Critical Review Form
Therapy

Ukholkina GB, Kostyanov IY, Kuchkina NV, et al. Oxygen therapy in combination with endovascular reperfusion during the first hours of acute myocardial infarction: clinical and laboratory findings. International Journal of Interventional Cardioangiology 2009;9:45e51.

Objectives: To assess "effect of 30-40% oxygen inhalation on the course of AMI after endovascular reperfusion of myocardium."

Methods: An open-label prospective trial was conducted in which 137 patients with acute myocardial infarction (AMI) were randomized to either ambient room air (N = 79) or 3-6 L/min of inhaled oxygen by nasal cannula (N = 58). The patients receiving oxygen were further divided into two groups: 28 patients received oxygen for 30 minutes prior to and 3 hours after coronary intervention, while 30 patients received oxygen only for 3 hours after intervention.

Inclusion criteria:

1) **Q-wave MI.**
2) **Uncomplicated MI.**
3) **Enrollment within 12 h after the onset of chest pain.**

Exclusion criteria:

1) **Complicated MI (pulmonary edema, cardiogenic shock).**
2) **Congestive heart failure.**
3) **Chronic obstructive pulmonary disease, anemia with HGB below 90 g/l).**

Primary outcome measures included:

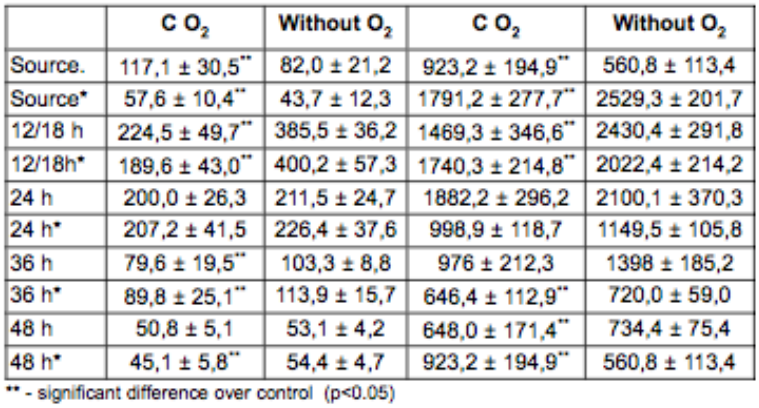
1) **Mortality**
2) **Recurrent AMI**
3) **Post-infarction angina**
4) **Circulatory failure**
5) **Heart rhythm and conduction disorders within one hour after intervention and during hospital stay**
6) **Pericarditis**

Secondary outcome measures included:

1) **Relative area and growth of necrotic zone and ischemic damage zone**
2) **Global and local myocardial contraction**
3) **Left ventricular geometry: end-diastolic volume (EDV), end-systolic volume (ESV).**

Pulse-oximetry readings were recorded on admission, within 2 days of admission, and on day 10. 12-lead ECG tracings were recorded on admission and at the end of days 1, 2, and 10 to assess necrotic zone size (by number of leads showing Q-waves or QS-complexes) and ischemic damage zone size (by number of leads showing ST-elevation and total ST-elevation). 48-lead ECG mapping was performed on day 10 to assess necrotic zone size. CPK and CPK-MB were measured on admission and at 12, 18, 24, 36, and 48 hours after the onset of chest pain. Left ventriculography was performed within one hour of admission to assess left ventricular ejection fraction (LVEF), stroke volume (SV), EDV, ESV, and contraction index (CI). Echocardiography was performed on day 5 to evaluate LVEF, SV, EDV, ESV, and CI.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, though they do not describe how the randomization sequence was generated.
2.	Was randomization concealed (blinded)?	No. This was an open-label study, and no attempts were made to conceal randomization from either subjects or treating physician, which could potentially lead to performance bias. It is not stated if data collectors or outcome assessors were blinded.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. However, patient who failed revascularization were withdrawn from the study and NOT analyzed. Failure to use an intention to treat protocol could potentially have biased the results, though we can't say in which direction as the authors do not state how many subjects from each group were withdrawn.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. While the groups were similar with respect to age, medical history, infarction area, and method of revascularization, there were significant differences with respect to signs of congestive heart failure (10% in the oxygen group vs. 1% in the control group, $p < 0.08$) and time between onset of chest pain and intervention (4.59 hours in the oxygen group vs. 3.90 hours in the control group, $p < 0.052$), leading to bias in favor of the control group. Longer duration of occlusion prior to revascularization has been shown to increase mortality (Newby 1996, Brodie 2010, Boersma 1996), increase infarct size (Reimer 1977, Milavetz 1998), and decrease LVEF (De Luca 2004).
B.	**Did experimental and control groups retain a**	

