Critical Review Form
Therapy

Rawles J, Kenmure ACF. Controlled trial of oxygen in uncomplicated myocardial infarction. British Medical Journal 1976;1:1121–3.

Objectives: **To evaluate the effect of supplemental oxygen therapy in acute myocardial infarction on "the severity of infarction, the incidence of arrhythmias, and the use of analgesics." (p. 1122)**

Methods: **Prospective, randomized controlled trial performed in the coronary care unit (CCU) in patients with suspected myocardial infarction (MI) in the preceding 24 hours. The CCU restricted admission to patients < 65 years of age. Additional exclusion criteria included:**

1) **Evidence of right or left heart failure**
2) **Chronic bronchitis or emphysema or any shortness of breath**
3) **Transfer to the CCU for treatment of arrhythmias**
4) **Cardiac arrest prior to admission**
5) **Cardiogenic shock.**

Two hundred consecutive patients with suspected MI were enrolled and were randomized by numbered sealed envelope to receive oxygen or room air. Oxygen at a rate of 6 L/min or compressed air was administered by medium concentration mask; the cylinders were shrouded to prevent the patient or medical staff from being aware of treatment group.

Myocardial infarction was defined by the presence of any two of the following criteria:

1) **"Classical history of gripping pain across the chest unaffected by position, respiration, rest, or glyceryl trinitrate and lasting more than half an hour"**
2) **Rise in serum aspartate aminotransferase (AST) above 20 IU/ml**
3) **An electrocardiogram (ECG) showing sequential ST and T-wave changes with or without pathologic Q-waves.**

There 95 patients randomized to receive compressed air and 105 to receive supplemental oxygen. MI was ruled out in 18 patients in the air group and 25 patients in oxygen group. Analysis of these excluded patients reveals a higher arterial oxygen pressure and higher number of doses of diamorphine given to those in the oxygen group; otherwise the two groups were similar.

An ECG was performed on every patient for two minutes out of every hour, and the heart rate, presence of arrhythmias, and ectopic beats were recorded. Pain was treated with 5 mg doses of intramuscular (IM) diamorphine, and a retrospective record was made of the number of doses required by each patient. The maximum AST level was recorded for all patients. 17 patients had systolic time intervals (STIs) measured around noon on the day of admission on oxygen or room air, then again 24 hours later when on room air.

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. Patients were randomized through the use of sealed envelopes. However, they do not describe how the randomization sequence was generated.
2.	Was randomization concealed (blinded)?	Yes. Randomization was concealed through the use of shrouded cylinders containing either compressed air or oxygen. It is possible that the shrouds could be removed, leading to performance bias. It is also unclear if outcome assessors or data collectors were blinded.
3.	Were patients analyzed in the groups to which they were randomized?	No. Myocardial infarction was confirmed after randomization occurred, and 18 patients in the air group and 25 in the oxygen group were found not to have MI and were not included in the analysis. Failure to use an intention to treat protocol could potentially have biased the results in favor of the air group.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. While patients were similar with respect to age and gender, there is no data regarding other prognostic factors (such as history of comorbidities, existing cardiovascular disease, or congestive heart failure).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. Patients were blinded by the use of shrouds over the canisters. It is possible that the shrouds could have been removed and patients and/or physicians became aware of allocation, but this seems unlikely.
2.	Were clinicians aware of group allocation?	No. Patients were blinded by the use of shrouds over the canisters. It is possible that the shrouds could have been removed and patients and/or physicians became aware of allocation, but this seems unlikely.
3.	Were outcome assessors aware of group allocation?	Uncertain. While it is not explicitly stated that outcome assessors were blinded to treatment, it seems likely that outcome assessors included the physicians and nurses caring for the patients, who were blinded.
4.	Was follow-up complete?	Yes. No specific follow-up duration was specified, but all patients were followed throughout their hospitalization.
II.	**What are the results**	

