Clinical Evaluation of Alternative-Site Glucose Measurements in Patients After Major Cardiac Surgery

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OBJECTIVE — Tight glycemic control improves outcome in critically ill patients but requires frequent glucose measurements. Subcutaneous adipose tissue (SAT) has been characterized as promising for glucose monitoring in diabetes, but it remains unknown whether it can also be used as an alternative site in critically ill patients. The present study was performed to clinically evaluate the relation of glucose in SAT compared with arterial blood in patients after major cardiac surgery.

RESEARCH DESIGN AND METHODS — Forty critically ill patients were investigated at two clinical centers after major cardiac surgery. Arterial blood and SAT microdialysis samples were taken in hourly intervals for a period of up to 48 h. The glucose concentration in dialysate was calibrated using a two-step approach, first using the ionic reference technique to calculate the SAT glucose concentration (SATg) and second using a one-point calibration procedure to obtain a glucose profile comparable to SAT-derived blood glucose (BgSAT). Clinical validation of the data was performed by introducing data analysis based on an insulin titration algorithm.

RESULTS — Correlation between dialysate glucose and blood glucose (median 0.80 [interquartile range 0.68–0.88]) was significantly improved using the ionic reference calibration technique (SATg vs.blood glucose 0.90 [0.83–0.94]; $P < 0.001$). Clinical evaluation of the data indicated that 96.1% of glucose readings from SAT would allow acceptable treatment according to a well-established insulin titration protocol.

CONCLUSIONS — The results indicate good correlation between SATg and blood glucose in patients after major cardiac surgery. Clinical evaluation of the data suggests that with minor limitations, glucose from SAT can be used to establish tight glycemic control in this patient group.

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Maintaining critically ill patients within strict glycemic limits can dramatically reduce mortality, risk of infection, and other complications and also has substantial socioeconomic impact (1–3). Due to administration of varying doses of parenteral and enteral nutrition, intravenous infusion of medications that affect glucose metabolism, and development of acute insulin resistance during sepsis, tight glycemic control can only be granted by frequent blood glucose monitoring. Although most critically ill and hospitalized patients have routinely placed venous or arterial access lines, glycemic control is still inadequate. The unmanageable workload for the nursing staff and the prevalent fear of hypoglycemia among critical care physicians hinders the implementation of glycemic control in the intensive care unit (ICU) (4).

For diabetic patients, alternative-site glucose testing to achieve better, continuous, or automated feedback control of glycemia has been sought for a long time (5–7). Thanks to minimal invasiveness and good correlation with blood glucose, subcutaneous adipose tissue (SAT) is probably the most investigated alternative sampling site (8–13). Glucose monitoring in SAT would provide more frequent information about glycemia (trend information) and would therefore also be of benefit for critically ill patients.

Microdialysis of SAT has been well established for the investigation of the interstitial fluid glucose profile in relation to blood glucose in healthy individuals and diabetic patients (9). Due to critical illness of patients in the ICU, the perfusion status of various tissue regions is altered (14–16), and hence, the suitability of adipose tissue as an alternative sampling site for glucose also has to be questioned. The aim of the present study was to clinically evaluate the relation between glucose concentrations in SAT and arterial blood using hourly point-to-point analysis in post–cardiac surgery patients at the ICU for a period of up to 48 h. A novel data analysis was introduced to clinically evaluate whether glucose measurements from SAT can be used to establish tight glycemic control in this patient group.

