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Acute Myocardial Infarction With Hyperoxemic Therapy (AMIHOT)

A Prospective, Randomized Trial of Intracoronary Hyperoxemic Reperfusion After Percutaneous Coronary Intervention

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Objectives This study sought to determine whether hyperoxemic reperfusion with aqueous oxygen (AO) improves recovery of ventricular function after percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Background Hyperbaric oxygen reduces myocardial injury and improves ventricular function when administered during ischemia-reperfusion.

Methods In a prospective, multicenter study, 269 patients with acute anterior or large inferior AMI undergoing primary or rescue PCI (<24 h from symptom onset) were randomly assigned after successful PCI to receive hyperoxemic reperfusion (treatment group) or normoxemic blood autoreperfusion (control group). Hyperoxemic reperfusion was performed for 90 min using intracoronary AO. The primary end points were final infarct size at 14 days, ST-segment resolution, and Δ regional wall motion score index of the infarct zone at 3 months.

Results At 30 days, the incidence of major adverse cardiac events was similar between the control and AO groups (5.2% vs. 6.7%, p = 0.62). There was no significant difference in the incidence of the primary end points between the study groups. In post-hoc analysis, anterior AMI patients reperfused <6 h who were treated with AO had a greater improvement in regional wall motion (Δ wall motion score index = 0.54 in control group vs. 0.75 in AO group, p = 0.03), smaller infarct size (23% of left ventricle in control group vs. 9% of left ventricle in AO group, p = 0.04), and improved ST-segment resolution compared with normoxemic controls.

Conclusions Intracoronary hyperoxemic reperfusion was safe and well tolerated after PCI for AMI, but did not improve regional wall motion, ST-segment resolution, or final infarct size. A possible treatment effect was observed in anterior AMI patients reperfused <6 h of symptom onset. (J Am Coll Cardiol 2007;50:397–405) © 2007 by the American College of Cardiology Foundation

Hyperbaric oxygen improves ventricular function and reduces tissue injury when administered during evolving myocardial infarction (1,2). Experimental data suggest that this effect is mediated, in part, by decreasing tissue edema, reducing formation of lipid peroxide radicals, altering nitric oxide synthase expression, and inhibition of leukocyte adherence and plugging in the microcirculation (3–7). How-

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Abbreviations and Acronyms

AMI = acute myocardial infarction

AO = aqueous oxygen

PCI = percutaneous coronary intervention

RWMSI = regional wall motion score index

TIMI = Thrombolysis In Myocardial Infarction

ever, use of hyperbaric oxygen chambers is impractical for patients with acute myocardial infarction (AMI). Recently, a novel site-specific method for achieving regional hyperoxemia has been developed using infusion of blood mixed with aqueous oxygen (AO) (8). In experimental models, intracoronary AO hyperoxemic reperfusion has been shown to improve microvascular flow and left ventricular function and to reduce infarct size when administered after coronary reperfusion (8–11). In a previous study we showed that hyperoxemic reperfusion using this technique was safe and feasible after primary percutaneous coronary intervention (PCI) for AMI (12). More recently, 2 small clinical studies have shown that treatment with AO in patients with anterior AMI improves left ventricular function and remodeling (13,14). Accordingly, the present study was designed to determine whether hyperoxemic reperfusion with AO would improve ventricular function and microcirculatory flow, or limit infarct size after primary or rescue PCI for AMI.

Methods

Study population. From January 2002 to December 2003, 269 patients with AMI were randomly assigned to PCI with or without adjunctive hyperoxemic reperfusion. Patients were eligible for enrollment up to 24 h from symptom onset. All patients had chest pain >30 min duration with ST-segment elevation ≥1 mm in 2 contiguous leads. Patients with inferior AMI were required to have ≥1 mm reciprocal ST-segment depression in 2 precordial leads (V_1 through V_4). Clinical exclusion criteria were cardiogenic shock or requirement for an intra-aortic balloon pump before or during PCI, coronary artery bypass surgery within 1 month, severe cardiac valvular stenosis, pericardial disease, cardiomyopathy, severe pulmonary disease with an arterial pO_2 <80 mm Hg on supplemental oxygen, and pregnancy. Angiographic exclusion criteria were Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the infarct vessel at initial angiography, saphenous vein graft culprit lesion, significant left main disease (>50% diameter stenosis), infarct related artery supplying a small amount of myocardium, inability to stent the culprit lesion, and TIMI flow grade <2 after PCI. The study was approved by the institutional review board at each center. Written informed consent was obtained from each patient before enrollment.

