Original articles

Blood sugar changes in diabetic patients undergoing hyperbaric oxygen therapy

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Key words
Diabetes, hyperbaric oxygen, blood sugar levels

Abstract
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Introduction: We have conducted a prospective, single-cohort observational study of blood sugar levels (BSL) before and after hyperbaric oxygen therapy (HBO_2) in diabetic patients.
Methods: BSL was measured immediately before and after HBO_2 for between four and 15 consecutive treatments in each individual. Primary analysis compared the mean change in BSL for each patient. Secondarily, we analysed the change for each individual treatment. Glycosylated haemoglobin (HbA1c) was measured before the first treatment, and then after ten treatments, to determine any alterations in diabetic control over the trial period.
Results: Twenty-seven patients were studied over a total of 237 treatment episodes. The mean change in the BSL after a single HBO_2 session was a reduction of 2.04 $mmol.l^{-1}$ (95% confidence limits (CL) 1.49 to 2.58, $p < 0.0001$). Problematic reductions in BSL occurred more often in patients requiring insulin than in those not requiring insulin. The number of treatment sessions in which the BSL drop was >4.0 $mmol.l^{-1}$ and/or intervention was required was 44/133 (33%) in the insulin group and 17/104 (16%) in the non-insulin group ($\chi^2 = 8.6$, DF = 1, $p = 0.003$). Eleven HBO_2 sessions were associated with symptomatic hypoglycaemia requiring glucose administration while in the hyperbaric chamber; nine in insulin-requiring subjects, two in non-insulin-requiring. There was a small, non-significant mean reduction in HbA1c of 0.22 % ($p = 0.06$) over the course of treatment.
Conclusions: HBO_2 reduces BSL in both non-insulin-requiring and insulin-requiring diabetics. Diabetic control overall is unchanged over a course of ten treatments. Problematic hypoglycaemia is more common in patients requiring insulin. We recommend daily monitoring of BSL prior to HBO_2 and prophylactic glucose in some form if the BSL is <8 $mmol.l^{-1}$.

Introduction

As evidence emerges to support the efficacy of hyperbaric oxygen therapy (HBO_2) for the treatment of the diabetic foot, diabetic patients are coming to constitute a significant proportion of those treated in hyperbaric facilities worldwide.[1–3]

Some authors have shown significant reductions in blood sugar level (BSL) in these patients during HBO_2,[4,5] while others suggest we should expect none.[6,7] The numbers of diabetic patients reported to date are small, and most published work has been restricted to those diabetics requiring regular insulin administration. Furthermore, if there is a significant relationship between HBO_2 and BSL, it remains unclear whether changes in BSL are variable in the population but predictable in the individual, or variable both for the individual and the population.

The ability to identify those patients most prone to problematic reductions in BSL would greatly assist clinical management and potentially eliminate unnecessary testing in patients identified as not at risk.

The mechanism by which HBO_2 might result in a reduction in BSL remains unclear though several possibilities have been proposed.[8–11] Whatever the mechanism, the clinical implications of any fall in BSL are important because early hypoglycaemia may be masked in the chamber by other physiological responses to HBO_2 or may be mistaken for oxygen toxicity.

We considered that further clinical investigation was required to quantify any fall in BSL in our own practice and to assist in the development of a rational protocol for the routine treatment of both insulin-requiring and non-insulin-requiring diabetics during HBO_2.

Consequently, we have conducted a prospective observational study of BSL before and after each hyperbaric treatment session in diabetics presenting for HBO_2, along with an estimation of glycosylated haemoglobin (HbA1c) concentrations before and after a course of HBO_2.

