be altered depending upon the type of blood sample and the BG analyzer used.

This study was limited by the small sample, the use of a convenience sample, and a single cohort of postoperative open-heart surgical patients. As such, the study results might not be generalizable to other critically ill patient populations due to the variability of the hematocrit, the pO_2, the pCO_2 and the pH among postoperative open-heart surgical patients.

Accuracy of capillary glucose values in patients with shock was evaluated in a study by Sylvain, Pokorny, English, Benson, Whitley, Ferenczy, et al. (1995). These researchers tested the following two research hypotheses: (1) No differences would be observed in the mean glucose values obtained by the fingerstick (capillary) method, venous specimens analyzed using a BGM, and venous samples analyzed in the hospital laboratory; (2) There would be no differences in the treatments and diagnoses which patients receive as a result of three glucose measurements. A convenience sample (n=38; M/F=22/16) of patients was selected from medical and surgical trauma ICUs and the Emergency department of a large tertiary care referral center in the United States. Subjects were: 18 years of age and older, had a hematocrit between 25% and 60%, had a physician's order for fingerstick and laboratory blood glucose measurement and showed evidence of inadequate tissue perfusion (defined as decreased capillary blood flow resulting in decreased nutrition and respiration at the cellular level). Signs of inadequate tissue pressure were: Systolic BP $\leq$ 80 mmHg; sinus tachycardia; temperature <36.4°C rectally; acute confusion; urine output <30 mls/hour; pale, dusky skin; cool, clammy skin.

Subjects ranged in age from 26 to 82 years with a mean of 66.48 years; ten (26.3%) had a history of diabetes, and a total of twenty seven (71.1%) were on vasoactive medications.

A venous whole blood sample was obtained and tested using a One Touch II® BGM (Lifescan, Inc. Milpitas, Calif), while the remainder of the sample was sent to the hospital laboratory for analysis (Astra®; Beckman Corp, Brea, Calif). Within four minutes of obtaining the venous sample, a capillary sample was obtained and tested on the same BGM. Mean capillary BG value (n=38) was 9.85 mmol/L (SD=6.27); mean venous BG value (n=35) was 11.58 mmol/L (SD=6.52); and the mean for venous samples sent to the hospital laboratory (n=37) was 14.12 mmol/L (SD=16.10). The authors suggested a 20% variance is acceptable, due to the differences between venous whole blood versus serum analyses, and capillary versus venous blood sampling. The results indicated that the mean hospital laboratory venous glucose levels were significantly higher from the sampling ($p<0.004$). Of the capillary BG values, 31.6% were outside a 20% variance. There was no significant difference between the mean hospital laboratory venous glucose and the mean BGM venous glucose.

Additionally, Sylvain et al. (1995) found that using the values from capillary samples, all the study subjects would have received a smaller dose of insulin (using sliding scale insulin), than if insulin doses had been based on venous hospital laboratory values. Thirty-two percent of the subjects would have received an incorrect insulin dose. The researchers recommend insulin doses should be given based on either venous BGM results or hospital laboratory venous glucose results rather than capillary blood sampling with inadequate tissue perfusion.

The purpose of this study was to determine the accuracy of capillary BG sampling in critically ill patients with shock. The researchers identified no clear definition of shock, so they proposed seven signs to indicate a shock state and the study subjects were required to have three of more of these signs. Due to the very general nature of the signs identified by these researchers, it is very likely some study subjects had inadequate tissue perfusion due to other pathophysiological changes (inadequate blood flow due to inadequate cardiac output) or possibly due to medications (vasopressors). Additionally, these researches used only venous and capillary blood samples; as a standard of care, most critically ill patients have indwelling arterial catheters from where blood samples are obtained. Venous and arterial BG are not the same and cannot be used interchangeably.

Chaisson (1995) compared arterial and capillary BG to test whether or not capillary BG sampling was appropriate or necessary when critically ill patients had an existing arterial line. A correlational study design used a convenience sample (n=75) of post-cardiac surgical patients. The subjects ranged in age from forty to eighty years old. There were three glucose values obtained from each subject. Upon admission to the cardiothoracic ICU, an arterial blood sample was obtained via an arterial line, and from this sample, blood was sent to the hospital laboratory and a drop of the remaining arterial blood was tested using the Accu-Chek III®(Boehringer-Mannheim, Indianapolis, IN) BGM. The arterial BG sample was analyzed within ten minutes in the hospital laboratory, which used a hexokinase method of glucose determination. The third glucose value was obtained by fingerstick capillary method and tested using a BGM. This BGM uses an oxidase-peroxidase reaction to measure glucose. Error tolerance criteria for BGMs is

within ±0.83mmol/L of the reference measurement for glucose levels ≤5.55 mmol/L and within ±15% of the reference measurement for glucose levels >5.55 mmol/L; 95% of glucose meter measurements should fall within these error tolerances (Louie et al., 2000). In this study a difference of more than 15% in either the capillary or arterial value using the BGM (as compared to the hospital laboratory value) was considered significant. Of the 75 capillary values, 34% (n=26) fell outside of the 15% range and of the arterial values, 17% (n=13) fell out of the 15% range.

On the basis of these findings, Chiasson (1995) recommended the use of arterial blood to assess glucose levels with a BGM, specifically the Accu-Chek lll®. Changes to nursing practice, such as using arterial blood samples for sampling of BG, can benefit patients as there is less discomfort and less interruption of patient sleep and activities as compared to using capillary samples. The author concluded more time would be available for nurses to provide direct patient care by testing arterial blood with a BGM rather than capillary samples.

Only one type of BGM was used in this study, limiting the generalizability of the findings. Chiasson (1995) identified the possibility that the surgical patients in the study could be considered anemic (hematocrit <35%) due to large volumes of fluids infused in the operating room. The low hematocrit of these surgical patients may affect BG values obtained by BGMs.

The clinical performance of two different BGMs, the SureStepPro® (LifeScan, Inc, Calif) and the Precision G® (Medisense, Abbott Laboratory Diagnostics, Inc, Bedford, Mass) were assessed in a study by Louie, Tang, Sutton, Lee & Kost (2000). Heparinized arterial blood samples were obtained from critically ill patients (n=247) in

the operating room, emergency department or critical care unit at major urban medical center. The first patient blood samples (n=141) were used to study the effects of two critical care variables, the partial pressure of oxygen (pO_2) and hematocrit on the performance of the BGMs. The remainder of the samples (n=106) were used to compare two different test strip lots used with BGMs. The primary reference instrument used for plasma glucose measurements was the YSI 2700® glucose analyzer (Yellow Springs Instruments, Inc, Yellow Springs, Ohio). The secondary reference instrument used for plasma glucose measurements was the Synchron CX-7® (Beckman Coulter, Inc, Brea, CA), a clinical laboratory analyzer. The researchers postulated that 95% of the BGM measurements should fall within a range of 15% when compared to standard laboratory measures (error tolerance criteria). Louie et al., (2000) found both BGMs displayed a relatively high clinical accuracy, as compared to the primary reference instruments, as 91% to 95% of Precision G® and 98% to 100% of SureStepPro® measurements satisfied the error tolerance criteria. However, it was observed that the effects of hematocrit and pO_2 could alter glucose measurements in critically ill patients. Both BGMs performed best when the hematocrit was between 30% and 40% and pO_2<150 mmHg. Hematocrit <25% can overestimate blood glucose levels and hematocrit >60% can underestimate BG levels. Blood pO_2 levels exceeding 150 mmHg may result in underestimated glucose measurement. Louie et al. (2000) suggested standardization of materials and methods is needed before comparing glucose measurements performed by BGMs with other BG analyzers. They concluded that health care providers must be aware of the potential differences between the reference and comparison methods in BGM evaluation and clinical decision-making.

Assessing the accuracy of the One Touch® BGM (LifeScan, Johnson & Johnson) in a Canadian critical care unit was the focus of a pilot study by Ray, Hamielec and Mastracci (2001). In this study, critically ill adults (n=10; aged 48-75 years) had pairs of arterial blood samples obtained within one minute of each other by the attending ICU nurse. One sample was tested using a BGM, while the other sample was immediately sent to the hospital laboratory in a plasma separation tube for analysis. Sequential samples were taken at intervals of at least 12 hours of one another, with a total of 105 paired arterial glucose values obtained. Mean laboratory and BGM glucose levels were 10.3 mmol/L (SD=3.2) and 10.3 mmol/L (SD=3.1), respectively. There was a strong and significant positive correlation between the laboratory and BGM measurements concentration (intraclass correlation coefficient=0.86; $p<0.0001$). The overall mean laboratory-BGM difference was -0.04 mmol/L using 95% confidence limits (-2.3 mmol/L and 2.2 mmol/L). The authors reported that bedside glucose testing of arterial whole blood samples may be an accurate alternative to laboratory plasma glucose measurement among critically ill patients, within approximately 2.3 mmol/L of certainty.

However, only ten patients participated in this study; none had hematocrit concentration assessed, eight patients had diabetes, six had Type 2 diabetes, one had Type 1 diabetes and one had corticosteroid-induced diabetes. Three subjects were identified as being in shock (septic shock in one patient, the type of shock was not identified in the other two patients). In addition, arterial whole BG results obtained by a BGM were compared to plasma results using a plasma glucose analyzer, so two different types of blood samples were used. It is not clinically acceptable that a BGM may

overestimate or underestimate a BG concentration by approximately 2.3 mmol/L, this discrepancy could cause inappropriate interventions in managing patients BG levels.

Summary

Many different practices exist in critical care units for obtaining and testing BG samples. A standard has not been established to determine the most accurate way to monitor BG in critically ill patients. Little consensus exists in the literature to advocate one type of sampling (capillary, venous or arterial) over another. Similarly, the type of analytical instrument that provides the most accurate and reliable determination of BG in critically ill patients has not been determined. Multiple sampling techniques and differences between BG analytical instruments enhance the risk for clinical misinterpretation and inappropriate interventions; and more importantly, they place critical care patients at unnecessary risk for hypoglycemia or hyperglycemia.

Among critically ill patients, the use of intensive insulin therapy requires extensive nursing efforts, including frequent bedside capillary and arterial glucose monitoring (Brown & Dodek, 2001; Goldberg et al., 2004). Additionally, this therapy requires the initiation, maintenance and termination of IV insulin drips by critical care registered nurses. Even after normoglycemia has been achieved, the need for monitoring BG levels and adjustment of insulin dose remains (Van den Berghe, 2003), as signs and symptoms of hypoglycemia may be masked in critically ill patients (Mizock, 2003).

A review of contemporary health care literature has identified the importance of maintaining normal BG among critically ill patients to decrease morbidity and mortality. However, the variation in BG sampling techniques and BG analytical instruments presents confusing and at times, conflicting results. Without reliable and valid BG

testing, strategies to maintain normal BG levels are seriously limited and increase the risk of either hyperglycemia or hypoglycemia in critically ill patients.

Chapter 3 Methods

Study Design

A prospective comparative within-subjects repeated measures study design was used to compare: (1) capillary BG readings analyzed by three different BGMs and the YSI® BG analyzer; (2) arterial BG readings analyzed by three different BGMs, the Chiron 865® blood gas analyzer and the YSI 2300 Stat Plus® BG analyzer.

Study Subjects

Subjects (n=60) were recruited from the GSICU (general systems intensive care unit) a large urban tertiary care hospital. GSICU is a 30 bed combined medical/surgical adult intensive care unit. There are approximately 108 to 130 admissions per month to GSICU, and the average length of stay per patient is 5 to 7 days (Dr. Chin, personal communication, December 23, 2004). It is usual to have about 75% of all patients in this ICU on blood glucose monitoring and most of these patients require insulin infusions to maintain normoglycemia. An *a priori* sample size calculation was not possible because there was no information on the variances of the measures to be used. However, with a within-subjects repeated measures design, a sample of n=60 subjects should be adequate for addressing the study questions.

The patient inclusion criteria included: a physician's order for BG monitoring and presence of an arterial indwelling catheter. Patients were excluded from participation in this study if they were less than 18 years of age or TPN therapy. The researcher determined if a patient met the inclusion/exclusion criteria of the study. For patients meeting these criteria, the researcher explained the purpose of the study and what was required of participants to the patient, significant other, or a family member, answered

any questions related to study participation and then obtained informed consent (Appendix A) and provided an information letter (Appendix B).

Each study participant had a capillary and an arterial BG drawn on three separate collection times in one day. BG samples were collected in the morning (T_1), at noon (T_2) and in the afternoon (T_3). No subject participated in the study more than once.

Data Collection

Patient Characteristics

Data collected on entry to the study included the patient's: age, sex, admission diagnosis, comorbidities, APACHE II score, medications, hematocrit, blood pressure, pO_2, pCO_2 and pH. This data was obtained from the patient's chart. The patient's capillary and arterial blood glucose levels were measured and recorded by the researcher using the SureStepFlexx® (BGM #1) (Appendix C).

It was not possible to obtain all the capillary blood required to test on the three BGMs along with the YSI 2300 Stat Plus®, (on three separate occasions) from all of these subjects. Therefore, 13 subjects (22%) were excluded, because of impaired finger capillary perfusion and/ or significant edema. Similarly, on two separate occasions, indwelling arterial catheters were removed before arterial BG sampling was completed. Therefore, an additional two subjects were excluded. Data analysis was completed from the information obtained from the remaining 45 study subjects (75%), who participated in the entire study.

Instrument Calibration

Before the data collection was done, within-day (intra-assay) precision testing was completed on each BGM using high and low control glucose solutions and test strips

provided by each of the manufacturers for their respective meters. Within-day precision was evaluated using the control glucose solutions and test strips six times each day, for six days, using high and low control glucose solutions for BGMs # 1, # 2 and # 3. For between-day (inter-assay) precision, on each day of data collection, all BGMs were tested with high and low control glucose solution (normal glucose solution with BGM # 3 only) and test strips provided by the manufacturers. Within-day and between-day precision testing is described using the coefficient of variation (CV) (defined as the standard deviation/mean times 100%).

Results from an accurate BGM should demonstrate linear behavior comparable with validated comparative methods and a slope close to 1.0 (Chen, Nichols, Duh & Hortin, 2003). Method accuracy of each BGM should be evaluated using ordinary least-squares linear regression of meter glucose results against each of the comparative methods (Chen, Nichols, Duh & Hortin, 2003).

