

# Oxygen therapy for acute myocardial infarction: a systematic review and meta-analysis

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## ABSTRACT

Oxygen (O<sub>2</sub>) is widely recommended in international guidelines for treatment of acute myocardial infarction (AMI), but there is uncertainty about its safety and benefits. A systematic review and meta-analysis were performed to determine whether inhaled O<sub>2</sub> in AMI improves pain or the risk of death. Cochrane CENTRAL Register of Controlled Trials, MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL were searched from start date to February 2010. Other sources included British Library ZETOC, Web of Science, ISI Proceedings, relevant conferences, expert contacts. Randomised controlled trials of inhaled O<sub>2</sub> versus air in patients with suspected or proven AMI of < 24 h onset were included. Two authors independently reviewed studies to confirm inclusion criteria met, and undertook data abstraction. Quality of studies and risk of bias was assessed according to Cochrane Collaboration guidance. Main outcomes were death, pain, and complications. Measure of effect used was the RR. Three trials (n=387 patients) were included. Pooled RR of death on O<sub>2</sub> compared to air was 2.88 (95%CI 0.88 to 9.39) on ITT analysis and 3.03 (95%CI 0.93 to 9.83) in confirmed AMI. While suggestive of harm, this could be a chance occurrence. Pain was measured by analgesic use. Pooled RR for the use of analgesics was 0.97 (95%CI 0.78 to 1.20). Evidence for O<sub>2</sub> in AMI is sparse, of poor quality and pre-dates advances in reperfusion and trial methods. Evidence is suggestive of harm but lacks power and excess deaths in the O<sub>2</sub> group could be due to chance. More research is required.

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The cornerstone of contemporary management of acute myocardial infarction (AMI) presenting with ST-segment elevation is reperfusion therapy. Other recommended treatments include aspirin, nitrates, morphine and oxygen. Although oxygen administration is mentioned in most AMI guidelines, recommendations are inconsistent.<sup>1–9</sup>

The rationale for providing oxygen in AMI is to improve oxygenation of ischaemic myocardial tissue. This has face validity but is there supporting evidence? A systematic review, including non-randomised studies, did not confirm that oxygen reduces acute myocardial ischaemia (some evidence suggested it may actually increase ischaemia).<sup>10</sup> A systematic review of the effect on infarct size concluded 'There is little evidence by which to determine the efficacy and safety of high flow

oxygen therapy in MI. The evidence that does exist suggests that the routine use of high flow oxygen in uncomplicated MI may result in a greater infarct size and possibly increase the risk of mortality'.<sup>11</sup>

A recent narrative review<sup>12</sup> also suggested that oxygen may do more harm than good. The British Heart Foundation's response to this was: 'The current practice of giving high-flow oxygen is an important part of heart attack treatment. Best practice methods have been developed and refined over the years to ensure the best possible outcome for patients. There is not enough evidence to change the current use of oxygen therapy in heart attacks'.<sup>13</sup> This view is consistent with that held by many clinicians who treat AMI.<sup>14 15</sup>

Given the uncertainty surrounding this widely used treatment, we undertook a systematic review to look at the effect on patient-centred clinical outcomes of giving oxygen to people with suspected AMI.

## METHODS

The protocol was registered at the Cochrane Library.<sup>16</sup>

## Eligibility criteria

Study design: randomised controlled trials, with any length of follow-up.

Participants: patients treated in a prehospital or a hospital setting for suspected or confirmed uncomplicated AMI of less than 24 h onset, regardless of co-therapies (eg, reperfusion), provided these were the same in both arms.

Intervention: inhaled oxygen, at normal pressure, for 1 h or more, at any stage within 24 h after the onset of AMI. Hyperbaric and aqueous oxygen therapy trials were excluded.

Comparator: air.

Publication status: any.

Language: any.

Years: any.

## Information sources

We searched the Cochrane CENTRAL Register of Controlled Trials, MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL, UK National Research Register (NRR) to 2007, the NRR Archive and NIHR CRN portfolio, Current Controlled Trials metaRegister and <http://ClinicalTrials.gov/>. Other sources included British Library ZETOC, Web of Science, ISI Proceedings, annual meetings and conferences of the American College of Cardiology, American Heart Association, British Cardiovascular Society and European Society of Cardiology.

