Effects of pressure on whole blood glucose measurements using the Bayer Glucometer 4 blood glucose meter

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Edge CJ, Grieve AP, Ginnins N, O'Sullivan F, Bryson P. Effects of pressure on whole blood glucose measurements using the Bayer Glucometer 4 blood glucose meter. Undersea Hyperbaric Med 1996; 23(4):221-224.--The effect of pressure was investigated on the readings of whole blood glucose obtained from the Bayer Glucometer 4 blood glucose meter which uses the hexokinase enzymatic reaction. Sixteen subjects (eight normal and eight insulin-dependent diabetics) were exercised in a hyperbaric chamber at a depth of 3.7 atm abs. Venous blood samples were monitored at regular intervals for whole blood glucose concentration as measured by a Glucometer 4 inside the chamber. The blood samples were immediately placed in an airlock and taken to 1 atm abs, where whole blood glucose concentrations were measured using an identical instrument. The remaining blood was then analyzed in duplicate for serum glucose concentration using standard laboratory methods. The results show a significant difference between whole blood glucose concentrations measured at pressure and those measured at atmospheric pressure. Significant differences are also observed between whole blood glucose concentrations measured under pressure and serum blood glucose concentrations measured at atmospheric pressure.

hyperbaric glucose measurement, diabetes, hexokinase, exercise

Hyperbaric oxygen (HBO_2) therapy has been used to treat ischemic, non-healing wounds in diabetic patients who have no significant large-vessel occlusive disease (1,2). In such patients, HBO_2 increases the partial pressure of oxygen to the affected tissues, thereby improving the rate of repair. During HBO_2, there is a risk that diabetic patients may become hypoglycemic. Clinically significant hypoglycemic levels may cause the patient to exhibit seizure-like activity, and Springer (3) reported that whole blood glucose concentration (WBGC) decreased by an average of 51 mg/dl (2.8 mmol/liter) in 25 insulin-dependent diabetics after HBO_2 therapy.

In recent years, several methods have been developed to measure glucose concentrations in whole blood. The commonest method has been to use the enzyme glucose oxidase, which oxidizes glucose and O_2 to form glucuronic acid and hydrogen peroxide. The hydrogen peroxide then reacts with a chromogen to form a colored compound, which is monitored photometrically. Another reaction uses glucose dehydrogenase which oxidizes glucose in the presence of NAD to form gluconolactone and NADH. The NADH reacts with a tetrazolium salt to produce a chromogen. A variant on this reaction uses the enzymes hexokinase and glucose-6-phosphate dehydrogenase to produce the chromogen. Both increased and decreased partial pressures of O_2 will affect those enzymatic reactions which involve oxygen (4, 5).

In an early study looking at the effect of an increased partial pressure of O_2 on the glucose oxidase reaction, Zel (6) noted that Chemstrip blood sugar values were altered by the hyperbaric environment, when abnormally elevated values were obtained. This elevation persisted even if the blood samples were transferred from the chamber and the values obtained outside of the hyperbaric environment. Price et al. (7) evaluated the accuracy of five commercially available glucometers in the hyperbaric environment. Four of the glucometers used the glucose oxidase reaction and the fifth used the glucose dehydrogenase. All the instruments were shown to be affected by the increased partial pressure of O_2. Unfortunately, the analysis presented in the paper does not allow the agreement between different instruments to be evaluated, but only the strength of the relation between the instruments (8).

From 1992 onward, persons with well-controlled insulin-

dependent and non-insulin-dependent diabetes mellitus have been permitted to scuba-dive under the medical rules of the British Sub-Aqua Club (BSAC), the Sub-Aqua Association (SAA), and the Scottish Sub-Aqua Club (SSAC). Major medical problems that could be suffered by diving diabetics include decompression illness (DCI) and hypoglycemia. The symptoms and signs resulting from the two medical problems may be confused, and it is important that blood glucose can be measured quickly and accurately in the chamber when the patient is being recompressed.