Cardiac catheterization and coronary intervention. All patients received aspirin 300 mg orally, intravenous heparin 5,000 U, and low-flow nasal oxygen before cardiac catheterization. Coronary intervention was performed using standard equipment and techniques. Heparin was administered to maintain the activated clotting time >250 s. All patients were treated with stent implantation. Glycoprotein receptor inhibitors were administered at the operator's discretion.

Hyperoxemic reperfusion. The study randomization was performed after completion of PCI. Patients were required to have TIMI flow grade 2 or 3 after PCI with no evidence of coronary dissection. Study allocations were assigned by the research study coordinator, using sequentially numbered, opaque, sealed envelopes. The study assignments were generated from a master computer-generated randomization list, unique for each study center.

Hyperoxemic reperfusion was performed for 90 min using a custom extracorporeal circuit using AO (TherOx Inc., Irvine, California). Details of the Aqueous Oxygen System have been previously reported (12). Blood for the AO system circuit was drawn from the sidearm of a 9-F arterial sheath in a coaxial configuration, or alternatively a 5-F sheath placed in the contralateral femoral or radial artery, and was mixed with AO in a polycarbonate chamber to achieve an elevated pO_2 of 760 to 1,000 mm Hg. Hyperoxemic blood was delivered to the patient via a 5.3-F intracoronary infusion catheter (Tracker-38, Target Therapeutics, Fremont, California) positioned in the proximal segment (1 to 2 cm) of the infarct-related artery (Fig. 1). The blood flow rate was 75 ml/min. During hyperoxemic reperfusion, the systemic arterial pO_2 was measured every 30 min, and the infusion of AO was adjusted accordingly.

Data management and analysis. Study data, collected prospectively by research coordinators, were verified against source documentation by independent trial monitors. An independent committee, blinded to treatment assignment, adjudicated all adverse clinical events. All investigators had access to study data.

Echocardiographic analysis. Regional left ventricular function was measured by serial contrast 2-dimensional echocardiography. Studies were performed immediately after PCI (before AO infusion), at 24 h, at 1 month, and at 3 months. For the baseline study, patients were supine; for all other studies, patients were placed in the left lateral decubitus position. Echocardiographic imaging was performed with commercially available equipment. Studies were recorded on super-VHS tape and analyzed at the Mayo Clinic Echocardiographic Core Laboratory. Left ventricular wall motion was assessed using a 16-segment model according to the recommendation of the American Society of Echocardiography (15). Segments were graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The regional wall motion score index (RWMSI) of the infarct zone was derived by the formula: RWMSI = sum of segment scores/number of abnormal segments. The ΔRWMSI of the infarct zone was calculated as the difference in the RWMSI between the baseline and 3-month study. If the 3-month study was not evaluable, the 1-month wall motion score was used to calculate the ΔRWMSI. Calculations were performed off line by 2 observers blinded

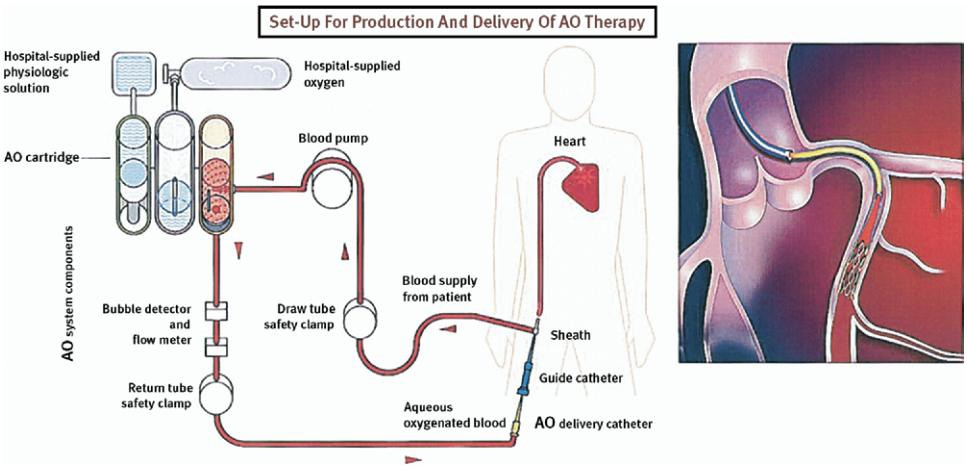

Figure 1 **Diagram of the AO System Circuit**

AO = aqueous oxygen.

to clinical details and treatment assignment. In the event of disagreement, a third observer was asked to adjudicate the findings.

