Effect of Mild Chronic Hyperbaric Pressure on Blood Antioxidant Levels Among Jordanian Smoker and Non- Smoker Males

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Abstract

Objective: Hyperbaric oxygen treatment and cigarette smoking are known to increase oxidative stress via the production of reactive oxygen species. Jordan, having different altitudes, offers an ideal geographical site to study the effect of mild chronic hyperbaric pressure (mHB), smoking and their combination on the level of antioxidants in humans.

Methods: The levels of the antioxidants, glutathione in the whole blood and the erythrocyte antioxidant enzymes, were assessed in non-smoker and smoker male subjects living in the Dead Sea area in the Jordan Valley which represents Earth's lowest point on land (423 m below sea level) and compared with male subjects living in the Amman area (766 m above sea level).

Results: It was found that chronic mHB caused a significant increase in the levels of glutathione and glutathione peroxidase (~ 35% to 50%) and catalase (up to 20%) in smokers and non-smokers but resulted in a decrease in glutathione reductase (~ 25%) in both groups. However, smoking habit did not affect the level of antioxidants except for a slight change in a few cases.

Conclusions: It is concluded that tolerance to mild chronic hyperbaric atmosphere involved induction of the antioxidants glutathione, glutathione peroxidase and catalase. In addition, the increased level of GSH may provide further protection to peripheral cells from any damage by the resulting mild increase in tissue O2 concentration in the subjects living under chronic mHB. Meanwhile, our results suggest that smoking appears to have little or no effect on the level of antioxidants in the blood.

Keywords: Antioxidants; Mild Hyperoxia; Smoking; Erythrocyte Enzymes.

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Introduction

The human body is constantly under attack by reactive oxygen species (ROS) that includes free radicals. ROS are highly reactive molecules generated by the redox reactions that occur as part of normal aerobic cell metabolism and by exposure to certain environmental factors [1,2]. An imbalance between the production of ROS and anti-oxidant capacity leads, to a state of "oxidative stress" that damages DNA, proteins and lipids.

The action of hyperoxia and cigarette-smoke

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are known to be stressful for living organisms. Under hyperoxic conditions, the generation of oxygen-free radicals is markedly increased. The excess production of partially reduced species of oxygen, which includes superoxide ion (O2), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$) and peroxynitrite ($ONOO^-$) is one of the postulated causes of tissue injury by hyperoxia [1,3,4,5] On the other hand, smoking has been implicated as a risk factor for numerous chronic diseases. Cigarette smoke contains large amounts of oxidants and free radicals that could cause oxidative damage to critical biological substances.

Cellular antioxidants act in concert to detoxify ROS which include the three main antioxidant enzymes (AOE), Superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), a group of low molecular weight antioxidants including reduced glutathione (GSH), ascorbic acid, α-tocopherole, β-carotene, uric acid and bilirubin and macromolecules such as ferritin, ceruloplasmin and albumin [3,6]. Hyperbaric oxygen (HBO) therapy is increasingly used in the treatment of a variety of medical conditions. The therapeutic uses include, decompression sickness, gas embolism, carbon monoxide poisoning, wound healing and many other applications. Traditionally HBO therapy involves intermittent inhaling up to 100% oxygen at a pressure greater than 1 atmosphere absolute (1 ATA), 2.0 to 3.0 ATA[7,8,9]. HBO treatments also leads to increased reactive oxygen species formation that cause cellular damage with lipid, protein and DNA oxidation[10] . More recently the use of mild – pressure hyperbaric therapy (mHBT) has become very popular among the general public and especially among athletes to improve the over-all well being and to treat sport- related injuries[11,10]. mHBT uses hyperbaric pressure that is less than 1.5 ATA (< 1140 mm Hg). In fact a recent study indicated that after mHBT, oxidative stress was decreased[11]. Also, mHBT treatment decreased blood lactate level and fatigue in athletes, shortened recovery period from acute leg pain and produced striking improvements in behavior in autistic children [11,12] It seems different pressures are used for different conditions but, for neuro-rehabilitation, the lower pressures of 1.2 to 1.3 ATA have benefits. On the other hand, treatment of an infected wound or an acute carbon monoxide exposure requires deeper pressure of 2.5 ATA and 100% O2 therapy [7,10]. It appears that mHBT is quite safe, but its effect on the antioxidant defense and enzymes is not yet known[11,12]. Also oxygen and pressure dosing studies are still lacking. Jordan topographically offers an ideal place for studying the effect of mild chronic hyperbaric pressure on humans. Jordan has population groups living in Amman, 766 m above sea level and at the Dead Sea level, 432 m below sea level (Earth's lowest point on land); barometric pressures are 697.5 mm Hg and 794.7 mm Hg, respectively. In addition, the level of AOE in healthy human subjects, smokers or nonsmokers, was not determined in any of the Middle Eastern region populations. In the present report we aimed to study the effect of the chronic mild hyperbaric pressure on the level of whole blood GSH and the erythrocyte AOE, GR, G6PD and 6-PGD in male smokers and non- smokers .

