Review Article

Oxygen Treatment in Intensive Care and Emergency Medicine

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Summary

Background: Oxygen treatment is often life-saving, but multiple studies in recent years have yielded evidence that the indiscriminate administration of oxygen to patients in the intensive care unit and emergency room can cause hyperoxia and thereby elevate mortality.

Methods: This review is based on prospective, randomized trials concerning the optimum use of oxygen in adult medicine, which were retrieved by a selective search in PubMed, as well as on pertinent retrospective studies and guideline recommendations.

Results: 13 prospective, randomized trials involving a total of 17 213 patients were analyzed. In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and in ventilated intensive-care patients, normoxia was associated with a lower mortality than hyperoxia (2% vs. 9%). In patients with myocardial infarction, restrictive oxygen administration was associated with a smaller infarct size on cardiac MRI at 6 months compared to oxygen administration at 8 L/min (13.1 g vs. 20.3 g). For patients with stroke, the currently available data do not reveal any benefit or harm from oxygen administration. None of the trials showed any benefit from the administration of oxygen to non-hypoxemic patients; in fact, this was generally associated with increased morbidity or mortality.

Conclusion: Hypoxemia should certainly be avoided, but the fact that the liberal administration of oxygen to patients in intensive care units and emergency rooms tends to increase morbidity and mortality implies the advisability of a conservative, normoxic oxygenation strategy.

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In emergency situations, oxygen therapy can be life-saving for patients with hypoxemia, but harmful effects of exposure to high oxygen concentrations (oxygen toxicity) have long been known (e1, e2). Within a few years of the introduction of oxygen therapy, the issue of potential oxygen toxicity was raised (e3). Today, we know that increased concentrations of oxygen free radicals cause cellular damage which can lead to apoptosis or necrosis, especially in the presence of other factors, such as, for example, infection. Cell death triggers the release of mediators, causing, in combination with oxygen free radicals, further cell damage; thereby a vicious cycle is initiated and maintained (e2).

In recent years, several studies have shown that hyperoxia is associated with increased mortality in various subgroups of critically ill patients (1, e4, e5). In a multivariate analysis of more than 30 000 patients with a hospital mortality of 31% (1) above an arterial partial pressure of oxygen (paO₂) of 123 mmHg, the odds ratio for mortality was 1.23 (95% confidence interval [CI] : [1,13; 1,34]). Previous reviews have focused on special patient groups

and not taken into account data from the most recently published large prospective randomized trials (e6–e9). Therefore, this article provides an overview of the role of oxygen therapy in the management of various conditions in intensive care and emergency medicine.

Methods

This review is based on pertinent publications that were retrieved by a selective search for prospective randomized trials on the target ranges of normobaric oxygen administration to treat adult intensive care or emergency patients. The search was performed in the PubMed database; the search criteria are listed in the eTable. Two of the authors (J. G., V. F.) independently identified studies on outcome parameters. To compensate for the scarcity of studies on this topic, selective retrospective studies as well as recommendations of specialist societies were also included (Table 1). Ongoing studies were searched and identified in the study registries of the United States (ClinicalTrials), Europa (EudraCT) and the United Kingdom (ISRCTN) (Table 2).

TABLE 1

Overview of the recommendations for oxygen therapy for selected acute conditions

Condition	Recommendation	Medical society
Acute exacerbation of COPD	Target: SpO ₂ 88–92%	British Thoracic Society (35)
	Target: SpO ₂ 91–92%	German Respiratory Society (29)
Myocardial infarction	O ₂ administration if SpO ₂ <90%	European Society of Cardiology und American Heart Association (30, 31, 36, 37)
Cardiogenic shock	Target: SpO ₂ 95–98% *	German Cardiac Society (DGK) (38)
Post-resuscitation	O ₂ therapy if SpO ₂ <94%, target: SpO ₂ 94–98%	European Resuscitation Council (32)
	Lowest O ₂ administration to achieve SpO ₂ ≥ 94%	American Heart Association (39)
Stroke	No routine administration of O ₂ , but seek to achieve SpO ₂ > 94%	American Stroke Association (33)
Ventilated intensive care patients	Lowest O ₂ administration to achieve SpO ₂ of 90–94% / paO ₂ of 60–80 mmHg	German Society of Anesthesiology and Intensive Care Medicine (DGAI) (34)
Carbon monoxide intoxication	Administration of 100% oxygen until patient is symptom-free; above COHb of 25–30%, hyperbaric oxygenation should be considered	Centers for Disease Control and Prevention (40)

*Guideline is currently being revised.

