Increased Cardiac Events with Use of Supplemental Oxygen
Therapy for Adult Patients Suffering From Uncomplicated STEMIs

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Pacific University

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Increased Cardiac Events with Use of Supplemental Oxygen Therapy for Adult Patients Suffering From Uncomplicated STEMIs

Abstract

Background: Although providers have been using supplemental oxygen therapy in the treatment of myocardial infarction for over 100 years, there are currently no current guidelines established for the treatment of normoxic patients. Research has shown possible worsened outcomes for uncomplicated myocardial infarctions when oxygen is used; including worsened ischemic area and increased arrhythmias. The aim of this systematic review is to evaluate the research on whether or not supplemental oxygen therapy can cause increased cardiac events for patients presenting with an uncomplicated AMI.

Methods: An exhaustive search of the literature was performed using MEDLINE-Ovid, Web of Science, and ClinicalKey. Key words included myocardial infarction, oxygen, and oximetry.

Results: Out of the 16 relevant articles found, only two articles fit all inclusion and exclusion criteria. Both studies showed evidence of increase infarct size and cardiac arrhythmias with supplemental oxygen use in uncomplicated myocardial infarctions. The overall quality of evidence was found to be moderate. Further studies are needed to show the long-term morbidity and mortality.

Conclusion: The use of supplemental oxygen in an uncomplicated AMI has been shown to cause an increase in infarct size as well as increased cardiac arrhythmias and recurrent myocardial infarcts. Although there is evidence to support short term worsened cardiac events, there are currently no studies for long-term morbidity and mortality. Further research is required to determine the long-term effects of oxygen supplementation for normoxic patients with acute myocardial infarctions.

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Subject Categories
Medicine and Health Sciences

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Increased Cardiac Events with Use of Supplemental Oxygen Therapy for Adult Patients Suffering From Uncomplicated STEMIs

Matthew W. Barton

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Mark Pedemonte, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
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Acknowledgements

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List of Abbreviations

ACCF.......................................................... American College of Cardiology Foundation
AHA.......................................................... American Heart Association
AMI.......................................................... Acute myocardial infarction
CMR.......................................................... Cardiac magnetic resonance imaging
COPD......................................................... Chronic Obstructive Pulmonary Disease
MONA..................................................... Morphine, oxygen, nitroglycerine, aspirin
NO.......................................................... Nitric Oxide
STEMI.......................................................ST-Segment-Elevation myocardial infarction
Increased Cardiac Events with Use of Supplemental Oxygen Therapy for Adult Patients Suffering From Uncomplicated STEMI

BACKGROUND

Supplemental oxygen therapy is administered for more than 90% of patients presenting with an acute myocardial infarction (AMI)\(^1\) and has been for over 100 years.\(^2\) However, due to research on therapeutic oxygen showing ambiguous results, the 2013 ACCF/AHA guidelines do not currently have any recommendation for its use in therapy for normoxic patients.\(^3\)

Human studies on this topic stem all the way back to 1976, where it was found that oxygen therapy might be beneficial in myocardial ischemia,\(^4\) especially when used for patients with oxygen saturations <90%.\(^5\) In hypoxic conditions, the increased oxygen is thought to be due to supplying the surrounding hypoxic tissue with needed oxygen.\(^6\) However, in normoxic myocardium, data has shown that supplemental oxygen leads to a decrease in cardiac output and coronary outflow.\(^6\)\(^-\)\(^8\)

This physiologic effect with normoxic myocardium is due to hyperoxia, the over saturation of hemoglobin molecules at a PO\(_2\) of approximately 90 mmHg.\(^8\) Supplemental oxygen therapy delivered through a facemask increases blood PO\(_2\) to approximately 250 mmHg; resulting in oversaturation of the hemoglobin and excess free oxygen in the blood stream.\(^8\) The free oxygen then forms reactive oxygen species (ROS) that reacts with nitric oxide, leading to the inactivation of its vasodilatory effects and continued constriction of the coronary blood flow. The theory of this physiologic effect has been further supported through lab results that showed increased lactate levels in the coronary venous system following 100% oxygen supplementation in myocardial infarctions.\(^7\)
With the mixed results found over the last 100 years, it is unknown whether the tradition of using oxygen therapy is beneficial or harmful to patients, and the harm of oxygen therapy has not been further evaluated until recently. The aim of this systematic review is to evaluate the research on whether or not supplemental oxygen therapy can cause increased cardiac events for patients presenting with an uncomplicated AMI.

