

STATE-OF-THE-ART REVIEW

Oxygen Therapy in Patients With Acute Heart Failure



Friend or Foe?

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ABSTRACT

Supplemental oxygen, a therapy that has been used for more than a century, is recommended in all practice guidelines in the management of hypoxemic (peripheral oxygen saturation <90% to 94% or partial arterial oxygen pressure <60 mm Hg) patients with acute heart failure, but its use in normoxemic patients is controversial. Several pre-clinical and early clinical studies have shown the detrimental effects of oxygen therapy and subsequent hyperoxia in patients with normal oxygen saturation levels. These effects are suggested to be gauged by the increased production of reactive oxygen species and the related oxidative stress and by the reductions in coronary blood flow and myocardial oxygen consumption resulting from hyperoxia-induced vasoconstriction in the cerebral, coronary, and systemic vasculature. Considering these findings, recent practice guidelines are diverging from the previous consensus that oxygen should be administered routinely in patients with cardiac disease, but this new direction is also based on expert opinions rather than evidence such as well-designed trials. In this review, the authors summarize current evidence regarding the cardiovascular effects of supplemental oxygen therapy, particularly evidence from the field of acute heart failure, and delineate knowledge gaps in the field and future directions in research. (J Am Coll Cardiol HF 2016;4:783-90)
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Hear failure (HF) is a highly prevalent chronic disease, and the majority of patients present for the first time or repetitively to the hospital through the emergency department (ED) with “acute” symptoms (1,2). Clinicians treating patients with acute heart failure (AHF) have few proven therapies at their disposal and thus rely on established clinical practice. However, many of these routine clinical practices have little evidence base beyond that of low-quality, non-randomized evidence. Diuretic agents and oxygen are often used concurrently despite the lack of high-quality evidence supporting either of these interventions. Although evidence has emerged from recent AHF trials and cohorts on the risks and potential benefits of emerging pharmacological agents, many

clinical questions remain unanswered. For example, noninvasive mechanical ventilation was used widely and thought to be a potential therapy for AHF, but when it was tested in a larger randomized controlled trial (RCT), there was no additional mortality benefit over standard oxygen therapy in this strategy (3). However, a recent Cochrane review did show an overall benefit for noninvasive mechanical ventilation in reducing hospital mortality, endotracheal intubation, and adverse events compared with standard oxygen therapy (4).

Supplemental oxygen has been used in the management of patients with cardiac disease and investigated for more than a century (5). The rationale for supplemental oxygen therapy in these patients was to improve oxygenation of diseased myocardial tissue.

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**ABBREVIATIONS
AND ACRONYMS**

- AHF** = acute heart failure
- ED** = emergency department
- FiO₂** = fraction of inspired oxygen
- HF** = heart failure
- RCT** = randomized controlled trial
- ROS** = reactive oxygen species

Although most clinicians are concerned about hypoxia (Table 1) in the acute setting, early clinical work demonstrates the negative consequences of hyperoxygenation in normoxemic patients with HF. Observational studies have shown supplemental oxygen therapy to be prescribed in at least one-half of patients with AHF in the ED, regardless of oxygen saturation level (6). Whether supplementary oxygen provides benefit or produces harm in patients with AHF remains uncertain.

**GUIDELINE RECOMMENDATIONS ON
SUPPLEMENTAL OXYGEN THERAPY**

Practice guidelines have emphasized that the symptoms of AHF should be relieved as rapidly as possible (2,7,8). Considering the contradictory findings regarding supplemental oxygen therapy, more recent practice guidelines are diverging from the previous consensus that oxygen should be administered routinely in patients with cardiac disease. However, this new direction is also based on expert opinion rather than well-designed RCTs (7,9-11). The recommendations of different practice guidelines on oxygen therapy in hypoxemic and normoxemic patients with AHF are summarized in Table 2. This topic has been studied in many other non-HF critically ill patient populations (12). For example, the recent American Heart Association guideline on cardiopulmonary resuscitation in patients with cardiac arrest stated that “after restoring the spontaneous circulation, the inspired oxygen should be titrated to minimize the risk of hyperoxemia” (13).