ST-segment resolution. Continuous electrocardiographic monitoring was performed with Northeast Monitoring NEMON 180+ 12-lead digital electrocardiographic monitors placed at the time of enrollment. Standard 12-lead electrocardiograms were acquired every 60 s on 128-MB flash RAM cards. The Duke method of continuously updated ST-segment recovery analysis was performed by the ECG Core Laboratory at the Duke Clinical Research Institute as has previously been described (16). Curve area taken from the ST-segment level versus time trend curve was measured as μV-min above recovery ST-segment level for 3 h from the time of randomization (end of PCI). Larger curve areas represent worsened ischemic ST-segment changes, longer lasting ischemic ST-segment changes, or both. Curve areas of 0 represent no ischemic ST-segment changes over post-PCI recovery ST-segment levels over the time period (3 h) continuously monitored.

Infarct size. Final infarct size was measured 14 to 21 days after PCI using ^{99m}Tc-sestamibi single photon emission computed tomography imaging. Images were obtained with single-head or multihead gamma cameras with images acquired in a 64 × 64 matrix. All images were analyzed at the Mayo Clinic Nuclear Core Laboratory using previously described methods (17–19).

Study end points and definitions. The primary safety end point was the incidence of death, reinfarction, target vessel revascularization, and stroke at 30 days. The primary efficacy end points of the study were: 1) change in RWMSI of the infarct zone at 3 months (ΔWMSI); 2) ST-segment curve area 3 h after PCI; and 3) final myocardial infarct size at 14 to 21 days. Reinfarction was defined as the recurrence of clinical symptoms or new electrocardiographic changes accompanied by an increase in creatine kinase-MB levels >2 times baseline. Target vessel revascularization was defined as urgent revascularization of the target vessel by either PCI or coronary artery bypass surgery. Patients assigned to hyperoxemic reperfusion who received <60 min AO therapy were considered failure-to-treat cases.

Statistical analysis plan. The study hypothesis was that patients undergoing PCI for AMI would have improved regional wall motion, improved (reduced) ischemic ST-segment 3-h curve areas, and a reduction in infarct size compared with patients undergoing primary PCI alone. The study was designed to detect the following differences with 80% power using a 1-sided significance level of 5%: 1) 0.2-U improvement in RWMSI of the infarct zone; 2) 50% improvement in ST-segment curve area; and 3) a reduction in mean final infarct size of 5% of the left ventricle. The sample size estimation of 250 patients was based on analysis of each of the 3 efficacy end points, with an assumed patient dropout rate of <10%. Based on historic data and the above assumptions, it was calculated that 114 patients per group were required to detect a difference in ST-segment curve area or final infarct size, and 52 patients per group were required to detect a difference in RWMSI (12,17,19). The primary efficacy end points were analyzed in all intent-to-treat patients who had evaluable studies. The RWMSI data were compared using the unpaired Student *t* test. Before analysis, data were examined for baseline differences to determine whether appropriate transformations were necessary. The ST-segment curve area data were highly skewed over the entire population, limiting the utility of parametric analysis. Therefore, ST-segment data were compared by categorizing the area under the ST-segment deviation time curve into 4 categories (0, 1 to 2,000, 2,000 to 5,000 and >5,000). Proportions of patients with areas in each of these intervals were compared between the study

groups using the Armitage chi-square test. Analysis of infarct size was performed using the Wilcoxon signed rank test because of the skewed distribution of infarct size (18). Secondary analyses were also performed on prespecified subgroups, including age, prior thrombolytic therapy, infarct location, time-to-treatment, left ventricular ejection fraction, and baseline TIMI flow grade. Continuous variables were examined using the Student *t* test, whereas categorical data were evaluated using the chi-square test for homogeneity. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with the NCSS 2004 software package (Kaysville, Utah).

Results

Clinical data. A total of 289 patients were enrolled at 23 investigational sites in 3 countries. Of the 289 patients, 20 were enrolled in a roll-in phase to familiarize the investigators with the infusion technique, and 269 were randomly assigned to PCI with or without hyperoxemic reperfusion (Fig. 2). Of the 269 randomized patients, 135 were assigned to the control arm and 134 to the treatment arm. Of the 134 patients assigned to the treatment arm, 123 patients received >60-min hyperoxemic reperfusion. The baseline clinical characteristics of the 2 study groups were well matched (Table 1).

Angiographic and procedural data. Approximately 90% of patients in each study group had complete occlusion (TIMI flow grade 0 or 1) of the infarct-related artery at initial angiography (Table 2). All patients were treated with stent implantation; 234 (87%) received a glycoprotein receptor inhibitor. There was no significant difference in the use of abciximab or eptifibatide between the study groups. After stent implantation, 92% of patients in the control group and 96% of patients in the AO group had TIMI flow grade 3 in the infarct vessel.