RESEARCH DESIGN AND METHODS

— A total of 40 adult patients from two different ICUs were included in the study. All patients were investigated after major cardiac surgery (coronary artery bypass grafting 70%, valve replacement 15%, both 5%, and aortic replacement 10% of patients). Patients were investigated until the end of ICU stay but for a maximum period of 48 h (median 48 h [range 15–48]). Patient characteristics are depicted in Table 1. The study was approved by the local ethics committee at Charles University

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Abbreviations: BgSAT, subcutaneous adipose tissue–derived blood glucose; ICU, intensive care unit; SAT, subcutaneous adipose tissue; SATg, SAT glucose concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline characteristics*

	Graz	Prague	Total
Patients (*n*)	20	20	40
Age (years)	68.6 ± 7	66.0 ± 11	67.3 ± 9
Female (*n*)	5	3	8
Ethnicity (Caucasian)	20	20	40
BMI (kg/m^2) (*n*)	28.2 ± 4.9	27.0 ± 4.0	27.6 ± 4.4
History of diabetes (*n*)	6	10	16
Systolic blood pressure (mmHg)	108 ± 10	119 ± 10	114 ± 11
Diastolic blood pressure (mmHg)	54 ± 5	57 ± 5	55 ± 5
Heart rate (bpm)	90 ± 10	88 ± 7	89 ± 9
APACHE II score	10.1 ± 3.2	11.4 ± 4.5	10.7 ± 3.9

Data are means ± SD. APACHE II, Acute Physiology And Chronic Health Evaluation II score (4).

Prague and at Medical University Graz. Signed informed consent was obtained from all patients before surgery and before any trial-related activities.

The study started with a screening visit before surgery to obtain characteristic information about the patients, including demographic data, medical history, concomitant medication, body composition, vital signs, and laboratory analysis from routine laboratory assessment. Patients fulfilling the inclusion criteria (increased blood glucose levels at admission to the ICU [>120 mg/dl]) were included after admission to the ICU. Tight glycemic control was established based on arterial blood glucose measurements. For sampling of interstitial fluid a microdialysis catheter (CMA 60; CMA Microdialysis, Solna, Sweden) was inserted into the SAT on the left or right side of the umbilical region. After insertion, the catheter was connected to a microinfusion pump (CMA 107; CMA Microdialysis) (17,18). Experiments started at least 60 min after insertion of the microdialysis catheter. The dialysis catheter was constantly perfused at a flow rate of 1 μl/min with an isotonic solution of 5% mannitol (19). Dialysate was continuously sampled and collected in hourly fractions (e.g. from time 0800 until 0900) in interstitial sampling vials (CMA Microdialysis) throughout the study period. Blood samples from an arterial line were collected in hourly intervals (e.g. at time 0800 and 0900) at the same time when SAT sampling vials were changed. Experiments ended when patients were transferred from the ICU upon decision of the treating physician but at the latest 48 h after start of the study.

Arterial blood glucose samples were analyzed using standard point-of-care testing devices (Graz: Omni S; Roche Diagnostics, Basel, Switzerland; Prague: ABL 700; Radiometer Medical, Copenhagen, Denmark). Fractionized samples from SAT dialysate were stored at −70° C immediately after sampling and analyzed at a central laboratory (Joanneum Research, Graz, Austria). Dialysate samples were analyzed for glucose using a Cobas Mira Analyzer (Roche Diagnostics, Basel, Switzerland) using standard enzymatic assays (Roche Diagnostics, Mannheim, Germany). Sodium (dialysate sodium) and potassium were analyzed using a flame photometer (Instrumentation Laboratory, Vienna, Austria). Intrarun (interrun) coefficients of variation were 1.3% (1.6%) and 0.4% (0.4%) for glucose and sodium, respectively.

