Effect of hyperbaric oxygen therapy on blood pressure in patients undergoing treatment

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ABSTRACT

Introduction: Hyperbaric oxygen (HBO_2) therapy is generally safe and well tolerated. However, known side effects do exist. Elevation in the blood pressure of patients undergoing HBO_2 therapy is a less defined potential side effect. We sought to better quantify effects of HBO_2 on blood pressure (BP) in patients undergoing HBO_2.

Methods: A retrospective chart review was performed on quality assurance data captured on all patients undergoing HBO_2 between March 2012 and October 2015 at a large tertiary referral university hospital hyperbaric center.

Results: We identified 155 patients who received 3,147 hyperbaric oxygen treatments. For all treatments there was an overall increase in the median systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) following treatment (Table 2). No statistically significant difference was found when comparing patients with and without hypertension. Calcium channel blockers (CCB) and beta-blockers (BB) were found to have an agonizing effect while ACE inhibitors (ACEI) were found to have a protective effect (Table 4). The change in SBP was less with each additional treatment in patients undergoing more than one treatment.

Discussion: The current study demonstrates that absolute rises in blood pressure do occur as a result of HBO2 therapy. However, the extent of this effect is not large. BB and CCB had agonizing effects while ACEI had a protective effect. Finally, there was a protective effect with more treatments.

INTRODUCTION

Hyperbaric oxygen (HBO_2) therapy can be delivered in monoplace or multiplace chambers for a wide range of medical conditions. Patients breathe 100% oxygen at higher than atmospheric pressure, causing systemic hyperoxia that improves cellular oxygen supply by raising the diffusion gradient from tissue to cell [1]. One hundred percent oxygen at a pressure of 3 atmospheres absolute (ATA) increases arterial oxygen tension to more than 2,000 mmHg PO_2 (partial pressure of oxygen). Resting tissue oxygen tensions are quadrupled in this scenario. Clinically, areas of the body that are difficult to adequately perfuse under stressful conditions become better oxygenated as oxygen is free in solution. This has implications in severe anemia and when oxygenation of hemoglobin is impaired, such as during carbon monoxide poisoning [2].

HBO_2 therapy promotes neovascularization by increasing local growth factors and stimulating bone marrow progenitor stem cell release [3]. It has also been shown to have benefit in ischemia-reperfusion injury by reducing intravascular leukocyte adhesion [4]. Despite the increased plasma oxygen carriage and improved flow in the microvasculature, HBO_2 causes significant vasoconstriction, which has been shown to reduce tissue edema [5]. HBO_2 also augments leukocyte oxygen-

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dependent peroxidase killing of bacteria, especially anaerobes [2]. The Undersea and Hyperbaric Medical Society has a list of a variety of approved indications for HBO_2 therapy.

HBO_2 therapy is generally safe and well tolerated. However, known side effects do exist. It is important to quantify the risk from these side effects for both provider decision-making and patient informed consent. Oxygen toxicity seizures are a rare side effect that occurs in approximately 1 in 3,000 treatments and has been shown to increase in frequency with increased treatment pressure [3]. More common side effects include middle ear barotrauma, sinus barotrauma, confinement anxiety, reversible myopia, and a potential worsening of cataracts [6]. Middle ear barotrauma is the most common side effect and was found in 43% of patients undergoing HBO_2 although 84% were minor cases (TEED 1 or 2) [7].

Elevation in the blood pressure of patients undergoing HBO_2 therapy is a less defined potential side effect. To date, few studies have set out to evaluate this effect. Studying the effects of HBO_2 on patient blood pressure and influences that may exacerbate the effect would further broaden the safety of HBO_2. The intent of the current study was to collect and analyze data on the effect on blood pressure of patients undergoing HBO_2 therapy. In addition, we sought to elucidate potential agonizing factors such as treatment pressure, medications, and existing medical conditions on patient blood pressure.

METHODS

A retrospective chart review was performed on quality assurance data captured on HBO_2 per protocol treatments for all patients between March 2012 to October 2015 at a large tertiary referral university hospital hyperbaric and wound care center. All patients were treated with 100% oxygen in a monoplace chamber. Duration and depth of pressure for each treatment were determined by the ordering physician. Data collected included age, gender, diagnosis, maximum treatment pressure, pre- and post-treatment blood pressure, history of hypertension, anti-hypertensive medications, other significant past medical history, and current tobacco use. Mean arterial pressure was calculated using MAP = (systolic blood pressure/SBP + 2 (diastolic blood pressure/DBP))/3. IBM SPSS Statistical version 22 was used for data analysis. Summary demographic statistics, non-parametric analysis for group comparisons of non-normally distributed data, and simple linear regression analysis for prediction equations was conducted. An a priori $p < 0.05$ was set for statistical significance. The study was granted an exemption by the Institutional Review Board for the protection of human subjects.