<table>
<tr><td></td><td>similar prognosis after the study started (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were patients aware of group allocation?</td><td>Yes. There was no attempt at blinding.</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>Yes. There was no attempt at blinding.</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>Uncertain. There is no mention of whether or not outcome assessors were blinded to intervention.</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>Yes. All patients were followed for 10 days.</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>Mortality:
There was one death in the oxygen group (1.7%, 95% CI 0.3%-9%), and none in the control group (0%, 95% CI 0%-5%). Can’t calculate relative risk with 0 events in the control group.
Table 5, CPK and MB-CPK levels:
 
<table>
<tr><th></th><th>C O_2</th><th>Without O_2</th><th>C O_2</th><th>Without O_2</th></tr>
<tr><td>Source.</td><td>117,1 ± 30,5**</td><td>82,0 ± 21,2</td><td>923,2 ± 194,9**</td><td>560,8 ± 113,4</td></tr>
<tr><td>Source*</td><td>57,6 ± 10,4**</td><td>43,7 ± 12,3</td><td>1791,2 ± 277,7**</td><td>2529,3 ± 201,7</td></tr>
<tr><td>12/18 h</td><td>224,5 ± 49,7**</td><td>385,5 ± 36,2</td><td>1469,3 ± 346,6**</td><td>2430,4 ± 291,8</td></tr>
<tr><td>12/18h*</td><td>189,6 ± 43,0**</td><td>400,2 ± 57,3</td><td>1740,3 ± 214,8**</td><td>2022,4 ± 214,2</td></tr>
<tr><td>24 h</td><td>200,0 ± 26,3</td><td>211,5 ± 24,7</td><td>1882,2 ± 296,2</td><td>2100,1 ± 370,3</td></tr>
<tr><td>24 h*</td><td>207,2 ± 41,5</td><td>226,4 ± 37,6</td><td>998,9 ± 118,7</td><td>1149,5 ± 105,8</td></tr>
<tr><td>36 h</td><td>79,6 ± 19,5**</td><td>103,3 ± 8,8</td><td>976 ± 212,3</td><td>1398 ± 185,2</td></tr>
<tr><td>36 h*</td><td>89,8 ± 25,1**</td><td>113,9 ± 15,7</td><td>646,4 ± 112,9**</td><td>720,0 ± 59,0</td></tr>
<tr><td>48 h</td><td>50,8 ± 5,1</td><td>53,1 ± 4,2</td><td>648,0 ± 171,4**</td><td>734,4 ± 75,4</td></tr>
<tr><td>48 h*</td><td>45,1 ± 5,8**</td><td>54,4 ± 4,7</td><td>923,2 ± 194,9**</td><td>560,8 ± 113,4</td></tr>
</table>
** - significant difference over control (p<0.05)
Table 6, based on 12-lead ECG findings:
Change in necrotic zone size at 24 hours: control group 1.46 ± 0.142, oxygen group 0.58 ± 0.199 (p < 0.001).
Change in necrotic zone size at day 10: control group 1.38 ± 0.149, oxygen group 0.32 ± 0.152 (p < 0.001).
Change in ischemic zone size between days 2 and 10: control group -0.04 ± 0.019, oxygen group -1.00</td></tr>
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		± 0.207 ($p < 0.001$). • Change in ischemic zone size by day 10: control group -1.04 ± 0.185, oxygen group -1.75 ± 0.240 ($p < 0.05$). Table 7, based on 48-lead ECG mapping: **O_2** | **No O_2** | **O_2** | **No O_2** Necrotic area: By end of day 1 ($p<0,005$) | By end of day 10 ($p<0,0001$) Increase: 27 (47%) | 63 (80%) | 24 (43%) | 59 (75%) No changes of decrease: 31 (53%) | 16 (20%) | 31 (57%) | 20 (25%) Ischemic damage area: Between days 2 and 10 ($p<0,01$) | By day 10 ($p<0,05$) Decrease: 25 (45%) | 18 (23%) | 43 (75%) | 46 (58%) No changes or increase: 30 (55%) | 61 (77%) | 14 (25%) | 33 (42%) Table 8, based on 48-lead ECG mapping on day 10: • Relative necrotic area in patients with anterior MI: control group 13.23 ± 1.7, oxygen group 8.61 ± 1.5 ($p < 0.02$). • Relative necrotic area in patients with posterior MI: control group 7.76 ± 0.9, oxygen group 4.37 ± 1.2 ($p < 0.015$). Table 9, Ventriculography and ECHO findings **Without O_2** | **Two inhala-tions** | **Single inhalation** | **O_2** Ventriculography findings EF, %: 51.9 ± 1.34 | 53.1 ± 2.29 | 49.3 ± 2.57 | --- SV, ml: 90.6±7.50 | 74.8±5.17* | 84.4±6.30 | ESV, ml: 85.9 ± 3.45 | 66.2 ± 5.17*° | 87.3 ± 7.12 | --- EDV, ml: 176.8 ± 5.25 | 141.3 ± 7.80*° | 172.8 ± 9.52 | --- Contraction index: 2.15 ± 0.065 | 2.14 ± 0.115 | 2.11 ± 0.123 | --- Echocardiography findings EF, %: 51.9 ± 1.19 | 52.4 ± 1.79 | 48.2 ± 2.10 | 50.2 ± 1.45 SV, ml: 73.4±2.15 | 64.0±2.87* | 68.6±2.91 | 66.5±2.1* ESV, ml: 70.0 ± 3.46 | 61.00 ± 4.82*° | 82.1 ± 7.53 | 73.4 ± 4.89 ESD, mm: 3.97 ± 0.16 | 3.73 ± 0.12° | 4.17 ± 0.50 | 4.0 ± 0.104 EDV, ml: 146.7 ± 4.29 | 124.8 ± 6.60*° | 150.7 ± 7.62 | 140.8 ± 5.50 EDD, mm: 5.42 ± 0.14 | 5.08 ± 0.12*° | 5.53 ± 0.12 | 5.4 ± 0.090 Contraction index: 2.18 ± 0.100 | 2.16 ± 0.208 | 2.11 ± 0.163 | 2.12 ± 0.126 Segments: 5.8 ± 0.431 | 5.82 ± 0.820 | 6.15 ± 0.741 | 5.9 ± 0.534
2.	How precise was the estimate of the treatment effect?	See above.