**METHODS**

An exhaustive search of the literature was performed using MEDLINE-Ovid, Web of Science, and ClinicalKey. Keywords used included: myocardial infarction, oxygen, and oximetry. Studies were required to be done on human participants, be written in English, include patients with an uncomplicated STEMI diagnosis, take ischemic area measurements by labs or imaging, record reoccurrence rates of AMI, and monitor for cardiac arrhythmias. Bibliographies of studies and other relevant articles were searched for further sources. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). ⁹

**RESULTS**

A total of 16 articles were reviewed for relevancy. Four articles fit inclusion criteria that were all randomized controlled trials. ¹⁰-¹³ One of the studies¹¹ found may have contained topic material, but was excluded due to not being in the English language. Another article was found that contained all of the inclusion criteria, but was excluded due to being a pilot study without final results.¹³ No additional articles were found by searching the references of the included studies. See Table I for a break down of the GRADE criteria used for each included article.

**Rawles and Kenmure (1976)**
This double-blinded, randomized control trial looked at two hundred consecutive patients presenting to the cardiac unit with an uncomplicated myocardial infarction within the last 24 hours. The patients were split into two groups upon presentation, one that received supplemental oxygen at 6L/min via mask (N=105) and the other that was placed on 6L/min compressed air via mask (N=95) for 24 hours. The air units were covered to allow for blinding. The participants were only allowed known oxygen therapy if they developed left ventricular failure or cardiac arrest during their stay in the unit, at which point they were unhooked from the blinded unit and attached to a wall mounted oxygen therapy. The participants were then left in their initial therapy groups for intent to treat protocol.

The study excluded any patients that had heart failure, chronic obstructive pulmonary disorder (COPD) or breathlessness due to any other cause. The patients were then diagnosed with AMI if they had >30 minutes of chest pain unaffected by position, respirations, rest, glyceryl trinitrate, rise in serum aspartate aminotransferase levels above 20 IU/ML, and abnormal ECGs with sequential ST and T wave changes with or without Q waves. Any patients included in the study originally that were found to have a different diagnosis than AMI were then excluded (18 in the compressed air group and 25 in the oxygen group).

Every participant had ECGs recorded for two minutes every hour for the first 24 hours. Heart rate, arrhythmias, and ectopic beats were noted from the recordings. Any other arrhythmias were also recorded. Serial aspartate aminotransferase levels were taken from every patient. The results were then analyzed using $\chi^2$ test with Yate’s correction for comparison of frequencies and Student t test for comparison of mean values.
Mean age, sex distribution, mean aspartate aminotransferase, arrhythmias, and deaths were recorded by Rawles and Kenmure and are available in Table II below. Results showed the mean serum aspartate aminotransferase level to be significantly higher (P<0.05) in the oxygen group (99.9; 95% CI 85.7-114.1) than it was in the compressed air group (80.7; 95% CI 67.5-93.9). It was also noted that there was a statistically significant (P<0.05) increase in the occurrence of sinus tachycardia in the oxygen group than in the compressed air group (23 patients vs. 11 patients). Death was also recorded, and it was found that patients in the supplemental oxygen group had increased mortality compared to the compressed air group (9 deaths vs. 3 deaths).


This multicenter, blinded, and computer randomized control study included 441 confirmed STEMI patients. It was done to look at whether normoxic (O2 saturation ≥94%) patients presenting with a STEMI diagnosis are harmed by use of supplemental oxygen therapy. The primary end point was AMI size and was monitored by use of troponin I and creatine kinase levels in STEMI patients with or without oxygen. Secondary end points included recurrent AMIs, cardiac arrhythmias (sustained and non-sustained ventricular and atrial tachycardia), AMI size via cardiac magnetic resonance imaging (CMR), and mortality.