Calculations and calibration

The basis for the data analysis was fractionized samples of SAT dialysate glucose concentrations. In addition, corresponding hourly measurements of arterial blood glucose were averaged between beginning (e.g. time 0800) versus end (e.g. time 0900) of the interstitial sampling interval. The measured glucose concentration in SAT dialysate was calibrated using a two-step calibration approach, first using the ionic reference technique (14,19) to calculate the actual glucose concentration in SAT (SATg) (dialysate glucose → SATg) and second using a one-point calibration procedure to obtain a glucose profile comparable to arterial blood glucose (SATg → SAT-derived blood glucose [BgSAT]). In brief, the ionic reference calibration technique accounts for the fact that the measured dialysate glucose concentration is lower than the actual SATg. SATg is calculated for each sample using the relation SATg = dialysate glucose × plasma sodium/dialysate sodium (19), considering the recovery of interstitial fluid in the collected dialysate of microdialysis samples. For the plasma sodium concentration, a constant concentration was applied for all patients (see CONCLUSIONS). SATg, as calculated using the ionic reference technique, is lower compared with the actual arterial blood glucose concentration (19,20). Therefore, as a second calibration step, SATg was calibrated to blood glucose using a one-point calibration procedure. Using this procedure, the ratio between the first SATg reading and the average of the two corresponding blood glucose readings was used to calculate BgSAT. The one-point calibration procedure was chosen to establish a critical evaluation of BgSAT measurements (21).

Statistical analysis

Pearson coefficient of correlation was used to describe the relation between dialysate glucose versus blood glucose and SATg versus blood glucose. Normal distribution of data were tested using Shapiro-Francia test. Statistical comparisons were performed with Student's *t* test for paired/unpaired data if normal distribution could be guaranteed; otherwise, the Wilcoxon rank-sum test was used for unpaired data comparison. P values < 0.05 were considered statistically significant.

Clinical evaluation (insulin titration error grid analysis)

To clinically evaluate whether glucose readings from interstitial fluid of SAT can be used for the establishment of tight glycemic control, a novel data analysis was introduced. The procedure, as indicated in Fig. 1*A*, is based on the widely accepted insulin titration guideline as used by Van den Berghe (22). A simplified version of this guideline was incorporated into a standard graph defining the *x*-axis as the reference blood glucose and the *y*-axis as the corresponding glucose value to be evaluated, in our case glucose concentrations obtained from SAT. Paired glucose readings from individual patients (*x*-axis: arterial blood glucose; *y*-axis: BgSAT) are indicated in Fig. 1*B*. In addition, the suggested actions of the insulin titration guideline in relation to the corresponding blood glucose range are indicated on both axes, respectively (Fig. 1). Based on the resulting grid, clinical experts of participating centers were able to define different zones according to the severity of violation of the guideline from a clinical perspective (insulin titration error grid analysis). Zones were defined as acceptable treatment if the general procedure of

