Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction

Dion Stub, MBBS, PhD; Karen Smith, BSc, PhD; Stephen Bernard, MBBS, MD; Ziad Nehme, BEmergHlth(Pmedic); Michael Stephenson, RN, BHlthSc, Grad Dip (MICA); Janet E. Bray, RN, PhD; Peter Cameron, MBBS, MD; Bill Barger, MACAP; Andris H. Ellims, MBBS, PhD; Andrew J. Taylor, MBBS, PhD; Ian T. Meredith, BSc, MBBS, PhD; David M. Kaye, MBBS, PhD; on behalf of the AVOID Investigators*

Background**—**Oxygen is commonly administered to patients with ST-elevation–myocardial infarction despite previous studies suggesting a possible increase in myocardial injury as a result of coronary vasoconstriction and heightened oxidative stress.

Methods and Results**—**We conducted a multicenter, prospective, randomized, controlled trial comparing oxygen (8 L/min) with no supplemental oxygen in patients with ST-elevation–myocardial infarction diagnosed on paramedic 12-lead ECG. Of 638 patients randomized, 441 patients had confirmed ST-elevation–myocardial infarction and underwent primary end-point analysis. The primary end point was myocardial infarct size as assessed by cardiac enzymes, troponin I, and creatine kinase. Secondary end points included recurrent myocardial infarction, cardiac arrhythmia, and myocardial infarct size assessed by cardiac magnetic resonance imaging at 6 months. Mean peak troponin was similar in the oxygen and no oxygen groups (57.4 versus 48.0 µg/L; ratio, 1.20; 95% confidence interval, 0.92–1.56; P=0.18). There was a significant increase in mean peak creatine kinase in the oxygen group compared with the no oxygen group (1948 versus 1543 U/L; means ratio, 1.27; 95% confidence interval, 1.04–1.52; P=0.01). There was an increase in the rate of recurrent myocardial infarction in the oxygen group compared with the no oxygen group (5.5% versus 0.9%; P=0.006) and an increase in frequency of cardiac arrhythmia (40.4% versus 31.4%; P=0.05). At 6 months, the oxygen group had an increase in myocardial infarct size on cardiac magnetic resonance (n=139; 20.3 versus 13.1 g; P=0.04).

Conclusion**—**Supplemental oxygen therapy in patients with ST-elevation–myocardial infarction but without hypoxia may increase early myocardial injury and was associated with larger myocardial infarct size assessed at 6 months.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01272713.

(*Circulation*. 2015;131:2143-2150. DOI: 10.1161/CIRCULATIONAHA.114.014494.)

Key Words: myocardial infarction ■ oxygen ■ ST-segment elevation myocardial infarction

Since the first report of supplemental oxygen for angina in 1900,[1] oxygen therapy has commonly been used in the initial treatment of patients with ST-segment–elevation myocardial infarction (STEMI). This is based on the belief that supplemental oxygen may increase oxygen delivery to ischemic myocardium and hence reduce myocardial injury and is supported by laboratory studies,[2,3] an older clinical trial,[4] the apparent benefit of hyperbaric oxygen,[5] and clinical trials of intracoronary aqueous oxygen.[6] Other studies, however, have suggested a potential adverse physiological effect of supplemental oxygen, with reduced coronary blood flow,[7] increased coronary vascular resistance,[8] and the production of reactive oxygen species contributing to vasoconstriction and reperfusion injury.[9,10] A recent meta-analysis of 3 small, randomized trials suggested a possible increase in adverse outcomes with supplemental oxygen administration.[11] More recently, a study comparing high-concentration oxygen with titrated oxygen in patients with suspected acute myocardial infarction (AMI) found no difference in myocardial infarct size on cardiac

Editorial see p 2101
Clinical Perspective on p 2150

Received November 26, 2014; accepted April 17, 2015.

From The Alfred Hospital, Melbourne, Australia (D.S., S.B., J.E.B., A.H.E., A.J.T., D.M.K.); Baker IDI Heart and Diabetes Institute, Melbourne, Australia (D.S., A.H.E., A.J.T., D.M.K.); Western Health, Melbourne, Australia (D.S.); Ambulance Victoria, Melbourne, Australia (K.S., S.B., Z.N., M.S., B.B.); Monash University, Melbourne, Australia (K.S., S.B., Z.N., M.S., M.E.B., P.C., I.T.M., D.M.K.); University of Western Australia, Western Australia, Australia (K.S.); and Monash Medical Centre, Melbourne, Australia (I.T.M.).

*See the online-only Data Supplement for a complete list of investigators.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.014494/-/DC1.

Correspondence to Karen Smith, BSc, PhD, Department of Research and Evaluation, Ambulance Victoria, 31 Joseph St, Blackburn North 3130, Victoria, Australia. E-mail Karen.smith@ambulance.vic.gov.au

magnetic resonance imaging (CMR).[12] Importantly, there are no studies evaluating the effects of supplemental oxygen therapy in the setting of contemporary therapy for STEMI, specifically acute coronary intervention.

With these results taken together, there remains considerable uncertainty over the utility of routine supplemental oxygen in uncomplicated AMI, with no clear recommendation for oxygen therapy in normoxic patients in the latest American Heart Association STEMI guidelines.[13] Despite its potential adverse physiological effects, supplemental oxygen continues to be administered to almost 90% of patients with suspected AMI.[14] The aim of this study was to compare supplemental oxygen therapy with no oxygen therapy in normoxic patients with STEMI to determine its effect on myocardial infarct size.

Methods

Study Design

The Air Versus Oxygen in Myocardial Infarction (AVOID) study was a multicenter, prospective, open-label, randomized trial. The study was conducted by Ambulance Victoria and 9 metropolitan hospitals that provide 24-hour percutaneous coronary intervention services in Melbourne, Australia, between October 2011 and July 2014. The trial design was registered with clinicaltrials.gov (http://www.clinicaltrials.gov; NCT01272713) and has been reported previously.[15]

Study Oversight

The study conformed to the Australian National Health and Medical Research Council framework for the conduct of clinical trials in the emergency setting. The study was approved by the Human Research Ethics Committees of all participating hospitals using a process of delayed consent. Before prehospital enrollment, patients were given brief information and the opportunity to opt out of the trial. Informed consent by the patient or next of kin was sought after stabilization in hospital. The study was designed by the authors, who wrote all drafts of the manuscript and vouch for the integrity and completeness of the data and analyses and for the fidelity of this report. None of the sponsors had access to the study data or had any role in the design or implementation of the study or the reporting of the data. All primary efficacy and safety outcome measures, including mortality, cardiac arrest, and unplanned intubations, were assessed by an independent Data Safety Monitoring Committee (see the list of investigators in the online-only Data Supplement). The Data Safety Monitoring Committee performed an interim analysis after 405 randomizations and recommended continuing the trial to the planned target.

Patient Population

Paramedics screened patients with chest pain to determine their eligibility for enrollment. Patients were included if they were adults ≥18 years of age, had chest pain beginning <12 hours before assessment, with prehospital ECG evidence of STEMI, as determined by the paramedic, defined as ST-segment elevation of ≥0.1 mV in 2 contiguous limb leads, ≥0.2 mV in 2 contiguous chest leads, or new left bundle-branch block pattern. Patients were excluded if any of the following was present: oxygen saturation <94% measured on pulse oximeter,[16] bronchospasm requiring nebulized salbutamol therapy with oxygen, oxygen administration before randomization, altered conscious state, or planned transport to a nonparticipating hospital. Patients who met the inclusion criteria in the field and were allocated to a treatment arm were excluded after hospital arrival if physician assessment indicated that the patient did not have a STEMI.

Randomization and Masking

Computer-generated block randomization was performed with ambulances carrying opaque envelopes numbered externally, concealing treatment assignment. Individuals involved with the delivery of oxygen therapy before hospital arrival and in hospital were not blinded to treatment assignment. Six-month follow-up of all patients was performed by a central coordinator blinded to treatment assignment. Investigators undertaking data analysis were masked to treatment assignment for primary end points and 6-month telephone follow-up.

Procedures

Patients in the oxygen group were administered supplemental oxygen via face mask at 8 L/min by paramedics. This therapy continued until transfer from the cardiac catheterization laboratory to the cardiac care ward. Patients randomized to the no oxygen arm received no oxygen unless oxygen saturation fell below 94%, in which case oxygen was administered via nasal cannula (4 L/min) or face mask (8 L/min) to achieve an oxygen saturation of 94%. All patients received aspirin 300 mg orally by paramedics. Additional antiplatelet therapy and choice of anticoagulation and percutaneous intervention strategy were at the discretion of the treating interventional cardiologist, according to hospital protocol. Blood sampling was done at baseline and then every 6 hours for the first 24 hours and every 12 hours to 72 hours after admission to assess cardiac troponin I (cTnI) and creatine kinase (CK) concentration. Contrast-enhanced CMR at 6 months was offered to all patients with confirmed STEMI who agreed to travel to the core site for scanning and had no contraindications for CMR.

Data were collected from patient case notes and electronic records onto trial-specific case record forms. All randomized patients were accounted for through daily audits of prehospital and hospital data to cross-check against all cardiac catheterization laboratory activations at each institution.

