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RECENT ADVANCES IN ICU

Trials on oxygen targets in the critically ill patients: do they change our knowledge and practice?

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In the last decades, the description of the U-shaped association between PaO_2 and mortality [1] highlighted the potential dangers of high PaO_2 levels (hyperoxaemia) in critically ill patients. Subsequent randomised controlled trials (RCTs) have generated conflicting results. Earlier trials favoured conservative oxygen therapy; two moderate-sized RCTs both reported an 8% absolute decrease in mortality compared to either a liberal oxygenation group [2] or to septic patients exposed to an FiO_2 of 100% for 24 h (HYPERS2S) [3]. A meta-analysis of 25 RCTs performed in acutely ill patients found a 1.21 (95% CI 1.03–1.43) increase in relative risk for hospital mortality with liberal oxygen therapy [4]. Two later and larger RCTs (ICU-ROX and HOT-ICU), however, failed to show any mortality difference [5, 6], while two other moderate-sized RCTs (O2-ICU and LOCO2) even trended towards a better clinical outcome in the liberal oxygenation groups [7, 8]. Important limitations of these trials include heterogeneous populations and the use of different arterial oxygenation targets that generally compared mild hypoxaemic against normoxaemic targets. The only conclusion that can be currently drawn is that extremes of oxygenation are disadvantageous. A fairly broad range of less extreme values appear to be safe and any clinical impact is likely to be minor.

Several important questions remain. Are there specific subpopulations which benefit from a higher or lower arterial oxygenation target? Since the nadir of the U-shaped PaO_2-mortality association was in the mild hyperoxaemic range at around 130 mmHg [1], is the optimal target higher than currently investigated? What upper limit of hyperoxaemia can be considered safe?

Recent trials

Three large RCTs assessing PaO_2 targets in different critically ill populations of patients are summarised in Table 1. The BOX trial [9] enrolled 789 adult patients comatose after out-of-hospital cardiac arrest (OHCA) admitted to two Danish hospitals. After admission, mechanically ventilated patients were randomised to a higher (97–105 mmHg) or lower (67–75 mmHg) PaO_2 target (median duration 60 h). Both primary (death or hospital discharge with coma) and secondary endpoints, including adverse events, did not differ between the two PaO_2 groups. The limited data on PaO_2 levels showed a minimal difference (~6–11 mmHg) between the two groups over the first 48 h as median PaO_2 levels exceeded 75 mmHg in the conservative group.

The EXACT trial [10] assessed two different SpO_2 targets, 90–94% vs 98–100%, in the immediate management of patients with return of spontaneous circulation (ROSC) after OHCA in two Australian emergency medical services. The protocol was initiated within 40 min after ROSC and terminated after the first blood gas analysis taken in the intensive care unit (ICU). Hospital survival, the primary endpoint, was higher (47.9 vs 38.3%; $p = 0.05$) in patients randomised to a higher SpO_2 target. This group also suffered fewer hypoxaemic episodes (16.1 vs 31.3% $p < 0.001$) pre-ICU admission. Unfortunately, the study was stopped prematurely due to the coronavirus disease 2019 (COVID-19) pandemic after enrolling a third of the planned sample size. The authors also acknowledged difficulties in providing an accurate

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Table 1 Characteristics of patients included, setting, oxygenation protocols and outcomes of the three recent trials on oxygen targets in critically ill patients

TRIAL	BOX trial	EXACT trial	PILOT trial
Type of population	Adult patients comatose after out of hospital cardiac arrest resuscitation	Adult with return of spontaneous circulation after out of hospital cardiac arrest	Adult undergoing invasive mechanical ventilation in ED with planned admission to ICU, or in ICU (12% cardiac arrest, 30% sepsis-septic shock, 60% with respiratory failure)
Sites, country	2 hospitals, Denmark	2 emergency medical services, 15 hospitals, Australia	1 hospital, United States
Patients (*n*)	789	425	2541
Time of randomization	Median (IQR) 146 (113–187) min after cardiac arrest	Median (IQR) 64 (51–80) min after cardiac arrest	Median (IQR) 0 (0–5) hours after initiation of mechanical ventilation
Target lower group	PaO_2 9–10 kPa (68–75 mmHg)	SpO_2 90–94%	SpO_2 90% (88–92%)
Target intermediate group	No	No	SpO_2 94% (92–96%)
Target higher group	PaO_2 13–14 kPa (98–105 mmHg)	SpO_2 98–100%	SpO_2 98% (96–100%)
Achievement lower group	Median PaO_2 between 11–12.5 kPa (83–94 mmHg) from 6 to 48 h[a]	At the end of protocol: median (IQR) SpO_2 98 (95–100) %; PaO_2 13 (10–19.5) kPa 97 (73–146) mmHg)	Median (IQR) SpO_2 94 (92–96)
Achievement intermediate group	No	No	Median (95% CI) SpO_2 95 (94–97)
Achievement higher group	Median PaO_2 between 13–14 kPa (98–105 mmHg) from 6–48 h[a]	At the end of protocol: median (IQR) SpO2 99 (97–100) %; PaO_2 15 (11–23,5) kPa 114 (83–177) mmHg)	Median (95% CI) SpO_2 97 (96–98)
Differences in O_2 targets between groups	SpO_2 0.5–2.3%[b] (approx 1.5–2 kPa (11–15 mmHg)[a]	End of protocol difference in median SpO_2 2%, PaO_2 2 kPa (15 mmHg)	SpO_2 Median (95% CI): Higher vs Intermediate: 2.0 (1.8–2.2)% Higher vs Lower: 3.2 (3.0–3.5)% Intermediate vs Lower: 1.2 (1.0–1.5)
Duration of protocol	From hospital admission to extubation: median time (IQR) 57 (39–110) and 60 (IQR 40–111) hours in lower and higher target groups, respectively	From return of spontaneous circulation to first blood gas analysis in intensive care unit: median ~ 240 (180–320) min	Early after intubation until extubation, transfer to other unit, or end of the 2 month study period: half the patients ~ 72 h
Limitations in the oxygenation protocol	Similar PaO_2 in the 2 groups in the first 4 h; data available only for the first 48 h; no analysis on PaO_2 differences between groups	Limitations in accurate FiO_2 titration and compliance to protocol for methods available in EMS. Similar SpO2 in the last hours of treatments (after hospital admission)	PaO_2 values available for approx. 20% of patients at day 1 and even less during the other study days, with decreasing differences between groups during the study
Primary endpoint	Death or hospital discharge with disability or coma: 32.0% and 33.9% in lower and higher target groups, respectively. (HR 0.95; 95% CI 0.75–1.21; $p = 0.69$)	Survival to hospital discharge: 38.3% and 47.9%; unadjusted OR 0.68 [95% CI 0.46–1.00]; ($p = 0.05$) in lower and higher target groups	Ventilator-free days through day 28 (median, IQR): 20 (0–25) days in lower target group, 21 (0–25) days in intermediate target group, 21 (0–26) in higher target group ($p = 0.81$)
Mortality	At 90 days: 28.7% and 31.1% in lower and higher target groups, respectively	As above	At 28 days: 34.8%, 34%, 33.2% in the lower, intermediate and higher groups, respectively

