



## Controversies in cardiovascular medicine

# Oxygen therapy in acute coronary syndrome: are the benefits worth the risk?

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Oxygen supplementation is a standard treatment for all patients who present with acute coronary syndrome, regardless of oxygen saturation levels. Most of the data regarding the function of oxygen in myocardial infarction is based on a limited number of basic and clinical studies. We performed a systematic literature review that explores the basic and clinical data on the function of oxygen in ischaemic heart disease and myocardial infarction. This review discusses many aspects of oxygen treatment: (i) basic studies on the effects of oxygen in ischaemia and the potential cardiovascular effects of oxygen metabolites; (ii) clinical trials that have assessed the value of inhaled oxygen, supersaturated oxygen, and intracoronary injection of hyperoxaemic solutions in myocardial infarction; and (iii) the haemodynamic effects of oxygen in various clinical scenarios and its direct effects on the coronary vasculature. Our findings suggest that there are conflicting data on the effects of oxygen treatment. Further, the potential harmful effects of oxygen must be considered, particularly in myocardial infarction. These findings question the current guidelines and recommendations and emphasize the need for large clinical trials.

**Keywords** Oxygen therapy • Acute coronary syndrome • Myocardial infarction

## Introduction

Oxygen supplementation is a well-accepted therapy for hypoxaemic patients, because it increases the delivery of oxygen to cells and is thus believed to reverse the effects of hypoxia. Nevertheless, the value of oxygen therapy in patients with preserved oxygen saturation is unknown; further, it might even be hazardous under certain conditions (e.g. in pre-term neonates).<sup>1,2</sup>

Oxygen supplementation is a standard component of treatment in patients with acute heart disease. Hypoxaemic patients benefit from oxygen insufflation, because hypoxia can induce general and brain ischaemia.<sup>3</sup>

However, most patients who present with acute coronary syndrome (ACS) are not hypoxaemic,<sup>4</sup> and the value of oxygen therapy in these patients remains unknown.

The 2004 American (AHA/ACC) ST-elevation myocardial infarction (STEMI) guidelines recommend that oxygen be administered to hypoxaemic STEMI patients (SaO<sub>2</sub> <90%, level of evidence B) and state that “it is reasonable to administer supplemental oxygen to all patients during the first 6 hours” (level of

evidence C).<sup>5</sup> More recently published updates do not address the administration of oxygen.<sup>6</sup>

The current European non-ST-elevation myocardial infarction (NSTEMI)-ACS guidelines recommend oxygen supplementation if oxygen saturation is <90%.<sup>7</sup> The recently published European STEMI guidelines suggest a different cut-off that defines hypoxia and advocate oxygen therapy only if oxygen saturation levels are <95%.<sup>8</sup> The recommendations in both guidelines are supported with a low level of evidence (C).

Awareness of the controversial effects of oxygen in normoxic ACS patients has increased,<sup>9,10</sup> an issue that the new guidelines address. However, the recommended practice remains unknown.

In this article, we systematically review basic data and animal and human studies that have assessed the effects of oxygen on cardiovascular parameters.

## Methods

We performed a literature search, involving the follow-up of references, using PubMed. First, we evaluated all studies that have been published in

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PubMed since 1960 in which the terms “oxygen treatment and acute myocardial infarction (MI)” or ‘oxygen and coronary’ appeared in the title. Of all hits, three were randomized control trials. We then tracked down the references from these studies to obtain further data (Figure 1). We focused on studies that evaluated the effects of oxygen on cardiovascular parameters and reported haemodynamic data.

We discuss the basic data on the biological and cardiovascular effects of oxygen and the clinical data on the value of oxygen in MI.

## Preclinical data

Most oxygen in the blood is bound to haemoglobin. The relationship between the partial pressure of oxygen in the bloodstream and haemoglobin saturation is reflected in the oxygen–haemoglobin dissociation curve—at levels >60 mm Hg, the standard dissociation curve is relatively flat, and the overall oxygen content of the blood does not change significantly, even with large increases in the partial pressure of oxygen.<sup>11</sup> During routine oxygen supplementation, the rise in dissolved plasma oxygen cannot be monitored, and more importantly, the effects of increased oxygen levels in the blood are unknown.