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Yes. The patients in the study were low-risk patients with AMI (onset of symptoms less than 12 hours prior to presentation). Patients were excluded for pulmonary edema, cardiogenic shock, COPD, or severe anemia. Mean age was 55.6 in the oxygen group and 53.5 in the control group.
2.	Were all clinically important outcomes considered?	No. While mortality was addressed as a primary outcome, the study lacked statistical power to show a difference between the groups. Instead, the study focused on many surrogate outcomes, including infarct size based on ECG findings, necrotic area based on 48-lead ECG mapping and biochemical markers, and indicators of cardiac function based on ventriculography and ECHO findings. More clinically useful markers of functional status and quality of life, such as the Kansas City Cardiomyopathy Questionnaire and the Quality of Life after Myocardial Infarction (QLMI) instrument, were not examined. Hospital length of stay, cast, and long-standing conduction and rhythm disturbances that would affect quality of life and/or require long-term management were also not considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. No significant difference in mortality or other patient-important outcomes was demonstrated. The clinical impact of those differences that were demonstrated is unclear. For example, a statistically significant difference in CPK-MB levels was demonstrated at 12-18 hours (224.5 in the control group vs. 385.5 in the oxygen group), however at 24 and 48 hours there was no statistically significant difference observed; it is unclear how to interpret the clinical importance of this finding. Just as importantly, it can be difficult to interpret the statistical significance of results when multiple outcomes are considered.

Limitations:

1) **The study was underpowered to detect a difference in mortality between the oxygen and room air groups. The performance of an *a priori* power analysis and larger study may provide further insight into the effects of oxygen on mortality in AMI. Other outcome measures (MB-CPK levels, ECG findings,**

ventriculography and ECHO results) represent surrogate outcomes, which may not translate to changes in patient-important outcomes.

2) **The authors do not describe how the randomization sequence was generated. More importantly, the lack of blinding results in a high risk of performance bias.**

3) **The difference in prognostic factors (longer duration of symptoms and increased incidence of signs of CHF) should bias the results in favor of the control group, although despite this fact many of the outcomes were improved in the oxygen group.**

4) **The use of multiple outcomes increases the probability that a statistically significant difference will be observed by change alone (rather than due to an actual underlying treatment effect). The primary outcome of mortality showed no statistically significant difference.**

Bottom Line:

This small, non-blinded, randomized control trial evaluating the use of oxygen compared to room air in the management of acute MI showed no statistically significant difference in mortality between the two groups. There were statistically significant differences in many secondary outcome measures which favored oxygen therapy, including lower MB-CPK levels at 12/18 hours; smaller increase in necrotic area at 24 hours and 10 days and larger decrease in ischemic zone at day 10, based on ECG findings; lower ESV, EDV, and SV by ventriculography prior to intervention; and lower SV on ECHO performed on day 5. Further research would be needed to confirm the statistical and clinical significance of these secondary outcome measures.