Statistical Analysis

For the baseline characteristics, variables that approximated a normal distribution were summarized as mean±SD, and groups were compared by Student *t* tests. Nonnormal variables were represented as median and first and third quartiles, and groups were compared by the Wilcoxon rank-sum test with exact inference. Binomial variables were expressed as proportions and 95% confidence intervals (CIs), and groups were compared by χ^2 tests. Definitions of the end points used in this study are provided in Table I in the online-only Data Supplement. The primary end point was myocardial injury, measured by peak cTnI and CK. The area under the curve (AUC_{72}) for cTnI and CK concentrations in serum was also measured. Secondary end points, measured at hospital discharge and at 6 months, included ECG ST-segment resolution, mortality, major adverse cardiac events (death, recurrent myocardial infarction, repeat revascularization, and stroke), and myocardial infarct size on CMR (n=139) at 6 months. For the primary end point, we calculated geometric means and ratios (95% CI) for cTnI and CK release, and a Student *t* test was carried out on the log-transformed data with comparison of groups obtained after back-transformation. To estimate the AUC_{72} for cTnI and CK release, we used trapezoidal integration, with multiple imputation using the Markov Chain Monte Carlo method for patients with ≥1 missing biomarker assays (Figure I and Table II in the online-only Data Supplement).[17,18]

The robustness of our AUC_{72} estimations was assessed with a series of sensitivity analyses. First, we conducted trapezoidal integration for the AUC measurement as above and considered additional covariates for the imputation model as follows: age, sex, Thrombolysis in Myocardial Infarction flow before the procedure, left anterior descending culprit artery, symptom-to-intervention time, and procedural success. In the second sensitivity analysis, a repeated-measures analysis was used to estimate the overall profile of cTnI/CK release over the 72-hour window. All available biomarker data were analyzed by use of linear mixed-effects regression with patient as a random effect, together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects. For this analysis, the nonsignificant interaction term between treatment group and time of assay was removed from the model. In the final sensitivity analysis, trapezoidal integration was used for the estimation of AUC. Patients with ≥1 missing biomarker assays were replaced by linear interpolation and extrapolation (Table II in the online-only Data Supplement).[19] Infarct size assessed by CMR at 6 months was compared across groups with the Student *t* test on the log-transformed data with comparison of groups obtained after back-transformation. Group differences in the median CMR infarct size were also compared across groups with the Wilcoxon rank-sum test. Finally, we used Spearman rank correlations to assess the relationship among cTnI, CK, and CMR infarct size (Table III in the online-only Data Supplement).

For the primary end point we hypothesized that withholding oxygen may influence myocardial injury by 20%.[20,21] Assuming a mean peak cTnI level of 75±35 µg/L,[22] for a statistical power of 90% and a probability of a type I error of 0.01 with a 2-sided test, a sample size of 326 (163 in each group) was calculated. This sample was increased to allow the positive predictive value of prehospital diagnosis of STEMI to be <100% and protocol violations. The final recruitment target was 600 prehospital randomizations, with 490 (245 patients in each arm) meeting inclusion criteria on arrival to hospital.

The primary analysis was performed on an intention-to-treat basis for all patients with confirmed STEMI after emergent coronary angiogram. Analysis of all randomized patients was also performed to examine differences in baseline characteristics (Table IV in the online-only Data Supplement). Analysis of the primary end point and all cardiac biomarker analyses were performed by an independent statistician blinded to treatment allocation. We assessed whether the distribution of the main clinical variables was similar between groups, taking into account whether they later fulfilled eligibility criteria (Table V in the online-only Data Supplement). To examine possible bias resulting from exclusion after randomization of patients with an alternative diagnosis to STEMI and the possible effect of the intervention on the diagnosis itself, we compared baseline and procedural characteristics and secondary end points available in patients included in the analysis with those who were excluded (Table VI in the online-only Data Supplement). Similarly, to examine whether missing data introduced selection bias, we compared baseline and procedural characteristics and secondary end points between included patients and patients who did not undergo the 6-month CMR (Table VII in the online-only Data Supplement).

Results

The study profile is shown in Figure 1. Of 836 adult patients with chest pain screened for the trial, 638 patients were randomized by paramedics. Of these, 50 were subsequently excluded because of prehospital protocol violations (35 patients), patient refusal of consent for trial participation (14 patients), and repeat enrollment (1 patient). After arrival at the emergency department, a further 118 patients were excluded from the analysis of primary end point after physician assessment of patient and ECG indicated an alternative diagnosis to STEMI.

The remaining 470 patients who were eligible to continue in the study underwent emergent coronary angiography. Primary end-point data are reported on the 441 patients (oxygen group, 218 patients; no oxygen group, 223 patients) with confirmed STEMI.

The baseline characteristics and vital signs between the treatment groups were well matched (Table 1). Patient treatments after randomization are shown in Table 2. Patient-reported pain scores, opioid requirements, and hemodynamics were similar between the 2 groups (Table VIII in the online-only Data Supplement). The majority of patients (99.5%) allocated to oxygen received oxygen at 8 L/min, whereas a small proportion of patients (7.7%) in the no oxygen group required oxygen at 4 L/min either before or on arrival to the cardiac catheterization laboratory (Figure II in the online-only Data Supplement). There was a significant difference in oxygen saturations (P<0.001) during the intervention period (Figure III in the online-only Data Supplement).

The time from onset of symptoms to intervention was similar in the 2 groups, with a median time of 150.5 minutes (interquartile range, 125.0–213.8 minutes) in the oxygen

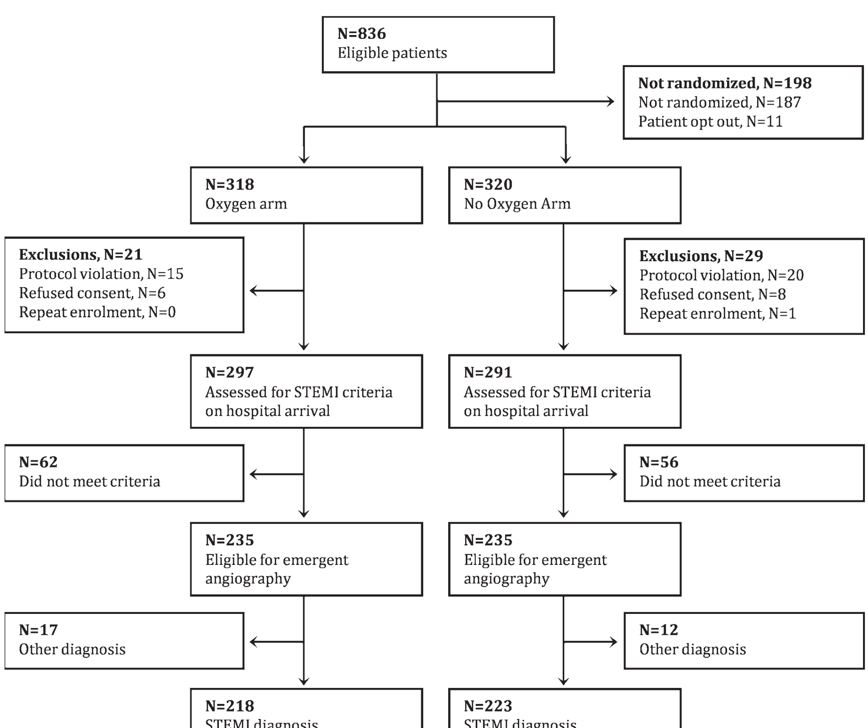

Figure 1. Patient selection and randomization flowchart. STEMI indicates ST-segment–elevation myocardial infarction.

Table 1. Baseline Characteristics of Patients With Confirmed STEMI

Characteristic	Oxygen Arm (n=218)	No Oxygen Arm (n=223)
Age, mean (SD), y	63.0 (11.9)	62.6 (13.0)
Male, n (%)	174 (79.8)	174 (78.0)
Body mass index, median (IQR), kg/m²*	27.4 (25.1–31.1)	27.7 (24.7–30.8)
Past history and risk factors, n (%)		
Diabetes mellitus	37 (17.0)	41 (18.4)
Hypertension	130 (59.6)	123 (55.2)
Dyslipidemia	121 (55.5)	118 (52.9)
Current or ex-smoker†	141 (65.3)	165 (74.3)
Peripheral vascular disease	4 (1.8)	11 (4.9)
Stroke	11 (5.0)	15 (6.7)
Ischemic heart disease	38 (17.4)	40 (17.9)
Previous PCI	24 (11.0)	26 (11.7)
Previous CABG	4 (1.8)	3 (1.3)
Medication only	8 (3.7)	12 (5.4)
Creatinine > 120 μmol/L	17 (7.8)	19 (8.5)
Status on arrival of paramedics		
Heart rate, median (IQR), bpm	74.0 (61.0–84.0)	72.0 (60.0–80.3)
Systolic blood pressure, median (IQR), mm Hg	130.0 (105.0–150.0)	130.0 (110.0–150.0)
Oxygen saturation, median (IQR), %	98.0 (97.0–99.0)	98.0 (97.0–99.0)
Pain score, median (IQR)	7.0 (5.0–9.0)	7.0 (5.0–8.0)

CABG indicates coronary artery bypass grafting; IQR, interquartile range; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Available in 280 of 441 patients.

†*P* for difference <0.05.

group compared with 162.0 minutes (interquartile range, 130.0–240.0 minutes) in the no oxygen group (P=0.09). Procedural details, including infarct-related artery, site of arterial access, use of thrombus aspiration, administration of glycoprotein IIb/IIIa antagonists, and stent implantation, were similar between the groups (Table 2).

In patients with confirmed STEMI, the geometric mean peak cTnI was 57.4 μg/L (95% CI, 48.0–68.6) in the oxygen group compared with 48.0 μg/L (95% CI, 39.6–58.1) in the no oxygen group, with a ratio of oxygen to no oxygen of 1.20 (95% CI, 0.92–1.56; P=0.18). Similar findings were obtained for AUC_{72} (Table 3). In the repeated-measures analysis, an ≈20% difference in the geometric mean for cTnI was consistent across all assay times (P value for group×time interaction=0.93; Figure 2). The ratio for oxygen to no oxygen cTnI based on the model that ignores the group×time interaction was highly significant at 1.28 (95% CI, 1.04–1.56; P=0.02; Table II in the online-only Data Supplement).