**SUPPLEMENTAL OXYGEN THERAPY:
CURRENT EVIDENCE**

HF STUDIES. Three small studies in patients with chronic HF are key to understanding the potential effects that would mimic the acute setting. Mak et al. (14) studied patients with stable coronary artery disease (n = 12) and those with HF (n = 16). They found that extreme hyperoxia (fraction of inspired oxygen [FiO₂] = 100%) was associated with impairment of cardiac relaxation and increased left ventricular filling pressures in patients with and without HF. In the HF cohort of the study, hyperoxia was associated with several negative hemodynamic changes, such as an increase in systemic vascular resistance, and reductions in cardiac output, stroke volume, and coronary sinus blood flow. Park et al. (15) (n = 13) showed that high-flow oxygen (~5 l/min, FiO₂ = 40%) reduced both cardiac output and heart rate and caused a trend toward increased

TABLE 1 Definitions	
Term	Definition
SaO ₂	Oxygen content in an arterial blood gas
SpO ₂	Peripheral oxygen saturation (measured by pulse oximetry), which is an estimate of arterial oxygen saturation and refers to the amount of oxygenated hemoglobin in the blood
PaO ₂	Partial pressure of oxygen
FiO ₂	Fraction of inspired oxygen; in terms of oxygen therapy, the term refers to the amount of oxygen a patient breathes in (21% = room air = 0.21, 24% = 1 l/min by nasal cannula = 0.24)
Hypoxia	Lack of oxygen at the level of the organ, tissue, or compartment; the term generally refers to SaO ₂ <90% to 94% or PaO ₂ <60 mm Hg
Hyperoxia	High oxygen content (either excess O ₂ or higher than normal physiological pO ₂)
Hyperoxemia	High oxygen tension in blood
ROS	Reactive oxygen species; chemically reactive molecules containing oxygen, such as superoxide, peroxide, hydroxyl and peroxy radicals, which are generated by enzymatic and nonenzymatic catalysis

systemic vascular resistance with no change in stroke volume compared with room air (FiO₂ = 21%). Both studies concluded that excessive supplemental oxygen may be detrimental to cardiac function. Finally, Haque et al. (16) observed reductions in stroke volume and cardiac output and an increase in pulmonary capillary wedge pressure with hyperoxia in patients admitted with AHF (baseline peripheral oxygen saturation = 92.6%), which began as early as 24% FiO₂, equivalent to 1 l/min of supplemental oxygen. Although the effect of oxygen may vary among patients with HF with reduced ejection fraction and those with HF with preserved ejection fraction, the available evidence is all from patients with HF with reduced ejection fraction (14-16), and no single study has investigated the effect of supplemental oxygen in the setting of HF with preserved ejection fraction. Finally, and although the practice of supplementing oxygen in patients with AHF is common, there have been no published cohort studies or RCTs establishing the role of hyperoxia in patients with AHF.

RELATED FINDINGS FROM ACUTE CORONARY SYNDROME STUDIES. Research involving patients with acute coronary syndromes has shown potential harm of excess oxygen administration (Table 3). Farquhar et al. (17) performed a systematic review of 6 studies (including 6 healthy subjects and 61 patients with cardiac disease) and reported that hyperoxia from high-concentration oxygen therapy caused marked reduction in coronary blood flow (8% to 29%) through an increase in coronary vascular resistance (mainly at the level of microvascular vessels). Cabello et al. (18) performed a meta-analysis including 4 RCTs

TABLE 2 Guideline Recommendations Regarding Oxygen Therapy in Hypoxemic and Normoxemic Patients With Heart Failure

Guideline (Ref. #)	Year	Recommendation on O ₂ Therapy in Hypoxemic Patients	Recommendation Class	Level of Evidence	Recommendation on O ₂ Therapy in Normoxemic Patients	Recommendation Class	Level of Evidence
ACCF/AHA (2)	2013	Not mentioned	NA	NA	Not mentioned	NA	NA
ACCF/AHA (48)	2009	O ₂ therapy should be administered to relieve symptoms related to hypoxemia	Class I	C	Not mentioned	NA	NA
HFSA (9)	2010	Routine administration of supplemental O ₂ in the presence of hypoxia is recommended	Class I	C	Routine administration of supplemental O ₂ in the absence of hypoxia is not recommended	Class III	C
ESC (11)	2012	O ₂ may be given to treat hypoxemia (SpO ₂ <90%)	Class I	C	Oxygen should not be used routinely in nonhypoxemic patients	Class III	C
CCS (7)	2012	Supplemental O ₂ therapy should be considered for patients who are hypoxemic (SaO ₂ <90%)	Strong	Moderate	Oxygen should be used cautiously in normoxic patients	NA	NA
ACCP consensus (10)	2010	Supplemental O ₂ can provide relief of dyspnea for patients who are hypoxemic at rest or during minimal activity	Class I	Clear consensus (~75% agreement)	Use of supplemental O ₂ for nonhypoxemic patients with advanced lung and heart disease	Class III	47% agreement
NICE (49,50)	2014	Not mentioned	NA	NA	Not mentioned	NA	NA
NHFA/CSANZ (51)	2011	No clear recommendation statement, however suggested oxygenation for hypoxemic patients	NA	NA	Not mentioned	NA	NA

