

Accuracy of continuous subcutaneous glucose monitoring with the GlucoDay[®] in type 1 diabetic patients treated by subcutaneous insulin infusion during exercise of low versus high intensity

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SUMMARY

Aim: The GlucoDay allows continuous glucose monitoring by subcutaneous microdialysis in sedentary conditions. To validate it when glycaemia may undergo rapid and dramatic changes, we investigated its accuracy during two exercise sessions with markedly different glucose disposal rates.

Methods: Nine male diabetic patients, aged 32-61, treated by insulin pumps, first underwent a standard maximal exercise-test designed for determining the maximal oxygen consumption and the first ventilatory threshold (V_{t1}). Then two 30 min steady-state workloads at 15% below and 15% above the V_{t1} were performed in random order with the GlucoDay, and measurement of CHO oxidation rates was made by indirect calorimetry.

Results: CHO oxidation during exercise at +15% V_{t1} was higher (+943.5 mg/min, ie +45.5%, $P < 0.01$) than during exercise at -15% V_{t1} . No hypoglycaemia occurred. Due to breakages of 39% of subcutaneous probes, eleven steady-state sessions in 7 subjects allowed to compare 141 paired glucose (sensor vs. venous) determinations. The Clarke error grid situates 92.9% of glucose values within the A zone and 6.4% within the B zone, while only one pair of values (0.7%) falls in the D zone. Venous glucose tended to decrease more rapidly than sensor glucose during exercise. Bland-Altman plots evidence for a few cases of underestimation of venous glucose at high intensity.

Conclusions: This study showed satisfactory accuracy of the GlucoDay during exercise. A slight lag time in sensor values likely explains a few discrepancies that do not appear as clinically meaningful. Reduction of probe fragility and confirmed sensor accuracy in hypoglycaemia would further support applicability of GlucoDay at exercise.

Key-words: Glucose sensor • Microdialysis • Exercise • Insulin pump • Indirect calorimetry.

Fayolle C, Brun JF, Bringer J, Mercier J, Renard E. Accuracy of continuous subcutaneous glucose monitoring with the GlucoDay[®] in type 1 diabetic patients treated by subcutaneous insulin infusion during exercise of low versus high intensity
Diabetes Metab 2006;32:313-320

RÉSUMÉ

Exactitude de la surveillance continue du glucose sous-cutané par le GlucoDay[®] chez des patients diabétiques de type 1 traités par perfusion sous-cutanée d'insuline durant un exercice de faible ou haute intensité

Objectif : Le GlucoDay permet une surveillance continue du glucose par microdialyse sous-cutanée dans des conditions sédentaires. Pour le valider lorsque la glycémie est exposée à des variations rapides et importantes, nous avons exploré son exactitude durant deux séances d'exercice physique avec utilisation du glucose très différente.

Méthodes : Neuf patients diabétiques masculins, âgés de 32 à 61 ans, traités par pompe à insuline, ont d'abord réalisé un exercice physique maximal standard destiné à déterminer la consommation maximale d'oxygène et le premier seuil ventilatoire (V_{t1}). Ensuite deux épreuves d'exercice de 30 minutes en plateau à 15 % en dessous et 15 % au dessus du V_{t1} ont été réalisées en ordre aléatoire avec le GlucoDay, et mesure des taux d'oxydation glucidique par calorimétrie indirecte.

Resultats : L'oxydation glucidique durant l'exercice à +15 % V_{t1} a été plus importante (+943.5 mg/min, soit +45.5 %, $P < 0.01$) que durant l'exercice à -15 % V_{t1} . Aucune hypoglycémie n'est survenue. Suite à la fracture de 39 % des sondes sous-cutanées, onze séances d'exercice en plateau chez 7 sujets ont permis de comparer 141 valeurs appariées de la glycémie (d'après le sensor et le sang veineux). La grille d'erreur de Clarke situe 92,9 % des valeurs de glucose appariées dans la zone A et 6,4 % des valeurs dans la zone B, tandis qu'un seul couple de valeurs (0,7 %) est dans la zone D. La glycémie veineuse tendait à décroître plus rapidement que la glycémie d'après le sensor durant l'exercice. L'analyse selon Bland-Altman montrait quelques cas de sous-estimation de la glycémie veineuse lors de l'exercice de haute intensité.