Subjects and methods

The study was approved by the Ethics Committee of the

TABLE 1. DEMOGRAPHIC DATA FOR PARTICIPATING SUBJECTS

	Insulin-requiring	Non-insulin-requiring	All diabetics
Age in years (mean)	35–79 (63.4)	39–83 (62.1)	35–83 (62.9)
Duration of diabetes in years (mean)	7–44 (22.1)	0.2–25 (6.0)	0.2–44 (15.4)
Male:Female	12:1	10:4	22:5

Prince of Wales Hospital (Randwick, Australia) and was conducted in accordance with NHMRC guidelines. All diabetic patients presenting to the Prince of Wales Hospital Department of Diving and Hyperbaric Medicine over a period of 12 months from January 1999 to January 2000 were considered for inclusion, and all consenting patients were enrolled in the study if they were over 18 years old and accepted for HBO_2.

BSL was measured using Medisense^R Precision QID™ glucometer (Abbott, MA, USA) immediately before and after HBO_2 for 10 consecutive sessions where possible. This instrument is commonly employed for serial estimations of BSL in diabetic inpatients and has been demonstrated to show acceptable accuracy and high concordance between operators (correlation coefficient 0.98).[12] We performed a preliminary study in non-diabetic control subjects and confirmed reliability in our clinical setting (unpublished data). Capillary blood was collected via finger prick in all patients no more than 15 minutes before HBO_2 and repeated no more than 15 minutes following HBO_2. Standard measurement procedure was used according to the manufacturer's instructions.

In a subset of five subjects (17 pairs of readings), BSL was estimated twice on non-treatment days at the same times as the pre- and post-HBO_2 samples in order to compare any alterations in BSL independent of HBO_2. HbA1c was measured in all patients prior to commencing the course of HBO_2 and again following the tenth treatment.

In order to identify any difference in the relationship of HBO_2 and BSL in different types of diabetes, we also compared changes in insulin-requiring and non-insulin-requiring diabetics. Finally, we investigated the quality of BSL control by comparison of HbA1c levels before and after ten treatment sessions.

STATISTICAL ANALYSIS

No sample size calculations were performed prior to commencing the data collection. Differences in mean BSL between groups were compared using Students *t*-test and for each individual using the paired *t*-test. Differences in proportions were compared using χ^2 analysis of 2 x 2 tables and any differences in daily BSL were investigated using one-way ANOVA with adjustment for multiple comparisons using the treatment number (from 1 to 10) as the within-group factor. Simple linear regression was used to investigate any relationship between initial BSL and post-treatment BSL. Results will be given as mean or proportion with 95% confidence limits (CL).

Results

All eligible patients consented to the study, and 27 patients undertook a total of 237 individual sessions of HBO_2 during the study period. Demographic data are shown in Table 1.

Thirteen patients required regular insulin administration prior to enrolment, while 14 did not. Of those who did not require insulin, eight were on regular oral hypoglycaemic agents (metformin, glibenclamide, gliclazide either singly or in combination) and six were controlled with diet alone. All patients were referred for the treatment of diabetic wounds in the lower extremities except one insulin-requiring patient treated for acute visual loss and two non-insulin-requiring patients with retinal artery occlusion. Twenty-three patients completed a minimum of nine sessions of HBO_2, while one insulin-requiring patient completed five sessions and three non-insulin-requiring patients completed four, four and six sessions respectively.

The range of BSLs before and after treatment for each patient is summarized in Table 2. The mean pre-HBO_2 BSL for insulin-requiring patients was 9.7 $mmol.l^{-1}$, while the mean BSL for non-insulin-requiring diabetics was 9.1 $mmol.l^{-1}$. This difference was not significant ($p = 0.14$). There was a mean reduction in BSL for each individual subject after HBO_2 of 2.04 $mmol.l^{-1}$ (95% CL 1.49 to 2.58, $p < 0.0001$). The mean reduction in BSL in insulin-requiring diabetics was 2.61 $mmol.l^{-1}$ (95% CL 3.5 to 1.68, $p < 0.0001$), and in non-insulin-requiring diabetics 1.5 $mmol.l^{-1}$ (95% CL 2.06 to 0.93, $p < 0.0001$). This difference between diabetic types was also statistically significant ($p = 0.03$).

