Interventional Cardiology

Initial Experience With Hyperoxemic Reperfusion After Primary Angioplasty for Acute Myocardial Infarction

Results of a Pilot Study Utilizing Intracoronary Aqueous Oxygen Therapy

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OBJECTIVES The purpose of this study was to evaluate the feasibility and safety of intracoronary hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction (MI).

BACKGROUND Hyperoxemic therapy with aqueous oxygen (AO) attenuates reperfusion injury and preserves left ventricular (LV) function in experimental models of MI.

METHODS In a multi-center study of patients with acute MI undergoing primary angioplasty (PTCA), hyperoxemic blood (pO_2: 600 to 800 mm Hg) was infused into the infarct-related artery for 60 to 90 min after intervention. The primary end points were clinical, electrical and hemodynamic stability during hyperoxemic reperfusion and in-hospital major adverse cardiac events. Global and regional LV function was evaluated by serial echocardiography after PTCA, after AO infusion, at 24 h and at one and three months.

RESULTS Twenty-nine patients were enrolled (mean age: 58.9 ± 12.6 years). Hyperoxemic reperfusion was performed successfully in all cases (mean infusion time: 80.8 ± 18.2 min; mean coronary perfusate pO_2: 631 ± 235 mm Hg). There were no adverse events during hyperoxemic reperfusion or the in-hospital period. Compared with baseline, a significant improvement in global wall motion score index was observed at 24 h (1.68 ± 0.24 vs. 1.48 ± 0.24, $p < 0.001$) with a trend toward an increase in ejection fraction ($48.6 \pm 7.3\%$ vs. $51.8 \pm 6.8\%$, $p = 0.08$). Progressive improvement in LV function was observed at one and three months, primarily due to recovery of infarct zone function.

CONCLUSIONS Intracoronary hyperoxemic reperfusion is safe and well tolerated after primary PTCA. These preliminary data support the need for a randomized controlled trial to determine if hyperoxemic reperfusion enhances myocardial salvage or improves long-term outcome. (J Am Coll Cardiol 2002;39:387–92) © 2002 by the American College of Cardiology

Left ventricular (LV) function is the most important determinant of survival after acute myocardial infarction (AMI) (1–4). Early and sustained restoration of flow in the infarct-related artery salvages jeopardized myocardium, reduces infarct size and preserves LV function (2,5–8). It is not uncommon, however, to observe a relatively modest improvement in ventricular function despite successful recanalization of the infarct vessel. It is clear that the presence of normal angiographic epicardial flow does not guarantee adequate myocardial perfusion (9). Failure to re-establish myocardial flow may be due to reperfusion injury, ischemia-induced microvascular damage or distal embolization from the lesion site (10,11). Regardless of the mechanism, failure to restore effective myocardial perfusion is associated with poor recovery of LV function (9,12).

Although oxygen free radicals are generated on normoxemic reperfusion, paradoxically, reperfusion injury can be attenuated by treatment with high oxygen tensions (13,14). Experimental data suggest this effect is mediated, in part, by antagonism of lipid peroxidation (15), inhibition of postcapillary venule leukocyte plugging (16) and increasing functional capillary density (13). Aqueous oxygen (AO) is a recently discovered liquid phase combination of water and medical grade oxygen that can be mixed with blood at ambient pressure to correct hypoxemia or produce hyperoxemia with small amounts of carrier solution (17). Regional organ or tissue perfusion is achieved using a blood loop (TherOx Inc., Irvine, California), permitting precise control of the pO_2 when AO is mixed with arterial blood in the circuit. In experimental models of MI, hyperoxemic reperfusion with AO has been demonstrated to attenuate microvascular injury and preserve LV function (17).

Abbreviations and Acronyms

AMI = acute myocardial infarction
AO   = aqueous oxygen
BP   = blood pressure
EF   = ejection fraction
LV   = left ventricle
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis In Myocardial Infarction
WMSI = wall motion score index

The purpose of this study was to evaluate the safety and feasibility of performing intracoronary hyperoxemic reperfusion using AO after primary angioplasty for AMI.

