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ORIGINAL ARTICLE

Point Accuracy of Interstitial Continuous Glucose Monitoring During Exercise in Type 1 Diabetes

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Abstract

Background: Previous studies of aerobic exercise have found lower sensor accuracy during exercise. Whether or not resistance exercise would also be associated with lower sensor accuracy has not yet been examined. This study sought to investigate the accuracy of continuous glucose monitoring sensor values at rest, during aerobic exercise, and during resistance exercise.

Subjects and Methods: Twelve individuals with type 1 diabetes performed 45 min of aerobic exercise, resistance exercise, or no exercise/rest followed by 60 min of recovery while monitored by continuous glucose monitoring systems.

Results: Sensors underestimated plasma glucose to the greatest extent during rest (-1.29 ± 1.39 mmol/L, $P < 0.001$) and resistance exercise (-0.71 ± 1.35 mmol/L, $P < 0.001$) and least during aerobic exercise (-0.11 ± 1.71 mmol/L, $P = 0.416$).

Conclusions: Optimal accuracy observed with aerobic exercise might arise from augmented blood flow better equilibrating plasma and interstitial fluid or from the combination of systematic sensor underestimation and sensor lag time.

Background

Although exercise is commonly recommended for people with type 1 diabetes, it can also increase the risk of hypoglycemia.[1] Continuous glucose monitoring (CGM) represents a potential tool to manage such risk,[2–6] but its accuracy and clinical utility have been questioned in the setting of exercise.[7] One possible limitation of common CGM technologies is that blood glucose concentration is estimated from the sampling of glucose in the interstitial fluid. Previous work has implied that a delay exists in sensing rapid changes in glucose, due to the amount of time required for glucose levels to equilibrate between plasma and interstitial fluid.[7–9] We therefore hypothesized that CGM sensor inaccuracy would be exaggerated by the rapid decreases in plasma glucose (PG), particularly during aerobic (AER) exercise.[10] We sought to add to current literature by performing a crossover clinical study examining CGM sensor point-accuracy during and after AER and resistance (RES) exercise compared with rest. A preliminary report of these results was presented in abstract form at the 2012 Canadian Diabetes Association Professional Conference.[11]

Subjects and Methods

The study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board, in accordance with the Declaration of Helsinki. Participants performed three separate sessions, all starting at 5 p.m.: (1) control (CON, seated rest for 45 min), (2) AER (45 min of treadmill running at 60% peak O_2 consumption [$\dot{V}O_{2peak}$]), and (3) RES (45 min of weight lifting) each followed by 60 min of monitored recovery. Participants were guided to standardize their food and insulin intake for 24 h before and 24 h after exercise.[10]

Blood was collected using intravenous catheters at the time intervals listed in Figure 1. PG was analyzed on frozen (−80°C) samples using the hexokinase timed endpoint method on the Unicel® DxC600 Synchron® Analyzer (Beckman Coulter Inc., Fullerton, CA) and SYNCHRON CX® Systems glucose reagent (catalog number 442640). Interstitial glucose was measured using the CGMS® System Gold™ (Medtronic, Northridge, CA). This system was chosen in order to minimize the occasional lost sensor signal seen with the wireless systems. The use of the blinded system also