The number of treatment sessions in which the BSL drop was >4.0 $mmol.l^{-1}$ and/or intervention with glucose was required was 61/237 (26%). Of these, 44/133 (33%) were in the insulin-requiring group and 17/104 (16%) in the non-insulin-requiring group. This difference in the

TABLE 2. BLOOD SUGAR LEVEL (BSL) BEFORE AND AFTER HBO_2 IN ALL PATIENTS

Patient and insulin requirement		BSL range (mmol.l^{-1}) before HBO_2	BSL range (mmol.l^{-1}) after HBO_2	BSL range (mmol.l^{-1}) change during HBO_2
1	Insulin	8.0-14.9	5.4-10.8	-1.3 to -6.6
2	Non-insulin	6.7-12.9	6.0-8.9	+1.1 to -6.1
3	Non-insulin	5.0-13.7	4.1-15.0	+4.8 to -3.9
4	Insulin	4.5-17.2	4.0-12.4	+2.1 to -5.1*
5	Non-insulin	4.1-15.4	2.7-12.4	+1.4 to -4.7
6	Non-insulin	5.5-13.7	4.6-12	+2.2 to -2.2
7	Non-insulin	6.1-9.6	3.7-7.6	+0.1 to -3.8
8	Insulin	9.1-13.8	7.1-13.2	+2.1 to -5.0
9	Insulin	3.7-10.1	2.9-7.4	+0.3 to -4.1
10	Insulin	5.4-14.5	5.8-14.9	+0.7 to -4.9
11	Insulin	4.5-20.1	1.4-16.9	+0.3 to -9.8*
12	Non-insulin	3.6-12.3	4.8-12.9	+9.3 to -2.8*
13	Insulin	6.4-13.1	4.3-8.9	+0.4 to -5.4
14	Insulin	4.5-10.2	2.6-8.5	+2.3 to -3.2*
15	Insulin	5.4-18.1	4.4-10.6	-0.2 to -7.5
16	Insulin	3.6-14.7	5.3-16.6	+6.2 to -4.7*
17	Non-insulin	5.4-12.4	3.4-7.9	-1.4 to -4.7
18	Insulin	5.4-11.7	2.7-7.5	-0.8 to -6.6*
19	Non-insulin	8.6-15.7	4.7-12.4	+2.3 to -5.7
20	Non-insulin	7.2-10.0	7.3-10.1	+2.9 to -1.5
21	Non-insulin	4.8-10.7	3.3-7.3	+2.1 to -4.6
22	Non-insulin	6.0-10.1	4.4-9.7	+3.7 to -5.7
23	Insulin	5.8-12.2	4.6-8.3	+1.0 to -3.7
24	Insulin	5.4-11.8	3.1-7.9	-0.3 to -6.1
25	Non-insulin	5.6-8.1	4.0-5.4	-0.4 to -3.8
26	Non-insulin	8.0-15.0	8.1-11.0	+3.0 to -4.0
27	Non insulin	7.4-13.5	7.3-11.4	+4.0 to -5.2

*Patient required glucodin and sugar for hypoglycaemia during treatment

proportion of sessions associated with significant hypoglycaemia was statistically significant (χ^2 = 8.6, DF = 1, p = 0.003).

While subjects underwent a total of 237 treatment sessions, 11 individual sessions were excluded from further analysis because glucose was administered during the hyperbaric session to treat symptomatic hypoglycaemia (nine episodes in insulin-requiring subjects and two in non-insulin-requiring subjects). The mean change in BSL in the remaining 226 treatments was 2.13 mmol.l^{-1} (95% CL 1.82 to 2.44, p <0.0001), similar to the overall mean. The changes in BSL following these 226 episodes of HBO_2 are shown in Figure 1.