The Bayer Glucometer 4 blood glucose meter (Bayer PLC, Basingstoke, UK) uses the hexokinase reaction to measure glucose levels in whole blood. This enzyme system has not been evaluated for accuracy of glucose measurement under increased partial pressures of O_2. Therefore, this study was undertaken to compare the WBGC measured in the hyperbaric chamber under pressure using a Glucometer 4 blood glucose meter with the WBGC as measured using the same glucometer model at atmospheric pressure.

The WBGC measured at pressure in the hyperbaric chamber was also compared with the serum blood glucose concentration (SBGC) as measured using standard laboratory techniques.

METHODS

Experimental methods: Eight sex- and age-matched normal subjects (six male and two female, mean age 26.8 yr) and eight insulin-dependent diabetic (IDDM) subjects (mean age 27.9 yr) took part in a clinical trial to assess the effect of pressure on glycemic control. The subjects were randomly assigned either to an exercise regime in a hyperbaric chamber at 3.7 atm abs on the first day of the trial, followed by the same exercise regime in a room at 1 atm abs on the following day, or vice versa. The hyperbaric chamber and the room were controlled for temperature (28°–32°C) and humidity (50–70%) throughout the course of the exercise.

Glucometer 4 blood glucose meters were cleaned and calibrated according to the method given with the test glucose solutions provided with the glucometers. The calibration exercise was carried out on the evening before testing on the following day, and all three control solutions were used for calibration purposes. Every test performed on the glucometers fell within the stipulated ranges given with the test solutions.

On the day when the subject was performing exercise in the chamber under pressure, the subject was fasted from midnight on that day of the study. At 0730 h, 2 ml of blood was drawn from a forearm vein via a cannula for serum glucose measurements. After this procedure, the subject was then allowed a normal breakfast, together with the standard dose of insulin which the subject would normally take before a dive. At 0830 h, 2 ml of blood was taken as above. One drop of this blood was then used to measure the WBGC using the glucometer inside the chamber,and a further drop of blood was used to measure the WBGC using the glucometer outside the chamber. The remainder of the blood was used to measure in duplicate the serum glucose concentration using standard laboratory techniques. The chamber was then pressurized over 2 min to 3.7 atm abs and the subject performed 12 min of exercise on an exercise bicycle. Blood was withdrawn from the forearm vein at 5, 10, and 15 min after the start of the pressurization of the chamber. WBGC was measured using the glucometer inside the chamber, the syringe containing blood was then immediately passed out of the chamber via the medical lock and the WBGC measured using the glucometer outside the chamber. The remainder of the blood was used to measure serum glucose concentration in duplicate as before. After the exercise had been completed, the subject was brought to atmospheric pressure over a period of 2 min. A final sample of blood for WBGC and serum glucose concentration was taken 20 min after the start of the descent in the chamber.

Subjects were accompanied in the chamber throughout the study by a chamber attendant. A medical practitioner familiar with the study was in attendance on the outside of the chamber at all times. The study had approval from the local ethics committee, and all the subjects taking part in the study gave their signed, informed consent.

Statistical methods: An analysis was carried out comparing the WBGC obtained from the glucometer inside the chamber with those obtained from the glucometer outside the chamber. Additionally, a comparison was made between the WBGC obtained from the glucometer inside the chamber with the serum glucose concentrations determined in the laboratory. The method used was a generalization of the method of Bland and Altman (8) that allowed for repeated measurements over time from the same subject and for differences between diabetic subjects and controls.