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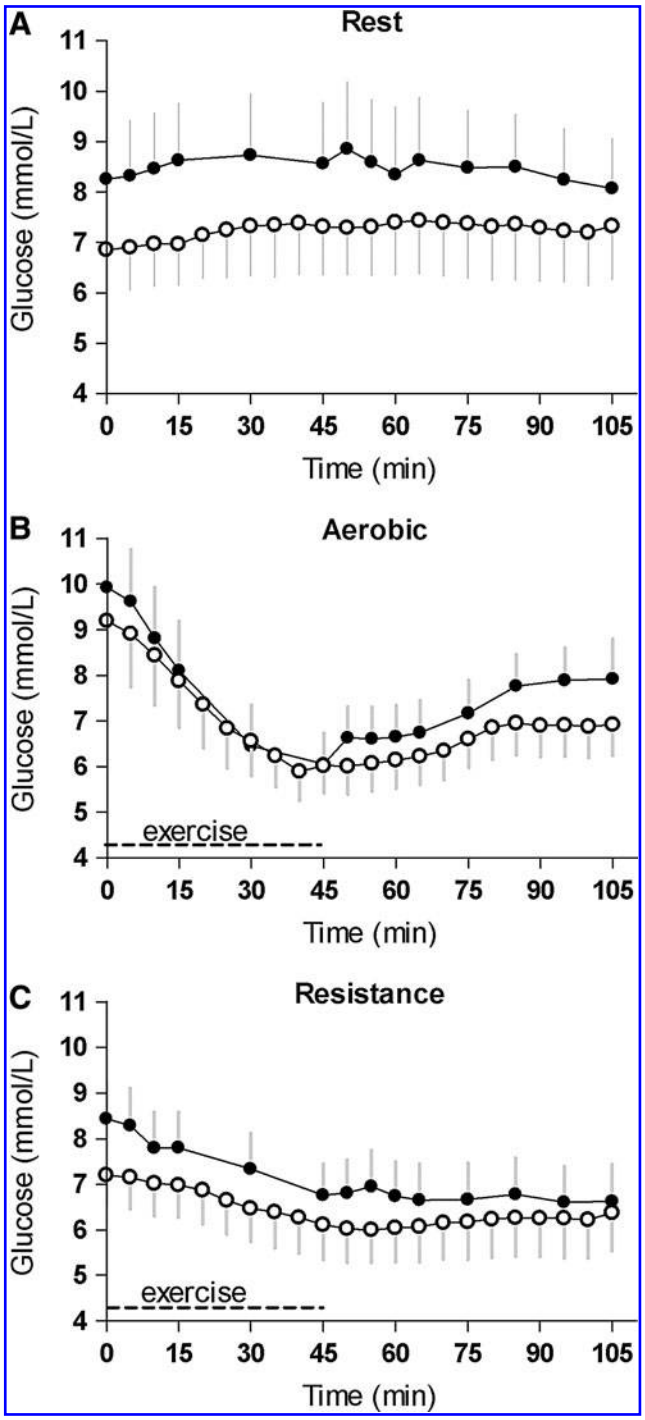

FIG. 1. Changes in sensor (white circles) and plasma (black circles) glucose during 45 min of **(A)** no exercise, **(B)** aerobic exercise, and **(C)** resistance exercise. Each treatment was followed by 60 min of recovery.

allowed us to observe changes in blood glucose in the absence of any behavior modifications that would be made if real-time interstitial glucose levels were visible to the participant. Sensors were inserted subcutaneously in the abdomen or gluteal area 24 h before the sessions. Participants were instructed to perform four calibrations daily based on capillary glucose tests. The mean numbers of daily calibrations were 3.6, 3.2, and 3.2 for the CON, RES, and AER intervals, respectively. Sensor values were downloaded using a Com-Station and Solutions Software version 3.0 (Medtronic).[10]

Analysis was performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC). Agreement between PG and simultaneous sensor values was assessed by the method of Bland and Altman.[12]

Results

Twelve (10 male, two female) physically active, complication-free participants (mean ± SD; age, 31.8 ± 15.3 years; $\dot{V}O_{2peak}$, 51.2 ± 10.8 mL/kg/min; diabetes duration, 12.5 ± 10 years; hemoglobin A1c, 7.1 ± 1.1%) were studied. During the first 45 min (exercise or rest), mean PG remained unchanged from 8.4 ± 3.5 to 8.6 ± 3.8 mmol/L in CON (paired *t* test, $P = 0.585$) but decreased from 8.4 ± 2.7 to 6.8 ± 2.3 mmol/L in RES ($P = 0.008$) and from 9.2 ± 3.4 to 5.8 ± 2.0 mmol/L in AER ($P = 0.001$) (Fig. 1). During the recovery period, PG remained unchanged from 8.6 ± 3.8 to 8.1 ± 3.1 mmol/L ($P = 0.426$) in CON and from 6.8 ± 2.3 to 6.6 ± 2.7 mmol/L in RES ($P = 0.784$) but increased from 5.8 ± 2.0 to 8.0 ± 2.4 in AER ($P = 0.004$). Of 168 potential pairs of plasma and sensor values, 151 (89%), 150 (89%), and 153 (91%) were available from CON, RES, and AER, respectively. Sensor values generally underestimated exercise and recovery PG (Table 1)—with mean underestimation being greatest during CON (−1.29 ± 1.39 mmol/L, $P < 0.001$) and RES (−0.71 ± 1.35 mmol/L, $P < 0.001$) and smallest during AER (−0.11 ± 1.71 mmol/L, $P = 0.416$) and its recovery—but generally reflected changes in PG associated with these conditions (Fig. 1). The magnitude of bias (underestimation) was proportionately small, as indicated by the mean and SD values shown as percentages in Table 1.