METHODS

Patient population. From April to December 1999, 29 patients with AMI undergoing primary angioplasty were enrolled in this prospective, multi-center study. All patients presented within 24 h from symptom onset and had chest pain lasting >30 min duration with ST-segment elevation >1 mm in two limb leads or >2 mm in the precordial leads. Exclusion criteria were: cardiogenic shock (blood pressure [BP] <80 mm Hg for >30 min not responsive to fluids or systolic BP <100 mm Hg with vasopressors), requirement for an intra-aortic balloon pump before or during coronary angioplasty, significant left main disease (>50% diameter stenosis), use of a non-balloon or stent device, Thrombolysis In Myocardial Infarction (TIMI) flow grade <2 after intervention, coronary artery bypass surgery within one month, severe cardiac valvular stenosis or insufficiency, pericardial disease, non-ischemic cardiomyopathy and pregnant women. Written informed consent was obtained from each patient before the procedure. The local institutional review board at each center approved the trial.

Catheterization. Before catheterization all patients received low flow nasal oxygen, aspirin 300 mg orally and heparin 5,000 U intravenously. Diagnostic coronary arteriography was performed via the femoral approach according to the Judkins technique, and arteries were visualized in multiple projections. The infarct-related artery was identified by localization of the electrocardiographic findings, site of the coronary occlusion or hemodynamically significant lesion and by analysis of the wall motion defect by ventriculography. Coronary intervention was performed using 7F or 8F guide catheters and standard guidewires and balloon catheters. Heparin was given to maintain the activated clotting time greater than 250 s. Stent deployment and use of glycoprotein receptor antagonists were permitted at the physician's discretion.

AO system. Hyperoxemic reperfusion was commenced after the coronary intervention was completed. Before the procedure, AO solution was prepared on site in a custom fluid vessel (TherOx, Inc., Irvine, California) to a concentration of 1 ml O_2/ml Lactated Ringer's solution. Aqueous oxygen was transferred into the AO system circuit via a custom syringe pump (TherOx, Inc., Irvine, California). In phase I of the study (nine patients), blood for the AO system circuit was withdrawn from a 4F or 6F sheath in the contralateral femoral artery or radial artery into 1/8-inch (internal diameter) PVC tubing (Baxter Healthcare Corp., Irvine, California) via a two-roller peristaltic tubing pump (Pemco, Inc., Cleveland, Ohio). Blood was delivered at 100 ml/min to a polycarbonate-mixing chamber (TherOx, Inc., Irvine, California) where it was directly mixed with AO. The AO flow rate was 1.5 to 3.0 ml/min (mean: 2.9 ± 0.5 ml/min) to achieve a blood pO_2 of 600 to 800 mm Hg in the mixing chamber (verified by blood-gas analysis). Hyperoxemic blood was then delivered to the patient via a 3/32-inch (internal diameter) PVC tubing (Qosina, Edgewood, New York) connected to a 7F Vector guide catheter (Medtronic, Inc., Minneapolis, Minnesota). The priming volume of the AO system circuit was 60 ml. The phase I treatment time was 60 min.

In phase IA of the study, the AO system circuit was nearly identical, with the following exceptions: 1) a 4F coronary infusion catheter (Tracker-38, Target Therapeutics, Fremont, California) was subselectively positioned in the infarct-related artery; 2) due to the subselective nature of the infusion, the blood flow rate of the peristaltic pump was decreased to 75 ml/min; and 3) the phase IA treatment time was 90 min.

During hyperoxemic reperfusion, femoral and pulmonary arterial pressures and saturations, systemic pO_2, electrocardiograms and echocardiograms were obtained every 15 min. Selective infarct vessel angiography was repeated after completion of the intracoronary infusion. Patients were monitored in the intensive care unit after the procedure and were treated according to local management guidelines.

Angiographic analysis. Quantitative angiography was performed using an automated edge detection system (CAAS II, Pie Medical, Maastricht, the Netherlands). Calibration was based on the dimension of a contrast-filled catheter. Multi-vessel coronary disease was defined as >50% stenosis in one or more vessels remote from the infarct artery. Patency of the infarct-related artery was classified according to the TIMI criteria (18).