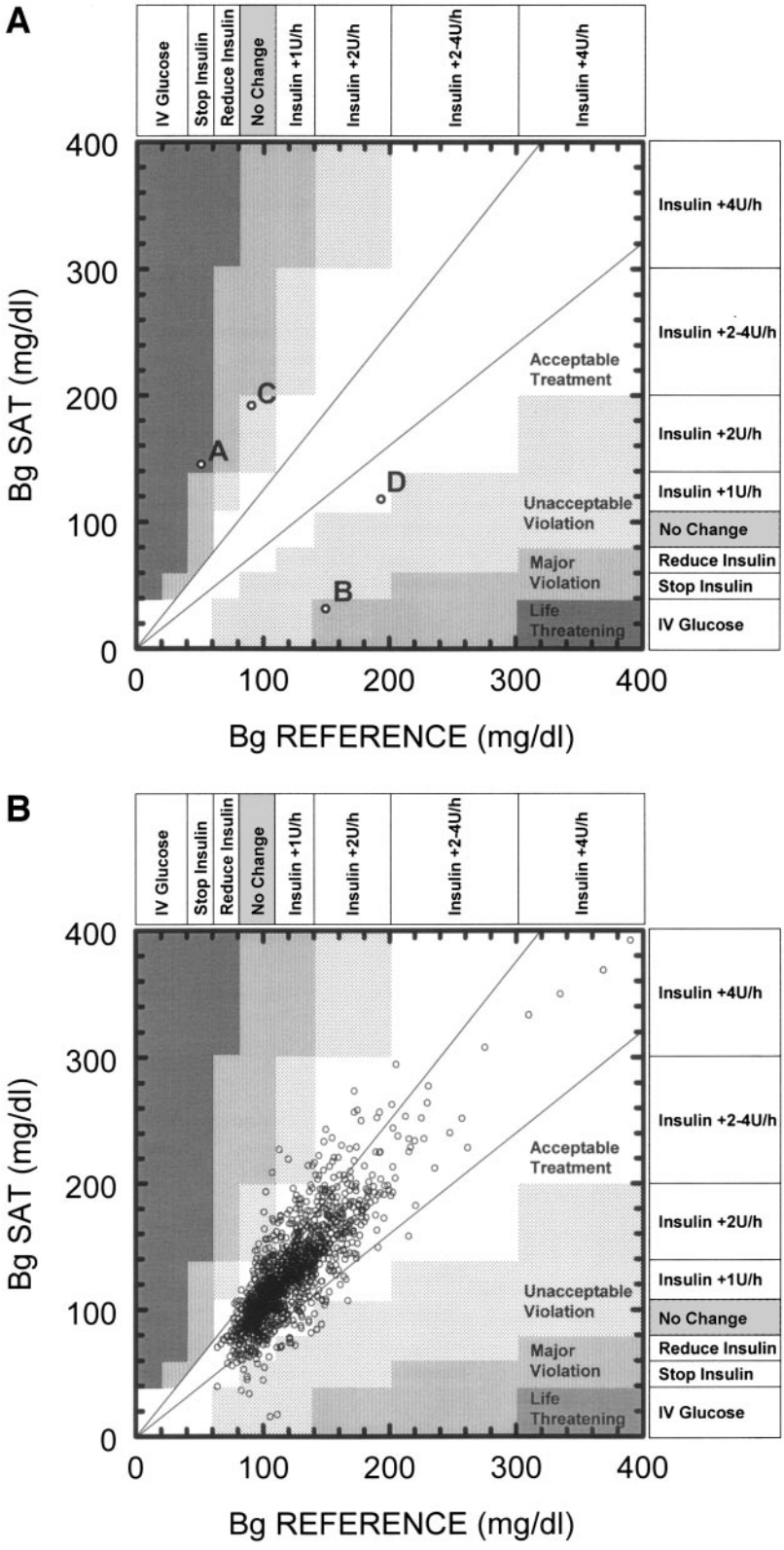

Figure 1—A: *Schematics for the clinical evaluation of subcutaneous glucose measurements using the insulin titration error grid analysis. Reference arterial blood glucose (Bg) concentrations and BgSAT are indicated on the* x- *and* y*-axis, respectively. Glucose ranges on* x- *and* y*-axis are related to major treatment actions as suggested by the Leuven insulin titration guideline (22). Based on these treatment actions, different zones according to the severity of violation of the titration algorithm have been defined. Examples A–D are described in the* RESEARCH DESIGN AND METHODS *section.* B: *Clinical evaluation of subcutaneous glucose measurements using insulin titration error grid analysis. A total of 96.1% of the data were found in the acceptable treatment zone, 3.8% of the data in the clinical unacceptable zone, and 0.1% of the data in the major violation zone.*

tight glycemic control was not violated, unacceptable violation if the guideline was violated but without any direct hazard for the patient, major violation in case of direct hazard for the patient because of a false treatment decision, and life threatening if the life of the patient might be directly endangered because of the false treatment decision. A relative measurement error of ±20% was tolerated for the whole range of glucose readings (23). Examples A–D, as indicated in Fig. 1*A*, represent examples for paired glucose measurements and shall illustrate the validation strategy. Example A: blood glucose 50 mg/dl; guideline suggests termination of insulin infusion. BgSAT 142 mg/dl; actual treatment will be to in-

Table 2—*Individual glucose readings as measured in arterial blood and interstitial fluid dialysate*