Although the elevation in dissolved oxygen can increase the delivery of oxygen to tissues, it can also enhance the formation of reactive oxygen species (ROS).<sup>12</sup> These highly reactive molecules, which are the products of normal oxygen metabolism, can cause significant damage to cells. In ischaemia, ROS are a significant factor in post-ischaemic injury, because they trigger leucocyte chemotaxis and inflammation.<sup>13</sup> Reactive oxygen species also damage electron transport complexes in the mitochondria,<sup>14</sup> and increased ROS levels in experimental ischaemia and reperfusion effect cell death.<sup>15</sup>

With regard to the interaction between vascular smooth muscle cells and cardiac myocytes, myocytes that are exposed to high oxygen concentrations produce increasing amounts of angiotensin I, enhancing vascular tone. However, myocytes that have been exposed to low-oxygen concentrations secrete adenosine,

reducing vascular tone.<sup>16</sup> This novel observation suggests that myocytes act as oxygen sensors and modulate vascular tone according to the needs of the myocardium, limiting the adverse effects of hypoxia and the extensive formation of ROS.

Other detrimental effects of ROS are related to their electrophysiological effects—oxidative stress with hydrogen peroxide promotes early afterdepolarizations and triggered activity, inducing lethal types of arrhythmia, such as ventricular tachycardia and ventricular fibrillation<sup>17</sup> (Figure 2). Although ROS are harmful, no antioxidant has proved to be efficacious in any cardiovascular disease.

## Clinical data

The clinical data on the value of oxygen in MI are based on animal and human studies. Experiments in animal models have demonstrated a beneficial effect of high oxygen in MI. For instance, the effects of intermittent occlusion of the left anterior descending artery in various fractions of inspired oxygen were evaluated in a canine model. An inspired oxygen fraction of 0.4 decreased ST-segment elevation, myocardial creatine phosphokinase (CPK) levels, and ischaemic injury, as evaluated by histology. Notably, higher fractions of inspired oxygen did not improve myocardial injury further.<sup>18</sup>

A separate animal study demonstrated that oxygen reduced infarct size by 38% and increased post-reperfusion ejection fraction (EF), leading the authors to postulate that high-oxygen tension decreases myocardial ischaemia, despite the risk of exacerbating reperfusion injury through elevated free radical levels.<sup>19</sup> A pivotal clinical trial by Madias and Hood<sup>20</sup> enrolled 17 patients with acute anterior transmural MI, in which oxygen inhalation increased PaO<sub>2</sub> by four-fold and lowered ST-segment elevation by 16% with no other clinical effects (Table 1).

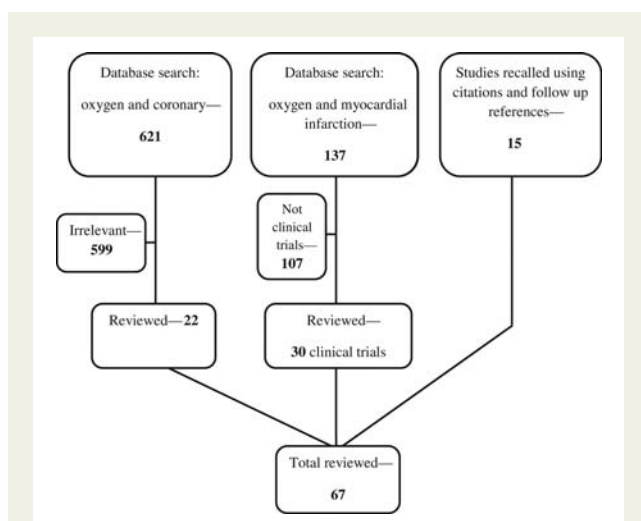
## Hyperbaric oxygen insufflation

Recent clinical studies have examined the effects of very high oxygen levels using hyperbaric oxygen. Hyperbaric oxygen therapy entails the intermittent inhalation of 100% oxygen at >1 atmosphere of pressure. This treatment elevates plasma concentrations of dissolved oxygen, an effect that can normalize or increase oxygen tension to hyperoxic levels in ischaemic tissue.<sup>21</sup>