Echocardiographic analysis. Two-dimensional echocardiography was performed after primary angioplasty, during and immediately after the AO infusion, at 24 h, and at one and three months. During the AO infusion patients were supine; for all other studies, patients were placed in the left lateral decubitus position. Echocardiographic imaging was performed with commercially available equipment, and studies were recorded on videotape. Calculations for global and regional wall motion were performed both on- and off-line (Kodak ImageVue Compact Workstation, Allendale, New Jersey). Parasternal long-axis, short-axis, four-chamber and two-chamber views were included for analysis. Post-treatment studies were analyzed in random sequence by two observers blinded to clinical details and outcome. In the event of conflicting wall motion scores, studies were

reread until a consensus was reached between observers, or a third observer was asked to adjudicate the findings.

The LV wall was divided into 16 segments and regional wall motion for each segment was scored according to the recommendation of the American Society of Echocardiography (19). Segments were graded as 1 = normal (or hyperkinetic), 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic. The LV ejection fraction (EF) was estimated by tracing the endocardial contour in end-diastole and end-systole according to biplane Simpson's rule. Global and regional wall motion score indexes (WMSI) were derived by the formula: WMSI = sum of the segment scores/number of segments scored.

Study end points. The primary end points were clinical (chest pain, ST elevation, abnormal flow in the infarct-related artery), electrical (heart block, ventricular arrhythmia) or hemodynamic (changes in heart rate, systemic or pulmonary artery pressures) instability during the AO infusion and in-hospital clinical events including death, bleeding, recurrent ischemia, target vessel revascularization and new or progressive heart failure. Major bleeding was defined as intra-cranial hemorrhage or the need for blood transfusion. Predefined secondary end points were global and regional LV function at 24 h, one month and three months. Clinical follow-up was obtained in all patients at 30 days.

Statistical analysis. Statistical analysis was performed using SAS software (version 6.12, Cary, North Carolina). Results are expressed as mean ± SD or percentage. Changes in hemodynamic parameters, WMSI and EF were evaluated using repeated measures analysis of variance. If significance was found, post-hoc analysis was performed using Tukey's highest significant difference test. A p value ≤0.05 was considered statistically significant.

RESULTS

Clinical and angiographic data. Twenty-nine patients (24 men, 5 women, mean age: 58.9 ± 12.6 years) were enrolled in this study (Table 1). Nineteen patients (65%) had infarction of the anterior wall. The mean time to reperfusion was 5.4 ± 3.8 h from symptom onset. Stenting was performed in almost all patients (93%) and most received a glycoprotein receptor antagonist (76%). The peak creatine kinase level and mean hospital stay were 3,264 ± 2,868 IU/l and 5.9 ± 2.9 days, respectively.

After percutaneous transluminal coronary angioplasty (PTCA) or stenting, 26 patients (90%) had a successful angiographic result with TIMI grade 3 flow. The mean diameter stenosis after intervention was 4.9 ± 6.1%. One patient had an improvement in epicardial flow (TIMI flow grade 2 to 3) after the AO infusion (Fig. 1).

Hyperoxemic reperfusion. Hyperoxemic blood was infused successfully in all patients (mean infusion time: 80.8 ± 18.2 min). The mean loop flow and pO$_2$ of the coronary perfusate were 82 ± 13 ml/min and 631 ± 235 mm Hg, respectively. Despite the high pO$_2$ of the

