JACC: ADVANCES VOL. 1, NO. 3, 2022

STATE-OF-THE-ART REVIEW

CRITICAL CARE CARDIOLOGY

Oxygen Supplementation and Hyperoxia in Critically Ill Cardiac Patients

From Pathophysiology to Clinical Practice

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ABSTRACT

Oxygen supplementation has been a mainstay in the management of patients with acute cardiac disease. Although hypoxia is known to be detrimental, the adverse effects of artificially high oxygen levels (hyperoxia) have only recently been recognized. Hyperoxia may induce harmful hemodynamic effects, including peripheral and coronary vasoconstriction, and direct cellular toxicity through the production of reactive oxygen species. In addition, emerging evidence has shown that hyperoxia is associated with adverse clinical outcomes. Thus, it is essential for the cardiac intensive care unit clinician to understand the available evidence and titrate oxygen therapies to specific goals. This review summarizes the pathophysiology of oxygen within the cardiovascular system and the association between supplemental oxygen and hyperoxia in patients with common cardiac intensive care unit diagnoses, including acute myocardial infarction, heart failure, shock, cardiac arrest, pulmonary hypertension, and respiratory failure. Finally, we highlight lessons learned from available trials, gaps in knowledge, and future directions. (JACC Adv 2022;1:100065)

Oxygen supplementation has been a foundational therapy for cardiac disease since Professor Charles Steel reported the resolution of angina with oxygen inhalation in 1900.[1] Over the subsequent 100 years, oxygen therapy was used routinely, especially for acute myocardial infarction (AMI), because of the widespread belief that supplemental oxygen counteracts the reduced blood flow from coronary obstruction and improves oxygen delivery.[2] Although hypoxia, defined as low oxygen levels at tissues and organs (**Figure 1**), has long been known to be detrimental to organ function,[3] the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 6, 2022; revised manuscript received July 5, 2022, accepted July 6, 2022.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2022.100065

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

AMI = acute myocardial infarction

CICU = cardiac intensive care unit

CS = cardiogenic shock

ECMO = extracorporeal membrane oxygenation

FiO_2 = fraction of inspired oxygen

HF = heart failure

ICU = intensive care unit

IMV = invasive mechanical ventilation

NSTEMI = non-ST-segment elevation myocardial infarction

PaO_2 = partial pressure of oxygen

PH = pulmonary hypertension

PPV = positive pressure ventilation

ROSC = return of spontaneous circulation

SaO_2 = oxygen saturation

STEMI = ST-segment elevation myocardial infarction

VA = venoarterial

potential harm of hyperoxia, defined as supraphysiologic oxygen at tissues and organs, has only recently been described. In addition, many clinicians share the misperception that oxygen supplementation is harmless,[4,5] resulting in upward of 84% of hospitalized patients being exposed to hyperoxia.[6]

As the understanding of oxygen supplementation has evolved, so too has the patient population in the cardiac intensive care unit (CICU), which now includes a complex, heterogenous mix of patients often complicated by multiorgan failure.[7-9] Respiratory failure is common in contemporary CICU populations, caused by both cardiac and noncardiac diseases.[10,11] Although the management of respiratory failure in the CICU has recently been reviewed,[12] there is less guidance concerning the effects of supplemental oxygen and hyperoxia in the CICU. However, it is critical for clinicians managing patients with acute cardiovascular disease to have a practical understanding of the effects of oxygen supplementation and potential harm of hyperoxia. Hence, we review the pathophysiology of oxygen in the cardiovascular system, examine clinically important subsets of cardiac patients, and review available studies as they relate to supplemental oxygen use and hyperoxia in the modern CICU patient population. Where possible, we have included societal guideline recommendations at the end of each section. When recommendations are absent or data are less robust, we have stated so, offered guidance, and detailed gaps in knowledge.

HIGHLIGHTS

- Although oxygen therapy is ubiquitous in the CICU, few guidelines address the effects of hyperoxia.
- Hyperoxia should be avoided in the CICU as it has multiple detrimental hemodynamic effects.
- Clinical trials are needed to establish oxygenation targets in CICU subpopulations.

CARDIOVASCULAR PATHOPHYSIOLOGY OF HYPOXIA AND HYPEROXIA

The fundamental function of the cardiovascular system is to provide oxygen and nutrients to the tissues and organs. Oxygen is carried predominantly in red blood cells bound to hemoglobin, with a small amount of oxygen dissolved in plasma. Once hemoglobin is completely saturated with oxygen, further oxygen supplementation will only serve to increase the amount of oxygen dissolved in blood (**Figure 2**). Importantly, excess oxygen dissolved in blood contributes little to the overall oxygen content but potentially enhances its toxic effects through the production of reactive oxygen species.[13] In addition, other methods of increasing oxygen delivery, such as blood transfusions, have largely found benefit or noninferiority from a restrictive strategy (hemoglobin levels 7-8 g/dL) compared with liberal transfusion strategy (hemoglobin level 10 g/dL) in numerous patient populations, including patients with AMI.[14,15] In the REALITY randomized trial of patients presenting with AMI, a transfusion threshold of 8 g/dL was found to be noninferior to a transfusion threshold of 10 g/dL for major cardiovascular outcomes at 30 days.[14] Nevertheless, anemia is associated with higher mortality,[16] including in patients with AMI.[17] Management of anemia in the patient with cardiovascular disease should be individualized (eg, evaluation for acuity of the drop, symptoms, or evidence of ongoing refractory ischemia) and prompt investigation for the etiology. The ongoing MINT trial (NCT02981407), which aims to enroll 3,500 patients with AMI and a hemoglobin <10 g/dL to a restrictive or liberal transfusion goal, may clarify future practice. Similarly, there is no evidence to suggest benefit in increasing cardiac output with inotropes and/or mechanical support above a mean arterial pressure of 65 mm Hg improves outcomes.[18]

Both hypoxia and hyperoxia may contribute to hemodynamic changes in patients with cardiopulmonary disease. Hypoxia increases heart rate via sympathetic stimulation and reduces systemic vascular resistance via tissue and endothelial release of vasodilatory metabolites.[19,20] In contrast to the peripheral circulation, hypoxia induces pulmonary vascular vasoconstriction, mediated by mitochondria sensing low oxygen tension in pulmonary artery smooth muscle cells.[21] Although hypoxic pulmonary vasoconstriction evolved to optimize ventilation-perfusion matching, it can become severely maladaptive in syndromes such as acute respiratory distress syndrome, resulting in increased afterload on the right ventricle and resultant right ventricular failure.[22,23] Moreover, exposure to chronic hypoxia is implicated in adverse pulmonary vascular remodeling