### Search strategy

Databases were searched from their start date to February 2010. The strategy specified in the protocol was amended to increase sensitivity by truncating the term 'oxygen'. See appendix 1 (available online only) for full strategy.

### Study selection

Two authors independently reviewed titles and abstracts of identified studies to see if they met the inclusion criteria. If this could not be decided from the title or abstract study reports were obtained in full. There were no discrepancies.

### Data collection process

Data were abstracted using a piloted data extraction form independently by two reviewers and entered by one reviewer and checked by two others. Differences were resolved by discussion.

### Data items

The primary outcome was prespecified as mortality; secondary outcomes were pain (or opiate use as a proxy), quality of life and any other reported patient-centred outcomes. Surrogate outcomes such as arrhythmias, infarct size and arterial oxygen saturation were not collected.

### Risk of bias in individual studies

We used the Cochrane Collaboration two-part tool.<sup>17</sup> We considered six domains: sequence generation; allocation concealment; blinding (participants, personnel and outcome assessors); incomplete outcome data; selective outcome reporting and other potential threats to validity. For each trial the design characteristics relating to each domain we judged the

risk of bias associated with the main outcome using a nominal scale: 'Yes' (low risk of bias) 'No' (high risk of bias) or 'Unclear' (uncertain risk of bias), for all the relevant outcomes in the relevant domains.

### Risk of bias across studies

We assessed the overall risk of bias for every outcome by each domain using the following scale: low ('Yes' in all domains), unclear ('Unclear' for one or more domains) and high ('No' for one or more domains).

When meta-analysis was undertaken, we summarised the risk of bias across studies. Disagreements were resolved by consensus.

### Summary measures

We calculated risk difference and RR of death. As the trials were old, we anticipated that control event rates would be higher than those expected currently and therefore prespecified that we would preferentially report the RR. Intention-to-treat (ITT) analysis was performed whenever possible.