RESULTS

During the study period, 155 patients received 3,147 HBO_2 treatments. Patient demographic information including patient comorbidities and indications for HBO_2 treatment are shown in Table 1. For all treatments (N=3147) there was an overall increase in the median SBP, DBP, and MAP following treatment (Table 2).

Of all HBO_2 treatments, 58.3% were administered with patients that had previously been diagnosed with hypertension. No statistically significant difference was found when comparing the pre/post change of SBP (7.00 vs. 6.00, p=0.38), DBP (4.00 vs. 4.00, p=0.13), or MAP (5.33 vs. 4.67, p=0.12) between patients diagnosed with hypertension and those not diagnosed with hypertension, respectively.

The pre/post HBO_2 treatment change in SBP, DBP and MAP were found to have a statistically significant difference when the different HBO_2 treatment pressures were considered ($\chi2$ (2, N=3147) = 31.5, p<.0001; $\chi2$ (2, N=3147) = 17.7, p<.0001; $\chi2$ (2, N=3147) = 30.0, p<.0001 respectively). The median change in SBP, DBP and MAP for all treatments at each HBO_2 treatment pressure is shown in Table 3. Individual treatment pressure group comparisons showed that the median change in SBP, DBP, and MAP between a maximum treatment pressure of 2.0 atmospheres absolute (ATA) and 2.5 ATA were statistically significant ($p < 0.001$). There was not a statistically significant difference in median change in SBP, DBP, and MAP between 2.0 ATA and 2.8 ATA (p = 0.31, 0.05, 0.09 respectively) nor between 2.5 ATA and 2.8 ATA (p = 0.57, 0.38, 0.87 respectively).

When taking into consideration each patient's (N=155) change in SBP, DBP, and MAP over the course of all of their treatments there was no difference found in the median change in SBP, DBP and MAP for patients with or without history of the following comorbidities: diabetes mellitus, coronary artery disease, peripheral vascular disease, diabetic neuropathy, and cerebrovascular disease. For treatments in which the patient

Table 1: Patient demographic characteristics, existence of comorbidities and indications for HBO_2 therapy

PATIENT CHARACTERISTICS		
	median	IQR
age (years)	57	47 - 65
	frequency	percent
male	103	66.5
female	52	33.5
COMORBIDITIES		
diabetes mellitus	54	34.8
coronary artery disease	33	21.3
peripheral vascular disease	18	11.6
cerebrovascular disease	15	9.7
diabetic neuropathy	21	13.5
tobacco use	61	39.4
hypertension	85	54.8
HBO_2 INDICATION		
diabetic foot ulcer	37	23.9
late-effect radiation injury	47	30.3
osteoradionecrosis of mandible	7	4.5
emergent	52	33.5
chronic refractory osteomyelitis	9	5.8
other	3	1.9

was previously diagnosed with hypertension (N = 1835), patients taking calcium channel blockers showed an increased change in SBP ($p = 0.01$), DBP ($p < 0.001$), and MAP ($p < 0.001$). Patients taking beta blockers had a statistically significant change in SBP ($p < 0.001$) while those taking an ACE inhibitor showed a statistically significant decrease in MAP ($p = 0.02$). There was no significant difference in the change in SBP, DBP, or MAP in patients diagnosed with hypertension whether or not they were taking alpha agonists or angiotensin receptor blockers (Table 4).

Table 2: Median change in systolic blood pressure, diastolic blood pressure and mean arterial pressure for all treatments

	median change (mmHg)	95% CI
systolic blood pressure	7.00	6.50 – 7.77
diastolic blood pressure	4.00	3.00 – 4.00
mean arterial pressure	5.00	4.33 – 5.33

For the majority of patients (N = 153) in this study we captured blood pressure data ranging from 1 – 57 total treatments for each patient (Median = 14; IQR = 2 - 35). A simple linear regression was calculated to determine if the number of treatments a patient had undergone had a significant effect on the mean change in SBP, DBP and MAP. A significant regression equation was found for SBP ($F(1, 56) = 14.19$, $p < 0.001$), with an $R2 = 0.20$. For each additional treatment a patient completed the mean change in SBP was decreased by 0.102 mmHg (95% CI: -0.156 - -0.048). A significant regression equation was found for MAP ($F(1, 56) = 9.86$, $p = 0.001$) with an $R2 = 0.15$. For each additional treatment a patient completed the mean change in MAP was decreased by 0.05 mmHg. (95% CK: -0.08 – -0.18). There was not a significant regression equation for change in DBP ($F(1,56) = 2.34$, $p = 0.13$.

