Coronary Care

CARDIOLOGY

Cardiology 1998;90:131–136

Received: April 22, 1998
Accepted after revision: May 15, 1998

Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction: The 'HOT MI' Randomized Multicenter Study

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Abstract

In a previous pilot study, we demonstrated that adjunctive treatment with hyperbaric oxygen (HBO) appears to be feasible and safe in patients with acute myocardial infarction (AMI) and may result in an attenuated rise in creatine phosphokinase (CPK), more rapid resolution of pain and ST changes. This randomized multicenter trial was organized to further assess the safety and feasibility of this treatment in human subjects. Patients with an AMI treated with recombinant tissue plasminogen activator (rTPA) or streptokinase (STK), were randomized to treatment with HBO combined with either rTPA or STK, or rTPA or STK alone. An analysis included 112 patients, 66 of whom had inferior AMIs (p = NS). The remainder of the patients had anterior AMIs. The mean CPK at 12 and 24 h was reduced in the HBO patients by approximately 7.5% (p = NS). Time to pain relief was shorter in the HBO group. There were 2 deaths in the control and 1 in those treated with HBO. The left ventricle ejection fraction (LVEF) on discharge was 51.7% in the HBO group as compared to 48.4% in the controls (p = NS). The LVEF of the controls was 43.4 as compared to 47.6 for those treated, approximately 10% better (no significant difference). Treatment with HBO in combination with thrombolysis appears to be feasible and safe for patients with AMI and may result in an attenuated CPK rise, more rapid resolution of pain and improved ejection fractions. More studies are needed to assess the benefits of this treatment.

Key Words
Myocardial infarction
Thrombolysis
Hyperbaric oxygen

Introduction

Hyperbaric oxygenation (HBO) is an inhalation therapy in which the patient inspires pure oxygen at >1 atm absolute pressure. A hermetic chamber is used to pressurize the inspired oxygen. HBO treatment increases plasma concentrations of dissolved oxygen, and this effect may normalize or even increase oxygen tensions to hyperoxic levels in ischemic tissue [1, 2]. HBO is a useful modality for treatment of diseases in which tissue oxygen availability is decreased, such as osteoradionecrosis, compromised skin grafts, carbon monoxide poisoning, and acute traumatic ischemia (e.g. crush injury) [3, 4]. Studies using HBO in the animal model of compartment syndromes demonstrate a preservation of skeletal muscle and adenosine triphosphatase activity [5, 6]. In animal stud-

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0008–6312/98/0902–0131$15.00/0

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ies, HBO also reduces the ischemic effects of coronary artery occlusion [7–10]. However, prior human trials detected little substantial benefit from HBO without concomitant thrombolysis [11–14]. The only controlled trial, done in the prethrombolytic era, revealed a trend but no statistically significant mortality benefit when standard methods of analysis were used [15]. The failure of these studies to demonstrate a benefit of HBO may be due to the fact that HBO alone does not prevent thrombus formation, which is the major cause of acute myocardial infarction (AMI) [16]. Thrombolytic agents are now increasingly used for the adjunctive management of acute coronary artery occlusion in order to reduce mortality and help prevent myocardial damage [17–21]. In general, these studies demonstrate only modest improvements in left ventricular ejection fraction (LVEF) [22–25]. Because myocardial necrosis following AMI is caused by tissue hypoxia or anoxia, it seems reasonable to hypothesize that thrombolytic therapy in combination with HBO will limit the amount of ischemic injury in acute thrombotic coronary artery occlusion. The animal study published by Thomas et al. [26] provides encouraging evidence for the validity of this hypothesis. In our previous randomized pilot 'HOT MI' study [27] we demonstrated the feasibility and safety of the combination of recombinant tissue plasminogen activator (rTPA) and HBO treatment. The following randomized multicenter study was designed to further assess the benefit of thrombolysis in combination with HBO in patients with AMI.

