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ORIGINAL ARTICLE

Intravascular Microdialysis as a Method for Measuring Glucose and Lactate during and after Cardiac Surgery

Fanny Möller, M.D., Jan Liska, M.D., Ph.D., Fredrik Eidhagen, M.D., and Anders Franco-Cereceda, M.D., Ph.D.

Abstract

Background:

The aim was to evaluate intravascular microdialysis as a method for measuring blood glucose and lactate in a clinical setting during and after cardiac surgery.

Methods:

Ten patients undergoing cardiac surgery were included. A microdialysis catheter was percutaneously placed in the superior vena cava or right atrium. Glucose and lactate values measured by the microdialysis technique were analyzed and compared with reference methods, i.e., arterial and venous blood gas values, once every hour up to 24 hours postoperatively. Laboratory plasma glucose was additionally analyzed every 4 hours for reference value.

Results:

Mean absolute differences were low between microdialysis and reference methods for both glucose and lactate values. All microdialysis glucose values were in the clinically acceptable zone of error grid analysis when compared with plasma glucose values. Accuracy of glucose values was 92% according to International Organization for Standardization criteria.

Conclusions:

Intravascular microdialysis is a novel and promising technique for real-time and accurate measurement of glucose and lactate during and after open heart surgery. Development of sensor technology may allow for continuous measurement of blood glucose and lactate using intravascular microdialysis.

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Author Affiliation: Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital Stockholm, Sweden

Abbreviations: (CI) confidence interval, (CVC) central venous catheter, (CVP) central venous pressure, (EGA) error grid analysis, (IIT) intensive insulin therapy, (ISO) International Organization for Standardization, (SICU) surgical intensive care unit

Keywords: glucose, heart surgery, lactate, microdialysis

Corresponding Author: Fanny Möller, M.D., Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, S-171 76 Stockholm, Sweden; email address *fanny.moller@ki.se*

Hyperglycemia associated with insulin resistance is common in critically ill patients, regardless of previously diagnosed diabetes. The underlying mechanism is thought to be associated with peripheral insulin resistance, hyperinsulinemia, increased gluconeogenesis, and impaired insulin-mediated glucose uptake, defined as stress diabetes.[1,2] In 2001, Van den Berghe and colleagues[3] published a study on intensive insulin therapy (IIT) in critically ill patients. This study attracted a great deal of attention for its demonstration of a reduction in in-hospital mortality by 34% by maintaining blood glucose values between 4.4 and 6.1 mmol/liter with IIT during intensive care. However, since then, doubt about IIT has been raised because of the increased risk for hypoglycemia and the difficulties of analyzing blood glucose values accurately and frequently enough. The mortality risk reduction has also been questioned.[4,5] It seems that surgical intensive care unit (SICU) patients benefit the most from IIT.[6] Special interest has been addressed to cardiac surgery patients and glucose control intraoperatively and postoperatively.[7,8]

Lactate is a well-known marker for ischemia and can be used as a prognostic factor for patients with a low cardiac output or patients with septicemia.[9] The routine method for measuring lactate values intraoperatively and in the SICU is the same as for glucose—through blood gas analysis.

This study was designed to assess efficacy of intravascular microdialysis for continuous sampling of blood glucose and lactate and determine the usefulness of this technique, in combination with an offline measuring device, for monitoring these analytes during surgery and postoperative intensive care.

Microdialysis

Tissue microdialysis was introduced in 1972 by Delgado and associates.[10] The technique is based on diffusion over a semipermeable membrane that is impermeable to macromolecules but permeable to low molecular weight compounds, such as glucose and lactate. A gentle flow of isotonic fluid within the membrane initiates diffusion and creates equilibrium between the test location and dialyzate fluid. Dialyzate can then be collected and analyzed. Intravascular microdialysis is an extension of the technique, which offers the possibility to monitor *in vivo* low molecular weight compounds in the bloodstream without blood sampling.[11] Hence, microdialysis offers the possibility to monitor low molecular weight compounds without blood sampling.