Blood pressures deemed high enough to warrant concern were defined to exceed 180 mmHg systolic and 100 mmHg diastolic blood pressure. In 36 patients representing 130 treatments the systolic blood pressure surpassed 180 mmHg after HBO_2. In 41 patients representing 139 treatments the diastolic blood pressure exceeded 100 mmHg after HBO_2. None of the patients sustaining SBP over 180 mmHg or DBP over 100 mmHg

Table 3: Median change in systolic blood pressure, diastolic blood pressure and mean arterial pressure for treatments at different maximum treatment pressure

	2.0 ATA (N=1207)	2.5 ATA (N=1870)	2.8 ATA (N=70)
systolic blood pressure (mmHg) (95% CI)	8.00 (7.00 – 9.00)	5.00 (4.00 – 6.00)	6.50 (-0.50 – 12.5)
diastolic blood pressure (mmHg) (95% CI)	5.00 (4.00 – 6.00)	3.00 (3.00 – 4.00)	1.00 (0.00 – 5.00)
mean arterial pressure (mmHg) 95% CI	6.33 (5.33 – 7.33)	4.00 (3.33 – 4.67)	3.50 (-0.50 – 7.33)

Table 4: Influence of antihypertensive medication by medication class on the median change in systolic and diastolic blood pressure and mean arterial pressure for treatments of patients diagnosed with hypertension

	treatments with patients taking medication class (95% ci)	treatments with patients not taking medication class (95% ci)
calcium chanel blockers (mmHg)	**n = 375**	**n = 1460**
systolic blood pressure	9.00 (6.00 – 10.00)	6.00 (5.00 – 7.00)
diastolic blood pressure	7.00 (6.00 – 8.00)	4.00 (3.00 – 4.00)
mean arterial pressure	7.67 (6.33 – 9.33)	4.67 (3.67 – 5.33)
ACE inhibitors (mmHg)	**n = 693**	**n = 1142**
systolic blood pressure	6.00 (4.00 – 7.00)	7.00 (6.00 – 8.00)
diastolic blood pressure	3.00 (2.00 – 4.00)	5.00 (4.00 – 6.00)
mean arterial pressure	4.00 (3.33 – 5.33)	6.00 (5.00 – 6.67)
beta-blockers (mmHg)	**n = 1064**	**n = 771**
systolic blood pressure	8.00 (7.00 – 9.00)	5.00 (4.00 – 7.00)
diastolic blood pressure	4.00 (3.00 – 6.00)	4.00 (3.00 – 5.00)
mean arterial pressure	6.00 (4.67 – 6.67)	4.67 (3.67 – 5.67)
alpha agonists (mmHg)	**n = 29**	**n = 1806**
systolic blood pressure	8.00 (-0.50 – 15.00)	7.00 (6.00 – 8.00)
diastolic blood pressure	8.00 (4.00 – 12.00)	4.00 (3.00 – 5.00)
mean arterial pressure	9.33 (0.33 – 11.67)	5.33 (4.33 – 6.00)
angiotensin receptor blockers (mmHg)	**n = 437**	**n = 1398**
systolic blood pressure	7.00 (6.00 – 9.00)	7.00 (5.00 – 8.00)
diastolic blood pressure	5.00 (3.00 – 6.00)	4.00 (3.00 – 5.00)
mean arterial pressure	6.67 (5.17 – 7.33)	4.67 (4.00 – 5.67)

Figure 1: Median DBP changes for post-DBP >100 mmHg and median SBP changes for post-SBP >180 mmHg