Of the 226 treatment sessions where in-chamber intervention to correct hypoglycaemia was not required, subjects with insulin-requiring diabetes accounted for 124 (55%). Of these, 112 (90%) were associated with a reduction in BSL that was measured post HBO_2. Seventy-one out of 124 (57%) sessions were associated with a reduction of >2 mmol.l^{-1}, 31/124 (25 %) with >4 mmol.l^{-1}, and 4/124 (3%) required treatment for hypoglycaemia. Non-insulin-requiring patients accounted for 102 (45%) of sessions. Of these, 80 (78%) were associated with a reduction in BSL, 13/102 (13%) had a BSL drop >4.0 mmol.l^{-1}, and 2/102 (2%) required intervention.

The relationship between the starting BSL and change over the course of a single HBO_2 session was investigated using correlation and regression (Figure 2). There was a significant relationship in that the higher the pre-HBO_2 BSL, the greater the reduction that can be expected following HBO_2 (correlation coefficient -0.45, p <0.0001). The relationship can be described by the regression equation:

Change in BSL (mmol.l^{-1}) = -0.37 x pre-treatment BSL (mmol.l^{-1}) +1.33

BSL was recorded in five patients (17 pairs of samples) on days during which no HBO_2 was administered. A reduction

FIGURE 1
CHANGE IN BLOOD SUGAR LEVEL (BSL) PRE- TO POST-HBO$_2$ SESSION IN 237 DIABETIC PATIENTS

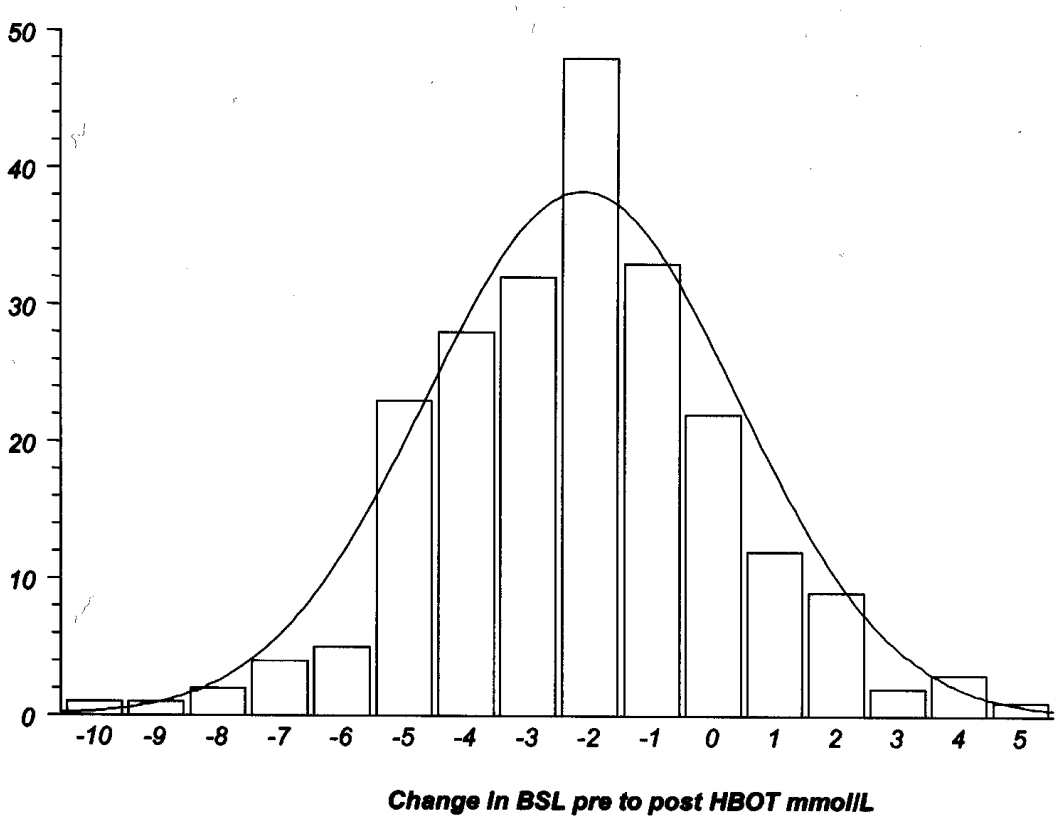
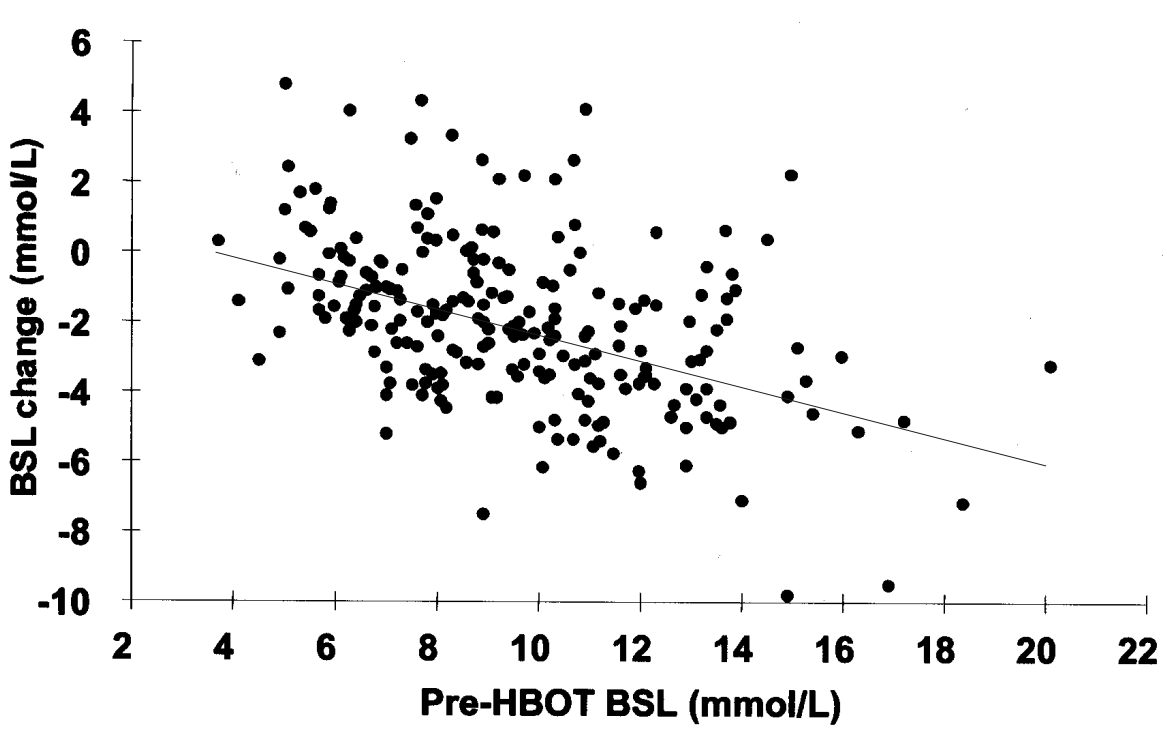


FIGURE 2
BLOOD SUGAR LEVEL (BSL) CHANGE PRE- TO POST-HBO$_2$ PLOTTED AGAINST THE PRE-HBO$_2$ BSL
(Correlation coefficient -0.45 , p <0.0001)