To determine inclusion into the study, paramedics in the field were used to determine if a patient was suffering from a STEMI according to 12-lead ECG (ST elevation of ≥0.1mV in 2 contiguous limb leads, ≥0.2mV in contiguous chest leads, or new LBBB pattern). They then opened a randomized opaque envelope to determine if the patient was to be given 8L/min oxygen via mask (N=218) or to be left on room air (N=223). The room air group was only
allowed oxygen therapy during the trial if their O₂ saturation fell below 94% at which point oxygen was titrated to maintain a saturation of 94%. Only 7.7% of the room air group needed oxygen therapy at any given time. Further inclusion criteria outside of ECG results included being ≥18 years of age and having chest pain for <12 hours. Exclusion criteria were if the patient had an O₂ saturation less than 94% at presentation, had a recent nebulizer therapy that used O₂, had O₂ therapy given before randomization, had altered mental status, had planned transport to a nonparticipating hospital, or was ruled to not have a STEMI by the physician upon arrival to the hospital. A flow chart of exclusion criteria can be seen with Figure I.¹²

The general characteristics for every participant were monitored (Table III). Serial troponin I and creatine kinase assays were taken at baseline, every six hours for the first 24 hours, and then every 12 hours until 72 hours post admission. Median peak levels were then used to determine comparisons for the two groups. Area under the curve (AUC) for serum levels was also conducted using trapezoidal integration with multiple imputations using the Markov Chain Monte Carlo method for patients missing ≥1 biomarker assay. Geometric means, ratios and 95% CI were done for each primary end point using Student t tests on log-transformed data with comparison of groups obtained after back-transformation. Secondary end points were then measured at discharge and again at 6 months. Geometric means of the infarct size at 6 months was compared across groups using the Student t test on the log-transformed data with comparison of groups obtained after back-transformation. Group differences were then compared using the Wilcoxon rank-sum test. The relationship between the troponin I and creatine kinase results were then compared to the CMR results using the Spearman rank correlations.¹²
The primary end point results (Table IV) found that the differences between the mean peaks for troponin I were not statistically significant (P=0.18) between the two groups (57.4 vs 48.0 µg/L; ratio 1.20; 95% CI 0.92-1.56). However, the creatine kinase was found to be significantly elevated (P=0.01) for the patients given oxygen (1948 vs 1543 U/L; ratio 1.27; 95% CI 1.04-1.52).12

Secondary end points studied found that in-hospital recurrent myocardial infarctions (5.5% vs 0.9%; P=0.006) and cardiac arrhythmias (40.4% vs 31.4%; P=0.05) were increased in the oxygen group. However, during the 6-month follow up, the two groups did not appear to have any differences. Myocardial infarct size studied through use of CMR found baseline characteristics to be similar at discharge. There were 139 patients (65 oxygen and 74 room air) who were then able to return to clinic to have a 6-month follow up CMR performed. These results showed a significant (P=0.04) increase in infarct size for the patients given oxygen supplementation (20.3g vs 13.1g). During their stay in the hospital, mortality results showed that the oxygen group had 4 deaths (1.8%) and the room air group had 10 (4.5%).12

The authors state the limitations of the study to be the inability to blind all participants, exclusion of participants due to physician rule out of STEMI, and small follow up for CMR results. The cardiology team, patients and paramedics were all unable to be blinded to treatment. However, the follow up coordinator, data analyst, and the statistician were all blinded to treatment groups. This should be substantial enough blinding to limit any biases in results. The exclusions due to physician rule out of STEMI were similar numbers in both groups (oxygen N=79; room air N=68) and had similar enough baseline characteristics to have substantial selection bias not occur. Limited CMR follow up was due to patients being unable to make the
return visit to the base hospital. Although the follow up numbers were similar for each group, the total population was relatively small. As a secondary end point, this does not limit the study, as further evaluation of mortality and morbidity is required. 12

