Glucose Monitoring at the Arm

Risky delays of hypoglycemia and hyperglycemia detection

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OBJECTIVE — We have examined whether rapid changes in blood glucose (BG) result in clinically relevant differences between capillary BG values measured at the forearm and the fingertip and whether local rubbing of the skin before blood sampling can diminish such differences.

RESEARCH DESIGN AND METHODS — Capillary BG samples were collected every 15 min for 3–5 h from the fingertip and the forearm of 17 insulin-treated diabetic patients and analyzed with different glucose monitors (FreeStyle, One Touch Ultra, and Soft-Sense). In a subgroup of patients ($n = 8$), local rubbing of the forearm skin was performed before blood sampling. A rapid increase in BG was induced by oral administration of glucose, and subsequently, a rapid decrease in glucose was induced by intravenous administration of insulin.

RESULTS — In the fasting state, the BG values at the fingertip and at the forearm were similar (7.8 ± 2.4 vs. 7.2 ± 2.3 mmol/l, $P = 0.06$). However, during rapid increase in glucose, BG values at the fingertip were consistently higher than at the forearm (maximal difference 4.6 ± 1.2 mmol/l, $P < 0.001$). During rapid decrease in glucose, lower BG values were recorded at the fingertip (maximal difference to forearm 5.0 ± 1.0 mmol/l, $P < 0.001$). At the forearm, BG was delayed by a median of 35 min ($P < 0.01$) in relation to the fingertip. Rubbing of forearm skin decreased the observed differences but with a large intraindividual and interindividual variability. There were no obvious device-specific differences.

CONCLUSIONS — To avoid risky delays of hyperglycemia and hypoglycemia detection, BG monitoring at the arm should be limited to situations in which ongoing rapid changes in BG can be excluded.

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Alternate site testing of capillary blood glucose (BG), i.e., at sites other than the fingertip, has been requested by individuals with diabetes to reduce the pain associated with finger-pricking and by their physicians to increase compliance with self-monitoring of blood glucose (SMBG). SMBG is an essential part of diabetes management, e.g., for insulin adjustments, and plays an important role in the detection of impending hypoglycemia. Blood samples for SMBG are usually obtained by pricking the fingertip, where BG closely follows arterial BG concentrations. However, pricking the fingertip is painful and uncomfortable, even with modern lancing devices.

Sampling at sites less densely innervated than the fingertip is associated with significantly reduced pain (1–3) and is consequently an attractive alternative. So far, this has been hindered by the minute blood volume (≤3 μl) obtainable from these sites. Recently, several new SMBG devices (Accu-Check Active, Roche Diagnostics, Indianapolis, IN; AtLast, Amira, Scotts Valley, CA; FreeStyle, TheraSense, Alameda, CA; Glucometer Elite XL in combination with Microlet Vaculance, Bayer, Tarrytown, NY; One Touch Ultra, LifeScan, Milpitas, CA; Soft-Sense, Abbott, Bedford, MA) with sample volumes between 0.3 and 2.6 μl received approval from the U.S. Food and Drug Administration for alternate site testing at the forearm, upper arm, abdomen, thigh, and calf. They have been marketed with considerable efforts in Europe and America under the assumption that capillary BG measurements at alternate sites do not differ from the usual measurements at the fingertip.

We were alerted by patients with diabetes who reported discrepancies between clinical symptoms of hypoglycemia with hypoglycemic values at the finger and normoglycemic SMBG values measured at the forearm (e.g., 2.8 vs. 5.6 mmol/l) (4). Neither standardized quality control assessments of technical performance (2,5) nor patient device handling resulted in any obvious explanation of the reported discrepancies. Because the clinical circumstances pointed to the critical role of rapid BG changes, we studied *1*) whether rapid BG changes result in clinically relevant BG differences between the forearm and the fingertip, and 2) whether local rubbing of the forearm skin (recommended by some manufacturers to increase blood volume) diminishes such differences.