FIGURE 1 Common Oxygen Definitions in Clinical Research

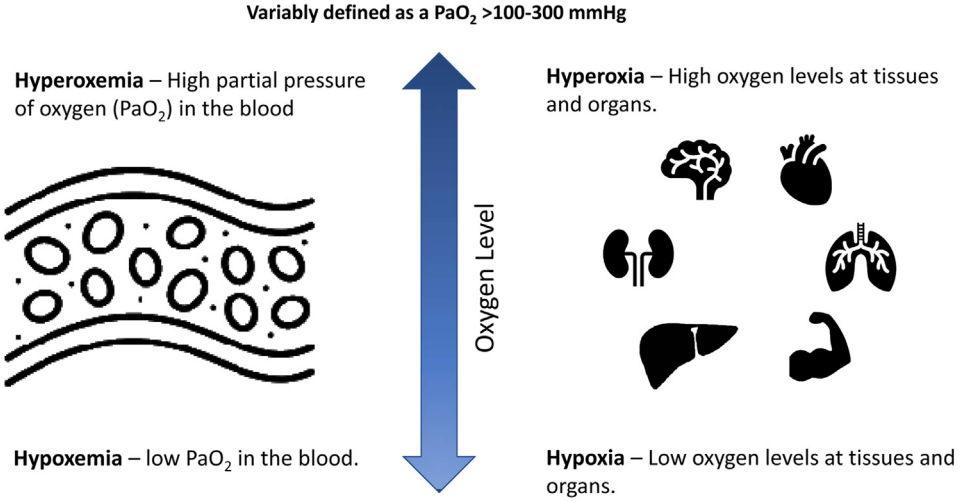
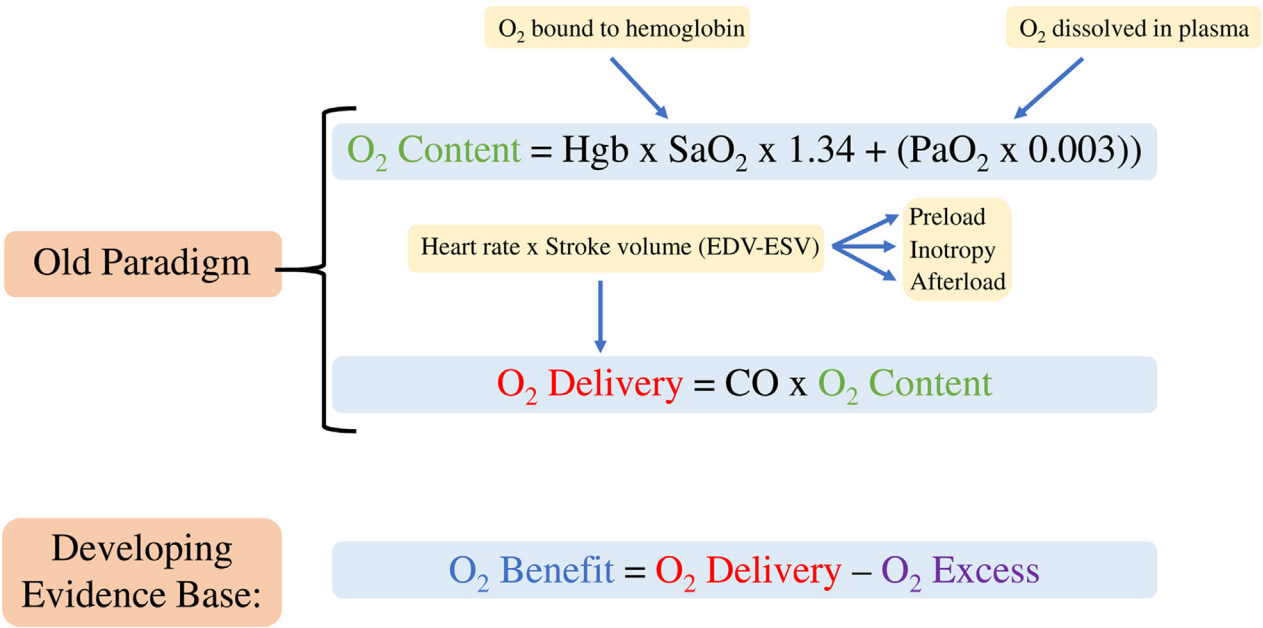
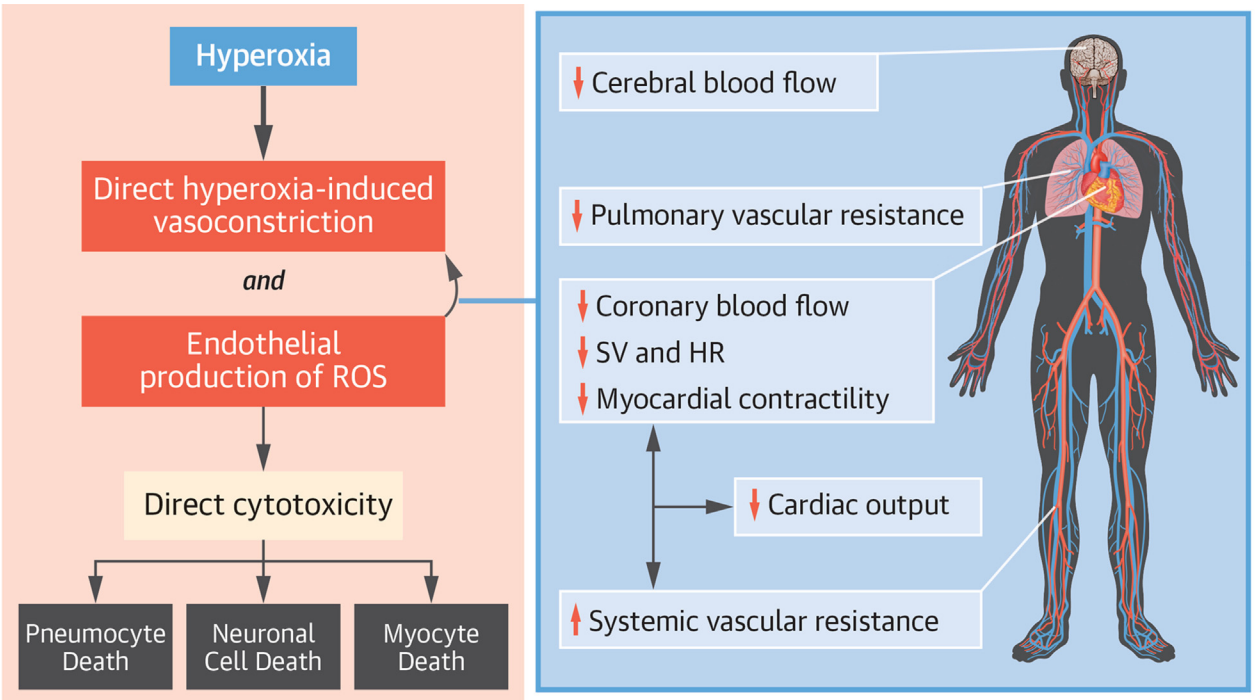


FIGURE 2 Oxygen Content, Delivery, and Benefit vs Harm



EDV = end diastolic volume; ESV = end systolic volume; Hgb = hemoglobin; PaO_2 = partial pressure of oxygen; SaO_2 = arterial oxygen saturation.

CENTRAL ILLUSTRATION **Potential Systemic Effects of Hyperoxia on Patients With Acute Cardiovascular Disease**



Thomas A, et al. JACC Adv. 2022;1(3):100065.

The 2 key systemic effects of hyperoxia include direct hyperoxia-Induced vasoconstriction and the generation of endothelial ROS, which can reduce nitric oxide levels and cause further vasoconstriction.[26,99] In addition, ROS are directly toxic and may cause pneumocyte, neuronal, and myocyte death.[100,101] Through vasoconstriction, hyperoxia can decrease cerebral and myocardial blood flow while increasing systemic vascular resistance.[24] The increase in afterload activates pressure-sensitive baroreceptors, ultimately decreasing heart rate and subsequently cardiac output.[24] HR = heart rate; BP = blood pressure; ROS = reactive oxygen species; SV = stroke volume.