**DISCUSSION**

Part of a treatment plan for a STEMI is that each patient is given morphine for pain, oxygen, nitroglycerine for vasodilation, and aspirin for anticoagulation effects (MONA). 14 Although no current guidelines have recommendations for oxygen use in all AMI patients, the use of supplemental oxygen therapy by physicians for all patients presenting with AMIs is high. 1

Currently there have been no influential studies to show improved or worsened long-term outcomes with oxygen use. Even with the lack of evidence, providers are still continuing to use supplemental therapy for more than 90% of patients. 1 Some providers have taken to symptomatic relief studies for reasoning behind supplementing its use. For example, both analgesic effects and anxiolytic effects of oxygen have been thought to occur in patients presenting with an AMI. 15 However, a recent study in 2013 has shown that there does not seem to be any analgesic effects when oxygen is compared to room air use in STEMIs. 16 If providers are going to use supplemental oxygen therapy without any strong evidence supporting the use of oxygen being beneficial, it must be determined if there is harm that can occur from its use.

The only evidence directed at the harm of oxygen therapy were those discussed in this review. Both articles 10,12 showed indications of worsened cardiac events due to supplemental oxygen therapy use. Increased serum cardiac enzymes with oxygen use was observed in both studies, a finding that implies an increased ischemic area of the heart. This finding was also backed up by CMR that showed an average of approximately 7g increase in infarct size after 6
months when compared to AMI patients on room air. ¹² Not only did patients on oxygen have increased infarct sizes, but research also noted increased arrhythmias and recurrent myocardial infarctions while in the hospital. ¹² Therefore, it can be concluded that there is an increase in cardiac events with the use of supplemental oxygen in an uncomplicated AMI. Unfortunately, at this time it is not evident whether or not supplementary oxygen has increased risk for long-term morbidity and/or mortality. Although these findings might lead to further morbidities for patients, it cannot be certain from the available information if they will result in any long-term effects. Further studies on the morbidity and mortality effects of supplemental oxygen are still required before official guidelines should be implemented for or against the use of oxygen in AMI.

These studies ¹⁰,¹² were evaluated using the GRADE criteria, and the results can be seen in Table 1. The Rawles and Kenmure study had the biggest limitation due to age. As it is from 1976, there were less evidence-based criteria required for studies at that time, less technology, and fewer lab tests available. For example, it is not indicated how many patients required supplemental oxygen therapy after having cardiac arrest or left ventricular heart failure. Although the patients were treated with intent to treat for results, the difference in which patients were requiring the oxygen could result in a bias in the results. Also, the lack of pulse oximetry technology limits the study as to whether the patients were hypoxic or normoxic at presentation, a criterion that currently has ACCF/AHA guidelines for supplemental oxygen use. Another notable flaw in the Rawles and Kenmure study is the use of aspartate aminotransferase to monitor heart ischemia. Although aspartate aminotransferase is found in the highest concentration in heart tissues, it is also found in erythrocytes, liver, muscle, pancreas, and kidneys. ¹⁷ With a diagnosis of AMI, it is likely the increased levels were from the heart tissue;
however, with the given information, it is impossible to tell for sure where the increased aspartate aminotransferase came from. With these limitations, the Rawles and Kenmure study cannot stand-alone for whether or not oxygen therapy is harmful for AMI patients.

The Stub et al study 12 was found to have a few limitations in their work as well. One limitation was the use of 8L/min oxygen, as decided per Australian protocol. Although it is not a direct limitation of the information, it is still unknown if low oxygen supplementation or other methods of oxygen deliver carry the same risks found. A non-substantial selection bias was also discussed as a limitation in this article. Because STEMIs had to be determined in the field by a paramedic, there was a resultant loss of participants from the provider ruling out an AMI. Because of the limited quantity of participants allowed to participate, this could have lead to a resultant selection bias. However, selection bias is not substantial because each group lost approximately the same amount of participants. Another limitation is the high loss of follow up for the CMR at 6 months. Although populations were almost even for each group when it came to follow up, the decrease in sample size is not significant enough to determine whether oxygen use can have increased risk associated with long term results.