Table 1. Baseline Clinical and Angiographic Characteristics (n = 29)

	n (%)
Age (yrs)	58.9 ± 12.6
Men	24 (82.7%)
Hypertension	11 (38%)
Diabetes	6 (21%)
Hyperlipidemia	11 (38%)
Current smoker	15 (52%)
History MI	6 (21%)
Previous PTCA	4 (14%)
Previous CABG	0 (0%)
Rescue PTCA	7 (24%)
Mean time to reperfusion from symptom onset (h)	5.4 ± 3.8
Mean time to reperfusion from arrival in catheterization laboratory (min)	35.3 ± 16.9
Infarct vessel	
LAD	19 (65%)
RCA	8 (28%)
Circumflex	2 (7%)
Vessel disease	
1	11 (38%)
2	11 (38%)
3	7 (24%)
Initial TIMI flow	
0/1	22 (76%)
2	7 (24%)
3	0 (0%)
Mean infarct vessel stenosis (%)	96.2 ± 6.7
Stent	27 (93%)
Glycoprotein IIb/IIIa antagonist	22 (76%)

CABG = coronary artery bypass grafting; LAD = left anterior descending coronary artery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

coronary perfusate, there was only a modest increase in mean systemic arterial pO$_2$ from baseline levels (150 ± 74 mm Hg vs. 170 ± 83 mm Hg, p = 0.01) (Table 2).

Primary and secondary end points. Hyperoxemic reperfusion was well tolerated in all patients. No clinical, electrical or hemodynamic instability was observed during the AO infusion (Table 2). There was a small but significant decrease in mean pulmonary wedge pressure at the end of the infusion compared with after angioplasty (21 ± 9 mm Hg vs. 16 ± 7 mm Hg, p = 0.04) (Table 2). There were no procedure-related complications.

During the in-hospital period, one patient developed congestive heart failure, which was treated with conventional therapy, and one patient required a blood transfusion because of bleeding at the femoral access site. There were no other adverse events during the hospitalization period.

At 30-day clinical follow-up there were no deaths, nor did any patients experience reinfarction, recurrent ischemia or need repeat target vessel revascularization.

LV function analysis. GLOBAL LV FUNCTION. Baseline and follow-up echocardiograms were performed in 28 (96%) patients (one patient was excluded because of technical difficulty with imaging). The EF and global WMSI immediately after angioplasty were: 48.6 ± 7.3% and 1.68 ± 0.24,
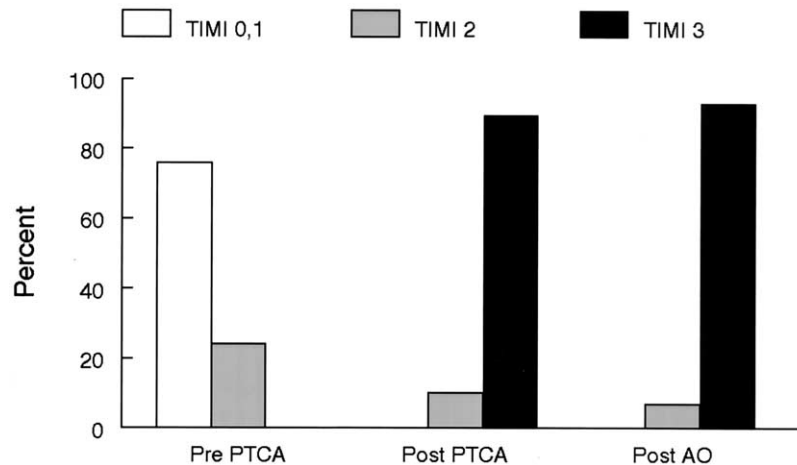
Figure 1. Infarct vessel Thrombolysis In Myocardial Infarction (TIMI) flow grade: before coronary angioplasty (PTCA), after PTCA and after the aqueous oxygen (AO) infusion.

respectively. A significant improvement in WMSI was demonstrated at 24 h (WMSI: 1.48 ± 0.24, p < 0.001) with a trend toward an increase in EF (51.8 ± 6.8%, p = 0.08) (Fig. 2 and 3). Progressive improvement in ventricular function was demonstrated at one and three months compared with baseline: WMSI one month: 1.39 ± 0.24 (p < 0.001), EF one month: 54.4 ± 6.6% (p < 0.001), WMSI three months: 1.34 ± 0.26 (p < 0.001) and EF three months: 56.0 ± 8.3% (p < 0.001).