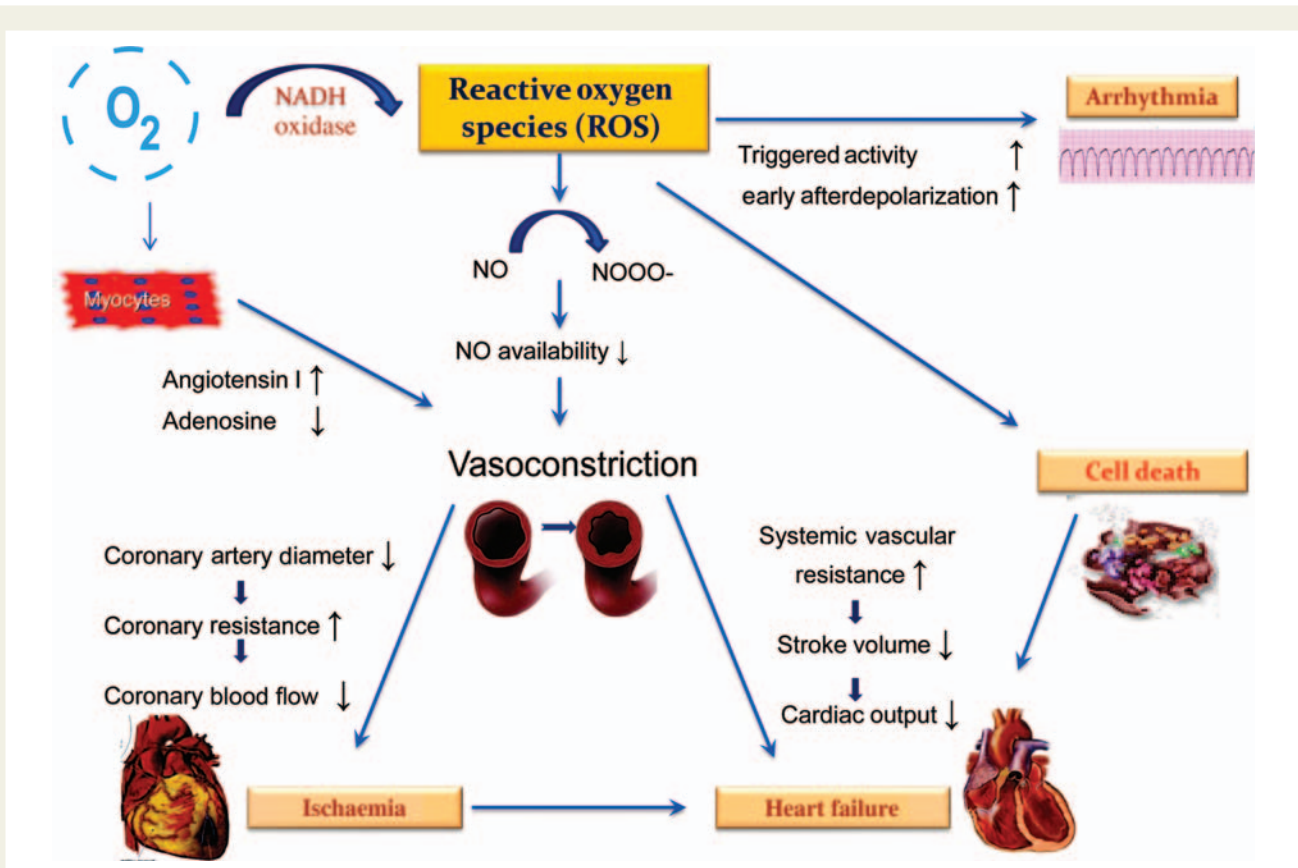
Two randomized trials in MI patients who were treated with thrombolysis have reported conflicting results regarding the effects of oxygen. One study enrolled 74 patients and showed a significant decline in the end-systolic volume index by 20% and improved cardiac output (CO) by 10%.<sup>22</sup> However, the HOT MI study, which enrolled 112 patients, demonstrated a shorter time to pain relief and a non-significant rise in EF, with no significant decrease in CPK levels.<sup>23</sup> Diastolic properties and left ventricular (LV) stiffness were also unaffected by oxygen therapy.<sup>24</sup> No other trials with hyperbaric oxygen have been published.

