

EDITORIAL



What's new in oxygen therapy?

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Introduction

From 'elixir of the life' to the **first cause of aging** and death, the history of oxygen in modern science and medicine is a fascinating example of controversial hypotheses, uncertain findings and **wrong theories**. The debate continues, especially in critically ill patients who frequently receive oxygen supplementation for preventing or treating tissue hypoxia. In these patients, the **appropriate oxygen dose** (i.e. quantity and duration) remains **unclear** and may substantially vary in specific sub-populations. We present a brief state-of-the-art update on oxygen therapy in emergency, intensive care and non-intensive care settings.

Although the **rationale for using oxygen therapy** was **not well developed** nor supported by **convincing data**, administering oxygen to non-hypoxaemic patients presenting to the emergency department with acute medical emergencies was a common practice. This led researchers to conduct several randomized controlled trials (RCTs) to determine the efficacy and safety of oxygen therapy in this context.

Oxygen therapy in acute stroke

There are **six RCTs** that examined the effect of oxygen therapy on mortality and physical function outcomes [1]. The largest was the stroke oxygen study (SO₂S) randomized clinical trial [2] which randomized **8003** patients with **acute ischaemic stroke** to one of three arms: continuous oxygen, nocturnal oxygen or no oxygen [2]. Oxygen administration did not improve the modified Rankin scale (mRS) scores in patients with acute stroke [odds ratio (OR) 0.97, 95% CI 0.89–1.05]. Similarly, when the total body of evidence was evaluated across six RCTs,

oxygen therapy did not improve physical function (mRS score) in patients with stroke (proportional OR 1.02, 95% CI 0.93–1.12) [1]. Different thresholds for oxygen therapy ranged between 30% and 100% oxygen; therefore, a threshold for benefit or harm could not be determined without an individual patient data meta-analysis.

Oxygen therapy in cardiac ischaemia and cardiac arrest

The rationale for oxygen therapy in non-hypoxaemic patients with cardiac ischaemia is to decrease the acute ischaemic injury and the infarct area [3]. Although prominent international **guidelines recommended** using **oxygen** in patients with cardiac ischaemia, the **recommendations were not supported by convincing evidence**. Several studies showed that **hyperoxaemia** was associated with **coronary vasoconstriction** and reduced myocardial oxygen consumption [4]. Aiming to inform clinical practice, a landmark RCT (DETO2X-AMI) randomized **6629** non-hypoxaemic patients with acute myocardial infarction to receive either continuous supplemental oxygen or no oxygen [5]. Oxygen therapy did **not reduce mortality** or re-hospitalization. The main limitation of this trial is imprecision as the sample size was **not powered** to firmly **exclude harm**. A **recent systematic review** identified six RCTs (**7778** patients) in a cardiac ischaemia population, and a single RCT (17 patients) in cardiac arrest [1]. When the effect on mortality was evaluated across all trials, oxygen therapy did not improve survival (RR 1.13, 95% CI 0.83–1.55); of note, the point estimate showed a **13% increase in mortality**, and the **CI could not exclude a 55% increase in mortality**.

Recent **guidelines** issued a **strong recommendation against using oxygen** therapy in non-hypoxaemic patients [peripheral oxygen saturation (SpO₂) **≥ 93%**] with **cardiac ischaemia or stroke**. In addition, they issued a **strong recommendation for discontinuing oxygen when SpO₂ ≥ 96%** [6].

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Table 1 How conservative is the oxygenation targets in the ICU trials?

RCTs	Status	Number of patients recruited	Inclusion criteria	Oxygen target(s) in the conservative group
Girardis [9]	Terminated after an unplanned interim analysis	434 out of 660	Expected length of stay in the ICU of 72 h	SpO ₂ up to 98% PaO ₂ 70–100 mmHg
Asfar [10]	Terminated after a planned interim analysis	442 out of 800	Mechanical ventilation and septic shock	SpO ₂ up to 97%
Panwar [11]	Completed	103	Mechanical ventilation	SpO ₂ up to 92%
ICU-ROX (ACTRN12615000957594)	Completed but no results reported yet	1000	Mechanical ventilation	SpO ₂ 91–96%
LOCO2 (NCT02713451)	Active, not recruiting	205 out of 850	ARDS according to the Berlin definition	PaO ₂ 55–70 mmHg SpO ₂ 88–92%
HOT-ICU (NCT03174002)	Recruiting	1504 out of 2928	FiO ₂ at least 0.50 or at least 10 L per minute in an open system	PaO ₂ 60 mmHg
ICU-Conservative O2 trial (EU DRAC T 2018-002525-35)	Starts recruiting in May 2019	Expected 1000	Mechanical ventilation and expected length of stay in the ICU of 72 h	SpO ₂ up to 98% PaO ₂ 70–100 mmHg