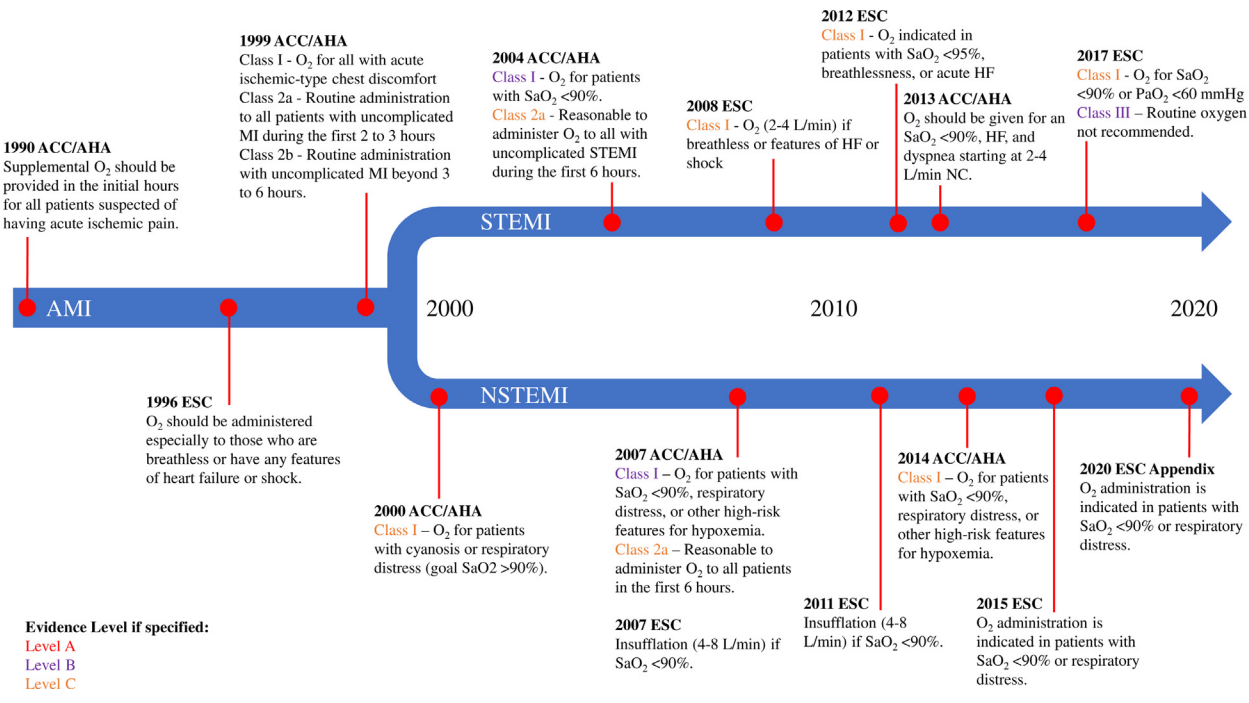
and the development of fixed precapillary pulmonary hypertension (PH).

Hyperoxia is also associated with several notable systemic effects (**Central Illustration**).[24] Hyperoxia has been shown to cause vasoconstriction in multiple organ beds, with an average increase in the systemic vascular resistance of 250 to 550 dyne $\times$ s $\times$ cm^{-5} and a 10% to 30% decrease in blood flow in the coronary, cerebral, and vascular systems.[25-27] Although multiple mechanisms have been proposed, hyperoxia appears to drive vasoconstriction primarily by decreasing the production and bioavailability of nitric oxide through excessive production of reactive oxygen species.[28] In addition, hyperoxia increases parasympathetic tone, via the baroreceptor reflex, in response to vasoconstriction and central chemoregulation, which causes a decline in heart rate and subsequent rate-related decrease in cardiac output.[27,29] In chronic heart failure (HF), patients with hyperoxia have a blunted heart rate response, a greater elevation in systemic vascular resistance, and a reduction in cardiac output, primarily driven by a decline in stroke volume.[24,30] Similar effects have been observed in patients with coronary artery disease, with subsets showing substantial reductions in cardiac function when exposed to hyperoxia.[31]

UNIQUE PATIENT POPULATIONS IN THE CICU

ACUTE MYOCARDIAL INFARCTION. Over the last 30 years, professional societies have shifted from recommending the routine use of supplemental oxygen in all patients with AMI, including both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), to treating only those with hypoxia (**Figure 3**). This departure from the routine use of supplemental oxygen in normoxic AMI patients has been driven by several clinical trials. Mechanistically, the scientific rationale behind oxygen therapy is to

FIGURE 3 Evolution in Major Societal Guideline Recommendations for Oxygen Supplementation in Patients With Acute Myocardial Infarction



AMI = acute myocardial infarction; HF = heart failure; NC = nasal cannula; STEMI = ST-segment elevation myocardial infarction.

augment oxygen delivery to the ischemic myocardium in the setting of impaired coronary blood flow and thereby attenuate infarct size. However, this hypothesis was largely derived from animal models and small clinical studies. More recent higher quality data now suggests that routine use of supplemental oxygen therapy in normoxic AMI patients is not beneficial and may lead to harm.

In 1976, the first prospective trial of oxygen therapy in suspected AMI was performed before the revascularization era and found significantly larger infarcts, as measured by aspartate aminotransferase, in the oxygen-treated group.[32] More recently, in 2015, the Australian Air vs Oxygen in Myocardial Infarction trial randomized 441 normoxic STEMI patients to oxygen via face mask (8 L/min) or no supplemental oxygen. Patients who received supplemental oxygen had larger infarct sizes on cardiac magnetic resonance imaging, greater myocardial injury (as assessed by cardiac biomarkers), and more frequent recurrent AMI (**Table 1**).[33] In contrast, the SOCCER (Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion) study, which randomized 100 normoxic STEMI patients to supplemental oxygen (10 L/min) or room air, found no significant differences in infarct size, myocardium at risk, or myocardial salvage index as assessed by cardiac magnetic resonance imaging.[34]

The largest study of oxygen therapy in patients with AMI was the DETO2X-AMI trial, which was a pragmatic, registry-based randomized trial of 6,629 patients in Sweden.[35] Patients with suspected AMI without hypoxemia were randomized to routine use of supplemental oxygen (6 L/min) for 6 to 12 hours delivered by open face mask vs room air. At 1-year, all-cause mortality was similar between groups, and routine oxygen administration did not reduce the prespecified composite of all-cause death, HF hospitalization, or cardiovascular death within 1 year. Notably, these findings were consistent across all 11 prespecified subgroups, regardless of baseline characteristics or AMI type.

As a result of these accumulated data, oxygen supplementation in normoxic patients with AMI is no longer standard of care. We concur with the 2017 STEMI guidelines from the European Society of Cardiology, which recommend oxygen therapy only for patients with an oxygen saturation (SaO_2) <90% (Class I) as well as their Class III recommendation against routine oxygen use (**Table 2**).[36] The 2013 American College of Cardiology/American Heart

TABLE 1 Notable Clinical Studies on Oxygenation in Cardiac Intensive Care Unit Populations

First Author (Study)	Year	Study Type	Study Size	Comparison	Main Outcomes
STEMI					
Ranchord et al,[102] (OPTIMISE)	2012	2-center RCT	136	6 L/min or O_2 to achieve SaO_2 93-96%	No difference in cardiac biomarkers or infarct size
Stub et al,[33] (AVOID)	2015	Multicenter RCT	441	8 L/min O_2 via face mask vs no O_2 unless SaO_2 <94%	Increase in recurrent AMI, arrythmias, cardiac biomarkers, and infarct size at 6 mo in the O_2 arm
Khoshnood et al,[34] (SOCCER)	2018	2-center RCT	95	10 L/min O_2 vs no O_2 unless SaO_2 < 94%	No difference in myocardium at risk or resulting infarct size assessed by CMR
AMI					
Hofmann et al,[35] (DETO2X-AMI)	2017	Multicenter RCT	6,629	6 L/min O_2 for 6-12 h vs no O_2 unless SaO_2 <90%	No difference in 1-y mortality or rehospitalization with AMI (including STEMI, n = 2,807)
Cardiac arrest					
Kuisma et al[103]	2006	Multicenter RCT	28	100% vs 30% FiO_2 for 60 min post-ROSC	No difference in overall serum markers of neuronal injury, but higher levels in the 100% O_2 group who did not undergo TTM
Kilgannon et al[54]	2010	Multicenter cohort	6,326	Hyperoxia[a] vs normoxia or hypoxia on the first ICU ABG	Hyperoxia was independently associated with increased in-hospital mortality compared with either normoxia or hypoxia
Roberts et al[52]	2018	Multicenter cohort	280	Early hyperoxia[a] (first 6 h) vs no hyperoxia	Early hyperoxia was independently associated with poor neurologic function at hospital discharge
Acute HF					
Minana et al[93]	2011	Single-center prospective	588	PaO_2 as a continuous variable and hypoxemia[b] vs normoxia on initial ABG	PaO_2 not associated with mortality. Hyperoxia not assessed.
Sepehrvand et al[43]	2019	Open-label, single-center RCT	50	High (≥96%) vs low (90-92%) SpO_2 targets	No difference in NT-proBNP levels, patient-reported dyspnea, patient global assessment, in-hospital mortality, or 30-d readmission
Chu et al[42]	2020	Singe-center retrospective	335	Hypoxemic (<75 mm Hg) vs normoxemic (75-100 mm Hg) vs and hyperoxemic (>100 mm Hg) patients	No difference in the proportion of patients undergoing mechanical ventilation, LOS, or in-hospital mortality
Yu et al[41]	2021	Multicenter propensity matched	2,922	Oxygen therapy vs room air in normoxemic patients	No difference in ICU or hospital mortality. The oxygen group had a longer ICU and hospital LOS
Hypoxic RF					
Barrot et al,[76] ($LOCO_2$)	2020	Multicenter RCT	205	PaO_2 target of 55-70 mm Hg vs 90-105 mm Hg for the first 7 d	Primary outcome of 28-d mortality was not different. Stopped early due to a statistically significant increased mortality in 90-d in the conservative group
Mackle et al,[73] (ICU-ROX)	2020	Multicenter RCT	1,000	Conservative vs usual care O_2 until ICU discharge or 28 d	No difference in mortality or ventilator free days
Schjorring et al,[78] (HOT-ICU)	2021	Multicenter RCT	2,928	PaO_2 target of 60 mm Hg vs 90 mm Hg	No difference in mortality, AMI, or stroke at 90 d