There was a significant increase in the geometric mean peak CK in the oxygen group compared with the no oxygen group (1948 U/L [95% CI, 1721–2205] vs 1543 U/L [95% CI, 1341–1776]), with a ratio of oxygen to no oxygen of 1.26 (95% CI, 1.05–1.52; P=0.01). Significant findings were also found for geometric mean AUC_{72} (Table 3). The results of the repeated-measures analysis were similar to those for cTnI. A

Table 2. Procedural Details of Patients With Confirmed STEMI

Characteristic	Oxygen Arm (n=218)	No Oxygen Arm (n=223)
Status on arrival at the catheterization laboratory		
Oxygen saturation, median (IQR), %*	100.0 (99.0–100.0)	98.0 (96.0–99.0)
Oxygen being administered, n (%)*	208 (95.9)	17 (7.7)
Oxygen dose, median (IQR), L/min*	8.0 (8.0–8.0)	4.0 (2.0–8.0)
Preintervention oxygen duration, median (IQR), min*†	79.0 (59.3–94.0)	51.5 (41.3–91.8)
Cardiac arrest, n (%)	10 (4.6)	8 (3.6)
Inotrope use, n (%)	11 (5.0)	12 (5.4)
Intubation, n (%)	0	3 (1.3)
Thrombolysis, n (%)	2 (0.9)	0
Killip class ≥II, n (%)	23 (11.1)	27 (12.7)
Culprit artery, n (%)		
LAD	82 (38.0)	74 (33.8)
LCx	21 (9.7)	31 (14.2)
RCA	100 (46.3)	101 (46.1)
Other	11 (5.1)	15 (6.8)
Extent of coronary disease, n (%)		
Single vessel	95 (43.8)	84 (37.7)
Multivessel	122 (56.2)	139 (62.3)
LMCA Involvement	9 (4.1)	7 (3.1)
Preprocedural TIMI flow 0/1, n (%)	191 (89.3)	191 (88.0)
Postprocedural TIMI flow 2/3, n (%)	208 (98.1)	211 (95.9)
Procedural details, n (%)		
Radial intervention	72 (33.2)	74 (33.3)
Stent implanted	202 (92.7)	201 (90.1)
Drug-eluting stent	112 (51.4)	114 (51.1)
Glycoprotein IIb/IIIa inhibitor	97 (44.5)	90 (40.4)
Thrombus aspiration	107 (49.1)	105 (47.1)
Intra-aortic balloon pump	7 (3.2)	12 (5.4)
CABG	5 (2.3)	9 (4.0)
Time intervals, median (IQR), min		
Call to hospital arrival	55.0 (46.0–69.0)	56.5 (48.0–68.8)
Paramedic on scene to hospital arrival	45.0 (35.0–55.0)	46.0 (38.0–57.0)
Symptom to intervention	150.5 (125.0–213.8)	162.0 (130.0–240.0)
Hospital arrival to intervention	54.0 (39.0–66.3)	56.0 (42.0–70.8)
Length of stay, median (IQR), d	4.0 (4.0–5.0)	4.0 (3.0–5.0)

CABG indicates coronary artery bypass grafting; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

**P* for difference <0.05.

†Duration on oxygen therapy from randomization to first procedural intervention (eg, aspiration, ballooning) measured in patients who received oxygen therapy.

consistent 20% increase in the geometric mean CK was found in the oxygen group regardless of assay time (Figure 3), which was significant when collapsed over time (ratio of oxygen to no oxygen, 1.20; 95% CI, 1.05–1.38; P=0.007; Table II in the online-only Data Supplement). Peak cTnI and CK measurements were highly correlated (r=0.87, P<0.001; Table III in the online-only Data Supplement), with a similar trend across clinically relevant subgroups (Figure IV in the online-only Data Supplement).

Clinical end points in hospital and at 6 months were monitored for safety (Table 4). By hospital discharge, there were 4 deaths (1.8%) in the oxygen group compared with 10 deaths (4.5%) in the no oxygen group (P=0.11). In the oxygen group, there was an increase in the rate of in-hospital recurrent myocardial infarctions (5.5% versus 0.9%; P=0.006) and major cardiac arrhythmias, defined as sustained and nonsustained ventricular and atrial tachyarrhythmia (40.4% versus 31.4%; P=0.05). At the 6-month follow-up, the rate of adverse outcomes did not differ between the groups, with appropriate medical therapy in both groups (Table IX in the online-only Data Supplement).

CMR was performed on 139 patients (32%) at 6 months. Baseline characteristics of those patients in the oxygen (n=65) and no oxygen (n=74) groups were similar (Table X in the online-only Data Supplement), as were the characteristics of those patients who did and did not undergo CMR (Table VIII in the online-only Data Supplement). No patient had evidence of a myocardial infarction in 2 arterial territories or myocardial scarring in a nonischemic pattern. Left ventricular dimensions and ejection fraction were similar between the 2 groups. The median infarct size was increased in the oxygen group compared with the no oxygen group (20.3 g [interquartile range, 9.6–29.6 g] versus 13.1 g [interquartile range, 5.2–23.6 g]; P=0.04). When expressed as a proportion of left ventricular mass, the difference in median infarct size was 12.6% (interquartile range, 6.7%–19.2%) in the oxygen group compared with 9.0% (interquartile range, 4.1%–16.3%) in the no oxygen group (P=0.08), with the ratio of geometric means approaching significance at 1.38 (95% CI, 0.99–1.92; P=0.06). cTnI and CK measurements taken at the index admission were significantly correlated with infarct size at 6 months (Table III in the online-only Data Supplement).

Discussion

The AVOID study was conducted to determine whether the routine administration of supplemental oxygen in patients with STEMI in both the prehospital and early in-hospital setting is associated with beneficial or harmful effects. We demonstrated that, in normoxic patients, routine oxygen administration was not associated with a reduction in symptoms or a diminution in infarct size according to the cTnI and CK profiles. Rather, our data suggest that routine high-flow oxygen supplementation may be accompanied by harm, as reflected by a significant increase in CK and larger infarct size determined by CMR at 6 months.

Although there have been significant advances in therapies for AMI, our findings are similar to those reported by Rawles and Kenmure[20] >40 years ago. In their study, inhaled oxygen

Table 3. Measures of Infarct Size in Patients With Confirmed STEMI

End Point	Oxygen Arm (n=218)	No Oxygen Arm (n=223)	Ratio of means (Oxygen/No Oxygen)	*P* Value
cTnI				
Sample size, n	200	205		
Median peak (IQR), μg/L	65.7 (30.1–145.1)	62.1 (19.2–144.0)		
Geometric mean peak (95% CI), μg/L	57.4 (48.0–68.6)	48.0 (39.6–58.1)	1.20 (0.92–1.55)	0.18
Median AUC_{72} (IQR), μg/L	2336.4 (965.6–5043.1)	1995.5 (765.7–4426.0)		
Geometric mean AUC_{72} (95% CI), μg/L	2000.4 (1692.8–2363.9)	1647.9 (1380.1–1967.6)	1.21 (0.95–1.55)	0.12
Creatine kinase, U/L				
Sample size, n	217	222		
Median peak (IQR), U/L	2073 (1065–3753)	1727 (737–3598)		
Geometric mean peak (95% CI), U/L	1948 (1721–2205)	1543 (1341–1776)	1.26 (1.05–1.52)	0.01
Median AUC_{72} (IQR), U/L	64 620 (35 751–107 066)	51 757 (29–141–10 6029)		
Geometric mean AUC_{72} (95% CI), U/L	60 395 (54 185–67 316)	50 726 (44 861–57 358)	1.19 (1.01–1.40)	0.04
Infarct size on CMR*				
Sample size, n	61	66		
Median (IQR), g	20.3 (9.6–29.6)	13.1 (5.2–23.6)		0.04
Geometric mean (95% CI), g	14.6 (11.3–18.8)	10.2 (7.7–13.4)	1.43 (0.99–2.07)	0.06
Median (IQR) proportion of LV mass, %	12.6 (6.7–19.2)	9.0 (4.1–16.3)		0.08
Geometric mean (95% CI) proportion of LV mass, g	10.0 (8.1–12.5)	7.3 (5.7–9.3)	1.38 (0.99–1.92)	0.06
ECG ST-segment resolution >70%, measured 1 d after hospital admission, n (%)	132 (62.0)	149 (69.6)		0.10

AUC indicates area under the curve; CI, confidence interval; CMR, cardiac magnetic resonance imaging; cTnI, cardiac troponin I; IQR, interquartile range; LV, left ventricular; and STEMI, ST-segment–elevation myocardial infarction.

*CMR conducted at six-month follow-up in 139 of 441 patients.

therapy at 6 L/min increased myocardial injury as measured by aspartate aminotransferase release in patients with AMI. Our results differ from a recent study by Ranchord and colleagues[12] of high-flow oxygen (6 L/min) compared with titrated oxygen in patients with STEMI. In their study of 136 patients, there was no difference in infarct size by troponin or CMR. One limitation of that study was that randomization and allocation to different levels of oxygen therapy occurred only after hospital presentation, and most subjects had routinely received oxygen therapy by paramedics for an average of 60 minutes.[12]

It has been suggested that oxygen may provide both psychological and physiological benefits to anxious patients during an AMI.[23] Our data suggest that there was no difference in chest pain scores or the requirement for additional opioid analgesics in the prehospital period in patients not administered oxygen. There are, however, proposed mechanisms that support our finding of increased myocardial infarct size in patients administered high-flow oxygen.[24] High-flow oxygen has been shown to reduce epicardial coronary blood flow,[7] to increase coronary vascular resistance,[8] and to affect the microcirculation, leading to functional oxygen shunting.[25]

Our results also suggest that withholding routine oxygen therapy is safe in normoxic patients with an AMI. A previous study reported a rate of hypoxia in AMI patients of 70%[26]; however, our study found that only 7.7% of patients allocated to no oxygen required oxygen supplementation on arrival to the cardiac catheterization laboratory for an oxygen saturation of <94%.