Error tolerance criteria are also used to evaluate the accuracy of BGM's. For BGMs, the error tolerance criteria should be within ±0.83 mmol/L of the reference measurement for glucose levels ≤5.55 mmol/L and within ±15% of the reference measurement for glucose levels >5.55 mmol/L. It is expected that at least 95% of glucose meter measurements (Louie et al., 2000) should fall within these error tolerances. This means that 95% of all BG measurements below 5.55 mmol/L should be within the reference range ±0.83 mmol/L and glucose values above 5.55 mmol/L must be within the reference range ±15%. According to the American Diabetes Association (1996) error tolerance criteria should be within ±5% mmol/L of the reference measurement for glucose levels ≤5.55 mmol/L and within ±5% of the reference measurement for glucose

levels >5.55 mmol/L (Chen, Nichols, Duh & Hortin, 2003). In 2003, the International Organization for Standardization (ISO) guidelines for acceptable performance criteria for BGMs recommend that for glucose concentrations <4.2 mmol/L, the percentage of results within ±0.28 mmol/L, ±0.56 mmol/L and ±0.83 mmol/L of the reference values be reported; and for glucose concentrations ≥4.2 mmol/L, results be expressed as the percentage of values falling within the following intervals: ±5%, ±10%, ±15% and ±20% of the reference instrument.

The BGM used to monitor BG at the critically ill patient's bedside was the LifeScan SureStepFlexx (BGM #1), as this is the BGM currently used to test whole capillary and arterial blood samples within the critical care units in Capital Health. Calibration for this BGM is performed at the time of manufacture and quality control is done every 24 hours against standard high and low glucose solutions provided by the manufacturer (Sharon Froment, personal communication, February 7, 2005). BGM #1 uses a photometry test method, with glucose oxidase as the enzyme (Louie et al., 2000). In photometric reflectance instruments, such as BGM #1, the color intensity detected by the photometer is proportional to the glucose concentration in the sample on the test strip (Louie et al., 2000). According to the Lifescan Canada Ltd. product information (1998), a small drop of blood is applied to a SureStepPro® test strip and glucose oxidase on the test strip triggers the oxidation of glucose in the blood sample. Gluconic acid and hydrogen peroxide are produced as a result of this reaction. Peroxidase on the test strip then causes the hydrogen peroxide to react with dyes to produce a blue color in the presence of oxygen. The blue color is visible through the confirmation dot on the back of the test strip; the darker the blue, the higher the glucose level in the blood sample. BGM

#1 measures the color intensity of the confirmation dot. This analysis averages 30 seconds (LifeScan, product information, 1998).

Extremes in hematocrit can affect test results and, according to LifeScan product information, BGM #1 is accurate within a hematocrit range of 25% to 60% and, sample types can be arterial, venous, neonate or capillary. The LifeScan product information (1998) indicates the range of the SureStep Brand Meters to be 0 to 27.8 mmol/L, above this range the meters read HIGH.

The second BGM that was used to measure whole capillary and arterial BG is the Accu-Chek Inform® (Roche Diagnostics, Indianapolis, IN). The Accu-Chek Inform® (BGM #2) uses amperometric technology and glucose dehydrogenase as the enzyme to measure glucose concentrations. Glucose dehydrogenase causes the oxidation of glucose to gluconolactone, and the nicotinamide adenine dinucleotide phosphate (NADH) formed with this reaction is proportional to the glucose concentration in the sample (Burtis & Ashwood, 2001). Unlike glucose oxidase, oxygen is not involved in this reaction pathway; thus there is much less interference with different levels of oxygen in the blood (Burtis & Ashwood, 2001).

According to information obtained from Roche Diagnostics website (November 18, 2004) (www.roche.com) with the Accu-Chek BGMs, 95.4% of all blood glucose measurements below 5.55 mmol/L are within the laboratory reference range ±0.83 mmol/L and glucose values above 5.55 mmol/L are within the laboratory reference range of ±15%. Extremes in hematocrit can affect test results; BGM #2 is accurate within a hematocrit range of 20% to 60% and sample types can be arterial, venous, neonate or capillary. BGM #2 will determine BG values in the range of 0.6 to 33.3 mmol/L. Quality

control for BGM #2 is performed every 24 hours against standard high, normal and low glucose solutions provided by the manufacturer.

The third BGM that was used to measure whole capillary and arterial BG was the Abbott TheraSense Freestyle® (TheraSense, Inc, Alameda, California). According to the Therasense website (November 23, 2004) (www.therasesense.com), BGM #3 uses a coulometric electrochemical sensor, which measures all the glucose in a blood sample, permitting the use of a very small sample size (0.3 microliters). The Freestyle test strip automatically pulls a sufficient blood sample and a confirmation beep is heard when the sample is adequate. BG results are obtained within 15 seconds. The Freestyle test strip uses the glucose dehydrogenase enzyme and as this enzyme is oxygen-independent, the glucose value obtained is unaffected by blood pO_2. Additionally, other substances such as uric acid, aspirin and acetaminophen do not interfere with the BG value.

The YSI 2300 Stat Plus® was the primary reference instrument used in this study. It was developed in 1975 by Yellow Springs Instruments as a whole blood glucose analyzer and is used by healthcare companies to ensure accuracy of BGMs (December 23, 2004) (www.ysi.com). The YSI® is used as the standard for measurement of whole blood glucose and is frequently the primary reference instrument used when analyzing BGMs accuracy (Louie et al., 2000; Stork et al., 2005;). Many research groups working on other types of glucose sensors use YSI® readings as their reference method (Vesper et al. 2005).

According to Burtis & Ashwood (2001) the YSI® uses glucose oxidase placed between two membranes. When the blood sample is introduced, glucose diffuses through the first membrane and reacts with the glucose oxidase to produce hydrogen peroxide

(H_2O_2), which diffuses through the second smaller-pore membrane where it is oxidized. The current generated is directly proportional to the glucose concentration in the blood. Figure 2 was obtained from the YSI® Life Sciences website (November 23, 2004) (www.ysi.com).

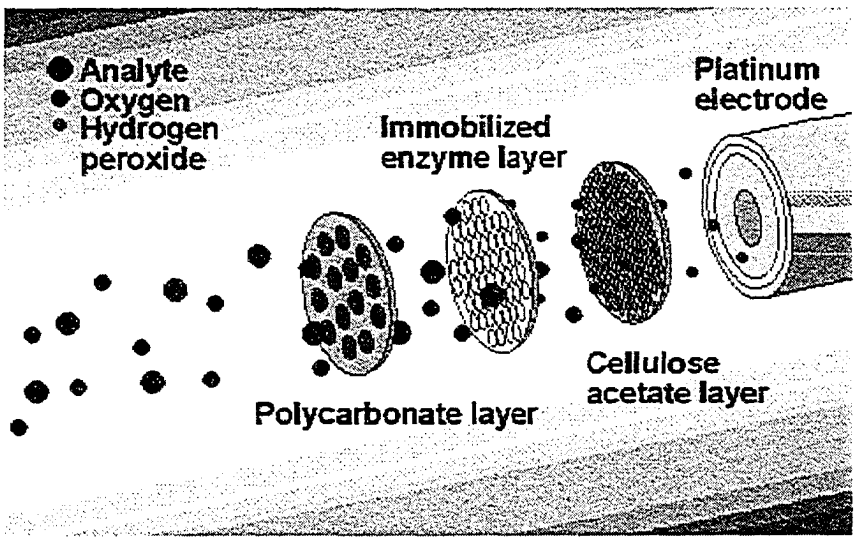


Figure 2. YSI® Blood Glucose Analyzer

The secondary reference BG instrument for this study was the Bayer Chiron 865® blood gas analyzer. This analyzer is used for the determination of pH, pCO_2, pO_2, glucose, hemoglobin, sodium, potassium, calcium, chloride and other calculated parameters. In critical care units, this analyzer is typically used for the measurement of arterial blood gases and may be used to determine levels of electrolytes and glucose from arterial samples. The Chiron 865® blood gas analyzer measures glucose with an electrochemical biosensor and the reported glucose concentration is free from the effects of interfering substances (Fogh-Anderson & D'Orazio, 1998). This analyzer measures glucose by an interaction with glucose oxidase on the surface of a measuring electrode that forms H_2O_2 and gluconic acid, which then causes the oxidation of H_2O_2 to oxygen.

The loss of electrons in the oxidation of H_2O_2 creates a current flow that is directly proportional to the glucose concentration in the sample (Carol Shalapay, personal communication, September 8, 2004). Daily calibration for this blood gas analyzer is carried out automatically according to a pre-programmed schedule.

Staff Involvement

Prior to initiating data collection, the medical and nursing staff were provided relevant study information. This included the study objectives and rationale and how the study was to be conducted (i.e., the inclusion criteria for patient selection, number and type of samples collected, data collections times, BG analyzers used, who collected and analyzed the BG samples, and recording of results). The researcher provided this information through inservices and provision of written materials. Staff had opportunity to ask questions. An information binder about the study was kept in the GSICU along with contact numbers for the researcher.

Collection of BG Samples

Certification in the use of BGMs by registered nurses is mandated by Laboratory Services as part of a quality control program. Certification consists of information being provided on BGMs, when and how to perform quality control tests, operating information, performing a patient test, care and maintenance of the meter, error messages, use of test strips and test strip holders, data management, precautions and infection control. The researcher was certified in the use of the BGMs #1, #2 and #3.

Testing was performed in the morning (0800-0900), at noon (1200-1300) and in the afternoon (1600-1700). BG levels are routinely monitored as 0800, 1200 and 1600 in GSICU. At the designated collection time, the researcher obtained both a capillary and

arterial sample, and then analyzed the samples using the bedside BGM #1. All arterial blood samples were obtained from an indwelling arterial catheter. The values obtained from these samples were recorded by the researcher (Appendix C). Within 5 minutes of obtaining the patient blood samples, the researcher took the remaining capillary and arterial samples and immediately gave them to the technologist in the POC lab in GSICU. These samples were analyzed within 20 minutes using BGMs #1, #2 and #3, the Chiron 865® blood gas analyzer (with arterial samples only) and the reference instrument, the YSI 2300 Stat Plus®. As the rate of glycolysis is approximately 7% per hour (Voss et al., 1996), samples tested by the technologist were done within 20 minutes of collection. The technologist was responsible for calibration of all these instruments. It was important to randomize the instrument sampling order to eliminate any a systematic confound caused by glycolysis (Voss et al., 1996); therefore, the technologist rotated the order of testing to achieve randomization using the different instruments. The BG values obtained from these samples were recorded by the technologist using the data collection sheet outlined in Appendix D. Therefore, three sets of data (morning, noon, afternoon) per patient were collected and recorded.

Data Analysis

Data was entered and analyzed using the Statistical Package for the Social Sciences (SPSS, Version 13) software package. Descriptive statistics (mean±SD, variance, range and percentages) were used to summarize demographic variables, and BG measurements obtained. A p-level of 0.05 was used to determine statistical significance. A three factor repeated (sample, instrument, time) measures ANOVA was used to

examine potential differences between arterial whole BG concentrations versus capillary whole BG concentrations measured by three BGMs and two POC analytical instruments.

To determine precision (within-day and between-day) of the instruments, the coefficient of variation (CV) (defined as the standard deviation/mean times 100%) was calculated (Voss et al., 1996). Intra-assay (within-day) CV was calculated for the results of the same glucose control solutions analyzed sequentially six times daily for 5 days for each of the BGMs, and the other two reference instruments. Inter-assay (between-day) precision was calculated for the results of the same glucose control solutions analyzed on each day of the study, for each of the BGMs, and the other two reference instruments.

To determine accuracy of the BGMs least squares linear regression (LSLR) was done to determine the line of identity, including the slope, y-intercept and the coefficient of determination. According to Voss et al. (1996), when the slope is 1.00, there is a perfect relationship between BGMs and the YSI 2300 Stat Plus®, and that is referred to as the line of identity. When the slope is not 1.00 (the regression line) the difference between the YSI 2300 Stat Plus® and BGM increases proportionately with increasing glucose concentrations. The y-intercept should equal 0, when the y-intercept does not equal 0 this implies a constant error exists across the range of glucose values (Voss et al. 1996). Therefore a positive or negative y-intercept indicates a corresponding positive or negative constant error. The coefficient of determination (R^2) is used to quantify the relationship between variables. The closer R^2 is to 1.00, the closer the relationship between the variables.

Systematic error (SE) which is also referred to as bias was calculated and reported. SE reflects the difference between the average of repeated measurements by a

BGM and the actual glucose concentration (Voss, 1996). It is calculated at clinically relevant concentrations of glucose. Thus, SE can be calculated using a low BG value to represent hypoglycemia, a normal BG value to represent normoglycemia and a high BG value to represent hyperglycemia, reflecting these BG values in critically ill patients. For this study 5.55 mmol/L was chosen to represent normoglycemic levels and 10 mmol/L was chosen to represent hyperglycemic levels (Dr. Chin, personal communication, September 3, 2005). SE was not calculated at a hypoglycemic level, because of the lack of hypoglycemic values found in this study. According to Voss et al. (1996), if the regression is perfect and the slope =1.00 and y-intercept=0.0, the SE will be 0. SE is calculated by multiplying the value of the slope by a clinically relevant concentration of glucose, adding the value of the y-intercept and then subtracting the chosen clinically relevant concentration of glucose (Voss, 1996). For example, if the slope and y-intercept were 0.8949 and 0.9849, respectively, at a concentration of 5.55 mmol/L, the SE is 7% and at a concentration of 10 mmol/L, the SE is 2%.

The standard error of the estimate ($S_{y/x}$) was calculated to determine the dispersion of data points around the regression line. If $S_{y/x}=0$ then every point lies exactly on the regression line (Voss et al. 1996), so an increase in the $S_{y/x}$ indicates an increased dispersion of data (imprecision) about the calculated regression line. Random error (RE) was calculated to determine imprecision of the BGMs. It is calculated by multiplying the $S_{y/x}$ by 1.96 (expressed as a percent) (George Cembrowski, personal communication, September 7, 2005). Total error (random + systematic error) was then estimated in order to examine the accuracy of the different BGMs and the Bayer Chiron

865® blood gas analyzer. The instrument yielding the least total error was assessed as being the most accurate.

Mountain plots (folded empirical cumulative distribution) were also used to graphically display the error distribution. The mountain peak represents the median of the BG values; the horizontal distance from 0 to the peak is the bias; the spread of points about the median represent variation. According to the NCCLS (2003) guidelines, mountain plots allow the observer to visualize central tendencies and variations and provides a visual comparison of BGM performance. Lastly, the International Standard Organization (ISO) (2003) performance criteria for BGMs was used to examine accuracy of BGM #1, BGM #2, BGM #3, the Bayer Chiron 865® blood gas analyzer when compared to the BG reference instrument, the YSI 2300 Stat Plus® analyzer.