Hyperoxemic reperfusion. Among the 134 patients randomly assigned to receive hyperoxemic reperfusion after stenting of the infarct-related artery, 117 (87%) completed a 90-min AO infusion, 6 (4%) received a 60- to 90-min AO infusion, and 11 (8%) received <60 min AO therapy. Of these 11 patients, 8 received an incomplete infusion because of technical issues with the AO system (most commonly a kinked line caused system shutdown), 1 patient had a low baseline pO_2 and was excluded from receiving therapy, 1 patient had the AO infusion halted to treat another lesion in the infarct vessel, and 1 patient did not receive the infusion because of a system malfunction. Hyperoxemic reperfusion was well tolerated. No hemodynamic or electrical instability was observed during the infusion.

Adverse events. At 30 days, the primary safety end point had occurred in 5.2% of the control group and 6.7% of those assigned to hyperoxemic reperfusion (p = 0.62) (Table 3). One patient developed stent thrombosis in the proximal left anterior descending artery during the AO infusion. This patient had significant disease at the ostium of the left anterior descending artery that impaired antegrade flow into the artery after the AO infusion catheter was positioned subselectively in the vessel. Further balloon dilatation was performed with a good anatomical result, and there were no

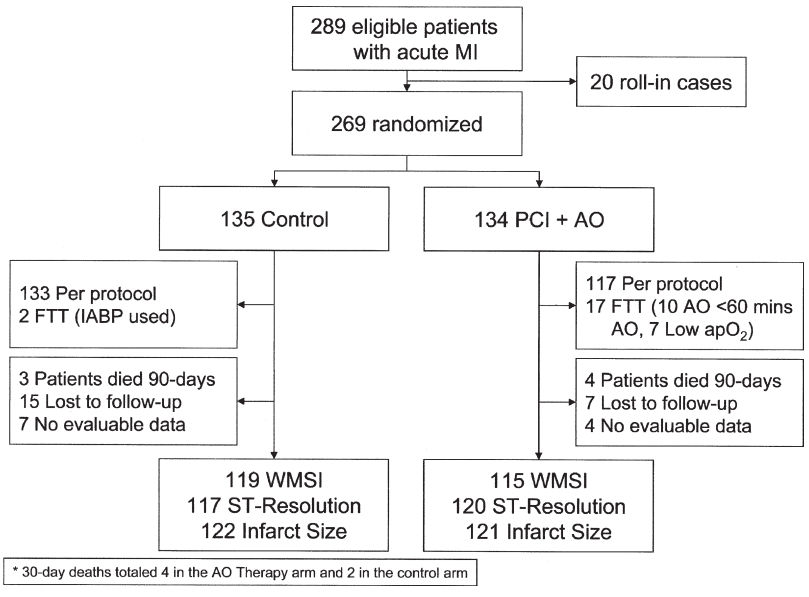

Figure 2 Clinical Recruitment Algorithm

AO = aqueous oxygen; FTT = failure to treat (see text for definition); IABP = intra-aortic balloon pump; MI = myocardial infarction; PCI = percutaneous coronary intervention; WMSI = wall motion score index.

Table 1 Clinical Characteristics of the Patients

	Control Group (n = 135)	AO Group (n = 134)	p Value
Age, yrs (mean ± SD)	60 ± 12	60 ± 13	0.99
Age, yrs (median, IQR)	59 (33–94)	60 (35–89)	
Female	36 (26.7%)	36 (26.9%)	0.97
Diabetes mellitus	15 (11.1%)	17 (12.7%)	0.69
Hypertension	66 (48.9%)	71 (53.0%)	0.48
Hyperlipidemia	56 (45.5%)	65 (54.2%)	0.18
Current smoker	57 (42.2%)	58 (43.3%)	0.50
Previous MI	14 (10.4%)	18 (13.4%)	0.44
Previous PCI	10 (7.4%)	16 (11.9%)	0.21
Previous CABG	2 (1.5%)	2 (1.5%)	0.99
Previous CHF	3 (2.3%)	3 (2.3%)	0.99
Prior thrombolytic therapy	21 (15.6%)	15 (11.2%)	0.29
Anterior MI	76 (56.3%)	81 (60.4%)	0.49
Killip class			
I	127 (94.1%)	118 (88.1%)	0.23
II	7 (5.2%)	13 (9.7%)	
III	1 (0.7%)	3 (2.2%)	
IV	0 (0.0%)	0 (0.0%)	
Time (median ± IQR)*			
From symptom onset to hospital arrival (min)	120 ± 180	109 ± 240	0.87
Door-to-balloon (min)	89.5 ± 73.5	90.5 ± 62.8	0.50
From symptom onset to reperfusion (min)	248 ± 231	260 ± 295.5	0.54
Peak creatine kinase (IU/l)	2,610 ± 1,985	2,449 ± 1,935	0.51

*Wilcoxon rank test. First balloon inflation was not recorded; door-to-balloon times were recorded using time of first contrast injection.