Conclusions : Cette étude montre lors de l'exercice une exactitude satisfaisante du GlucoDay. Un discret délai de réponse dans les valeurs du sensor explique probablement quelques différences qui n'apparaissent pas cliniquement significatives. Une moindre fragilité des sondes et la confirmation de l'exactitude en hypoglycémie soutiendraient plus avant l'utilisation du GlucoDay[®] lors de l'exercice.

Mots-clés : Détecteur de glucose • Microdialyse • Exercice physique • Pompe à insuline • Calorimétrie indirecte.

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Received: September 1st, 2005; accepted: January 2nd, 2006.

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Current guidelines for the management of diabetes emphasize the need for a closer control of blood glucose in order to achieve near-normality [1-3]. One of the greatest difficulties in reaching this goal by insulin therapy is that much more information on daily blood glucose variations is required to allow a better adjustment of insulin delivery. The major patient complaints about frequent self measurement of blood glucose are the inconvenience and discomfort of finger-pricking and, in some countries, the high cost of the strips, all of which limit the number of measurements taken per day. Therefore, the development of "Holter-style" sensor systems that continuously monitor glucose level and may provide almost online data is likely to represent an important technical progress for achieving this task. However, for being suitable in clinical practice, these devices should offer perfect accuracy in terms of estimation of glycaemia. The GlucoDay system (A. Menarini Diagnostics, Florence, Italy) is composed of a subcutaneous microdialysis probe connected to a portable unit that contains glucose-oxidase for measurement of recovered interstitial glucose. The system takes a glucose measurement every second and stores an average value every 3 min, allowing continuous monitoring. The performance of the GlucoDay has been previously evaluated at rest in hospital setting and results have been shown to be quite satisfactory [4]. However, little is known about this accuracy during exercise, a physiological situation where glycaemia undergoes rapid dramatic changes, although an increasing number of type 1 diabetic patients are nowadays practising various sports.

On the whole, there are two opposite situations during exercise: low intensity, prolonged exercise, which implies the oxidation of lipids as an energetic fuel, but results in a progressive decline in blood glucose [5], and high intensity exercise that uses predominantly carbohydrate and determines a huge glycolytic flux [6], but is also associated in physiological conditions with high rates of glycogenolysis and gluconeogenesis in order to overcome the glucose needs, so that they frequently induce hyperglycaemia [7].

In this study we thus aimed at validating the GlucoDay system during exercise at both low and high intensity in type 1 diabetic patients treated by continuous subcutaneous insulin infusion.

Research design and methods

Patients

The study was carried out on 9 male type 1 diabetic subjects, aged from 32 to 61 years regularly attending our out-patient clinic. Patients had the following characteristics: age: 38.00 ± 0.29 yrs, weight: 78.20 ± 0.21 kg, height: 1.76 ± 0.02 m, BMI: 25.27 ± 0.06 kg/m², fat mass: $17.0 \pm 0.2\%$. They had been treated for over several years by external pump (HTRON V100 from Roche Diagnostics, Mannheim, Germany, in 3 patients; D-TRON Plus also from Roche Diagnostics in one patient; Medtronic-MiniMed model 508 from Medtronic-MiniMed, Northridge, CA, in five patients). The insulin used in these infusion devices was always the insulin lispro analogue Humalog, U-100 from Lilly France, Puteaux, France. Only one patient had microalbuminuria (urinary albumin >20 mg/24 h). Their duration of diabetes was 18-38 yrs (mean $\pm$ SEM: 24.7 ± 1.8). All were regularly active with at least 1 hr of sports each week.

Protocol of the study

On the first day (D₀), patients performed the standardized exercise-test for the determination of maximal oxygen consumption (VO_{2max}) and first ventilatory threshold (VT₁), as described below. On the eighth day (D₈) and the sixteenth day (D₁₆) the 30 min steady-state exercise bouts at either low intensity (15% below the VT₁) or high intensity (15% above the VT₁) were performed in random order.

For both D₈ and D₁₆ sessions, patients were admitted to our hospital on the preceding day in the evening for setting of the GlucoDay system. A microfiber was set under local anesthesia in the subcutaneous tissue of the periumbilical region, and was connected with the GlucoDay portable unit, as detailed elsewhere [4]. After stabilization, sensor signal was calibrated against one blood glucose value according to manufacturer's recommendations. A small polyethylene catheter was also inserted into an antecubital vein for blood sampling.