Ethical Considerations

Support for the study was obtained from the Medical Director and Patient Care Manager of GSICU, University of Alberta Hospital. Ethical approval was obtained from the Health Research Ethics Board, University of Alberta. Once eligible patients were identified, the researcher approached the patient, significant other, or family to explain the study and its purpose, and informed consent was obtained (Appendix A). The researcher clearly indicated that participation was voluntary, and that the patient was free to withdraw from the study at any time with no impact on the quality of patient care. There were no individual benefits other than the advancement of knowledge related to the study. When the researcher was collecting blood samples, she was not involved in direct patient care. There was a small risk of bruising and tenderness at the puncture site, but this was minimized by gentle pressure following capillary sampling. Subject

confidentiality will be maintained by assigning code numbers and the data collected will remain secure in a locked filing cabinet for 7 years. If this study is accepted for publication, neither the institution nor the study subjects will be identified.

Chapter 4 Findings

Characteristics of the Study Subjects

A summary of the sample population characteristics is shown in Table 1. The mean age of subjects (n=45) was 57 years (SD±17.1), with age ranging between 19 and 88 years. The subjects were predominantly male (n=29). The male to female ratio was 29:16. All subjects were patients in the GSICU during the study. The primary diagnosis (n=21, 47%) was respiratory failure. Among the remaining patients, 11% were diagnosed with trauma, 9% with liver failure, 7% with sepsis/septic shock, 7% post surgery, and 4% with drug/alcohol overdose. The remaining diagnoses (15%) included meningitis, decreased level of consciousness, diabetic ketoacidosis, stroke, gastrointestinal bleed, multi-organ disease and Chronic Obstructive Pulmonary Disease. Eighty-four percent of the patients were intubated and receiving mechanical ventilation support. Fifty-one percent (n=23) of these patients were receiving continuous enteral tube feeds. The mean APACHE II score (a composite measurement of severity of illness where higher scores represent greater severity of illness) was 20 (SD±6.7), with scores ranging from six to thirty-six (maximum score=63).

Mean temperature of study subjects was 36.7°C with a range of 35°C to 39.3°C. Mean arterial blood pressure (MAP) was 91 mmHg with a range of 58 mmHg to 144 mmHg. Hematocrit ranged from 21% to 51% (normal: 40% to 50%), with a mean of 31% (SD±6.38). From arterial blood gas analysis, mean pH was 7.42 (normal: 7.35 to 7.45) and ranged from 7.25 to 7.55. Mean pO_2 was 84% (normal: 80% to 100%) with a range of 51% to 150%, the mean pCO_2 was 43% (normal: 35% to 45%) with a range of 16% to 79%.

Of the 45 subjects, 20% had a comorbid diagnosis of diabetes mellitus identified in their medical record. In this particular GSICU, all patients are targeted to maintain BG between 4.5 mmol/L and 8 mmol/L, and standard practice is to initiate continuous intravenous Novolin Toronto insulin infusions to maintain BG levels between the identified values. During the study period, 47% of subjects were on continuous insulin infusions, 9% were on either norepinephrine or vasopressin continuous infusions or both to support their blood pressure and three subjects (7%) were on dobutrex continuous infusions in an attempt to improve cardiac contractility.

Precision Testing of the Analytical Instruments

For each of the BGMs and the YSI 2300 Stat Plus® within-day and between- day precision studies were completed. The results of these precision studies are found in Table 2. Using the low and high glucose control solutions provided by the respective manufacturers, the between-day coefficient of variation (CV) ranged from 0.7% to 8% and the within-day testing CV ranged from 1% to 7%. BGM #2 and BGM #3 exceeded the manufacturers recommended CVs for both within-day and between-day precision studies. According to Burnett (1975) a meaningful measure of the precision of a quantitative method must include the inherent precision of the measurement technique along with the outlier frequency. The outliers are identified and segregated. Therefore re-analysis was completed by removing two out of a total of thirty-eight of the BG values that were identified outliers (Burnett, 1975). This re-analysis obtained CVs <5% for both BGM #2 and #3 (Table 3).

Measurement of BG Results: A Comparison between Capillary Samples Versus Arterial Samples Using Lifescan SureStepFlexx® BGM

Table 4 summarizes the BG values (mean ±SDs) of capillary and arterial samples as measured by BGM #1 and BGM #1POC. For BGM #1, the mean arterial BG values (in mmol/L) at T_1, T_2 and T_3 were (7.12±1.77), (7.16±1.66), and (6.97±1.56) respectively. Mean capillary BG tested at the same times were (7.18±1.73), (7.21±1.68), and (7.02±1.73). The overall mean for arterial BG was 7.08 mmol/L and for capillary BG was 7.14 mmol/L.

In contrast, mean arterial BG values obtained with BGM #1POC at T_1, T_2, and T_3 revealed a mean of (7.06±1.74), (7.09±1.47), and (6.96±1.64) mmol/L respectively. Mean capillary BG tested with BGM #1POC at the same sampling times were (7.42±1.84), (7.36±1.68), and (7.33±1.77). The overall mean for arterial BG was 7.04 mmol/L and for capillary BG was 7.37 mmol/L.

To examine the effects of time of sample collection and the type of sample, a 3 × 2 factor (time × sample) repeated measures analysis of variance (ANOVA) was completed. For BGM #1, there were no significant differences in mean BG values between capillary versus arterial samples (F=.88; df =1,44; p=0.35), among the test-times (F=.52; df=1,44; p=0.64) and no significant interaction effect between sample and test-time (F=.01; df=1,44; p=0.93)

However, with BGM #1POC, there was a significant difference found between capillary and arterial BG values (F=41.05; df=1,44; p=0.00). An inspection of the mean capillary and arterial BG levels at T_1, T_2 and T_3 showed that capillary levels were consistently higher than those obtained from arterial sampling (Table 4). There were no

significant differences in BG values across testing times (F=.24; df=2,88; p=0.79). The interaction between sample type and test-time was nonsignificant (F=.49, df=8,352; p=0.86).

Least squares linear regression (LSLR) was used to determine the slope and y-intercept of BGM #1 and BGM #1 POC when compared with the YSI 2300 Stat Plus®. According to Voss et al. (1996) when the slope is 1.00, there is a perfect relationship between BGMs and the YSI 2300 Stat Plus® (line of identity), and the y-intercept should equal 0. The coefficient of determination (R^2) was used to quantify the relationship between variables (BG instrument as compared to YSI 2300 Stat Plus®). The closer R^2 is to 1.00, the more similar the variables are to each other.

Figures 3 and 4 provide a visual representation of the slope and y-intercept of BGM #1 and BGM #1 POC. Figure 1 shows the line of identity and the regression line for capillary BG compared with the arterial BG using BGM #1, and the resulting regression equation is $y=0.91x + 0.6$ with $R^2=0.87$. Figure 2 shows the line of identity and the regression line for capillary BG compared with arterial BG using BGM #1POC. The regression equation is $y=0.88x + 0.5$ with $R^2=0.91$. The line of identity represents a perfect relationship between the BGM and the reference instrument, the regression line represents the actual relationship between the BGM and the reference instrument.

The standard error of the estimate ($S_{y/x}$) reflects the random error of the data points around the original data. If $S_{y/x}=0$ then every point lies exactly on the regression line, so an increase in the $S_{y/x}$ indicates an increased dispersion of data (imprecision) about the calculated regression line (Voss et al., 1996). For BGM #1 at bedside using

capillary versus arterial BG samples the $S_{y/x}$ was 0.61, with BGM #1 in POC lab the $S_{y/x}$ was 0.53.

Systematic error (SE) which also is referred to as bias was calculated. According to Voss et al. (1996) if the regression is perfect and the slope =1.00 and y-intercept=0.0, the SE will be 0. Table 6 displays the SE using 5.55 mmol/L as the critical value and Table 7 displays the SE using 10 mmol/L as the critical value.

Mountain plots (folded empirical cumulative distribution) were also used to graphically display the error distribution. These plots depict the magnitude and distribution of errors in BG measurement. The *x* axis of each of the mountain plots represents the percentage deviation of each BG value obtained from the BGMs compared with the YSI 2300 Stat Plus®. The peak represents the median difference. If the BG measurement instrument and reference instrument are unbiased, the mountain will be centered over zero. Long tails in the plot reflect large random differences. The mountain base can be measured at the ± 2.5 percentile limit, representing the inner 95% of the population. It is important that the base not exceed ± 20%, as that is the maximum allowable error for BG >4.2 mmol/L (ISO, 2003).

The mountain plot depicted in Figure 5 shows the percentage difference of the capillary BG values obtained from BGM #1 and BGM #1POC compared with the YSI 2300 Stat Plus®. The median of BGM #1POC (8%) exceeds that of BGM #1 (3%). Therefore, BGM #1POC capillary BG values on average will be 5% higher than BGM #1. The dispersion of the error of BGM #1POC is less than that of BGM #1 with 95% of the observations being within -2% to 22%. For BGM #1, there is a greater negative

dispersion with the lower 2.5 percentile limit being -11%. The upper 2.5 percentile limit is roughly equivalent to that of BGM #1POC.

In Figure 6, the mountain plot illustrates the percentage difference of the arterial BG values obtained from BGM #1 and BGM #1POC compared with the YSI 2300 Stat Plus®. The median of BGM #1 is slightly higher (4%) than that of BGM #1POC (3%). The dispersion of error is less with BGM #1POC with 95% of the observations within -4% to 16%. For BGM #1, there is a greater negative dispersion with the lower 2.5 percentile limit being -9%. The upper 2.5 percentile limit is the same as that of BGM #1POC.

For BG values ≥4.2 mmol/L, the most frequent error tolerance criteria to determine acceptability of BGMs is within ±20% of the reference instrument and for those values <4.2 mmol/L the criteria is within ±0.83 mmol/L of the reference instrument (ISO,2003) (Table 5). In this study, for BG values ≥4.2 mmol/L, 94% of capillary samples tested with BGM #1 and 93% of those tested with BGM #1POC were within ±20% of the YSI 2300 Stat Plus®. However, only 58% of capillary samples tested with BGM #1POC and 70% of those tested with BGM #1 fell within ±10% of the YSI 2300 Stat Plus®. With arterial BG samples, 99% of those tested with BGM #1 and 100% tested with BGM #1POC were within ±20% of the YSI 2300 Stat Plus®. Using the tighter performance criteria of ±10% of the YSI 2300 Stat Plus®, 85% of those tested with BGM #1POC and 80% tested with BGM #1 met this criterion (Table 6).

Comparative Measurement of Capillary BG Using Three BGMs and the YSI 2300 Stat Plus® Glucose Reference Analyzer

A 4 x 3 factor (instrument x time) repeated measures ANOVA was used to examine the capillary BG values obtained over 3 sampling times and analyzed by three different BGMs and the YSI 2300 Stat Plus® analyzer (the reference analyzer). There was a significant main effect of instrument (BGM) (F=37.76; df=4,176 p=0.00). The planned comparisons of each BGM with the YSI 2300 Stat Plus®, revealed significant differences in the BG values between the three BGMs and the values obtained by the reference analyzer. Individual results were as follows: for BGM #1 (F=15.83; df=1,44; p=0.00); for BGM #2 (F=24.24; df=1,44; p=0.00); for BGM #3 (F=28.54; df=1,44; p=0.00). For all of the BGMs there were no significant differences found with the different test times (F=0.14; df=2,88; p=0.87) nor with the interaction of instrument and time (F=0.50; df=8,352; p=0.86).

LSLR was used to determine the slope, y-intercept and coefficient of determination of each of the three BGMs when compared with the YSI 2300 Stat Plus® using capillary samples. Figure 7 shows the line of identity and the regression line for BGM #1, the regression equation is y=0.89x + 0.98 with R^2=0.88. The crossover relationship between the line of identity and the regression line shows with BG values <8 mmol/L, BGM #1 would provide BG values higher than the YSI 2300 Stat Plus® and with BG values >11 mmol/L, BGM #1 would provide BG values lower than the YSI 2300 Stat Plus®. Figure 8 shows the line of identity and the regression line for BGM #2, the regression equation is y=0.99x -0.19 with R^2=0.94. The parallel relationship between the line of identity and the regression line shows BGM #2 would consistently provide

lower BG values than the YSI 2300 Stat Plus®. Figure 9 shows the line of identity and the regression line for BGM #3, the regression equation is y=1.07x –0.23 with R^2=0.94. The $S_{y/x}$ values for each of the three instruments were 0.60 for BGM #1, 0.45 for BGM #2, and 0.50 for BGM #3.

Figure 10 depicts the capillary BG sample mountain plots for BGM #1, 2 and 3 compared to the YSI 2300 Stat Plus® analyzer. The mountain bases range from -11% to + 20% with BGM #1; from -17% to + 9% with BGM #2; and, from -5% to + 20% with BGM #3. The medians representing the 3 BGMs are not centered close to zero, the median for BGM #2 shows a negative bias, with BGM #1 and BGM #3 a positive bias.

Comparative Measurement of Arterial BG Using Three BGMs, the Bayer Chiron 865® Blood Gas Analyzer and the YSI 2300 Stat Plus® Glucose Reference Analyzer

A 5 x 3 factor (instrument x time) repeated measures ANOVA was used to compare the arterial BG as obtained by each of the three BGMs, the Bayer Chiron 865® blood gas analyzer and the YSI 2300 Stat Plus® analyzer (reference analyzer). There was a significant main effect of instrument (F=51.68; df=5,220; p=0.00). The planned comparisons (each BGM versus the reference), revealed significant differences in the BG values between each of the three BGMs and the values obtained by the reference analyzer. The individual ANOVA results were as follows: for BGM #1 (F=24.14; df=1,44; p=0.00.); for BGM #2 (F=159.23; df=1,44; p=0.00); for BGM #3 (F=4.53 df=1,44; p=0.04). For all of the BGMs there were no significant differences in BG values for the different sampling testing times (F=0.30; df=2,88; p=0.74) nor with the interaction effect of instrument and time (F=0.97; df=10,440; p=0.47).