RESEARCH DESIGN AND METHODS

Participants

Insulin-treated patients with diabetes were consecutively recruited between December 2000 and April 2001 among inpatients from the German Diabetes Research Institute (Duesseldorf, Germany) who were undergoing routine hypoglycemia awareness testing ($n = 20$). Decision for hypoglycemia awareness testing was independently made by the caring physicians. Three patients refused to participate due to the required additional BG sampling. A total of 17 patients participated in the study: 2 women, 15 men; age range 20–59 years (median 38);

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

13 patients with type 1 diabetes, 4 patients with type 2 diabetes; duration of diabetes 2 weeks to 28 years (median 13). Diabetes-specific complications were absent in 12 patients, whereas mild microvascular complications were observed in 5 patients (retinopathy in 5, sensorimotor neuropathy in 2, microalbuminuria in 2). Five patients reported impaired awareness of hypoglycemia.

BG measurements

Capillary BG samples were analyzed with SMBG devices approved for quantitative glucose measurements in capillary blood taken from the fingertip as well as the forearm. For BG measurements, the following SMBG devices were used: FreeStyle (TheraSense, Alameda, CA) requiring a sample volume of 0.3 μl (10 patients), MediSense Soft-Sense (Abbott, Bedford, MA) requiring a sample volume of 2.6 μl (4 patients), and One Touch Ultra (LifeScan, Milpitas, CA) requiring a sample volume of 1.0 μl (3 patients).

In all patients, additional capillary whole blood samples (20 μl) from the fingertip were collected in parallel to the SMBG device samples and analyzed in our clinical chemistry laboratory by a hexokinase-based method (Gluco-quant; Roche Diagnostics, Mannheim, Germany). These laboratory values matched the respective fingertip values measured with the examined SMBG devices (Figs. 1 and 2; Table 1). The technical performance of all BG monitors within the study was evaluated (6) and was within the limits expected for SMBG devices [median (quartiles) of relative glucose deviation (i.e., capillary BG from the fingertip: SMBG monitor value divided by clinical chemistry lab value) was 0.9% (−1.9; 5.8) for Free Style, 2.9% (−3.6; 7.6) for Soft-Sense, and 3.7% (−0.8; 8.9) for One Touch Ultra].

Procedures

After an overnight fast and on their individual basal insulin, the patients' prebreakfast rapid-acting insulin was omitted, and the breakfast was replaced by an oral glucose load (Dextro O.G-T.; Hoffmann-LaRoche, Grenzach-Wyhlen, Germany), equivalent to 75 g glucose, to achieve BG values of 16–22 mmol/l. The glucose load was reduced to half in those patients with a baseline fingertip BG >10 mmol/l to reach comparable BG values of 16–22 mmol/l. Then, the patient's usual