## Hyperoxaemic reperfusion therapy

Inconsistent data have been generated by studies on the effects of intracoronary injection of hyperoxaemic solutions during MI.



**Figure 1** Data collection for the systematic review. Systematic review, comprising a database search using specific terms and follow-up references.



**Figure 2** Potential mechanisms of the harmful effects of oxygen. High oxygen levels promote the formation of reactive oxygen species, increase angiotensin I, and decrease adenosine levels. These consequences, as well as the possible direct effects of high oxygen, can alter the coronary vasculature and influence haemodynamic parameters. Further, reactive oxygen species can augment the harmful effects of oxygen by promoting arrhythmia and tissue injury.

**Table 1** Effects of oxygen in myocardial infarction

Trial and year	Number of subjects	Study intervention	Outcome	Additional treatment
Madias and Hood <sup>20</sup> (1976)	17	Inhalation of oxygen	Reduction in ST segment elevation	—
Rawles and Kenmure <sup>39</sup> (1976)	157	Inhalation of oxygen	Higher serum aspartate aminotransferase levels and higher incidence of sinus tachycardia	—
Wilson and Channer <sup>40</sup> (1997)	50	Inhalation of oxygen	No effect	Thrombolysis
Ukholkina et al. <sup>41</sup> (2005)	137	Inhalation of oxygen	Decrease in combined end point (death, heart failure, angina and tissue damage)	PCI
Dekleva et al. <sup>22</sup> (2004)	74	Hyperbaric oxygen	EF improved and end-systolic volume was decreased	Thrombolysis
Stavitsky et al. <sup>23</sup> (1998)	112	Hyperbaric oxygen	Decreased time to pain relief but with no significant decrease in creatine phosphokinase levels	Thrombolysis
Vlahovic et al. <sup>24</sup> (2004)	74	Hyperbaric oxygen	No effect on left ventricular diastolic filling	Thrombolysis
Dixon et al. <sup>25</sup> (2002)	29	Injection of intracoronary hyperoxaemic blood	Improved global wall motion score	Primary PCI
O'Neill et al. <sup>26</sup> (2007) and Stone et al. <sup>27</sup> (2009)	269	Injection of intracoronary hyperoxaemic blood	No effect. May reduce infarct size in patients with large MIs treated early	Primary PCI
Warda et al. <sup>28</sup> (2005)	42	Injection of intracoronary hyperoxaemic blood	At 30 days, EF significantly increased. Other parameters remained unchanged	Primary PCI

Trials evaluating the effects of oxygen delivered in various forms in patients presenting with myocardial infarction. PCI, percutaneous coronary intervention; EF, ejection fraction; MI, myocardial infarction.

Hyperoxaemic reperfusion therapy is a treatment in which arterial blood is removed, supersaturated with oxygen, and reinfused into the bloodstream at the site of cardiac injury.<sup>25</sup>

In a pilot study, intracoronary hyperoxaemic blood (PaO<sub>2</sub>: 600–800 mmHg) that was infused into the infarct-related artery improved the global wall motion score from 1.68 to 1.48.<sup>25</sup> However, in the prospective, multicentre AMIHOT trial, there was no difference in the final infarct size, ST-segment resolution, or regional wall motion score between the oxygen-treated and control groups.<sup>26</sup> Despite the lack of a difference in primary outcome, *post hoc* subgroup analyses suggested that oxygen reduces the infarct size (from 26 to 20%, as measured by nuclear imaging) in patients with large MIs who were treated within 6 h of symptoms onset.<sup>27</sup>