LSLR was used to determine the slope, y-intercept and coefficient of determination for arterial BG samples for the three BGMs and the Bayer Chiron 865® compared with the YSI 2300 Stat Plus®. Figure 11 shows the line of identity and the regression line for BGM #1: the regression equation is y=0.92x + 0.77 with R^2=0.94. The crossover relationship between the regression line and the line of identity indicates at BG levels up to 8 mmol/L, BGM #1 will have a positive bias and at BG levels >12 mmol/L, BGM #1 will have a negative bias. Figure 12 shows the line of identity and the regression line for BGM #2: the regression equation is y=0.96x -0.26 with R^2=0.96. The parallel relationship between the regression line and the line of identity indicates there will be a constant negative bias in BG values tested with BGM #2. Figure 13 shows the line off identity and the regression line for BGM #3: the regression equation is y=1.02x –0.1 with R^2=0.97. Figure 14 shows the line of identity and the regression line for the Bayer Chiron 865®: the regression equation is y=1.05x –0.28 with R^2=0.96. The $S_{y/x}$ for each of the four instruments were 0.41 for BGM #1, 0.33 for BGM #2, 0.29 for BGM #3 and 0.36 for the Bayer Chiron 865®.

Figure 13 depicts the mountain plots for BGM #1, BGM #2, BGM #3 and the Bayer Chiron 865® compared with the YSI 2300 Stat Plus® for arterial BG samples. The mountain bases range from -10% to +15 % with BGM #1; from -19% to + 3% with BGM #2; from -7% to + 10% BGM #3; and from -10% to +10% with the blood gas analyzer (Bayer Chiron 865®). The median of BGM #3 and the Bayer Chiron 865® are centered close to zero difference, the median for BGM #2 shows a negative bias and for BGM #3, a positive bias.

Performance Criteria for BGMs

The International Organization for Standardization (ISO, 2003) performance criteria for BGMs has set out reporting recommendations based on variance at lower ranges of BG values, as well as upper ranges. Results are presented separately for glucose concentrations <4.2 mmol/L and ≥4.2 mmol/L because different criteria apply. Tables 5 and 6 summarize the performance criteria of BG instruments used in this study

The ISO recommends for glucose concentrations <4.2 mmol/L that the percentage of results within ±0.28 mmol/L, ±0.56 mmol/L and ±0.83 mmol/L of the reference values be reported. For the capillary BG samples tested in this study, only 4 out of a total of 540 capillary BG values were <4.2 mmol/L. Of these BG values, there was 2/4 within ±0.28 mmol/L, and 1/4 within ±0.56 mmol/L of the capillary YSI 2300 Stat Plus® BG values. To determine acceptability of BGMs when BG <4.2 mmol/L the most frequent error tolerance criteria is ±0.83 mmol/L of the BG value from the reference instrument. One out of the four capillary BG values from BGM #3 exceeded this criterion. Therefore out of a total of 540 capillary BG values only 1 BG value was not within ±0.83 mmol/L of the BG value obtained by the YSI 2300 Stat Plus®.

For the arterial BG samples, only 8 out of a total 675 arterial BG values were <4.2 mmol/L. Of these BG values, there were 4/8 within ±0.28 mmol/L, and 6/8 within ±0.56 mmol/L of the arterial YSI 2300 Stat Plus® BG values. In total, only 2 arterial BG values exceeded the ±0.83 mmol/L error tolerance criteria. Both of these were arterial BG samples tested with BGM #2. Overall, there were < 1% of BG values <4.2 mmol/L, yet 25% of these arterial BG values were higher than the maximum error tolerance criterion of ±0.83 mmol/L when compared to the YSI 2300 Stat Plus® BG values (Table 5).

For glucose concentrations ≥4.2 mmol/L, The ISO (2003) recommends that the percentage of values falling within specific intervals (±5%, ±10%, ±15% and ±20%) be reported. The most frequent error tolerance criteria to determine acceptability of BGMs is within ±20% of the reference instrument. Overall, arterial samples produced better accuracy than capillary samples, in particular with values within ±15% or ±20%. BGM #3 was the most accurate, with 85% of the values ≥4.2 mmol/L within the ±5% interval, 95% within ±10% and ±20% and 100% within the ±20% interval. In contrast, only 49% of the values obtained from the currently used BGMs (BGM #1) fell within the 5% range, while 80% fell within ±10% and 99% within ±20% (Table 6).

In order to compare BGM performance and the Bayer Chiron 865® with the YSI 2300 Stat Plus®, the total error (systematic error + random error, expressed in %) was estimated. Random error was calculated using the standard error of the estimate ($S_{y/x}$) for each BG instrument. Systematic error is calculated at different clinically relevant BG concentrations, for this study, 5.55 mmol/L and 10 mmol/L were used. Table 7 displays total error analysis with capillary and arterial BG samples at a BG concentration of 5.55 mmol/L. With capillary samples at this concentration, BGM #2 has the lowest percentage of total error (14%), and BGM #1, the highest (17%). With arterial samples, BGM #3 has the lowest percentage of total error (8%), and BGM #2, the highest (16%). Table 8 displays total error analysis with capillary and arterial BG samples at a BG concentration of 10 mmol/L. With capillary samples at this concentration, BGM #2 has the lowest total error (11%), and BGM #3 the highest (15%). With arterial samples BGM #3 has the lowest total error (7%), BGM #2, the highest (14%).

Table 1. Characteristics of Study Subjects

Study Subjects ($n = 45$)		n	%
Gender	Male	29	64.0
	Female	16	36.0
Admission Diagnosis	Respiratory Failure	21	47.0
	Trauma	5	11.0
	Liver Failure	4	9.0
	Sepsis/Septic Shock	3	7.0
	Post Surgery	3	7.0
	Drug/Alcohol Overdose	2	4.0
	Other*	7	15.0

	Mean	Range
Age (years)	57	19-88
Apache 11 score (points)	20.22	6-36
Hematocrit (%)	31.0	21-51
Partial Pressure of Oxygen (pO2) [%]	84	51-150
Partial Pressure of Carbon Dioxide (pCO2) [%]	43	16-79
pH	7.42	7.25-7.55
Temperature (°C)	36.7	35-39.3
Mean Arterial Pressure (MAP) [mmHg]	91	58-144

*Other: Meningitis, Decreased Level of Consciousness, Diabetic Ketoacidosis, Stroke, Gastrointestinal (GI) Bleed, Multi-Organ Disease, Chronic Obstructive Pulmonary Disease (COPD)

Table 2. Between-Day and Within-Day Precision Testing Results

Between-Day Precision Testing						
	Low Glucose Controls			High Glucose Controls		
	Mean ± SD	CV (%)	Manufacturers' CV (%)	Mean ± SD	CV (%)	Manufacturers' CV (%)
BGM #1	2.5 ± 0.10	4.2	4.4	19 ± 0.55	2.9	4.5
BGM #2	3.2 ± 0.24	7.5	4.8	18.4 ± 0.78	4.2	2.8
BGM #3	2.4 ± 0.10	4.2	5.6	19.3 ± 1.50	7.8	3.6
YSI 2300 Stat Plus®	3.4 ± 0.03	0.9	2	15 ± 0.10	0.7	2
Within-Day Precision Testing						
	Low Glucose Controls			High Glucose Controls		
	Mean ± SD	CV (%)	Manufacturers' CV (%)	Mean ± SD	CV (%)	Manufacturers' CV (%)
BGM #1	2.6 ± 0.08	3.1	< 5	19.1 ± 0.60	3.3	< 5
BGM #2	3.3 ± 0.20	5.8	< 5	19 ± 0.80	4.4	< 5
BGM #3	2.4 ± 0.20	7.2	< 5	19 ± 0.50	2.8	< 5
YSI 2300 Stat Plus®	3.2 ± 0.04	1.2	2	15.2 ± 0.20	1.3	2

BGM #1: LifeScan SureStepFlexx®
BGM #2: Roche Accu-Chek Inform®
BGM #3: Abbott FreeStyle®

Table 3. Second Analysis: Between-Day and Within-Day Precision Testing Results

Between-Day Precision Testing						
	Low Glucose Controls			High Glucose Controls		
	Mean ± SD	CV (%)	Manufacturers' CV (%)	Mean ± SD	CV (%)	Manufacturers' CV (%)
BGM #1	2.5 ± 0.10	4.2	4.4	19 ± 0.55	2.9	4.5
BGM #2	3.1 ± 0.15	4.8	4.8	18.4 ± 0.78	4.2	2.8
BGM #3	2.4 ± 0.10	4.2	5.6	19 ± 0.68	3.6	3.6
YSI 2300 Stat Plus®	3.4 ± 0.03	0.9	2	15 ± 0.10	0.7	2
Within-Day Precision Testing						
	Low Glucose Controls			High Glucose Controls		
	Mean ± SD	CV (%)	Manufacturers' CV (%)	Mean ± SD	CV (%)	Manufacturers' CV (%)
BGM #1	2.6 ± 0.08	3.1	< 5	19.1 ± 0.60	3.3	< 5
BGM #2	3.2 ± 0.15	4.6	< 5	19 ± 0.80	4.4	< 5
BGM #3	2.1 ± 0.10	4.7	< 5	19 ± 0.50	2.8	< 5
YSI 2300 Stat Plus®	3.2 ± 0.04	1.2	2	15.2 ± 0.20	1.3	2

BGM #1: LifeScan SureStepFlexx®
BGM #2: Roche Accu-Chek Inform®
BGM #3: Abbott FreeStyle®

Table 4. Summary Table of Mean Blood Glucose Values (±SD) by Analytical Instrument and Sampling Time

INSTRUMENT		Sample (n=45)	TIME		
			T_1	T_2	T_3
ARTERIAL BLOOD GLUCOSE	BGM #1	Mean	7.12	7.16	6.97
		SD	1.77	1.66	1.56
	BGM #1 POC	Mean	7.06	7.09	6.96
		SD	1.74	1.47	1.64
	BGM #2	Mean	6.37	6.33	6.18
		SD	1.86	1.57	1.67
	BGM #3	Mean	6.98	6.94	6.80
		SD	2.00	1.68	1.75
	Chiron Bayer 865®	Mean	6.95	6.94	6.87
		SD	2.00	1.77	1.85
	YSI®	Mean	6.88	6.93	6.72
		SD	1.87	1.63	1.74
CAPILLARY BLOOD GLUCOSE	BGM #1	Mean	7.18	7.21	7.02
		SD	1.73	1.68	1.73
	BGM #1 POC	Mean	7.42	7.36	7.33
		SD	1.84	1.68	1.77
	BGM #2	Mean	6.64	6.68	6.58
		SD	1.92	1.80	1.79
	BGM #3	Mean	7.19	7.19	7.12
		SD	2.17	1.90	1.90
	YSI®	Mean	6.96	6.87	6.79
		SD	1.98	1.71	1.66

T_1: 8:00-9:00 a.m. T_2: 12:00-1:00 p.m. T_3: 4:00-5:00 p.m.

BGM #1: LifeScan SureStepFlexx® at the patient's bedside
BGM #1 POC: LifeScan SureStepFlexx® in the Point-of-Care Lab
BGM #2: Roche Accu-Chek Inform®
BGM #3: Abbott FreeStyle®
Chiron Bayer 865®: Blood Gas analyzer
YSI®: YSI 2300 Stat Plus® analyzer

Table 5. Instrument Accuracy for Blood Glucose Concentrations <4.2 mmol/L

Capillary Samples (n=4)			
	Within ± 0.28 mmol/L	Within ± 0.56 mmol/L	Within ± 0.83 mmol/L
BGM # 1	0/1	1/1	1/1
BGM # 2	1/1	1/1	1/1
BGM # 3	1/2	1/2	1/2
Arterial Samples (n=8)			
BGM # 1	1/1	1/1	1/1
BGM # 2	2/5	2/5	3/5
BGM # 3	1/2	2/2	2/2

Table 6. Instrument Accuracy for Blood Glucose Concentrations >4.2 mmol/L

Capillary Samples (n=540)				
	Within ± 5 %	Within ± 10 %	Within ± 15 %	Within ± 20 %
BGM # 1	56/135 (41 %)	94/135 (70 %)	117/135 (87 %)	126/135 (94 %)
BGM # 1 POC	45/135 (33 %)	79/135 (58 %)	108/135 (80 %)	125/135 (93 %)
BGM #2	65/135 (48 %)	111/135 (82%)	128/135 (95 %)	132/135 (98 %)
BGM # 3	74/135 (55 %)	113/135 (84 %)	123/135 (91 %)	130/135 (96 %)
Arterial Samples (n=675)				
BGM # 1	66/135 (49 %)	108/135 (80 %)	127/135 (94 %)	134/135 (99 %)
BGM # 1 POC	85/135 (63 %)	114/135 (85 %)	128/135 (95 %)	135/135 (100%)
BGM #2	31/135 (23 %)	86/135 (64 %)	123/135 (92 %)	135/135 (100%)
BGM # 3	**114/135 (85 %)**	128/135 (95 %)	134/135 (99 %)	135/135 (100%)
Bayer Chiron 865® Blood Gas Analyzer	81/135 (60 %)	129/135 (95 %)	133/135 (98 %)	134/135 (99 %)

BGM #1: LifeScan SureStepFlexx®
BGM #2: Roche Accu-Chek Inform®
BGM #3: Abbott FreeStyle®