RESULTS

A plot of the WBGC measured in the chamber against the WBGC measured out of the chamber is shown in Fig. 1, together with a line denoting equality of the results. The increased variability in the results as the WBGC is increased implies that the concentrations do not follow a normal distribution. Therefore, to perform parametric statistical analysis on the data, the data were transformed using logarithms to base e (natural logarithms, represented as ln). Figure 2 shows a plot of the log transformed data, in

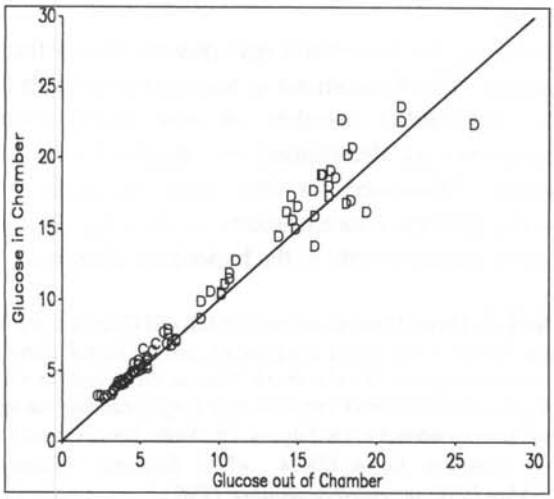

FIG. 1—A plot of the WBGS measured using the Glucometer 4 inside the hyperbaric chamber at 3.7 atm abs vs. the WBGC measured using an identical instrument outside the chamber at 1 atm abs. The line of equal concentrations is shown. *C* denotes the WBGC measured on control subjects; *D* denotes WBGC measured in diabetic subjects.

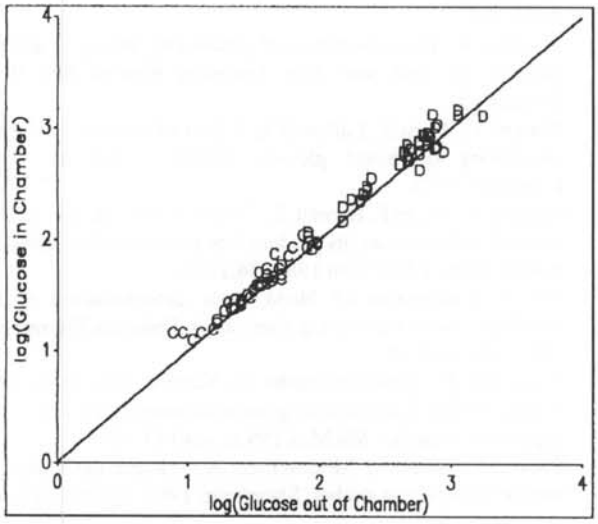

FIG. 2—A plot of the data from Fig. 1 that has been log transformed. The line of equal concentrations is shown. *C* denotes the WBGC measured in control subjects; *D* denotes WBGC measured in diabetic subjects.

which the variability is seen to be greatly diminished. Following a similar analysis to Bland and Altman (Grieve AP, manuscript in preparation), a plot of the difference in ln(WBGC) from the two glucometers vs. the average of the ln(WBGC) from the two glucometers is shown in Fig. 3. From this distribution, the average ratio is 3.5% [95% confidence interval (CI) 1.4–5.4%]. The limits of agreement [defined by $\exp(d \pm 1.96s)$, where d is the mean of the differences in logs and s is their standard deviation] is −11.2%:20.7%.

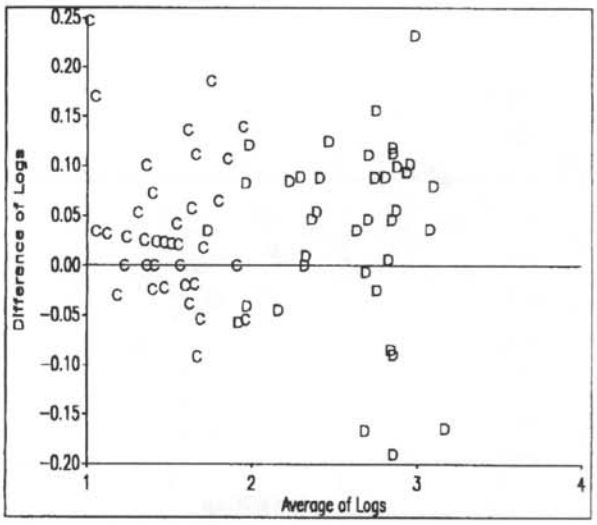

FIG. 3—A plot of the diffrence in ln (WBGC measured inside the chamber) and ln (WBGC measured outside the chamber) vs. the mean of ln (WBGC measured inside the chamber) and ln (WBGC measured outside the chamber). *C* denotes the WBGC measured in control subjects; *D* denotes WBGC measured in diabetic subjects.