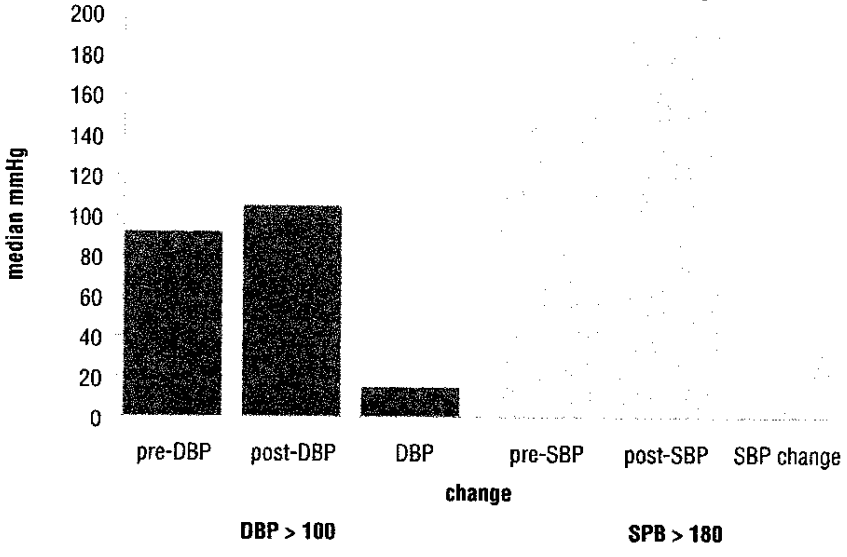


Figure 2: Comparison of treatment DBP pre-, post- and change between patients with a post-DBP >100 mmHg vs. ≤ 100mmHg

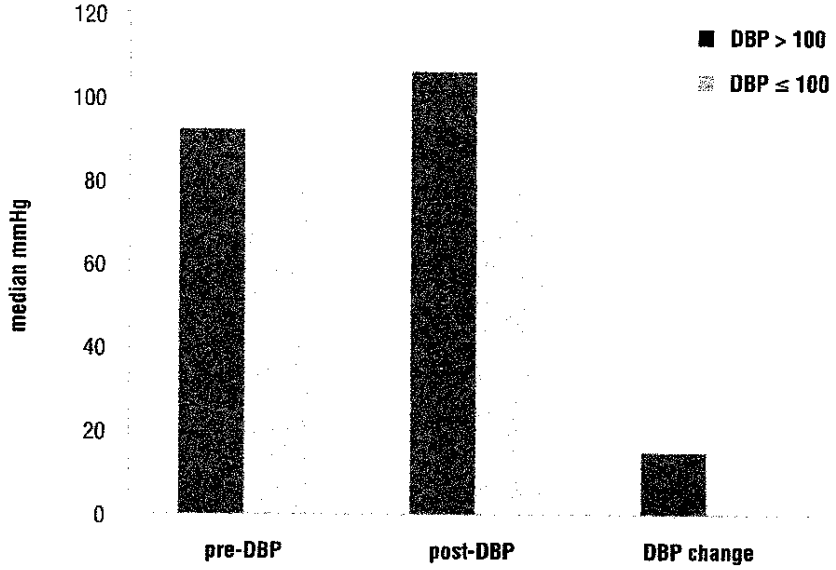
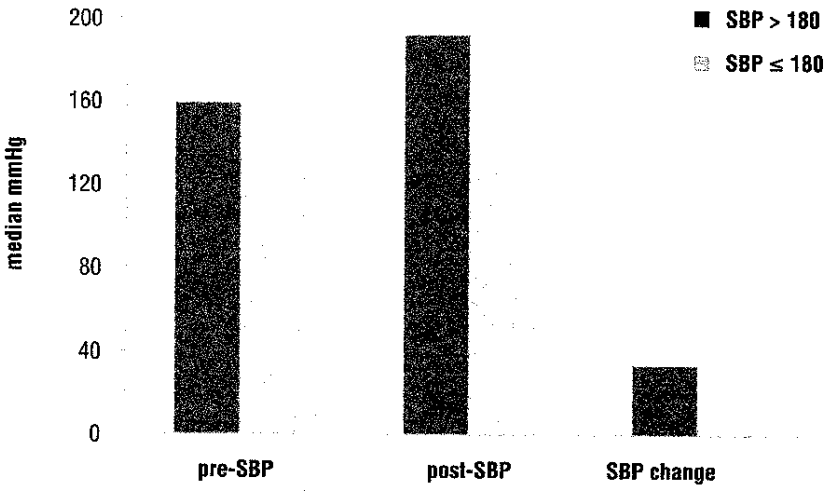


Figure 3: Comparison of treatment SBP pre-, post- and change between patients with a post-SBP >180 mmHg vs. ≤ 180 mmHg



experienced clinical or laboratory signs of hypertensive urgency or emergency. Figure 1 shows the median pre-, post- and change in DBP for treatments when patients' post-DBP > 100 and median pre-, post- and change in SBP for treatments when patients' post-SBP > 180. Figures 2 and 3 show the difference in pre-, post- and change in DBP between treatments with patients whose post treatment DBP > 100 vs. ≤ 100 and pre-, post- and change in SBP between treatments with patients whose post-treatment SBP > 180 vs. ≤ 180 respectively.