Table 7. Total Error Analysis With Blood Glucose Equal to 5.55 mmol/L

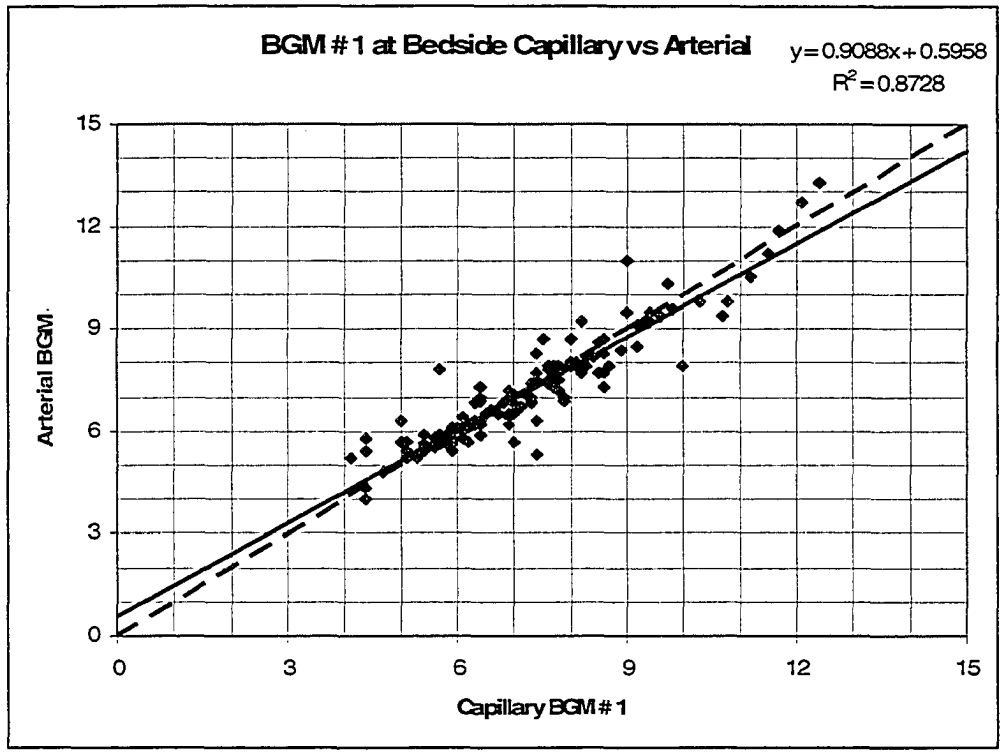
CAPILLARY BG SAMPLES	Systematic Error	Random Error %	Total Error %
BGM #1	0.4 mmol/L 7%	10%	17%
BGM #2	0.3 mmol/L 5%	9%	14%
BGM #3	0.3 mmol/L 5%	10%	15%
ARTERIAL BG SAMPLES			
BGM #1	0.4 mmol/L 7%	8%	15%
BGM #2	0.5 mmol/L 9%	7%	16%
BGM #3	0.1 mmol/L 2%	6%	8%
Bayer Chiron 865® Blood Gas Analyzer	0.1 mmol/L 2%	7%	9%

Table 8. Total Error Analysis With Blood Glucose Equal to 10 mmol/L

CAPILLARY BG SAMPLES	Systematic Error	Random Error %	Total Error %
BGM #1	0.2 mmol/L 2%	10%	12%
BGM #2	0.2 mmol/L 2%	9%	11%
BGM #3	0.5 mmol/L 5%	10%	15%
ARTERIAL BG SAMPLES			
BGM #1	0.0 mmol/L 0%	8%	8%
BGM #2	0.7 mmol/L 7%	7%	14%
BGM #3	0.1 mmol/L 1%	6%	7%
Bayer Chiron 865® Blood Gas Analyzer	0.2 mmol/L 2%	7%	9%

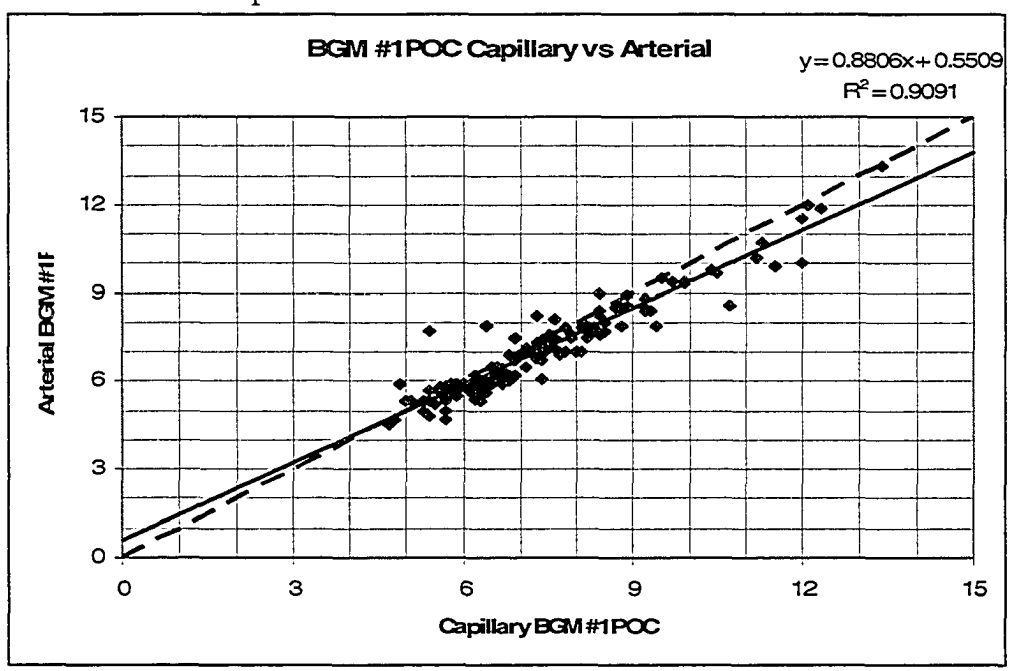
BGM #1: LifeScan SureStepFlexx®
BGM #2: Roche Accu-Chek Inform®
BGM #3: Abbott FreeStyle®

Figure 3. BGM #1 at Bedside Capillary Blood Glucose Values Compared to Arterial Blood Glucose Values



Dotted Line: Line of Identity Solid Line: Regression Line

Figure 4. BGM #1Point-of-Care Lab Capillary Blood Glucose Values Compared to Arterial Blood Glucose Values



Dotted Line: Line of Identity Solid Line: Regression Line

Figure 5. Mountain Plot: Capillary Blood Glucose Values BGM #1 and BGM #1POC Compared to YSI 2300 Stat Plus®

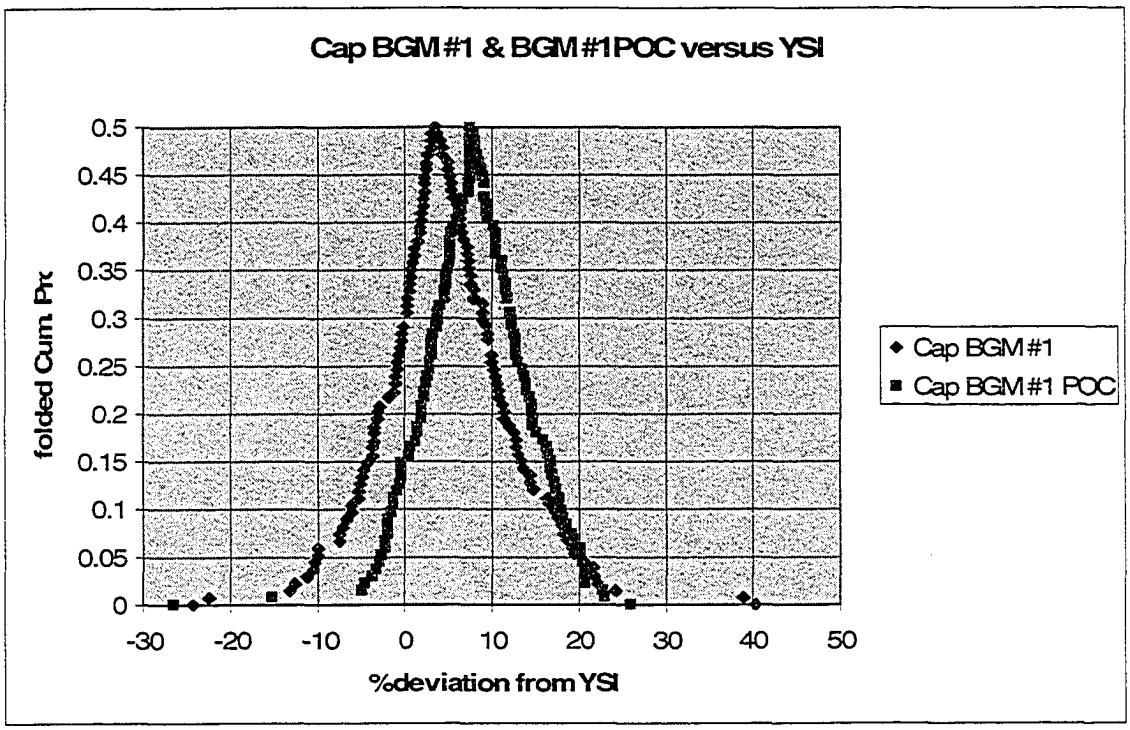


Figure 6. Mountain Plot: Arterial Blood Glucose Values BGM #1 and BGM #1POC Compared to YSI 2300 Stat Plus®

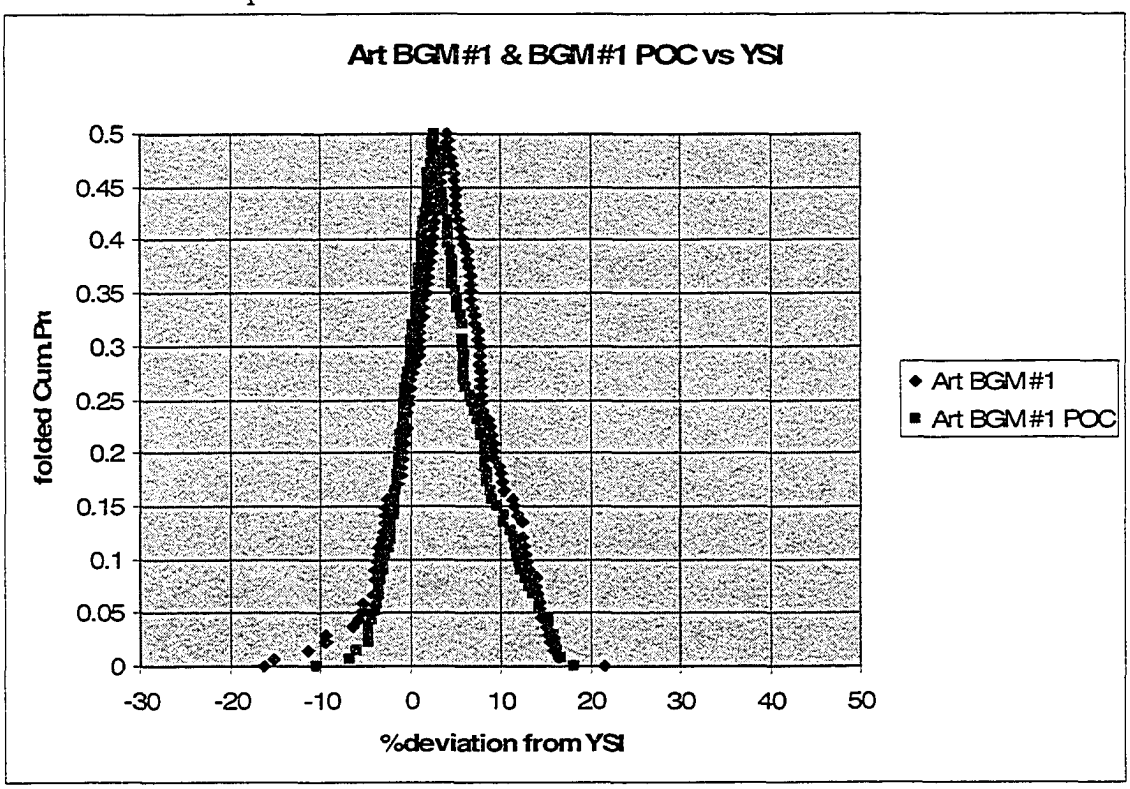
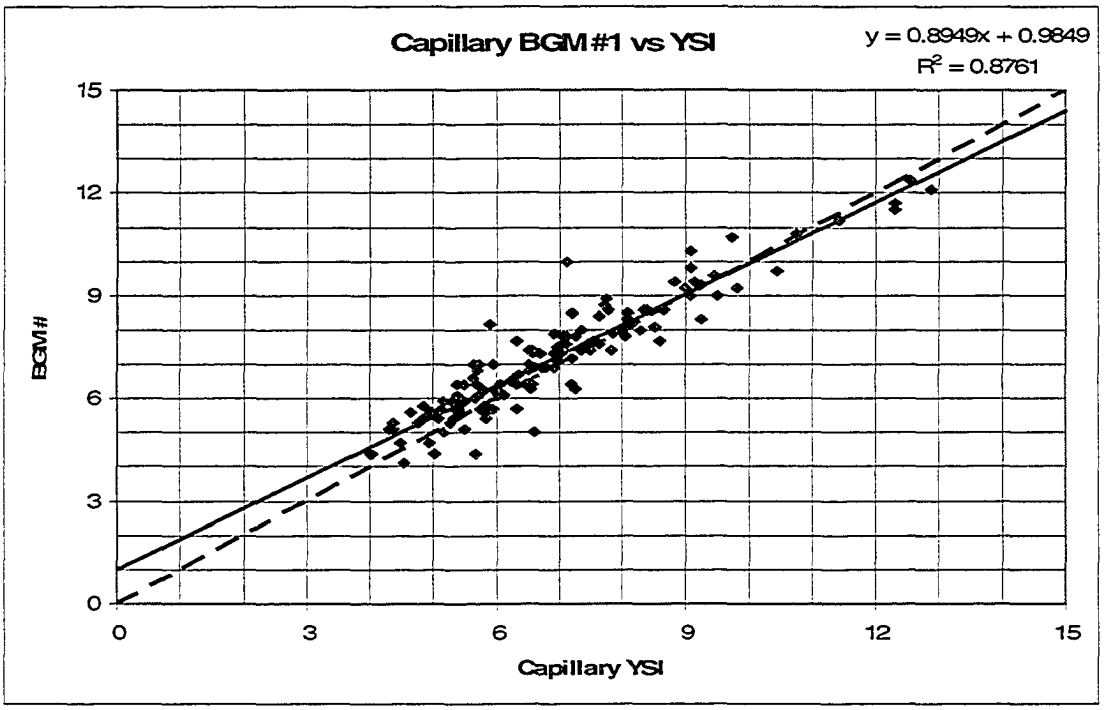
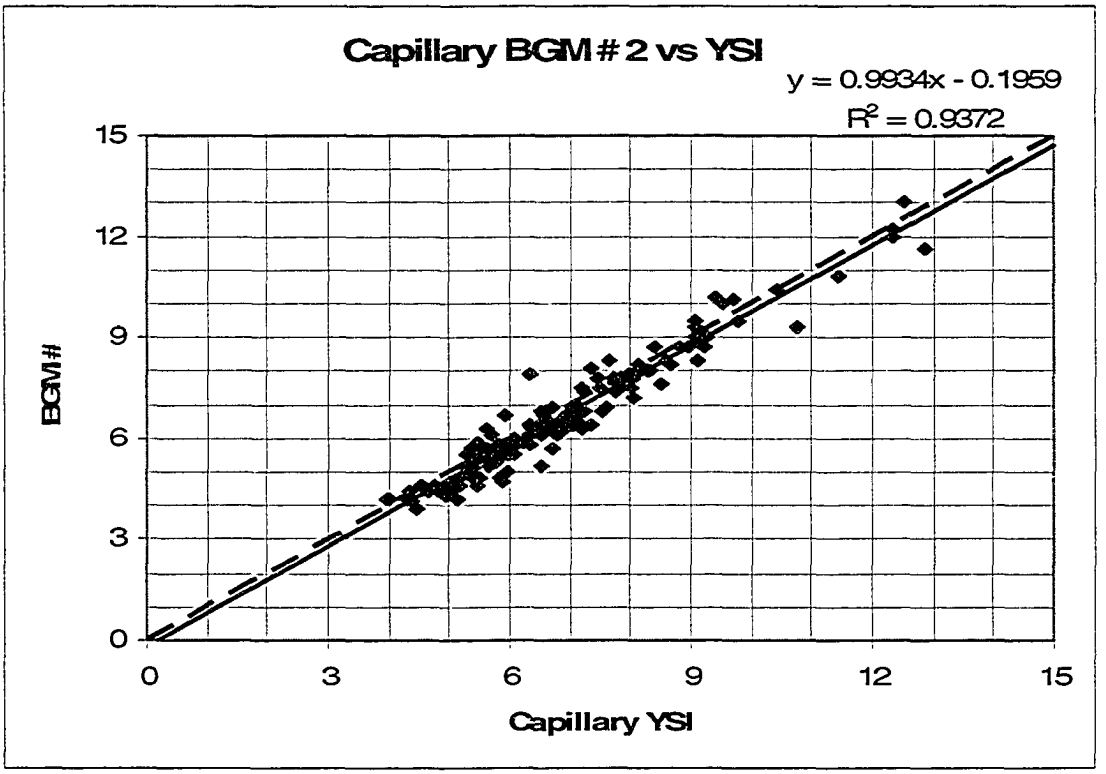


