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Effect of cumulative oxygen exposure on myocardial injury following ST-elevation myocardial infarction: results from the AVOID trial.

Running title: Effect of oxygen therapy on myocardial injury

Ziad Nehme *BEmergHlth(Hons)* ^{*†‡}, Dion Stub *MBBS PhD* ^{§||}, Stephen Bernard *MBBS MD* ^{*†§}, Michael Stephenson *BHlthSc GradDip(MICA)* ^{*}, Janet E. Bray *PhD* [†], Peter Cameron *MBBS MD* ^{†§}, Ian T. Meredith *MBBS PhD* ^{†¶}, Bill Barger *MACAP* ^{*}, Andris H. Ellims *MBBS PhD* ^{§||}, Andrew J. Taylor *MBBS PhD* ^{§||}, David M. Kaye *MBBS PhD* ^{†§||}, and Karen Smith *BSc PhD* ^{*†#},
for the AVOID Investigators ^{††}.

^{*} Ambulance Victoria, Melbourne, Australia; [†] Monash University, Melbourne, Australia; [§] The Alfred Hospital, Melbourne, Australia; ^{||} Baker IDI Heart Diabetes Institute, Melbourne, Australia; [¶] Monash Medical Centre, Melbourne, Australia; [#] University of Western Australia, Western Australia, Australia;

^{††} See Supplementary Appendix for a full list of AVOID Investigators.

‡ Address for correspondence:

Ziad Nehme
Department of Research and Evaluation
Ambulance Victoria
31 Joseph Street
Blackburn North
Victoria 3130, Australia.
T: +61 3 9896 6083
F: +61 3 9011 7739
E: ziad.nehme@ambulance.vic.gov.au

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Abstract

Background

While routine supplemental oxygen therapy may increase myocardial injury following ST-elevation myocardial infarction (STEMI), the effect of the dose and duration of oxygen exposure on myocardial injury remains unclear.

Objectives

To evaluate the effect of cumulative oxygen exposure on myocardial injury after STEMI

Methods

This was a prospectively defined sub-study of the multicenter, prospective, randomized, controlled trial, of 441 STEMI patients who were allocated to routine oxygen therapy (8L/min via facemask) or no supplemental oxygen. The primary endpoint was myocardial infarct size as assessed by cardiac enzymes, troponin (cTnI) and creatine kinase (CK). Oxygen therapy was commenced after randomization by paramedics, and continued for up to 12 hours post procedural intervention in hospital. Cumulative oxygen exposure was calculated as the area under the dose*time curve (AUC) for oxygen administration over the first 12 hours, and then assessed for its association with cTnI/CK release using multivariable linear regression.

Results

After adjustment for potential confounders, every 100 liter increase in supplemental oxygen exposure was associated with a 1.4% (95% CI: 0.6%-2.2%, $p<0.001$) and 1.2% (95% CI: 0.7%-1.8%, $p<0.001$) increase in the mean peak cTnI and CK respectively. Excluding patients who developed cardiogenic shock, recurrent myocardial infarction or desaturations ($SpO_2 < 94\%$) during admission, every 100 liter increase in oxygen exposure was associated with a 1.2% (95% CI: 0.2%-2.1%, $p=0.01$) increase in the mean peak cTnI and a 1.0% (95% CI: 0.4%-1.7%, $p=0.003$) increase in the mean peak CK.

Conclusion

Every liter of supplemental oxygen administered in the first 12 hours after STEMI was associated with a small but significant rise in cTnI and CK. Monitoring the dose and duration of oxygen administration could help limit further myocardial injury in patients with STEMI.

Key Words

Myocardial Infarction; oxygen inhalation therapy; air; randomised controlled trials

Abbreviations

AMI, acute myocardial infarction; AUC, area under the curve; AVOID, Air Versus Oxygen In myocarDial infarction; CK, creatine kinase; CMR, cardiac magnetic resonance imaging; cTnI, troponin I; ECG, electrocardiography; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Introduction

~~In spite of routine clinical practice, the use of~~ Although several studies of supplemental oxygen therapy ~~in patients suffering acute myocardial infarction (AMI) has recently been associated with~~ have indicated the presence of deleterious physiological and clinical outcomes, ~~its use remains common in routine clinical practice for patients suffering acute myocardial infarction (AMI). Recently, in a recent analysis of~~ the multicenter, prospective, randomized, Air Versus Oxygen in myocardial infarction (AVOID) controlled trial, normoxic ~~ST-elevation myocardial infarction (STEMI)-patients~~ with ST-elevation myocardial infarction (STEMI) randomized to routine supplemental oxygen experienced a significant increase in myocardial injury compared to patient's breathing room air (1). The findings come almost four decades after Rawles and Kenmure demonstrated in a double-blind randomized controlled trial that inhaled oxygen therapy increased myocardial injury in patients with AMI compared with breathing compressed air (2). Furthermore, supportive data from smaller physiological studies also show that supplemental oxygen may reduce coronary perfusion and heighten oxidative stress (3-6).

The threshold ~~for at~~ which oxygen therapy ~~could~~ begins to increase myocardial injury following AMI remains unclear. To date, both the dose and duration of treatment of oxygen therapy has varied considerably across clinical studies. Earlier physiological studies have opted for relatively high concentrations of supplemental oxygen of 10 to 15 liters per min (L/min) delivered in short periods of time (7), a practice which varies from those adopted in contemporary clinical trials (8-10). In the AVOID trial, patients randomized to the oxygen group received oxygen therapy at 8 L/min via facemask in the prehospital setting, while in-hospital oxygen use was indexed to local hospital protocols (9). This resulted in heterogeneous oxygen administration which reflects real-world utility of oxygen therapy in the setting of AMI.