Our study was not powered for clinical end points. The statistical differences noted for in-hospital recurrent myocardial infarctions and major cardiac arrhythmias and the nonsignificant difference in mortality need to be confirmed. The currently enrolling Swedish registry–based randomized trial of oxygen in AMI is powered for mortality and will provide evidence for the effects of supplemental oxygen on cardiovascular morbidity and mortality.[27] The AVOID trial was also not designed to assess the impact of lower concentrations of supplemental oxygen that may be administered via nasal cannulas. Patients in the oxygen arm received 8 L/min oxygen therapy via face mask. This was chosen to maintain consistency with existing emergency medical services treatment protocols in Australia. Although the dose of 8 L/min is substantially lower than those used in other emergency medical services systems[28] and earlier physiological studies,[29] the dose is similar to what has been used in earlier clinical trials.[12,30]

The AVOID study was a pragmatic clinical trial, which by design required randomization in the prehospital setting by paramedics before detailed patient consent. The use of delayed consent in clinical trials in patients with STEMI has been the subject of significant recent controversy[31] but has been deemed to be a suitable method of conducting ethical, pragmatic, comparative-effectiveness trials of emergency interventions.[32] Our process of consent was approved by the Human Research Ethics committees of all participating hospitals and was well received by patients.

Our study has several limitations. First, treatment allocation was not blinded to paramedics, patients, or in-hospital cardiology teams. However, the analysis of the primary end point was performed by a statistician who was blinded to treatment group. Our study was powered to detect group differences in initial myocardial injury as reflected by the cardiac biomarker profiles rather than major adverse cardiac events. Given the relatively low mortality observed in our trial, an outcomes-based study would require a much larger number of patients. The study had a pragmatic design facilitating prehospital enrollment by paramedics, which led to a number of patients who did not have STEMI being excluded from the primary end-point analysis after randomization. The proportion of excluded patients was comparable to those in other prehospital STEMI trials,[33,34] and the characteristics of excluded patients compared with those included in the analysis were similar, suggesting that substantial selection bias did not occur. In addition, not all patients in our study underwent CMR at 6 months after infarct because of contraindications to and the availability of CMR at a single central site that made

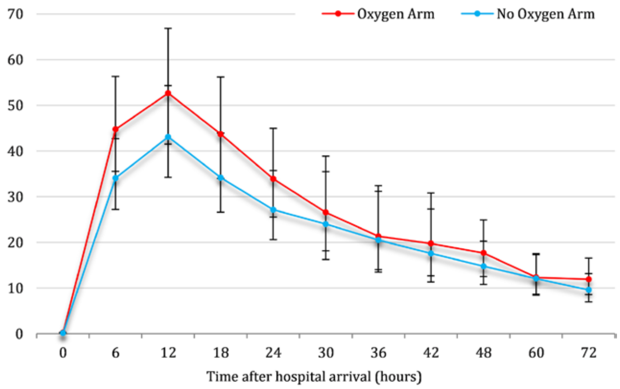

Figure 2. Geometric mean (95% confidence interval) for cardiac troponin I (cTnI) release (μg/L) over 72 hours in patients with confirmed ST-segment–elevation myocardial infarction. A repeated-measures analysis was used to estimate the overall profile of cTnI release over the 72-hour window. All available biomarker data were analyzed with linear mixed-effects regression with patient as a random effect, together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects.

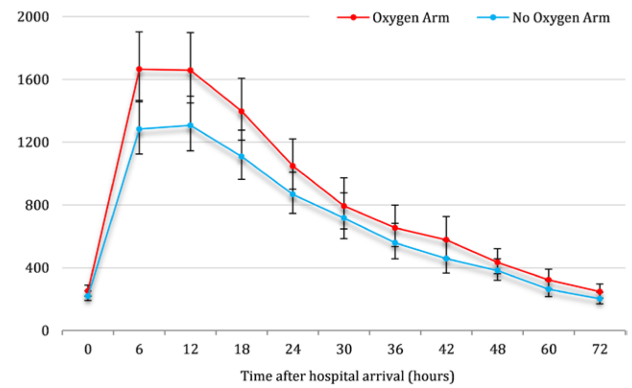

Figure 3. Geometric mean (95% confidence interval) for creatine kinase release (U/L) over 72 hours in patients with confirmed ST-segment–elevation myocardial infarction. A repeated-measures analysis was used to estimate the overall profile of CK release over the 72-hour window. All available biomarker data were analyzed with linear mixed-effects regression with patient as a random effect, together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects.

Table 4. Adverse Clinical End Points at Hospital Discharge and the 6-Month Follow-Up in Patients With Confirmed STEMI

Clinical End Point	Oxygen Arm (n=218)	No Oxygen Arm (n=223)	*P* Value
At hospital discharge, n (%)			
Mortality, any cause	4 (1.8)	10 (4.5)	0.11
Cardiac cause	4 (1.8)	7 (3.1)	…
Massive hemorrhage	0	2 (0.8)	…
Sepsis	0	1 (0.4)	…
Recurrent myocardial infarction	12 (5.5)	2 (0.9)	0.006
Stroke or transient ischemic attack	3 (1.4)	1 (0.4)	0.30
Cardiogenic shock	20 (9.2)	20 (9.0)	0.94
Coronary artery bypass grafting	5 (2.3)	9 (4.0)	0.30
Major bleeding	9 (4.1)	6 (2.7)	0.41
Arrhythmia	88 (40.4)	70 (31.4)	0.05
At the 6-mo follow-up, n (%)*			
Mortality, any cause	8 (3.8)	13 (5.9)	0.32
Cardiac cause	6 (2.9)	9 (4.1)	…
Massive hemorrhage	0	2 (0.9)	…
Sepsis	0	1 (0.5)	…
Renal failure	1 (0.5)	0	…
Cancer	0	1 (0.5)	…
Recurrent myocardial infarction	16 (7.6)	8 (3.6)	0.07
Stroke or transient ischemic attack	5 (2.4)	3 (1.4)	0.43
Repeat revascularization	23 (11.0)	16 (7.2)	0.17
MACEs	46 (21.9)	34 (15.4)	0.08

MACE indicates major adverse cardiac events (all-cause mortality, recurrent myocardial infarction, repeat revascularization, stroke); and STEMI, ST-segment–elevation myocardial infarction.

*Fourteen of 441 were lost to follow-up.

travel difficult for many patients. Given this limited availability, it was not feasible to perform the originally planned CMR scan during index presentation to measure myocardial salvage and infarct size as a proportion of area at risk. All cardiac enzymes were performed with the same cTnI and CK assays; we did not use a core laboratory for all enzyme analyses or analyses of angiographic data. However, our findings suggest a strong correlation between both sets of cardiac biomarker data.

Although oxygen therapy is appropriate in hypoxemic patients with complicated AMI, it should be noted that oxygen is a drug with possibly significant side effects. To date, clinical trial data supporting its routine use in normoxemic patients with AMI have not been robust enough to inform clinical guidelines with sufficient levels of evidence, particularly in the setting of contemporary interventional reperfusion practices.

Conclusions

Our study does not demonstrate any significant benefit of routine oxygen therapy for reducing myocardial infarct size, improving patient hemodynamics, or alleviating symptoms. Instead, we identified some evidence for increased myocardial injury when oxygen was administered during uncomplicated AMI.

Acknowledgments

We are grateful to all the paramedics and hospital staff who contributed to the AVOID study for their dedication, commitment, and hard work. The Data Safety Management Committee members were Christopher Reid, PhD, Monash University; Richard Harper, MBBS, PhD, Monash Medical Center; and David Garner, BHlthSc (MICA), Ambulance Victoria, Doncaster, Australia. Steve Vander Hoorn assisted with the statistical analysis.

Sources of Funding

The AVOID study was funded by grants from Alfred Foundation, FALCK Foundation, and Paramedics Australia. Drs Stub and Bray are supported by cofunded National Health and Medical Research Council/National Heart Foundation fellowships (No. 1090302/100516 and No. 1069985/100136). Drs Smith, Bernard, Cameron, Ellims, Taylor, Meredith, and Kaye are supported by National Health and Medical Research Council of Australia grants.

Disclosures

None.

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CLINICAL PERSPECTIVE

The Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction (AVOID) trial has important implications for the management of patients with suspected acute myocardial infarction during both their prehospital and in-hospital treatment pathways. Although oxygen may benefit the hypoxemic patient with complicated acute myocardial infarction, evidence supporting its routine use in normoxemic patients is of low quality and predates contemporary reperfusion practices. Recent physiological studies have highlighted the potential adverse effects of supplemental oxygen, including a reduction in coronary blood flow, increased coronary vascular resistance, and the production of reactive oxygen species. The AVOID study, taken in conjunction with these recent physiological studies, does not demonstrate any significant benefit of routine oxygen use in terms of myocardial infarct size, patient hemodynamics, or reported symptoms. Instead, the AVOID trial identified a signal for increased myocardial injury during uncomplicated acute myocardial infarction with the routine use of supplemental oxygen. Oxygen should be treated like all other medical therapies, balancing efficacy and side-effect profile. On the basis of this data, the largest collection so far, we recommend that prehospital and hospital care providers review their current practice concerning supplemental oxygen. Until larger studies are available, international guidelines should consider updating recommendations, highlighting the lack of benefit for oxygen therapy and the potential for harm in acute myocardial infarction unless oxygen saturations are <94%.

Circulation

American Heart Association

Air Versus Oxygen in ST-Segment–Elevation Myocardial Infarction

Dion Stub, Karen Smith, Stephen Bernard, Ziad Nehme, Michael Stephenson, Janet E. Bray, Peter Cameron, Bill Barger, Andris H. Ellims, Andrew J. Taylor, Ian T. Meredith and David M. Kaye
on behalf of the AVOID Investigators*

Circulation. 2015;131:2143-2150; originally published online May 22, 2015;
doi: 10.1161/CIRCULATIONAHA.114.014494
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Supplementary Appendix

Air Versus Oxygen In ST-Elevation Myocardial Infarction

Complete list of AVOID Investigators

Chief Investigators
Stephen Bernard, MBBS, MD; Karen Smith, BSc, PhD.

Steering Committee
Dion Stub, MBBS PhD; Ziad Nehme, BEmergHlth(Pmedic)(Hons); Michael Stephenson, RN, BHlthSc, Grad Dip (MICA); Janet Bray, RN, PhD; Bill Barger, MACAP; Ian Meredith, BSc, MBBS, PhD; Peter Cameron, MBBS, MD; David Kaye, MBBS, PhD.