Each steady-state exercise session was performed 2 hr after a standardized breakfast and the insulin bolus to cover the breakfast was reduced by 50%. Insulin basal delivery was stopped 1 hr before the beginning of exercise and during all its duration. During the period that followed exercise, a basal insulin delivery was restored but it was maintained 25% below its usual rate until lunch-time. Before the exercise session, the calibration of the GlucoDay was performed with one blood venous glucose value. The GlucoDay system was removed 1 hr after the cessation of exercise. Patients left the hospital at 12:00 after the exercise test.

Subjects, who were all interested by this assessment of their glucoregulatory adaptation to exercise, gave informed consent, and the study was conducted in accordance with the guidelines of the local ethics committee.

Abbreviations

CHO:	carbohydrates
VE:	ventilation
VCO ₂ :	carbon dioxide output in the breath
VO ₂ :	oxygen consumption
VO ₂ MAX:	maximal oxygen consumption
VT ₁ :	first ventilatory threshold

Exercise testing

Materials for exercise testing

The patients performed each test on the same electromagnetically braked cycle ergometer (Ergoline 500, Bosch, Berlin, Germany). Gas volumes, i.e., ventilation ($\dot{V}_E$), O_2 consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) in inspired and expired air, were measured with a computer-based breath-to-breath exercise analysis system (ZAN 600 Ergo test, EMO International, La Rochelle, France) using a mouthpiece and nose clip system. Reproducibility of gas analysis has been studied in 10 subjects tested twice. The coefficients of variation measured at steady state at a fixed intensity for the respiratory exchange ratio (RER) ranged between 2.8% (low values) and 4.75% (high values) [7,8].

Aerobic capacity and ventilatory threshold (test 1)

Each subject's $\dot{V}O_{2\max}$ was measured during an 8 to 12-min incremental exercise test. The theoretical maximal aerobic power ($W_{\max Th}$), which is the power corresponding to the theoretical $\dot{V}O_{2\max}$, was calculated [9]. This equation takes anthropometric characteristics and sex into account. The initial power output was 20% of $W_{\max Th}$ for 3 min and was increased by 10% every minute until maximal exercise was reached, which was evaluated in terms of maximal heart rate, RER (>1.15) and $\dot{V}O_2$ stability. Pedal frequency was maintained between 60 and 70 rpm throughout the test. The highest $\dot{V}O_2$ value was considered as $\dot{V}O_{2\max}$ and the highest power output reached was considered as the maximal workload ($W_{\max}$). The first ventilatory threshold (V_{t1}) was determined with the usual criteria, i.e. a change of slope in the relationship between $\dot{V}O_2$ and $\dot{V}CO_2$, and a rise in the ratio between ventilatory flow rate and $\dot{V}O_2$ [10].

Steady state exercise bouts

For the two following tests, the subjects had to perform a 30-min exercise. The tests were performed in random order. The subjects were instructed to come for the second test under the same conditions as the first one in terms of meal and physical activity to exclude bias by these factors. After the initial rest period, they were instructed to pedal for 30 min at an intensity corresponding to either 15% below their V_{t1} (low intensity exercise) or 15% above their V_{t1} (high intensity exercise). Gas volumes were collected 10 min before the test and throughout testing. After stopping the exercise bout, the subjects returned to reclining position for 60 min and the measurements of sensor glucose and venous glucose were continued during all this period of recovery.

Calorimetric calculations

The rates of substrate oxidation of CHO and lipid were calculated from gas exchange measurements by using nonprotein RER values, according to the following equations [11]:

$$\text{lipid (mg.min}^{-1}\text{)} = 1.6946 \dot{V}O_2 - 1.7012 \dot{V}CO_2,$$

$$\text{CHO (mg.min}^{-1}\text{)} = 4.585 \dot{V}CO_2 - 3.2255 \dot{V}O_2$$

with gas volume expressed in milliliters per minute. These equations are based on the assumption that protein breakdown contributes little to energy metabolism during exercise. Reproducibility of these measurements during this protocol has been studied in 10 subjects tested twice. Coefficients of variation were: for the lipid oxidation rates 18% (low intensity) and 28% (high intensity); for the CHO oxidation rates 17% (low intensity) and 15% (high intensity) [8].

Biochemical determinations

Venous blood samples were stored in fluoride tubes for subsequent glucose determination, using the reference standard method (Beckman, Fullerton, CA). During the two steady-state sessions, venous blood glucose and blood lactate were measured every 6 min since time -12 min, and then, after cessation of exercise, at intervals of 12 min for 1 hr during recovery. When each venous sampling was performed, glucose values given by the sensor system, and the corresponding time shown on the monitor, were noted.