Methods

The study was approved by the scientific research and ethics committee of the University of Jordan (5/3/2/1595). Blood samples were collected from male smoker and non-smoker volunteers of dwellers at both the

Amman region and the Dead Sea region at the Jordan Valley (Earth's lowest point on land) after obtaining informed consent. A total number of 202 male volunteers, (age range was 20–40 years), were included in this study. Most subjects were economically middle class people, apparently healthy, not suffering from any known chronic disease and had no history of favism. They were mainly students and office workers in both regions with a few working in agriculture in the Jordan Valley (Dead Sea region). All smokers were chosen from among people who have been smoking at least one pack (20 cigarettes) a day for at least the past five years. Blood samples were collected in EDTA-containing tubes. One milliliter of the collected blood was immediately used for the estimation of GSH and hemoglobin (Hb)[13]. The blood was then centrifuged at 2500 x g for ten minutes at 4°C.The saline-washed erythrocyte of the blood were then stored in different aliquots at -70°C for quantitative enzyme assays. The optimum level of the erythrocyte enzymes GR, GPx, G6PD, 6-PGD, catalase and SOD were determined as described by Beutler[13] using Cary 100 uv-vis spectrophotometer. G6PD activity was measured with correction for 6-PGD activity[13]. All enzymatic assays were performed at 30°C except for SOD at 25°C. G6PD deficient subjects were excluded from calculations of all the erythrocyte parameters studied in Table 1.

Statistical methods: All analyses were performed by SPSS software, Version 18 (SPSS Inc., Chicago, IL). Based on a table provided by Cohen[14], we needed at least 39 subjects in each of the four groups, Amman nonsmokers, Amman smokers, Dead Sea nonsmokers and Dead Sea smokers to find a statistically significant difference at an alpha level of 0.05. Moderate effect size (0.25) and a power of 0.80 were assumed. The analysis of variance (ANOVA) was used to compare the level of antioxidants in the four groups. To determine factors independently associated with the level of various antioxidants, a multivariate analysis was performed using a linear regression model of three variables, mHBO, smoking and age. P-values of less than 0.05 were considered statistically significant.

Table 1. The levels of antioxidants in the blood of smokers and non smokers living in Amman and Dead Sea area

Antioxidant	Amman Nonsmokers (n = 46)		Amman Smokers (n= 61)		Dead Sea Nonsmokers (n = 45)		Dead Sea Smokers (n = 50)		P
	Mean ±	SD	Mean ±	SD	Mean ±	SD	Mean ±	SD	
GSH	6.99 ±	1.11[a]	7.12 ±	1.2[a]	9.34 ±	1.59[b]	9.41 ±	1.84[b]	0.000
GR	9.52 ±	1.75[a]	9.82 ±	1.94[a]	7.36 ±	1.61[b]	7.32 ±	1.36[b]	0.000
GPx	25.25 ±	4.09[a]	23.11 ±	4.31[a]	35.76 ±	8.14[b]	34.1 ±	8.23[b]	0.000
G6PD	6.94 ±	1.27[a]	7.69 ±	1.53[b]	7.3 ±	1.13[ab]	7.04 ±	1.11[a]	0.012
PGD6	7.33 ±	1.28[a]	7.59 ±	1.26[a]	7.36 ±	0.87[a]	7.14 ±	0.95[a]	0.223
CATALASE	25.05 ±	4.22[a]	23.03 ±	4.1[b]	27.96 ±	5.86[c]	28.07 ±	5.98[c]	0.000

GSH µmole/gm Hb; all antioxidant enzymes Unit/ gm Hb at 30 °C
The differences between values with the same superscript are not statistically significant
GSH: Glutathione, GR: Glutathione reductase, GPx: Glutathione peroxidase, G6PD: Glucose- 6- phosphate dehydrogenase, PGD6: 6-phosphogluconate dehydrogenase

Results

The over-all age range of subjects were, 20 to 40 yr. The mean age of the various groups were: Amman area non smokers 26.0 ± 6.0 yr; Amman area smokers 27.7 ± 6.3 yr; Dead Sea area non smokers 29.6 ± 6.0 yr. and Dead Sea area smokers 31.4± 6.3 yr. The mean age of both Dead Sea dwellers groups were significantly higher than the mean age of Amman non smoker group, but the mean age of smokers was not significantly different in either areas.