Methods

Patients

Patients (n = 10) were subjected to routine cardiac surgery, coronary artery bypass grafting (n = 9) and aortic valve replacement (n = 1) at the Karolinska University Hospital between April and May 2009. Three patients had a medical history of diabetes on admission, one of which had treatment with insulin (**Table 1**). All patients gave their consent to participate after being given oral and written information about the study. The Regional Ethics Committee of Stockholm approved the study and its protocol (ethical registration number 2007/1268-31).

Patients were prepared with standard procedures for surgery and anesthesia induction. A triple-lumen central venous catheter (CVC) was inserted in the right internal jugular vein, which enabled continuous measurement of central venous pressure (CVP), administration of medication, and blood sampling. An arterial line in the radial artery was used to measure arterial pressure and for collecting blood samples.

Catheter and Microdialysis System

Microdialysis was performed with a 4 Fr intravascular catheter (Dipylon Cardiac Catheter, CMA Microdialysis AB, Solna, Sweden). The catheter (length 67 cm) has a semi-permeable microdialysis membrane (length 40 mm and diameter 4 Fr) located at its distal end. The membrane is made of polyarylethersulphone and has a molecular weight cut-off of approximately 20,000 Dalton. The ratio of the concentration of molecules on both sides of the

Table 1.
Patient Characteristics[a]

Sex	
Male/female	8/2
Age (years)	65 ± 10
Body mass index	25 ± 3
History of diabetes	3
Treated with insulin	1
Treated with oral antidiabetics	2

[a] Values are presented as mean ± standard deviation.

membrane is defined as the recovery. The ideal recovery is 100%, i.e., levels are equal on both sides of the membrane. Recovery for lactate and glucose using the microdialysis catheter is 100% (company data on file). Dialyzate was collected in microvials (CMA Microdialysis AB) in the outlet lumen of the microdialysis catheter. Microvial dialyzate was analyzed for glucose and lactate values using the ISCUS Clinical Microdialysis Analyzer (CMA Microdialysis AB). The ISCUS is calibrated using solutions with known glucose and lactate concentrations.

Microdialysis was prepared as follows: a 6 Fr introducer (IntroFlex, Edward Lifesciences, Irvine, CA) was placed in the right internal jugular vein next to the CVC. The microdialysis catheter was then inserted in the superior vena cava, i.e., 20 cm (n = 10) into the introducer to allow the complete membrane to be exposed to the blood stream. The actual length at insertion and at removal of the catheter was registered for each patient. After insertion, perfusion of the catheter was initiated with a continuous flow of sterile isotonic solution (Ringer Acetate 0.3 ml/h) with the use of a pump (Alaris GH Guardrails, CardinalHealth, Dublin, OH).

Study Design

The study was designed to compare glucose and lactate values with reference methods of arterial blood gas and venous blood gas. Analyses were performed every hour starting at arrival into the SICU and were terminated after a maximum of 24 h or when the patient was discharged from the SICU. In addition, the plasma glucose was analyzed every 4 h in nine patients.

The following procedure was performed every hour after arrival into the SICU until the end of the study: a microvial was inserted into the microdialysis catheter to sample dialyzate for a period of 5 min. Correction was not made for the time lag of the sampling period. Hemodynamic parameters, including mean arterial pressure, heart rate, and CVP, were recorded. In addition, arterial and venous blood gas samples were analyzed for glucose and lactate values using a blood gas analyzer (ABL800 FLEX, Radiometer Medical, Copenhagen, Denmark). Plasma glucose values were analyzed by the hospital's laboratory every 4 h in nine patients.

After arrival to the SICU, patients received 10% glucose infusion (1 ml/kg/h) for up to 24 h postoperatively. The infusion was administered through the CVC. Blood glucose levels were maintained with insulin infusions. Other standard infusions were propofol for sedation, prophylactic antibiotics, and morphine. Patients also received inotropic or vasodilating drugs and diuretics as needed. At removal of the microdialysis catheter the membrane was inspected for potential clotting.