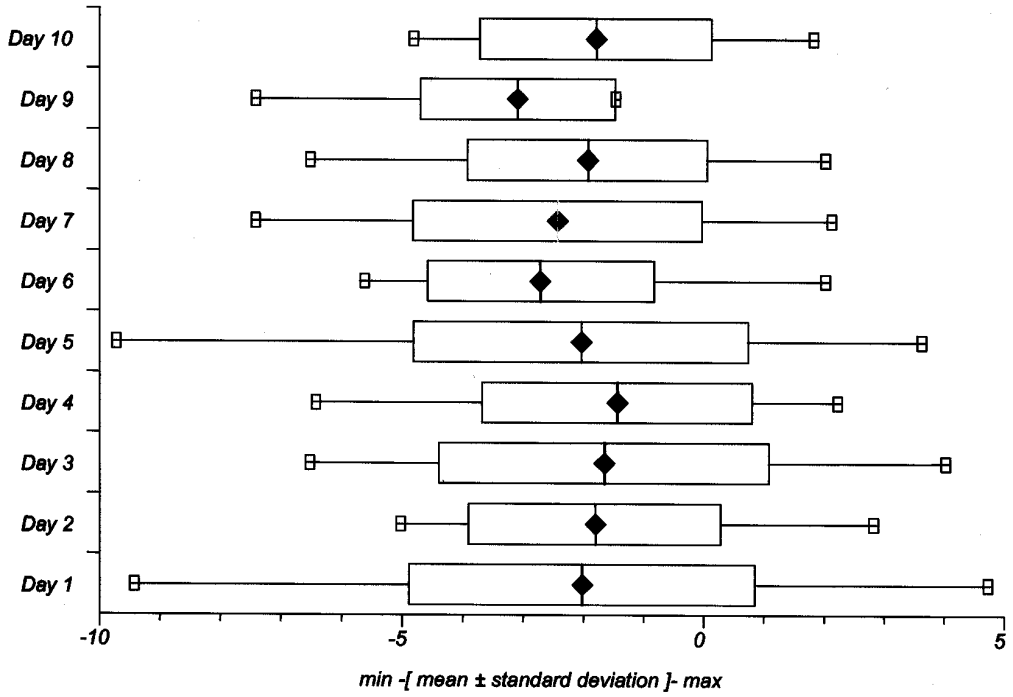


FIGURE 3
DAILY CHANGE IN BLOOD SUGAR LEVEL IN DIABETIC PATIENTS OVER THE STUDY PERIOD

in BSL was recorded in five (29%) sample pairs, two (12%) were >2 mmol.l^{-1}, while none were >4 mmol.l^{-1} or required intervention. The proportion of pairs showing a drop of >2 mmol.l^{-1} was significantly smaller in this group compared to the proportion associated with HBO_2 (11% versus 54%, $\chi^2 = 4.3$, $p = 0.04$).

The mean reduction in BSL following treatment did not significantly alter with treatment number during the course ($F = 0.94$, $p = 0.49$) (Figure 3). However, there was wide variability in the daily BSL measurements in each patient, and drops were unpredictable even in the same patient on consecutive days (Table 2).

Seventeen of the 23 patients who completed ten sessions of HBO_2 had HbA1c estimations following completion of the tenth session. Six patients were missed, four of whom were insulin-requiring and two non-insulin-requiring. In the 17 in whom the HbA1c was estimated, mean HbA1c prior to commencing HBO_2 was 7.78%, and there was a small, non-significant mean reduction in HbA1c of 0.22% (SD 0.43, 95% CL 0.01 to -0.44, $p = 0.06$) over the course of treatment.

Discussion

We have performed a prospective study into the effect of HBO_2 on the BSL in a population of 27 diabetics. There was a significant reduction in BSL in both insulin-requiring and non-insulin-requiring patients. The reductions in insulin-requiring patients were significantly greater and more often required active intervention.