(Table 1) shows significantly higher levels of GSH /gr.Hb (133%) and GPx (141 to 147%) and catalase (112 to 120%) in both groups of dwellers living under mild chronic hyperbaric pressure in the Dead Sea region (794.7 mm Hg) as compared to dwellers at Amman level (697.5 mm Hg). On the contrary, GR levels were significantly reduced by the increased atmospheric pressure in both groups of smokers and non smokers in the Dead Sea area (75 to 77 % of Amman level). However, there were no significant differences seen between smokers and non- smokers, in both regions, in all the studied parameters except a slight but significant decrease in catalase (8%) and an increase (10%) in G6PD among smokers in the Amman area but not in the Dead sea region (Table 1). Smoking did not affect the level of SOD when studied among Amman dwellers only. (data not shown).

Discussion

The erythrocyte is at an increased risk from oxidative stress because it is continually exposed to high oxygen tension. Three percent of oxyhemoglobin is oxidized to methemoglobin daily with the concomitant production of superoxide anion. In human, most of the studies were carried to measure the activities of antioxidant enzymes of the erythrocyte in smokers, patients suffering from genetic anemia and patients with dementia. Each oxidant appears to affect a different pattern of antioxidant enzyme response[3,4]. Some antioxidant enzymes may respond to oxidative stress by a compensatory increase in their activities while others may undergo some inactivation as a result of oxidative-induced damage.

HBO therapy has long been known and recommended for a wide range of medical conditions. Despite the positive clinical results, oxygen toxicity is a side effect of HBO treatment which might increase the production of ROS, as shown by increased production of stress markers, that may overcome the antioxidant capacity resulting in a state called oxidative stress. HBO therapy seems to be an excellent model system for the investigation of oxidative stress and its biological consequences. The cellular response to oxidative stress has been principally investigated in animal models and only a few studies have evaluated the effect of HBO in humans[10]. More recently, some physicians started using mild hyperbaric pressure therapy of 1.3 to 1.5 ATA (mHBT) chambers for various treatments. These are frequently mistaken for hospital HBO chambers despite the big difference in specifications between them. mHBT is believed to be safe as no study so far indicated the production of oxidative stress with such treatment. Although mHBT chambers have become recently widely used, few studies were done on their biological effect. The mechanism of mHBT action needs to be explored and its effect on the level of the major antioxidant enzymes in human is not

known. Jordan offers an ideal geographical region to study the effect of chronic exposure to mHBO among the dwellers of the Dead Sea region. Our results for smokers and non-smokers living under mild chronic hyperbaria showed a significant increase in the levels of GPx (~50%), GSH (~35%) and catalase (10 to 20%) but a decrease in GR (~25%). An increase in GPx and a decrease in GR were also seen in patients with chronic disorders associated with oxidative stress like thalasseamia and G6PD deficiency. Paradoxically, other antioxidants, that include vitamins and GSH were all decreased in the blood of patients with various types of genetic anemia like sickle cell anemia, thalassemia and G6PD deficiency[6, 17]. It is also interesting to state that HBO therapy has been used in the treatment of Crohn's disease [18] . Frazer and Niv[19] reported that even mHBO environment was highly effective in managing patients with severe Crohn's disease, who were unresponsive to medical treatment, after staying 1-3 weeks at mHBO environment of the Dead Sea region . This may indicate that people living under mild hyperbaric pressure in the Dead Sea for extended periods of time may have the advantage of intermittent exposure to high pressure oxygen (HBO) in the therapeutic chambers.

Exposure of experimental animals to hyperoxia resulted in a variable increase in one or more of the AOE. The different responses in AOE activities depend on the OAE, organ or cell types within the same organ and incubation time[5,1,20,21,4]. In bacteria, exposure to hyperbaric oxygen resulted in an increase in all three AOE [1]. However, in transformed E.coli, it was shown that the large increase in the activity of a single enzyme like SOD was not enough to provide resistance to oxidant challenge [22]. Therefore, the activities of AOE must be balanced to provide enough resistance to oxidant damage. Thus, resistance to oxidant challenge due to a single AOE is definitely not possible. Hence adaptation to hyperoxia as was shown for bacteria and experimental animals involved induction of more than one antioxidant[1,22,21]. Similarly, our subjects living under a mild chronic hyperbaric atmosphere in the Dead Sea region exhibited a significant increase, at least in GPx and GSH and a slight increase in catalase. Although GR activity was reduced by 25%, all together, there was a maintenance of a net balance of the antioxidants in the blood of the Dead Sea dwellers. It is likely that even chronic mHBO can induce low levels of oxidative stressors (ROS). The induced low level of ROS is enough to induce protective gene expression to defend cells from environmental and endogenous stressors as was shown that HBO treatment (2.4 ATA and 100% O2) induced antioxidants genes expression of human microvascular endothelial cell line[23]. Previous studies from our department showed also that people living under mild chronic hyperbaric atmosphere in the Dead Sea region have compensatory lower levels of RBC counts, Hb concentration, PCV% and 2,3-bisphosphoglycerate level in their blood than people living in the Amman area [24,25].