AO = aqueous oxygen; CABG = coronary artery bypass grafting; CHF = congestive heart failure; IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention.

clinical sequelae. Patients in the AO group also had a higher incidence of vascular access complications than control patients, mainly because of hematomas (6.0% vs. 3.0%). This was most likely related to the larger sheaths used in some patients in the AO group, and the requirement for additional anticoagulation during the 90-min infusion.

Regional wall motion. Of the 269 randomized patients, 234 (87%) completed echocardiographic follow-up at 3

Table 2 Angiographic and Procedural Data

	Control Group (n = 135)	AO Group (n = 134)	p Value
Infarct-related artery			
Left anterior descending coronary artery	76 (56.3%)	81 (60.4%)	0.63
Right coronary artery	48 (35.6%)	42 (31.3%)	
Circumflex artery	8 (5.9%)	10 (7.5%)	
Other	3 (2.2%)	1 (0.7%)	
Initial diameter stenosis	100 ± 1%	100 ± 0%	0.12
Initial TIMI flow grade			
0/1	121 (89.7%)	117 (87.3%)	0.76
2	14 (10.4%)	17 (12.4%)	
3	0 (0.0%)	0 (0.0%)	
Stent implanted	135 (100%)	134 (100%)	1.00
Glycoprotein IIb/IIIa inhibitor	114 (84.4%)	120 (89.5%)	0.46
Abciximab	81 (71.1%)	77 (64.2%)	0.26
Eptifibatide	33 (28.9%)	43 (35.9%)	0.26
Final diameter stenosis (%)	0 ± 10	0 ± 10	0.90
Final TIMI flow grade			
0/1	0 (0.0%)	0 (0.0%)	0.13
2	11 (8.1%)	5 (3.7%)	
3	124 (91.9%)	129 (96.3%)	

AO = aqueous oxygen; TIMI = Thrombolysis In Myocardial Infarction.

Table 3 Clinical Data at 30 Days

	Control Group (n = 135)	AO Group (n = 134)	p Value
Death	2 (1.5%)	4 (3.0%)	0.45
Reinfarction	3 (2.2%)	3 (2.2%)	1.00
Target vessel revascularization	3 (1.5%)	3 (1.5%)	1.00
Stroke	2 (1.5%)	1 (0.7%)	1.00
Composite end point (major adverse cardiac event)	7 (5.2%)	9 (6.7%)	0.62

AO = aqueous oxygen.

months and had studies evaluable by the core laboratory. The mean RWMSI of the infarct zone at baseline was similar between study groups (control 2.67 ± 0.26 vs. AO 2.64 ± 0.30, p = NS). At 3 months, the ΔRWMSI of the infarct zone was −0.57 ± 0.48 in the control group and −0.62 ± 0.53 in the AO group (p = 0.24) (Fig. 3). In secondary analysis, patients reperfused <6 h had a trend toward a higher ΔRWMSI in the AO group compared with controls (Table 4). The interobserver variability of the RWMSI was 0.29 ± 0.27.

ST-segment resolution. Continuous digital electrocardiographic data were available in 237 patients (88%). In the overall patient group, the area under the ST-segment deviation time curve for 0 to 3 h after PCI was similar in the control and AO groups (Fig. 4).

Infarct size. Two hundred forty-three patients (90%) had infarct size measured at follow-up. At 14 days, the median infarct size was 13% of the left ventricle in the control group (interquartile range 0 to 39) and 11% of the left ventricle in the AO group (interquartile range 0 to 38) (p = 0.30) (Fig. 5). In secondary analysis, patients with age <59.5 years, time to reperfusion <6 h, and initial TIMI flow grade 2 had a smaller infarct size in the AO group compared with control patents (Table 5). A larger infarct size was observed in the subgroup of patients reperfused 6 to 24 h who received AO; however, this group had a higher proportion of anterior MI and a longer mean time to reperfusion.

