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# Physiological Influences on Off-Finger Glucose Testing

GEOFF McGARRAUGH, M.S.,[1] DAVID PRICE, M.D.,[2] SHERWYN SCHWARTZ, M.D.,[3] and RICHARD WEINSTEIN, M.D.[4]

## ABSTRACT

**Products for monitoring blood glucose that allow extraction from sites other than the finger have recently been introduced. The FreeStyle™ Blood Glucose Monitor requires only 0.3 μL of blood, and allows extraction from the hand, arm, and leg, as well as the traditional finger site. Differences in circulatory physiology of the off-finger test sites lead to differences in the measured blood glucose concentration. The first study involved 160 clinic visits by 120 unique subjects with type 1 or type 2 diabetes. FreeStyle measurements were compared to YSI Model 2300 Stat Plus Glucose Analyzer plasma measurements using venous blood, capillary blood from the finger, and capillary blood from the arm. In a second study, the time course of glucose variation was tested by simultaneous measurements on the arm and finger taken every 15 min for 6 h. Thirteen subjects with type 1 diabetes were studied in two 6-h sessions. When FreeStyle was compared to YSI using venous samples and finger samples, the regression statistics were very similar. But when FreeStyle with arm samples was compared to YSI with finger samples, the regression equation was similar, but the scatter in the data was statistically significantly greater at the 95% confidence interval. By studying the time course of glucose changes, the difference between finger and arm measurements was attributed to a time lag in the glucose response on the arm with respect to glucose response on the finger. The lag was observed when the glucose concentration was increasing or decreasing, and the lag time varied from subject-to-subject in the range of 5–20 min. Using the Clarke Error Grid Analysis, the difference between arm and finger glucose measurements was not clinically significant. However, when the glucose concentration is decreasing rapidly into a state of hypoglycemia, the lag in measurements on the arm could delay detection of hypoglycemia. When specifically testing for hypoglycemia, the finger may be the preferable test site.**

## INTRODUCTION

SELF-MONITORING OF BLOOD GLUCOSE (SMBG) is a necessary part of the treatment plan of people with diabetes mellitus. Frequent blood glucose testing is necessary for intensive insulin therapy, which is the most effective means of obtaining glycemic control.[1] Barriers to frequent testing include the pain associated with the finger stick necessary for obtaining blood for the test and the accumulated trauma to the fingers. New glucose monitoring systems have recently been developed that allow sample extraction from

[1]TheraSense Inc., Alameda, California.
[2]Endocrine Associates, Santa Rosa, California.
[3]Diabetes and Glandular Diseases, San Antonio, Texas.
[4]Diablo Clinical Research Inc., Walnut Creek, California.

other sites than the finger in order to overcome this barrier.

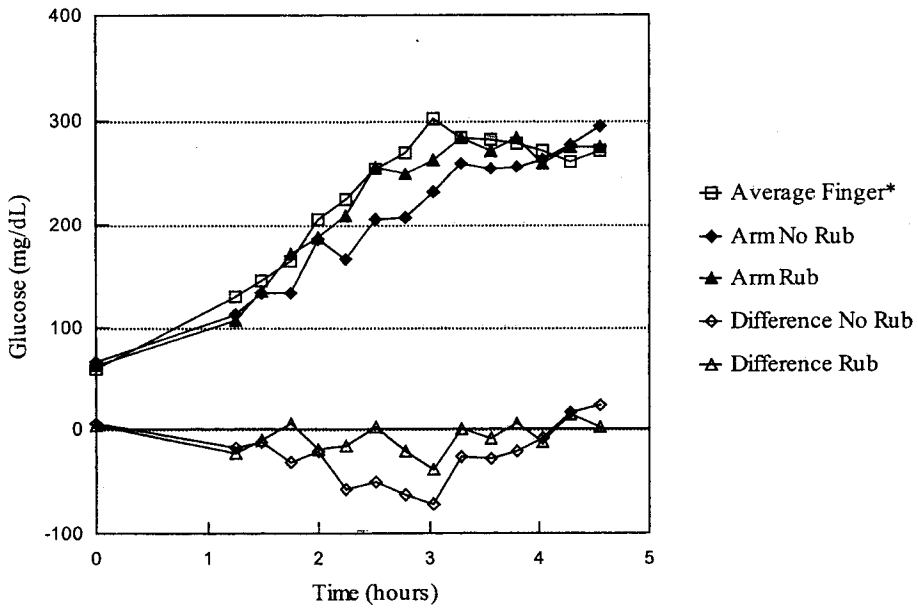
The FreeStyle™ Blood Glucose Monitoring System was designed to use a very small sample size, 0.3 μL. Early in the development of the product it was clear that it was possible to obtain sufficient blood from the forearm to perform the glucose measurements with excellent precision. It was also observed that the glucose results from blood extracted from the arm and finger were not perfectly correlated. The studies reported here are part of a continuing effort to characterize and understand the differences in glucose concentrations between blood samples from different test sites.