It is not known whether the deleterious effects of oxygen therapy in AMI are dependent on the dose and duration of its administration. In this sub-study of the AVOID trial, we evaluate the effect of cumulative oxygen exposure on biochemical and radiological measures of myocardial injury in patients with STEMI.

Methods

Design, setting, and participants

The AVOID trial randomised 638 prehospital suspected STEMI patients between October 2011 and July 2014, who were transferred to 9 percutaneous coronary intervention (PCI) capable hospitals in Melbourne, Australia. The trial design was registered with clinicaltrials.gov (NCT01272713) and details of the design, protocol, and main trial results have been published previously (1,11). The collection and use of trial data was approved by the Alfred Health Human Research Ethics Committee and nine reviewing ethics and governance committees across participating hospitals.

Patients were randomised by paramedics according to the following criteria: Age ≥ 18 years; Chest pain symptoms < 12 hours prior; prehospital electrocardiography (ECG) evidence of STEMI, including: 1) ST-segment elevation of ≥ 0.1 mV in two contiguous limb leads, or 2) ≥ 0.2 mV in two contiguous chest leads, or 3) new left bundle branch block pattern. The key exclusion criteria were hypoxaemia on room air ($SpO_2 < 94\%$ measured on pulse oximeter), oxygen administration prior to randomization, altered conscious state, or planned transport to a non-participating hospital. The intention-to-treat analysis included 441 patients with confirmed STEMI following emergent coronary angiogram.

Randomization and interventions

Patients were randomly assigned to the oxygen and no oxygen treatment groups using opaque envelopes concealing treatment assignment. In the oxygen group, paramedics administered supplemental oxygen via face mask at 8 L/min, which continued to arrival at hospital. After hospital arrival, oxygen administration continued according to hospital treatment protocols. In the no oxygen group, patients received no supplemental either prehospital or in-hospital unless their oxygen saturations fell below 94%. Oxygen was then indicated to maintain a target oxygen saturation of 94%. Details of oxygen use were recorded in the case report form at regular intervals, including at randomization, at hospital arrival, at the catheterization laboratory, and at two hourly intervals thereafter up to 12 hours post procedural intervention. Individuals involved with the delivery of oxygen therapy pre-hospital and in-hospital were not blinded to treatment assignment, due to the impracticality and potential risk of concealing oxygen treatment.

Study outcomes

Definitions of the endpoints used in the AVOID trial have been published in the supplementary appendix of the main trial (1). The AVOID trial utilized highly correlated co-primary endpoints of peak cTnI and CK. To obtain a comprehensive picture of the treatment effect, the area under the curve (AUC_{72}) for cTnI and CK concentration in serum for the first 72 hours were also measured. Blood sampling was conducted at baseline and then six hourly for the first 24 hours and 12 hourly out to 72 hours after admission. Secondary endpoints measured at hospital discharge and 6 months, included ECG ST-segment resolution; mortality, and; major adverse cardiac events (death, recurrent myocardial infarction, repeat revascularization and stroke). At 6 months, a contrast enhanced cardiac magnetic resonance imaging (CMR) scan was offered to all patients who were agreeable to travel to the core site for scanning and had no contraindications for CMR. Data on CMR infarct size was available for a total of 139 (31.5%) patients.

Statistical analysis

All statistical analyses were performed using IBM® SPSS® Statistics 21. The primary analysis was performed on 441 patients with confirmed STEMI following emergent coronary angiogram. Oxygen exposure in liters was calculated using trapezoidal integration for the area under the dose*time curve over the first 12 hours. We used spearman rank correlations to compare the

relationships between myocardial injury and varying measures of supplemental oxygen exposure (see Table 2 in supplementary appendix). The cumulative oxygen exposure between baseline and 12 hours (AUC_{12}) had the strongest correlation with measures of myocardial injury and was used for all analyses.

For the comparison of baseline characteristics, procedural details and clinical outcomes, we stratified patients into equal tertiles on the basis of cumulative supplemental oxygen exposure (AUC_{12}). The final groups included patients with: no supplemental oxygen exposure ($n=128$); low supplemental oxygen exposure of between 1 and 1160 liters ($n=105$); moderate supplemental oxygen exposure of between 1161 and 2376 liters ($n=104$), and; high supplemental oxygen exposure of > 2376 liters ($n=104$). As an example, high oxygen exposure was equivalent to receiving at least 8 L/min of supplemental oxygen therapy for approximately 5 hours. Variables that approximated a normal distribution were summarized as mean $\pm$ SD, and groups compared using ANOVA. Non-normal variables were represented as median and first and third quartiles (Q1, Q3), and groups were compared using the Wilcoxon rank sum test. Binomial variables were expressed as proportions and 95% confidence intervals (CI) and groups compared using χ^2 tests.

To estimate the total cTnI and CK release in the first 72 hours we used trapezoidal integration of area under the curve (AUC_{72}). Missing biomarker assays were replaced with multiple imputation using the Markov Chain Monte Carlo method (12,13). The adjusted effect of AUC_{12} cumulative oxygen exposure on biochemical measures of myocardial injury (peak and AUC_{72} cTnI/CK) were assessed using linear regression models. The models were adjusted for additional covariates which were known predictors of myocardial injury: age, gender, pre- and post-intervention TIMI flow, killip class, culprit artery, and symptom-to-intervention time (14). Radiological measures of infarct size assessed by CMR at 6-months (infarct mass in grams and infarct size as a proportion of left ventricular mass) were assessed using the same method. All analyses were carried out using log-transformed outcome data with comparison of the treatment effect obtained after back-transformation.