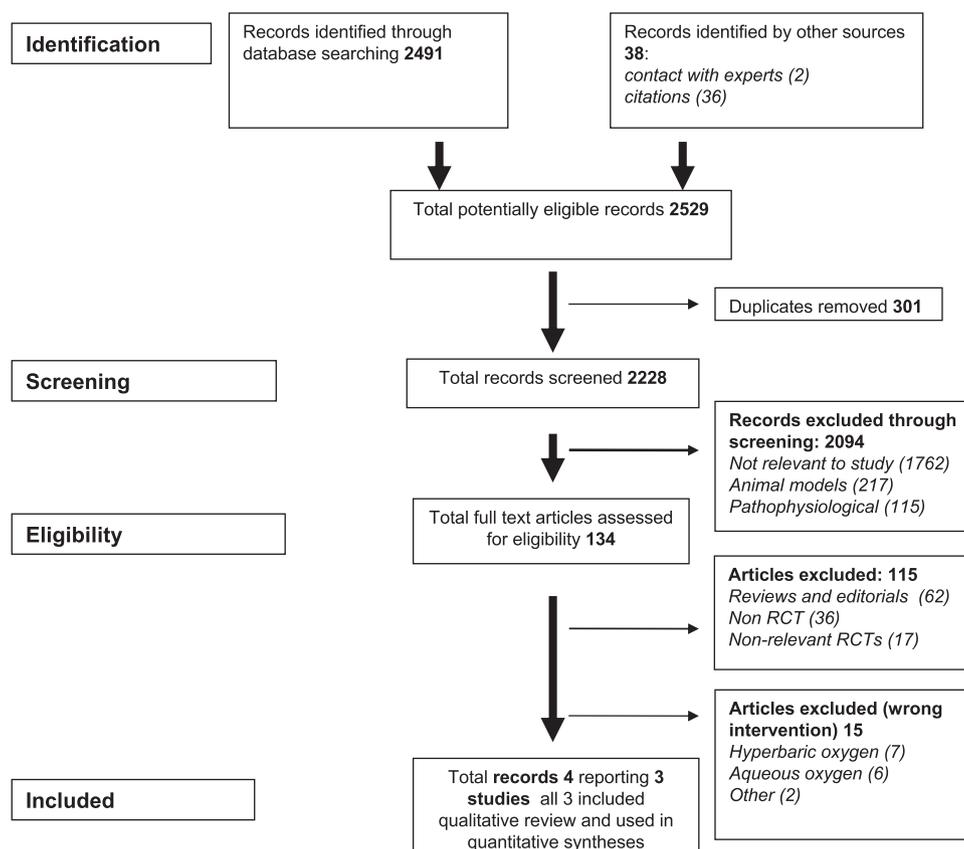
### Synthesis of results

We used RevMan 5.0. Meta-analyses were performed when clinically sensible and data available using a fixed effects model. ITT analysis was the primary analysis but we also looked at results in patients with confirmed AMI. We assessed heterogeneity by visual inspection and the  $I^2$  statistic ( $I^2 < 60\%$  was considered moderate).

### Additional analyses

We undertook a best-case worst-case sensitivity analysis for missing data on death for confirmed AMI and ITT populations.

**Figure 1** Flow diagram of study selection. RCT, randomised controlled trial.



## RESULTS

### Study selection

We identified 2529 articles. The removal of duplicates left 2228. Based on title and abstract, 2094 were excluded, 134 full papers were retrieved. A further 115 were excluded, leaving four papers reporting three trials<sup>17–20</sup> that met the inclusion criteria (figure 1 gives reasons for exclusions).

### Study characteristics

All three studies were parallel design randomised controlled trials (RCT). One<sup>18</sup> was double blind, the others were open label. Table 1 shows the main characteristics of the included studies.

#### Rawles and Kenmure, 1976

This study was the largest (N=200) and had the best methodology. It was performed in the pre-reperfusion era. Patients with suspected AMI were randomly assigned and followed to discharge.<sup>18</sup>

#### Wilson and Channer, 1997

This was a small RCT of 50 people with confirmed uncomplicated AMI, followed to discharge. Its primary purpose was to look at the effect of oxygen on hypoxaemia and it did not record most of the outcomes of interest to this review. It was reported along with a postal survey on the use of oxygen and pulse oximetry in 252 cardiac care units in the UK.<sup>19</sup>

#### Ukholkina *et al*, 2005

This study was published in English<sup>20</sup> and Russian.<sup>21</sup> It is the only trial performed in the percutaneous coronary intervention (PCI) era and included 137 patients with confirmed uncomplicated AMI. Its primary purpose was to look at infarct size. Patients were followed for 10 days.

### Risk of bias within studies

Risk of bias for each study is summarised in figure 2. The reasons underlying these classifications are given below.

#### Rawles and Kenmure, 1976

There is no description of how the randomisation sequence was generated. Allocation was concealed using numbered sealed envelopes. The groups had similar baseline characteristics. Blinding of patients and staff was by shrouding gas cylinders. There is no information on how effective this was. If patients required oxygen due to severe hypoxaemia or cardiac arrest, blinding was not broken—the tube was attached to a wall supply of oxygen. While the primary outcome of this review, death, is not subject to observer bias, the possibility of performance bias due to unblinding cannot be excluded. The patients withdrawn from the study are not reported, so we cannot estimate the possible impact of performance bias on outcomes. Nursing staff were not aware that routine recording of opiate administration would be used as a proxy measurement of pain.<sup>18</sup>

There was no loss to follow-up, but randomisation was undertaken before the diagnosis was confirmed. Of the 105 people randomised to oxygen and the 95 to air, AMI was not confirmed in 25 and 18 patients, respectively. Characteristics of those in whom AMI was not confirmed were similar in both groups and there were no deaths in these individuals. No selective reporting bias was identified.