[a]Defined as a PaO_2 >300 mm Hg. [b]Defined as a PaO_2 <60 mm Hg.

ABG = arterial blood gas; AMI = acute myocardial infarction; CMR = cardiac magnetic resonance; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; LOS = length of stay; RCT = randomized controlled trial; RF = respiratory failure; ROSC = return of spontaneous circulation; STEMI = ST-segment elevation myocardial infarction; TTM = targeted temperature management.

Association STEMI guidelines, which preceded the DETO2X-AMI trial results, recommend oxygen therapy starting at 2 to 4 L/min for patients with a SaO_2 <90%, HF, or dyspnea (no class recommendation),[37] which are similar to the most recent American College of Cardiology/American Heart Association and European Society of Cardiology NSTEMI recommendations.[38,39]

ACUTE HF AND CARDIOGENIC SHOCK. Oxygen therapy is widely recommended for hypoxic patients with acute heart failure (AHF),[40] yet provision of supplemental oxygen therapy to normoxic patients with AHF may result in hyperoxia and potential harm. In a propensity-matched analysis of 2,922 normoxic intensive care unit (ICU) patients with AHF, supplemental oxygen did not confer a

TABLE 2 Current Major Societal Guidelines for the Appropriate Use of Supplemental Oxygenation and Avoidance or Management of Hyperoxia

Patient Population	Society	Year	Supplemental Oxygen Recommendation	Hyperoxia Recommendation
General CICU				
	AHA	2020	Titrate supplemental oxygen to an SpO_2 >90% or PaO_2 >60 mm Hg	PaO_2 >150 mm Hg should be avoided
AMI				
STEMI	ACC/AHA	2013	Oxygen should be given for an SaO_2 <90%, heart failure, or dyspnea starting at 2-4 L/min nasal cannula	Caution with COPD and CO_2 retention
	ESC	2017	Oxygen for SaO_2 <90% or PaO_2 <60 mm Hg (Class I, Level of Evidence: C)	Routine oxygen not recommended (Class III, Level of Evidence: B)
NSTEMI	ACC/AHA	2014	Oxygen should be administered to patients with an SpO_2 >90%, respiratory distress, or other high-risk features (Class I, Level of Evidence: C)	None
	ESC	2020	Oxygen administration is indicated in patients with SaO_2 <90% or respiratory distress	Routine oxygen is not recommended if SpO_2 >90%
Cardiac arrest				
	AHA	2020	Titrate SaO_2 to a target of 92%-98% (Class 2b, Level of Evidence: B)	Avoid hyperoxemia
	ERC/ESICM	2021	Titrate oxygen to an SaO_2 goal of 94%-98% or PaO_2 of 75-100 mm Hg (strong recommendation, very low certainty evidence)	Avoid hyperoxemia following return of spontaneous circulation (weak recommendation, low certainty evidence)
Heart failure				
	ACC/AHA	2013/2017	None	None
	ESC	2021	Oxygen is recommended in patients with an SpO_2 >90% or PaO_2 >60 mm Hg (Class I, Level of Evidence: C)	Oxygen should not be administered in nonhypoxemic patients
Cardiogenic shock				
	AHA	2017	None	None
	ESC	2019	None	None
Pulmonary HTN				
	ACC/AHA	2009	Oxygen is recommended if SaO_2 <90%	None
	ESC	2015	Supplemental oxygen if chronic PaO_2 <60 mm Hg (Class 1, Level of Evidence: C)	None

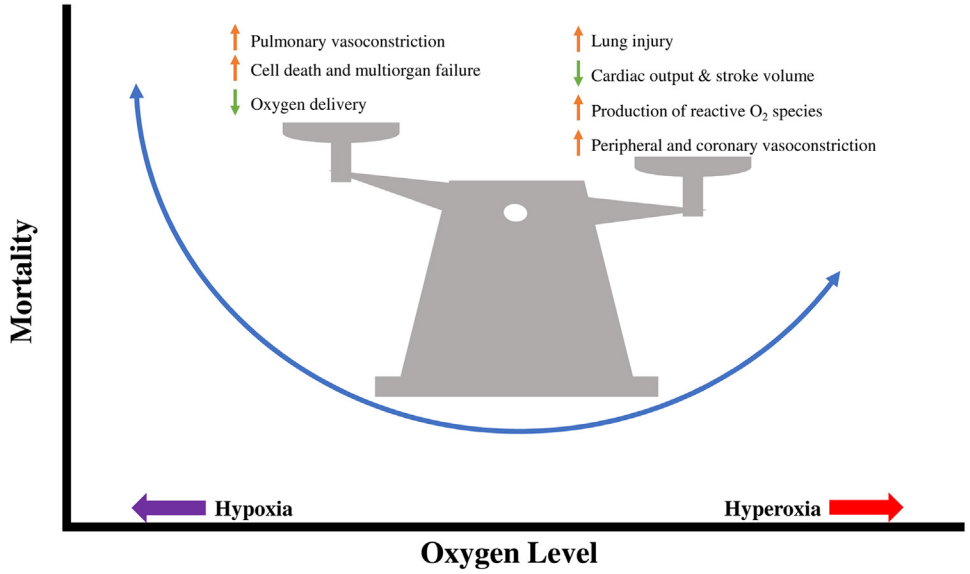
ACC = American College of Cardiology; AHA = American Heart Association; AMI = Acute myocardial infarction; COPD = Chronic obstructive lung disease; ERC = European Resuscitation Council; ESC = European Society of Cardiology; ESICM = European Society of Intensive Care Medicine; NSTEMI = non-ST-segment elevation myocardial infarction; PaO_2 = partial pressure of oxygen; SpO_2 = arterial oxygen saturation; STEMI = ST-segment elevation myocardial infarction. **Green** = Class I, **orange** = Class II, **yellow** = no class recommendation, **red** = class III, **clear** = none.

survival benefit but was associated with longer hospital length of stay (Table 1).[41] Another study of 335 AHF patients categorized patients as hypoxemic (PaO_2 <75 mm Hg), normoxemic (PaO_2 = 75-100 mm Hg), and hyperoxemic (PaO_2 >100 mm Hg) based on their first arterial blood gas and then compared the rates of invasive mechanical ventilation (IMV), length of stay, and mortality. They found that 34% of patients with AHF were hyperoxemic, but that it was not associated with any of the primary outcomes.[42] In 2019, a small (N = 50) open-label pilot study randomized patients with AHF to either a high (SaO_2 ≥96%) or low (SaO_2 = 90%-92%) oxygen saturation. The study did not find a difference in N-terminal pro-brain-type natriuretic peptide, patient-reported dyspnea scale, or clinical outcomes between oxygen treatment groups.[43]

Patients in cardiogenic shock (CS) exhibit a significant impairment in systemic oxygen delivery due to ineffective cardiac output. Although it may seem intuitive that increasing the arterial oxygen content with supplemental oxygen would be beneficial,[44] there are limited data regarding the impact of oxygen supplementation or hyperoxia in this subgroup.