Statistical analyses

The performance of the GlucoDay was evaluated by comparing its readings (sensor values) to those obtained at the same time by the glucose oxidase method (reference values), with used Bland and Altman graphs [12-14], which plot the mean, over all data pairs, of the absolute value of the difference between the sensor and reference glucose, divided by the reference glucose. The mean ± 1.96 SD represented the 95% CI.

We also used the Clarke's Error Grid which separates a Cartesian diagram (in which the values generated by the continuous monitoring device (GlucoDay) are displayed on the y-axis, whereas the values received from the reference method are displayed on the x-axis) into five zones of clinical significance [15]. Zone A represents the glucose values that deviate from the reference values by 20% or are in the hypoglycaemic range (<70 mg/dl), when the reference is also within the hypoglycaemic range. Zone B (benign errors) is located above and below zone A; this zone represents those values that deviate from the reference values, which are incremented by 20%. The values that fall within zones A and B are clinically acceptable, whereas the values included in areas C-E are potentially dangerous, and there is a possibility of making clinically significant mistakes.

Data are expressed as means $\pm$ SEM.

Results

Clinical and technical results

Patients had a maximal power output of 300.0 ± 2.3 watts. Their $\dot{V}O_{2\max}$ was 44.40 ± 0.33 ml.min⁻¹kg⁻¹, i.e. $123.30 \pm 0.84\%$ of the theoretical $\dot{V}O_{2\max}$. The first ventilatory threshold (V_{t1}) fell at $57.70 \pm 0.24\%$ of the actual

$\text{VO}_{2\text{max}}$ and at $70.10 \pm 0.44\%$ of the theoretical $\text{VO}_{2\text{max}}$. Values of $\text{VO}_{2\text{max}}$ 23% above the theoretical norms and Vt_1 above 50% $\text{VO}_{2\text{max}}$ show that they were relatively fit due to their regular practice of exercise.

As shown in figure 1, exercise calorimetry evidenced during the high intensity session at +15% above the Vt_1 a rate of CHO oxidation higher by 943.5 mg/min ($P < 0.01$) ie 45.5% greater ($P < 0.001$) than during exercise at low intensity -15% below the Vt_1 . Figure 2 shows the blood lactate values during the two exercise sessions. Although both sessions elicit a rise in lactate above 2 mmol/l ($P < 0.001$), the high

intensity session clearly results in a much higher lactate response ($P < 0.001$).

Among the glucose sensors, 7 (39%) could not provide any data due to early breakages of the microfiber during exercise and were excluded from the analysis. No adverse event resulted from probe breakages. A total of 6 sessions at low intensity and 5 sessions at high intensity, ie a total of 141 couples of glucose determinations were considered suitable for the comparison study.

Figure 3 shows the variations of glucose as measured in venous blood and estimated from sensor values during each

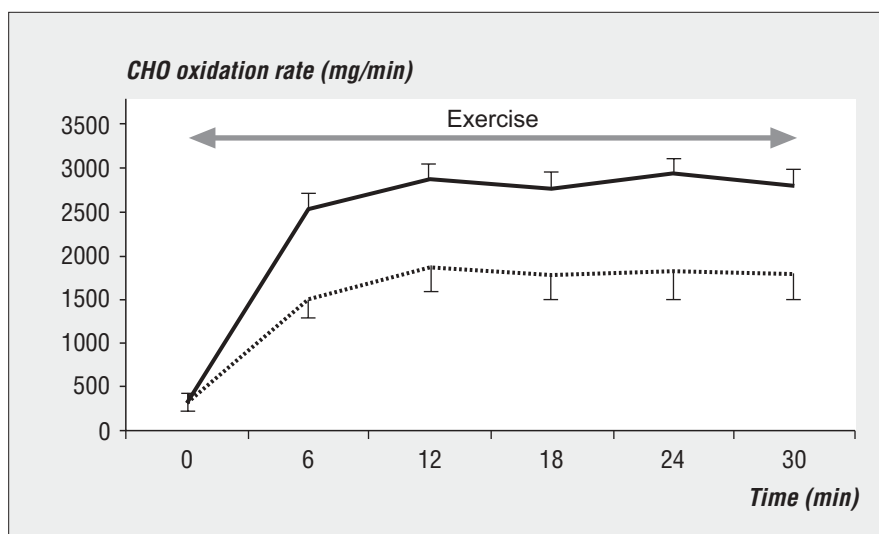


Figure 1

Rates of carbohydrate oxidation measured with indirect calorimetry during the low (dashed line) and high intensity (full line) sessions. Overall difference between the two sessions is highly significant ($P < 0.001$).