	Blood glucose (mg/dl)	Dialysate (mg/dl)	REC (%)	SATg (mg/dl)	*r* (blood glucose vs. dialysate)	*r* (blood glucose vs. SATg)
Median (interquartile range)	115 (98–141)	37 (14–58)*	59 (25–78)	66 (53–80)*	0.80 (0.68–0.88)	0.90 (0.83–0.94)
Min/max	64/390	2/237	4/118	10/293	0.26/0.96	0.49/0.99

Microdialysis recovery rate (REC) and SATg as calculated using the ionic reference technique (13,20). *r* indicates the Pearson coefficient of correlation of dialysate and SATg versus arterial glucose readings calculated for each individual patient. $n = 1{,}415$ patients; $^*P < 0.01$ vs. blood glucose.

crease the insulin infusion by 2 units/h. This case has been identified as a life-threatening situation for the patient because of the phycisians' unawareness of a critical hypoglycemic situation of the patient and the wrong treatment option of administering additional insulin to the patient. Example B: blood glucose 150 mg/dl; guideline suggests incrementing insulin infusion by 2 units/h. BgSAT 36 mg/dl; actual treatment will be to give an intravenous glucose bolus. This case was identified as a major violation of the titration guideline. Example C: blood glucose 85 mg/dl; the guideline suggests no change of the insulin infusion. BgSAT 195 mg/dl; actual treatment will be to increase the insulin infusion by 2 units/h. This case has been identified as unacceptable violation of the guideline because the increase of the insulin infusion may result in a dangerous situation for the patient. Example D: blood glucose 195 mg/dl; the guideline suggests increasing the insulin infusion by 2 units/h. BgSAT 120 mg/dl; actual treatment will be to increase the insulin infusion by 1 unit/h. This case was identified as acceptable treatment because the decision of the guideline was not severely violated. With this acceptable form of false treatment, tight glycemic control will be achieved but in a less aggressive manner.

RESULTS — A total of 40 patients were recruited into the trial. In none of the patients was reinsertion of a microdialysis system due to technical failure required. No adverse events related to the interstitial fluid glucose sampling occurred.

Comparison of dialysate and ionic reference calibrated (SATg) glucose profiles

Glucose concentrations as measured in SAT dialysate and glucose as calculated for SAT using the ionic reference technique (SATg) were clearly lower compared with arterial blood glucose concentrations (Table 2). These data confirm that an additional (second) calibration step of intersitital fluid glucose readings to describe blood glucose readings is required. To test whether the first calibration step (ionic reference technique) can be justified as interim calibration step in critically ill patients, correlations of individual glucose profiles between dialysate glucose versus blood glucose and SATg versus blood glucose were compared (Table 2). The results indicate that the correlation between dialysate glucose versus blood glucose could be significantly improved using the ionic reference calibration technique (dialysate vs. blood glucose: median 0.80 [interquartile range 0.68–0.88]; SATg vs. blood glucose: 0.90 [0.83–0.94]; $P < 0.001$).

After applying the second calibration step (one-point calibration), the relative differences between arterial blood glucose readings and BgSAT were calculated. Results indicated median −4.8% (interquartile range −14.7 to 2.9) difference between blood glucose and BgSAT readings. Figure 2 depicts eight representative patients, four patients with smallest (Fig. 2*A*) and four patients with largest (Fig. 2*B*) relative difference between blood glucose and BgSAT.

Clinical evaluation of BgSAT profiles

Clinical evaluation of BgSAT in comparison to blood glucose was performed using insulin titration error grid analysis as described in Fig. 1*A*. The analysis is based on a total of 1,415 pairs of blood glucose and BgSAT readings from 40 patients. A total of 96.1% of the interstitial fluid glucose readings were found in the acceptable treatment zone; 3.8% of the data were found in the unacceptable violation zone, and 0.1% of the readings were found in the major violation zone (Fig. 1*B*). Results of the analysis indicated that for a total of 3.9% of the glucose readings from SAT, safe implementation of tight glycemic control using the applied insulin guideline cannot be guaranteed.