Statistical Analysis

Correlation plots were made by plotting tested glucose and lactate values to the chosen reference value. Clarke error grid analyses (EGAs) were made to analyze the clinical relevance of microdialysis glucose values.[12] The EGA plots display paired samples in five different zones of different significance. Values in zone A are within 20% of the reference value and have no clinical implications. Values in zone B exceed 20% difference from reference value but lead to appropriate clinical decisions. Values in zone C may lead to unnecessary but harmless corrections. Values in zone D and E represent overestimation of hypoglycemia (failure to detect) or underestimation of hyperglycemia that may lead to incorrect clinical actions. In short, the more values in zone A and B, the more clinical accuracy of the method.

Glucose values were also evaluated according to the International Organization for Standardization (ISO) criteria. To meet this criteria, 95% of test glucose values have to be within ±20% of reference values if the reference value is >4.1 mmol/liter or within ±0.8 mmol/liter if the reference value is <4.1 mmol/liter.

Results

Mean follow-up time was 16.7 h (range 8–20 h). At removal of the microdialysis catheter, no clotting of the membrane was observed.

Glucose

Average glucose values over time are presented in **Figure 1**.

Correlation between Microdialysis and Arterial Blood Gas

Mean difference was -0.07 mmol/liter [95% confidence interval (CI) -1.5 to 1.4 mmol/liter]. Correlation is shown in **Figure 2A**. A total of 93% of the samples were within ISO criteria (**Table 2**). All test samples were within the AB zone in EGA (**Figure 3A**).

Correlation between Microdialysis and Venous Blood Gas

Mean difference was -0.09 mmol/liter (95% CI -1.9 to 1.7 mmol/liter). Correlation is shown in **Figure 2B**. A total of 89% of the samples were within ISO criteria (**Table 2**). Clarke EGA displayed one sample outside the AB zone (**Figure 3B**).

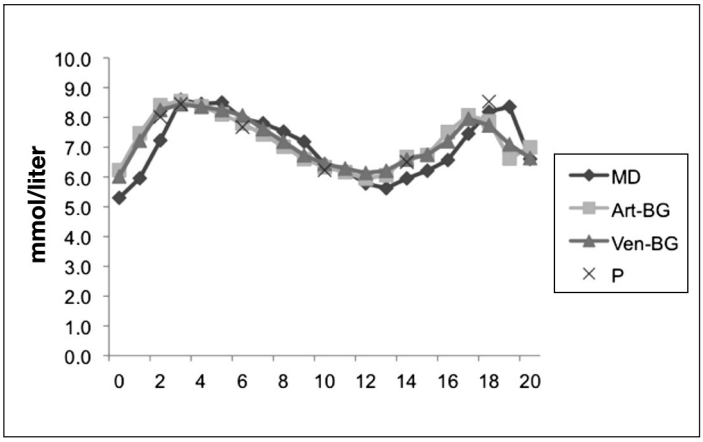

Figure 1. Average glucose values over time. Art-BG, arterial blood gas; MD, microdialysis; P, plasma glucose from laboratory; Ven-BG, venous blood gas.

Table 2.
Accuracy According to the International Organization for Standardization Criteria[a]

Test versus reference method	Total number of samples	ISO accuracy (%)	Test value higher (%)	Test value lower (%)
MD vs Art-BG	174	93	2	5
MD vs Ven-BG	174	89	3	8
MD vs P	36	92	6	2
Art-BG vsP	37	100	0	0
Ven-BG vs P	37	97	3	0
Ven-BG vs Art-BG	177	99	1	0

[a] Art-BG, arterial blood gas; MD, microdialysis; P, plasma glucose from laboratory; Ven-BG, venous blood gas.