ACCF = American College of Cardiology Foundation; ACCP = American College of Chest Physicians; AHA = American Heart Association; CCS = Canadian Cardiovascular Society; CSANZ = Cardiac Society of Australia and New Zealand; ESC = European Society of Cardiology; HFSA = Heart Failure Society of America; NA = not applicable; NICE = National Institute for Health and Care Excellence; NHFA = National Heart Foundation of Australia.

(n = 430) showing a 2-fold increase in the risk for death in patients with acute coronary syndromes given fixed supplemental oxygen (3 to 6 l/min or, in 1 study, manually titrated to achieve an oxygen saturation of 93% to 96%). We have updated this meta-analysis of RCTs by adding the most recent RCT, mentioned later, and have observed a lack of mortality difference between 2 approaches (Figure 1). Despite the equipoise observed in this analysis, it should be noted that the studies are mostly small, with divergent results; hence, further large-scale trials are indicated.

The AVOID (Air Versus Oxygen in Myocardial Infarction) trial randomized 441 patients with ST-segment elevation myocardial infarctions to either of supplemental oxygen (8 l/min via mask) or no additional oxygen and evaluated myocardial infarct size and clinical events (19). It showed that supplemental oxygen in patients with ST-segment elevation myocardial infarctions without hypoxia had increased myocardial injury and larger myocardial infarct size (55% larger) at 6 months (20). An ongoing trial in patients with acute coronary syndromes is the DETO₂X-AMI (Determination of the Role of Oxygen in

Acute Myocardial Infarction) trial, a registry-based RCT, recruiting up to 6,600 normoxic patients with suspected AMI who are randomized to either 6 l/min supplemental oxygen using a face mask for 6 to 12 h or room air; results are expected in 2017 (21).

POTENTIAL MECHANISMS OF HYPEROXIA-INDUCED CARDIOVASCULAR EFFECTS

Although hypoxia happens frequently in nature (e.g., various disease states, altitude), hyperoxia is a man-made phenomenon, and humans have not developed any evolutionary adaptation to respond to hyperoxia. Hence, we sense hyperoxia by a conglomerate of factors that are “responding to the stress of unnaturally high local O₂ levels” (22). The cardiovascular effects of hyperoxia are mediated by 2 main phenomena: the endothelial production of reactive oxygen species (ROS) and hyperoxia-induced vasoconstriction in the cerebral, coronary, and systemic vasculature. Although inflammation was proposed as a mechanism of hyperoxia-related effects in some

TABLE 3 Clinical Studies on Oxygen Therapy in Acute Coronary Syndromes

First Author (Year), Country (Ref. #)	Study Design and Sample Size	Participants	Intervention	Comparator	Effect of Hyperoxia
Bourassa et al. (1969), Canada (52)	Single-arm intervention, n = 23	CAD	FiO ₂ = 1.0, mouthpiece with a Sanborn metabulator, 6 min	Room air	Decreased cardiac index by 14%, 3.7 ± 1.3 vs. 3.2 ± 0.9 l/min/m ²
Ganz et al. (1972), United States (53)	Single-arm intervention, n = 9	CAD	10-15 l/min, face mask, 7 min	Room air	Decreased cardiac index by 10%, 2.9 ± 0.1 vs. 2.6 ± 0.1 l/min/m ²
Rawles and Kenmure (1976), United Kingdom (54)	Double-blind RCT, n = 200	Suspected AMI presenting within 24 h of onset of pain	6 l/min O ₂ , MC mask, 24 h	6 l/min air at normal pressure, MC mask, 24 h	Increased infarct size determined by AST by 19%, 80.7 ± 6.6 vs. 99.9 ± 7.1
Wilson and Channer (1997), United Kingdom (55)	Open-label RCT, n = 50	Confirmed uncomplicated AMI	4 l/min O ₂ , face mask, 24 h	Air breathed normally	No difference in arrhythmia or ST-segment changes
Ukholkina et al. (2005), Russia (56)	Open-label RCT, n = 137	Confirmed uncomplicated AMI	3-6 l/min O ₂ (FiO ₂ = 30%-40%), nasal cannula, 3 h	Air breathed normally	
McNulty et al. (2005), United States (57)	Single-arm intervention, n = 18	Stable coronary artery disease	FiO ₂ = 1.0, face mask, 15 min	Room air	Decreased coronary blood flow by 29%, 45 ± 14 vs. 32 ± 7 cm ³ /min
McNulty et al. (2007), United States (58)	Single-arm, before-after intervention, n = 12	Stable angina pectoris	FiO ₂ = 1.0, face mask, 10 min	Room air	Decreased coronary blood flow by 20%, 91 ± 31 vs. 73 ± 28 cm ³ /min
Ranchord et al. (2012), New Zealand (59)	Open-label RCT, n = 136	Confirmed uncomplicated AMI	6 l/min O ₂ , MC mask, 6 h	O ₂ titrated to SaO ₂ of 93%-96%, nasal prongs or mask	Nonsignificant difference in infarct size assessed by troponin T level 2.2 ± 1.8 vs. 2.9 ± 2.8 ng/ml or MRI infarct 12.5 ± 10.9% vs. 13.1 ± 9.7%
Stub et al. (2015), Australia (20)	Open-label RCT, n = 441	Confirmed uncomplicated AMI	8 l/min O ₂ , Hudson mask, until the end of acute PCI	Air breathed normally	Median CK 2,073 U/l (IQR: 1,065-3,753 U/l) vs. 1,727 U/l (IQR: 737-3,598 U/l)
Khoshnood et al. (2015), Sweden (60)	Single-blind RCT, n = 100	Normoxemic patients with confirmed STEMI	10 l/min O ₂ , OxyMask, until the end of acute PCI	Room air	In progress

