Monitoring Blood Glucose with Microdialysis of Interstitial Fluid in Critically Ill Children

To the Editor:

Hyperglycemia, a common feature in critically ill patients, was traditionally perceived as an adequate stress response reflecting the severity of the disease state and was treated only if glycemia exceeded 11–13.5 mmol/L. In recent studies in intensive care patients, we showed that tight glycemic control (TGC) with intensive insulin therapy (IIT) reduced the risk of organ failure and death (1). In critically ill children, peak blood glucose (BG) and duration of hyperglycemia are associated with risk of mortality (2). Implementing TGC and avoiding hypoglycemia with intensive insulin therapy requires frequent BG sampling. Microdialysis of interstitial fluid (ISF) is a promising approach to reduce diagnostic blood loss. Continuously sampling dialyzed ISF and converting the ISF glucose concentration (IFG) to a BG value is a promising new method for glucose monitoring in diabetes patients. We conducted a prospective clinical trial in critically ill children to evaluate the feasibility of prolonged subcutaneous microdialysis and the correlation between BG and IFG.

The study was approved by the Institutional Ethical Review Board. Twenty children were enrolled after written informed consent was obtained from the parents. A CMA 60 microdialysis catheter (CMA Microdialysis) was inserted subcutaneously. This catheter has a dialyzing membrane with a molecular cutoff of 20 kDa and was continuously perfused with a 5% mannitol solution at a flow rate of 1 μL/min. BG was determined on an ABL 715 blood gas analyzer (Radiometer) and dialysate glucose (DG) values with a Cobas Mira Analyzer (Roche). Both techniques use the enzyme glucose dehydrogenase. Because of the used flow rate of 1 μL/min, the concentration in the dialysate reaches only partial equilibration and thus does not reflect the absolute concentration in the extracellular fluid. Therefore, IFG was calculated using the ionic reference technique (3). This technique is based on the simultaneous measurement of glucose and ions in the samples. The ionic recovery can be calculated as the ratio of sodium in the sample to the sodium concentration in plasma, using an ion-free perfusate. Assuming that recovery rates of glucose and sodium were the same, we calculated the glucose concentration of the ISF as IFG = dialysate glucose × plasma sodium/dialysate sodium. Thus, the relative recovery of a particular substance is the concentration of this substance in the dialysate expressed as percentage of the concentration of this substance in the surrounding tissues. Mean age and body weight were 3.4 years and 14.5 kg. No complications with the technique occurred. Median microdialysis recovery rate was 89% (P25–P75:75–94%).

Fig. 1. Bland–Altman analysis.

The bias is 29.4 mg/dL (1.6 mmol/L). This bias represents the mean of the systematic distribution of the values. To achieve TGC, this bias of 29.4 mg/dL is inaccurate for safe clinical implementation in ICU. Bias SD (1.96) represents the limits of agreement. A potential difference reaching between 105.8 and −46.9 mg/dL (5.9 and −2.6 mmol/L) is unacceptable for clinical use in ICU-settings applying TGC.
Differences between BG and DG and IFG respectively were significant (P <0.0001). Correlation between BG and DG (r² = 0.79) was not significantly improved with the ionic reference technique (r² = 0.86) (P = 0.37). Bland–Altman analysis comparing IFG to BG is shown in Fig. 1.

Microdialysis of adipose tissue adequately reflects BG in the setting of diabetes (4) and healthy volunteers. In this study in critically ill children, the correlation between BG and IFG was moderate. Bland–Altman analysis, however, indicated that the microdialysis technique is unsuitable to replace frequent blood sampling to safely monitor TGC in this patient group. The difference using IFG for BG was unacceptable in the clinically relevant glycemic ranges and this difference could be both negative or positive (Fig. 1); thus hyper- and/or hypoglycemia may be undiagnosed when only IFG is measured and therapeutic adjustments are based on this value. These results confirm those of previous studies (5) concluding that the correlation between BG and IFG of adult intensive care unit (ICU) patients is not as good as in healthy or diabetic individuals. It remains speculative whether this is a result of the particular patient population with disturbed microvasculature and treatment with vasoactive drugs. We used a flow rate of 1 μL/min to avoid the delay in detection of changes in IFG that occurs at lower flow rates and to avoid an insufficient hourly sample volume. Higher flow rates, however, can lead to local depletion of metabolites and dilution of the dialysate. Lower flow rates facilitate the capture of true interstitial glucose concentrations during glucose fluctuations. No drugs known to interfere with the used methodology of glucose measurements were administered.

Before microdialysis of the subcutaneous adipose tissue can be safely implemented for TGC in pediatric intensive care units, more studies are necessary to identify interfering factors and to optimize the performance of the current technology.

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References

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Detection and Characterization of Putative Metastatic Precursor Cells in Cancer Patients

To the Editor:

Metastasis is the major cause of cancer-related death. Single disseminated tumor cells (DTC) can be detected in the bone marrow and peripheral blood years before the occurrence of clinically detectable metastases. Recent clinical studies, however, have clearly indicated that a significant fraction of breast cancer patients with DTC never develop distant metastases (1). Thus, DTC detected by sensitive immunocytochemical and molecular assays may be apoptotic or may lack stem cell properties and never give rise to an overt metastasis. The ability to detect and characterize viable DTC is therefore of utmost importance.

We applied a novel technique for the detection and ex vivo characterization of single viable DTC derived from epithelial tumors. Our technique for detection of specific secreted proteins, epithelial immunospot (EPISPOT), is an adaptation of the enzyme-linked immunospot assay. EPISPOT detects only viable tumor cells and can detect protein secretion at an individual cell level, allowing the direct determination of protein-secreting cell (SC) frequencies. Immunospots are the protein fingerprint left only by the viable SCs. Cell culture is needed for a sufficient amount of secreted marker proteins to accumulate to form immunospots; dying tumor cells do not secrete adequate amounts of protein and thus are not detected.

We first studied blood samples from breast and prostate cancer patients with gross metastases. SCs for the circulating tumor antigens mucin 1 (MUC1) or prostate-specific antigen (PSA) were detected in the majority of patients with metastatic breast (100%) and prostate (83.3%) cancer, respectively, whereas such SCs were not observed in healthy controls or in patients with benign prostatic hyperplasia (2). Consistent with our previous findings, the EPISPOT assay revealed viable DTC in the peripheral blood of 65% of prostate cancer patients, even in the absence of overt...