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

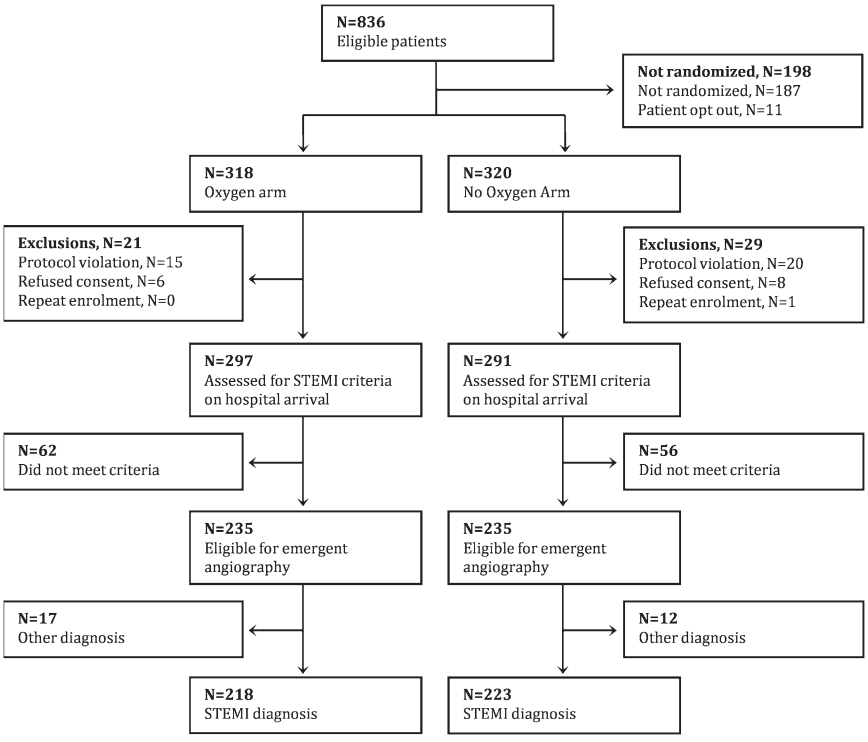

Figure 1. Patient selection and randomization flowchart. STEMI indicates ST-segment–elevation myocardial infarction.

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.

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.

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

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

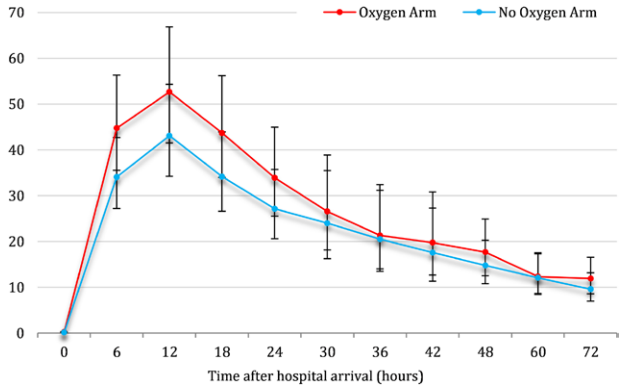

Figure 2. Geometric mean (95% confidence interval) for cardiac troponin I (cTnI) release (μg/L) over 72 hours in patients with confirmed ST-segment–elevation myocardial infarction. A repeated-measures analysis was used to estimate the overall profile of cTnI release over the 72-hour window. All available 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.

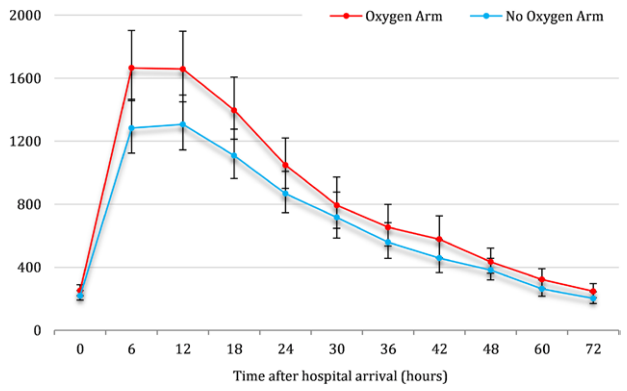

Figure 3. Geometric mean (95% confidence interval) for creatine kinase release (U/L) over 72 hours in patients with confirmed ST-segment–elevation myocardial infarction. A repeated-measures analysis was used to estimate the overall profile of CK release over the 72-hour window. All available biomarker 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.