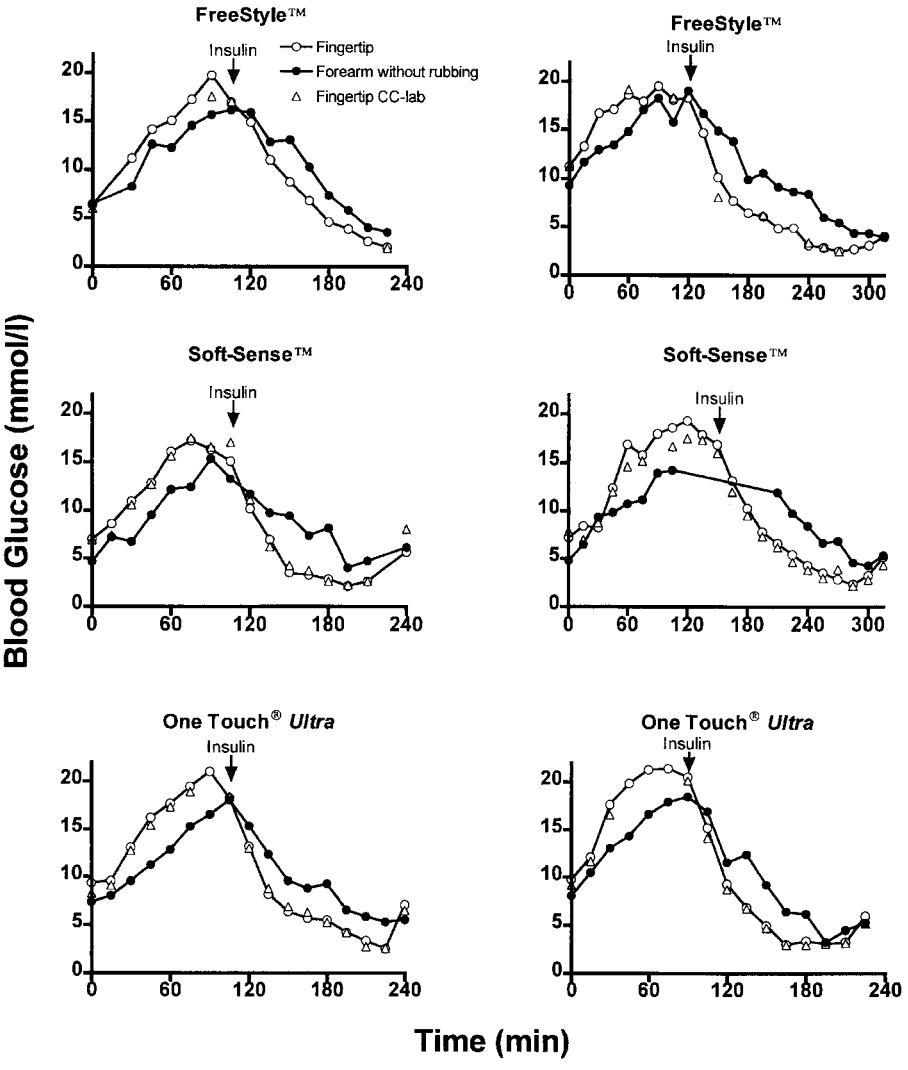

Figure 1—*Representative study BG profiles from the forearm and the fingertip of six patients with diabetes. Changes in BG were induced with 75 g oral glucose (t = 0) and by intravenous insulin injection. BG was analyzed using three different BG monitors as well as a clinical chemistry laboratory (CC-lab) method.*

short-acting insulin was injected intravenously at an individual dose (6–40 units) to induce a fast decrease in BG (>0.1 mmol · l^{-1} · min^{-1}) down to hypoglycemic values (≤3.5 mmol/l). Hypoglycemia was treated by oral administration of glucose.

Capillary blood samples were collected by a trained research nurse in parallel (within 3 min) from the fingertip (lateral pulps of fingers 2–4) and the forearm (ventral and dorsoradial surface) every 15 min. In each patient, the same BG monitor was used for capillary BG measurements at both sites. The forearm skin was not rubbed before BG sampling, as recommended by some manufacturers, to avoid any disturbance of the normal regional blood flow. In a subset of patients (n = 8), additional blood samples were collected from the other forearm after a research nurse rubbed the forearm skin area (≈20 cm^2), which was subsequently used for lancing. The rubbing required 5–10 s and aimed to result in marked warming and redness of the skin area.

All procedures were followed in accordance with the standards of the Ethical committee at the Heinrich-Heine University (Duesseldorf, Germany), and written informed consent was obtained from each participant before the study.

Data analysis

Glucose profiles were analyzed separately for the increase part, i.e., from the ingestion

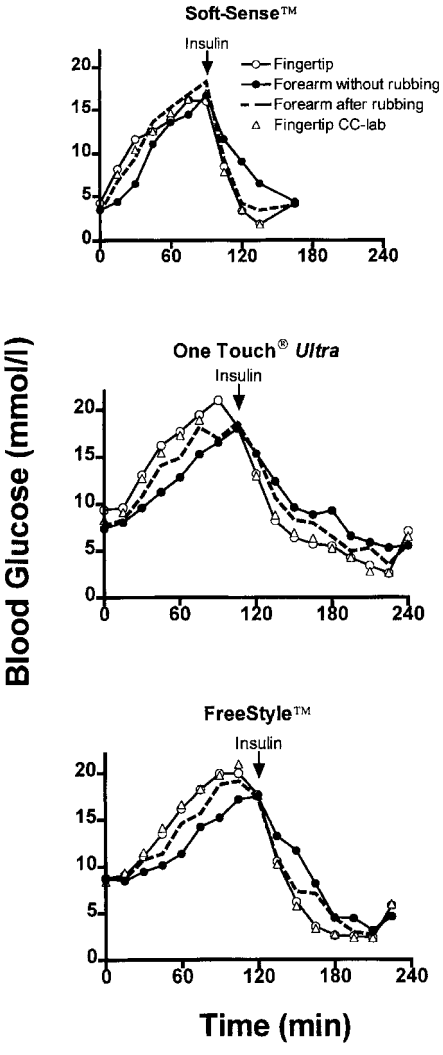

Figure 2—*Effect of rubbing on forearm BG values: representative study BG profiles from three patients with diabetes. BG changes were induced and measured as described in Fig. 1.*

of the glucose load to the BG maximum measured at the fingertip, and the decrease part, i.e., from insulin injection to the BG minimum measured at the fingertip.