IQR interquartile range, *EMS* emergency medical service

[a] Estimated from Fig. 1A ref [9]

[b] Table S5 of the article ref [9]

FiO_2 and following the protocol in an out-of-hospital setting. As with the BOX trial, differences in SpO_2 between the two groups on arrival in the Emergency Department (97% vs 99%) and at protocol end (98% vs 99%) were minimal.

The cluster crossover PILOT trial [11] evaluated three different SpO_2 targets [90% (88–92%) vs 94% (92–96%) vs 98% (96–100%)] in mechanically ventilated adult patients in one US hospital. More liberal targets were allowed during transport or procedures. The protocol was applied to approximately half the patients for at least 72 h. The three groups did not differ, either for primary outcome (i.e. ventilation-free days through day 28), secondary outcomes or adverse events. Unfortunately, between-group differences in SpO_2 were lower than intended, ranging between 1 and 3% among groups rather than a 4% separation. This was particularly relevant to the lowest SpO_2 group where the median SpO_2 value was 94%. Surprisingly, PaO_2 data were available for only 20% of included patients on day 1 and even less over the following days.

As with any other drug, benefit and harm from oxygen therapy depend on total dose, i.e. the percentage of O_2 within the inspired gas mixture and exposure duration, and patient's factors that may increase susceptibilities to oxygen toxicity, such as severe brain injuries [12]. Beyond the substantial overlap between groups in SpO_2 and/or PaO_2 achieved during the study, it is relevant to note that the time of exposure to different O_2 levels is short ranging from few to 48–72 h for most of the patients included in the trials, resulting in a minimal difference in total O_2 exposure among groups.

Take-home messages

In virtually all trials to date in critically ill patients, liberal and conservative oxygenation targets have not been extreme and, accordingly, little effect has been seen on clinical outcomes. The impact of greater degrees of hyperoxaemia or hypoxaemia remains uncertain, as does any differential effect in pre-specified patient subsets, such as those surviving cardiac arrest.

Many more studies on oxygenation targets are in progress, of which Mega-ROX is the largest, targeting a sample size of 40,000 patients [13]. The hypothesis being tested here is that conservative oxygen therapy (91–95% SpO_2) in patients requiring unplanned mechanical ventilation reduces in-hospital all-cause mortality by at least 1.5% when compared with liberal oxygen therapy (lower SpO_2 limit of at least 91%, no specified upper limit, and a minimum use of 0.3 FiO_2 while the patient remains intubated). Within the overall trial there will be three nested RCTs in pre-specified patient subgroups: suspected hypoxic ischaemic encephalopathy (HIE), sepsis, and acute brain injuries other than HIE. However, we express the same concerns here as with previous studies in terms of achieving adequate separation between groups to demonstrate any clear outcome difference. Furthermore, whether a small clinical impact, even if statistically significant, is sufficient to change routine clinical practice is questionable, especially considering that practice outside a trial protocol is likely to be even less rigorous.

A study we would like to see performed is one that incorporates a mild hyperoxaemia target, e.g. 120–130 mmHg, corresponding to the nadir of the U-shaped-relationship with mortality. Alternatively, perhaps preferably, and as is being recognised after multiple negative RCTs in sepsis, a more directed and biological approach to study design may yield greater advances. Patients could be stratified into liberal and conservative targets by a biomarker identifying, for example, brain injury, endothelial activation, or excessive reactive oxygen species production where either a high or low oxygen target may be postulated as beneficial or detrimental. Such an approach does, however, require prior studies to identify suitable biomarkers with repeated blood sampling to delineate the baseline biological signature of enrolled patients and to assess the impact of oxygenation targets, given the heterogeneity of other management practices. So-called pragmatic trials, where no attempt is made to appreciate the underlying biology, have been uniformly disappointing to date. This repeating pattern is likely to continue unless a different trial strategy is adopted. In the waiting period for the new trials, we suggest considering oxygen as a powerful drug that should be carefully titrated for maintaining the patient in the nadir part of the U-Shaped relationship, that is, for most of the critically ill patients included in the normoxia-mild hyperoxaemia range.

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Declarations

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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