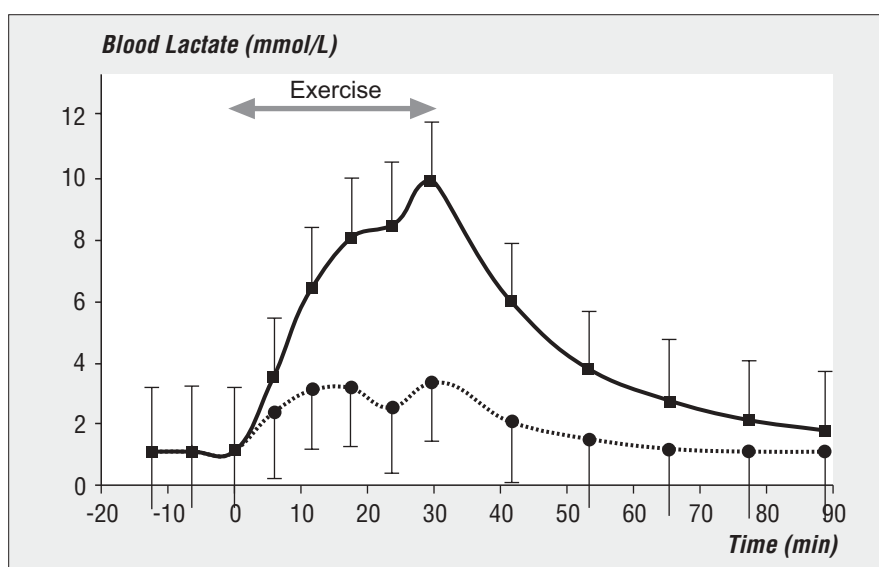
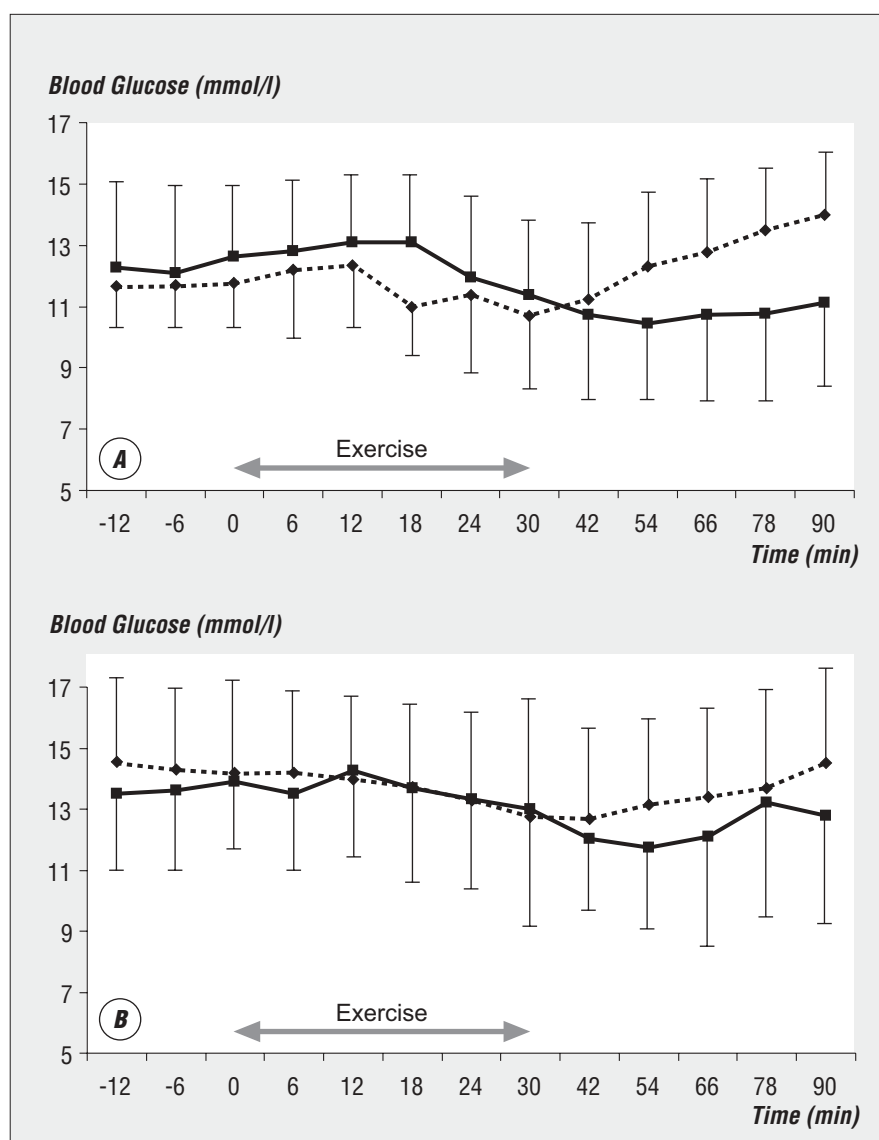