Looking at each subject separately, we can predict an average drop in BSL during the course of a single HBO_2 exposure of about 2 mmol.l^{-1}, and our analysis predicts that 95% of diabetic patients will experience an average drop in BSL of between 1.5 and 2.6 mmol.l^{-1}. However, there is a greater variability in the changes in BSL following a single exposure. Furthermore, we cannot predict in which treatment an individual is more likely to experience a clinically significant problem. No patient with a pre-HBO_2 BSL greater than 8 mmol.l^{-1} required intervention for hypoglycaemia. Our figures are broadly in agreement with a previous small study in Australian patients.[4]

It might be suggested that we have detected a change in BSL that reflects normal variation over time in diabetics or, indeed, the normal population. Published work does confirm that BSL may vary by up to 2 mmol.l^{-1} postprandially in non-diabetic volunteers.[13] However, in these normal subjects there is an initial elevation after a meal, with the BSL returning to baseline over two hours. While testing non-diabetics might show a reduction in BSL during an HBO_2 session, such reductions would only be noted with treatment immediately after a meal, and from slightly elevated values down to normal. Symptomatic hypoglycaemia would be most unlikely. These hypotheses should be confirmed by further clinical investigations.

The published data on expected BSL variation over two hours in diabetics in the absence of a specific intervention are surprisingly sparse. To assess any such changes in our patient population, we examined the BSL over a two-hour

period on non-treatment days in some of our study group. Compared with changes associated with HBO_2, reductions in BSL were smaller, less frequent and did not require intervention in this group. These results confirm that HBO_2 is associated with specific effects on BSL in diabetics. Further, if the reductions we report in this study were common to all diabetics, we would expect such changes to be well reported and to result in modifications to standard diabetic treatment protocols.

We chose to estimate BSLs with the Medisense^R Precision QID™ glucometer as an accurate and expedient means of measuring BSLs in this patient population. This device was previously reported to be unreliable in the presence of high blood PO_2.[14] Each electrode contains the enzyme glucose oxidase, which catalyses the oxidation of glucose to produce gluconic acid. During the reaction, electrons are transferred to the electrode surface. The resulting current is measured by the sensor. This method was found to result in falsely low BSLs in the hyperbaric environment with high PO_2.[14] However, in late 1997 the measurement strips were modified specifically to function reliably under conditions of varying oxygen tension.[15] In addition, BSLs were measured in our patients once outside the chamber, at which time their PaO_2 would be approaching more normal physiologic levels.

The mechanisms by which HBO_2 might result in a reduction in BSL remain unclear. Possibilities include stimulation of residual insulin production,[8] suppression of glucose production by the liver,[9] improvement in tissue metabolism, and suppression of the glucagon response to a BSL fall.[10,11]

There is evidence to suggest increased insulin production is not a likely candidate.[4] This is certainly consistent with our findings, as there is a trend towards greater reductions in the BSL of patients who require insulin. If increased insulin production contributed to lower BSL in diabetics, we might expect the reverse to be true because non-insulin-requiring diabetics have better preserved insulin-manufacturing capability with which to respond.

Reduced glucose absorption and/or production secondary to the effects of hyperoxia on the cardiovascular system are a possibility. HBO_2 is known to cause vasoconstriction and a decrease in global cardiac output of up to 30%.[16] While the specific effect on splanchnic blood flow in humans is unknown, animal data have demonstrated a decrease.[17] Decreased flow could theoretically decrease gut absorption of nutrients, while decreased hepatic blood flow might affect gluconeogenesis and glycogenolysis.

Suppression of glucose production by the liver was proposed as the chief mechanism for hypogylycaemia in one Russian paper. However, the patients were tested before and after a full course of HBO_2, and the proposed mechanism of decreased hepatic production was not fully elucidated.[9] In the non-diabetic population with normal regulation of insulin production, a decrease in blood glucose will trigger a decrease in insulin production and the release of glucagon and catecholamines. However, suppression of the glucagon response to hypoglycaemia is well described in diabetics and the catecholamine response is similarly blunted.[18] This means that a decrease in glucose production or absorption would result in a significant decrease in BSL, particularly in the presence of exogenous hypoglycaemic agents.