COHb, carboxyhemoglobin; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; O₂, oxygen; paO₂, arterial partial pressures of oxygen; SpO₂, oxygen saturation by pulse oximetry

Results

Using this search strategy, a total of 13 prospective randomized trials (2–14) with altogether 17 213 patients were included for analysis (*eFigure, Table 3*).

Chronic obstructive pulmonary disease (COPD)

One study on patients with acute exacerbation of COPD was identified. It included 405 patients treated in the prehospital situation with titration of oxygen therapy to pulse-oximetry oxygen saturation (SpO₂) levels between 88% and 92%, using oxygen flow rates of 8 to 10 L/min (2). In the group treated with titrated oxygen therapy, mortality was reduced from 9% to 2% (risk ratio 0.22) and the mean pH value was found increased by 0.12 compared to the group having received high-dose oxygen therapy.

Myocardial infarction

Five randomized studies with a total of 7458 patients evaluated the use of supplemental oxygen in patients with myocardial infarction. A first randomized study, carried out in 1976, evaluated 157 patients with uncomplicated myocardial infarction who were treated for 24 hours with 6 L/min oxygen versus ambient air. No significant differences with regard to mortality (ambient air: 4% versus oxygen: 11%) or the reduction of cardiac arrhythmia were found (3).

Among 136 patients with ST-segment elevation myocardial infarction (STEMI) without hypoxemia, mortality (6 L/min: 1% versus titrated: 3%) and infarct size did not differ significantly between oxygen therapy titrated to the SpO₂ target of 93% and oxygen administration of 6 L/min; however, the authors noted

that the sample size was inadequate to detect a difference between the two treatments (4).

A small randomized study evaluating 95 patients treated with either 10 L/min oxygen or ambient air found no benefit of oxygen administration (left-ventricular infarct size 16 ± 10% versus 16 ± 11%) (6).

In the AVOID study, STEMI patients were already randomized in the prehospital situation to receive either 8 L/min oxygen (the oxygen group) or to only receive oxygen if SpO₂ levels were <94% (5). Of the 441 patients included in this study, those in the oxygen group showed a significant increase in creatine kinase levels, more re-infarctions and more arrhythmias. Furthermore, cardiac MRI at 6 months after myocardial infarction showed an increased infarct size (20.3 g versus 13.1 g).

In 2017, the so far largest study on this topic with more than 6000 patients was published (DETO2X-AMI). This randomized study evaluated the impact of routine oxygen supplementation at a rate of 6 L/min versus no oxygen in patients with STEMI or non-ST-segment elevation myocardial infarction (NSTEMI) with SpO₂ levels of ≥ 90% on morbidity and mortality (7). No differences were found for mortality after 1 year (oxygen: 5.0% versus ambient air: 5.1%), reinfarction (3.8% versus 3.3%), atrial fibrillation (2.8% versus 3.1%), and cardiogenic shock (1.0% versus 1.1%).

Post-resuscitation

No randomized studies evaluating the effect of oxygen administration on post-resuscitation outcome have so

TABLE 2

Ongoing studies

Name	Target group	Design	Reference	Endpoints
LOCO ₂ (Liberal Oxygenation versus Conservative Oxygenation in ARDS)	ARDS, 850 pts	paO ₂ 90–105 mmHg vs. paO ₂ 55–70 mmHg	NCT02713451	Mortality day 28
HO ₂ TorNO ₂ T (Hyperoxic O ₂ Therapy vs. Normoxic O ₂ Therapy in Sepsis)	Sepsis, 50 pts	O ₂ 15 L/min vs. O ₂ therapy if SpO ₂ <94%	NCT02378545	Mortality day 90
O ₂ -ICU (Optimal Oxygenation in the Intensive Care Unit)	SIRS, 385 pts	paO ₂ 105–135 mmHg vs. paO ₂ 60–90 mmHg	NCT02321072	Daily changes of Se- quential Organ Failure Assessment Score (SOFA)
REOX (Reoxygenation After Cardiac Arrest)	CPR, 280 pts	Correlation of oxygen ex- posure with biomarkers	NCT01881243	Biomarkers
REOX II (Reoxygenation After Cardiac Arrest II)	CPR, 75 pts	Fast optimization of paO ₂ , outcome comparison with patients from REOX	NCT02698826	Biomarkers, modified Rankin scale

ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation; O₂, oxygen; paO₂, arterial partial pressure of oxygen; pts, patients; SIRS, systemic inflammatory response syndrome

far been published, except for a pilot study with only 28 analyzed patients (8). It is known that during cardiopulmonary resuscitation an initially high paO₂ increases the likelihood of restoration of spontaneous circulation (15). However, during the further course of treatment, hyperoxia during the first 24 hours seems to increase mortality, as suggested by 2 meta-analyses (16, 17). The largest two cohort studies included here analyzed 6326 (e4) and 12 108 patients (18), respectively. In the latter study, the negative effect of hyperoxia was no longer detectable after multivariate analysis for severity.

Stroke/intracerebral hemorrhage

So far, 3 randomized studies on oxygen therapy in patients with stroke, including a total of 8343 patients, have been published. In a pilot study, 289 stroke patients were randomly assigned to two groups, receiving over a period of 72 hours either no oxygen or 2–3 L/min oxygen. No difference was found between the 2 groups (modified Rankin scale [mRS]) 3 versus 3) (9, e10). By contrast, another study found an mRS improvement associated with oxygen administration; however, the study was small, including only 51 patients (10). A quasi-randomized trial with 550 stroke patients, receiving either no oxygen or for 1 day supplemental oxygen at a rate of 3 L/min found no differences between the two groups with regard to mortality and neurological outcome after 1 year (19).

In the recently published SO₂S study, 8003 stroke patients were randomly assigned to one of 3 groups: Over a period of 72 hours, oxygen was given (1) only at night, (2) continuously or (3) not at all. After 90 days, no difference in mRS scores was found between the groups (11); this also applied to subgroups differing in disease severity. One point of criticism of this study is that it included many patients with

comparatively mild stroke (median score on the National Institutes of Health Stroke Scale [NIHSS] of 5).

Until now, no randomized study on oxygen therapy in patients with intracerebral hemorrhage has been published. A post-hoc analysis of a prospective randomized hypothermia trial with patients after severe traumatic brain injury indicated a potential positive effect of hyperoxia; however, both groups of this study had very high paO₂ levels (242 versus 193 mmHg) and consequently no normoxic values (20).

So far, several retrospective analyses have been published, none of which has shown an advantage of hyperoxia. Among 2643 ventilated patients with stroke, no correlation between mortality and paO₂ was found (21), while in 2894 patients hyperoxia (paO₂ of ≥ 300 mmHg) during the first 24 hours was an independent risk factor for in-hospital mortality (22). In patients with traumatic intracerebral hemorrhage, paO₂ levels ≥ 300 mmHg were associated with increased mortality (23) and in another study this association was also found for paO₂ levels >200 mmHg (24); however, if hyperoxia is defined as paO₂ levels of >100 mmHg or >150 mmHg, there is no association between mortality and hyperoxia (25, 26).

Intensive care patients

Three prospective randomized trials in intensive care patients, including a total of 979 persons, were identified. In the first study (OXYGEN-ICU), 434 intensive care patients with a length of stay in an intensive care unit (ICU) of 3 days or longer were analyzed (12). Two thirds of the evaluated patients received mechanical ventilation. In the conventional group (target: SpO₂ of 97–100%, median paO₂ = 102 mmHg),