Sensor accuracy was also examined in the subsets of PG readings obtained during hypoglycemia (< 4.0 mmol/L), hyperglycemia (> 10.0 mmol/L), and euglycemia (4.0–10.0 mmol/L). In brief, the median absolute differences between sensor and PG values approximated those of the entire dataset. During the CON session, median [interquartile range] differences were −2.8 [−3.7, −0.3] mmol/L, −0.7 [−1.5, −0.3] mmol/L, and −0.5 [−0.6, 0.1] mmol/L in hyperglycemia ($n = 51$), euglycemia ($n = 87$), and hypoglycemia ($n = 13$), respectively. During the RES session, median differences were −1.9 [−2.4, −1.0] mmol/L, −0.6 [−1.3, 1.0] mmol/L, and 0.3 [−0.3, 0.6] mmol/L during hyperglycemia ($n = 21$), euglycemia ($n = 114$), and hypoglycemia ($n = 15$), respectively. Similarly, during the AER session, median absolute differences were −0.9 [−1.4, 0] mmol/L, −0.4 [−1.2, 0.6] mmol/L, and 0.5 [0.4, 0.7] mmol/L during hyperglycemia ($n = 26$), euglycemia ($n = 117$), and hypoglycemia ($n = 10$), respectively.

Three participants inserted the sensors in the abdominal region for all of their testing sessions, while the remaining nine inserted them in the gluteal area. Sensor accuracy between the two sites was similar for all three testing sessions. During the CON session, the median absolute differences between sensor and PG values were −0.7 [−1.3, −0.3] mmol/L for the abdominal site ($n = 40$) versus −1.3 [−2.8, −0.3] for the gluteal site ($n = 111$). Throughout the RES session, the median absolute difference between CGM and PG values was −0.9 [−1.7, −0.4] mmol/L for sensors inserted in the abdomen ($n = 42$) and −0.3 [−1.7, 0.5] for sensor readings in the gluteal area ($n = 108$). Finally, during the AER session median

Table 1. Summary of Differences (Sensor Minus Plasma) and Distribution of Differences According to Intervention Phase in 12 Subjects with Type 1 Diabetes Mellitus (Exercise Followed by Recovery)

	Control	*Resistance exercise*	*Aerobic exercise*
Number of paired values	151	150	153
Mean ± SD sensor glucose	7.22 ± 3.06	6.45 ± 2.46	7.38 ± 2.78
Mean ± SD plasma glucose	8.51 ± 3.66	7.16 ± 2.55	7.49 ± 2.78
Absolute differences and their distributions			
Mean ± SD	−1.29 ± 1.39	−0.71 ± 1.35	−0.11 ± 1.71
Median [IQR]	−0.8 [−2.1, −0.3]	−0.5 [−1.7, 0.2]	−0.4 [−1.2, 0.5]
95% confidence intervals	−4.4 to 0.6	−0.93 to −0.49	−0.39 to 0.16
P value	< 0.001	< 0.001	0.416
Percentage differences and their distributions			
Mean ± SD (%)	−14.1 ± 13.2	−8.6 ± 17.1	−1.91 ± 30.6
Median [IQR] (%)	−15.8 [−25.5, −3.5]	−9.5 [−21, 4]	−5.6 [−14.7, 9.4]
95% confidence intervals (%)	−16.2 to −12	−11.4 to −5.9	−3 to 6.85
P value	< 0.001	< 0.001	0.445