Some limitations to this systematic review paper include the inclusion of only two articles on the topic resulting in a decreased precision in the results. However, the strong evidence found in the Stub et al study, 12 and the consistency seen between the two articles increases the precision. The only inconsistency observed while undergoing the research was seen in mortality. The Rawles and Kenmure study 10 found that patients on oxygen therapy had a three-fold increase in mortality (9 deaths vs. 3 deaths), whereas the Stub et al study 12 found more than double the amount of deaths for patients on room air than patients given oxygen (10
deaths vs. 4 deaths). This inconsistency may be insignificant given the relatively small numbers in each subgroup and the results being secondary outcomes in both studies. Due to these limitations, the overall quality of evidence included in this research is a moderate rating according to the GRADE scale.

The increased risk for morbidity and the inconsistency with mortality must be followed up on with larger studies that focus on them as primary outcomes. One study that is currently being worked on in Sweden is the DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial (DETO2X-AMI Trial) by Hofmann et al.\textsuperscript{13} This study will include 6600 normoxic AMI patients that are split into either 6L/min oxygen or room air. The study’s primary outcome will be 1-year all-cause mortality with secondary end points of 30-day mortality, cardiac events, and health economy. With the results of this new study\textsuperscript{13} it is hopeful that the question of whether or not supplemental oxygen therapy puts an AMI patient at increased risk of harm will be answered more clearly.

CONCLUSION

The use of supplemental oxygen in an uncomplicated AMI has been shown to cause an increase in infarct size as well as increased cardiac arrhythmias and recurrent myocardial infarcts while admitted in the hospital. Given this information, it is uncertain why there are no current guidelines for the use of supplemental therapy in uncomplicated AMIs. The number one rule for health providers is to do no harm to patients. However, even with this expectation of doing no harm to patients, supplemental oxygen therapy is still being used. Unfortunately, this may be due to the lack of information on the long-term morbidity and mortality of oxygen use. At this time there is not enough evidence to determine the long-term effects of supplemental oxygen use in
uncomplicated AMIs. Further large random control studies that are focused on the long-term effects of supplemental oxygen are needed before any guidelines should be implemented to regulate the use of oxygen in normoxic AMI patients.
References


Table I: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rawles and Kenmure(^\text{10})</td>
<td>RCT</td>
<td>Very Serious(^{a})</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td>N/A</td>
</tr>
<tr>
<td>Stub et al(^\text{12})</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Unlikely</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^{a}\) Study was performed in 1976

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Table II – Details of patients with define myocardial infarction. Rawles and Kenmure\(^\text{10}\)

<table>
<thead>
<tr>
<th></th>
<th>Air Group (95% CI)</th>
<th>Oxygen Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>77</td>
<td>80</td>
<td>NS</td>
</tr>
<tr>
<td>No of men</td>
<td>61</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>56.4 (54.8 – 58)</td>
<td>55.1 (53.3 - 56.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean serum AST level (IU/mL)</td>
<td>80.7 (67.5 – 93.9)</td>
<td>99.9 (85.7 - 114.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean heart rate/min</td>
<td>72.7 (68.9 – 76.5)</td>
<td>77.0 (73.6 - 80.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial ectopic beats</td>
<td>35</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>11</td>
<td>23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No of deaths in hospital</td>
<td>3</td>
<td>9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table III – Baseline Characteristics of Patients With Confirmed STEMI. Stub et al 12