TABLE 3a

Overview of completed prospective randomized trials on oxygen therapy

Name of study / first author	Design	Target group	Intervention	Control	Age intervention / control	Outcomes (primary endpoints)
COPD						
Austin et al. (2)	Single-center, cluster-randomized	Acute exacerbation of COPD, n = 405	Nasal O ₂ titrated, Target: SpO ₂ 88–92%, n = 179	Mask 8–10 L/min O ₂ , n = 226	69 ± 12 / 69 ± 11	Mortality prehospital or in-hospital: normoxia 2% vs. hyperoxia 9% (p = 0.02)
Myocardial infarction						
Rawles et al. (3)	Single-center, randomized	Myocardial infarction without pump failure, n = 157	Mask 6 L/min air, n = 77	Mask 6 L/min O ₂ , n = 80	56 ± 1 / 55 ± 1	No difference in mortality (air: 4% vs. oxygen: 11%)
Ranchord et al. (4)	Two-center, randomized	STEMI, n = 136	nasal O ₂ or mask titrated, target: SpO ₂ 93–96% n = 68	Mask 6 L/min O ₂ or more if SpO ₂ < 92%, n = 68	62 ± 13 / 60 ± 13	No difference in mortality at day 30 (6 L/min: 1% vs. titrated: 3%) or infarct size
AVOID ^{*1} (5)	Multicenter, randomized	STEMI, n = 441	No O ₂ , if SpO ₂ < 94%: nasal O ₂ 4 L/min or mask 8 L/min, n = 223	Mask 8 L/min O ₂ , n = 218	63 ± 13 / 63 ± 12	Higher troponin levels in oxygen group, infarction area (hyperoxia 20.3 g vs. normoxia 13.1 g; p = 0.04)
SOCCER ^{*2} (6)	Two-center, randomized	STEMI, n = 95	No O ₂ , if SpO ₂ < 94%: mask 10 L/min, n = 49	Mask 10 L/min O ₂ , n = 46	66 ± 12 / 64 ± 13	No difference in infarct size (left ventricular infarct size: 16 ± 10% vs. 16 ± 11%)
DETO ₂ X-AMI ^{*3} (7)	Multicenter, randomized	Myocardial infarction, n = 6629	No O ₂ , n = 3318	Mask 6 L/min O ₂ , n = 3311	68 (59–76) / 68 (59–76)	No difference in mortality after 1 year (oxygen: 5.0% vs. air 5.1%), re-infarction (3.8% vs. 3.3%), atrial fibrillation (2.8% vs. 3.1%), cardiogenic shock (1.0% vs. 1.1%)
post CPR						
Kuisma et al. (8)	Single-center, randomized	after ROSC, n = 28	FiO ₂ = 0.3, n = 14	FiO ₂ = 1.0, n = 14	62 ± 14 / 64 ± 8	No difference S-100 (after 24/48 h: FiO ₂ = 0.3: 0.21/0.23 µg/L vs. FiO ₂ = 1.0: 0.73/0.49 µg/L) and NSE (after 24/48 h: FiO ₂ = 0.3: 10.9/14.2 µg/L vs. FiO ₂ = 1.0: 13.0/18.6 µg/L)
Stroke						
Ali et al. (9)	Single-center, randomized	n = 289	No O ₂ , n = 141	If SpO ₂ > 93: 2 L/min O ₂ , otherwise 3 L/min O ₂ , n = 148	71 ± 12 / 73 ± 12	No difference in mortality after 6 months (no O ₂ : 14% vs. oxygen: 15%)
Mazdeh et al. (10)	Single-center, randomized	n = 51	No O ₂ , n = 25	Mask, FiO ₂ = 0.5, n = 26	Data not available	Modified Rankin scale after 6 months in oxygen group (mean: 2.7 vs. 3.3; p = 0.04)
SO ₂ S ^{*4} (11)	Multicenter, randomized	n = 8003	No O ₂ , n = 2668	O ₂ during night (n = 2667) or O ₂ during day and night (n = 2668)	72 ± 13 in all 3 groups	No difference in modified Rankin scale on day 90 (odds ratio no O ₂ vs. the two O ₂ groups: 0.97 [95% CI: 0.89; 1.05] for better value)

95% CI, 95% confidence interval; CPR, cardiopulmonary resuscitation; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; NSE, neuron-specific enolase (protein as a marker for brain damage); O₂, oxygen; paO₂, arterial partial pressure of oxygen; p/F, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; ROSC, return of spontaneous circulation; S-100, protein as a marker for brain damage; SpO₂, pulse-oximetry oxygen saturation; STEMI, ST-segment elevation myocardial infarction

^{*1} Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction

^{*2} Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion

^{*3} DETermination of the role of OXYgen in Acute Myocardial Infarction

^{*4} Stroke Oxygen Study

TABLE 3b

Continued: Overview of completed prospective randomized studies on oxygen therapy