Data from the Extracorporeal Life Support Organization registry, including adult patients from 2010 to 2015 receiving either venovenous-extracorporeal membrane oxygenation (ECMO) or extracorporeal cardiopulmonary resuscitation, found that hyperoxemia (defined as PaO_2 >100 mm Hg at 24 hours after ECMO initiation) was associated with higher in-hospital mortality.[45] No significant association between hyperoxia and outcomes was seen for venoarterial (VA)-ECMO in this study or in a smaller subsequent report, although these analyses are likely

FIGURE 4 U-Shaped Relationship Between Oxygen and Mortality in Cardiac Arrest



underpowered.[45,46] Conversely, another study demonstrated worse neurological outcomes and higher mortality among 132 patients receiving VA-ECMO who had hyperoxemia.[47] Data are most consistent among patients receiving extracorporeal cardiopulmonary resuscitation, with higher mortality observed among those with hyperoxia.[45,48,49]

Although the available data are the most limited for these populations, we believe it is prudent to avoid hyperoxemia and limit the administered fraction of inspirated oxygen (FiO_2) in patients with AHF and CS. However, optimal PaO_2 and SaO_2 are still unknown. Given that there are no data to suggest supplemental oxygen improves the sensation of breathlessness,[3] we refrain from administering oxygen therapy in normoxic patients with AHF or CS. For patients with CS receiving VA-ECMO, it is usually reasonable to maintain a similar FiO_2 on the mechanical ventilator and ECMO circuit in the absence of differential hypoxia ("harlequin syndrome").[50] However, it is important to note that these data are retrospective and oftentimes include small patient populations. Furthermore, ECMO physiology is complex, and oxygen levels may be confounded by the inclusion of a particularly sick patient population.

CARDIAC ARREST. After the restoration of circulation in patients after cardiac arrest, reperfusion triggers a multitude of downstream pathways that can precipitate or exacerbate anoxic injury through an imbalance in cerebral oxygen supply and demand.[51] Hypoxia and hyperoxia are common after cardiac arrest, with estimates upward of 63% and 37%, respectively.[52-54] Although the optimal PaO_2 level remains unknown, evidence suggests there is a U-shaped relationship between PaO_2 levels and mortality after cardiac arrest, with higher mortality at the extremes (**Figure 4**).[55] One proposed mechanism for hyperoxia-induced harm after cardiac arrest is the production of reactive oxygen species, which contribute to direct cellular injury.[13]

In 2010, a retrospective multicenter study found an association between hyperoxia and poorer outcomes after cardiac arrest (**Table 1**).[54] Compared with normoxemia or hypoxia, hyperoxemia (defined as a PaO_2 $\geq$300 mm Hg) was independently associated with higher in-hospital mortality. Furthermore, among hospital survivors, hyperoxemia compared with normoxemia was associated with a lower likelihood of independent functional status.[54] Subsequent observational studies have reported mixed associations between hyperoxia with clinical outcomes, likely reflecting variation in the study populations, as well as the definition and timing of hyperoxia.[56-58] In 2018, a prospective multicenter study used a standardized protocol for arterial blood gas measurements to better define the association between hyperoxia and outcomes after cardiac arrest.[52] Among

TABLE 3 Future/Ongoing Clinical Trials on Oxygen Supplementation

Study	Estimated Sample Size	Study Population	Comparison	Primary Outcome	Reported Expected Finish Date
UK-ROX	16,500	Hypoxic respiratory failure requiring IMV	Conservative O_2 (SpO_2 88%-92%) therapy vs usual oxygen therapy	90-d mortality	November 2023
MEGA-ROX	40,000	Hypoxic respiratory failure requiring IMV	Conservative O_2 (SpO_2 <94%) therapy vs usual oxygen therapy	In-hospital mortality	December 2025
AMIHOT III	434	Anterior AMI	Intracoronary hyperoxemic saturated O_2 therapy vs PCI	1-y rate of MACE	October 2025
ISO-SHOCK	60	STEMI complicated by cardiogenic shock	PCI/Impella + intracoronary hyperoxemic saturated O_2 vs PCI/Impella	30-d mortality	June 2025
BOX	800	Comatose out-of-hospital cardiac arrest	PaO_2 goal of 67.5-75 mm Hg vs 97.5-105 mm Hg	Mortality or severe anoxic brain injury at 3 mo	December 2021
RELIEPH[a]	300	Comatose out-of-hospital cardiac arrest	PaO_2 goal of 67.5-75 mm Hg vs 97.5-105 mm Hg	Pulmonary HTN at 30 d	December 2021
EXACT	1,416	Out-of-hospital cardiac arrest	SpO_2 goal 90%-94% vs 98%-100%	In-hospital mortality	December 2020

[a]Single-center substudy of the BOX trial.

AMI = acute myocardial infarction; HTN = hypertension; IMV = invasive mechanical ventilation; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

280 patients with in- and out-of-hospital cardiac arrest, 38% (n = 105) of patients developed hyperoxemia, defined as a PaO_2 >300 mm Hg, in the first 6 hours after return of spontaneous circulation (ROSC). Compared with normoxic patients, those exposed to hyperoxemia were more likely to have poor neurologic function (modified Rankin Scale >3) at discharge (77% vs 65%, respectively). Greater duration of hyperoxemia was further associated with poorer neurologic outcomes. The ongoing, multicenter, randomized Reduction of Oxygen after Cardiac Arrest trial may help refine oxygen targets in cardiac arrest (Table 3).[59]

In contrast to the potential adverse effects of hyperoxia after ROSC, a small observational study (which may be limited by unmeasured confounders) suggested that intra-arrest hyperoxemia is associated with higher rates of ROSC and lower mortality.[60] Currently, societal recommendations support the use of high FiO_2 during cardiac arrest because of limited lung perfusion during cardiopulmonary resuscitation.[3,61] However, following ROSC, it is advisable to avoid detrimental hyperoxia by monitoring pulse oximetry continuously and checking an arterial blood gas within 30 to 60 minutes to allow titration of the FiO_2 to a goal SpO_2/SaO_2 between 92% and 98% and a goal PaO_2 of 75 to 100 mm Hg.[61] This strategy is consistent with the most recent American Heart Association (Class IIb, Level of Evidence: B-R), European (strong recommendation, very low certainty evidence),[61,62] and Canadian guidelines (conditional recommendation, low-quality evidence) (Table 2).[63]

PULMONARY HYPERTENSION. The relevance of local alveolar and systemic hypoxia in PH pathogenesis, longitudinal patient care, and acute hemodynamics is well described and predominantly focuses on the pathologic role of hypoxia.[64,65] In contrast, there are limited data supporting either a pathologic or beneficial impact of hyperoxia. Although preclinical studies implicate chronic hyperoxia in the development of pulmonary artery smooth muscle cell proliferation, human studies indicate a functional and hemodynamic benefit to time-limited hyperoxia exposure in patients with precapillary PH such as pulmonary arterial hypertension and chronic thromboembolic disease.[66-68]

The most recent world symposium on PH recommends targeting a modest oxygen saturation of >90% for ICU patients with PH and right ventricular failure, driven in part by a desire to balance the potential benefits of avoiding hypoxia with the hemodynamic consequences of positive pressure ventilation (PPV).[69] Higher oxygen saturations (>95%) may be preferable in patients with significant precapillary PH, especially if this can be achieved with standard- or high-flow nasal cannula. However, the need to initiate PPV to achieve a higher SpO_2 goal risks hemodynamic derangements that often outweigh the benefits of modestly improved oxygenation. A notable exception is the PH patient with hypoxia due to derecruitment and low lung volumes (eg, lobar

collapse). In this setting, alveolar recruitment via PPV may both improve oxygenation and decrease right ventricular afterload by avoiding the detrimental effects of low lung volumes on PVR.[70] Thus, the astute CICU clinician must balance the relative importance of oxygenation with the hemodynamic sequelae of more aggressive PPV strategies on an individual patient basis. Although higher oxygenation targets are reasonable for patients not requiring or already receiving PPV, the hemodynamic risks of more aggressive respiratory support likely outweigh any potential benefits.