Stimulating blood perfusion by rubbing the forearm prior to blood extraction has a significant influence on the glucose value obtained. This is demonstrated by the data from a previous study shown in Figure 1.[2] In this example blood from the forearm without rubbing exhibited a measurably different glucose concentration than blood from the finger. When the forearm was rubbed prior to blood extraction, the difference was significantly reduced.

## MATERIALS AND METHODS

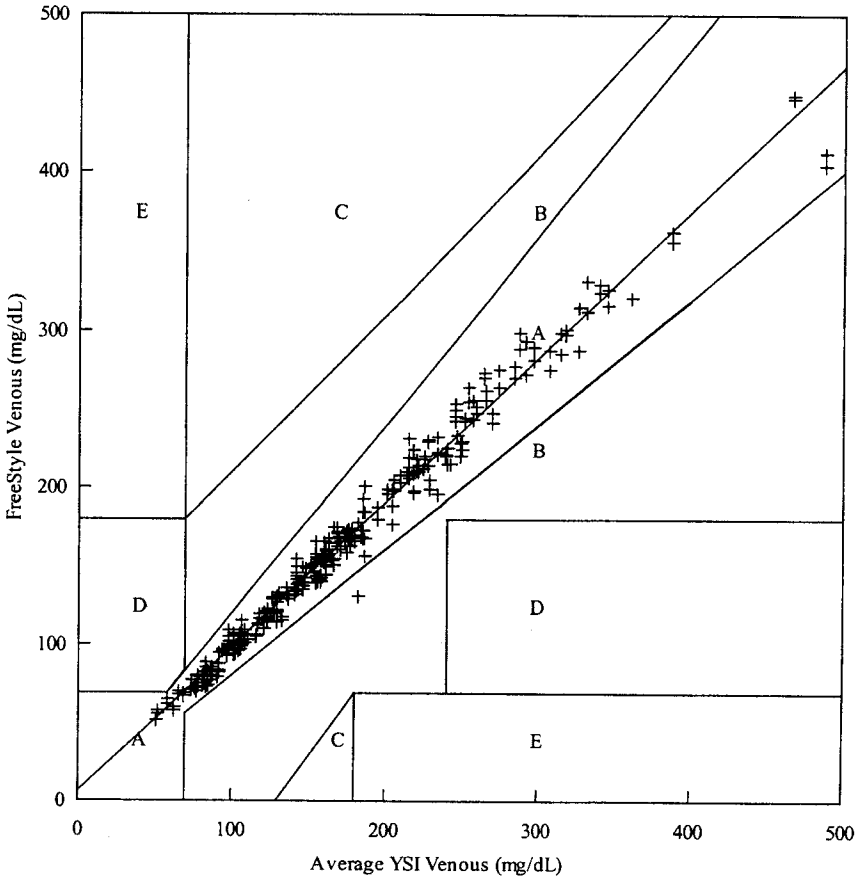
### *Study 1*

Subjects with both type 1 and type 2 diabetes were tested during a normally scheduled clinic visit. In each testing session, a trained technician obtained two FreeStyle glucose readings from finger sticks and two FreeStyle glucose readings from blood extracted from the dorsal surface of the forearm. Before lancing the arm, the test site was rubbed vigorously for a few seconds until the arm felt warm. A large sample of capillary blood was extracted from the finger, and plasma from this sample was analyzed for glucose on the YSI model 2300 Blood Glucose Analyzer (YSI Corporation, Yellow Springs, OH). Care was taken that all tests were performed over a short time period to avoid changes in blood glucose concentrations during the readings. A heparinized venous sample was also drawn, and the glucose was analyzed by FreeStyle and YSI. Duplicate FreeStyle readings were taken, and the YSI reading was performed on plasma separated from the whole blood sample. One hundred and sixty clinic sessions were conducted with 120 unique sub-




*The data points are the average of duplicate measurements.

FIG. 1. The influence of rubbing on the glucose readings of blood extracted from the arm.




Clarke Error Grid Analysis

| | Zone A | Zone B | Zone C | Zone D | Zone E |
|---|---|---|---|---|---|
| Readings | 316 | 1 | 0 | 0 | 0 |
| % | 99.7 | 0.3 | 0 | 0 | 0 |

**FIG. 2.** FreeStyle versus YSI using venous blood.

jects. After 20 testing sessions were conducted, the strip lot was changed, giving a total of eight unique strip lots.