Name of study / first author	Design	Target group	Intervention	Control	Age intervention / control	Outcomes (primary endpoints)
Intensive care patients						
Oxygen-ICU (12)	Single-center, randomized	Ventilated intensive care patients without patients with acute exacerbation of COPD or ARDS with p/F <150mmHg, n = 434	Target paO ₂ : 70–100 mmHg or SpO ₂ : 94–98%, n = 216	FiO ₂ ≥ 0.4, paO ₂ up to 150 mmHg, SpO ₂ : 97–100%, n = 218	63 (51–74) / 65 (52–76)	Mortality in ICU: normoxia 11.6% vs. 20.2% hyperoxia (p = 0.01)
HYPER2S (13)	Multicenter, randomized	Sepsis, n = 442	Target SaO ₂ : 88–95%, n = 223	FiO ₂ = 1.0, n = 219	66 ± 15 / 68 ± 13	Mortality on day 28: normoxia 35% vs. hyperoxia 43% (p = 0.12); secondary endpoints: serious adverse events: normoxia 76% vs. hyperoxia 85% (p = 0.02)
Panwar et al. (14)	Multicenter, randomized	Ventilated intensive care patients, n = 103	Target SaO ₂ : 88–92%, n = 52	Target: SaO ₂ ≥ 96%, n = 51	62 ± 15 / 62 ± 17	No difference regarding new organ dysfunction, mortality in ICU (restrictive 25% vs. liberal 24%) and on day 90 (restrictive 40% vs. liberal 37%, risk ratio of O ₂ -restrictive group 0.77 [95% CI: 0.40; 1.50])

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; NSE, neuron-specific enolase (protein as a marker for brain damage); O₂, oxygen; paO₂, arterial partial pressure of oxygen; p/F, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; SaO₂, arterial oxygen saturation; SpO₂, pulse-oximetry oxygen saturation; STEMI, ST-segment elevation myocardial infarction

the number of patient deaths was higher compared to the conservative group (target: SpO₂ of 94–98%, median paO₂ = 87 mmHg) in the ICU (20.2% versus 11.6%, risk ratio 0.57, p = 0.01; primary endpoint) and overall hospital mortality was also increased (33.9% versus 24.2%, risk ratio 0.71, p = 0.03). Furthermore, the median ventilation time was shorter among patients treated with less oxygen.

In a feasibility study, 103 mechanically ventilated intensive care patients were randomly assigned to either a conservative oxygenation strategy (SpO₂ of 88–92%) or a liberal oxygenation strategy (SpO₂ of ≥ 96%) (14). No significant differences were found between the groups with regard to new organ dysfunction, or ICU mortality or 90-day mortality.

The recently published HYPER2S study evaluating the administration of hypertonic versus isotonic saline and mechanical ventilation with hyperoxia versus with normoxia among ICU patients with septic shock was terminated early after inclusion of 442 patients because of safety concerns. In the hyperoxia group, a significantly higher rate of severe side effects, including muscle weakness and atelectasis, was noted (85% versus 76%, p = 0.02) (13).

Earlier, several retrospective studies indicated that hyperoxia was associated with increased mortality. An analysis of more than 36 000 intensive care patients with mechanical ventilation found that paO₂ levels of about 70–80 mmHg during the first day after hospital admission was associated with the lowest mortality. Mortality increased with both lower and

higher paO₂ levels. This effect persisted even after multivariate adjustment for disease severity (1).

In another retrospective analysis of more than 150 000 intensive care patients during the first 24 hours of ICU admission, these results were only partially confirmed as it was shown that after multivariate adjustment for disease severity a general association between hyperoxia and increased mortality was no longer present, only for hypoxia (27). In an observational study with 105 patients, restrictive oxygen supplementation was no longer associated with increased complications after reduction the oxygen target range (28).

Discussion

This review, which analyzed 13 prospective randomized trials, did not find evidence indicating an advantage of oxygen supplementation in non-hypoxemic patients in any of these studies. Since it was even associated with increased mortality or morbidity in the majority of studies, adjuvant oxygen therapy should always be critically assessed.