Materials and Methods

The study population consisted of patients admitted to the emergency departments at the following study locations: Long Beach Memorial Medical Center, Long Beach, Calif., USA; Zemun Clinical Hospital Center, University of Belgrade, Yugoslavia; Northridge Hospital Medical Center, Northridge, Calif., USA; Indian River Memorial Hospital, Vero Beach, Fla., USA, and Richland Memorial Hospital, Columbia, S.C., USA. These study participants, ranging in age from 18 to 80 years, showed symptoms and signs suggestive of an AMI and were treated at one of the above locations between August 1989 and December 1997. This diagnosis was predicated on the finding of ST elevation ≥ 1 mm in two adjacent ECG leads and chest pain ≥ 20 min but ≤ 6 h in duration unrelieved by sublingual nitroglycerin.

Exclusion criteria including suspected aortic dissection, recent surgery, recent peptic ulcer disease or stroke were standard for thrombolysis. Further exclusions pertaining predominantly to hyperbaric treatment included (1) severe claustrophobia; (2) chronic obstructive pulmonary disease (COPD) with marked CO_2 retention; (3) patients with Killip class IV myocardial infarctions (cardiogenic shock) or Killip class III myocardial infarction with shortness of breath not rapidly controlled with intravenous medications; (4) hemodynamically compromising ventricular or atrial tachyarrhythmias or bradyarrhythmias not responding rapidly to standard medical treatment; (5) patients with previous transmural anterior myocardial infarctions; (6) inability to equilibrate pressure in the middle ear space secondary to upper respiratory tract infections, allergic rhinitis or otitis.

The rTPA dose was 100 mg, starting with 60 mg in the first hour (of which 12 mg was administered as a bolus over the first 1–2 min) and 20 mg over each of the second and third hour, respectively. Patients weighing <65 or >85 kg received 1.25 mg/kg rTPA prorated ot the above schedule. Streptokinase (STK) was administered at the dose of 1.5 MU in 100 ml of normal saline in a soluset system over 60 min. Both groups received an enteric-coated aspirin (325 mg) before commencement of thrombolysis and 160 mg of aspirin daily thereafter at least for the duration of their hospital stay. Patients were anticoagulated with heparin as a 5,000-unit intravenous bolus just before termination of rTPA infusion. This was followed by an intravenous heparin infusion to maintain a partial thromboplastin time of 60–90 s for at least 3 days or until definitive intervention. Those receiving STK were not treated with heparin.

With a random number table, patients were randomized to thrombolytic therapy alone or thrombolytic therapy with HBO. The patients randomized to HBO were then immediately transferred to the hyperbaric unit for a single treatment. The patients were pressurized during a 30-min period up to 2 atm absolute pressure equivalent to 33 feet of sea water pressure. They remained at this pressure for 60 min and then they were depressurized to surface pressure over a 30-min period. Total time for the HBO treatment was 2 h. A critical care nurse and cardiology fellow or cardiologist were in attendance at all times. Small doses (≤ 5 mg total) of diazepam (Valium) were utilized intravenously as necessary for sedation. Monitoring of electrocardiograms, noninvasive blood pressures, and other vital signs was performed during HBO treatments in the same fashion as in the cardiac care unit. Those patients randomized to thrombolysis alone (the control group) were transferred to the cardiac care unit for routine monitoring and therapy. They received 6 liters of oxygen by nasal cannula, or 40% oxygen by face mask for at least 3 h after admission to the cardiac care unit. All patients received intravenous nitroglycerin in doses of 20–200 mg/min, titrated to pain and blood pressure.

Creatine phosphokinase (CPK) and CPK-MB samples were obtained upon admission and every 4 h for 24 h. Electrocardiograms were performed at 1-hour intervals for the first 3 h; thereafter every 4 h for 24 h and daily for 3 days after this. The time to pain relief was recorded. The time taken for resolution of ST elevation to ≤ 1 mm was estimated from recorded electrocardiograms. All patients underwent standard post-AMI management, including angiography, angioplasty, and coronary artery bypass when indicated. An LVEF was determined from a predischarge resting nuclear ventricular function study or an echocardiogram utilizing observer blinding.