*Study 2*

Subjects with type 1 diabetes were brought into a clinic in the morning and tested for blood glucose every 15 min. Each subject was followed for 5–6 h, including one meal. At each test time, the subject obtained two FreeStyle glucose readings from the finger and two FreeStyle glucose readings from the dorsal surface of the forearm. The readings were taken as close in time as possible. Fourteen subjects were tested. Each subject participated in two

TABLE 1. REGRESSION STATISTICS FOR COMPARISON OF FREESTYLE TO YSI[a]

| *Comparison* | *Intercept (mg/dL)* | *Slope* | *R* | *Standard error (mg/dL)* |
|---|---|---|---|---|
| Venous FreeStyle to venous YSI | 6.3 | 0.923 | 0.992 | 9.4 |
| Finger FreeStyle to finger YSI | 5.9 | 0.932 | 0.983 | 13.4 |
| Arm FreeStyle to finger YSI | 9.7 | 0.934 | 0.966 | 19.5 |

[a]In 160 clinic visits by 120 unique subjects, duplicate FreeStyle measurements were compared to YSI plasma measurements. Venous blood, capillary blood from the finger, and capillary blood from the arm were compared.

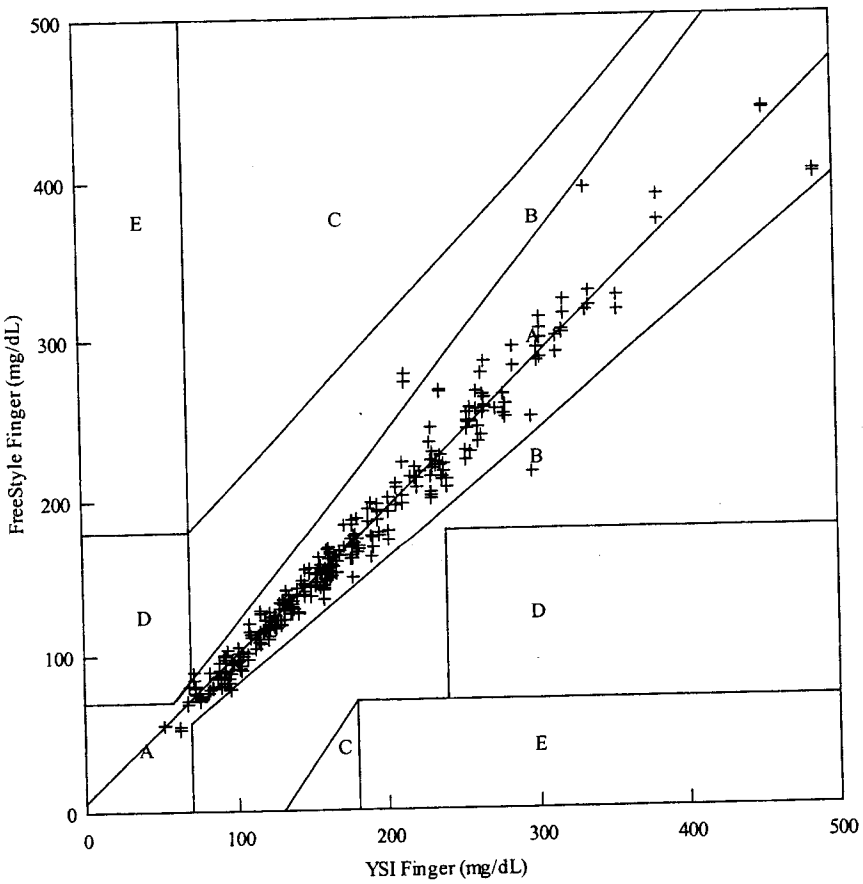
testing sessions, with the exception of one subject who was dropped from the study after 3 h due to bruising of the skin of the arm. Seven of the subjects ate normal meals and administered subcutaneous insulin by pump or syringe. Seven of the subjects ate high-sugar, low-fat meals and received intravenous insulin, with the objective of producing large swings in glucose concentration. Each subject used a single strip lot in the simultaneous arm and finger tests.

## RESULTS AND DISCUSSION

In study 1, the accuracy of the FreeStyle measurement technology is demonstrated by the analysis of venous blood samples. A graph of FreeStyle measurements of venous whole blood samples versus the YSI measurements of plasma extracted from that whole blood is shown in Figure 2, and the regression statistics are listed in Table 1. There is very close correlation of FreeStyle to YSI, with low scatter. The best measures of the scatter are the standard error of 9.4 mg/dL and the correlation coefficient of 0.992.