ARDS acute respiratory distress syndrome, ICU intensive care unit, PaO₂ partial pressure of arterial oxygen, SpO₂ peripheral oxygen saturation

Non-intensive care patients

Oxygen supplementation is widely used in hypoxic patients admitted to general wards, frequently without targeted prescription [7]. Although the disease severity and the oxygen concentration used are lower, it is plausible that inappropriate oxygen therapy may cause negative effects similar to those observed in critically ill patients. In addition, in general wards the monitoring of oxygen levels is commonly less precise than in patients admitted to intensive care unit (ICU). Therefore, the exposure to hypoxia and hyperoxia may be even more frequent and uncontrolled. Unfortunately, few data are available on oxygen therapy in this setting, particularly on adverse effects related to possible exposure to hyperoxia. Interestingly, a recent retrospective single-centre cohort study showed that early hyperoxaemia compared to normoxaemia was associated with larger in-hospital mortality and late ICU transfer in patients admitted to general wards. Moreover, as in critically ill patients, the total oxygen exposure (area under the curve of PaO₂ levels) was related to occurrence of new respiratory, hepatic and renal dysfunctions [8].

Oxygen therapy in ICU patients

Oxygen is the most common drug used in the ICU and often administrated liberally to give a margin of safety against life-threatening hypoxia. The life-saving properties of oxygen therapy in critically ill patients with hypoxaemic respiratory failure seem to have overshadowed the awareness of serious adverse events (SAEs) caused by oxygen. Emerging evidence points towards a reduced mortality in acutely ill adults treated with a conservative

oxygen strategy compared with a liberal oxygen therapy [1]. Noteworthy, a single-centre RCT [9] provided 32% of the weight in the mortality analysis in this recent systematic review and meta-analysis [1], but stopped early after a non-scheduled interim analysis. Adding to the evidence, the HYPERS2S trial [10], a two-by-two factorial multicentre RCT, found a higher risk of SAEs with hyperoxaemia and was also terminated early. In contrast, a pilot RCT showed no difference in mortality between conservative versus liberal oxygenation targets for mechanically ventilated patients [11]. Therefore, to what degree hyperoxaemia affects mortality in the ICU population remains uncertain.

We await the results of several studies in the ICU. The largest multicentre RCT in mechanical ventilation patients, the ICU-ROX trial (ACTRN12615000957594) completed recruitment (1000 patients) in November 2018, and the results are expected later in 2019. Additionally, the LOCO2 trial (NCT02713451) stopped recruiting and the results are expected soon. The HOT-ICU trial (NCT03174002), which is focused on patients with hypoxaemic respiratory failure, has randomized over half of the planned 2928 patients and is still ongoing (Table 1).

Undoubtedly, the overall body of evidence supports conservative use of oxygen, but the question remains as to how conservative the oxygen therapeutic goals should be. Table 1 provides an overview of how conservative the oxygenation targets is in the ICU RCTs. Until the results of ongoing trials are available, the optimal target of oxygen therapy in the ICU population is unknown.

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Compliance with ethical standards

Conflicts of interest

Dr. Girardis was the principal investigator of a completed trial [9] and a principal investigator of a coming trial (EUROACT 2018-002525-35) evaluating oxygen saturation targets for critical ill patients. Dr. Rasmussen is a principal investigator of an ongoing trial (NCT03174002) evaluating oxygen saturation targets for critically ill patients. Dr. Alhazzani co-authored a systematic review and a guideline on oxygen therapy for acutely ill patients.

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