#### Wilson and Channer, 1997

There is no description of how the randomisation was done. Allocation was concealed using sealed envelopes. The baseline

**Table 1** Characteristics of included studies

Trial and year	Study design and sample size	Clinical setting	Participants	Exclusions	Intervention	Comparator	Outcomes	Length of follow-up and parallel care
Rawles and Kenmure, 1976 <sup>18</sup>	Double-blind, RCT N=200	Single site coronary care unit in the UK	Suspected AMI presenting within 24 h of onset of pain	Patients with heart failure, bronchitis, emphysema, or other respiratory problems	Inhaled oxygen at normal pressure given at 6 l/min by MC mask for 24 h N: 105	Air at normal pressure given at 6 l/min by MC mask N: 95	Death, arrhythmias, use of analgesics, LOS	Discharge Pre-thrombolysis period
Wilson and Channer, 1997 <sup>19</sup>	Open label RCT N=50	Single site coronary care unit in the UK	Confirmed uncomplicated AMI	Patients with heart failure, cyanosis central or pulmonary disease requiring oxygen	Oxygen for 24 h administered via face mask at 4 l/min N: 25	Air breathed normally N: 25	Hypoxaemia, arrhythmias, analgesics, and cardiac enzymes	Discharge Thrombolysis period
Ukholkina and colleagues, 2005 <sup>20</sup> 21	Open label RCT N=137	Single site coronary care unit in Russia	Confirmed uncomplicated AMI	Patients with complicated MI, congestive heart failure, pulmonary disease, or anaemia	Oxygen for 3 h administered via nasal cannulae 3–6 l/min (Fio <sub>2</sub> 30–40%) N: 58	Air breathed normally N: 79	Death, recurrent AMI, post-infarction angina, heart failure, area of tissue damage measured by ECG mapping, cardiac enzymes	10 Days PCI era

AMI, acute myocardial infarction; Fio<sub>2</sub>, fractional inspired oxygen; LOS, length of stay; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomised controlled trial.

	Adequate sequence generation?	Allocation concealment?	Blinding? (Death)	Blinding? (Pain (or surrogate))	Blinding? (infarct size ECG)	Incomplete outcome data addressed? (Death)	Incomplete outcome data addressed? (infarct size ECG mapping)	Free of selective reporting?	Free of other bias?	Baseline characteristics
Rawles 1976	?	+	+	?	?	+	+	+	+	+
Ukholkina 2005	?	?	+	+	?	+	+	+	+	+
Wilson 1997	?	+	+	+	+	+	+	+	+	+

**Figure 2** Risk of bias.

characteristics showed the groups to be similar in mean age and smoking habits. The study was not blind. In total eight patients were excluded from the analysis: 1 death, 1 stroke, 4 withdrew consent and 2 because of incomplete data. Death was recorded, but the patient who died was excluded from the study and it was not reported whether they received oxygen. No other selective reporting was identified.<sup>19</sup>

#### Ukholkina *et al*, 2005

There is no description of how randomisation sequence was generated or whether allocation was concealed. Baseline characteristics differ in the two groups for: time to revascularisation (41 min shorter in the air group ( $P=0.052$ )) and Killip classification: (Killip class II was present in 10% oxygen vs 1% air group ( $P=0.08$ ) (class III and IV were excluded from the study)). Both are potential confounders which could have led to over-estimation of comparative mortality in the oxygen group.<sup>20 21</sup>

Blinding was not undertaken. The primary outcome, death, and other outcomes such as recurrent MI and pericarditis are hard outcomes and unlikely to be subjected to significant observer bias. It may have led to performance bias. The study has possible bias in infarct size estimation: CPK-MB was not measured at the same time from onset in all patients and PCI can alter biomarker release; no information is provided about number or blinding of observers, reliability and repeatability of measurements for ECG mapping. Furthermore, ECG-mapping for assessing infarct size was used only in a subset of patients.

No patients were lost to follow-up. There is no explicit data on patients excluded post-randomisation due to failed revascularisation, or the number of failed revascularisations per group. The mismatch between numbers reported in the tables and the text suggest two patients may have been excluded from the air group and four from the oxygen group. Data in table 3 of the study report did not make sense for 'No complications' for the

air group. We recalculated complication rates for this group for the outcome tables in our analysis.