Study Designs and Statistics

This project was designed as a prospective randomized clinical multicenter trial but was not conducted on an intention-to-treat basis because of the small sample size. The statistical tests used for comparison include Student's t test, χ^2 test with Yates' correction, or Fisher's exact test where appropriate. The study protocol had the approval of the institutional review board at Long Beach Memorial Medical Center. We were largely dependent on the data forwarded to us by the other participating centers. Some of the data sheets were not complete so we could use only available data for the statistical analy-

sis of the corresponding variables. All patients recruited at the American centers received rTPA and all patients from the Zemun Clinical Hospital Center, University of Belgrade, Yugoslavia, were treated with STK. We did not collect data from those whose physicians refused to have their patients included or those who were transferred out of our facility by their HMO soon after randomization.

Results

Of the 138 patients originally considered for the study, 16 were subsequently excluded. Four patients were excluded because of hemodynamic instability in the emergency room. Of these 3 were taken for emergent coronary angiography, and the 4th, randomized to HBO but not treated, died in the emergency room. Two patients were subsequently found to have no enzymatic evidence of AMI and were excluded. Three patients were excluded because careful review revealed that the time limit for rTPA administration had been exceeded (>6 h). One patient refused entry into the HBO chamber after consenting to the treatment, and 1 patient received the incorrect protocol. One patient, who subsequently died, could not receive HBO treatment since the chamber was already occupied by another research study patient. Four patients were excluded because of incomplete data sets (no predischarge LVEF). One patient received only half of the 2-hour HBO treatment due to feelings of claustrophobia in the HBO chamber, and he has been included in the HBO treatment group for analysis purposes.

The patient demographics, listed in table 1, reveal that the patients in each group are well matched. There was no significant difference between study groups with regard to the prevalence of diabetes, hypertension, chronic obstructive pulmonary disease, prior myocardial infarction, previous coronary bypass or smoking history. Time from initiation of rTPA to initation of HBO treatment averaged 71 min. Three patients from the Long Beach Medical Center in the control group and 4 in the HBO group had runs of nonsustained ventricular tachycardia (including accelerated idiventricular tachycardia). The distribution of AMI sites is not significantly different between study groups (table 1). The groups are also similarly matched for time of pain onset to the time of administration of thrombolytics. The HBO group had earlier resolution of chest pain, a lower rise in CPK, a greater predischarge LVEF, and 1 death. There were 2 deaths among those receiving rTPA alone. Only the time to pain resolution reached statistical significance. These data are summarized in table 2. Positive dynamics in ST change resolution was observed virtually in every patient treated with HBO (fig. 1). Unfortunately, we were unable to analyze the electrocardiographic data due to incomplete information from participating centers. There were no major bleeding complications in either group. Patients in both groups were evenly distributed in either Killip class I or II. There were no significant differences between the two groups

Table 1. Demographics (n = 112)

	Thrombolysis only (n = 63)	Thrombolysis + HBO (n = 59)	p value
Males	48 (76%)	49 (83%)	NS
Females	15 (24%)	10 (17%)	NS
Age, years	59 ± 11.7	58 ± 11.1	NS
Anterior AMI	29 (48%)	24 (41%)	NS
Inferior AMI	32 (52%)	34 (59%)	NS
Undetermined location	2 (3.2%)	1 (1.7%)	NS

Table 2. Clinical variables

	n	Thrombolysis only	n	Thrombolysis + HBO	p value
Deaths	63	2 (3.2%)	59	1 (1.7%)	NS
CPK on admission	44	394 ± 666.6	42	215 ± 181.9	NS
12-hour CPK	43	1,828 ± 1,654.9	41	1,690 ± 1,293.6	NS
24-hour CPK	36	1,093 ± 1,200.9	36	1,028 ± 769.8	NS
Maximum CPK	57	2,111 ± 1,641.7	53	1,698 ± 1,400.5	NS
Pain onset to TPA, min	38	199 ± 126	34	191 ± 165	NS
Time to pain relief, min	41	614 ± 428	40	261 ± 99	≤ 0.001
TPA to angiography time, h	23	40 ± 29	26	54 ± 42	NS
Ejection fractions	60	48.4 ± 12.9	57	51.7 ± 11.2	NS