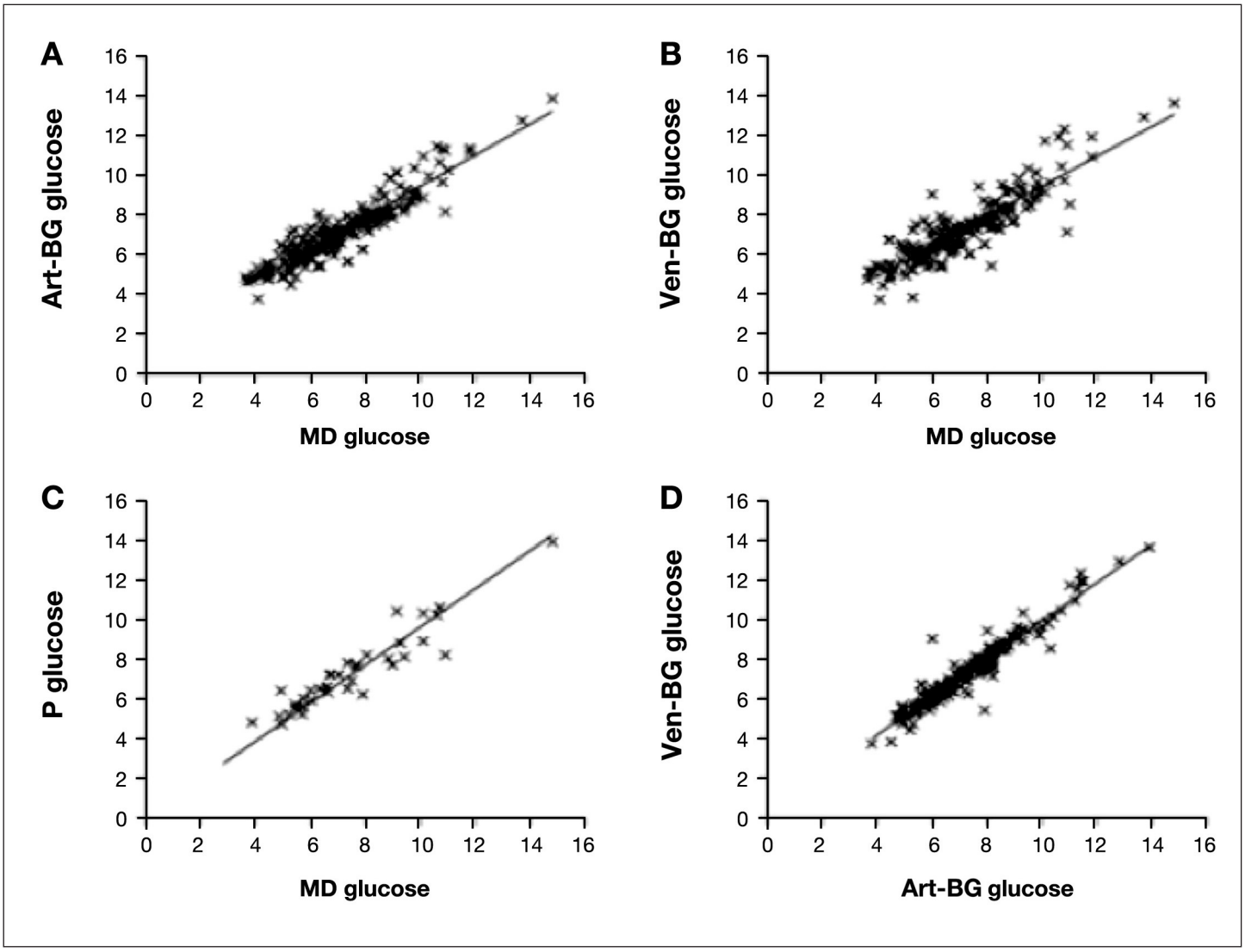

Figure 2. Correlation between glucose values (mmol/liter): **(A)** microdialysis versus arterial blood gas, **(B)** microdialysis versus venous blood gas, **(C)** microdialysis versus plasma, and **(D)** arterial versus venous blood gas. Art-BG, arterial blood gas; MD, microdialysis; P, plasma glucose from laboratory; Ven-BG, venous blood gas.