OXYGENATION FOR NONCARDIAC CRITICAL ILLNESS. CICU clinicians should also be familiar with best practices for managing oxygen therapy in the growing proportion of patients with noncardiac causes of respiratory failure (eg, infection, acute respiratory distress syndrome, and obstructive lung disease).[11,71] Among patients receiving IMV, several clinical trials have demonstrated the equivalence or superiority of a conservative vs a liberal oxygen strategy (**Table 1**).[72-78] In 2018, the Improving Oxygen Therapy in Acute-Illness meta-analysis assessed the association between liberal (median FiO_2 0.52) vs conservative (median FiO_2 0.21) oxygen therapy in over 16,000 patients from 25 randomized controlled trials. Liberal oxygen therapy was associated with increased in-hospital and 30-day mortality. In addition, as SpO_2 increased, so did in-hospital mortality.[6]

After this meta-analysis, 2 notable randomized clinical trials were published. The ICU-ROX trial randomized 1,000 patients who required IMV to either conservative therapy (SpO_2 targets >90% to <97%) or usual care with an acceptable lower SpO_2 of >90%.[73] There were no differences in ventilatory-free days or 180-day mortality (35.7% vs 34.5%) between the conservative oxygen and usual care groups, although the absolute difference in PaO_2 between treatment arms was small. Subsequently, the HOT-ICU trial randomized 2,928 patients who were receiving 10 L/min of oxygen or had an FiO_2 ≥50% to a PaO_2 of 60 (lower oxygenation group) or 90 mm Hg (higher oxygenation group).[78] There was no difference in the primary outcome of all-cause death within 90 days between the lower or higher oxygen treatment arms (42.9% vs 42.4%) and no differences in the incidence of new-onset shock, stroke, myocardial ischemia, or intestinal ischemia.[78] Taken together, the prior meta-analysis and subsequent clinical trials suggest that most critically ill adults requiring supplemental oxygen (including those receiving IMV) can be treated with a conservative oxygen strategy to avoid hyperoxia. In general, maintaining an SpO_2 of 88% to 95% is adequate, and few, if any, patients will require titration of oxygen to maintain SpO_2 >98%.

An important subgroup of critically ill patients who may be particularly harmed by a liberal oxygen strategy and subsequent hyperoxia are those with hypercarbic respiratory failure, such as chronic obstructive pulmonary disease. In these patients, chronic elevation in carbon dioxide (CO_2) results in a drive to breathe triggered primarily by hypoxia, with excess oxygen administration serving to decrease respiratory drive. Supplemental oxygen also destabilizes already optimized ventilation-perfusion matching, further exacerbating hypercarbia.[79] For these patients, we recommend careful titration of FiO_2 to maintain SpO_2 at 88% to 92% and no higher.

COVID-19 infection is associated with both cardiovascular complications and poorer outcomes for patients with cardiovascular disease.[80] Compared with the evidence for other causes of hypoxic respiratory failure, there is limited high-quality evidence to suggest oxygen targets should be any different in COVID-19. An ongoing RCT is comparing lower (60 mm Hg) vs higher (90 mm Hg) PaO_2 goals with a planned enrollment of 780 COVID-19 patients.[81] Until more data are available, consistent with the Surviving Sepsis Campaign Guidelines, we recommend an SpO_2 goal between 92% and 96% for patients with acute COVID-19 infection.[82]

CO_2 BALANCE IN CARDIOVASCULAR DISEASE

Although oxygenation is the focus of our review, it is relevant to briefly discuss the impact of CO_2 balance, specifically changes in the arterial partial pressure of CO_2 ($PaCO_2$), on the cardiovascular system. Compared with normocapnia ($PaCO_2$ = 35-45 mm Hg), acute hypercapnia ($PaCO_2$ >45 mm Hg) is associated with increased pulmonary vasoconstriction,[83] cerebral blood flow,[84] and myocardial blood flow.[85-87] Conversely, acute hypocapnia ($PaCO_2$ <35 mm Hg) has been associated with the opposite, including cerebral hypoperfusion,[88] a reduction in coronary blood flow,[89] and systemic arterial vasodilation.[90,91] However, most of these observations are derived from animal models, and CO_2 balance is one factor in a complex system, within which $PaCO_2$ is difficult to separate from the acid/base status and is often counterbalanced by other physiological

mechanisms.[92] Clinical outcomes may therefore be confounded by the underlying cause of the CO_2 disturbance and whether it is a primary or secondary phenomenon.

Investigations of $PaCO_2$ levels with clinical outcomes have been limited to retrospective analyses. Minana et al[93] found that hypercapnia (defined as a $PaCO_2$ >50 mm Hg) on the first arterial blood gas was not associated with mortality in 588 patients with AHF. Another report of 435 patients with AHF admitted to the CICU found that a $PaCO_2$ <31 mm Hg was associated with higher all-cause mortality.[94] Similarly, a study of more than 16,000 patients after cardiac arrest found that hypocapnia ($PaCO_2$ < 35 mm Hg) was independently associated with higher mortality, whereas hypercapnia ($PaCO_2$ >45 mm Hg) had similar outcomes to normocapnia.[95] Several studies including patients presenting with cardiac arrest have found a U-shaped relationship with harm associated with hypercapnia,[96] whereas others have reported potential benefit from mild hypercapnia.[57,97] Currently, there are 2 ongoing RCTs aimed at evaluating optimal $PaCO_2$ targets in patients with cardiac arrest (TAME: NCT03114033 and COMACARE: NCT02698917). Until these results are available, we would recommend avoidance of hypocapnia ($PaCO_2$ <35 mm Hg), especially in the cardiac arrest patient population. Mild hypercapnia appears safe when not associated with significant acidosis in most CICU populations except for patients with PH and/or right heart dysfunction because hypercapnia can exacerbate pulmonary vasoconstriction.

LESSONS LEARNED FROM CLINICAL TRIALS, GAPS IN KNOWLEDGE, AND FUTURE DIRECTIONS

Despite the multiple studies reviewed, additional evidence is still needed to help define optimal oxygen targets in the ICU. The liberal/usual care arms in many of these trials may not reflect the range of usual PaO_2 in clinical practice, highlighting the challenges in establishing meaningful differences in oxygenation targets between treatment arms.[98] Furthermore, many of the studies discussed were retrospective in nature, and poorer outcomes in the hyperoxia groups may have been confounded by sicker patient populations receiving a greater proportion of supraphysiological oxygen supplementation. The ongoing MEGA-ROX trial, which plans to enroll 40,000 patients with hypoxic respiratory failure requiring IMV to conservative (SpO_2 <94%) vs usual care may help address this question (**Table 3**). Furthermore, the wide variation in definitions for hyperoxia complicates the interpretation of the literature which is at times conflicting.

The prevalence of hyperoxia and its potential association with clinical outcomes in the heterogenous CICU patient population are not known and its generalizability is complicated by the significant variation in the composition of the CICU population. Other than for patients with AMI, most published data on hyperoxia in specific cardiac patient populations are retrospective, single center, and/or observational. In addition, available clinical trials from the general ICU may not be generalizable to the CICU patient population. For example, only 22 of 1,000 patients were reported as having a "cardiovascular comorbidity" in the ICU-ROX trial,[73] <7% of patients had either coronary heart disease or HF in the $LOCO_2$ trial,[76] and <15% of patients in the HOT-ICU trial had ischemic heart disease or HF.[78] Given the unique effects of hyperoxia on the cardiovascular system, it is crucial that future trials of oxygenation in critical illness include a greater proportion of patients with cardiac admission diagnoses and comorbidities.[24] More granular investigations, including the optimal lower and upper limits, the impact of "dose" and timing on outcomes, and the impact of FiO_2 relative to PaO_2 levels, are needed. Pragmatic trials leveraging the strengths of the electronic health record may be helpful to better understand these complex relationships.