CONCLUSIONS — With the present study it was demonstrated that in patients recovering from major cardiac surgery at the ICU, arterial blood glucose fluctuations are well described using interstitial fluid glucose measurements from SAT. Clinical evaluation of the data based on a well-accepted insulin titration guideline indicated that 96% of the glucose readings as derived from SAT would allow establishing tight glycemic control in the investigated patient group.

Numerous studies have been performed to test the suitability of glucose monitoring in interstitial fluid of SAT aimed to establish improved glycemic control in diabetes therapy (12,24–26). To date, few studies are available that evaluate the subcutaneous glucose concentration in critically ill patients (3,18), and to the best of our knowledge no study with point-to-point analysis of blood versus interstitial fluid glucose readings has been performed so far. Studies investigating more methodological aspects of tissue perfusion in critically ill patients with sepsis indicated impaired microvascular perfusion in these patient groups (14–16), which also might have an effect on the relation between blood and interstitial glucose concentrations. Results from the present study in patients at the surgical ICU suggest a close relationship between blood and interstitial fluid glucose, which is comparable as seen in previous studies in healthy volunteers and type 1 diabetic patients (9,12).

The present study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community. As part of the project, the present study was performed to directly evaluate the principle relation between arterial blood and interstitial fluid glucose concentrations using state-of-the-art laboratory analysis and point-to-point comparisons. Basis for the data analysis of the present study were samples of interstitial fluid dialysate, which were continuously collected in hourly fractions. A