AMI = acute myocardial infarction; AST = aspartate aminotransferase; CAD = coronary artery disease; CK = creatine kinase; FiO₂ = fraction of inspired oxygen; IQR = interquartile range; MC = medium concentration; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SaO₂ = peripheral oxygen saturation; STEMI = ST-segment elevation myocardial infarction.

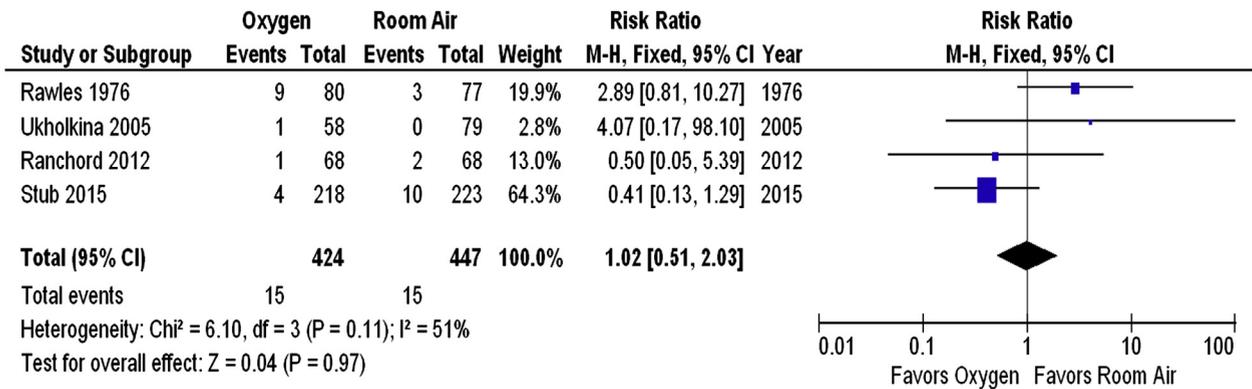
studies (23-25), it was not supported by others (26,27), and it seems to be a downstream impact of the oxidative stress.

When high tissue oxygen levels are present, ROS such as superoxide and hydrogen peroxide form to cause cellular tissue damage. Supplemental oxygen therapy and hyperoxia have been shown to exacerbate the formation and accumulation of excessive ROS (28,29). There are mainly 3 cellular sources for the production of ROS under hyperoxic conditions: 1) the mitochondrial electron transport chain, which can generate superoxide ions in a process of incomplete oxygen reduction and impaired electron transfer within the chain complexes (30); 2) nicotinamide adenine dinucleotide phosphate oxidases, which are expressed in the cellular membrane of the endothelial cells (31,32); and 3) through nonenzymatic reactions, similar to exposure to radiation (33). When the accumulated ROS outweighs the antioxidant capacity in

the tissue or body, it leads to oxidative stress and a cascade of adverse outcomes, including cardiac cell damage and death. Although AHF is a syndrome involving patients with different underlying etiologies and triggers, the mechanism to develop ROS and subsequent cardiac, pulmonary, and cerebral effects are similar.