Data were compared by a two-sided Wilcoxon's matched-pairs signed-rank test. If appropriate, *P* values were adapted according to the Bonferroni procedure. A *P* value <0.05 was considered statistically significant. Time delays in forearm BG increase and decrease were determined at a BG level of 3.5, 5.5, and 14 mmol/l, respectively. Unless otherwise stated, data are expressed as median (interquartile range).

RESULTS — With all three BG monitors, we observed similar capillary BG differences between the forearm and the fingertip during the increase part as well as the decrease part. Representative examples of all BG monitors are shown in Fig. 1. For further analysis, results of all BG monitors were combined.

At baseline, no relevant differences between BG values at the finger and forearm [7.7 (2.9) vs. 6.5 (2.4) mmol/l, $P = 0.06$] were observed. The increase in BG at the fingertip was consistently larger than that at the forearm [11.5 (2.4) vs. 8.4 (1.9) mmol/l, $P < 0.001$]. The rate of increase in BG measured at the fingertip was 0.13 ± 0.03 mmol $\cdot l^{-1} \cdot min^{-1}$. An individual maximal difference in BG between forearm and finger of 4.7 mmol/l (1.3) (range 2.6–7.6) was observed 30–90 min after the ingestion of glucose. The decrease in BG at the fingertip was also consistently larger than that at the forearm [15.0 (1.6) vs. 12.1 (2.4) mmol/l, $P < 0.001$]. The rate of decrease in BG measured at the fingertip was 0.17 ± 0.06 mmol $\cdot l^{-1} \cdot min^{-1}$. An individual maximal difference in BG between forearm and finger of 5.4 mmol/l (1.6) (range 3.4–6.6) was observed 15–75 min after administration of insulin. At the first hypoglycemic fingertip BG value (≤3.5 mmol/l), 80% of forearm BG values were ≥5.0 mmol/l (Table 1).

During the increase and decrease parts, BG at the forearm was lagging behind BG at the fingertip by a median of 27 min (6–91, $P < 0.001$), of 35 min (22–67, $P < 0.001$), and of 34 min (27–35, $P < 0.05$) at 14.0, 5.5, and 3.5 mmol/l, respectively.

There was a large intraindividual and interindividual variation of the rubbing effect on the finger-forearm BG difference in the subset of patients ($n = 8$) on which a rubbing procedure was performed. In these patients, the effect ranged from virtually no change of forearm BG to the establishment of full equilibration with the fingertip BG (Fig. 2). On average, the individual maximal difference between forearm and finger was reduced during the increase part from 4.5 ± 0.7 to 3.1 ± 1.1 mmol/l ($P < 0.05$) and during the decrease part from 4.8 ± 1.1 to 3.0 ± 0.9 mmol/l ($P < 0.01$).

CONCLUSIONS — Glucose monitoring at the arm is an attractive, nearly painless alternative to the more painful fingertip site. BG values from both sites are virtually equal at metabolic steady state. Unfortunately, due to rapid BG changes, transient but clinically relevant differences between forearm BG and the fingertip BG occur. During rapid BG changes, the forearm BG is lagging behind the fingertip BG by >30 min on average. As a result, the detection of hyperglycemia as well as hypoglycemia can be delayed. Clinical relevance is obvious, as even few delays of hypoglycemia detection could cause serious adverse events in diabetic patients, especially in those with impaired awareness of hypoglycemia.

Several systems for BG testing at alternate sites have been recently approved according to the provided evidence that BG values from these sites do not differ from values measured in blood samples collected at the fingertip. These results are related to the general design of standard study protocols for the technical and clinical evaluation of SMBG devices (7). They do not specify whether BG values must be taken during periods of slow or rapid BG changes. Actually, the BG measurements used for evaluation are normally taken for insulin dose adjustments and therefore focus on fasting and preprandial values, i.e., times usually not characterized by rapid BG changes. Therefore, it is not surprising that the observed differences during rapid BG changes were overlooked. Similarly, studies comparing glucose values measured in dermal interstitial fluid with those measured in blood were either done in the fasting state or during slow or moderate BG changes (8–12) and might therefore not have found significant differences.