References

1. Steele C. Severe angina pectoris relieved by oxygen inhalations. *BMJ*. 1900;2:1568.
2. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation*. 1975;52:360–368.
3. Kelly RF, Hursey TL, Parrillo JE, Schaer GL. Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion. *Am Heart J*. 1995;130:957–965.
4. Madias JE, Madias NE, Hood WB Jr. Precordial ST-segment mapping, 2: effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. *Circulation*. 1976;53:411–417.
5. Stavitsky Y, Shandling AH, Ellestad MH, Hart GB, Van Natta B, Messenger JC, Strauss M, Dekleva MN, Alexander JM, Mattice M, Clarke D. Hyperbaric oxygen and thrombolysis in myocardial infarction: the "HOT MI" randomized multicenter study. *Cardiology*. 1998;90:131–136.
6. O'Neill WW, Martin JL, Dixon SR, Bartorelli AL, Trabattoni D, Oemrawsingh PV, Atsma DE, Chang M, Marquardt W, Oh JK, Krucoff MW, Gibbons RJ, Spears JR; AMIHOT Investigators. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50:397–405. doi: 10.1016/j.jacc.2007.01.099.
7. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Beasley R. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J*. 2009;158:371–377. doi: 10.1016/j.ahj.2009.05.037.
8. Kenmure AC, Murdoch WR, Beattie AD, Marshall JC, Cameron AJ. Circulatory and metabolic effects of oxygen in myocardial infarction. *Br Med J*. 1968;4:360–364.
9. McNulty PH, Robertson BJ, Tulli MA, Hess J, Harach LA, Scott S, Sinoway LI. Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. *J Appl Physiol (1985)*. 2007;102:2040–2045. doi: 10.1152/japplphysiol.00595.2006.
10. Mak S, Azevedo ER, Liu PP, Newton GE. Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. *Chest*. 2001;120:467–473.
11. Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. 2010;6:CD007160.
12. Ranchord AM, Argyle R, Beynon R, Perrin K, Sharma V, Weatherall M, Simmonds M, Heatlie G, Brooks N, Beasley R. High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: a pilot randomized controlled trial. *Am Heart J*. 2012;163:168–175. doi: 10.1016/j.ahj.2011.10.013.
13. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ,

Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425. doi: 10.1161/CIR.0b013e3182742cf6.

14. Beasley R, Aldington S, Weatherall M, Robinson G, McHaffie D. Oxygen therapy in myocardial infarction: an historical perspective. *J R Soc Med*. 2007;100:130–133. doi: 10.1258/jrsm.100.3.130.
15. Stub D, Smith K, Bernard S, Bray JE, Stephenson M, Cameron P, Meredith I, Kaye DM; AVOID Study. A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Verses Oxygen In myocarDial infarction study (AVOID Study). *Am Heart J*. 2012;163:339–345.e1. doi: 10.1016/j.ahj.2011.11.011.
16. O'Driscoll BR, Howard LS, Davison AG, British Thoracic S. BTS guideline for emergency oxygen use in adult patients. *Thorax*. 2008;63(suppl 6):vi1–vi68.
17. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10:585–598.
18. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399. doi: 10.1002/sim.4067.
19. Morris TP, Kahan BC, White IR. Choosing sensitivity analyses for randomised trials: principles. *BMC Med Res Methodol*. 2014;14:11. doi: 10.1186/1471-2288-14-11.
20. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1:1121–1123.
21. Ukholkina GB, Kostianov IIu, Kuchkina NV, Grendo EP, Gofman IaB. Effect of oxygenotherapy used in combination with reperfusion in patients with acute myocardial infarction [in Russian]. *Kardiologiia*. 2005;45:59.
22. Chia S, Senatore F, Raffel OC, Lee H, Wackers FJ, Jang IK. Utility of cardiac biomarkers in predicting infarct size, left ventricular function, and clinical outcome after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2008;1:415–423. doi: 10.1016/j.jcin.2008.04.010.
23. Atar D. Should oxygen be given in myocardial infarction? *BMJ*. 2010;340:c3287.
24. Kones R. Oxygen therapy for acute myocardial infarction—then and now: a century of uncertainty. *Am J Med*. 2011;124:1000–1005. doi: 10.1016/j.amjmed.2011.04.034.
25. Reinhart K, Bloos F, König F, Bredle D, Hannemann L. Reversible decrease of oxygen consumption by hyperoxia. *Chest*. 1991;99:690–694.
26. Wilson AT, Channer KS. Hypoxaemia and supplemental oxygen therapy in the first 24 hours after myocardial infarction: the role of pulse oximetry. *J R Coll Physicians Lond*. 1997;31:657–661.
27. Hofmann R, James SK, Svensson L, Witt N, Frick M, Lindahl B, Östlund O, Ekelund U, Erlinge D, Herlitz J, Jernberg T. DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial. *Am Heart J*. 2014;167:322–328. doi: 10.1016/j.ahj.2013.09.022.
28. Joint Royal Colleges Ambulance Liaison Committee, Ambulance Service Association. *UK Ambulance Service Clinical Practice Guidelines (2006)*. 2006. http://www.jrcalc.org.uk/guidelines.html. Accessed May 5, 2015.
29. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Beasley R. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J*. 2009;158:371–377. doi: 10.1016/j.ahj.2009.05.037.
30. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1:1121–1123.
31. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, Andron M, Appleby C, Fisher M, Khand A, Kunadian B, Mills JD, Morris JL, Morrison WL, Munir S, Palmer ND, Perry RA, Ramsdale DR, Velavan P, Stables RH; HEAT-PPCI Trial Investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014;384:1849–1858. doi: 10.1016/S0140-6736(14)60924-7.
32. Shaw D. HEAT-PPCI sheds light on consent in pragmatic trials. *Lancet*. 2014;384:1826–1827. doi: 10.1016/S0140-6736(14)61040-0.
33. Bøtker HE, Kharbanda R, Schmidt MR, Bøttcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet*. 2010;375:727–734. doi: 10.1016/S0140-6736(09)62001-8.
34. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med*. 2014;371:1016–1027. doi: 10.1056/NEJMoa1407024.

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%.