To assess the potential impact of selection bias, we constructed a series of sensitivity analyses by excluding sub-groups which could confound the treatment effect, including: 1) patients randomized to the no oxygen arm; 2) patients with a desaturation ($SpO_2 < 94\%$) recorded at any time in the first 12 hours; 3) patients who developed cardiogenic shock, recurrent myocardial infarction or a desaturation ($SpO_2 < 94\%$), and; 4) patients with any adverse clinical outcome during admission.

Results

Study population

Study flow and patient selection is shown in Figure 1 of the supplementary appendix. A total of 441 patients with confirmed STEMI after emergency coronary angiogram were analyzed for primary endpoint data. Of the 223 patients randomized to the no oxygen group, 102 (45.7%) patients received oxygen at some stage in the first 12 hours post randomization, including 46 patients with evidence of hypoxaemia ($\text{SpO}_2 < 94\%$) and 56 patients with no documented hypoxaemia. All 218 patients randomized to the oxygen group received oxygen therapy. Figure 1 shows the distribution of cumulative oxygen exposure (AUC_{12}) for the first 12 hours in the overall population and by treatment arms. The median cumulative oxygen exposure was 1746 liters (IQR: 960 to 2858) in the overall population, but was higher in patients randomized to the oxygen group compared to the no oxygen group (2258 liters vs. 960 liters, $p < 0.001$).

Baseline and procedural characteristics

With the exception of dyslipidemia, demographics and past medical history did not differ significantly after stratification of patients into cumulative oxygen exposure groups (Table 1). Patients with high oxygen exposure described higher baseline pain scores, but had similar findings with respect to the extent of coronary artery disease and procedural details (Table 2). Both symptom-to-intervention time and door-to-intervention did not differ between groups. Length of hospital stay was higher in patients with high oxygen exposure ($p < 0.001$).

Adverse clinical outcomes

Table 3 shows the adverse clinical outcomes experienced at hospital discharge and 6 months follow-up. At hospital discharge, recurrent myocardial infarction, cardiogenic shock, major bleeding and arrhythmias were experienced more frequently in patients receiving oxygen, with the highest proportion of events occurring in the high oxygen exposure group. The median time to recurrent myocardial infarction after admission was 2 days (IQR: 1-4). With the exception of recurrent myocardial infarction, adverse outcomes at 6 months were similar across groups.

Unadjusted relationship between oxygen exposure and myocardial injury

The distribution of biochemical measures of myocardial injury across oxygen exposure groups are shown in Figure 2. The difference in the unadjusted geometric mean peak/ AUC_{72} for cTnI and CK was statistically significant across oxygen exposure groups.

Adjusted relationship between oxygen exposure and myocardial injury

The effect of every 100 liters of supplemental oxygen exposure on biochemical and radiological measures of myocardial injury are described in Table 4. After adjustment for potential confounders of myocardial injury, every 100 liters of oxygen exposure was associated with a 1.4% (95% CI: 0.6%-2.2%, $p < 0.001$) and 1.2% (95% CI: 0.7%-1.8%, $p < 0.001$) increase in the geometric mean peak cTnI and CK respectively. Similar estimates for the increase in AUC_{72} cTnI and AUC_{72} CK release were also found. A 1.2% (95% CI: 0.1%-2.3%, $p = 0.03$) increase in the geometric CMR infarct mass and a 0.9% (95% CI: -0.05%-1.9%, $p = 0.06$) increase in the infarct size as a proportion of left ventricular mass was observed in a sub-group of 139 patients undergoing a 6-month CMR.

For the sensitivity analyses, excluding sub-groups which could potentially confound the treatment effect resulted in a slight diminution of the treatment effect (Table 4). In patients randomised to the oxygen group, the effect of every 100 liters of supplemental oxygen exposure was exposure was associated with a 1.4% (95% CI: 0.2%-2.7%, $p = 0.02$) increase in the geometric mean peak cTnI and a 1.0% (95% CI: 0.2%-1.9%, $p = 0.02$) increase in the geometric mean peak CK. Similarly, after excluding patients who developed cardiogenic shock, recurrent myocardial infarction or desaturations ($\text{SpO}_2 < 94\%$) during admission, every 100 liters of

supplemental oxygen exposure was associated with a 1.2% (95% CI: 0.2%-2.1%, p=0.01) increase in the geometric mean peak cTnI and a 1.0% (95% CI: 0.4%-1.7%, p=0.003) increase in the geometric mean peak CK. Excluding all patients with any adverse outcome at hospital discharge resulted in similar findings (data not shown).

Discussion

In this sub-study of the AVOID trial, we examined the effect of cumulative oxygen exposure on biochemical and radiological measures of myocardial injury in patients with STEMI. Our measure of oxygen exposure accounts for both the dose and duration of oxygen treatment, and has been evaluated in previous clinical studies (15,16). The area under the 12 hour oxygen dose*time curve was strongly correlated with measures of myocardial injury, and performed better than peri-interventional measures of oxygen exposure which only account for oxygen supplementation in the early stages of reperfusion. These observations suggest that increases in myocardial injury in relation to oxygen exposure are cumulative over the duration of treatment, and not necessarily related to reperfusion. This may explain why Rawles and Kenmure also demonstrated an elevated signal for myocardial injury in patients exposed to oxygen therapy for 24 hours after AMI without reperfusion (17).