REGIONAL LV FUNCTION. The WMSI was analyzed according to infarct and non-infarct zones. The WMSI of the infarct zone was 2.18 ± 0.32 after primary PTCA and 2.02 ± 0.37 (p = NS) immediately after hyperoxemic reperfusion (Fig. 4). At 24 h a significant improvement in infarct zone function was observed (WMSI: 1.84 ± 0.41, p < 0.001), with sustained improvement at one month (WMSI: 1.68 ± 0.44, p < 0.001) and three months (WMSI: 1.63 ± 0.43, p < 0.001) compared with baseline. No significant change in WMSI was observed in the non-infarct zone.

DISCUSSION

The primary purpose of this study was to evaluate the feasibility and safety of performing hyperoxemic reperfusion in patients undergoing primary angioplasty for AMI. The main finding of the study was that hyperoxemic reperfusion using AO after recanalization of the infarct vessel is safe and well tolerated. Although this study was not designed to evaluate the clinical efficacy of hyperoxemic reperfusion, results of the LV analysis suggest this therapy may promote healing and lead to early recovery of function in the infarct zone.

Rationale for this study. Hyperbaric oxygen therapy has been shown to reduce reperfusion injury and limit infarct size in experimental models of AMI (20). This benefit has been confirmed in clinical studies, with a reduction in arrhythmia, improved ST-segment resolution and decrease in creatine kinase release (21–23). However, using hyperbaric oxygen chambers in the setting of AMI is not only cumbersome but is limited by cost, access and concern about pulmonary toxicity. In light of these issues, the introduction of AO has been a major advance because this therapy can be used to produce hyperoxemia on a regional basis.

Although the precise biochemical and cellular mechanisms have yet to be fully elucidated, the effects of hyperbaric oxygen appear to be mediated, in part, by an increase in capillary density in post-ischemic tissue (13) and by a reduction in leukocyte adherence in post-capillary venules (16). More recently, hyperbaric oxygen therapy has been

Table 2. Hemodynamic Parameters and pO$_2$ During the AO Infusion

	Baseline	15 min	30 min	45 min	60 min	75 min	90 min
BP systolic	124.0 ± 16.4	122.2 ± 17.4	123.0 ± 19.8	123.2 ± 18.0	124.8 ± 16.7	122.7 ± 14.7	122.8 ± 17.3
BP diastolic	80.5 ± 11.2	78.4 ± 10.9	78.2 ± 11.1	80.5 ± 9.7	79.3 ± 9.3	80.5 ± 10.0	80.7 ± 11.9
Heart rate (beats/min)	78.4 ± 11.3	71.5 ± 11.3	71.5 ± 12.8	71.1 ± 13.4	73.8 ± 10.6	72.1 ± 15.4	73.2 ± 14.9
PA systolic	36.2 ± 12.7	31.5 ± 12.4	31.6 ± 9.0	31.2 ± 10.2	31.4 ± 9.4	31.0 ± 12.3	31.3 ± 10.3
PA diastolic	19.3 ± 5.3	17.2 ± 6.4	17.6 ± 7.0	17.5 ± 7.1	16.2 ± 6.4	16.5 ± 7.5	16.3 ± 5.4
PCW	21.4 ± 9.0	17.6 ± 7.5	18.4 ± 6.6	17.1 ± 8.3	16.6 ± 6.2	17.9 ± 8.2	16.0 ± 6.9*
Systemic pO$_2$	149.4 ± 73.6	170.0 ± 83.0	174.5 ± 72.4	174.0 ± 84.6	174.9 ± 79.8	166.9 ± 59.7	166.7 ± 78.6†
Loop pO$_2$	631.8 ± 235.7	684.9 ± 187.8	725.2 ± 196.1	719.9 ± 177.3	728.8 ± 186.7	746.1 ± 206.7	751.4 ± 188.4