Site Investigators
Ian Meredith, BSc, MBBS, PhD, Monash Medical Centre, Clayton, Australia; Adam Hutchinson, MBBS, PhD, Monash Medical Centre, Clayton, Australia; Paul Antonis, MBBS, Monash Medical Centre, Clayton, Australia; Sarah Gutman, MBBS, Monash Medical Centre, Clayton, Australia; Nitesh Nerlekar, MBBS, Monash Medical Centre, Clayton, Australia; Colin Machado, MBBS, Monash Medical Centre, Clayton, Australia; Harendra Wijesekera, MBBS, Monash Medical Centre, Clayton, Australia; Kiran Munnur, MBBS, Monash Medical Centre, Clayton, Australia; Anthony Dart, BA, BM, BCh, D Phil, Alfred Hospital, Melbourne, Australia; James Shaw, MBBS, PhD, Alfred Hospital, Melbourne, Australia; Stephen Duffy, MBBS, PhD, Alfred Hospital, Melbourne, Australia; Andrew Taylor, MBBS, PhD, Alfred Hospital, Melbourne, Australia; James Hare, MBBS, PhD, Alfred Hospital, Melbourne, Australia; Leah Iles, MBChB PhD, Alfred Hospital, Melbourne, Australia; Andris Ellims, MBBS, Alfred Hospital, Melbourne, Australia; Teressa Lancefield MBBS, Alfred Hospital, Melbourne, Australia; Prabath Joseph-Francis, MBBS, Alfred Hospital, Melbourne, Australia; Gishel New, MBBS, PhD, Box Hill Hospital, Box Hill, Australia; Melanie Freeman, MBBS, Box Hill Hospital, Box Hill, Australia; Louise Roberts, RN, Box Hill Hospital, Box Hill, Australia; Robert Whitbourn, MBBS, BMedSc, MD; St Vincent's Hospital, Fitzroy, Australia; Omar Farouque, MBBS, PhD, Austin Hospital, Heidelberg, Australia; Louise Brown, RN, Austin Hospital, Heidelberg, Australia; Leeanne Grigg, MBBS, Royal Melbourne Hospital, Carlton, Australia; Monique R Watts, MBBS, Royal Melbourne Hospital, Carlton, Australia; Geoff Toogood, MBBS, Frankston Hospital, Frankston, Australia; Robert Lew, MBBS PhD, Frankston Hospital, Frankston, Australia; Mark Freilich, MBBS, Frankston Hospital, Frankston, Australia; Rodney Teperman, MBBS, Frankston Hospital, Frankston, Australia; Rahul Sharma, MBBS, Frankston Hospital, Frankston, Australia; Sandeep Prabhu, MBBS, Frankston Hospital, Frankston, Australia; Greg Szto, MBBS Peninsula Private Hospital, Frankston, Australia; Nicholas Cox, MBBS, Western Hospital, Footscray, Australia; Salvatore Rametta, MBBS, Western Hospital, Footscray, Australia; Vanessa Lee, RN, Western Hospital, Footscray, Australia.

Data Safety Committee
Christopher Reid, PhD, Monash University, Prahran, Australia; Richard Harper, MBBS, PhD, Monash Medical Centre, Clayton, Australia; David Garner, BHlthSc (MICA), Ambulance Victoria, Doncaster, Australia.

Table S1. Definitions of outcomes used in the AVOID study.	
Death	Deaths were classified as cardiac or non-cardiac. Examples of cardiac death included myocardial infarction, cardiogenic shock, arrhythmia, or dissection. A non-cardiac cause of death was the result of sepsis, pneumonia, cancer or non-cardiac haemorrhaging. Non-cardiac causes of death which occurred after the index admission were classified as non-cardiac deaths. Causes of death were verified through medical records and autopsy findings (if necessary). Deaths occurring after the index admission were verified through telephone follow-up with the patient's next-of-kin.
Recurrent myocardial infarction	The diagnosis of recurrent myocardial infarction was made using the following criteria: 1. Occurred after the index admission; **AND** 2. Recurrence of ischemic chest discomfort and/or new ST segment elevation, in at least two contiguous limbs leads (≥ 1 mm) or chest leads (≥ 2mm), or new left bundle branch block (LBBB) pattern; **AND** 3. A 50% increase in the serum cardiac enzyme level in a patient with a previously established peak value, and where the result is greater than 3 × 99th percentile Upper Reference Limit (URL) **OR** 4. Angiographic evidence of new thrombus, or either complete or partial vessel occlusion.
Stroke or transient ischemic attack	Neurological deficits classified by a clinician as stroke or transient ischaemic attack. Strokes were classified as haemorrhagic or ischaemic on the basis of brain imaging.
Major adverse cardiac event	A major adverse cardiac event was defined as death from any cause, recurrent myocardial infarction, recurrent revascularisation, and stroke.
Cardiogenic shock	Evidence of inadequate tissue perfusion in the setting of adequate intravascular volume, characterised by persistent hypotension (systolic blood pressure ≤ 90 mm Hg), with or without altered mental status and peripheral hypoperfusion, requiring either pharmacologic or mechanical circulatory support.
Major bleeding	Clinically overt bleeding associated with either one of the following: 1. A drop in haemoglobin of > 3 g/dL; 2. Haemodynamic compromise; 3. Requires blood transfusion; 4. Intracranial haemorrhage. Bleeding occurring after the index admission was classified as major bleeding when associated with death, hospital admission, blood transfusion, or intracranial haemorrhage.
Repeat revascularization	Any subsequent revascularisation (i.e. percutaneous coronary intervention or coronary artery bypass grafting) of any lesion which occurs after the index admission and verified at 6 months follow-up.
Target vessel revascularization	Any subsequent revascularisation (i.e. percutaneous coronary intervention or coronary artery bypass grafting) which occurs after the index admission, and involves the target lesion treated at the index admission.
Readmissions	Re-hospitalisations occurring for any reason after the index admission.
ST segment resolution at 1 day after admission	The reduction in ST-segment elevation one day after the admission as a proportion of the initial pre-procedural ECG.
Major Cardiac Arrhythmia	Defined as sustained and non-sustained ventricular and atrial tachyarrhythmia requiring medical intervention

Table S2. Sensitivity analyses of area under the curve estimation for cTnI and CK release in patients with confirmed STEMI.				
	Oxygen Arm	**No Oxygen Arm**	**Ratio of Means (Oxygen/No Oxygen)**	**P-Value**
Geometric Mean AUC_{72} (95% CI) cTnI, mcg/L				
Primary analysis*	2000.4 (1692.8 – 2363.9)	1647.9 (1380.1 – 1967.6)	1.21 (0.95 – 1.55)	0.12
Sensitivity analysis 1†	1978.3 (1683.6-2324.6)	1620.2 (1354.2-1938.5)	1.22 (0.96 – 1.55)	0.10
Sensitivity analysis 2‡	NA	NA	1.28 (1.04 – 1.56)	0.02
Sensitivity analysis 3∫	2164.4 (1824.8 – 2567.2)	1820.4 (1518.1 – 2183)	1.19 (0.93 – 1.53)	0.17
Geometric Mean AUC_{72} (95% CI) CK, U/L				
Primary model*	60395 (54185 - 67316)	50726 (44861 - 57358)	1.19 (1.01 – 1.40)	0.04
Sensitivity analysis 1†	60749 (5414 - 67699)	51168 (45232 - 57883)	1.19 (1.01 – 1.40)	0.04
Sensitivity analysis 2‡	NA	NA	1.20 (1.05 – 1.38)	0.007
Sensitivity analysis 3∫	69937 (62494 – 78266)	58760 (51891 – 66538)	1.19 (1.01 – 1.41)	0.04

NA denotes not applicable.

* Trapezoidal integration was used for the estimation of AUC_{72}. Data for patients with one or more missing biomarker assays were replaced by multiple imputation using the Markov Chain Monte Carlo (MCMC) method. Analyses were conducted on the log-transformed data, with comparisons obtained by back-transformation.

† Trapezoidal integration was used for the estimation of AUC_{72}, as per the primary analysis. For this sensitivity analysis, the imputation model included additional baseline covariates were associated with cTnI/CK release and missingness of data. The imputation model considered additional covariates as follows: age, gender, TIMI flow pre procedure, LAD culprit artery, symptom to intervention time and procedural success.

‡ A repeated measures analysis was used to estimate the overall profile of cTnI/CK release over the 72 hour window. All available biomarker data were analyzed using linear mixed-effects (LMM) regression with patient as a random effect together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects. For this analysis, the non-significant interaction term between treatment group and time of assay was removed from the model.

∫ Trapezoidal integration was used for the estimation of AUC_{72}, as per the primary analysis. Patients with one or more missing biomarker assays were replaced by linear interpolation and extrapolation.

Table S3. Spearman's rank correlation coefficient between derived endpoints*

	Peak CK	AUC_{72} CK	Peak cTnI	AUC_{72} cTnI
AUC_{72} CK	0.95	-	-	-
Peak cTnI	0.87	0.81	-	-
AUC_{72} cTnI	0.89	0.86	0.97	-
CMRI Infarct size	0.65	0.59	0.68	0.70

* All correlations are significant ($p<0.001$).