Figure 2

Blood lactate concentrations during the low (dashed line) and high intensity (full line) sessions. Overall difference between the two sessions is highly significant ($P < 0.001$).

**Figure 3**

Glucose variations as measured in venous blood (dashed line) and estimated from sensor values (full line) during low (panel A) and high intensity (panel B) sessions. Data are mean $\pm$ SEM.

exercise session. As expected, there was during the low intensity session a gradual decrease in blood glucose. Since patients had stopped their insulin infusion 1-hr before exercise, they all started exercise with high blood glucose values (between 11 and 16.5 mmol/l) and individual profiles of glycaemia were extremely variable, although a general trend to decrease was evidenced during the last 20 min of exercise, followed by a further increase after exercise cessation. A moderate delay during the decrease in glycaemia can be evidenced between blood glucose (which falls first) and sensor glucose (which falls 3-4 min later). Sensor glucose increased also after blood glucose during recovery. No hypoglycaemia occurred during exercise sessions in any patient.

There is a highly significant linear correlation between blood and sensor values for the 141 couples of samples

available ($r=0.931$, $P<0.001$). This correlation is not shown on a separate figure since it can be seen on the Clarke's error grid of figure 4 that situates 92.9% of the paired glucose determinations within the zone A and 6.4% within the zone B. Only one paired glucose determination (0.7%) is in zone D: it corresponds to a high intensity exercise.

Comparison of the two blood glucose determinations during the 30 min exercise sessions shows no overall significant difference, but an average underestimation at high intensity (mean difference -1.44 ± 0.61 mmol/l, $P<0.02$) and overestimation at low intensity (mean difference 0.91 ± 0.23 mmol/l, $P<0.0001$) with the GlucoDay. As shown in figures 5 and 6, the Bland-Altman plots for the two sessions (high and low intensity, respectively) both demon-

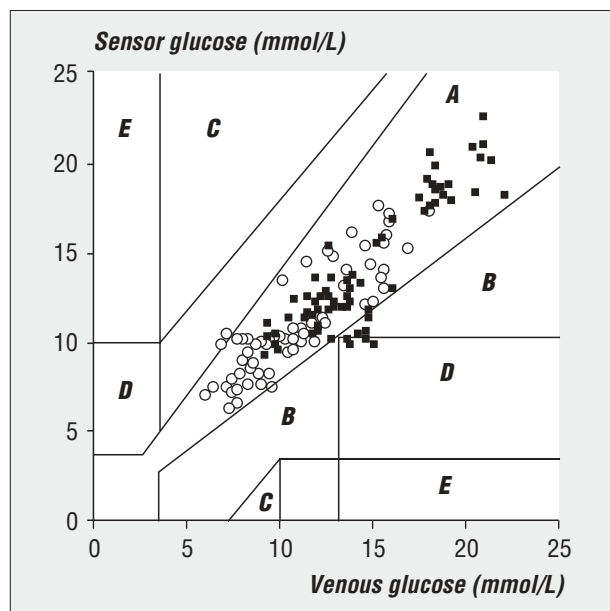


Figure 4

Clarke's error grid analysis for all determinations ($n=141$). 92.9% of glucose paired values fell within the A zone and 6.4% within the B zone, while only one pair of values (0.7%) obtained during high intensity exercise fell on the edge of the D zone. Open circles: low intensity exercise. Full squares: high intensity exercise.

strate a satisfactory concordance of the two methods, but the plot for high intensity exercise also shows a tendency to underestimate blood glucose with 7 values falling below the expected range of ± 1.96 SD, while 4 values for low intensity were above the expected range.