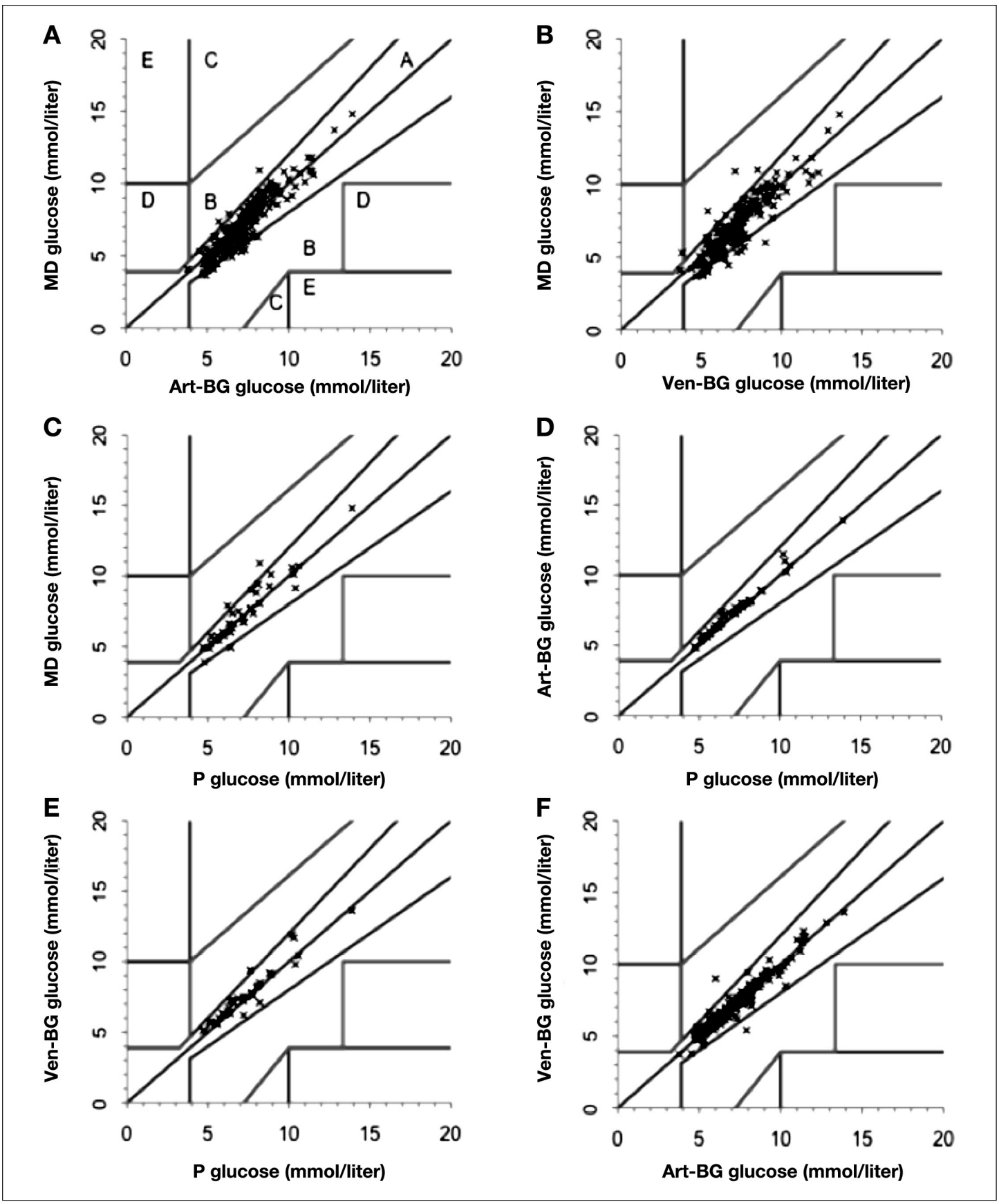

Figure 3. Clarke EGAs of **(A)** microdialysis versus arterial blood gas, **(B)** microdialysis versus venous blood gas, **(C)** microdialysis versus plasma, **(D)** arterial blood gas versus plasma, **(E)** venous blood gas versus plasma, and **(F)** venous versus arterial blood gas. Art-BG, arterial blood gas; MD, microdialysis; P, plasma glucose from laboratory; Ven-BG, venous blood gas.