The clinical accuracy is assessed using the Clarke Error Grid Analysis.[3] The definitions of the zones in the Error Grid are as follows:

Zone A: within ±20%, clinically accurate
Zone B: error greater than ±20%, but would lead to benign or no treatment




Clarke Error Grid Analysis

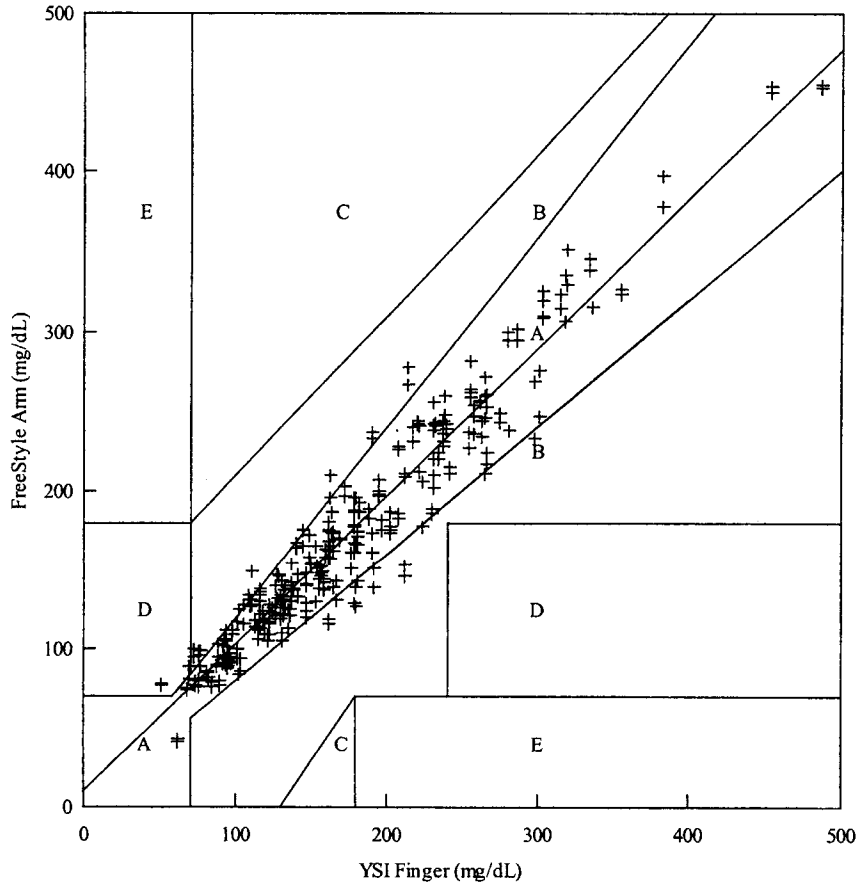
| | Zone A | Zone B | Zone C | Zone D | Zone E |
|---|---|---|---|---|---|
| Readings | 310 | 4 | 0 | 0 | 0 |
| % | 98.7 | 1.3 | 0 | 0 | 0 |

FIG. 3. FreeStyle versus YSI using capillary blood from the finger.

Zone C: error would lead to over correction of hypo- or hyperglycemia
Zone D: potentially dangerous failure to detect hypo- or hyperglycemia
Zone E: Erroneous treatment of hypo- or hyperglycemia.

All but one reading in Figure 2 is in Zone A of the error grid, indicating excellent clinical accuracy.

In this same study, measurements on the finger (FreeStyle to YSI) are compared. This relationship is graphed in Figure 3, and the regression statistics are listed in Table 1. The Error Grid Analysis demonstrates the same clinical accuracy as the venous samples. The regression equation is nearly identical to that determined with venous samples, but the scatter is somewhat greater, with a standard error of 13.4 mg/dL and a correlation coefficient of 0.983. The increase in scatter is not significant at the 95% confidence level, but there is a likely reason for the scatter to be higher for this comparison. The tests were not performed on the identical sample at the same time. The FreeStyle-to-YSI venous comparison (Fig. 2) was made using blood taken from a single Vacutainer tube. The FreeStyle-to-YSI finger comparison was made using blood taken from three finger sticks. Although care was taken to perform the tests over the shortest possible period of time, there could be a time difference of 5–10 min between the finger sticks for the FreeStyle and that for the YSI. During that time




Clarke Error Grid Analysis

| | Zone A | Zone B | Zone C | Zone D | Zone E |
|---|---|---|---|---|---|
| Readings | 278 | 33 | 0 | 3 | 0 |
| % | 88.5 | 10.5 | 0 | 1.0 | 0 |

**FIG. 4.** FreeStyle using capillary blood from the arm versus YSI using capillary blood from the finger.

the subject's blood glucose could change a little, causing more scatter in the data.