DISCUSSION

The current study demonstrates that absolute rises in blood pressure do occur as a result of HBO_2 therapy. However, the overall extent of this effect is not large when one considers the numerous factors that transiently elevate or depress blood pressure in the course of a day.

Several ideas exist as to how HBO_2 may account for elevated post-procedural blood pressures. Tissue hyperoxia causes peripheral vasoconstriction which results in an elevated systemic vascular resistance [9]. In addition, high levels of oxygen may reduce nitric oxide synthase in alveolar walls, further contributing to vasoconstriction and the attendant rise in blood pressure under conditions of hyperoxia [10]. Endothelin-1, a potent vasoconstrictor produced by endothelial cells, has been noted to increase under the influence of hyperbaric oxygen as well [11]. Walker, et al. found that HBO_2 caused an antidiuretic affect and a decline in urinary PGE2 excretion in conscious dogs, effectively attenuating a prostaglandin vasodilatory influence [12].

Al-Waili, et al. proposed an additional side effect to the well-documented adverse effects of HBO_2 in their study on the effects of hyperbaric oxygen on vital signs in patients with diabetes and hypertension. They found a statistically significant elevation in blood pressure, but contrary to our current study they also found the effect significantly higher in patients with diabetes, hypertension (HTN) and both diabetes and HTN compared to controls. They also found antihypertensive medication such as beta-blockers had an agonizing effect on blood pressure following HBO_2 [8].

In our study patients taking beta-blockers and calcium channel blockers had agonizing effects on blood pressure, whereas ACE inhibitors seemed to have a protective effect. Non-selective beta-blockers, by virtue of beta-2 blockade, may attenuate vasodilation in the vasculature that occurs by activation of these receptors, thus potentiating vasoconstriction and a subsequent rise in blood pressure [8]. We did not stratify selective vs. non-selective drugs in this class. It would be interesting to determine if there is a more robust effect of non-selective beta-blockers on blood pressure in patients undergoing HBO_2 treatment than our results showed.

Patients who had a post-DBP >100 mmHg and post-SBP >180 mmHg were shown to have a higher pre-HBO_2 blood pressure and a more dramatic increase in their blood pressure. These patients who were at higher risk had a median pre-DBP >90 mmHg and pre-SBP > 160 mmHg. Based on these results one may risk-stratify patients with a pre-HBO_2 blood pressure > 160/90 mmHg as being at increased risk of having a clinically relevant increase in blood pressure from their HBO_2 treatment. That said, it should be noted that none of the patients in this study developed hypertensive urgency or emergency.

A paradoxical effect of larger median changes in SBP, DBP and MAP was observed at lower treatment pressure in this study when comparing treatment at 2.0 ATA versus 2.5 ATA. This is counterintuitive and should be confirmed with further study. A statistically significant change in SBP, DBP, and MAP was not found when comparing 2.0 ATA versus 2.8 ATA or 2.5 ATA vs. 2.8 ATA. This lack of statistical significance is likely due to a lower number of treatments at 2.8 ATA in this study. Higher treatment pressures presumably predispose patients to a greater risk of complications, thus future work is warranted to determine how reproducible this effect is.

Clinically, one should consider the risk of congestive heart failure exacerbation from HBO_2 therapy. HBO_2 may increase this risk due to increased systemic vascular resistance and a decrease or differential disturbance in cardiac output between ventricles, compromising cardiac function. This imbalance or drop in cardiac function causes pulmonary congestion [13]. Acute pulmonary edema is not to be expected in patients undergoing HBO_2 therapy, except perhaps in heart failure patients [14]. No patient experienced acute pulmonary edema during or following HBO_2 in the present study, suggesting this is a rare side effect likely related to patients with very low ejection fraction.

Finally, there was actually a protective effect with more treatments. The change in SBP was less with each additional treatment in patients undergoing more than one treatment. This effect was very small, but in conditions requiring 40-60 treatments, the cumulative effect becomes more noticeable. Thus, although there was an absolute increase of 7 mmHg averaged across all treatments in SBP, this elevation decreases with each additional HBO_2 treatment. For patients experiencing 40 HBO_2 treatments this could result in a decrease in their SBP of 4 mmHg by their last treatment.

CONCLUSION

In conclusion, HBO_2 appears to be a safe therapy used in the treatment of a diverse list of indications. The current study underscores the long-term safety of HBO_2 therapy including the majority of patients who require multiple treatments. More importantly, it allows physicians to reassure patients that although blood pressure after the treatment may rise, this risk is minor and becomes less pronounced with ongoing therapy.

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Conflict of interest statement

Authors declare no conflicts of interest exist with this submission.

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