In a pre-specified analysis of the AHIMOT trial, by echocardiographic evaluation of 20 patients in the oxygen group and 22 patients in the control group, LV volume remained unchanged and 30-day EF increased significantly in the oxygen group, the latter of which was unchanged in the control group. Other parameters remained constant.<sup>28</sup>

## Haemodynamic effects of oxygen therapy

In addition to the clinical efficacy of oxygen therapy in patients with MI, its cardiovascular and haemodynamic effects have been studied (Table 2). Most studies suggest that oxygen does not have beneficial haemodynamic effects and is even harmful. In normoxaemic patients (SaO<sub>2</sub> >90%) with MI, oxygen therapy decreases CO and stroke volume (SV)<sup>29</sup> and raises systemic vascular resistance (SVR). Notably in hypoxaemic patients with MI, oxygen therapy increased CO.<sup>29</sup> A separate study showed that the administration of 100% oxygen in patients with coronary artery disease (CAD) resulted in an increase of lactate production presumably due to decreased coronary flow.<sup>30</sup>

In contrast, in healthy subjects oxygen therapy increased SVR, with no change in other haemodynamic parameters.<sup>31</sup>

A recent imaging study evaluated CO, SV, and calculated LV perfusion by MRI in healthy volunteers who were treated with oxygen. Oxygen therapy caused a significant 23% decline in LV perfusion.

Similarly, CO decreased by 10% due to a decrease in the heart rate, with no significant changes in SV.<sup>32</sup>

## Effects of oxygen on coronary vasculature

There is less controversy regarding the effects of oxygen on coronary vasculature. Studies from the 1970s suggest that oxygen decreases the coronary sinus blood flow in both healthy subjects and patients with CAD, an effect that was attributed to increased LV coronary resistance<sup>33</sup> (Figure 2).

Further, vascular tone is directly related to oxygen levels—whereas oxygen therapy decreases the coronary blood flow, hypoxia elevates it. It was suggested that hypoxia induces vasodilatation,<sup>34</sup> but in patients with CAD, oxygen reduced coronary blood flow velocity and increased coronary resistance by 23%, without significantly changing the diameter of capacitance arteries.<sup>35</sup> Notably, vitamin C, an antioxidant, prevents hyperoxia-induced vasoconstriction, underscoring the function of ROS in the pathogenesis of oxygen-induced vasoconstriction.<sup>36,37</sup>

The vasoconstrictory effects of oxygen are especially hazardous during coronary stenting, because underestimation of the diameter of the coronary artery is a common cause of stent thrombosis and sudden cardiac death.<sup>38</sup>

## Randomized controlled clinical trials

Although some studies have suggested that oxygen is beneficial in MI, only three randomized controlled clinical trials that have compared inhaled oxygen vs. air in patients with acute MI have been published (Table 1).

The first study, performed by Rawles and Kenmure<sup>39</sup> in the pre-revascularization era, was a controlled blinded study that randomized 105 patients to oxygen and 95 to air, but MI was not confirmed in 25 and 18 patients, respectively. Oxygen was delivered at 6 L/min for 24 h. The mean partial pressure of oxygen in the blood was 65 ± 2 mmHg in the air-treated group and 136 ± 11 mmHg in

**Table 2** Haemodynamic effects of oxygen

Trial and year	Number of subjects	Clinical scenario	Outcome
Bourassa et al. <sup>30</sup> (1969)	50	Patients with CAD	Decrease in coronary blood flow
Sukumalchantra et al. <sup>29</sup> (1969)	59	Normoxaemic patients with acute STEMI	Decrease in CO and SV, increased SVR.
Mak et al. <sup>31</sup> (2001)	28	Healthy subjects	Increased SVR
Bodetoft et al. <sup>32</sup> (2010)	16	Healthy subjects	Decrease in CO and LV perfusion
Ganz et al. <sup>33</sup> (1972)	15	Patients with CAD and healthy subjects	Decrease in coronary sinus blood flow
Momen et al. <sup>34</sup> (2009)	11	Healthy subjects	Decreased coronary blood flow
McNulty et al. <sup>35</sup> (2007)	12	Patients with CAD	Decreased coronary blood flow velocity and increased coronary resistance