Post-hoc analysis. In post-hoc analysis, anterior AMI patients reperfused <6 h who were treated with AO had a greater improvement in regional wall motion (ΔRWMSI = −0.54 ± 0.49 in the control group vs. −0.75 ± 0.57 in the AO group, p = 0.03), more complete ST-segment resolution, and a smaller median infarct size (23% of left ventricle in the control group [interquartile range 0 to 56] vs. 9% of left ventricle in the AO group [interquartile range 0 to 49], p = 0.04), compared with normoxemic control patients (Figs. 3 to 5).

Discussion

In the present study, treatment with hyperoxemic reperfusion after PCI for AMI did not result in improved regional wall motion, more complete ST-segment resolution, or reduced infarct size; however, the therapy was safe and well tolerated.

There are several possible explanations for why the present study failed to meet the primary efficacy end points. First, the trial had a broad window for enrollment and included patients presenting up to 24 h from symptom onset. By comparison, most other studies evaluating adjuncts to reperfusion therapy have enrolled only patients presenting within 6 h. The broad inclusion window used in the present trial was based on data from an experimental study in which pigs treated with AO 24 h after reperfusion

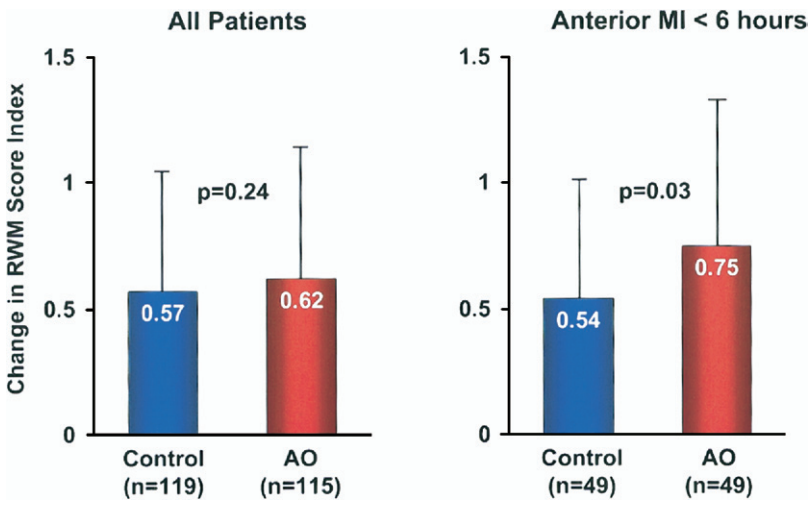

Figure 3 Echo Wall Motion Changes

Change in wall motion score index of the infarct zone at 3 months in patients assigned to undergo percutaneous coronary intervention with or without hyperoxemic reperfusion (intent-to-treat analysis). Results are shown for the overall study group and patients with anterior acute myocardial infarction (MI) <6 h. AO = aqueous oxygen group; RWM = regional wall motion.

Table 4 Change in Regional Wall Motion Score Index of the Infarct Zone at 3 Months

	Control Group (n = 119)	AO Group (n = 115)	p Value
All patients	−0.57 ± 0.48 (119)	−0.62 ± 0.53 (115)	0.24
Age <59.5 yrs*	−0.57 ± 0.45 (64)	−0.66 ± 0.56 (61)	0.16
Age ≥59.5 yrs	−0.57 ± 0.51 (55)	−0.57 ± 0.49 (54)	0.49
Thrombolytic	−0.45 ± 0.51 (19)	−0.36 ± 0.48 (14)	0.30
No thrombolytic	−0.59 ± 0.47 (100)	−0.65 ± 0.53 (101)	0.19
Anterior MI	−0.57 ± 0.48 (68)	−0.67 ± 0.55 (71)	0.13
Nonanterior MI	−0.57 ± 0.49 (51)	−0.53 ± 0.49 (44)	0.35
Time to reperfusion <6 h	−0.55 ± 0.48 (86)	−0.69 ± 0.55 (79)	0.06
Time to reperfusion 6 to 24 h	−0.62 ± 0.49 (33)	−0.47 ± 0.47 (36)	0.11
LVEF <40%	−0.56 ± 0.47 (43)	−0.58 ± 0.49 (42)	0.45
LVEF >40%	−0.58 ± 0.49 (76)	−0.64 ± 0.55 (73)	0.22
Initial TIMI flow grade 0/1	−0.56 ± 0.45 (106)	−0.61 ± 0.54 (100)	0.21
Initial TIMI flow grade 2	−0.69 ± 0.66 (13)	−0.66 ± 0.49 (15)	0.44