Cigarette smoke is a major public health hazard because it is known to contain numerous oxidants and free radicals, capable of producing oxidative damage to critical biological substances. In addition, smokers have increased numbers of phagocytes that generate ROS. Human red blood cells are vulnerable targets for electrophilic and oxidant foreign compounds. Several studies reported that smoking and its oxidative stress did not

influence the AOE level in human blood[26,27] . However in some other studies, a decrease has been observed due to the possible oxidative damage of some of the AOE, mainly catalase and GPx. The reported decrease in "AOE" was controversial and ranged from a decrease in only one to three AOE[14, 15,28]. A recent study showed that moderate smoking (4 to 6 cigarettes per day) had actually caused increased activity of SOD, catalase and GPx but reduced level of GSH [29]. Using ANOVA, our results did not show any significant change in the optimum level of any of the AOE, G6PD, 6-PGD and whole blood GSH level in the smokers living under chronic mHBO in the Dead sea region or in the Amman area who smoked at least 20 cigarettes a day. Multiple linear regression results confirmed the results obtained by ANOVA and showed that smoking was an independent predictor of GPx only where as age was an independent predictor of GSH and catalase though to a much lesser extent than mHBO effect (data not shown). This rules out the possibility that the greater effect of mHBO has masked the effect of the age and smoking habit on the antioxidants levels. Finally, although we cannot explain the discrepancy among the various workers on the effect of smoking on the AOE level in the blood, but as the level of these enzymes were shown to be influenced by age, gender and other genetic factors, it seems that these factors should be carefully controlled in such studies. Our subjects were all males, apparently healthy and their age range was from 20 to 40 yr.

Conclusion

Chronic exposure to mild hyperbaric pressure is associated with increase in blood level of key antioxidant enzymes and GSH in both smokers and nonsmokers. The potential of using this mild hyperbaric environment of the Dead Sea region in the Jordan Valley for the management of some chronic diseases associated with oxidative stress like Crohn's disease should be investigated.

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تأثير زيادة الضغط الجوي الطفيفة والمزمنة على مستويات مضادات الأكسدة في الدم على الذكور المدخنين وغير المدخنين الأردنيين

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الملخص

الهدف: من المعروف أن تدخين السجائر والمعالجة بالاكسجين بضغط مرتفع يؤديان إلى الإجهاد التأكسدي عن طريق زيادة إنتاج أنواع من الاكسجين التفاعلي. يعد الأردن بما يضم من ارتفاعات جغرافية متعددة موقعا مثاليا لدراسة تأثير كل من التدخين والزيادة الخفيفة المزمنة في الضغط الجوي على مستوى مضادات الأكسدة في الإنسان.

الطريقة: تم تقييم مستوى مضادات الأكسدة التي تشمل كلا من الجلوتاثيون في الدم والانزيمات المضادة للأكسدة في خلايا الدم الحمراء لدى مجموعتين من الذكور المدخنين وغير المدخنين الذين يقطنون في منطقة البحر الميت التي تمثل اخفض بقعة في العالم (423م تحت سطح البحر) ومجموعتين من الذكور الذين يقطنون في عمان (766م فوق مستوى سطح البحر).

النتائج: وجد ان الزيادة المزمنة والطفيفة في الضغط الجوي أدت إلى زيادة ملحوظة في مستوى الجلوتاثيون والجلوتاثيون بيروكسيديز (35%-50%) والكاتاليز (لغاية 20%) لدى المدخنين وغير المدخنين، في حين حصل انخفاض في مستوى الجلوتاثيون ريدكتيز (25%) لدى المجموعتين. ومع ذلك، لم تؤثر عادة التدخين في مستوى مضادات الاكسدة فيما عدا تغييرات طفيفة في مستويات بعضها.

الاستنتاجات: يستدل من هذه النتائج ان تحمل الزيادة الطفيفة في الضغط الجوي تتجلى في تحفيز إنتاج الجلوتاثيون والجلوتاثيون بيروكسيداز والكاتالاز. علاوة على ذلك، فإن زيادة الغلوتاثيون قد تكون لتوفير حماية إضافية للخلايا المحيطية ضد أي أذى قد تسببه الزيادة الطفيفة للأكسجين.

الكلمات الدالة: مضادات الأكسدة، التدخين، الأنزيمات المضادة للأكسدة في خلايا الدم الحمراء.