Correlation between Microdialysis and Plasma Glucose Analyzed by the Hospital's Laboratory
Mean difference was 0.19 mmol/liter (95% CI -1.4 to 1.8 mmol/liter). Correlation is shown in **Figure 2C**. A total of 92% of the samples were within ISO criteria (**Table 2**). All test samples were within the AB zone in EGA (**Figure 3C**).

Correlation between Arterial Blood Gas and Plasma Glucose Analyzed by the Hospital's Laboratory
Mean difference was 0.27 mmol/liter (95% CI -0.3 to 0.9 mmol/liter). All samples (100%) were within ISO criteria (**Table 2**). All test samples were within the AB zone in EGA (**Figure 3D**).

Correlation between Venous Blood Gas and Plasma Glucose Analyzed by the Hospital's Laboratory
Mean difference was 0.29 mmol/liter (95% CI -0.9 to 1.4 mmol/liter). A total of 97% of the samples were within ISO criteria (**Table 2**). All test samples were within the AB zone in EGA (**Figure 3E**).

Correlation between Venous Blood Gas and Arterial Blood Gas
The arterial blood gas value was chosen as the reference value. Mean difference was 0.09 mmol/liter (95% CI -0.9 to 1.0 mmol/liter). Correlation is shown in **Figure 2D**. A total of 99% of the samples were within ISO criteria (**Table 2**). All test samples were within the AB zone in EGA (**Figure 3F**).

Lactate

Average lactate values over time are presented in **Figure 4**.

Correlation between Microdialysis and Arterial Blood Gas
Mean difference was 0.33 mmol (95% CI -0.3 to 0.9 mmol/liter). Correlation is shown in **Figure 5A**.

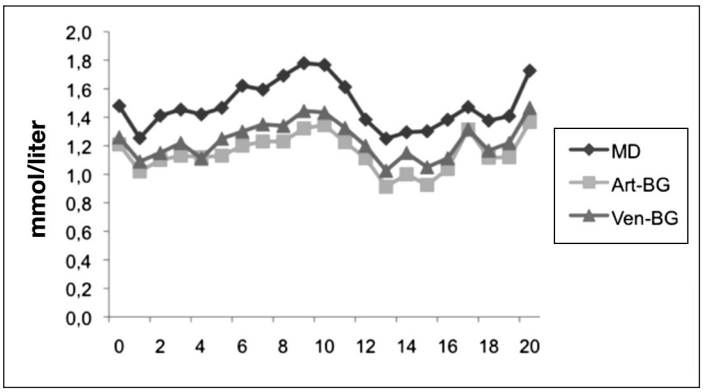

Figure 4. Average lactate values over time. Art-BG, arterial blood gas; MD, microdialysis; Ven-BG, venous blood gas.

Correlation between Microdialysis and Venous Blood Gas
Mean difference was 0.24 mmol (95% CI -0.3 to 0.8 mmol/liter). Correlation is shown in **Figure 5B**.

Correlation between Venous Blood Gas and Arterial Blood Gas
Mean difference was 0.09 mmol (95% CI -0.1 to 0.3 mmol/liter). Correlation is shown in **Figure 5C**.

Discussion

In this study, we have evaluated intravascular microdialysis as a method for measurement of glucose and lactate during and after cardiac surgery compared with conventional blood sampling. Results indicate that intravascular microdialysis can be used for metabolic monitoring of patients undergoing cardiac surgery, and therefore provide information to keep glucose values in a safe range with IIT and also to give an early sign of perioperative and postoperative ischemia (lactate). In the SICU, blood glucose is analyzed repeatedly to adjust glucose and insulin infusions. A reliable and easy method to measure blood glucose frequently is needed for practical reasons. If proven to be useful and accurate, intravascular microdialysis could have the potential to replace the present standard methods of analyzing blood glucose.