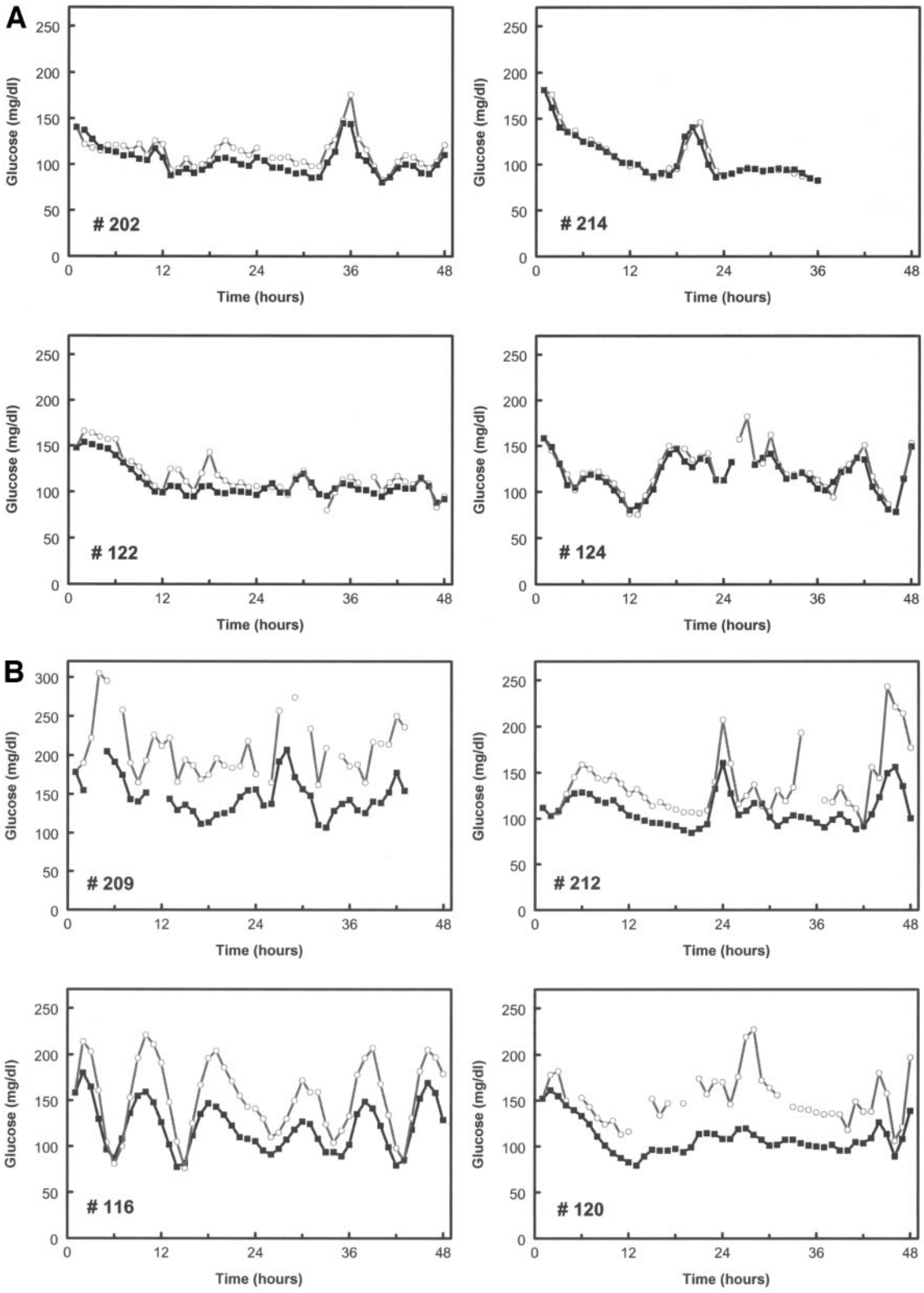

Figure 2—*Individual glucose profiles according to best* (A) *and worst* (B) *relation between arterial blood glucose and BgSAT based on individual method of residual analysis. Data indicate arterial blood glucose* (■) *and BGSAT calibrated to first arterial blood glucose reading* (□). *Numbers in graphs indicate patient IDs.*

prospective calibration technique (ionic reference technique) was used to calculate the interstitial fluid glucose concentration (19). To avoid the necessity of individual plasma sodium measurements, plasma sodium was assumed constant, a prerequisite that is likely to be violated in critically ill patients. In the present study a maximum intrapatient coefficient of variation (CV) for plasma sodium of 2.3% and an interpatient CV of 4.6% was observed. Regardless of these fluctuations of plasma sodium, the correlation between interstitial fluid and blood glucose readings could be substantially improved using the ionic reference technique. This finding clearly suggests that the calibration technique is useful when applied in the investigated patient group.

For the clinical evaluation of glucose data from SAT, a novel approach, an insulin titration error grid analysis was introduced. The objective of the analysis is to provide clinical evaluation criteria for alternative-site versus reference glucose measurements for critically ill patients. The analysis is based on a widely used insulin titration protocol as proposed by Van den Berghe (22). To integrate the insulin titration protocol into a standard two-dimension *x*-*y* graph, the titration guideline was simplified with respect to actions per range and at the same time also slightly extended, i.e., an additional action for glucose exceeding 300 mg/dl was introduced. Analysis of the present data using the analysis indicated that a total of 3.9%, representing 55 of 1,415 blood glucose readings, were outside the clinical acceptable treatment zone. The data suggest that establishment of tight glycemic control according to the implemented guideline and based on glucose readings from interstitial fluid would not have been violated for 96% of the acquired data pairs. Further analysis indicated that data in the unacceptable treatment zone was mostly due to patients, as indicated in Fig. 2*B*. Instability of the microdialysis catheter (25) during the initial phase of the experiment in combination with the applied one-point calibration procedure might explain differences of the subcutaneous glucose signal compared with arterial blood glucose readings as seen in these patients. Additional refinement of the technology (e.g., more frequent calibration intervals) will be required to further improve the relation between blood and interstitial glucose readings.

We summarize that the relation between arterial blood glucose and glucose as derived from interstitial fluid measurements was similar in patients after major cardiac surgery as previously reported for healthy volunteers and type 1 diabetic patients. Critical evaluation of the interstitial glucose data suggests that with minor limitations, glucose from SAT can be used to establish tight glycemic control in patients after major cardiac surgery.

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