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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