Table S4. Baseline characteristics of all randomized patients.*

Characteristic	Oxygen Arm N=312	No Oxygen Arm N=312	P-Value
Age in years, median (IQR)	63.5 (54.0, 73.0)	62.0 (53.0, 71.0)	0.28
Males, n (%)	240 (76.9)	242 (77.6)	0.85
Body mass index, median (IQR) †	27.4 (25.0, 31.0)	27.5 (24.7, 30.1)	0.80
Status on arrival of paramedics			
Heart rate, median (IQR)	76.0 (64.0, 88.0)	72.0 (62.0, 84.0)	0.28
Systolic blood pressure (mmHg), median (IQR)	130.0 (108.0, 150.0)	130.0 (110.0, 150.0)	0.57
Oxygen saturation (%), median (IQR)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)	0.50
Pain score, median (IQR)	6.0 (4.8, 8.0)	6.0 (4.0, 8.0)	0.17
Status on arrival at hospital			
Heart rate, median (IQR)	75.0 (64.0, 84.5)	74.0 (63.0, 84.0)	0.48
Systolic blood pressure (mmHg), median (IQR)	130.0 (118.3, 148.8)	130.0 (115.0, 145.0)	0.13
Oxygen saturation (%), median (IQR)	99.0 (99.0, 100.0)	98.0 (97.0, 99.0)	<0.001
Pain score, median (IQR)	2.0 (0.0, 4.0)	2.0 (0.5, 3.5)	0.77
Hospital diagnosis, n (%) ‡			
ST elevation myocardial infarction	220 (75.1)	227 (78.0)	0.41
Non-ST elevation myocardial infarction	11 (3.8)	13 (4.5)	0.66
Unstable angina	4 (1.4)	3 (1.0)	0.71
Pericarditis	9 (3.1)	6 (2.1)	0.44
Apical ballooning	4 (1.4)	8 (2.7)	0.24
Chest pain, non-specific	20 (6.8)	13 (4.5)	0.22
Arrhythmia	4 (1.4)	5 (1.7)	0.73
Syncope	6 (2.0)	7 (2.4)	0.77
Other	15 (5.1)	9 (3.1)	0.22
All-cause mortality during hospital admission, n (%)	5 (1.6)	11 (3.5)	0.13

IQR denotes interquartile range.

* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

Table S5. Baseline characteristics of randomized patients by enrolment criteria.*

Characteristic	All randomized patients N=624	Assessed for STEMI criteria on hospital arrival N=588	Confirmed STEMI on emergent coronary angiogram N=441
Age in years, median (IQR)	63.0 (54.0, 72.0)	63.0 (54.0, 72.0)	63.0 (54.0, 71.0)
Males, n (%)	482 (77.2)	457 (77.7)	348 (78.9)
Body mass index, median (IQR) †	27.4 (24.9, 30.8)	27.4 (24.9, 30.8)	27.5 (24.9, 30.9)
Status on arrival of paramedics			
Heart rate, median (IQR)	74.0 (62.5, 84.0)	74.0 (62.0, 84.5)	72.0 (60.0, 84.0)
Systolic blood pressure (mmHg), median (IQR)	130.0 (110.0, 150.0)	130.0 (110.0, 150.0)	130.0 (110.0, 150.0)
Oxygen saturation (%), median (IQR)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)
Pain score, median (IQR)	6.0 (4.0, 8.0)	6.0 (5.0, 8.0)	7.0 (5.0, 8.0)
Status on arrival at hospital			
Heart rate, median (IQR)	74.0 (64.0, 84.0)	74.0 (64.0, 84.0)	72.5 (64.0, 84.0)
Systolic blood pressure (mmHg), median (IQR)	130.0 (115.8, 146.0)	130.0 (116.3, 145.8)	130.0 (120.0, 148.0)
Oxygen saturation (%), median (IQR)	99.0 (99.0, 100.0)	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)
Pain score, median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	2.0 (1.0, 4.0)
Hospital diagnosis, n (%) ‡			
ST elevation myocardial infarction	447 (76.5)	443 (76.4)	441 (100.0)
Non-ST elevation myocardial infarction	24 (4.1)	24 (4.1)	0
Unstable angina	7 (1.2)	7 (1.2)	0
Pericarditis	15 (2.6)	15 (2.6)	0
Apical ballooning	12 (2.1)	12 (2.1)	0
Chest pain, non-specific	33 (5.7)	33 (5.7)	0
Arrhythmia	9 (1.5)	9 (1.6)	0
Syncope	13 (2.2)	13 (2.2)	0
Other	24 (4.1)	24 (4.1)	0
All-cause mortality during hospital admission, n (%)	16 (2.6)	15 (2.6)	14 (3.2)

IQR denotes interquartile range.

* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

Table S6. Baseline characteristics of patients included in the primary endpoint analysis and those excluded after randomization.*			
Characteristic	**Confirmed STEMI on emergent coronary angiogram N=441**	**Excluded after randomization N=183**	**P-Value**
Age in years, median (IQR)	63.0 (54.0, 71.0)	63.0 (50.0, 73.0)	0.86
Males, n (%)	348 (78.9)	134 (73.2)	0.12
Body mass index, median (IQR) †	27.5 (24.9, 30.9)	26.8 (24.4, 29.4)	0.30
Status on arrival of paramedics			
Heart rate, median (IQR)	72.0 (60.0, 84.0)	77.0 (66.0, 89.3)	0.003
Systolic blood pressure (mmHg), median (IQR)	130.0 (110.0, 150.0)	130.0 (110.0, 150.0)	0.36
Oxygen saturation (%), median (IQR)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)	0.60
Pain score, median (IQR)	7.0 (5.0, 8.0)	5.0 (1.0, 8.0)	<0.001
Status on arrival at hospital			
Heart rate, median (IQR)	72.5 (64.0, 84.0)	76.0 (64.0, 84.0)	0.41
Systolic blood pressure (mmHg), median (IQR)	130.0 (120.0, 148.0)	125.0 (111.3, 145.0)	0.06
Oxygen saturation (%), median (IQR)	99.0 (98.0, 100.0)	99.0 (98.0, 100.0)	0.61
Pain score, median (IQR)	2.0 (1.0, 4.0)	1.0 (0.0, 2.0)	<0.001
Hospital diagnosis, n (%) ‡			
ST elevation myocardial infarction	441 (100.0)	6 (4.2)	<0.001
Non-ST elevation myocardial infarction	0	24 (16.8)	<0.001
Unstable angina	0	7 (4.9)	<0.001
Pericarditis	0	15 (10.5)	<0.001
Apical ballooning	0	12 (8.4)	<0.001
Chest pain, non-specific	0	33 (23.1)	<0.001
Arrhythmia	0	9 (6.3)	<0.001
Syncope	0	13 (9.1)	<0.001
Other	0	24 (16.8)	<0.001
All-cause mortality during hospital admission, n (%)	14 (3.2)	2 (1.1)	0.13

SD denotes standard deviation; IQR, interquartile range.

* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

Table S7. Baseline characteristics and procedural details of patients with confirmed STEMI with and without CMRI data at six months follow-up.			
Characteristic	**Patients without MRI data N=302**	**Patients with MRI data N=139**	**P-Value**
Age in years, median (IQR)	64.0 (55.0, 74.0)	60.0 (53.0, 65.0)	<0.001
Males, n (%)	231 (76.5)	117 (84.2)	0.07
Body mass index, median (IQR)*	27.4 (24.7, 31.1)	27.7 (25.9, 30.7)	0.60
Previous IHD, n (%)	54 (17.9)	24 (17.3)	0.88
Diabetes mellitus, n (%)	59 (19.5)	19 (13.7)	0.13
Current or ex-smoker, n (%)	209 (69.9)	97 (69.8)	0.98
Status on arrival of paramedics			
Heart rate, median (IQR)	72.0 (60.0, 84.0)	72.0 (60.0, 84.0)	0.90
Systolic blood pressure, median (IQR)	130.0 (108.5, 150.0)	135.0 (110.0, 154.0)	0.51
Oxygen saturation, median (IQR)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)	0.11
Pain score, median (IQR)	7.0 (5.0, 8.0)	7.0 (5.0, 8.0)	0.59
Procedural details, n (%)			
LAD Culprit artery	101 (34.1)	55 (39.6)	0.27
Multi-vessel coronary disease	180 (59.8)	81 (58.3)	0.76
Pre-procedural TIMI flow 0/1	259 (88.7)	123 (88.5)	0.95
Post-procedural TIMI flow 0/1	12 (4.1)	1 (0.7)	0.06
Radial intervention	105 (35.0)	42 (30.2)	0.32
Stent implanted	270 (89.4)	133 (95.7)	0.03
Glycoprotein IIb/IIIa inhibitor	118 (39.1)	69 (49.6)	0.04
Thrombus aspiration	139 (46.0)	73 (52.5)	0.21
Length of stay (days), median (IQR)	4.0 (4.0, 5.0)	4.0 (3.0, 5.0)	0.09
Symptom-to-intervention time in minutes, median (IQR)	158.0 (127.0, 230.0)	156.0 (123.5, 219.8)	0.43
Geometric Mean Peak cTnI (95% CI), mcg/L	53.3 (45.3 – 62.7)	50.5 (40.5 – 62.9)	0.71
Geometric Mean Peak CK (95% CI), U/L	1719 (1530 – 1931)	1760 (1498 – 2066)	0.82

IHD denotes ischemic heart disease, TIMI thrombolysis in myocardial infarction, LAD left anterior descending, IQR interquartile range, CI confidence interval.

* Available in 280 of 441 patients.

Table S8. Paramedic treatment of patients with confirmed STEMI.			
	Oxygen Arm N=218	**No Oxygen Arm N=223**	**P-Value**
Status on arrival of paramedics			
Heart rate, median (IQR)	74.0 (61.0, 84.0)	72.0 (60.0, 80.3)	0.24
Systolic blood pressure (mmHg), median (IQR)	130.0 (105.0, 150.0)	130.0 (110.0, 150.0)	0.29
Oxygen saturation (%), median (IQR)	98.0 (97.0, 99.0)	98.0 (97.0, 99.0)	0.51
Pain score, median (IQR)	7.0 (5.0, 9.0)	7.0 (5.0, 8.0)	0.08
Status on arrival at hospital			
Heart rate, median (IQR)	75.0 (64.0, 86.0)	72.0 (62.5, 84.0)	0.32
Systolic blood pressure (mmHg), median (IQR)	130.0 (120.0, 148.0)	130.0 (118.0, 147.8)	0.45
Oxygen saturation (%), median (IQR)	100.0 (99.0, 100.0)	98.0 (97.0, 99.0)	<0.001
Pain score, median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.59
Oxygen being administered, n (%)	215 (99.5)	10 (4.5)	<0.001
Oxygen dose (L/min), median (IQR)	8.0 (8.0, 8.0)	4.0 (2.8, 8.0)	< 0.001
Morphine administered, n (%)	192 (89.3)	204 (91.5)	0.44
Morphine dose total (mg), median (IQR)	12.5 (8.0, 20.0)	11.3 (7.5, 15.0)	0.33
Fentanyl administered, n (%)	20 (9.3)	21 (9.4)	0.97
Fentanyl dose total (mcg), median (IQR)	137.5 (63.8, 218.8)	100.0 (80.0, 150.0)	0.45
Nitrates administered, n (%)	46 (21.3)	54 (24.2)	0.47
Nitrates dose total (mg), median (IQR)	0.6 (0.3, 1.3)	0.6 (0.3, 0.9)	0.44

IQR denotes interquartile range.