### Results of individual studies

#### Rawles and Kenmure, 1976

Some 8.6% of randomly assigned patients (11.2% with confirmed AMI) in the oxygen group died (one in the first 24 h while still on therapy) and 3.2% of randomly assigned patients (3.9% of those with confirmed MI) in the air group died (two of them in the first 24 h). The RR of death was 2.89 (95% CI 0.81 to 10.27) in the confirmed AMI and 2.71 (95% CI 0.76 to 9.73) in the ITT population.<sup>18</sup>

Diamorphine use was reported as a proxy for pain. It was administered in 54.3% of the oxygen group (71.3% of those with confirmed AMI). The average was 2.1 doses (SD 1.5), but it is unclear whether the denominator was those using diamorphine or all patients. In the air group, 54.7% received diamorphine (67.5% of those with confirmed AMI). The average was 2.0 doses (SD 1.4), but the denominator was unclear. The RR for the use of analgesia was 1.06 (95% CI 0.86 to 1.30) in confirmed AMI and 0.99 (95% CI 0.77 to 1.28) in the ITT population.

#### Wilson and Channer, 1997

There was one death, but we were unable to determine in which group this occurred. Both authors confirmed they no longer had the trial data and did not remember in which arm the death and the stroke occurred. Twenty five were randomly assigned into each group.<sup>19</sup>

Opiate use was recorded as a proxy for pain. Although 50 patients were randomly assigned, results were only reported for 42. Sixteen out of 22 patients (72.7%) in the oxygen group used opiates and 18 out of 20 patients (90%) in the air group used opiates. The RR of the need for analgesia was 0.81 (95% CI 0.60 to 1.08) in the reported groups and 0.89 (95% CI 0.61 to 1.30) on an ITT basis. There was no difference in ECG ST-segment changes between the groups.

#### Ukholkina *et al*, 2005

One patient out of 58 died in the oxygen group and none out of 79 in the air group. The RR of death was 4.07 (95% CI 0.17 to 98.10).

Complications of AMI (excluding angina) were reported in eight out of 58 (13.8%) in the oxygen group and 24 out of 79 (30.4%) in the air group. The RR of complications was 0.45 (95% CI 0.22 to 0.94).<sup>20 21</sup>

The authors used several techniques to estimate the infarct size. Although they conclude that oxygen 'reduced the area of necrosis and peri-infarction area, improved central haemodynamic, and decreased the rate of postoperative rhythm disorders as compared to patients breathing ambient air', we felt that this could not be concluded confidently because of the methodological weaknesses discussed above.

### Synthesis of results

There were only sufficient data to perform meta-analyses for death and opiate use from two of the three trials (Rawles and Kenmure<sup>18</sup> and Ukholkina and colleagues<sup>20 21</sup> for death and Rawles and Kenmure<sup>18</sup> and Wilson and Channer<sup>19</sup> for pain). There was no heterogeneity in the ITT analyses.

The meta-analysis showed a RR of death for patients in the oxygen group of 3.03 (95% CI 0.93 to 9.83) in confirmed AMI and 2.88 (95% CI 0.88 to 9.38) in the ITT population (figure 3).

The meta-analysis for analgesic use gives a RR of 0.99 (95% CI 0.83 to 1.18) in confirmed AMI and 0.97 (95% CI 0.78 to 1.20; figure 4) in the ITT population.



**Figure 3** Oxygen versus air. Death in hospital for all patients using intention-to-treat analysis (ie, including those who did not have an acute myocardial infarction).

### Risk of bias across studies

The risk of bias across studies is high. Risk of bias is 'unclear' for adequate sequence generation and allocation concealment and 'high' for blinding, completeness of outcome data, selective outcome reporting and other biases.

### Additional analysis

We did a sensitivity analysis for missing information on the arm in which the death occurred in the trial by Wilson and Channer.<sup>19</sup> The worst-case scenario assumes that the patient who died was in the oxygen arm and gives a RR of death of 2.88 (95% CI 0.88 to 9.38) using ITT analysis. The best-case scenario assumes that the patient who died received air, giving a RR of death of 2.06 (95% CI 0.67 to 6.37) using ITT analysis.