Figure 7. Capillary Samples BGM #1 Compared to YSI 2300 Stat Plus®



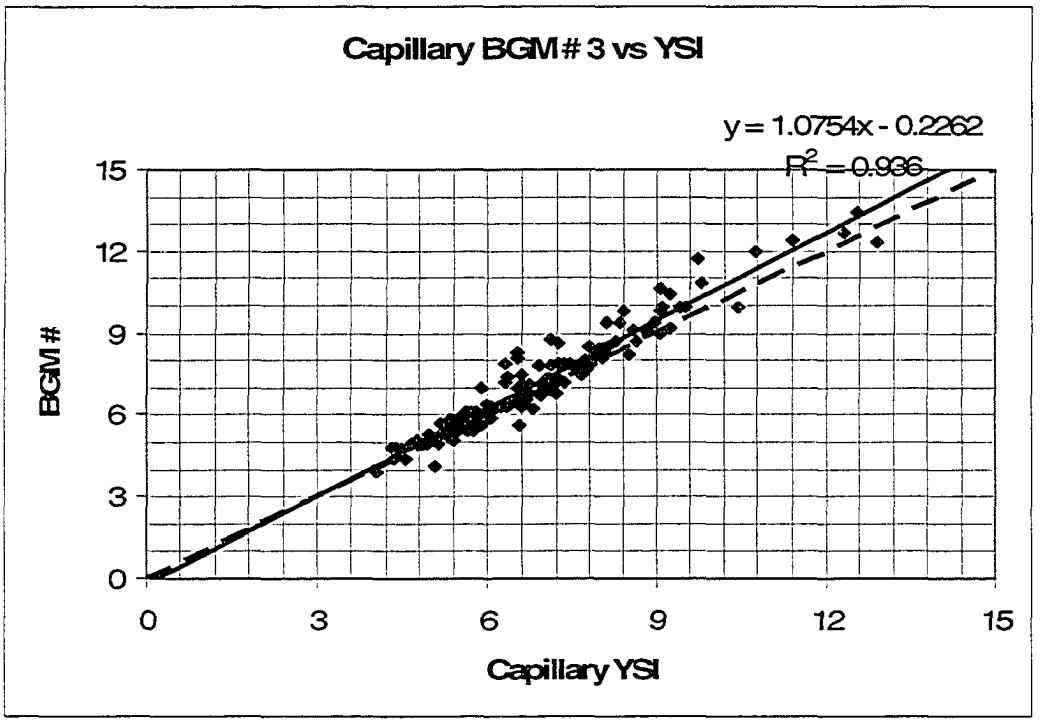
Dotted Line: Line of Identity Solid Line: Regression Line

Figure 8. Capillary Samples BGM #2 Compared to YSI 2300 Stat Plus®



Dotted Line: Line of Identity Solid Line: Regression Line

Figure 9. Capillary Samples BGM #3 Compared to YSI 2300 Stat Plus®



Dotted Line: Line of Identity Solid Line: Regression Line

Figure 10. Mountain Plots: Capillary Samples: BGMs Compared to YSI 2300 Stat Plus®

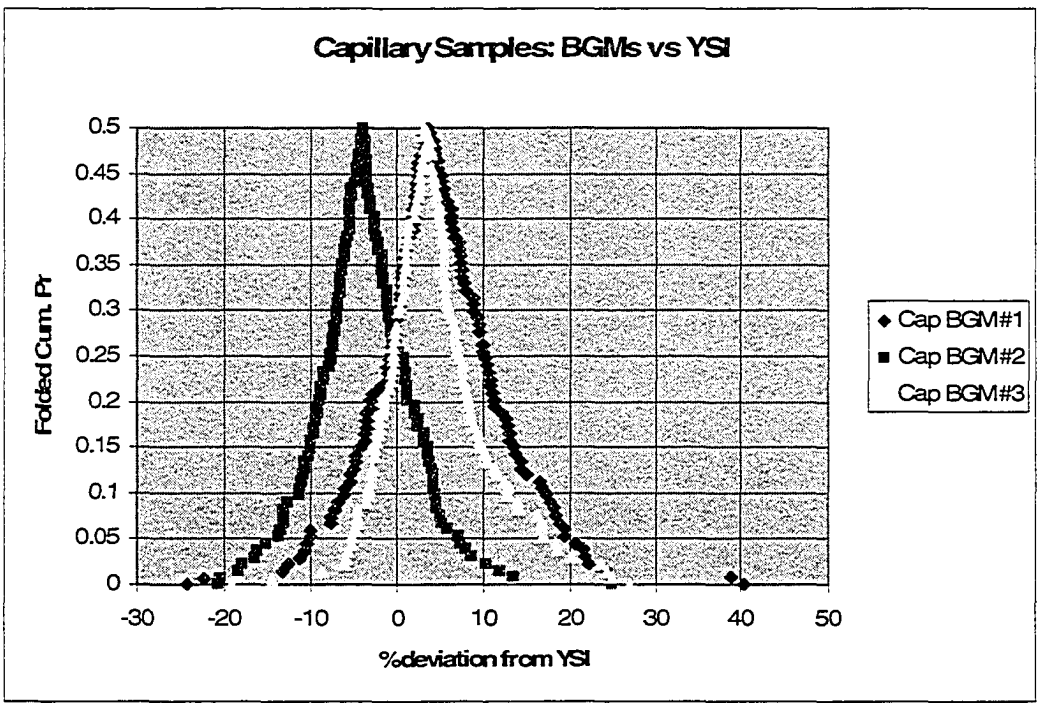
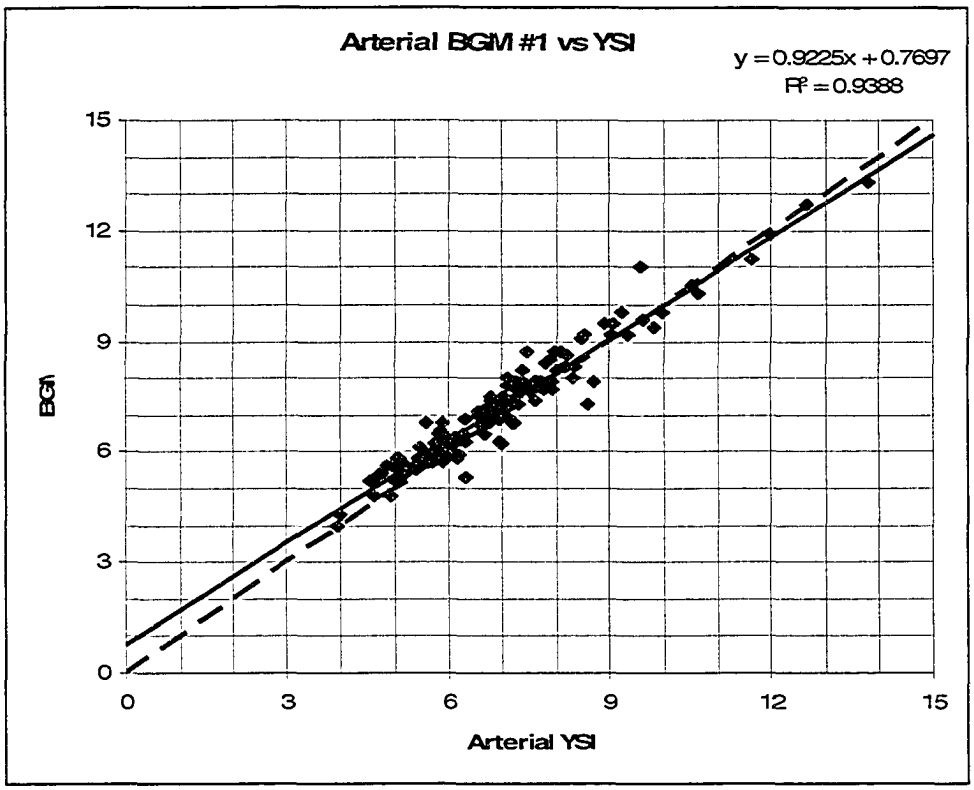
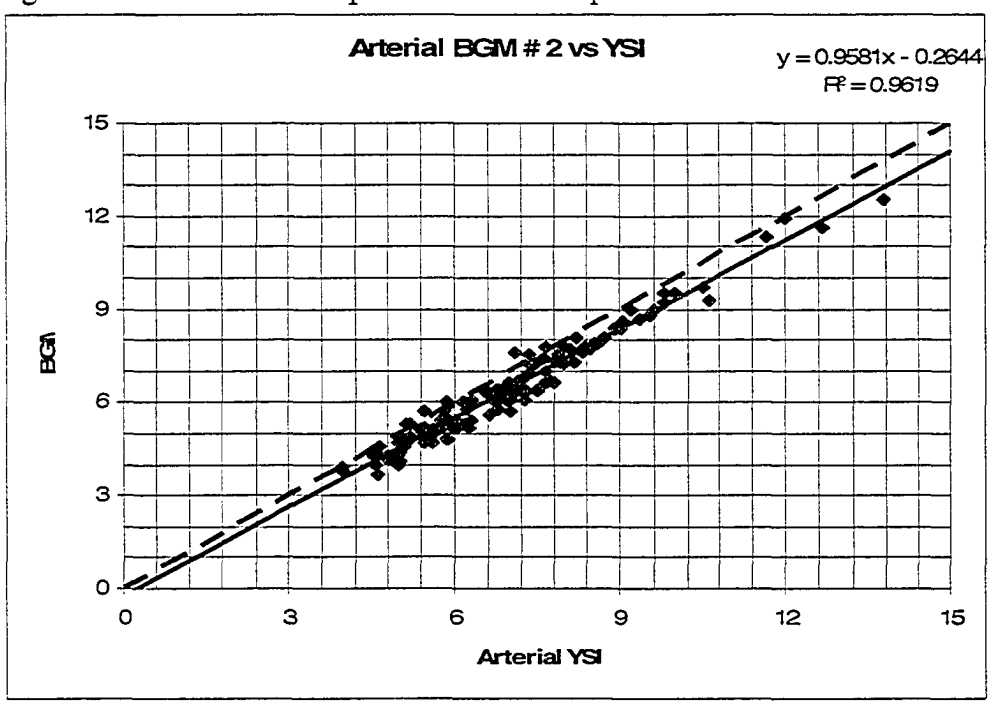


Figure 11. Arterial Samples BGM #1 Compared to YSI 2300 Stat Plus®



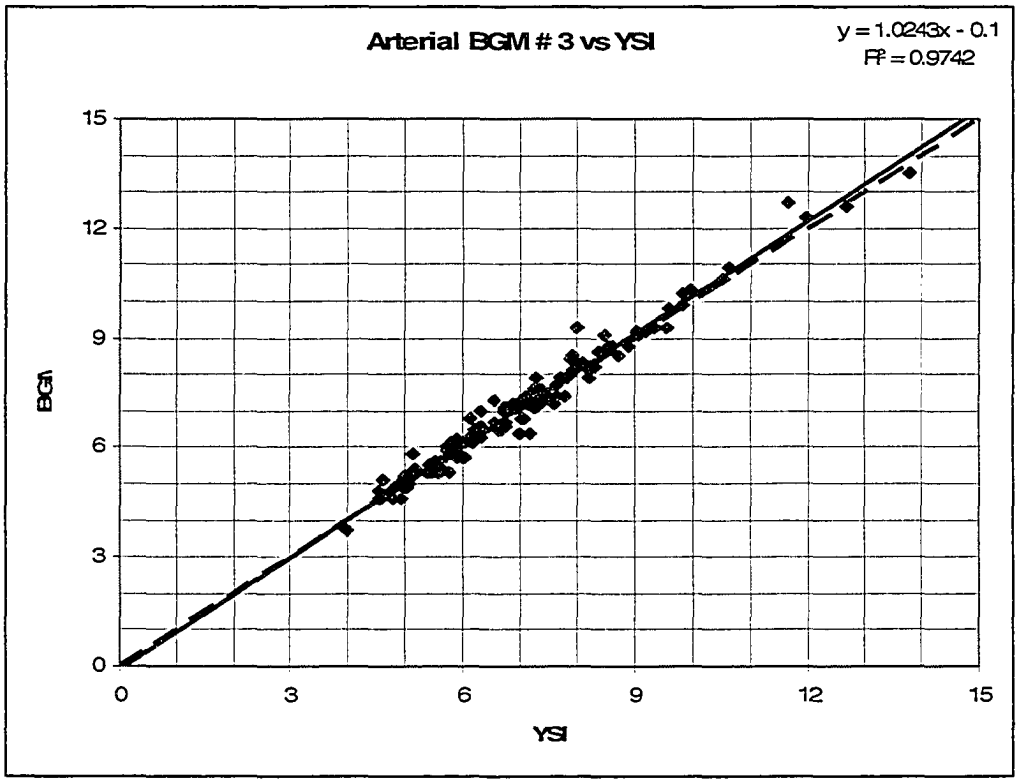
Dotted Line: Line of Identity Solid Line: Regression Line