To evaluate accuracy of glucose values measured by different methods, several aspects can be investigated: absolute difference between test and reference values, accuracy according to ISO criteria, or whether the values result in the same clinical intervention. Mean absolute difference between evaluated methods of glucose measurement was low in this study.

As expected, arterial blood gas and venous blood gas glucose values were both accurate enough to meet ISO criteria when compared with plasma glucose values (**Table 2**). Microdialysis values were 92%, 93%, and 89% accurate using plasma glucose, arterial blood gas, and venous blood gas, respectively, as reference data. Even though current accuracy is lower than required by the ISO norm (>95%), better results may be achieved after further technical improvement of the analyzing method.

Error grid analyses were plotted to obtain information of clinical relevance of glucose test values. When compared with laboratory plasma glucose as reference value, no other test method (microdialysis, arterial blood gas, and venous blood gas) had values affecting the patient clinically (**Figure 3**). Thus all values were within the AB zone of the EGA.

Other studies investigating glucose measurement accuracy have focused on point-of-care testing.[13–15] Kanji and coworkers[14] found 76.5% agreement between arterial blood gas glucose analysis and central laboratory glucose values. Agreement was defined as values resulting in the same clinical interventions. In our study, the agreement of both glucose analysis between arterial blood gas and microdialysis with laboratory plasma glucose values were more consistent. Arterial blood gas glucose values correlated well with conventional laboratory assessment, as shown by Corstjens and colleagues,[15] who demonstrated that 96.8% of paired samples were in the clinically acceptable zones A and B of the EGA. This finding further supports our results with 100% of paired samples (arterial blood gas and laboratory plasma glucose values) in the AB zone (**Figure 3D**) and 100% ISO accuracy (**Table 2**). Petersen and associates[16] found that arterial blood gas glucose values did not alter clinical care according to EGA when compared with laboratory plasma glucose, which also is in accord with our findings.

Increase in lactate can be used as an indicator of ischemia and is today most easily monitored by analyzing arterial or venous blood gases. The mean absolute difference was lowest when comparing arterial and venous blood gas lactate values and highest when comparing microdialysis to arterial blood gas lactate values. It is difficult to establish the accuracy of measured lactate values in our study, although our data suggest a high correlation between obtained microdialysis and blood gas values.