Until now, only few prospective randomized studies with adequate power have been published. The majority of recommendations for oxygen therapy is based on retrospective analyses which is a limitation of many studies. Furthermore, there is inconsistency in the paO₂ ranges used to define hypoxia, normoxia and hyperoxia. While in some studies, a paO₂ of >100 mmHg is already defined as hyperoxia, in others it is still considered within the normoxic

KEY MESSAGES

- Hyperoxia can increase mortality and morbidity.
- Patients without hypoxia should not receive routine oxygen supplementation.
- The therapeutic use of hyperoxia should be limited to special conditions, such as, for example, carbon monoxide intoxication.
- The current recommendations for the target range of oxygen therapy depend on the respective primary disease.
- To improve patient outcomes, a conservative oxygenation strategy accompanied by training measures should be implemented.

range which extends up to a paO_2 of 300 mmHg. Thus, comparability between studies is absent.

Even though paO_2 levels between 100 and 300 mmHg are no longer within the physiological range and can only be reached by artificially supplying oxygen, many researchers included them in their definitions of normoxia. Since in recent randomized studies the boundary between normoxia and hyperoxia is essentially identical with the one between physiological and non-physiological paO_2 levels, and a difference between the groups has been demonstrated, it is conceivable that various endpoints in the studies with “non-physiological” normoxia/hyperoxia boundaries could not be reached because those patients defined as normoxic were actually already hyperoxic.

Despite these potential negative effects of hyperoxia, it should not be forgotten that there are certain conditions, such as carbon monoxide (CO) intoxication which require the use of therapeutic hyperoxia (e11). However, the assumption that perioperative hyperoxia reduces the incidence of abdominal surgery-related wound infection proved to be wrong (e12), especially since patients treated with hyperoxia were even years later still at an increased risk of myocardial infarction (e13).

Prospective randomized trials comparing hypoxia with normoxia are not available due to ethical and medical concerns, as hypoxia can cause hypoxia-related organ damage. These concerns are supported by retrospective analyses demonstrating hypoxia-related increases in mortality among ICU patients (1, 27).

In patients with COPD, restrictive use of oxygen therapy is advisable because these patients characteristically are at risk of hypercapnic pulmonary failure. In these patients, hyperoxia may further decrease the respiratory drive, leading to increased hypercapnia. In addition—presumably as the result of a deterioration of the ventilation-perfusion ratio—improved perfusion of poorly ventilated alveoli ultimately increases the pulmonary shunt fraction. For these reasons, restrictive oxygen therapy has widely been adopted in clinical practice as the management strategy for

COPD patients for many years now. The target defined in the recently published German clinical practice guideline is an SpO_2 of 91–92% (29).

In patients with myocardial ischemia, resulting from an imbalance between oxygen availability and oxygen requirement, the strategy of oxygen supplementation appears to be plausible from the perspective of pathophysiology to improve symptoms, reduce ischemic tissue injury and ultimately mortality. However, since studies failed to demonstrate any benefit from oxygen therapy, it appears that the negative effects of hyperoxia, such as reperfusion damage due to free radicals (e14) and reduction in coronary perfusion, outweigh conceivable positive effects (e8). Therefore, the current European guidelines for the management of STEMI and NSTEMI do only recommend the use of oxygen therapy in patient with oxygen saturations of <90% (30, 31).

According to the current recommendations for post-cardiac arrest management, oxygen therapy should only be administered in patients with oxygen saturation levels of <94% (target: oxygen saturation levels of 94–98%) (32). Further studies on post-resuscitation management are being planned or ongoing to develop strategies to more precisely define the optimum oxygen partial pressure after resuscitation, for example the REOX study (NCT01881243) and the REOX-II study (NCT02698826).

According to the US guideline for stroke management, the routine use of oxygen therapy is not recommended; however, measures should be taken to achieve an oxygen saturation of >94% (33).

Even though the two largest randomized studies on ventilated ICU patients were terminated early, the Italian single-center study found a lower mortality in the group with restrictive oxygen therapy (11.6% versus 20.2%) (12). In any case, normoxia is not associated with an additional risk. Therefore, the recently published German clinical practice guideline for invasive ventilation recommends a paO_2 target range of 60–80 mm Hg (34). To also increase our understanding of the association between oxygenation and mortality in special patient populations, further studies are currently being planned or conducted, including, among others, the LOCO₂ study on acute respiratory distress syndrome (ARDS), the HO₂TorNO₂T study on sepsis and the O₂-ICU study on systemic inflammatory response syndrome (SIRS).