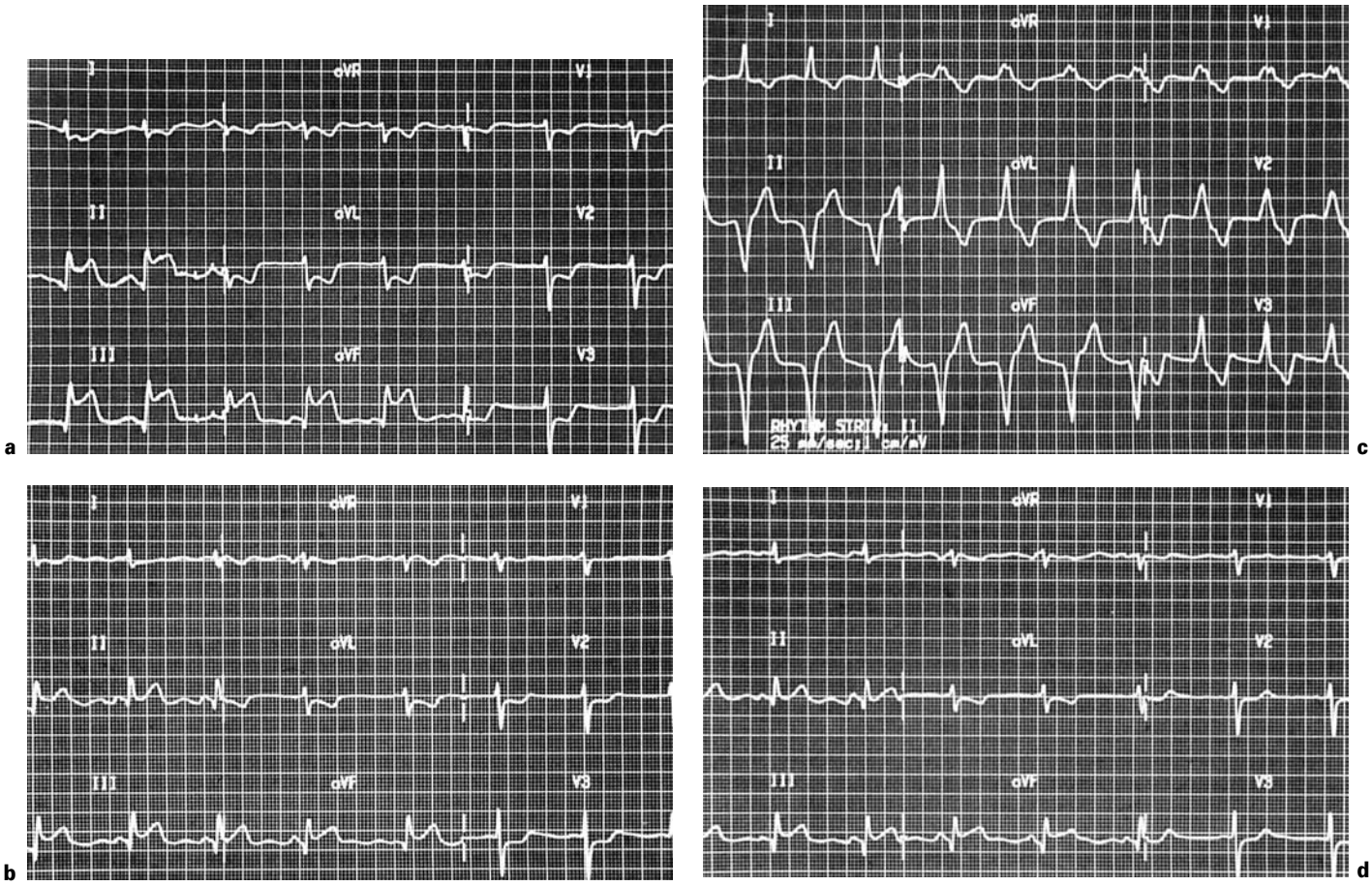

Fig. 1. Rapid resolution of ST changes after administration of HBO (**a, b, d**) and probable reperfusion arrhythmia at 15:10 (**c**) in patient 1 (August 28, 1989). **a** Immediately prior to HBO (14:05 h). **b** During HBO (14:18 h). **c** This reperfusion dysrhythmia typically occurs in the first h of HBO (15:10 h). **d** This recording was taken at the termination of HBO (16:03 h).