*Median value for group. Data shown are mean ± SD (n).
AO = aqueous oxygen; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

had a significant improvement in left ventricular function and infarct size compared with control animals (11). However, it is likely that this animal model has relatively limited applicability to clinical patients presenting late in the course of AMI. In addition, although a single randomized trial showed myocardial salvage in patients treated with PCI after 12 h (20), 43% of patients in that trial had initial TIMI flow grade 2 or 3, compared with only 11% with TIMI flow grade 2 in this study (patients with TIMI flow grade 3 were excluded). Second, hyperoxemic reperfusion (or any adjunct therapy) may be unnecessary in selected patient subgroups, such as those with inferior infarction. Data from this trial, and other recent mechanical reperfusion studies, suggest that the final infarct size in inferior AMI patients treated with PCI is typically <10% of the left ventricular mass. Given the smaller infarct size after mechanical reperfusion per se in such patients, the effect of any adjunct therapy will be very difficult to show without a very large number of patients (19), and may not have any significant impact on clinical outcome. Third, the time delay to initiate hyperox-

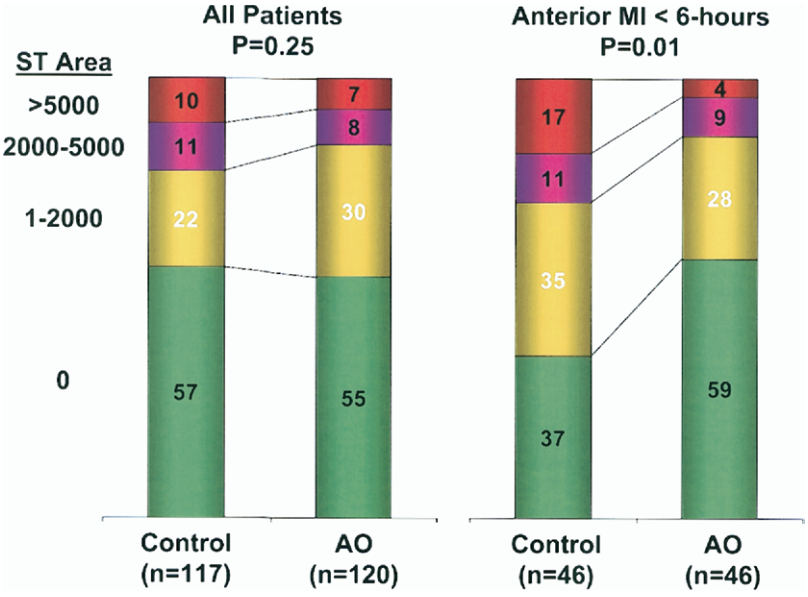

Figure 4 Changes in ST-Segment Elevation

The ST-segment resolution in patients assigned to undergo percutaneous coronary intervention (PCI) with or without hyperoxemic reperfusion (measured by the area under the ST-segment deviation vs. time curve 0 to 3 h after PCI; intent-to-treat analysis). Results are shown for the overall study group and patients with anterior acute myocardial infarction (MI) <6 h. A greater proportion of anterior MI patients in the aqueous oxygen (AO) group had improved ST-segment resolution compared with controls.

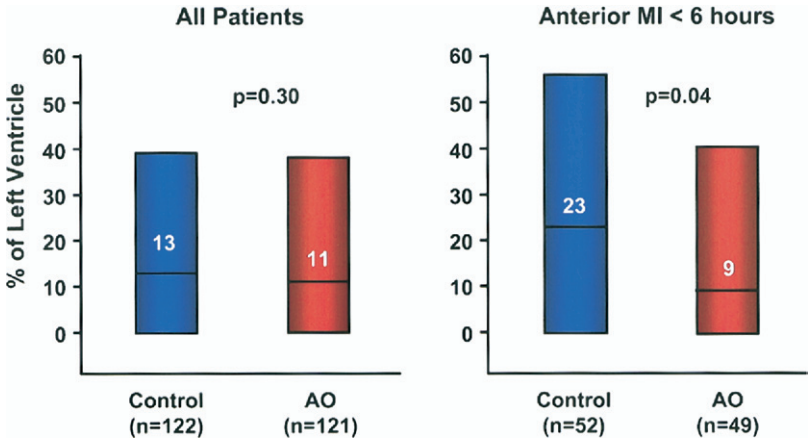

Figure 5 Changes in Nuclear Infarct Size

Final infarct size at 14 days in patients assigned to undergo percutaneous coronary intervention with or without hyperoxemic reperfusion (intent-to-treat analysis). Results are shown for the overall study group and patients with anterior myocardial infarction (MI) <6 h. AO = aqueous oxygen group.