CONCLUSIONS

Oxygen supplementation is common and frequently necessary for the management of critically ill patients in the CICU. A growing body of evidence has established that routine oxygen supplementation in patients with AMI is unnecessary and potentially harmful. Hyperoxia, especially in the vulnerable postresuscitation brain, is associated with higher mortality and worse neurologic outcomes. Although the optimal PaO_2 levels across various cardiac diagnoses are unknown, clinicians should avoid PaO_2 ≥300 mm Hg, with some experts believing that this maximum target should be substantially lower. For patients with PH and/or right ventricular failure, the SaO_2 should be maintained at >90% without resorting to the use of PPV. Ongoing clinical trials should better inform individualized oxygenation targets across a wide range of patients with cardiovascular disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Barnett has received research funding from AbbVie Inc, BeiGene, Ltd, United Therapeutics Corporation, and Acceleron Pharma; owns stock in Biogen Inc; and is a member of the ABIM critical care medicine test writing committee, and no ABIM examination questions are shared or otherwise disclosed in this article. Dr Solomon has received research support from the National Institutes of Health Clinical Center intramural research funds. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Steele C. Severe angina pectoris relieved by oxygen inhalations. *BMJ*. 1900;2:1568.

2. Kones R. Oxygen therapy for acute myocardial infarction-then and now. A century of uncertainty. *Am J Med*. 2011;124:1000–1005.

3. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax*. 2017;72:ii1–ii90.

4. Burls A, Emparanza JI, Quinn T, Cabello JB. Oxygen use in acute myocardial infarction: an online survey of health professionals' practice and beliefs. *Emerg Med J*. 2010;27:283–286.

5. Kelly CA, Lynes D, O'Brien MR, Shaw B. A wolf in sheep's clothing? Patients' and healthcare professionals' perceptions of oxygen therapy: an interpretative phenomenological analysis. *Clin Respir J*. 2018;12:616–632.

6. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391:1693–1705.

7. Bohula EA, Katz JN, van Diepen S, et al. Demographics, care patterns, and outcomes of patients admitted to cardiac intensive care units: the critical care cardiology trials network prospective North American Multicenter Registry of cardiac critical illness. *JAMA Cardiol*. 2019;4(9):928–935.

8. Miller PE, Thomas A, Breen TJ, et al. Prevalence of non-cardiac multimorbidity in patients admitted to two cardiac intensive care units and their association with mortality. *Am J Med*. 2021;134(5):653–661.e5.

9. Fuster V. The (R)evolution of the CICU: better for the patient, better for education. *J Am Coll Cardiol*. 2018;72:2269–2271.

10. Jentzer JC, van Diepen S, Barsness GW, et al. Changes in comorbidities, diagnoses, therapies and outcomes in a contemporary cardiac intensive care unit population. *Am Heart J*. 2019;215:12–19.

11. Metkus TS, Miller PE, Alviar CL, et al. Advanced respiratory support in the contemporary cardiac ICU. *Crit Care Explor*. 2020;2:e0182.

12. Alviar CL, Miller PE, McAreavey D, et al. Positive pressure ventilation in the cardiac intensive care unit. *J Am Coll Cardiol*. 2018;72:1532–1553.

13. Cornet AD, Kooter AJ, Peters MJ, Smulders YM. The potential harm of oxygen therapy in medical emergencies. *Crit Care*. 2013;17:313.

14. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA*. 2021;325:552–560.

15. Garfinkle M, Lawler PR, Filion KB, Eisenberg MJ. Red blood cell transfusion and mortality among patients hospitalized for acute coronary syndromes: a systematic review. *Int J Cardiol*. 2013;164:151–157.

16. Rayes HA, Vallabhajosyula S, Barsness GW, et al. Association between anemia and hematological indices with mortality among cardiac intensive care unit patients. *Clin Res Cardiol*. 2020;109:616–627.

17. Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, Eisenberg MJ. Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis. *Am Heart J*. 2013;165:143–153.e5.

18. Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J Cardiovasc Pharmacol Ther*. 2015;20:249–260.

19. Xie A, Skatrud JB, Puleo DS, Morgan BJ. Exposure to hypoxia produces long-lasting sympathetic activation in humans. *J Appl Physiol (1985)*. 2001;91:1555–1562.

20. Thomson AJ, Drummond GB, Waring WS, Webb DJ, Maxwell SR. Effects of short-term isocapnic hyperoxia and hypoxia on cardiovascular function. *J Appl Physiol (1985)*. 2006;101:809–816.

21. Dunham-Snary KJ, Wu D, Sykes EA, et al. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. *Chest*. 2017;151:181–192.

22. Bull TM, Clark B, McFann K, Moss M, National Institutes of Health/National Heart, Lung, and Blood Institute ARDS Network. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med*. 2010;182:1123–1128.

23. Metkus TS, Mathai SC, Leucker T, Hassoun PM, Tedford RJ, Korley FK. Pulmonary and systemic hemodynamics are associated with myocardial injury in the acute respiratory distress syndrome. *Pulm Circ*. 2020;10:2045894020939846.

24. Smit B, Smulders YM, van der Wouden JC, Oudemans-van Straaten HM, Spoelstra-de Man AME. Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. *Crit Care*. 2018;22:45.

25. Saadjian A, Paganelli F, Levy S. Hemodynamic response to oxygen administration in chronic heart failure: role of chemoreflexes. *J Cardiovasc Pharmacol*. 1999;33:144–150.

26. McNulty PH, King N, Scott S, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol*. 2005;288:H1057–H1062.

27. Haque WA, Boehmer J, Clemson BS, Leuenberger UA, Silber DH, Sinoway LI. Hemodynamic effects of supplemental oxygen administration in congestive heart failure. *J Am Coll Cardiol*. 1996;27:353–357.

28. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. *J Intern Med*. 2013;274:505–528.

29. Rousseau A, Bak Z, Janerot-Sjoberg B, Sjoberg F. Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man. *Acta Physiol Scand*. 2005;183:231–240.

30. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. *Heart*. 2010;96:533–538.

31. Guensch DP, Fischer K, Yamaji K, et al. Effect of hyperoxia on myocardial oxygenation and function in patients with stable multivessel coronary artery disease. *J Am Heart Assoc*. 2020;9:e014739.

32. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1:1121–1123.

33. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation*. 2015;131:2143–2150.

34. Khoshnood A, Carlsson M, Akbarzadeh M, et al. Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: the randomized SOCCER trial. *Eur J Emerg Med*. 2018;25:78–84.

35. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. 2017;377:1240–1249.

36. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in

patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.

37. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2013;61:e78–e140.

38. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64:e139–e228.

39. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367.

40. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

41. Yu Y, Yao RQ, Zhang YF, et al. Is oxygen therapy beneficial for normoxemic patients with acute heart failure? A propensity score matched study. *Mil Med Res*. 2021;8:38.

42. Chu MYS, Guo W, Lim KK, Lim BL. Effect of oxygen therapy on the risk of mechanical ventilation in emergency acute pulmonary edema patients. *Eur J Emerg Med*. 2020;27:99–104.

43. Sepehrvand N, Alemayehu W, Rowe BH, et al. High vs. low oxygen therapy in patients with acute heart failure: HiLo-HF pilot trial. *ESC Heart Fail*. 2019;6:667–677.

44. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e232–e268.

45. Munshi L, Kiss A, Cypel M, Keshavjee S, Ferguson ND, Fan E. Oxygen thresholds and mortality during extracorporeal life support in adult patients. *Crit Care Med*. 2017;45:1997–2005.

46. Ross P, Miller C, Sheldrake J, McGuiness W, Udy A, Burrell A. Hyperoxia in patients with cardiogenic shock after myocardial infarction supported with venoarterial extracorporeal membrane oxygenation. *Aust Crit Care*. 2021;34:55–59.

47. Al-Kawaz MN, Canner J, Caturegli G, et al. Duration of hyperoxia and neurologic outcomes in patients undergoing extracorporeal membrane oxygenation. *Crit Care Med*. 2021;49:e968–e977.

48. Bonnemain J, Rusca M, Ltaief Z, et al. Hyperoxia during extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest is associated with severe circulatory failure and increased mortality. *BMC Cardiovasc Disord*. 2021;21:542.