A similar analysis was performed for the comparison between the glucometer inside the chamber and the serum glucose concentration measured in the laboratory. Figure 4 shows a plot of the difference in ln (WBGC) and ln (average laboratory serum glucose concentration) vs. the average in ln(WBGC) and ln(average laboratory serum glucose concentration). The average ratio is −7.4% (95% CI −9.8% to −4.8%) with the limits of agreement −20.2%:7.6%.

DISCUSSION

The Glucometer 4 uses the enzymes hexokinase and glucose-6-phosphate dehydrogenase to measure glucose concentration. Such a reaction system should be less susceptible to interference by increased or decreased O_2 partial pressures. The difference between the WBGC measured at 3.7 atm abs and the WBGC measured at 1.0 atm abs is therefore somewhat unexpected and indicates that pressure does have the effect of increasing the measured value of WBGC when using the hexokinase reaction. The reasons for this result are unclear, but it may be that the increased partial pressure of O_2 reacts allosterically with one or more of the enzymes used in the reagent test strip so that an increased concentration of formazan (the brown colored compound detected by the glucometer) is produced.

As expected, a percentage difference was found between the Glucometer 4 and the SBGC, reflecting the fact that the Glucometer 4 was measuring WBGC rather than SBGC.

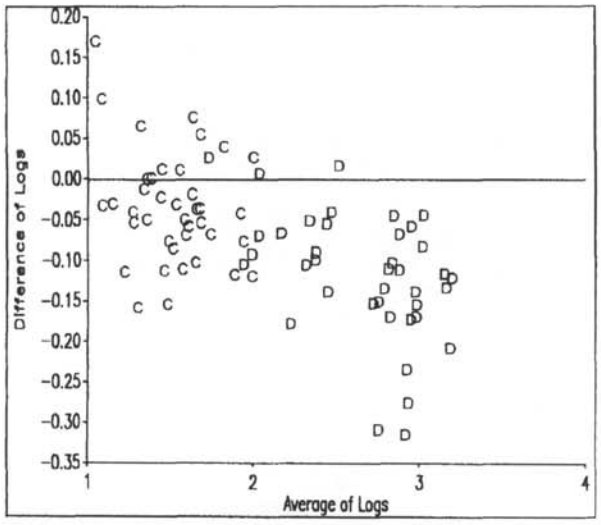

FIG. 4—A plot of the difference in ln (WBGC measured inside the chamber) and ln (mean SBGC) vs. the mean of ln (WBGC measured inside the chamber) and ln (mean SBGC). *C* denotes the glucose concentration measured in control subjects; *D* denotes glucose concentration measured in diabetic sibjects.

The value of −7.4% is in good agreement with previous results, and indicates that the WBGC is on average less than that measured for the SBGC. However, the limits of agreement between the measurements obtained under pressure and the laboratory serum results are rather large, and at lower blood glucose concentrations may become critical. The problem of wide limits of agreement is compounded at low SBGC by the Glucometer 4 giving a *high* reading for the blood glucose, which may thus delay the administration of antihypoglycemic measures. This is seen clearly in Fig. 4 at average log values of between 1.0 and 1.5 (glucose concentrations in the range of 2.7 to 4.5 mmol/liter). Price et al. (7) noted that the glucometers that they tested also gave falsely high readings when tested on glucose solutions in the concentration range of 1.4 to 2.8 mmol/liter.

In summary, the hyperbaric environment does affect the performance of the Glucometer 4, and the meter reads high in the hyperbaric chamber at low blood glucose concentrations as determined by standard laboratory techniques. Allowance for this must be made when measuring glucose concentrations in the range likely to precipitate seizure events in the hyperbaric chamber.

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