The relationship of arm FreeStyle measurements to finger YSI measurements is graphed in Figure 4, with the regression statistics listed in Table 1. According to the Error Grid Analysis, there would be little clinical difference between the arm and finger tests. There are a significantly greater number of readings in the B Zone of the grid, but these tend to be borderline cases, where the differences in treatment would be inconsequential. Only 1% of the readings are borderline excursions into the D Zone, and these will be considered in detail in the following discussion.

Comparing the finger FreeStyle-to-finger YSI data (Fig. 3) to the arm FreeStyle-to-finger YSI data (Fig. 4), the regression equation is very similar, but the scatter is significantly greater, with a standard error of 19.5 mg/dL and correlation coefficient of 0.966. The increase in scatter is statistically significant at the 95% confidence interval, suggesting that blood from the arm has a different glucose concentration than blood from the finger. The similarity in the regression equations suggests that the arm and finger glucose concentrations are the same on average, but the increase in scatter indicates that the correlation is not one-to-one. In the study, each subject's arm was rubbed vigor-

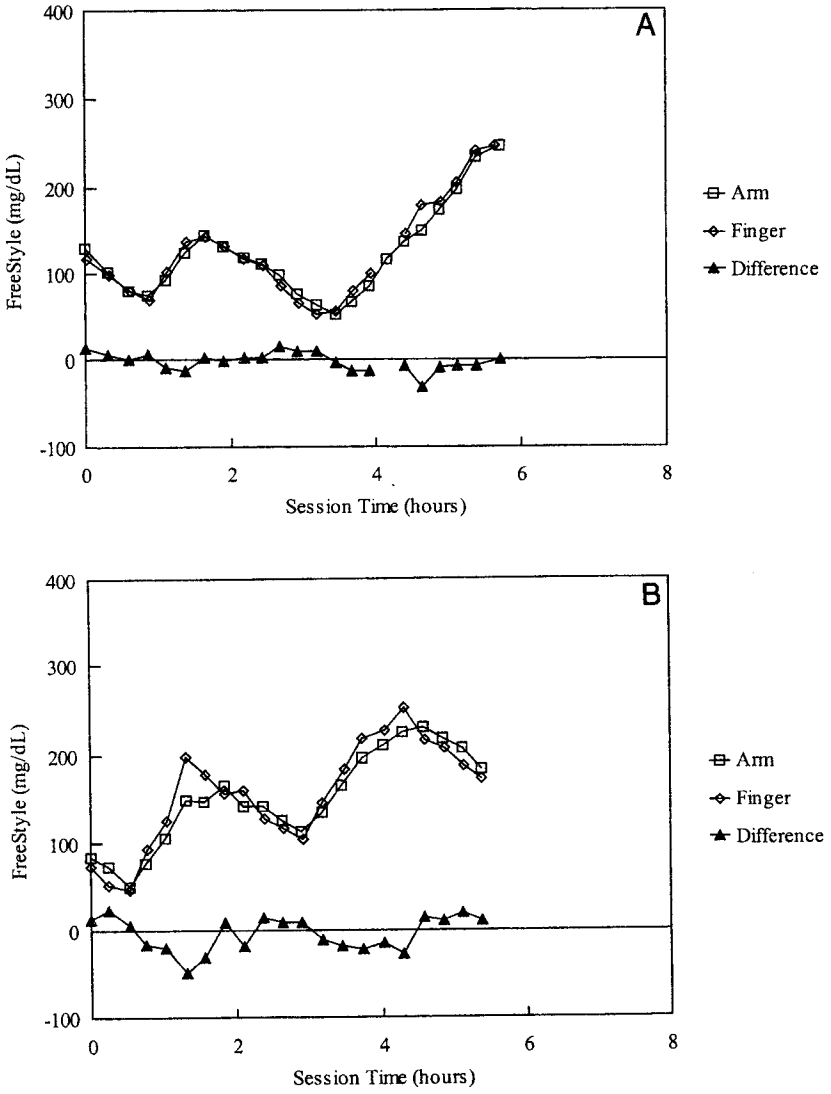



FIG. 5. (A) Glucose time profile with a subject that displays little lag time between arm and finger glucose measurements. (B) The second testing session with the subject from A.

ously prior to lancing. Our previous work indicated that rubbing the test site would reduce the difference between arm and finger glucose, but it is apparent from this study that the difference was not entirely eliminated by the rubbing technique.

As in study 2, other studies that followed the course of blood glucose over several hours have been very useful in characterizing the differences between arm and finger. The types of patterns observed are illustrated in Figures 5–7. In the figures the duplicate tests have been averaged to reduce random error and more clearly display the pattern of glucose changes. The data in Figure 5A,B are from the same subject in two testing sessions. There is little difference between the arm and finger for this subject, but on close inspection the changes in glucose are first observed on the finger and then the arm, with a lag on the order of 5 min. This is true when the glucose is increasing and decreasing.