There are several known mechanisms which could help explain why myocardial injury worsens with cumulative oxygen exposure. Since the early 1980s, oxygen-derived free radicals have been implicated in the pathogenesis of reperfusion injury, with studies showing that a sudden “burst” of oxygen free radical production shortly after reperfusion can promote further tissue damage and arrhythmias (18). In lung epithelium, the formation of reactive oxygen species increases rapidly after exposure to hyperoxia, but returns to pre-treatment levels within 30 minutes of oxygen cessation (19). The intensity of free radical production is also highly attenuated by the fraction of inspired oxygen, with higher doses of oxygen being exponentially associated with the production of reactive oxygen species (19,20). Supranormal arterial oxygen tension is also associated with a number of cardiovascular responses including a reduction in coronary blood flow and myocardial oxygen consumption, and an increase in coronary vascular resistance (7). Several studies have postulated that reactive oxygen species are responsible for the coronary vasoconstriction induced under hyperoxic conditions (21). Although intravenous injection with an antioxidant can rapidly reverse and prevent coronary vasoconstriction during hyperoxia (22), the effect may also be self-limiting after the normalization of blood oxygen tension (23).

Although the AVOID trial was not powered to detect differences in adverse clinical outcomes, there may be some evidence that oxygen increases the frequency of arrhythmias and recurrent myocardial infarctions after STEMI (1). In this sub-study, the frequency of arrhythmias and recurrent myocardial infarctions were highest in patients with high oxygen exposure. It ~~is~~ is not clear ~~if whether~~ the differences in adverse outcomes were the direct result of oxygen administration, or whether the presence of adverse outcomes influenced a greater use of oxygen by medical staff. Importantly, many of the adverse outcomes occurred outside the 12 hour oxygen administration period. In fact, almost 75% of recurrent myocardial infarctions occurred at least 2 days after admission. The rate of recurrent myocardial infarctions at 6 months follow-up also remained higher in the high oxygen exposure group compared to other groups. Furthermore, the results of our analyses were not significantly altered after the exclusion of patients whose adverse outcomes may have confounded the treatment effect.

Our results have important implications for the interpretation of results from oxygen studies in AMI. Unlike other clinical trials which assigned a standard dose of oxygen supplementation up to 24 hours after randomization of patients into the oxygen arm (8,10,17), the AVOID trial indexed oxygen dosing to local hospital protocols (9). The result was a highly heterogeneous oxygen exposure profile which rarely results in a patient receiving moderate to high concentrations of oxygen for 12 hours. For instance, a dose of 6 L/min delivered over 12 hours would yield a cumulative oxygen exposure of 4320 liters, which was only achieved by 5% of patients in our study, or 9% of patients randomized to the oxygen arm. This may suggest that patients are being weaned from moderate to high concentrations of oxygen soon after coronary intervention, and this reflects contemporary clinical practice in our region. Comparing these

findings to other trials is difficult because the frequency of cross-over between groups has not been reported in previous clinical trials (8,17).

What remains difficult to determine is what target oxygen saturation range is optimal for patients who experience desaturations during treatment. In the AVOID trial, as many as 46% of patients in the no oxygen group received oxygen in the first 12 hours. Although some patients were not indicated to receive oxygen therapy according to protocol, many experienced low range desaturations of 90-93% on pulse oximeter. It ~~is~~ is not yet known whether a lower oxygen saturation threshold of 90% can be utilized safely in patients with AMI, and is currently being evaluated by the Swedish-based clinical trial DETO2X-AMI (10). However, unlike recent clinical trials (1,8), an optimal oxygen saturation target after the development of hypoxemia has not been stated in the DETO2X-AMI trial, and this could create further uncertainty regarding the right approach to oxygen treatment.

Is it worth adding comment about the potential adverse effects of adding routine oxygen therapy peri/post routine PCI or PCI in other ACS – effects on CBF etc ?Dion

Limitations

The AVOID trial reported several limitations with respect to blinding of treatment, missing biomarker data, and the limited application of CMR scanning of infarct size (1). In our study, 8.2% of patients had missing cTnI assays and 0.5% had missing CK assays, which could not be imputed for the analysis. Although we attempted to limit the possibility of selection bias, it is not clear whether our sensitivity analyses and covariate adjustments completely account for illness severity factors which could lead to the administration of oxygen. Importantly, excluding patients with any adverse clinical outcome during admission (i.e. the “complicated” STEMIs) did not affect the impact of oxygen exposure on myocardial injury. Our CMR scans were completed in a small number of patients, and due to feasibility constraints we could not perform early CMR scans to consider other index measures of myocardial injury such as myocardial salvage and infarct size as a proportion of area at risk. Finally, we did not collect measures of arterial oxygen tension during admission and we are therefore unable to show how cumulative oxygen exposure is related to arterial oxygen tension.

Conclusion

In this sub-study of the AVOID trial, every liter of oxygen administered in the first 12 hours after STEMI was associated with a small but significant rise in cTnI and CK release. Monitoring the dose and duration of oxygen administration could help limit further myocardial injury in patients with STEMI. Efforts should now be focused on titrating oxygen therapy during treatment and identifying optimal oxygen saturation targets for patients with AMI.