*p = 0.04 vs. baseline; †p = 0.01 vs. baseline. All mesurements are mm Hg unless indicated.
AO = aqueous oxygen; BP = blood pressure; Loop pO$_2$ = pO$_2$ of blood infused into the infarct–related artery via the distal portion of the aqueous oxygen system circuit; PA = pulmonary artery pressure; PCW = pulmonary capillary wedge pressure.
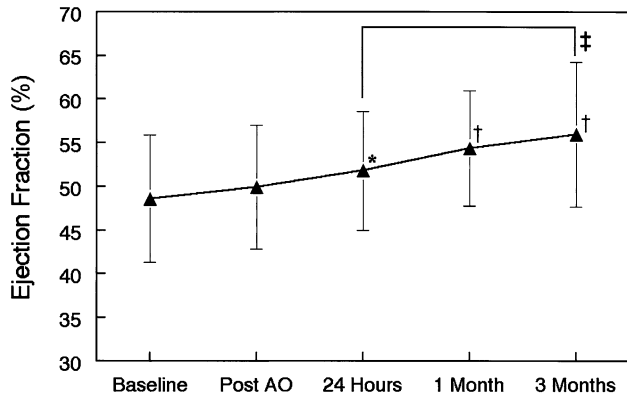
Figure 2. Global left ventricular ejection fraction immediately after primary percutaneous transluminal coronary angioplasty (baseline) and after hyperoxemic reperfusion with aqueous oxygen (AO). *p = 0.08 (vs. baseline); †p < 0.001 (vs. baseline); ‡p < 0.005 (vs. 24 h).

shown to impair cyclic guanosine monophosphate synthesis in activated neutrophils, thereby inhibiting β_2 integrin-dependent adherence (24). Despite concern about hyperoxemia increasing free radical production, biochemical data have demonstrated that the converse is true with hyperbaric oxygen enhancing a biochemical pathway that reduces formation of lipid peroxide radicals (15).

Experimental studies using AO. The effect of AO hyperoxemic reperfusion was initially investigated in a canine model of myocardial ischemia (17). Low coronary blood flow in the circumflex artery was delivered with a roller pump through the central lumen of a balloon occlusive catheter. A significant decrease in LV function was observed during low-flow hypoxemic and low-flow normoxemic perfusion, but this was prevented with hyperoxemic perfusion. In a subsequent study, the proximal left anterior descending or circumflex arteries of dogs were balloon occluded for 90 min. Hyperoxemic reperfusion with AO was associated with a significant improvement in two-dimensional echocardiography EF compared with controls (Spears JR, MD, unpublished data, 1997). The improvement in EF was unchanged 30 min after termination of hyperoxemic perfusion. More
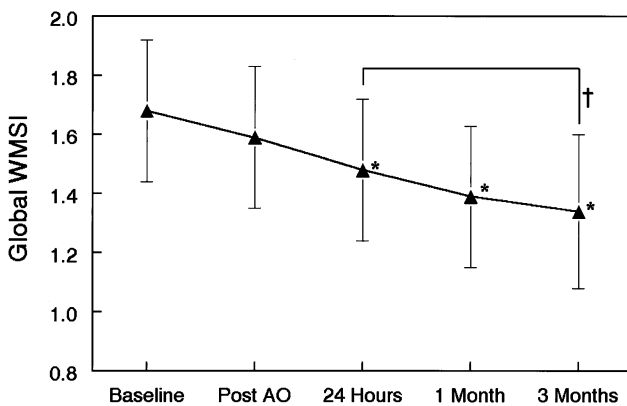

Figure 3. Global wall motion score index (WMSI) immediately after primary percutaneous transluminal coronary angioplasty (baseline) and after hyperoxemic reperfusion with aqueous oxygen (AO). *p < 0.001 (vs. baseline); †p < 0.005 (vs. 24 h).
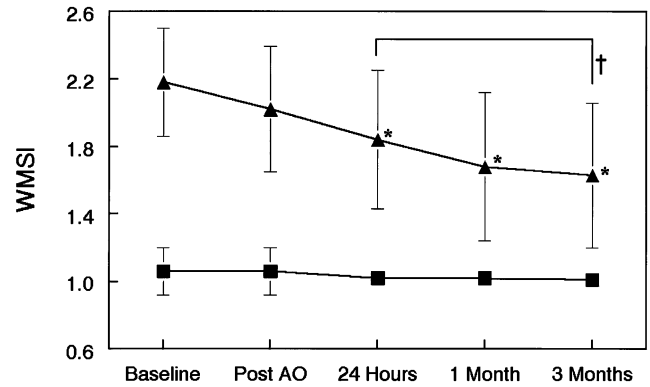