### DISCUSSION

Only three trials, involving a total of 387 patients, were found. None demonstrated that oxygen therapy in AMI does more good than harm. In both the ITT and the confirmed AMI meta-analyses, there were more deaths among those on oxygen than those on air, although this did not reach statistical significance and could simply be a chance occurrence. There was no clinically or statistically significant difference in analgesia use. In the meta-analysis for analgesic use in confirmed AMI we found moderate heterogeneity ( $I^2=54\%$ ) but it disappeared in the ITT analysis. While the two studies used in the meta-analysis had differences in design (blind vs open label) and attrition rates (higher in the study by Wilson and Channer),<sup>19</sup> it is not possible to investigate heterogeneity further with only two trials.

This review has a number of limitations. First, the evidence in support of such a widespread practice is surprisingly sparse and scattered. We were unable to analyse if there was any publication bias using formal methods as only three studies were found. The possibility that there are unpublished studies and or other published studies, especially in foreign languages, that are not indexed in the electronic databases cannot be excluded.

Second, the quality of included studies was generally poor and the risk of bias was high for both outcomes. Two studies (Rawles and Kenmure<sup>18</sup> and Wilson and Channer)<sup>19</sup> were old

and before the improvements in trial design, conduct and reporting that have taken place in the past decade. Therefore results must be interpreted with caution.

Third, the study by Rawles and Kenmure<sup>18</sup> was undertaken in the pre-reperfusion era and thus may not be applicable now. Moreover, case death rates from AMI have fallen over the past 30 years due to improved management including reperfusion and the use of medical treatments such as beta-blockers, aspirin or ACE inhibitors.<sup>22</sup>

Finally, the overall death rate among controls during hospital stay in the included studies was only 1.7%. This is lower than observed in contemporaneous routinely collected data.<sup>22</sup> While this may be explained by the fact that low-risk patients were recruited, it could also be due to a chance deficit of mortality in the control arm (which could have contributed to the apparent excess of deaths in the oxygen arm).

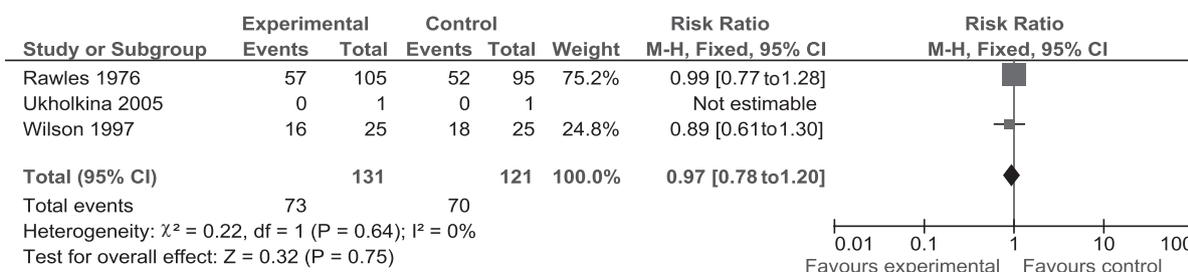
### CONCLUSION

The evidence in this area is sparse, of poor quality and pre-dates advances in reperfusion techniques and trial methods. What evidence there is, is suggestive of harm but lacks power and excess deaths in the oxygen group could be due to chance. Current evidence neither supports nor refutes the routine use of oxygen in patients with uncomplicated AMI.

### Implications for research

As long ago as 1950, it was demonstrated that the administration of pure oxygen via face mask not only failed to reduce the duration of angina pain, but also prolonged ECG changes indicative of acute myocardial ischaemia.<sup>23</sup> This topic was identified as requiring further research over three decades ago.<sup>24</sup> It is surprising that a definitive study has not been undertaken.

We searched <http://ClinicalTrials.gov/> and the WHO International Clinical Trials Registry Platform for ongoing trials of oxygen in AMI and identified two studies, from Australia and New Zealand, neither of which (one hospital based, the other pre-hospital, recruiting approximately 200 patients each) is powered for mortality. We have calculated that approximately 10 000 patients would need to be randomly assigned to receive



**Figure 4** Oxygen versus air. Opiate use (as a proxy measure for pain) for all patients using intention-to-treat analysis (ie, including those who did not have an acute myocardial infarction).

oxygen, and another 10 000 to air, to address the question of whether oxygen improves or increases mortality. We are working with colleagues from ambulance services, cardiology, emergency medicine and public health to plan such a trial. Given the widespread use of oxygen in AMI, the inconsistency in guideline recommendations about when and to whom it should be given, and the fact that the best current evidence is suggestive of potential clinically significant harm, the need to clarify this uncertainty is urgent.