Perspectives

Competency in medical knowledge

The use of routine oxygen therapy for uncomplicated STEMI is not recommended by American Heart Association treatment guidelines. Results from the AVOID trial suggest that routine supplemental oxygen may be associated with increased myocardial injury and poorer clinical outcomes after STEMI.

Competency in patient care

Routine supplemental oxygen can be withheld in normoxic STEMI patients without risk of adverse clinical outcomes. Patients who develop hypoxia during prehospital or in-hospital care should receive supplemental oxygen therapy titrated to normal or near-normal blood oxygen saturation levels.

Translational outlook

Further research is required to determine the optimal blood oxygen saturation target in hypoxic STEMI patients. The effect of routine oxygen therapy on mortality is currently being investigated by a Swedish-based registry trial DETO2X-AMI.

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Figure legends

- Figure 1: Frequency distribution for cumulative oxygen exposure (liters of oxygen) in the overall population and by treatment arm.
- Figure 2: Distribution of biochemical measures (cTnI/CK) across oxygen exposure groups. Black lines represent geometric mean peaks. P-values calculated using one-way ANOVA for the difference in log-transformed means.

Tables

Table 1. Baseline characteristics of patients with confirmed STEMI					
Characteristic	No oxygen exposure N= 128	Low oxygen exposure N= 105	Moderate oxygen exposure N= 104	High oxygen exposure N= 104	p-value
Age in years, mean (SD)	61 (12)	63 (13)	63 (12)	64 (12)	0.23
Males, n (%)	103 (80.5)	76 (72.4)	83 (79.8)	86 (82.7)	0.28
Past history and risk factors, n (%)					
Diabetes mellitus	18 (14.1)	25 (23.8)	21 (20.2)	14 (13.5)	0.13
Hypertension	64 (50.0)	66 (62.9)	59 (56.7)	64 (61.5)	0.18
Dyslipidemia	59 (46.1)	64 (61.0)	49 (47.1)	67 (64.4)	0.008
Current or ex-smoker	95 (74.8)	74 (70.5)	65 (63.7)	72 (69.2)	0.34
Peripheral vascular disease	4 (3.1)	4 (3.8)	1 (1.0)	6 (5.8)	0.29
Stroke	9 (7.0)	9 (8.6)	3 (2.9)	5 (4.8)	0.31
Ischemic Heart Disease	22 (17.2)	23 (21.9)	14 (13.5)	19 (18.3)	0.46
<i>Previous PCI</i>	14 (10.9)	15 (14.3)	8 (7.7)	13 (12.5)	0.49
<i>Previous CABG</i>	2 (1.6)	2 (1.9)	1 (1.0)	2 (1.9)	0.94
<i>Medication only</i>	7 (5.5)	6 (5.7)	3 (2.9)	4 (3.8)	0.71
Creatinine > 120 µmol/L	7 (5.5)	9 (8.6)	9 (8.7)	11 (10.6)	0.55
Status on arrival of paramedics					
Heart rate, median (IQR)	76 (64, 84)	72 (61, 84)	76 (60, 88)	70 (60, 83)	0.63
Systolic blood pressure, median (IQR)	140 (120, 159)	130 (105, 150)	130 (110, 150)	130 (101, 150)	0.09
Oxygen saturation, median (IQR)	98 (87, 99)	98 (96, 99)	98 (97, 99)	98 (97, 99)	0.15
Pain score, median (IQR)	7 (5, 8)	6 (5, 8)	7 (5, 9)	8 (5, 9)	0.04

SD denotes standard deviation, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, IQR interquartile range.

Table 2. Procedural details of patients with confirmed STEMI					
Characteristic	No oxygen exposure N= 128	Low oxygen exposure N= 105	Moderate oxygen exposure N= 104	High oxygen exposure N= 104	p-value
Status on arrival at the catheterization laboratory					
Oxygen saturation, median (IQR)	98 (97, 99)	98 (96, 100)	100 (98, 100)	100 (99, 100)	<0.001
Oxygen being administered, n (%)	0	55 (52.4)	85 (81.7)	100 (96.2)	<0.001
Oxygen flow rate (L/min), median (IQR)	0	6 (4, 8)	8 (6, 8)	8 (6, 8)	<0.001
Pre-intervention oxygen duration in minutes, median (IQR)*	0	58 (49, 74)	82 (62, 93)	85 (68, 101)	<0.001
Inotrope use, n (%)	4 (3.1)	5 (4.8)	6 (5.8)	8 (7.7)	0.47
Killip class ≥ II, n (%)	13 (10.7)	9 (9.1)	8 (8.2)	20 (19.4)	0.05
Extent of coronary disease, n (%)					
LAD culprit artery	38 (30.2)	37 (35.6)	39 (38.2)	42 (40.8)	0.37
Multi-vessel disease	76 (59.4)	62 (59.0)	56 (54.4)	67 (64.4)	0.54
LMCA Involvement	4 (3.1)	3 (2.9)	5 (4.9)	4 (3.8)	0.87
Procedural details, n (%)					
Pre-procedural TIMI flow 0/1	106 (84.8)	92 (92.0)	92 (90.2)	92 (88.5)	0.36
Post-procedural TIMI flow 2/3	122 (96.8)	98 (95.1)	100 (100.0)	99 (96.1)	0.21
Radial intervention	44 (34.6)	34 (32.4)	29 (28.2)	40 (38.5)	0.46
Stent implanted	118 (92.2)	91 (86.7)	98 (94.2)	96 (92.3)	0.24
Drug-eluting stent	65 (50.8)	50 (47.6)	61 (58.7)	50 (48.1)	0.35
Glycoprotein IIb/IIIa inhibitor	45 (35.2)	42 (40.0)	45 (43.3)	55 (52.9)	0.05
Thrombus aspiration	59 (46.1)	44 (41.9)	53 (51.0)	56 (53.8)	0.32
Intra-aortic balloon pump	4 (3.1)	3 (2.9)	4 (3.8)	8 (7.7)	0.27
CABG	2 (1.6)	7 (6.7)	1 (1.0)	4 (3.8)	0.07
Symptom-to-intervention time, median (IQR)	158 (128, 245)	159 (124, 213)	154 (124, 223)	159 (128, 227)	0.80
Door-to-intervention time, median (IQR)	54 (40, 70)	52 (35, 66)	56 (40, 69)	58 (44, 70)	0.32
Length of stay (days), median (IQR)	4 (3, 5)	4 (3, 5)	4 (4, 5)	5 (4, 6)	<0.001