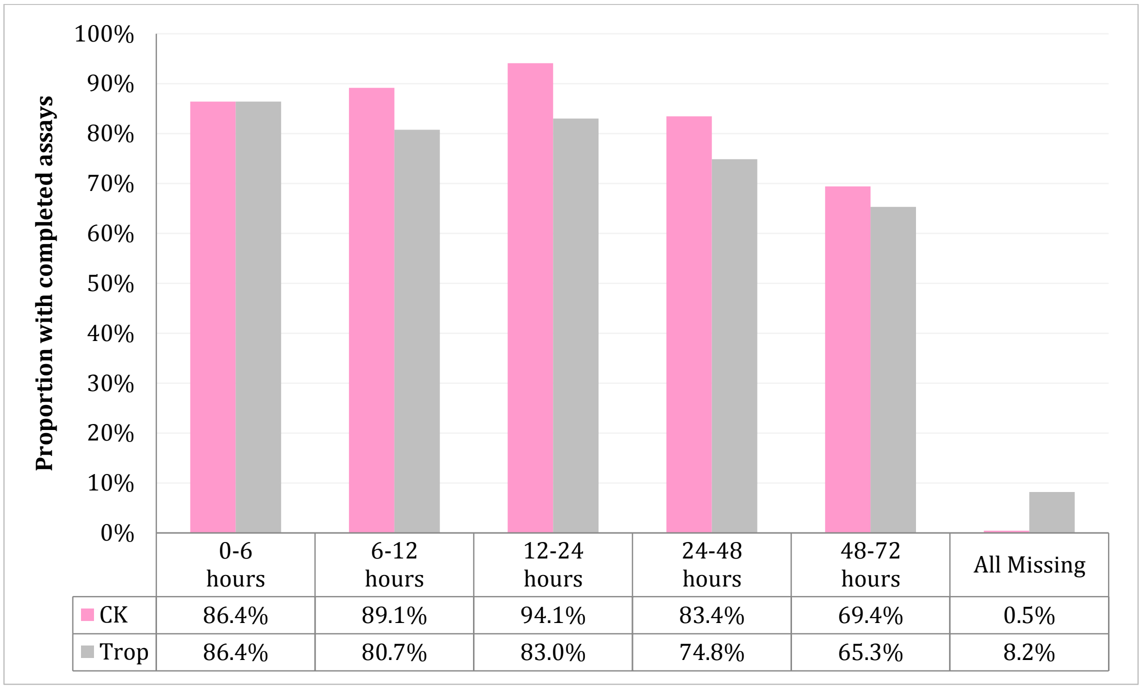
Table S9. Medical therapy at six months follow-up.

	Oxygen Arm N=218	No Oxygen Arm N=223	P-Value
Aspirin	172 (83.9)	181 (85.8)	0.59
Clopidogrel	84 (41.0)	82 (38.9)	0.66
Prasugrel	39 (19.0)	45 (21.3)	0.56
Ticagrelor	41 (20.0)	44 (20.9)	0.83
Aspirin + (Clopidogrel OR Prasugrel OR Ticagrelor)	151 (73.7)	159 (75.4)	0.69
Beta-blocker	161 (78.5)	171 (81.0)	0.52
Statin	182 (88.8)	182 (86.3)	0.44
ACE/ARB	166 (81.0)	169 (80.1)	0.82
Ca-channel blocker	10 (4.9)	9 (4.3)	0.77
Aldosterone antagonist	1 (0.5)	2 (0.9)	0.58
Diuretic	23 (11.2)	14 (6.6)	0.10
Anticoagulation	9 (4.4)	5 (2.4)	0.25

Table S10. Baseline characteristics and findings in 139 patients with confirmed STEMI undergoing cardiac magnetic resonance imaging (CMRI) at six months follow-up.			
Characteristic/measure	**Oxygen Arm N=65**	**No Oxygen Arm N=74**	**P-Value**
Age in years, mean (SD)	60.0 (10.7)	59.0 (9.9)	0.60
Males, n (%)	55 (84.6)	62 (83.8)	0.89
Body mass index, median (IQR)	26.8 (25.2, 30.8)	27.7 (24.8, 31.0)	0.90
Previous IHD, n (%)	12 (18.5)	12 (16.2)	0.73
LAD culprit artery, n (%)	27 (26.5)	55 (39.6)	0.43
Pre-procedural TIMI flow 0/1, n (%)	58 (89.2)	65 (87.8)	0.80
Post-procedural TIMI flow 0/1, n (%)	0	1 (1.4)	0.35
Symptom-to-intervention time in minutes, median (IQR)	147.0 (119.0, 221.5)	162.0 (129.0, 213.5)	0.32
Recurrent MI, n (%)	4 (6.2)	1 (1.4)	0.13
LV end diastolic volume, mean (SD)	180.4 (43.9)	178.1 (44.1)	0.75
LV end systolic volume, median (IQR)	84.3 (59.8, 108.1)	77.7 (56.9, 100.5)	0.34
LV stroke volume, mean (SD)	96.1 (21.8)	95.3 (20.8)	0.81
LV ejection fraction, mean (SD)	54.4 (9.5)	54.9 (10.0)	0.76
Pre-procedural TIMI flow 0/1	53.9 (9.7)	54.3 (9.8)	0.83
Pre-procedural TIMI flow 2/3	58.9 (6.9)	59.7 (10.9)	0.86
LAD culprit artery	52.7 (9.3)	52.8 (10.9)	0.96
Non-LAD culprit artery	55.8 (9.6)	56.2 (9.4)	0.85
Symptom to intervention ≤180mins	54.5 (9.9)	55.4 (9.3)	0.76
Symptom to intervention >180mins	54.2 (9.0)	55.0 (11.4)	0.80
Infarct size (grams), median (IQR)	20.3 (9.6, 29.6)	13.1 (5.2, 23.6)	0.04
Pre-procedural TIMI flow 0/1	20.7 (10.0, 31.4)	15.2 (6.3, 24.3)	0.06
Pre-procedural TIMI flow 2/3	16.2 (4.2, 25.0)	7.0 (2.3, 24.2)	0.64
LAD culprit artery	20.7 (10.6, 33.3)	20.1 (4.4, 632.3)	0.60
Non-LAD culprit artery	15.2 (7.4, 26.3)	10.6 (5.2, 18.9)	0.05
Symptom to intervention ≤180mins	20.3 (9.9, 29.1)	12.9 (6.2, 22.2)	0.10
Symptom to intervention >180mins	20.8 (8.2, 30.5)	13.1 (3.3, 25.8)	0.15
Infarct size (% of LV mass), median (IQR)	12.6 (6.7, 19.2)	9.0 (4.1, 16.3)	0.08
Pre-procedural TIMI flow 0/1	12.7 (6.9, 19.3)	9.5 (5.5, 16.3)	0.14
Pre-procedural TIMI flow 2/3	9.0 (3.4, 17.0)	5.9 (2.1, 14.1)	0.32
LAD culprit artery	13.5 (8.1, 21.0)	14.8 (3.3, 20.1)	0.64
Non-LAD culprit artery	11.9 (5.8, 17.2)	8.1 (4.1, 15.0)	0.13
Symptom to intervention ≤180mins	11.9 (6.3, 17.6)	9.4 (4.3, 16.2)	0.28
Symptom to intervention >180mins	12.8 (7.4, 20.4)	7.9 (2.5, 16.5)	0.13

LV denotes left ventricular, IHD ischemic heart disease, TIMI thrombolysis in myocardial infarction, LAD left anterior descending, IQR interquartile range, SD standard deviation, MI myocardial infarction.

Figure S1: Proportion of patients with completed biomarker assays for each time-point.



	0-6 hours	6-12 hours	12-24 hours	24-48 hours	48-72 hours	All Missing
CK	86.4%	89.1%	94.1%	83.4%	69.4%	0.5%
Trop	86.4%	80.7%	83.0%	74.8%	65.3%	8.2%

Figure S2. Proportion of patients receiving supplemental oxygen across study time points and treatment groups in patients with confirmed STEMI.