Conclusions

This study shows that the GlucoDay system gives accurate determinations of glycaemia during exercise at low or high intensity. The results of this comparison performed during exercise are quite similar to those of the multicentric evaluation of the GlucoDay in hospital setting in which 391 couples of glucose determinations were compared, showing 97% of the values in the clinically acceptable A-B zones, 3% in the C zone, and only one value (0.26%) in the D zone [4]. In the current investigations those percentages are respectively 99.3% (A+B zones) and 0.7% (D zone). Therefore, when the probe is not damaged during the muscular activity, the GlucoDay provides a quite accurate estimation of the values of blood glucose that would be given by the reference measurement.

These results suggest that the estimation of blood glucose by subcutaneous abdominal microdialysis provides an accurate follow-up of blood glucose variations during exercise. However, slight differences require some comments. It is clear that interstitial glucose on which sensor values are based and venous plasma glucose are two different compartments which reach equilibrium with some delay. This issue has been the matter of experimental studies in rats, leading to a quite complicated picture of the discrepancies between interstitial and plasma glucose [16]. It has been shown that in rats two different protocols of experimental hypoglycaemia result in discrepancies between interstitial glucose and venous glucose. When hypoglycaemia is induced by insulin, plasma glucose decreases first, and interstitial glucose decreases later. When hypoglycaemia is induced by phlo-

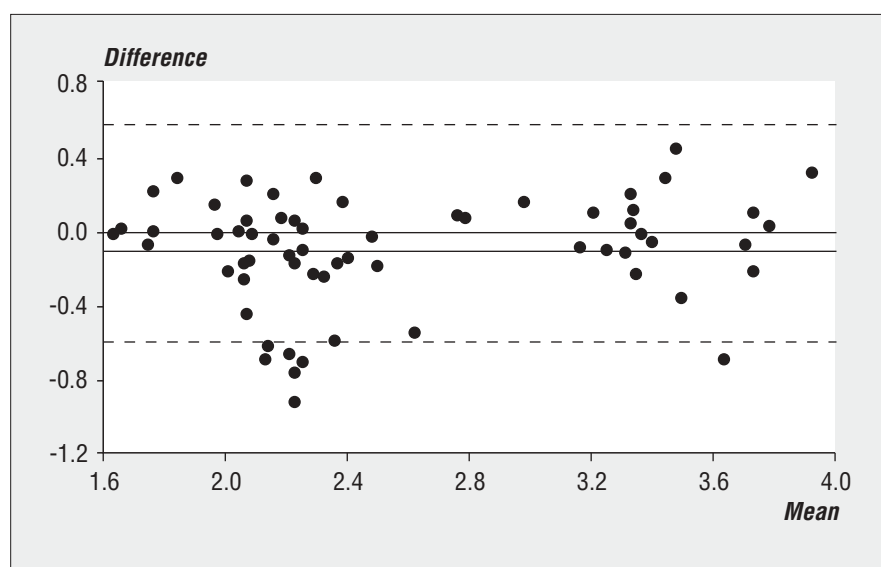


Figure 5

Bland-Altman difference plots showing the agreement between blood glucose estimations by the GlucoDay and reference venous blood glucose for high intensity exercise.