The data in Figure 6A,B are likewise from a single subject during two different testing sessions. In this case, the subject ingested high-carbohydrate, low-fat calories and received insulin intravenously, creating rapid changes in blood glucose concentration. In these data, the lag in the arm readings is more apparent, and the lag time is as much as 15 min. It is also ap-

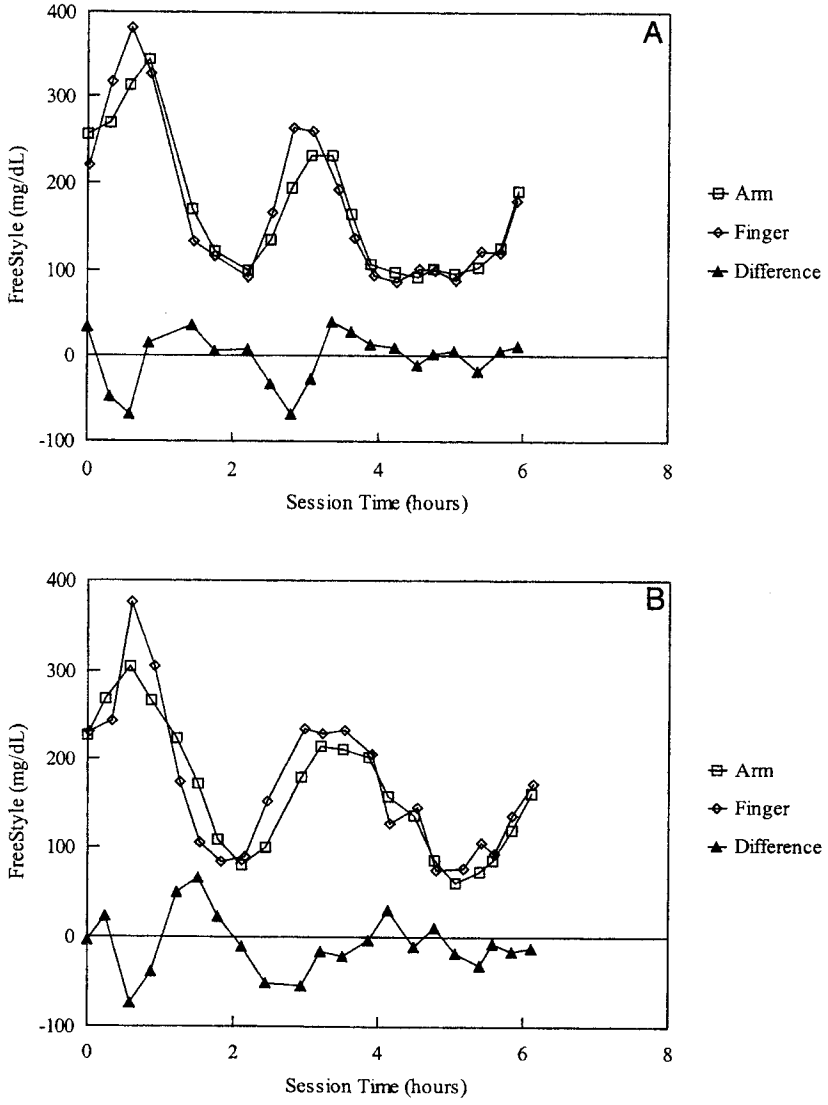



**FIG. 6.** (**A**) Glucose time profile with a subject that displays very large swings in glucose concentrations. (**B**) The second testing session with the subject from A.