49. Halter M, Jouffroy R, Saade A, Philippe P, Carli P, Vivien B. Association between hyperoxemia and mortality in patients treated by eCPR after out-of-hospital cardiac arrest. *Am J Emerg Med*. 2020;38:900–905.

50. Miller PE, Solomon MA, McAreavey D. Advanced percutaneous mechanical circulatory support devices for cardiogenic shock. *Crit Care Med*. 2017;45:1922–1929.

51. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. *Crit Care*. 2017;21:90.

52. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. *Circulation*. 2018;137:2114–2124.

53. Ebner F, Ullén S, Åneman A, et al. Associations between partial pressure of oxygen and neurological outcome in out-of-hospital cardiac arrest patients: an explorative analysis of a randomized trial. *Crit Care*. 2019;23:30.

54. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303:2165–2171.

55. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. *Crit Care*. 2015;19:348.

56. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. *Circulation*. 2011;123:2717–2722.

57. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. *Crit Care Med*. 2014;42:1463–1470.

58. Youn CS, Park KN, Kim SH, et al. The cumulative partial pressure of arterial oxygen is associated with neurological outcomes after cardiac arrest treated with targeted temperature management. *Crit Care Med*. 2018;46:e279–e285.

59. Bray JE, Smith K, Hein C, et al. The EXACT protocol: a multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients. *Resuscitation*. 2019;139:208–213.

60. Patel JK, Kataya A, Parikh PB. Association between intra- and post-arrest hyperoxia on mortality in adults with cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2018;127:83–88.

61. Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2020;142:S366–S468.

62. Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intensive Care Med*. 2021;47:369–421.

63. Wong GC, van Diepen S, Ainsworth C, et al. Canadian Cardiovascular Society/Canadian Cardiovascular Critical Care Society/Canadian Association of Interventional Cardiology position statement on the optimal care of the postarrest patient. *Can J Cardiol*. 2017;33:1–16.

64. Green S, Stuart D. Oxygen and pulmonary arterial hypertension: effects, mechanisms, and therapeutic benefits. *Eur J Prev Cardiol*. 2021;28:127–136.

65. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53(1):1801887.

66. Coflesky JT, Adler KB, Woodcock-Mitchell J, Mitchell J, Evans JN. Proliferative changes in the pulmonary arterial wall during short-term hyperoxic injury to the lung. *Am J Pathol*. 1988;132:563–573.

67. Ulrich S, Hasler ED, Saxer S, et al. Effect of breathing oxygen-enriched air on exercise performance in patients with precapillary pulmonary hypertension: randomized, sham-controlled cross-over trial. *Eur Heart J*. 2017;38:1159–1168.

68. Groth A, Saxer S, Bader PR, et al. Acute hemodynamic changes by breathing hypoxic and hyperoxic gas mixtures in pulmonary arterial and chronic thromboembolic pulmonary hypertension. *Int J Cardiol*. 2018;270:262–267.

69. Hoeper MM, Benza RL, Corris P, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801906.

70. Simmons DH, Linde LM, Miller JH, O'Reilly RJ. Relation between lung volume and pulmonary vascular resistance. *Circ Res*. 1961;9:465–471.

71. Jentzer JC, Alviar CL, Miller PE, et al. Trends in therapy and outcomes associated with respiratory failure in patients admitted to the cardiac intensive care unit. *J Intensive Care Med*. 2021;37:543–554.

72. Asfar P, Schortgen F, Boisrame-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med*. 2017;5:180–190.

73. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med*. 2020;382:989–998.

74. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA*. 2016;316:1583–1589.

75. Gelissen H, de Grooth HJ, Smulders Y, et al. Effect of low-normal vs high-normal oxygenation targets on organ dysfunction in critically ill patients: a randomized clinical trial. *JAMA*. 2021;326:940–948.

76. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med*. 2020;382:999–1008.

77. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2016;193:43–51.

78. Schjorring OL, Klitgaard TL, Perner A, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med*. 2021;384:1301-1311.

79. Hanson CW 3rd, Marshall BE, Frasch HF, Marshall C. Causes of hypercarbia with oxygen therapy in patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1996;24:23-28.

80. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28:583-590.

81. Molgaard Nielsen F, Lass Klitgaard T, Granholm A, et al. Higher versus lower oxygenation targets in COVID-19 patients with severe hypoxaemia (HOT-COVID) trial: protocol for a secondary Bayesian analysis. *Acta Anaesthesiol Scand*. 2022;66:408-414.

82. Alhazzani W, Evans L, Alshamsi F, et al. Surviving Sepsis Campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. *Crit Care Med*. 2021;49:e219-e234.

83. Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest*. 1996;109:1215-1221.

84. Grubb RL Jr, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO2 on cerebral blood volume, blood flow, and vascular mean transit time. *Stroke*. 1974;5:630-639.

85. Kazmaier S, Weyland A, Buhre W, et al. Effects of respiratory alkalosis and acidosis on myocardial blood flow and metabolism in patients with coronary artery disease. *Anesthesiology*. 1998;89:831-837.

86. Tzou WS, Korcarz CE, Aeschlimann SE, Morgan BJ, Skatrud JB, Stein JH. Coronary flow velocity changes in response to hypercapnia: assessment by transthoracic Doppler echocardiography. *J Am Soc Echocardiogr*. 2007;20:421-426.

87. Powers ER, Bannerman KS, Fitz-James I, Cannon PJ. Effect of elevations of coronary artery partial pressure of carbon dioxide (PCO2) on coronary blood flow. *J Am Coll Cardiol*. 1986;8:1175-1181.

88. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. *Stroke*. 1972;3:566-575.

89. Neill WA, Hattenhauer M. Impairment of myocardial O2 supply due to hyperventilation. *Circulation*. 1975;52:854-858.

90. Richardson DW, Kontos HA, Raper AJ, Patterson JL Jr. Systemic circulatory responses to hypocapnia in man. *Am J Physiol*. 1972;223:1308-1312.

91. Burnum JF, Hickam JB, Mc IH. The effect of hypocapnia on arterial blood pressure. *Circulation*. 1954;9:89-95.

92. Crystal GJ. Carbon dioxide and the heart: physiology and clinical implications. *Anesth Analg*. 2015;121:610-623.

93. Minana G, Nunez J, Banuls P, et al. Prognostic implications of arterial blood gases in acute decompensated heart failure. *Eur J Intern Med*. 2011;22:489-494.

94. Kato T, Kasai T, Suda S, et al. Prognostic effects of arterial carbon dioxide levels in patients hospitalized into the cardiac intensive care unit for acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2021;10:497-502.

95. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation*. 2013;84:927-934.

96. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Trzeciak S. Association between postresuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. *Circulation*. 2013;127:2107-2113.

97. Hope Kilgannon J, Hunter BR, Puskarich MA, et al. Partial pressure of arterial carbon dioxide after resuscitation from cardiac arrest and neurological outcome: a prospective multi-center protocol-directed cohort study. *Resuscitation*. 2019;135:212-220.

98. Angus DC. Oxygen therapy for the critically ill. *N Engl J Med*. 2020;382:1054-1056.

99. Sepehrvand N, Ezekowitz JA. Oxygen therapy in patients with acute heart failure: friend or foe? *J Am Coll Cardiol HF*. 2016;4:783-790.

100. Hafner C, Wu J, Tiboldi A, et al. Hyperoxia induces inflammation and cytotoxicity in human adult cardiac myocytes. *Shock*. 2017;47:436-444.

101. Thiel M, Chouker A, Ohta A, et al. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. *PLoS Biol*. 2005;3:e174.

102. Ranchord AM, Argyle R, Beynon R, et al. High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: a pilot randomized controlled trial. *Am Heart J*. 2012;163:168-175.

103. Kuisma M, Boyd J, Voipio V, Alaspaa A, Roine RO, Rosenberg P. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. *Resuscitation*. 2006;69:199-206.

KEY WORDS cardiac critical care, hyperoxia, oxygenation