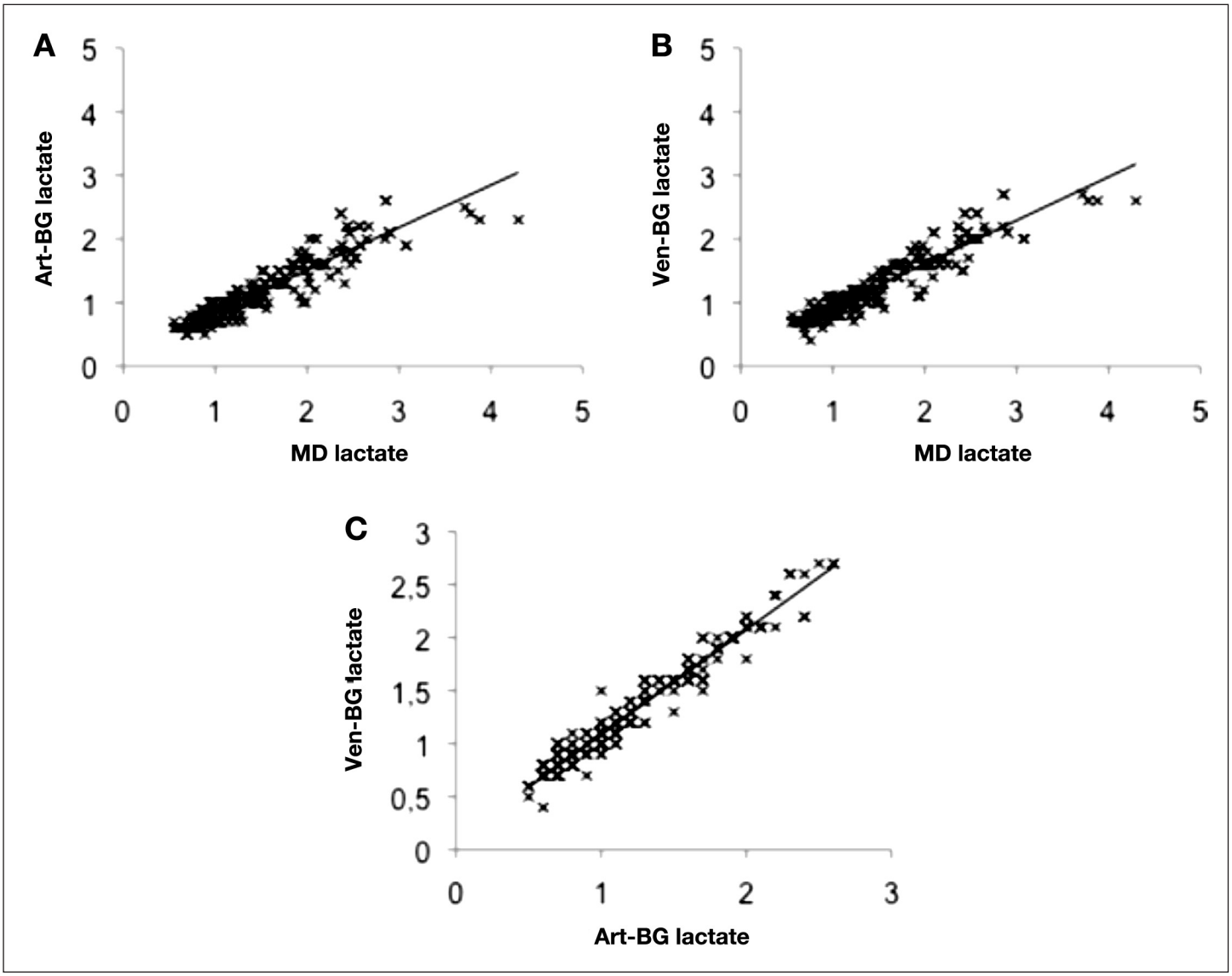

Figure 5. Correlation between lactate values: **(A)** microdialysis versus arterial blood gas, **(B)** microdialysis versus venous blood gas, and **(C)** arterial versus venous blood gas. Art-BG, arterial blood gas; MD, microdialysis; Ven-BG, venous blood gas.

It is noteworthy that there were consistent higher lactate levels when measured by microdialysis compared with reference levels. To what extent this relates to differences in analytical methods remains to be further studied. Furthermore, in a clinical setting, the trend of lactate values may be more clinically important than the actual momentary value.

It is notable that no clotting of the surface of the microdialysis membrane was apparent during the usage period of up to 24 hours. However, to what extent the catheter can be used for longer periods without anticoagulation remains to be studied.

Study Limitations

All patients received postoperative glucose infusions in the SICU. Glucose infusions were administered through the CVC, which was placed in proximity to the microdialysis catheter membrane. Ideal placement of the microdialysis catheter would be proximal to the CVC to avoid interference from the glucose infusion. However, this could not be achieved because the microdialysis catheter is longer than the CVC if the complete membrane is to be placed outside the introducer used in this study and fully exposed to the bloodstream. However, the lack of difference in glucose correlation regarding placement of the microdialysis catheter (right atrium or superior vena cava) in our results does not support this concern. Another weakness of the presently used technique of intravascular microdialysis is that it is carried out by sampling dialyzate for 5 minutes while blood gas analyses are instantaneous values, which may affect the results. This could be overcome by technical improvement with online and real-time microdialysis measurement.

Conclusions

This study shows that intravascular microdialysis is a promising new method for glucose and lactate measurement in a clinical setting. An online continuous microdialysis system with real-time measurement and minimal time lag would further simplify perioperative and postoperative metabolic monitoring of patients undergoing cardiac surgery. It is further suggested that this technology can be used to measure other clinically relevant small molecular-weight compounds.

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Disclosure:

Jan Liska and Anders Franco-Cereceda are stockholders of CMA Microdialysis AB, Solna, Sweden.

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