* Duration on oxygen therapy from randomization to first procedural intervention (e.g. aspiration, ballooning) measured in patients who received oxygen therapy. LAD denotes left anterior descending, LCx left circumflex, RCA right coronary artery, TIMI thrombolysis in myocardial infarction, CABG coronary artery bypass grafting, IQR, interquartile range.

Table 3. Adverse clinical end points at hospital discharge and six-month follow-up in patients with confirmed STEMI.					
Characteristic	No oxygen exposure N= 128	Low oxygen exposure N= 105	Moderate oxygen exposure N= 104	High oxygen exposure N= 104	p-value
At hospital discharge, n (%)					
All-cause mortality	4 (3.1)	4 (3.8)	3 (2.9)	3 (2.9)	0.98
Cardiac mortality	3 (2.3)	2 (1.9)	3 (2.9)	3 (2.9)	0.96
Recurrent myocardial infarction	0 (0.0)	1 (1.0)	4 (3.8)	9 (8.7)	0.001
Stroke or transient ischemic attack	0 (0.0)	1 (1.0)	2 (1.9)	1 (1.0)	0.50
Cardiogenic shock	6 (4.7)	8 (7.6)	10 (9.6)	16 (15.4)	0.04
Coronary artery bypass grafting	2 (1.6)	7 (6.7)	1 (1.0)	4 (3.8)	0.07
Major bleeding	2 (1.6)	5 (4.8)	0 (0.0)	8 (7.7)	0.01
Arrhythmia	30 (23.4)	37 (35.2)	42 (40.4)	49 (47.1)	0.002
ST-segment resolution > 70% †	85 (70.2)	72 (70.6)	72 (71.3)	52 (50.2)	0.003
At six-month follow-up, n (%)*					
All-cause mortality	6 (4.7)	5 (5.0)	4 (4.0)	6 (5.9)	0.94
Cardiac mortality	5 (3.9)	2 (2.0)	3 (3.0)	5 (4.9)	0.70
Recurrent myocardial infarction	3 (2.4)	3 (3.0)	5 (5.0)	13 (12.7)	0.003
Stroke or transient ischemic attack	1 (0.8)	3 (3.0)	3 (3.0)	1 (1.0)	0.45
Coronary artery bypass grafting	5 (3.9)	9 (8.9)	4 (4.0)	7 (6.9)	0.34
Repeat revascularization	12 (9.4)	7 (6.9)	11 (11.0)	9 (8.8)	0.79
Readmission	26 (20.5)	21 (20.8)	26 (26.0)	26 (25.5)	0.66
Major adverse cardiac event ‡	20 (15.7)	17 (16.8)	20 (19.8)	23 (22.5)	0.56

* 14 of 441 were lost-to-follow-up.

† Measured on ECG one day after hospital admission.

‡ MACE denotes any of the following: all-cause mortality, recurrent myocardial infarction, repeat revascularization or stroke.

Outcome measure	Unadjusted estimate (95% CI) *	P-value	Adjusted estimate 1 (95% CI) *†	P-value	Adjusted estimate 2 (95% CI) †‡	P-value	Adjusted estimate 3 (95% CI) †§	P-value	Adjusted estimate 4 (95% CI) † 	P-value
Logarithm peak cTnI	0.018 (0.011-0.026)	<0.001	0.014 (0.006-0.022)	<0.001	0.014 (0.002-0.027)	0.02	0.014 (0.006-0.022)	0.001	0.012 (0.002-0.021)	0.01
Logarithm AUC ₇₂ cTnI	0.019 (0.011-0.026)	<0.001	0.013 (0.006-0.021)	<0.001	0.013 (0.002-0.025)	0.02	0.013 (0.005-0.021)	0.001	0.012 (0.003-0.021)	0.007
Logarithm peak CK	0.016 (0.010-0.022)	<0.001	0.012 (0.007-0.018)	<0.001	0.010 (0.002-0.019)	0.02	0.013 (0.007-0.019)	<0.001	0.010 (0.004-0.017)	0.003
Logarithm AUC ₇₂ CK	0.013 (0.008-0.019)	<0.001	0.010 (0.005-0.015)	<0.001	0.008 (0.000-0.016)	0.04	0.010 (0.004-0.015)	0.001	0.008 (0.002-0.014)	0.006
Logarithm CMR infarct mass (g) ¶	0.014 (0.004-0.024)	0.005	0.012 (0.001-0.023)	0.03	0.010 (-0.006-0.025)	0.21	0.011 (-0.001-0.022)	0.07	0.010 (-0.002-0.023)	0.11
Logarithm CMR infarct percent (%) ¶	0.012 (0.003-0.021)	0.007	0.009 (0.000-0.019)	0.06	0.005 (-0.009-0.018)	0.48	0.009 (-0.002-0.019)	0.09	0.008 (-0.003-0.019)	0.16

cTnI denotes Troponin I, CK creatine kinase, CMR cardiac magnetic resonance imaging.