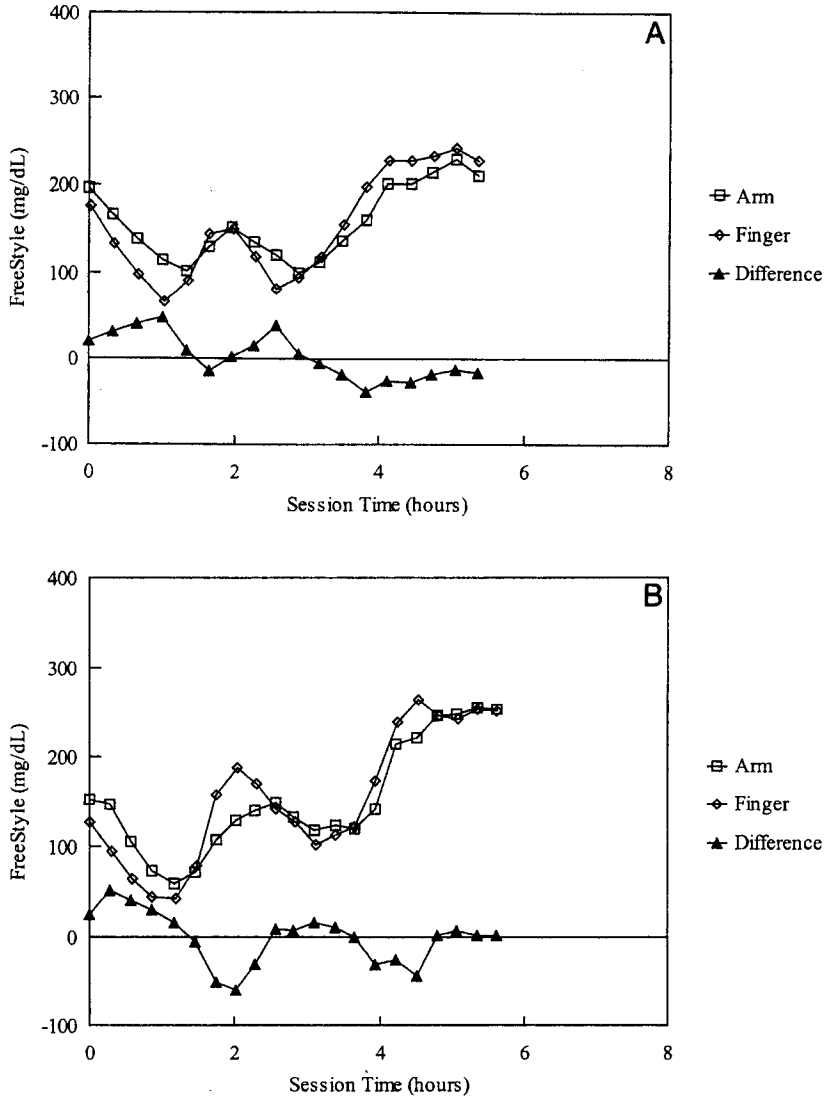



FIG. 7. (A) Glucose time profile with a subject that displays a significant lag time between arm and finger glucose concentrations. (B) The second testing session with the subject from A.

parent that, when the glucose in changing rapidly, the absolute difference between the finger and arm is maximum. When glucose is not changing, there is no difference.

Data in Figure 7A,B are also from a third subject, and show the delay between the finger and arm changes can be large—sometimes greater than 15 min. There are times when the arm readings are delayed to such an extent that the maximum and minimum values on the arm are significantly damped in relation to those on the finger.

For each of the subjects shown, the qualitative aspects of the lead-lag phenomenon was different, but the phenomenon was consistent for a given subject in both testing sessions. Likewise, all of the subjects in the study exhibited qualitatively similar glucose profiles from one session to the next.

The difference in arm and finger readings (arm-finger) is graphed versus the rate of change in glucose ($d_{glucose}/d_t$) for the entire study in Figure 8. In general, when the rate is negative (glucose decreasing) the arm is higher than the finger (finger leads the decrease), and when the rate is positive (glucose increasing) the arm is lower than the finger (finger leads the increase). The greater the rate of change, the greater the difference. Some of the scatter in the data is random error—calculating derivatives