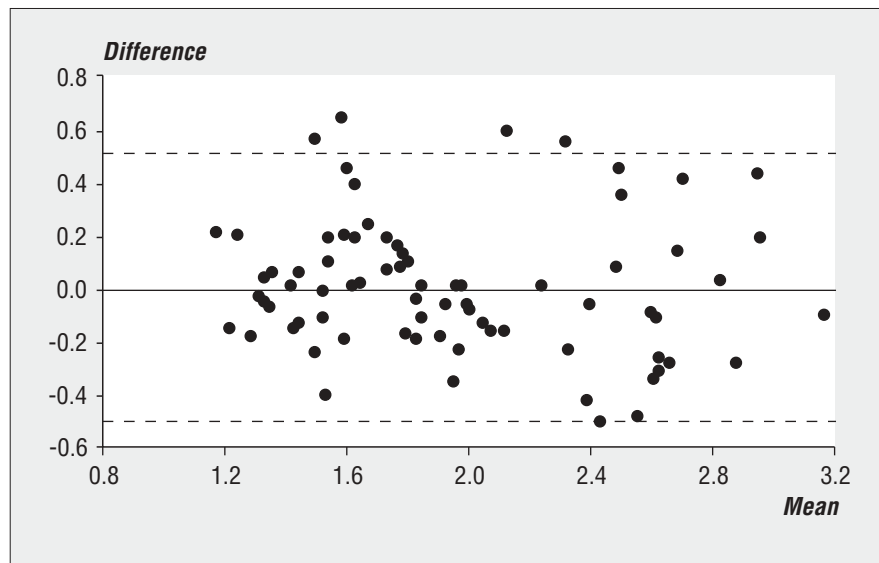


Figure 6

Bland-Altman difference plots showing the agreement between blood glucose estimations by the GlucoDay and reference venous blood glucose for low intensity exercise.

rizin, interstitial glucose decreases first, and plasma glucose decreases later. A model proposed by these investigators suggests that catecholamines may also interfere with this equilibrium, since it decreases glucose passage from interstitial tissue into the cell. Due to the complexity of this picture in experimental animals, it was difficult to predict the effects of the two kinds of exercise tested here. Our results show actually during exercise a similar evolution as after experimental insulin-induced hypoglycaemia, ie, plasma glucose decreases first, and interstitial glucose decreases later. However, in the conditions of our experiment, this discrepancy is very moderate and devoid of any clinical relevance.

Our choice to target the exercise sessions below and above the V_{t1} and to monitor them from indirect calorimetry is based on the notion that there is a marked difference in the pattern of utilization of energetic substrates between these two levels. At low intensity lipid oxidation takes a variable but generally important part while at high intensity CHO are the almost exclusive fuel and are oxidized at a high rate. The lactate responses (figure 2) show that a large quantity of CHO does not enter the Krebs cycle and is derived toward lactate. This may indicate that during this kind of exercise, there is an important flux of glucose through the glycolytic pathways, which may rapidly influence interstitial glucose levels. Thus, our two exercise sessions, despite mean profiles of glycaemia that are widely variable and thus not markedly different, involve, as expected, two different glucoregulatory patterns.

Actually, since no hypoglycaemia occurred during these exercise sessions, our study does not fully rule out the possibility that a very rapid fall in blood glucose below 2.8 mmol/l could fail to be detected in due time. Underde-

tection of postexercise hypoglycaemia has recently been reported with the CGMS [17]. On the basis of current studies on the GlucoDay and of our results, we think that there may be a delay of 3–4 min for the detection, but that a lack of detection of hypoglycaemia seems unlikely, since the multicentric study [4] has shown a good accuracy of this technique for low values of plasma glucose. However, a specific study on exercise hypoglycaemia would be needed in order to answer this question.

Our subjects were on the average rather fit, with a mean VO_{2max} at 123% of the theoretical expected value. They were all used to practise leisure sports. In fact, the second session consisting of 30 min at 15% above V_{t1} would have been difficult to complete for fully sedentary individuals. In addition, the purpose of our study was to examine what could occur during sports, and it was thus logic to study diabetics regularly practising sports. However, the glucoregulatory response could perhaps be slightly different in less fit subjects, and the accuracy of the GlucoDay in that context would also probably require a separate study. Besides, the noticeable fragility of microdialysis probes at exercise that we experienced with almost 40% breakages may have been related to the quite high intensity of both exercise sessions due to our patients' fitness. Microfiber resistance to mechanical stress due to physical activity definitely needs improvement in view of a clinical applicability of GlucoDay to allow glucose monitoring during sport practise in usual life conditions. Such improvement might also contribute to allow longer use of glucose monitoring using GlucoDay, which is currently limited to 48 hours according to the manufacturer's recommendations. Accuracy testing on a longer period should, however, also be

investigated. Finally, the size of the monitor, although well accepted in an investigational environment and during exercise on a cycle ergometer, would benefit from significant reduction to allow easy use in common and various sport activities.

On the whole, our study shows that glucose determinations by the Glucoday acceptably correlate with reference plasma measurements during low or high intensity exercise, and suggests that the technique of subcutaneous microdialysis yields a reliable estimation of blood glucose levels during exercise, at least in a controlled exercise environment. However, the ability of this technique to detect rapid falls in blood glucose reaching hypoglycaemic levels requires further investigation

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