Table 3. Patients who underwent angiography

	Thrombolysis only		Thrombolysis + HBO	
	n	%	n	%
Patients				
1-vessel disease	26	41.3	28	47.5
2-vessel disease	13	20.6	13	22
3-vessel disease	14	22.2	9	15.3
No angiogram	10	15.9	9	15.3
Patent arteries	42	66.7	47	79.7
Occluded arteries	14	22.2	8	13.6
Undetermined occlusion	7	11.1	4	6.8
TPA to angiography time	23	40 h	26	54 h

with respect to left main stenosis ($\geq 50\%$) or single-, double-, and three-vessel coronary artery disease (table 3). The frequency of revascularization with balloon angioplasty or coronary artery bypass grafting was similar in each group.

Discussion

The quantity of oxygen carried in the plasma and tissue fluid under hyperbaric conditions in this study is increased ± 10-fold compared to breathing room air. The net effect is an approximately 25% increase in the oxygen content of blood with an HBO treatment at 2 atm absolute pressure. HBO has been shown to increase tissue oxygen diffusion distance by a factor of 3 or 4 [28]. There is

consequently improved penetration of oxygen into hypoxic tissues casued by the facilitation of oxygen diffusion. Tissue oxygen tensions remain elevated for some hours following the cessation of HBO treatment [28]. Thus the tissues remain oxygenated after completion of the HBO treatment. This could result in sustained beneficial effects even after decompression and allow for improved myocardial salvage in that group of patients who have late reperfusion.

There is evidence that hyperoxia induces generalized vasoconstriction. It has been demonstrated in the context of limb circulation that blood flow is decreased by 8.9% at 2 atm absolute pressure as a result of vasoconstriction. Despite this, tissue oxygen still increases by 18% [29]. A recent study has demonstrated that progressive ischemic arteriolar vasoconstriction, seen in arterioles close to ischemic venules, is inhibited with HBO treatment in animals [30].

In the current study, either rTPA or STK was utilized as the only thrombolytic agent because it is reported to provide earlier coronary arterial patency [31]. This factor may offer the potential for more myocaridal salvage with the conjunctive use of HBO.

There was initially concern that an increase in free oxygen radical generation occasioned by the high oxygen tension state of HBO treatment would potentiate tissue reperfusion injury. The results from our study group of patients do not suggest that this mechanism occurs to any appreciable clinical degree in patients treated with HBO.

Recent investigational work by Zamboni et al. [30] has shown that reperfusion injury may actually be inhibited by HBO by a decrease in leukocyte venular endothelial adherence, release of toxic oxygen species and consequent arteriolar vascoconstriction. The result is that progressive arteriolar vascoconstriction is inhibited [30]. Thus far, this effect of HBO has only been studied in an in vitro rat skeletal muscle preparation.

Our study demonstrates lower maximum CPK levels and at both 12 and 24 h in the HBO-treated group (p = NS). Increased myocardial salvage seems to be the likely explanation given the higher predischarge LVEF in the HBO-treated group and the reduced time to pain relief.

In conclusion, we have demonstrated the feasibility and safety of a combination of rTPA or STK and HBO treatment in this randomized multicenter trial. All clinical data, although statistically nonsignificant, except time to pain resolution, were better in patients who received thrombolysis and HBO. No obvious acute adverse clinical sequelae of HBO-enhanced 'reperfusion injury' were observed. In order to attain a sufficient level of statistical significance this study needs to be repeated on a larger patient sample.

Acknowledgments

Thus study was funded in part by Genentech, San Francisco, Calif., USA, and the Memorial Foundation, Long Beach Memorial Medical Center.

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