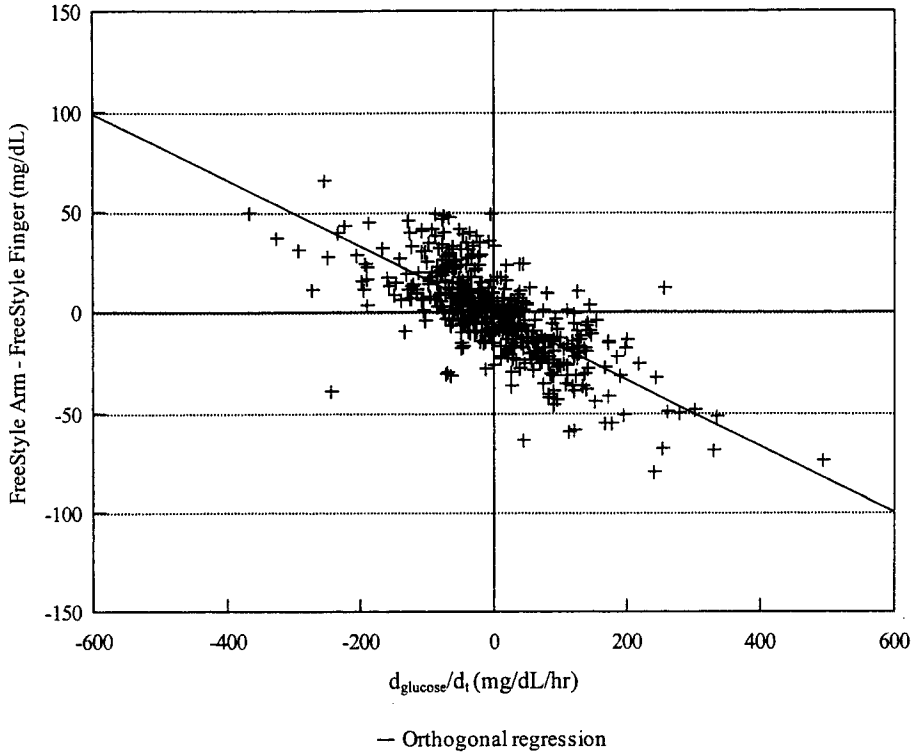



**FIG. 8.** The difference between arm and finger tests (arm-finger) as a function of the rate of change in glucose ($d_{glucose}/d_t$).

amplifies the measurement error. However, some of the scatter is due to the person-to-person differences noted above.

The circulatory physiology of the skin of the fingers and palm of the hand is distinctly different than that of the arm and legs. All skin tissue contains capillaries, but in the fingertips and palm of the hand there are short, direct vessels between the arteries and veins—arteriovenous anastomoses—in far greater abundance than occur in the skin of the arms and legs. The blood flow through these vessels is much higher than the flow through ordinary capillaries of the skin. The blood flow at the fingers has been measured at 33 ± 10 mL/g• min at 20°C, while the reported blood flow at the leg, forearm and abdomen skin is 4–6 mL/g• min at 19–22°C.[4] Perhaps it is the greater flow of blood through the fingertips that results in the more rapid equilibration of capillary and venous blood in the fingertips. When the test site is heated or rubbed, the increase in blood flow is significant,[4] and the blood that is brought to the surface may be more nearly equilibrated to venous blood.

The difference in blood glucose between arm and finger has a benign effect in most instances. For example, when intensive insulin therapy is used to keep blood glucose in tight control, insulin adjustments are made prior to meals, so that blood glucose concentration is not in flux and the difference between arm and finger is minimal.

Likewise, the average of postprandial glucose measurements, which is useful for adjusting medication, would not be greatly affected. If it is equally likely that the blood glucose is measured before, after, or during the peak glucose concentration, the individual readings are affected by the lag, but the average is not significantly changed. Although there are occasions when insulin adjustments are made on a single postprandial measurement, this must be careful, fine-tuning of the insulin dose based on an estimate of the on-board insulin. The error in glucose measurement is small compared

to the error in estimating the insulin dose. In these examples, the differences between arm and finger tests do not change clinical treatment for the patient.

When glucose is changing rapidly, the difference between arm and finger readings is greatest. Under these conditions, however, the timing of the test can have the most significant influence. A difference of ±15 min in the time the reading is taken will make a large difference in both the finger and arm results. The lag in the arm reading is generally inconsequential since it is impossible to gain a meaningful understanding of the glycemic state with a single measurement under rapidly changing conditions. However, if the blood glucose is falling quickly into a state of hypoglycemia, measuring blood glucose on the arm could delay detection of the hypoglycemic state. There are examples of this in Figure 7A,B. A failure to detect hypoglycemia as a person is preparing to drive, for instance, could have serious consequences. If a blood glucose test is performed specifically for the purpose of detecting hypoglycemia, the finger may be the preferable test site.

Our current research efforts include the further characterization of off-finger glucose testing. The characterization of sub-populations, such as children, gestational diabetics, and patients with peripheral vascular disease is the thrust of future work. Off-finger glucose testing is generating much interest due to the nearly painless nature of the blood acquisition, but the difference in circulatory physiology at different test sites has added some complexity that must be understood. Although the difference in the readings is insignificant under most circumstances, a detailed understanding of the physiological differences will help optimize off-finger testing.

## CONCLUSION

The blood glucose concentration from the off-finger sites is not always identical to that at the finger. Changes in glucose concentration detected on the forearm lag in time behind those changes at the finger. The lag time can be minimized by vigorously rubbing the test site, but there are differences from person to person. In this study, the lag ranged from 5 to 20 min. On average, the blood glucose concentrations from the arm and finger agree, and the lag time usually has no influence on clinical decisions. However, at times of rapidly decreasing glucose, the difference in concentration between arm and finger can be clinically significant. When glucose concentration is falling rapidly into a state of hypoglycemia, the lag in the arm readings could delay detection of hypoglycemia. If a patient is specifically testing for hypoglycemia, the finger may be the preferred test site.

## ACKNOWLEDGMENTS

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Address reprint requests to:
*Geoff McGarraugh*
*TheraSense Inc.*
*1360 South Loop Road*
*Alameda, CA 94502*

*E-mail:* geoff.mcgarraugh@therasense.com