* Primary analysis includes all patients (n= 441).

† Model adjusted for the following covariates: age, gender, culprit artery, killip class, pre- and post-intervention TIMI flow, and symptom-to-intervention time.

‡ Sensitivity analysis conducted in patients randomized to the oxygen treatment arm (n= 218).

§ Sensitivity analysis excludes patients with desaturations (SpO₂ < 94%) at any time in the first 12 hours after randomization (n= 361).

|| Sensitivity analysis excludes patients with cardiogenic shock or recurrent myocardial infarction during admission, or desaturations (SpO₂ < 94%) at any time (n= 325).

¶ Subgroup with available data at 6 months (n=139).

Figures

Figure 1: Frequency distribution for cumulative oxygen exposure (liters of oxygen) in the overall population and by treatment arm.

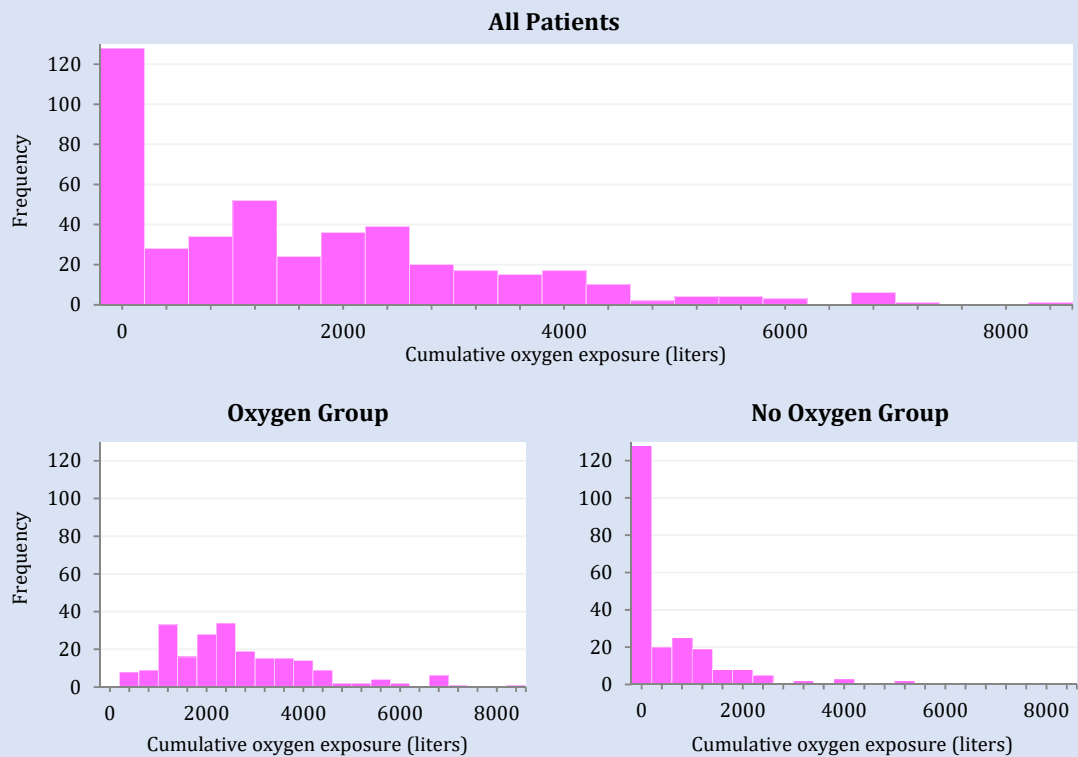
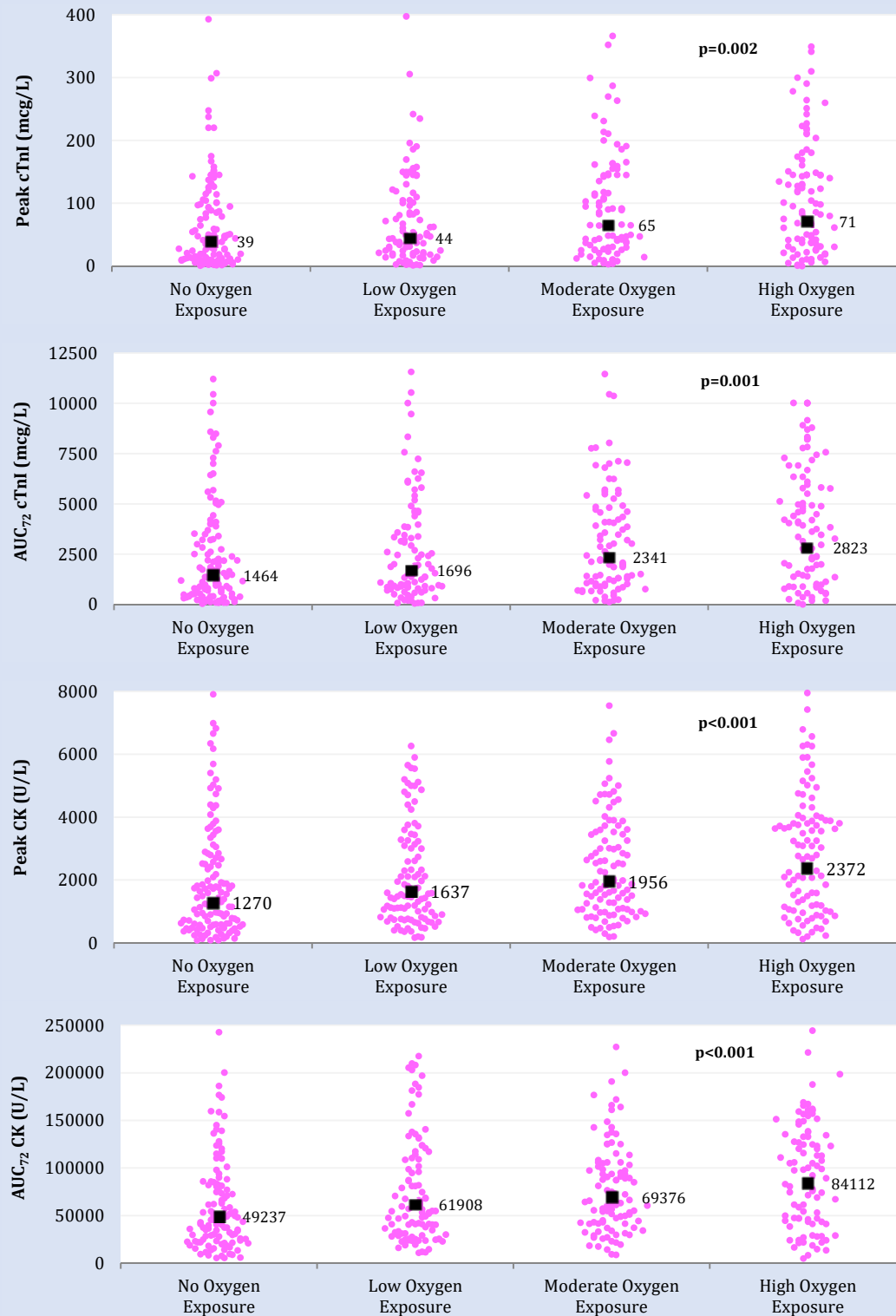