emic reperfusion after PCI may have affected the potential benefit of therapy. In an experimental study by Sterling et al. (1), no protection was observed when hyperbaric oxygen was administered late after reperfusion. Fourth, when regional wall motion abnormalities assessed by echocardiography were correlated with infarct size by sestamibi imaging in AMI patients treated with reperfusion therapy, recovery of regional myocardial function was slower than that of the perfusion defect (21). Regional myocardial function may remain abnormal unless transmural ischemia is almost completely reversed by reperfusion. Therefore, wall motion analysis at a longer follow-up period might have shown a more significant benefit from hyperoxemic therapy. Finally, one must also consider the possibility that the AO infusion as applied in this trial did not result in regional hyperoxemia or influence myocardial metabolism. Although this has not been specifically evaluated in clinical studies, experimental data suggest that higher arterial oxygen levels do increase oxygen extraction and reduce lactate production, suggesting a favorable effect on ischemic myocardium (8,10,22).

Effect in anterior myocardial infarction <6 h. Although hyperoxemic reperfusion was not found to be beneficial in the overall study group, a promising signal was identified in anterior AMI patients who were treated within 6 h of symptom onset. In this group, there was a significant improvement in infarct size, ST-segment resolution, and regional wall motion in patients who were treated with AO. The fact that there was a consistent and parallel improvement in microvascular reperfusion, regional function, and infarct size in the AO patients suggests that this was a treatment effect rather than a result of chance alone.

Table 5 Infarct Size at 14 Days

	Control Group (n = 122)	AO Group (n = 121)	p Value
All patients	13 ± 26 (122)	11 ± 28 (121)	0.30
Age <59.5 yrs*	13 ± 27 (66)	7 ± 20 (63)	0.02
Age ≥59.5 yrs	14 ± 27 (56)	17 ± 30 (58)	0.11
Thrombolytic	10 ± 26 (20)	15 ± 29 (15)	0.44
No thrombolytic	14 ± 25 (102)	11 ± 28 (106)	0.31
Anterior MI	19 ± 31 (71)	21 ± 35 (73)	0.31
Nonanterior MI	8 ± 14 (51)	7 ± 14 (48)	0.39
Time to reperfusion <6 h	18 ± 17 (89)	14 ± 17 (82)	0.04
Time to reperfusion 6 to 24 h	15 ± 14 (33)	23 ± 18 (39)	0.02
LVEF <40%	30 ± 26 (45)	20 ± 30 (47)	0.08
LVEF >40%	8 ± 15 (77)	7 ± 20 (74)	0.43
Initial TIMI flow grade 0/1	13 ± 26 (108)	16 ± 27 (105)	0.43
Initial TIMI flow grade 2	15 ± 32 (14)	0 ± 10 (16)	0.06

*Median value for group. Data shown are median ± IQR (n).
Abbreviations as in Table 4.

However, given the limitations of subgroup analysis, these observations should be considered exploratory and therefore need to be confirmed in a prospective study.

Study limitations. The main limitation of the study was the small sample size. Although the trial was sufficiently powered to show differences in each of the individual efficacy end points, the study was too small to detect treatment differences in patient subgroups. Second, inclusion of patients presenting up to 24 h from symptom onset was also a significant limitation as previously discussed. Third, a small number of patients assigned to hyperoxemic reperfusion did not receive a complete 90-min infusion of AO. Another potential limitation was that for patients with missing echocardiographic data at 3 months, the wall motion score from the 1-month study was used. Because progressive improvement in the wall motion score typically occurs up to 3 months from AMI, use of the 1-month value may underestimate any treatment effect. Finally, an important methodological limitation of the study was inclusion of 3 co-primary end points, which is considered unusual with contemporary clinical trial design. However, at the time the AMIHOT (Acute Myocardial Infarction with HyperOxemic Reperfusion) trial was planned there was little consensus regarding the ideal surrogate end points in clinical trials evaluating new adjuncts to reperfusion therapy, and for this reason 3 end points were selected.

Conclusions

This study shown that hyperoxemic reperfusion after PCI for AMI is safe and well tolerated but does not improve regional wall motion, improve ST-segment resolution, or reduce final infarct size. In post-hoc analysis, a possible treatment effect was observed in patients with anterior AMI <6 h. These data suggest that further investigation is required to determine whether hyperoxemic reperfusion will improve ventricular function or clinical outcome in anterior infarction.

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APPENDIX

For the names of the principal investigators and clinical sites participating in the AMIHOT trial, please see the online version of this article.