	(answer the questions posed below)?	
1.	How large was the treatment effect?	Mortality • For patients with confirmed MI: out of 77 patients in the air group, there were 3 (3.9%, 95% CI 1.3%-10.9%) deaths; out of 80 patients in the oxygen group there were 9 (11.3%, 95% CI 6%-20%) deaths for a relative risk (RR) of 2.89 (95% CI 0.81-10.27) for the use of oxygen. • For an intention to treat analysis on all patients randomized: out of 95 patients in the air group there were 3 (3.2%, 95% CI 1.1%-8.9%) deaths; out of 105 patients in the oxygen group there were 9 (8.6%, 95% CI 4.6%-15.5%) deaths for a RR of 2.71 (95% CI 0.76-9.73) for the use of oxygen. Pain • In the air group, 52 (67.5%, 95% CI 56.5%-76.9%) patient received diamorphine compared to 57 (71.3%, 95% CI 60.5%-80.0%) in the oxygen group, for a RR of 1.06 (95% CI 0.77-1.28). Biomarker • The mean maximum serum AST level was 80.7 in the air group and 99.9 in the oxygen group ($p < 0.05$). Cardiac function: • Mean PEP/LVET on day 1 was 0.43 in the air group and 0.35 in the oxygen group (no p-value given, listed as no statistically significant difference). • Mean PEP/LVET on day 2 was 0.44 in the air group and 0.37 in the oxygen group (no p-value given, listed as no statistically significant difference). Dysrhythmias: • No statistical difference was seen between the groups for any dysrhythmia except sinus tachycardia, which was seen in 11 (14.3%, 95% CI 8.2%-23.8%) patients in the air group and 23 (28.7%, 95% CI 19.5-40.1%) patients in the

		oxygen group for a RR of 2.01 (95% CI 1.05-3.84).
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?	No. Patients in the study were all less than 65 years of age, which would exclude a large portion of our patients. In addition, treatment of patients in this study (conducted in 1976) differed in many respects, most notably the use of revascularization (by thrombolysis and percutaneous coronary intervention) which was not used at that time but which has become the standard of care.
2.	Were all clinically important outcomes considered?	No. The study did not assess the risk of long-standing arrhythmia, conduction defect requiring pacemaker placement, and cost of care. Additionally, the use of validated Health-Related Quality of Life (HQRL) instruments such as the Kansas City Cardiomyopathy Questionnaire and the Quality of Life after Myocardial Infarction (QLMI) instrument would help assess the long-term impacts of oxygen use.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study was performed before the advent of revascularization for AMI became standard of care, was performed in a population very different from ours (notably those less than 65 years of age), failed to address many patient important outcomes, and was not powered to detect a potential affect on mortality.

Limitations:

1) **There is a significant difference in age between our patients and those in the study, in which patient > 65 were excluded. In one study on characteristic of patient with acute MI, patients over 65 represent 75.2% and 57.8% of patients with NSTEMI and STEMI respectively (McManus 2011)**
2) **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 (maximum AST, systolic time interval) represent surrogate outcomes, which may not translate to changes in patient-important outcomes.**

3) **While well-designed, this study was performed in 1976 when several aspects of care in AMI differed from current management strategies:**
    a. **The use of AST as a cardiac biomarker has been replaced in favor more sensitive and specific troponin assays. In this study, AST was used both in the confirmation of AMI and as an outcome measure.**
    b. **This study was performed before the advent of coronary reperfusion. Current standard of care in the treatment of AMI involves the use of thrombolysis or percutaneous coronary intervention to reperfuse infarcted and ischemic areas of myocardium. Additionally, newer medications have become standard in the treatment of AMI, including heparin and low-molecular weight heparins, newer anti-platelet agents, and glycoprotein iib/iiia inhibitors. These treatments have led to a decline in mortality and incidence of heart failure.**
4) **While this study was randomized and blinded, the authors do not describe how the randomization sequence was generated, and the blinding method could be broken easily, which could potentially lead to performance bias.**
5) **The authors do not reports adequate demographic data to compare the treatment groups.**

Bottom Line:

The use of supplemental oxygen led to a non-statistically significant trend towards increased mortality (RR 2.89; 95% CI 0.81-10.27), a significant increase in maximum AST (99.9 vs. 80.7, $p < 0.05$), no change in analgesic requirement (RR of 1.06; 95% CI 0.77-1.28), and no change in systolic time interval. Changes in management of AMI since the study's publication make interpretation of the results difficult.