Figure 12. Arterial Samples BGM #2 Compared to YSI 2300 Stat Plus®



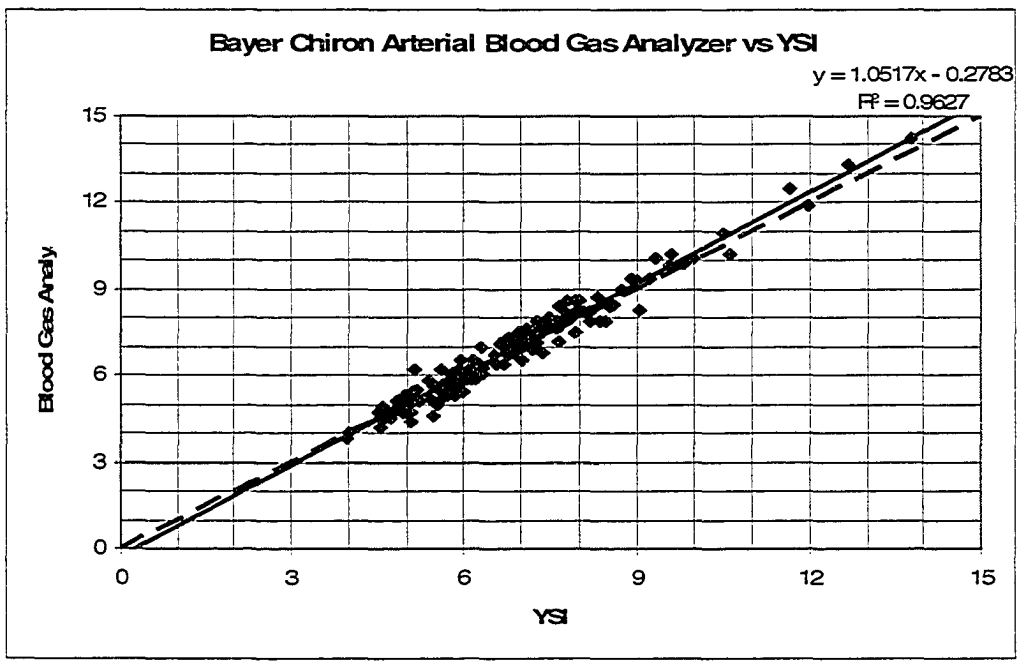
Dotted Line: Line of Identity Solid Line: Regression Line

Figure 13. Arterial Samples BGM #3 Compared to YSI 2300 Stat Plus®



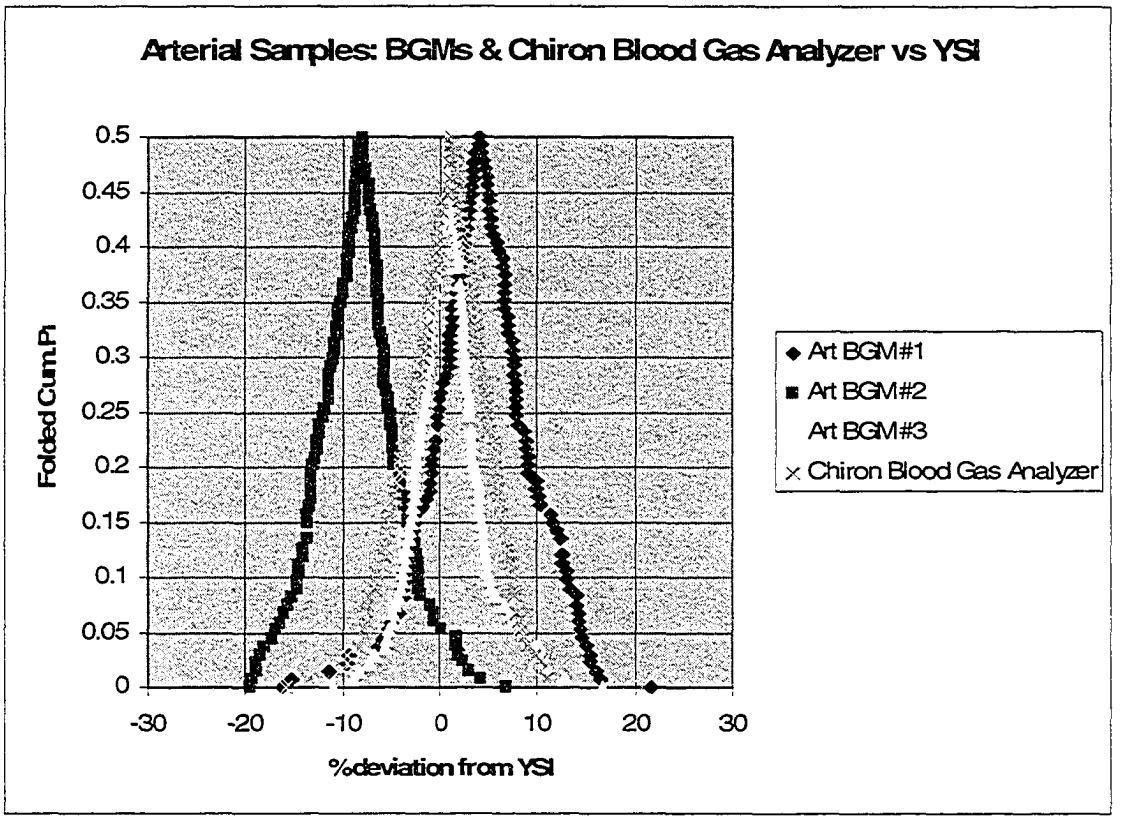
Dotted Line: Line of Identity Solid Line: Regression Line

Figure 14. Bayer Chiron Arterial Blood Gas Analyzer Compared to YSI 2300 Stat Plus®



Dotted Line: Line of Identity Solid Line: Regression Line

Figure 15. Mountain Plot Arterial Samples: BGMs and Blood Gas Analyzer Compared to YSI 2300 Stat Plus®



Chapter 5 Discussion

A prospective comparative within-subjects repeated measures study design was used to compare: (1) capillary blood glucose analyzed by three different BGMs (LifeScan SureStepFlexx® [BGM #1], Roche Accu-Chek Inform® [BGM #2], and Abbott Freestyle® [BGM #3]) and the YSI 2300 Stat Plus® analyzer which was used as the reference instrument; (2) arterial BG was also analyzed by BGMs #1-3, the Bayer Chiron 865® blood gas analyzer and the YSI 2300 Stat Plus® as the reference instruments.

The study population (n=45) had a mean age of 57 years of age, and were predominantly male. Many had a primary diagnosis of respiratory failure, requiring mechanical ventilation support and the mean APACHE II score was 20. These findings are consistent with literature describing characteristics of adult critically ill patients in a GSICU that participated in BG studies. For example in a study by Kulkarni et al. (2005) looking at agreement between two methods of BG measurement in critically ill patients, 54 patients were enrolled, 30 of these subjects were male, the mean age was 59 years of age and the mean APACHE II score was 21. Another study by Kanji et al (2004) looking at BG and insulin therapy in critically ill patients (n=100), reported the following demographic characteristics: 58% were male, the mean age of these patients was 63 years of age, with respiratory failure as a common diagnosis and 97% of all patients required mechanical ventilation support. The mean APACHE II score of these patients was 20.

Precision of BG Instruments

Overall, the coefficient of variation (CV) reflected clinically acceptable levels of precision (Carol Shalapay, personal communication, July 25, 2005). For the BGMs the

within-day and between-day CV values were 5% or less, after re-analysis was completed. The two identified outliers that were removed for the re-analysis may have been due to test strip lot-to-lot variability or user variability. For precision testing performed on the YSI 2300 Stat Plus® the CV values for within-day precision were <1% and the between-day values were 1%, reflecting a high degree of precision.

BG Monitoring in Critical Ill Patients

In the GSICU where data collection for this study occurred, current clinical practice is to use BGM #1 to determine capillary and arterial BG levels at the patient's bedside and the Bayer Chiron 865® blood gas analyzer is used to determine arterial BG values in the POC lab. Maintaining BG within a range specified by the physician is achieved through the use of continuous insulin infusions. These insulin infusions are titrated (adjusted) by RN's based on capillary or arterial BG results obtained using BGM #1 or arterial BG tested by the Bayer Chiron 865® blood gas analyzer. The decision to use either a capillary or arterial sample to determine the critically ill patient's BG level and whether to use BGM #1 or the Bayer Chiron 865® blood gas analyzer is entirely dependent upon the R.N. providing care for that specific patient. Consequently, variation in both sampling and instrument used to determine BG exists on a daily basis.

Relationship of Capillary and Arterial BG Tested Using

Lifescan SureStepFlexx® BGM (BGM # 1)

There was no significant difference found in the BG obtained using capillary and arterial samples, tested at the bedside. Neither the mean capillary or arterial BG values were significantly different from the values obtained with the YSI 2300 Stat Plus®. The mean arterial BG and the mean arterial YSI 2300 Stat Plus® were not significantly

different. These findings indicate at the bedside, there was very close agreement between mean capillary and arterial BG values as compared to a recognized reference instrument.

Kulkarni et al. (2005) looked at the relationship between capillary BG values using a BGM (n=493) and arterial BG values (n=493) using a blood gas analyzer in critically ill patients. The Bland-Altman method was used to demonstrate adequate agreement between measurements. Results were reported using the mean and SD, no *p* values were provided. The mean difference (bias) was 0.12 mmol/L (2.2%), with the arterial BG values being consistently higher. These authors concluded in a general population of critically ill patients there is statistical agreement between the BG levels measured by a BGM with capillary samples and levels measured by arterial blood gas analysis, suggesting no significant difference in BG levels obtained using capillary and arterial samples. However, the authors did not use a reference BG analyzer in this study nor were capillary and arterial BG samples compared using the same instruments. Their data differs from our results in that we consistently found capillary BG values to be higher than the arterial values (Table 3). Our research design was a significant expansion from that of these authors and may explain the differing results.

In the POC lab, there were significant differences found between mean capillary BG and the mean capillary YSI 2300 Stat Plus®, but not between mean arterial BG values and the mean arterial YSI 2300 Stat Plus®. One possible explanation for the discrepancy with capillary BG values, is a consistent bias with the single BGM used in the POC lab. In addition, the testing technique differed between the POC lab and the bedside. At the bedside the first drop (5 microliters) of capillary blood was immediately tested using BGM #1. Then, an additional 20 microliters of capillary blood had to be

obtained and put into a blood tube in order to have a sufficient capillary sample to test using BGM #1, #2, #3 and the YSI 2300 Stat Plus® in the POC lab. The technologist used a pipette to obtain the required sample volume from the blood tube and then the capillary blood was tested on the different instruments in the POC lab. Thus, neither the capillary BG sampling nor BG testing using BGM #1 and BGM #1POC was done at exactly the same time.

Chiasson (1995) compared arterial and capillary BG to the hospital laboratory BG in a convenience sample (n=75) of post-cardiac surgical patients. The objective of this study was to determine if there was a difference of greater than 15% in the capillary or arterial BG value using a BGM as compared to the hospital laboratory BG value. Of the 75 capillary values, 34% fell outside of the 15% range and of the arterial values, 17% fell out of the 15% range. Based on these findings, Chiasson recommended the use of arterial blood to assess BG levels with a BGM. Mean capillary and arterial BG levels were 17.8 mmol/L and 14.8 mmol/L respectively. An identified limitation of this study was that all the patients could have been considered anemic (hematocrit <35%), which could affect BG values obtained from the BGM. No comments on the difference between capillary and arterial BG were included in this study, however Chiasson did find an overall mean difference of 3 mmol/L, with the capillary BG values being higher. This is a much higher overall mean difference than found in our study. Chiasson did not differentiate instrument accuracy using BG concentrations of <4.2 mmol/L and ≥4.2 mmol/L as recommended by ISO (2003), as we did, and our study results found a much higher percentage of capillary and arterial BG values within ± 15% of the reference analyzer.

For BG values ≥4.2 mmol/L, the most frequent error tolerance criteria to determine acceptability of BGMs is within ±20% of the reference instrument and for those values <4.2 mmol/L the criteria is within ±0.83 mmol/L of the reference instrument (ISO, 2003). Overall, with the capillary BG values ≥4.2 mmol/L, 7% of those tested with BGM #1POC and 6% tested with BGM #1 exceeded ±20% (in comparison with the YSI 2300 Stat Plus®). Using arterial BG values, 100% of those tested with BGM #1POC and 99% met these criteria, indicating this meter to be more accurate with measurement of arterial BG.

In our study, there were no significant differences found when testing matched capillary and arterial BG using the YSI 2300 Stat Plus®. Additionally, a high degree of correlation was found between the capillary BG and arterial BG tested using the YSI 2300 Stat Plus®. These findings suggest capillary and arterial BG sampling can be interchanged when BG is measured using the YSI 2300 Stat Plus®. Unfortunately, the YSI 2300 Stat Plus® is not readily available nor used routinely to monitor BG in critically ill patients.

Relationship of Capillary BG Measured Using Three Different BGMs Compared to the YSI 2300 Stat Plus® Glucose Reference Analyzer

There were significant differences between capillary BG tested using BGM #1, BGM #2 and BGM #3 as compared to the YSI 2300 Stat Plus®. Obtaining capillary samples in critically ill patients can be difficult, due to impaired perfusion and significant edema that is often found in the fingertips of these patients. More than a single drop of capillary blood was required to measure BG levels using all three BGMs along with the YSI 2300 Stat Plus®, and it was sometimes difficult to obtain the volume of sample

required. BGM #1 showed a slightly positive constant error as compared to the YSI 2300 Stat Plus®, while BGM #2 and BGM #3 showed a slightly negative error. Thus capillary BG results obtained using BGM #1 would be slightly higher than BG values obtained using the YSI 2300 Stat Plus®, whereas with BGM #2 and BGM #3, BG results would be slightly lower.

A study by Kanji et al. (2004) looked at the efficiency and safety of a nurse-managed insulin protocol. BG was measured with capillary samples using BGM #2, insulin infusions were started when BG > 6.1 and adjusted according to a protocol.. Overall, 20% of the patients experienced hypoglycemia (defined as BG < 2.2 mmol/L). This is a much higher percentage then found in our study (<1%). Their higher rates of hypoglycemia could have resulted from dependency on capillary sampling and/or from such factors as instrument precision, user error and assumptions inherent in their research design.