Trials evaluating the effects of inhaled oxygen on various haemodynamic and vascular parameters in different clinical scenarios and in healthy subjects. CAD, coronary artery disease; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; STEMI, ST-elevation myocardial infarction; LV, left ventricle.



the oxygen-treated group. The endpoints for this study were death, arrhythmia, and the use of analgesics. There were nine deaths in the oxygen-treated group compared with three deaths in the air group, but this difference was not significant. There was no difference in analgesic use between groups, but the oxygen group had higher serum aspartate aminotransferase levels and a greater incidence of sinus tachycardia.

The second study, by Wilson and Channer,<sup>40</sup> was a small, randomized, but unblinded control trial of 50 patients (25 in each group) with confirmed uncomplicated MI who were followed to discharge. The incidence of hypoxaemia ( $\text{SaO}_2 < 90\%$ ) was 70% and that of severe hypoxaemia was 35% in those who were not treated with oxygen, compared with 27 and 4% in patients who were administered oxygen. There was no difference in ST-segment change between groups, and additional data were not available.

The last study, by Ukholkina *et al.*,<sup>41</sup> enrolled 137 patients who presented with MI and underwent percutaneous coronary intervention. This unblinded study assessed the effects of 30–40% oxygen inhalation (flow rate of 3–6 L/min) compared with air. Baseline saturation rates were comparable between groups (94% with oxygen vs. 93.4% with air). Hypoxaemia at baseline ( $\text{SaO}_2 < 94\%$ ) was noted in 37% of all patients and was associated with lower EF and SV. Oxygen-treated patients presented with more severe clinical features (10% in Killip class II vs. 1% with air). In addition, time to revascularization was 41 min longer in the oxygen group. The endpoints included death, heart failure, angina, and tissue damage, as measured by ECG and cardiac enzymes. More complications were reported in air- vs. oxygen-treated patients (30.4 vs. 13.8%, respectively), but the results of this study were limited, because the measurements of the infarct area in the air-treated group were unreliable.<sup>42</sup>

A recently published meta-analysis<sup>43</sup> reviewed three randomized controlled clinical trials and suggested that the significant methodological problems in these studies precluded any solid conclusions from being drawn.

## Is routine oxygen therapy during myocardial infarction really needed?

Oxygen is readily available and easy to use. Those who recommend routine oxygen therapy argue that oxygen therapy is harmless.<sup>44</sup> A recently published survey evaluated the physician's rationale for using oxygen in MI patients—approximately half of respondents believed that oxygen decreases mortality, while 25% believed that it reduces pain. Although 25% of physicians stated that oxygen has no effect, 96% of them chose to use oxygen in MI patients.<sup>45</sup>

The cost of oxygen treatment in patients with ACS needs to be examined. Basic calculations suggest that in-hospital oxygen treatment costs up to \$10 per day—higher in the pre-hospital setting—translating into a significant cumulative financial burden.

Recently, several scientific societies have reviewed and modified their guidelines on ACS management regarding oxygen supplementation—the new European guidelines now recommend oxygen therapy only in hypoxaemic patients.<sup>7,8</sup> Also, the Scottish

Intercollegiate Guidelines Network and the British National Clinical Guidelines Centre for acute and chronic conditions advocate oxygen therapy only in hypoxic patients ( $\text{SaO}_2 < 94\%$ ). These new revisions, however, are based on expert opinion (level C), not solid clinical data.

## Conclusions

Routine oxygen therapy in acute MI settings is a common practice. Whereas hypoxaemic patients undoubtedly benefit from oxygen insufflation, the level of evidence for this practice in normoxaemic patients is insufficient to determine its efficacy and safety.

Further, there is evidence that this therapy is ineffective and hazardous. Based on our increasing knowledge of the adverse effects of oxygen, particularly ROS, large-scale clinical studies are needed to evaluate the effects of oxygen supplementation and determine the appropriate guidelines for its use.

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