Data are expressed in mmol/L.
IQR, interquartile range.

absolute differences were −0.8 [−1.4, 0.5] mmol/L for abdominally inserted sensors ($n = 44$) versus −0.3 [−1.0, 0.5] for those used in the gluteal region ($n = 109$). In addition to the absolute median differences being quantitatively similar, none of the comparisons between abdominal and gluteal sites reached statistical significance.

Discussion

Although sensor values generally estimated PG with acceptable accuracy, contrary to our hypothesis we found neither AER nor RES impaired its accuracy. While we found that the sensor values slightly underestimated PG in our study rather than the slight overestimation seen in other studies,[6,8] the overall trends detected by CGM reflected the changes in PG associated with both exercise modalities. As the overall accuracy of CGM sensors is known to be quite good, it is not surprising that minor underestimations are found in some studies, whereas small overestimations are found in others. In addition to data presented in the previous studies, we also observed similar accuracy during hyperglycemia and hypoglycemia and with the use of abdominal insertion sites compared with gluteal sites.

Interstitial fluid glucose levels depend to a certain extent on both the level of glucose in the bloodstream as well as the amount of glucose uptake by the tissues. Theoretically, in the situation in which PG is rising, subsequent increases in interstitial glucose levels will depend on the rate of diffusion across the capillary endothelial barrier.[13] Conversely, falls in interstitial glucose may precede decreases in PG if glucose uptake in the peripheral tissues is augmented. However, physical activity is associated with an increase in metabolic heat production resulting in a subsequent increase in skin blood flow to transfer heat away from the body core.[14] This may consequently promote the equilibration of glucose concentration between plasma and interstitial fluid.[15]

The potential explanation for improved sensor accuracy during AER and RES compared with rest conditions is the blood flow-mediated equilibration of glucose between plasma and interstitial fluid during activity.[16] In contrast, previous literature has associated increased exercise intensity with worse sensor point-accuracy.[6,7,17] One study, however, used capillary glucose measures rather than plasma as the reference standard,[17] whereas the second tested a CGM method that has not entered into clinical practice.[7] The latter study found that CGM values (using microdialysis rather than glucose oxidase enzyme-based techniques) during 30-min exercise sessions underestimated venous glucose during high-intensity exercise but overestimated glucose during low-intensity intervals.[7] While one possibility for the discrepancy between these studies and ours may be that the conventional glucose oxidase-based sensors that we used may not be sensitive to the pH changes associated with high-intensity activity,[18] we cannot refute those findings as our participants did not perform such high-intensity exercise ($> \dot{V}O_{2peak}$ of 80%).

The alternative explanation for enhanced sensor point-accuracy during exercise is that it was observed for factitious reasons related to the combined systematic underestimation and the lag time observed with interstitial glucose. Where sensor values underestimate PG, point-accuracy will improve during declines in PG because of an estimated 4–20-min lag in the sensor values' decline explained by either delayed equilibration of interstitial fluid to plasma[7–9] or an intrinsic lag of CGM sensors.[19] Although best accuracy in our study was observed in AER, the session with the greatest decline in PG, against this hypothesis as the sole explanation for better accuracy was the finding that PG trends were qualitatively well represented by the sensor values during both the active exercise session and the recovery (Fig. 1).

Although this is, to our knowledge, the first study examining point-accuracy of CGM sensor values during both AER and RES with matched comparison with rest, it has some potential limitations. Adherence to sensor calibration was not complete, and, although not statistically significant, the small differences observed between anatomical sites of sensor insertion may have had a minor impact on results.

These data support that CGM point-accuracy is not impaired by AER or RES. On the contrary, blood flow-mediated equilibration between interstitial fluid and plasma or the combination of sensor lag time with its systematic underestimation may explain an apparent improvement in sensor accuracy associated with exercise.

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