In order to measure BGM accuracy, performance criteria from the International Organization for Standardization (ISO) (2003) was used. It is important to note only 1% of the BG values (4/540 capillary BG and 8/675 arterial BG) were below 4.2 mmol/L. This suggests critical care RN's working in this GSICU, are very good at preventing episodes of hypoglycemia. Of the BG samples <4.2 mmol/L, 75% (9/12) were within ± 0.83 mmol/L YSI 2300 Stat Plus®, the performance criteria commonly used to measure acceptability of BGMs. However, based on the small number of BG values <4.2 mmol/L found in this study, it is difficult to conclude that these BGMs are accurate when testing BG <4.2 mmol/L.

For capillary BG values ≥4.2mmol/L, BGM #3 demonstrated the highest percentage of values within ±5% and ±10% of the YSI 2300 Stat Plus® and BGM #2 demonstrated the highest percentage of BG values within ±15% and ±20% of the YSI 2300 Stat Plus®. When BG values were compared with the reference instrument, 94% of BGM #1, 98% of BGM #2, and 96% of BGM #3 satisfied the performance criteria of within ±20%. Management of BG levels in critically ill patients may require a more stringent performance criterion. Further studies are needed to determine the interventions that were missed or inappropriately done in response to BG values that fell outside of the set range.

The mountain plot comparing the percentage difference of the capillary BG values obtained from BGM #1, BGM #2 and BGM #3 as compared to the YSI 2300 Stat Plus®, demonstrate BG values obtained with BGM #2 on average will be lower, while those from BGM #1 and BGM #3 will be higher than the YSI 2300 Stat Plus®. Total error analysis, at a BG of 5.55 mmol/L and 10 mmol/L, found all 3 BGMs achieved a total error of <20%, with a range of 11% (BGM #2) to 17% (BGM #1). Overall, it is imperative the BGM values be consistently within 20% of the reference instrument, the YSI 2300 Stat Plus®. The findings of this study consistently show BG values obtained with all three BGMs to be <20% of the YSI 2300 Stat Plus®.

Relationship of Arterial BG Measured Using Three Different BGMs and the Bayer Chiron 865® Compared to the YSI 2300 Stat Plus® Glucose Reference Analyzer

There were significant differences between arterial BG obtained using BGM #1 BGM #2 and BGM #3 as compared to the YSI 2300 Stat Plus®. Similar to the capillary data, BGM #1 showed a slightly positive constant error as compared to the YSI 2300 Stat

Plus®, while BGM #2 and the Bayer Chiron 865® blood gas analyzer showed a slightly negative constant error. Thus, results obtained when testing arterial BG using BGM #1 would be slightly higher than BG obtained using the YSI 2300 Stat Plus®, while BG results from BGM #2, BGM #3 and the Bayer Chiron 865® blood gas analyzer would be slightly lower. With arterial sampling, there is much less scatter of points around the regression line than with capillary BG suggesting arterial sampling provides a more accurate BG value than capillary sampling.

Eighty-five percent of the arterial samples measured by BGM #3 were within ±5% of the YSI 2300 Stat Plus®, and 95% of the BG values were within ±10% of the of the YSI 2300 Stat Plus®, suggesting a high degree of accuracy at these levels. Results from the Bayer Chiron 865® blood gas analyzer at the ±10% were similar to the results from BGM #3. 100% of the BG values measured by BGM #2 and BGM #3 were within ±20% of the YSI 2300 Stat Plus®. These results were similar to those obtained by Louie et al (2000), although not directly comparable as those authors used different BGMs and clinical laboratory analyzer.

The mountain plot comparing the percentage difference of the arterial BG values obtained from BGM #1, BGM #2 and BGM #3 as compared to the YSI 2300 Stat Plus®, demonstrate BG values obtained with BGM #2 on average will be lower, while those from BGM #1 will be higher than the YSI 2300 Stat Plus®. There was only a 1% difference in the peak of the mountain plot representing BGM #3 and the Bayer Chiron 865® blood gas analyzer compared to the YSI 2300 Stat Plus®, demonstrating a high degree of accuracy with these two instruments. In addition, BGM #3 displayed the lowest

percent of total error. Based on these findings, with arterial BG sampling, it is very clear that BGM #3 is an excellent choice to accurately measure BG in critically ill patients.

Strengths and Limitations

The major strengths of this study are related to study design and include the following: 1) the use of a within-subjects repeated measures design which controlled for various clinical and patient covariates such as age, gender, reason for admission, acuity of illness, number and type of patient comorbid conditions; 2) the recruitment of a heterogeneous study population consisting of a mixed medical/surgical ICU population expanding the generalizability of the study findings; 3) all capillary and arterial samples were collected and tested at the patient's bedside by only one researcher using BGM #1. This was done to ensure consistency of BG collection and measurement. Similarly, all the arterial and capillary samples were measured by one researcher in the POC lab using the three BGMs and the YSI 2300 Stat Plus® to ensure consistency of BG collection and measurement; 4) all BG measurements were done within 20 minutes of collection to control for any effects of glycolysis; and 5) to control for time between sampling and analyses, the order of the various instrument was rotated. Attention was given to current clinical practice in the design of the research protocol. Venous BG samples were not included in this study as BG testing in critical care units is primarily done using capillary and arterial samples. Three different BGMs were used in this study, employing different methodologies for measuring BG. In addition, the Bayer Chiron 865® blood gas analyzer was used to measure arterial BG levels, as this is the analyzer currently used in this GSICU. The YSI 2300 Stat Plus® a recognized reference instrument, was used to determine accuracy of the BGMs. The data analysis performed in this study was

extensive, including repeated measures ANOVA, LSLR, precision testing, percentage differences and total error analysis. Using the different analytical techniques, both the study results and conclusions were consistent.

This study had some limitations which must be considered. The use of many different BGM #1 at the patient's bedside (usually there are about 10 different BGM #1 in use in this GSICU) was chosen in order to duplicate the current nursing practice of this GSICU in monitoring BG, but it could be argued the same BGM #1 should have been used to control for any potential contribution of multiple meters. The effect of hematocrit was not assessed in this study, however the different manufactures' product information claim different accuracy parameters by hematocrit: BGM #1 is reported accurate within a hematocrit range of 25% to 60% (LifeScan product information), whereas the manufactures of BGM #2 and BGM #3 claim their meters are accurate within a hematocrit range of 20% to 60% (Roche product information) and 0% to 60% (Abbott product information) respectively. The patients in this study had hematocrits ranging from 21% to 51%, so the effect of hematocrit on any of the meters should be minimal. The effects of other variables such as blood pH and pO_2 were not assessed.

Implications For Clinical Practice

The literature review revealed the importance of maintaining normal BG among critically ill patients to decrease morbidity and mortality (Van den Berghe et al., 2001; Krinsley, 2003; DiNardo et al., 2004). However, the variation found in BG sampling techniques and BG analytical instruments presents confusing and at times conflicting results. Very few studies have examined the impact of interchanging capillary and arterial BG sampling that occurs when measuring BG in critically ill patients. This study is

unique as it examined within each subject the relationship between capillary and arterial BG using three different BGMs (LifeScan SureStepFlexx®, Roche Accu-Chek Inform®, and Abbott Freestyle®), and a blood gas analyzer (Bayer Chiron 865®) as compared to a standard reference BG instrument (YSI 2300 Stat Plus®).

This study was designed to simulate existing nursing management related to BG in critically ill patients. Currently, when measuring BG levels, the R.N. may choose either capillary or arterial sampling. Depending upon the patient's status, it may be more appropriate to choose an arterial sample over a capillary sample or vice-versa. With an indwelling arterial catheter, a discard of 3 mls of arterial blood is required, in order to prevent the dilution effect from the solution used to maintain patency of the arterial catheter. Therefore, if multiple blood tests are required, a significant amount of blood may be discarded, which can cause a decrease in the patient's hemoglobin and hematocrit. Nevertheless, as most critically ill patients have indwelling arterial catheter, many nurses are reluctant to "poke" the patient's fingertip for a capillary sample. Therefore, it is imperative to ensure that BG results from capillary and arterial samples are interchangeable in critically ill patients. In this study, no statistically significant differences were found in capillary and arterial BG samples obtained from the same patient at the same time, and measured at the patient's bedside using BGM #1. Yet, in the POC lab, using the same type of BGM, and the same matched blood samples, statistically significant differences were found. These conflicting results require further investigation. Importantly, there were no statistically significant differences found when testing matched capillary and arterial BG using the YSI 2300 Stat Plus®. Consequently, it is unclear as to whether it is acceptable to interchange capillary and arterial BG samples

using BGMs, however it is acceptable to interchange capillary and arterial BG samples if testing is done using the YSI 2300 Stat Plus®.

How accurate is the BG obtained using capillary samples in critically ill patients? This study attempted to answer this question, by comparing the capillary BG obtained with three different BGMs to the BG obtained by the YSI 2300 Stat Plus®, as the reference instrument. The YSI 2300 Stat Plus® is the BG reference instrument used by the manufacturers of these three BGMs, along with the reference instrument used in many BG studies (Voss et al., 1996; Fogh-Anderson, 1998; McGarraugh & Putz, 2002). There were statistically significant differences found with each of the BGMs as compared to the YSI 2300 Stat Plus®. Based on these results, it cannot be recommended to use capillary samples over arterial samples to obtain BG levels in critically ill patients, if BG testing is done using BGM #1, BGM #2 or BGM #3.

On the other hand, when using arterial samples to obtain BG, BGM #3 was found to be a highly accurate meter for BG testing in critically ill patients. Furthermore, our results support the current practice in this GSICU of obtaining an arterial BG measurement with the Bayer Chiron 865® blood gas analyzer, as our data shows this blood gas analyzer to have a high degree of accuracy when compared to the YSI 2300 Stat Plus®. However, if blood sampling using the Bayer Chiron 865® blood gas analyzer is performed by Respiratory Therapists (as in this GSICU), reliance on this method would have workload implications. Nonetheless, it is important to note that the Bayer Chiron 865® blood gas analyzer can be used to validate the results obtained by BGMs in critically ill patients. If the RN questions the accuracy of the BG value obtained by a BGM, an arterial sample may be obtained and tested using the Bayer Chiron 865®

blood gas analyzer. If any discrepancy in BG values exists between these two methods, a recommendation can be made to use the BG value obtained by the Bayer Chiron 865® blood gas analyzer as the more accurate result.

Implications for Research

Further research into the accuracy of BGMs used to monitor BG levels in critically ill patients needs to occur in more than one GSICU. The effects of a number of potential covariates, such as hematocrit, pO_2, and pH on BGM performance must also be taken into consideration. The relationship of capillary and arterial BG requires further study, as these blood samples are frequently interchanged in critical care units. Studies designed to determine the best method to adjust continuous insulin infusions to maintain normoglycemia within critically ill patients are needed and these studies require BGMs that provide accurate BG measurements. The BG ranges purported in the Van den Berghe (2001) study were 4.4 mmol/L to 6.1 mmol/L. In this study, 71% of arterial BG values and 72% of capillary BG values were >6.1 mmol/L, and 1% of both arterial and capillary BG values were <4.4 mmol/L. Therefore more research is required to establish standardization of BG ranges in a heterogeneous critically ill patient population. The application of performance criteria for BGMs established with an outpatient diabetic population (BGM value within 20% of the BG reference instrument) must be examined to determine if a more stringent criterion (i.e.within 10%) for management of BG in critically ill patients is necessary.

Conclusion

Emerging data supports maintaining normal BG with continuous insulin infusions as a standard of care for critically ill patients. This intervention has been shown to have a

profoundly beneficial effect on morbidity and mortality in critically ill patients. RN's are in a position to greatly improve outcomes of critically ill patients, by utilizing this cost-effective therapy. However, maintaining normal BG levels can be quite challenging, because different analytical methods are not equally accurate in their measurement of BG in capillary and arterial blood. Without reliable and valid BG testing, strategies to maintain normal BG levels are seriously limited and increase the risk of either hyperglycemia or hypoglycemia in critically ill patients.

The accuracy of any laboratory result is only as good as the quality of the sample and the instrument upon which the analysis was done. Critical care nursing practice includes maintaining BG values in critically ill patients within a narrow range, therefore critical care RN's must be provided with the research and BG instruments necessary to achieve this goal. Based on the findings of this study, measurement of BG using arterial samples demonstrates a higher degree of accuracy when compared to capillary samples in critically ill patients. With arterial BG sampling, the Abbot Freestyle® (BGM #3) is the most accurate of the three BGMs evaluated in this study. In addition, the Bayer Chiron 865® blood gas analyzer is shown to be a highly accurate instrument to measure arterial BG.

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Appendix C

Data Collection Sheet

Patient study #_____Date:_____Admission Date:_____

Demographic Variables:

Age:_____Sex: ❑ Male ❑ Female. APACHE II Score:_____

Admission Diagnosis:_____

Comorbidities:

INSULIN @ 0800:_____1200:_____1600:_____

MEDICATIONS:_____

_____

Tube Feed: CRRT:

Laboratory data:

1. Hematocrit:_____ pO_2:_____pCO_2:_____pH_____
2. Hematocrit:_____ pO_2:_____pCO_2:_____pH_____
3. Hematocrit:_____ pO_2:_____pCO_2:_____pH_____

Patient data:

SureStepFlexx® BGM blood glucose value: Capillary sample

1:_____2:_____3:_____

SureStepFlexx® BGM blood glucose value: Arterial sample

1:_____2:_____3:_____

1. Temperature:_____ BP_____ MAP_____
2. Temperature:_____ BP_____ MAP_____
3. Temperature:_____ BP_____ MAP_____

Appendix D

Blood Glucose Values Measured and Recorded
by Laboratory Technician

SUBJECT #	Capillary Blood	Capillary Blood	Capillary Blood	Capillary Blood	Capillary Blood
BLOOD GLUCOSE ANALYZER	SureStepFlexx	AccuChek Inform	Freestyle	YSI	**Corrected** YSI
BG					
BG					
BG					

SUBJECT #	Arterial Blood	Arterial Blood	Arterial Blood	Arterial Blood	Arterial Blood	Arterial Blood
BLOOD GLUCOSE ANALYZER	SureStepFlex	AccuChek Inform	Freestyle	YSI	**Corrected** YSI	CHIRON 865 Blood Gas Analyzer
BG						
BG						
BG						

BG: Blood Glucose
BGMs: LifeScan SureStepFlexx®
Roche Accu-Chek Inform®
Abbott Freestyle®
YSI®: Yellow Springs Instrument
Chiron 865® Blood Gas Analyzer