Figure 2: Distribution of biochemical measures (cTnI/CK) across oxygen exposure groups. Black lines represent geometric mean peaks. P-values calculated using one-way ANOVA for the difference in log-transformed means.



Supplementary Appendix

Table 1. Complete list of AVOID Investigators

Stephen Bernard, MBBS, MD, Ambulance Victoria, Blackburn North, Australia;
 Karen Smith, BSc, PhD, Ambulance Victoria, Blackburn North, Australia;
 Dion Stub, MBBS PhD, Alfred Hospital, Melbourne, Australia;
 Ziad Nehme, BEmergHlth(Hons), Ambulance Victoria, Blackburn, Australia;
 Michael Stephenson, BHLthSc, Ambulance Victoria, Blackburn, Australia;
 Janet Bray, RN, PhD; Monash University, Melbourne, Australia;
 Bill Barger, MACAP; Ambulance Victoria, Blackburn North, Australia;
 Ian Meredith, MBBS, PhD, Monash Medical Centre, Clayton, Australia;
 Peter Cameron, MBBS, MD, Monash University, Melbourne, Australia;
 David Kaye, MBBS, PhD, Alfred Hospital, Melbourne, Australia;
 Andris Ellims, MBBS, Alfred Hospital, Melbourne, Australia;
 Andrew Taylor, MBBS, PhD, Alfred Hospital, Melbourne, 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, BCh, PhD, Alfred Hospital, Melbourne, Australia;
 James Shaw, MBBS, PhD, Alfred Hospital, Melbourne, Australia;
 Stephen Duffy, MBBS, PhD, Alfred Hospital, Melbourne, Australia;
 James Hare, MBBS, PhD, Alfred Hospital, Melbourne, Australia;
 Leah Iles, MB ChB PhD, Alfred Hospital, Melbourne, Australia;
 Teresa 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, 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.

Table 2. Spearman rank correlations for the association between measures of oxygen exposure and myocardial injury.

Outcome measure	Area under the curve (AUC) for oxygen exposure				
	Baseline to intervention	Baseline to 2 hours post-intervention	Baseline to 4 hours post-intervention	Baseline to 6 hours post-intervention	Baseline to 12 hours post-intervention
Peak cTnI	0.091	0.149 *	0.185 †	0.209†	0.228†
AUC ₇₂ cTnI	0.102 *	0.154 *	0.190 †	0.216 †	0.240 †
Peak CK	0.137 *	0.169 †	0.200 †	0.224 †	0.243 †
AUC ₇₂ CK	0.122 *	0.163 *	0.199 †	0.225 †	0.242 †
CMR infarct mass (g) ‡	0.241 *	0.258 *	0.286 *	0.290 *	0.293 *
CMR infarct percent (%) ‡	0.222 *	0.240 *	0.266 *	0.272 *	0.277 *

cTnI denotes Troponin I, CK creatine kinase, CMR cardiac magnetic resonance imaging.

* p<0.05 † p <0.001

‡ Subgroup with available data at 6 months (n=139).

Figure 1: Study flow-chart and patient selection.