The observed slower glucose kinetics at the forearm are most likely related to physiologically occurring site-specific differences in dermal circulation. In healthy individuals as well as those with type 1 and type 2 diabetes, dermal blood flow is 5–20 times higher at the fingertip than at the forearm (13–15). This is due to the fact that arteriovenous anastomoses within the dermis are numerous in glabrous (hairless) skin (e.g., fingertip) but nearly absent in nonglabrous (hairy) skin (e.g., forearm) (13,16). Therefore, the total exchange of blood within cutaneous venous plexus, from which blood obtained by skin-pricking is mainly derived (17), will take more time at the forearm than at the fingertip. This interpretation is supported by the ameliorating effect of local rubbing of the skin, which increases local blood flow.

Because our observations are based

Table 1—*Capillary forearm BG compared with the first hypoglycemic value (BG ≤3.5 mmol/l) at the fingertip*

Blood glucose (mmol/l)			
Forearm	Fingertip		
BG monitor	BG monitor	CC-lab	Clinical symptoms of hypoglycemia
9.4[S]	3.5[S]	4.2	Drowsiness
9.0[S]	3.3[S]	3.4	None
8.8[F]	2.9[F]	ND	None†
8.4[F]	3.1[F]	3.4	None†
7.9[F]	2.8[F]	ND	None†
6.6[S]	3.5[S]	ND	Visual disturbance, warmth
6.4[U]	3.0[U]	2.9	None†
6.2[F]	3.1[F]	ND	Hunger, drowsiness
5.9[U]	3.4[U]	2.8	Sweating, tremor
5.9[F]	2.4[F]	2.2	Hunger, drowsiness, dizziness
5.8[F]	3.3[F]	ND	Drowsiness
5.0[F]	2.2[F]	1.8	Sweating, nausea
4.5[F]	2.6[F]	2.7	None
4.1[F]	2.6[F]	ND	None†
3.9[S]	3.1[S]	3.2	None

Additional capillary blood samples from the fingertip were analyzed using a clinical chemistry laboratory method. Clinical symptoms of hypoglycemia are given according to patients' perception. Hypoglycemia was not reached in two patients (data not displayed). CC-lab, clinical chemistry laboratory; ND, not done; S, Soft-Sense; F, FreeStyle, U, One Touch Ultra; †known history of impaired awareness of hypoglycemia.

on physiological differences in local dermal blood flow, they presumably affect any glucose test system that relies on glucose values from the upper skin layer of the arm (18). This is in accordance with our observations in all three examined BG monitors and supported by findings of their manufacturers (19–21). Test systems that measure glucose concentration within dermal interstitial fluid, such as the recently approved GlucoWatch (Cygnus, Redwood City, CA) or noninvasive optical devices such as the Diasensor 1,000 (Biocontrol Technology, Indiana, PA) might possibly detect rapid changes in BG with that significant delay. Due to the similarity of dermal blood flow, BG samples taken at other nonglabrous skin areas (e.g., upper arm, abdomen, thigh, or calf) could be affected in a similar way.

Rubbing of the forearm skin can reduce differences in BG during rapid changes in BG. However, due to the considerable intra- and interindividual variability the effect of rubbing on the forearm BG value is unpredictable. Therefore, rubbing of forearm skin cannot be regarded as a reliable compensatory action.

We conclude that BG testing at the forearm under metabolic steady-state conditions (e.g., fasting state, preprandially) can be a reliable and valuable alternative to BG testing at the usual finger site. However, during rapid changes in BG, e.g., postprandially or insulin-induced, the forearm should not be used for BG testing due to risky delays in detection of hypoglycemia and hyperglycemia. In addition, we would not recommend relying on BG values from the forearm if there is any concern about hypoglycemia (e.g., when driving a car). Diabetic patients and their health care providers should be informed and trained specifically in the proper use of alternate site testing at the arm. Before recommending other alternate sites for BG testing, site-specific information about the reliability of BG results during rapid BG changes should be provided. Evaluation protocols should be extended appropriately to ensure that BG is tested during periods of sufficiently rapid change in BG. There is a need for more studies covering various aspects of daily life (e.g., physical exercise or vasoactive drugs) that might change the BG equilibration process at alternate sites.

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