Independent of the desired target range for oxygen therapy, the route of administration also plays an important role (e15). For example, one study demonstrated the superiority of high-flow oxygen through nasal cannula (50 L/min) over noninvasive ventilation via a face mask in patients with non-hypercapnic respiratory failure (e16). However, in case of hypercapnic respiratory failure, non-invasive ventilation is preferred as it offers advantages over invasive ventilation via an endotracheal tube (e17).

In a randomized controlled trial, oxygen therapy for non-hypoxemic palliative care patients with refractory dyspnea showed no advantages (e18). Thus, palliative oxygen should not be offered to this patient population.

Very recently, a meta-analysis of oxygen therapy including 25 studies with a total of 16 037 patients has been published, comparing a liberal with a conservative oxygen strategy in patients with non-elective hospital admission (e19). It showed an increased mortality (risk ratio for in-hospital mortality: 1.21; [95% confidence interval (CI): 1.03; 1.43]) in the group with liberal oxygen therapy; thus, supplemental oxygen should not be given to patients with SpO₂ levels above 94 to 96%.

Future studies should aim to identify the optimum pO₂ range to achieve the best possible outcome for patients. Furthermore, prospective randomized trials on oxygen therapy are needed to overcome the limitations of retrospective analyses.

Conflict of interest statement

Prof. Kluge received consultancy fees from Baxter, Fresenius und Xenios. He received reimbursement of travel and accommodation expenses as well as lecture fees from Baxter, Fresenius, Sorin, and Xenios. He received consumables for the conduct of clinical and preclinical studies from ETView Ltd und Fisher & Paykel as well as funds from Xenios.

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► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref2718

eFigure, eTable:
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CLINICAL SNAPSHOT

Acquired Perforating Collagenosis in Diabetes Mellitus

An 83-year-old woman complained of intense itch. On the left side of her trunk, there were multiple ulcerations with central, nodular keratinous plugs. Histopathological examination confirmed the suspected diagnosis of perforating collagenosis. Acquired perforating collagenosis is a condition in which collagenous connective tissue is transepidermally extruded. A Koebner phenomenon resulting from deep self-inflicted scratches is thought to be a possible mechanism for this condition, which is often associated with diseases such as chronic renal insufficiency, diabetes mellitus, herpes zoster, or scabies. This patient had an HbA1c value of 7.8%; chronic metabolic decompensation of her previously diagnosed diabetes mellitus was considered to have been a possible triggering factor for the skin condition. In the differential diagnosis of such cases, other pruritic skin diseases—e.g., prurigo diseases—must be excluded. The clinical presentation here, with sharply demarcated ulcerations, was typical, but skin biopsy was nonetheless essential for confirming the diagnosis. The

most important part of therapy is the treatment of the underlying disease. We also gave this patient topical glucocorticoids and systemic antihistamine drugs, alternatives include ultraviolet therapy or systemic allopurinol. The itch rapidly improved, and the skin lesions gradually healed.

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Supplementary material to:

Oxygen Treatment in Intensive Care and Emergency Medicine

by Jörn Grensemann, Valentin Fuhrmann, and Stefan Kluge

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eTABLE

Search criteria

Search terms	Number of hits
#1, "Search ((((((oxygen [Title] OR hyperoxia[Title] OR normoxia[Title] OR hypoxia[Title]))) AND (randomised or randomized controlled trial))) AND (myocardial infarction or nstemi or stemi))"	72
#2, "Search ((((((oxygen [Title] OR hyperoxia[Title] OR normoxia[Title] OR hypoxia[Title]))) AND (randomised or randomized controlled trial))) AND (intensive or critical care))"	384
#3, "Search ((((((oxygen [Title] OR hyperoxia[Title] OR normoxia[Title] OR hypoxia[Title]))) AND (randomised or randomized controlled trial))) AND (((cardiac arrest) or (resuscitation)))"	191
#4, "Search ((((((oxygen [Title] OR hyperoxia[Title] OR normoxia[Title] OR hypoxia[Title]))) AND (randomised or randomized controlled trial))) AND (((chronic obstructive (lung or pulmonary) disease) or (COPD)))"	247
#5, "Search ((((((oxygen [Title] OR hyperoxia[Title] OR normoxia[Title] OR hypoxia[Title]))) AND (randomised or randomized controlled trial))) AND ((traumatic brain injury) or stroke))"	148

PRISMA flowchart of literature search