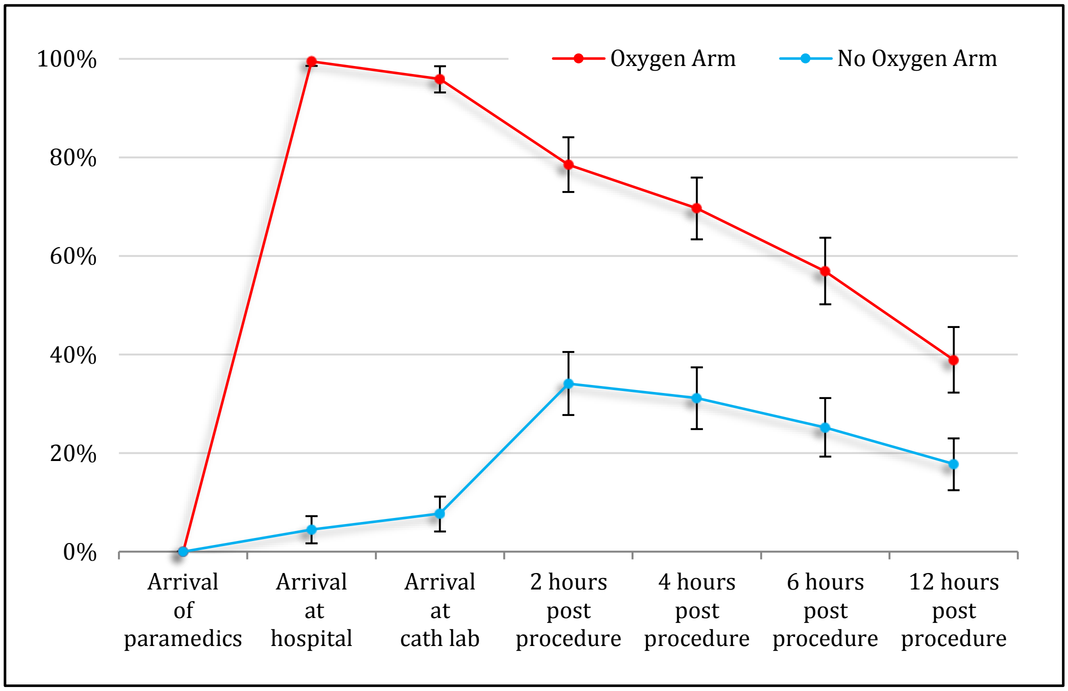


Figure S3. Geometric mean (95% CI) for peripheral blood oxygen saturation (SpO_2) across time points in patients with confirmed STEMI.

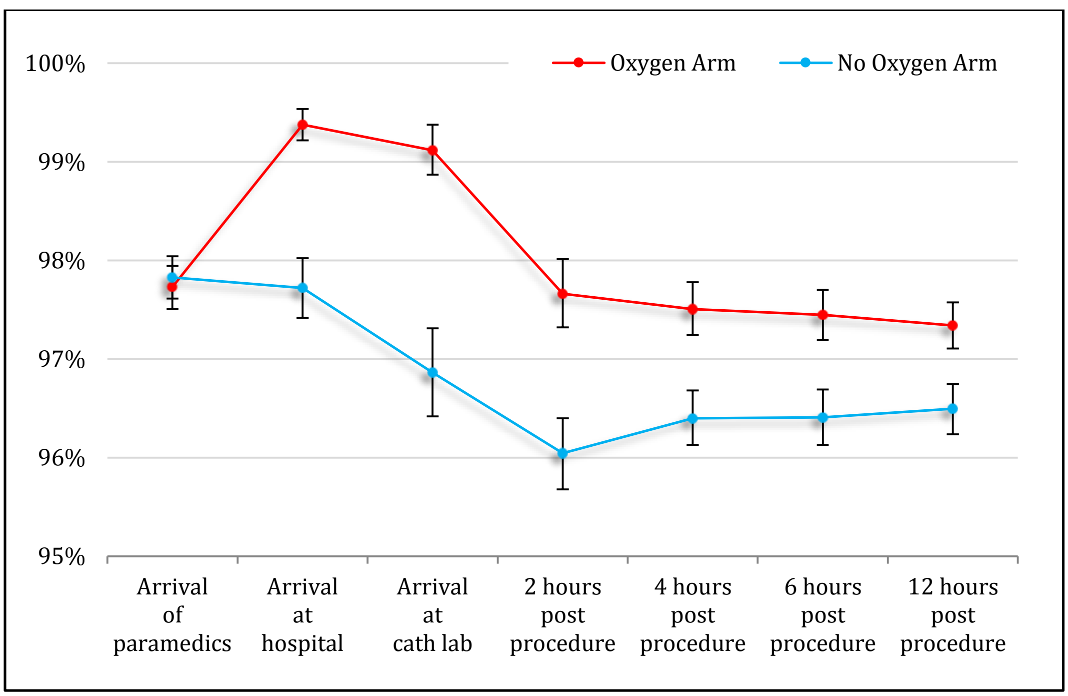
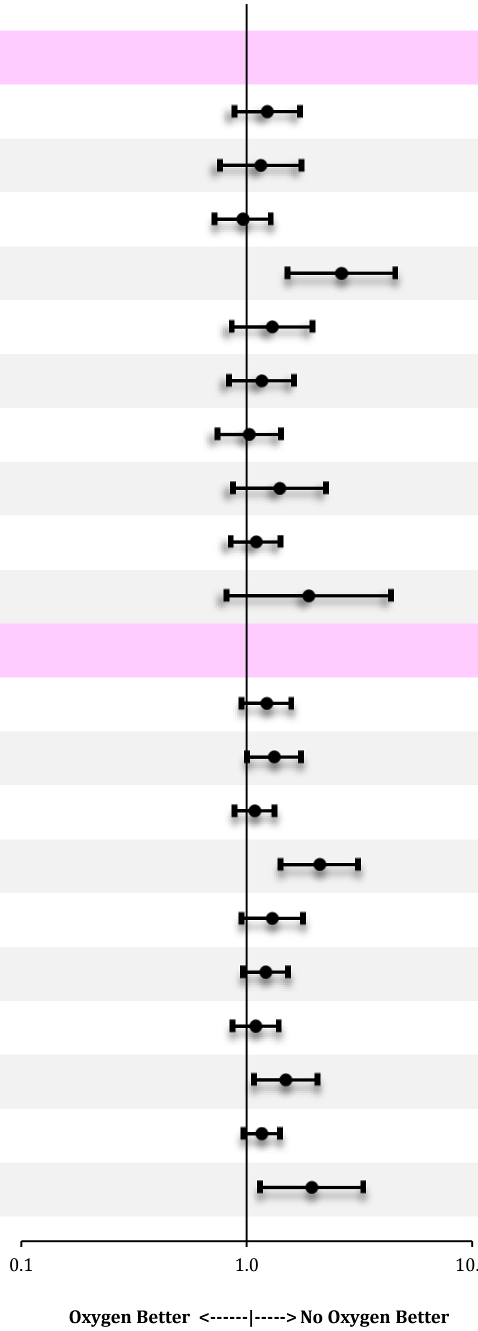


Figure S4: Ratio of geometric means (95% CI) for peak cTnI and peak CK release in patients with confirmed STEMI.

Characteristic	Sub-group	Ratio of means (Oxygen/No Oxygen)	P-value for interaction
Peak cTnI			
Age	< 65 years	1.24 (0.88 – 1.73)	0.81
	≥ 65 years	1.16 (0.76 – 1.76)	
Gender	Male	0.96 (0.72 – 1.29)	0.001
	Female	2.64 (1.52 – 4.57)	
Culprit Artery	LAD	1.30 (0.86 – 1.96)	0.69
	Non-LAD	1.17 (0.84 – 1.63)	
Symptom-to-intervention time	≤ 180 mins	1.03 (0.75 – 1.42)	0.29
	> 180 mins	1.40 (0.87 – 2.26)	
Pre-intervention TIMI flow	0 or 1	1.10 (0.85 – 1.42)	0.22
	2 or 3	1.89 (0.82 – 4.38)	
Peak CK			
Age	< 65 years	1.23 (0.95 – 1.58)	0.69
	≥ 65 years	1.33 (1.01 – 1.75)	
Gender	Male	1.09 (0.89 – 1.34)	0.003
	Female	2.11 (1.42 – 3.14)	
Culprit Artery	LAD	1.30 (0.95 – 1.78)	0.73
	Non-LAD	1.22 (0.97 – 1.53)	
Symptom-to-intervention time	≤ 180 mins	1.10 (0.87 – 1.39)	0.13
	> 180 mins	1.49 (1.08 – 2.07)	
Pre-intervention TIMI flow	0 or 1	1.17 (0.97 – 1.41)	0.07
	2 or 3	1.94 (1.15 – 3.30)	



TIMI denotes thrombolysis in myocardial infarction, LAD left anterior descending,

ST분절 상승 심근경색증 환자의 통상적인 치료 중 하나인 산소요법은 오히려 해로울 수 있다: AVOID 연구

신 준 한 교수 아주대학교병원 순환기내과

초록

배경

산소요법은 ST분절 상승 심근경색증(ST-segment elevation myocardial infarction, STEMI) 환자의 통상적인 치료 중 하나이지만, 기존의 일부 연구에서는 산소요법이 관상동맥의 수축을 유발하고 산화스트레스를 증강시켜서 심근손상을 악화시킬 가능성이 있다고 보고하였다.

방법 및 결과

본 연구는 다기관, 전향적, 무작위 치료군-대조군 연구로 응급 구조사가 출동한 현장에서 촬영한 심전도검사로 STEMI 진단을 받은 환자를 대상으로, 한 군은 안면마스크로 8L/min의 산소를 투여하였고, 다른 군은 산소를 투여하지 않았다. 총 638명의 환자 중 분석이 가능한 환자는 총 441명이었다. 일차종료점은 심근효소인 troponin I와 CK(creatine kinase)로 평가한 경색의 크기로 하였다. 이차종료점은 경색의 재발, 부정맥, 6개월째에 심장 MRI(magnetic resonance imaging)로 측정한 경색의 크기로 하였다.

산소투여군과 비투여군 간에 평균 최고 troponin I 농도는 차이가 없었다(57.4 vs. 48.0 μg/L; ratio, 1.20; 95% CI, 0.92-1.56; *P*=0.18). 그러나 평균 최고 CK는 산소투여군에서 유의하게 높았다(1,948 vs. 1,543 U/L; means ratio, 1.27; 95% CI, 1.04-1.52; *P*=0.01). 심근경색증의 재발률(5.5 vs. 0.9 %; *P*=0.006)과 부정맥의 발생(40.4 vs. 31.4 %; *P*=0.05)은 산소투여군에서 유의하게 높았다. 6개월째 경색의 크기 역시 산소투여군에서 의미 있게 컸다(20.3 vs. 13.1 g; *P*=0.04, 139명).

결론

저산소증이 없는 STEMI 환자에게 통상적인 산소요법을 사용하는 것은 조기 심근손상을 증가시키고 6개월째 경색의 크기를 증가시킨다.