Increased glucose utilization secondary to up regulation of oxidative pathways might explain the reduction in BSL, and there is some experimental evidence that this may be so, at least over a course of HBO_2. In a study involving 120 diabetic patients, Kakhnovskii measured glucose, lactate, pyruvate, malate dehydrogenase and lactate dehydrogenase over 15–18 days utilizing HBO_2 at 1.7 ATA (173 kPa), and demonstrated a link between increased tissue metabolism and increased glycolysis.[11] Efuni produced similar results in another series.[19] These studies also demonstrate that with the increase in oxidative capability there is a concomitant induction of enzymes in the gluconeogenic pathways, thus reducing the net effect on BSL over time.

HbA1c is an indicator of longer-term glucose control. It is formed following irreversible, non-enzymatic glycation of the haemoglobin A beta chain and is directly proportional to the ambient glucose concentration. In our subjects, HbA1c levels did not significantly change over the course of ten sessions of HBO_2. Although the absolute figures suggest there may be a small decrease, the measured reduction would not be clinically significant.

A larger study measuring HbA1c at the end of a longer period of HBO_2 may confirm this finding. If correct, this would be consistent with the premise that there was no significant change in the adequacy of diabetic control over this period and therefore no evidence for induction of metabolic pathways that may contribute to hypoglycaemia. The literature confirms that a change in HbAIc should be measurable after this period of time with a change in therapy or in BSL control.[20]

A novel mechanism not previously discussed in the literature involves the possible effect of hyperoxia on the carotid bodies. The carotid bodies are known to be responsive to oxygen tension and recent animal data suggest that they may have a significant role in the regulation of blood glucose. In a dog model in which the carotid bodies were removed, for example, Koyama reported significant impairment in glucagon release and a hypoglycaemic response to infusion of insulin.[21] It is possible that HBO_2 may affect carotid body function and alter the response to hypoglycaemia via this mechanism.

We are not aware of any studies specifically involving HBO_2 and the glucagon response to hypoglycaemia. In fact, as noted above, glucagon release in response to hypoglycaemia is lost early in insulin-requiring diabetic disease and therefore may not be of any significance in our patients.[18]

Growth hormone and cortisol also have important regulatory effects in glucose metabolism.[22] While Longoni looked at urinary cortisol levels in diabetic patients undergoing HBO_2 and found no changes, no-one has comprehensively examined growth hormone or cortisol responses in diabetic patients receiving HBO_2.[5] Inhibition of these hormones may possibly contribute to hypoglycaemia in patients with impaired glucose regulation.

Perhaps the most likely mechanism for hypoglycaemia is an increase in the insulin receptor sensitivity in response to HBO_2. Non-insulin-requiring diabetic patients have lower numbers of insulin receptors and tend to have resistance to insulin, whereas insulin-requiring diabetics have a higher number of insulin receptors and maintain sensitivity.[23] This would explain the greater drop in insulin-requiring diabetics compared to non-insulin-requiring diabetics. Despite a literature search we were unable to find previous work in regard to insulin receptors and the effects of HBO_2.

Our results show that, on average, diabetics having HBO_2 will drop their BSL by about 2 $mmol.l^{-1}$ during each treatment. However, there is considerable variability in this response, both between subjects and between treatment sessions in a single subject. Non-insulin-requiring diabetic patients are more predictable in their response than insulin-requiring diabetic patients and are less likely to drop their BSL sufficiently to require treatment.

We recommend all diabetics eat a meal within two hours of HBO_2 if possible and that a BSL estimation be performed prior to each treatment. Patients with insulin-requiring diabetes in whom the BSL is <8.0 $mmol.l^{-1}$ or with non-insulin-requiring diabetes with a BSL <6.0 $mmol.l^{-1}$ should be given glucose prior to entering the chamber. We continue to monitor our experience with these recommendations, but suggest that under this regimen symptomatic hypoglycaemia is very unlikely. It would be useful to confirm this suggestion in a subsequent larger study.

Regardless of aetiology, our study has demonstrated that important changes in BSL can occur in any diabetic patient undergoing HBO_2. Such changes cannot be predicted by previous response in an individual patient. Therefore, we advocate that BSL estimation should be mandatory in all diabetic patients prior to each HBO_2 session.

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