A strong a priori belief,<sup>14 15 25</sup> based on pathophysiological reasoning, that oxygen administration is beneficial, may have precluded the funding of a definitive trial to date.

### Potential mechanisms causing harm

It is biologically plausible that oxygen is doing harm. Potentially harmful mechanisms include the paradoxical effect of reducing coronary blood flow and increasing coronary vascular resistance;<sup>26 27</sup> reduced stroke volume and cardiac output;<sup>28</sup> other adverse haemodynamic consequences, such as increased vascular resistance from hyperoxia; and reperfusion injury from increased oxygen-free radicals.<sup>29 30</sup>

Potential mechanisms by which oxygen might harm cardiac patients have been explored in two recent reviews. In their systematic review, Farquhar *et al*<sup>30</sup> concluded that hyperoxia caused a significant reduction in coronary blood flow due to a mean increase in coronary vascular resistance, suggesting that hyperoxia is a potent vasoconstrictor stimulus to the coronary circulation, functioning at the level of microvascular resistance vessels. They also found that hyperoxia led to a reduction in myocardial oxygen consumption, due both to a reduction in oxygen delivery and myocardial oxygen demand, shown to be associated with reduced myocardial contractility (although they identify conflicting study results). Moradkhan and Sinoway,<sup>31</sup> in a narrative review, suggest that, with the widespread use of high concentration oxygen in cardiac patients to maintain oxygen saturations close to 100%, many patients are consequently exposed to significant periods of hyperoxia, resulting in coronary vasoconstriction as a result of the generation of reactive oxygen species, a fall in intracellular ATP concentrations mediating the opening of ATP-sensitive potassium channels, in turn causing hyperpolarisation of vascular smooth muscle cells and vasodilation. Hyperoxia may also induce vasoconstriction through acting directly on L-type calcium channels, and may affect the release of angiotensin II, with subsequent changes in endothelin 1 levels, increasing vascular tone. Hyperoxia is also thought to increase production of the potent vasoconstrictor 20-HETE. Moreover, in critically ill patients, high flow oxygen causes a redistribution of microcirculatory blood flow, with increased oxygen shunting and a reduction in oxygen consumption.<sup>31</sup>

### A new consensus?

Emerging guidelines are beginning to diverge from the previous consensus that oxygen should routinely be administered in AMI, but this 'new consensus' is largely based on expert opinion rather than robust evidence of what we should do.<sup>8 9 32–35</sup> A recent BMJ editorial argued that oxygen continue to be used routinely based on pathophysiological reasoning, as none of the studies in the review by Farquhar *et al*<sup>30</sup> included patients with AMI.<sup>36</sup> Clearly there is ongoing uncertainty about the role of oxygen in AMI.

Decades after the trial by Rawles and Kenmure,<sup>18</sup> we still do not know whether routine oxygen administration is beneficial, harmful, or irrelevant in AMI. Nor do we have robust evidence that oxygen is beneficial in 'complicated' patients such as those with shock or arrhythmia, and concern has been raised about

hyperoxia in patients resuscitated from cardiac arrest.<sup>37</sup> We need to generate good evidence, from adequately powered RCT to guide decisions on which patients, if any, should receive oxygen, at what dose and for how long.

Given widespread use, the inconsistency in recommendations about when and to whom it should be given, and the fact that the best current evidence is suggestive—but not conclusive proof—of potential harm from oxygen, the need to clarify this uncertainty is urgent.

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**Contributors** AB, JIE and SB designed the first protocol. JBC and JIE participated in protocol amendments. AB, JIE, JBC and SB participated in the data acquisition. AB, JIE, JBC and TQ participated in the analysis and interpretation of data. JBC, AB and JIE wrote the paper. TQ and SB revised the article critically. All the authors approved the version to be published. AB is the guarantor.

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