Figure 4. Wall motion score index (WMSI) of infarct and non-infarct zones at baseline and after hyperoxemic reperfusion with aqueous oxygen (AO). **Solid triangle** = infarct zone; **solid square** = non-infarct zone. *p < 0.01 (vs. baseline); †p = 0.01 (vs. 24 h).

recent data show that animals treated with AO hyperoxemic reperfusion have smaller infarct size with reduced myeloperoxidase levels, improved myocardial blood flow and preservation of endothelial cell morphology in the ischemic segment compared with animals undergoing normoxemic reperfusion (Spears JR, MD, unpublished data, 1999). These observations suggest that hyperoxemia may attenuate reperfusion microvascular ischemia and, thereby, limit tissue injury.

Recovery of LV function in previous studies. While the importance of infarct vessel patency for late recovery of ventricular function is well established (8), most studies have shown little or no improvement between early and late EF after reperfusion as a result of hyperkinesis in the non-infarct zone. For this reason, the WMSI is a more accurate method of assessing changes in global and regional LV function after reperfusion because it negates the effect of non-infarct zone hyperkinesis. Broderick et al. (25) used WMSI to evaluate 50 patients undergoing successful reperfusion therapy, with serial echocardiograms performed early (within 24 h) and late (mean: six days) after presentation. Overall, there was an improvement in WMSI (1.73 to 1.43, p < 0.001) but no significant change in LV EF. In this study we observed a trend toward improved EF 24 h after reperfusion (46.8 vs. 51.8%, p = 0.08) in addition to an early improvement in global WMSI. Although our study was not designed to assess the efficacy of hyperoxemic reperfusion, the improvement in infarct zone WMSI early after reperfusion was greater than expected from historic controls. While it is tempting to speculate this benefit was related to AO hyperoxemic reperfusion, this hypothesis needs to be tested in a randomized controlled trial.

Study limitations. Two different methods were used in this study to perform hyperoxemic reperfusion. After the first nine patients, the loop system was modified, and hyperoxemic blood was infused selectively into the infarct vessel via an intracoronary infusion catheter (rather than through the guide catheter) in order to optimize delivery of hyperoxemic blood to the infarct bed. Although no signif-

icant difference in global or regional wall motion was observed between the two delivery techniques, the small number of patients studied limits this analysis. For the same reason, we are unable to determine if hyperoxemic reperfusion has different effects in patient subgroups, such as those who received thrombolytic therapy or a glycoprotein receptor inhibitor.

There are several potential limitations with the echocardiographic analysis. First, assessment of ventricular function using the WMSI is semi-quantitative and requires optimal echocardiographic imaging to visualize all myocardial segments. However, this technique is well validated and provides a more accurate assessment of ventricular function than the EF alone. In this study, technically adequate images were obtained in the majority of patients, and the analysis was performed by two observers to minimize variability in interpretation. Second, significant hyperkinesis of the non-infarct zones was commonly observed during and immediately after primary angioplasty, which may have led to over-estimation of the baseline EF. In most cases, however, this had resolved by 24 h, suggesting that hyperkinesis had minimal effect on calculation of EF beyond the procedure itself. Myocardial contrast echocardiography was not performed in this study, although it would have been useful to further define the effects of AO on myocardial perfusion.

Implications. This is the first clinical study evaluating AO hyperoxemic reperfusion in AMI. This pilot study demonstrated that intracoronary hyperoxemic reperfusion is safe and well tolerated and may provide a new means to improve myocardial salvage after primary angioplasty. These preliminary data support the need for a randomized controlled trial of hyperoxemic reperfusion to evaluate the effect of this therapy on ventricular function and clinical outcome.

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