Hyperoxia, by reducing the production and the bioavailability of nitric oxide as a potent vasodilator, attenuates endothelial-mediated vasodilation and increases vascular tone. ROS-induced closure of adenosine triphosphate-dependent potassium channels (34) and activation of ligand-gated calcium channels (35) in vascular smooth muscle cells as well as a potential increase in endothelin-1 level and a decrease in the bioavailability of prostacyclin are some other mechanisms proposed for hyperoxia-related vasoconstriction (36,37). Hyperoxia-induced vasoconstriction leads to a decrease of 8% to 30% in

FIGURE 1 Forest Plot of Oxygen Versus Room Air Comparison for the Outcome of In-Hospital Death in Patients With Acute Myocardial Infarction



CI = confidence interval; M-H = Mantel-Haenszel.

the coronary blood flow, which outweighs the increase in blood oxygen content resulting from hyperoxygenation, leading to a reduction in oxygen delivery to the myocardium and hence worsening myocardial relaxation and contractility. Decreased cerebral blood flow occurs with increasing cerebral oxygen delivery in normoxic patients and leads to increased ventilation and possibly increased dyspnea (38,39). Also, the aforementioned hyperoxia-related decrease in cardiac output seems to be gauged by a reduction in heart rate rather than a decrease in stroke volume (15). The heart rate reduction has been shown to be mediated by an increase in parasympathetic activity and not related to the sympathetic nervous system (16,40-42). The **Central Illustration** summarizes some potential mechanisms of effect for supplemental oxygen therapy in patients with cardiac diseases. These mechanisms are discussed in greater detail elsewhere (36,39,43).

**FUTURE DIRECTIONS:
 IS ADDITIONAL OXYGEN EFFECTIVE,
 COST EFFECTIVE, OR EVEN SAFE?**

Oxygen therapy remains a cornerstone of AHF treatment in practice, but guidelines provide variable recommendations on its appropriate use, reflecting the lack of robust evidence on this “cornerstone” therapy (2,7,8). To produce a change in clinical practice given the long-standing and often fixed beliefs about the benefit of a “safe” therapy, studies beyond cohort studies must provide sufficient evidence to “reverse” the trend of giving oxygen to nonhypoxic patients. As an example, it was standard to perform neonatal resuscitation with 100% oxygen until

multiple RCTs demonstrated that room air results in a lower incidence of infant mortality and hypoxic-ischemic encephalopathy than 100% oxygen, leading to a dramatic change in guidelines and practice (44). There are still many unresolved questions regarding the optimal method of oxygen delivery, levels, and duration of therapy in any patient management framework, such as ambulances, EDs, and inpatient wards.

Additional considerations should also be given to the economic implications. Health care systems spending roughly \$100/day per patient on oxygen gas alone, without considering the physician, nursing, and respiratory therapist time to initiate, titrate, and discontinue therapy, increased complexity of routine care, and expendables such as nasal cannulas and oxygen bottles.

How should a trial be designed in this complex area? Both pre-hospital and ED- and hospital-based patients must be included, with the consideration of a short-term clinical outcome related to the intervention. Similar to the DOSE (Diuretic Optimization Strategies Evaluation) trial (45), as early as 3 to 5 days for a short-term surrogate outcome (e.g., natriuretic peptide level, ST-2, peak expiratory flow rate, dyspnea indexes) may be reasonable for a phase 2-like trial, but key outcomes should be measured until 30 days at a minimum. There are many possible designs, including (but not limited to):

1. an RCT with patient-level randomization of face mask at a set level (e.g., 6 l/min) versus no face mask, similar to the design of the AVOID trial (20);
2. an RCT with patient-level randomization at 2 separate oxygen delivery levels;

supplemental oxygen delivery. These hold promise for conducting oxygen titration studies with near constant adjustments and less heterogeneity of blood oxygen saturations (46,47). These systems can regulate the flow of oxygen every second on the basis of a pulse oxygen level through a sophisticated closed-loop algorithm that can increase or decrease oxygen flow on a second-to-second basis to prevent under- or overdelivery of oxygen. We are conducting an RCT addressing the issue of optimal supplemental oxygen titration and dosing targets in patients with AHF using a closed-loop automated oxygenation system (HiLo-HF [High Versus Low SpO₂ Oxygen Therapy in

Patients With Acute Heart Failure]; [NCT02518828](#)). Although this may answer some initial questions, many will remain unanswered, and many iterations and designs will be necessary to understand the complexity of the relationship of patients with AHF and our old friend (or foe) oxygen.

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