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oxygen (n=218)</th>
<th>Room Air (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>63 (11.9)</td>
<td>62.6 (13.0)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>174 (79.8)</td>
<td>174 (78.0)</td>
</tr>
<tr>
<td><strong>Body mass index, median (IQR), kg/m²</strong></td>
<td>27.4 (25.1–31.1)</td>
<td>27.7 (24.7–30.8)</td>
</tr>
<tr>
<td><strong>Past history and risk factors, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (17.0)</td>
<td>41 (18.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>130 (59.6)</td>
<td>123 (55.2)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>121 (55.5)</td>
<td>118 (52.9)</td>
</tr>
<tr>
<td>Current or ex-smoker†</td>
<td>141 (65.3)</td>
<td>165 (74.3)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4 (1.8)</td>
<td>11 (4.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>11 (5.0)</td>
<td>15 (6.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>38 (17.4)</td>
<td>40 (17.9)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>24 (11.0)</td>
<td>26 (11.7)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>4 (1.8)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Medication only</td>
<td>8 (3.7)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>Creatinine &gt;120 μmol/L</td>
<td>17 (7.8)</td>
<td>19 (8.5)</td>
</tr>
<tr>
<td><strong>Status on arrival of paramedics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, median (IQR), bpm</td>
<td>74.0 (61.0–84.0)</td>
<td>72.0 (60.0–80.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, median (IQR), mmHg</td>
<td>130.0 (105.0–150.0)</td>
<td>130.0 (110.0–150.0)</td>
</tr>
<tr>
<td>Oxygen saturation, median (IQR), %</td>
<td>98.0 (97.0–99.0)</td>
<td>98.0 (97.0–99.0)</td>
</tr>
<tr>
<td>Pain score, median (IQR)</td>
<td>7.0 (5.0–9.0)</td>
<td>7.0 (5.0–8.0)</td>
</tr>
</tbody>
</table>

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 IV – Measures of infarct Size in Patients With Confirmed STEMI

<table>
<thead>
<tr>
<th>End Point</th>
<th>Oxygen (n=218)</th>
<th>Room Air (n=223)</th>
<th>Ratio of means (Oxygen/Room Air)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size, n</td>
<td>200</td>
<td>205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median peak (IQR), μg/L</td>
<td>65.7 (30.1–145.1)</td>
<td>62.1 (19.2–144.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean peak (95% CI), μg/L</td>
<td>57.4 (48.0–68.6)</td>
<td>48.0 (39.6–58.1)</td>
<td>1.20 (0.92–1.55)</td>
<td>0.18</td>
</tr>
<tr>
<td>Median AUC\textsubscript{72} (95% CI), μg/L</td>
<td>2336.4 (965.6–5043.1)</td>
<td>1995.5 (765.7–4426.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean AUC\textsubscript{72} (95% CI), μg/L</td>
<td>2000.4 (1692.8–2363.9)</td>
<td>1647.9 (1380.1–1967)</td>
<td>1.21 (0.95–1.55)</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatine Kinase, U/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size, n</td>
<td>217</td>
<td>222</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median peak (IQR), U/L</td>
<td>2073 (1065–3753)</td>
<td>1727 (737–3598)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean peak (95% CI), μg/L</td>
<td>1948 (1721–2205)</td>
<td>1543 (1341–1776)</td>
<td>1.26 (1.05–1.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median AUC\textsubscript{72} (95% CI), μg/L</td>
<td>64,620 (35,751–107,066)</td>
<td>51,757 (29,141–106,029)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean AUC\textsubscript{72} (95% CI), μg/L</td>
<td>60,395 (54,185–67,316)</td>
<td>50,726 (44,861–57,358)</td>
<td>1.19 (1.01–1.40)</td>
<td>0.04</td>
</tr>
<tr>
<td>Infarct size on CMR*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size, n</td>
<td>61</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR), g</td>
<td>20.3 (9.6–29.6)</td>
<td>13.1 (5.2–23.6)</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Geometric mean peak (95% CI), g</td>
<td>14.6 (11.3–18.8)</td>
<td>10.2 (7.7–13.4)</td>
<td>1.43 (0.99–2.07)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median (IQR) proportion of LB mass, %</td>
<td>12.6 (6.7–19.2)</td>
<td>9.0 (4.1–16.3)</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Geometric mean (95% CI) proportion of LB mass, g</td>
<td>10.0 (9.1–12.5)</td>
<td>7.3 (5.7–9.3)</td>
<td>1.38 (0.99–1.92)</td>
<td>0.06</td>
</tr>
<tr>
<td>ECG ST-segment resolution &gt;70%, measured 1 d after hospital admission, n (%)</td>
<td>132 (62.0)</td>
<td>149 (69.6)</td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>

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

*CMR conducted six-month follow-up in 139 of 441 patients
Figure I – Patient selection and randomization flowchart. STEMI indicates ST-segment-elevation myocardial infarction