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REVIEW

Ventilation management in acute respiratory failure related to COVID-19 versus ARDS from another origin – a descriptive narrative review

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ABSTRACT

Introduction: It is uncertain whether ventilation in patients with acute respiratory failure related to coronavirus disease 2019 (COVID-19) differs from that in patients with acute respiratory distress syndrome (ARDS) from another origin.

Areas covered: We undertook two literature searches in PubMed to identify observational studies reporting on ventilation management––one in patients with acute respiratory failure related to COVID-19, and one in patients with ARDS from another origin. The searches identified 14 studies in patients with acute respiratory failure related to COVID-19, and 8 studies in patients with ARDS from another origin.

Expert opinion: In patients with acute respiratory failure related to COVID-19, ventilation management seems to be similar to that of patients with ARDS from another origin. The future lies in studies focused on personalized treatment of ARDS of all origins, including COVID-19.

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1. Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening complication in critically ill patients with high mortality and morbidity [1]. Sepsis, systemic inflammation, and pneumonia are the most common causes of ARDS [2]. Since December 2020, ICUs worldwide are overwhelmed with patients with acute respiratory failure related to coronavirus disease 2019 (COVID-19). Initially, COVID-19 was seen as a 'novel' disease and the acute respiratory failure it can cause as a 'new form' of ARDS [3]. It is increasingly understood, however, that acute respiratory failure related to COVID-19 has many issues in common with 'normal' ARDS [4].

In ARDS, so–called lung-protective ventilation is strongly advocated to limit lung injury caused by the ventilator [5]. Key components of lung-protective ventilation include the limitation of volumes and pressures, prevention of atelectasis while avoiding overdistension, proper use of prone positioning, and possibly also the use of conservative oxygenation targets. In patients that remain severely hypoxic, additive rescue therapies for hypoxemia can be applied, including muscle paralysis through continuous infusion of neuromuscular blocking agents (NMBAs), inhaled nitric oxide (iNO), or extra–corporeal membrane oxygenation (ECMO). It is very likely that lung–protection and possibly also the use of the abovementioned additive rescue therapies are also important in patients with acute respiratory failure related to COVID-19.

We here describe and compare ventilation management in patients with acute respiratory failure related to COVID-19 to that in patients with ARDS from another origin. Following a succinct overview of the evidence for benefit of the four abovementioned key components of lung-protective ventilation and additive rescue therapies, we summarize ventilation management as reported in several cohorts of patients with acute respiratory failure related to COVID-19, and in preceding international or multicenter cohorts of patients with ARDS from another origin.

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List of abbreviations

ARDS: acute respiratory distress syndromeCOVID-19: coronavirus disease 2019ECMO: extra–corporeal membrane oxygenationFiO_2: inspired oxygen fractionICU: intensive care unitiNO: inhaled nitric oxideNMBAs: neuromuscular blocking agentsPplat: plateau pressurePEEP: positive end–expiratory pressurePBW: predicted body weightSpO_2: pulse oximetryV_T: tidal volume

Article highlights

- Key components of lung-protective ventilation in ARDS patients include limitation of volumes and pressures, prevention of atelectasis while avoiding overdistension, proper use of prone positioning, and use of conservative oxygenation targets;
- PEEP and FiO_2 titrations remain debated in ventilated critically ill patients;
- Lower V_T are used in patients with acute respiratory failure due to COVID-19 than in ARDS of other origin;
- Higher PEEP with broad variation is currently used in COVID-19 patients;
- Higher FiO_2 is needed in COVID-19 patients;
- Prone positioning is used much more often patients with acute respiratory failure due to COVID-19 than in ARDS of other origin;
- It is unclear whether differences in ventilation management between patients with acute respiratory failure due to COVID-19 and in ARDS of other origin reflect protocol adherence or are the consequence of differences in pathophysiology; and
- There are no arguments to ventilate COVID-19 patients different from patients with ARDS of other origin.

2. Lung-protective ventilation

2.1. Smaller volumes and lower pressures

Ventilation with a higher tidal volume (V_T) [10 to 15 ml/kg predicted body weight (PBW)] was commonly used because use of a higher V_T improved oxygenation. However, animal studies showed that ventilation with a higher V_T causes disruption of lung structures and induced a local release of inflammatory mediators––a phenomenon frequently referred to as 'volutrauma'.

The first randomized clinical trials comparing ventilation with a higher V_T to ventilation with a lower V_T failed to show profit of this strategy in patients with ARDS [6–8]. One landmark randomized clinical trial from the United States, named 'ARMA', unmistakably demonstrated benefit from ventilation with a lower V_T [6 to 8 ml/kg PBW] when compared to ventilation with a higher V_T [12 ml/kg PBW]––ventilation with a lower V_T improved survival and shortened duration of ventilation in patients with ARDS [9]. These findings, confirmed in a metaanalysis that also included the preceding trials [10], brought about a revolutionary change in ventilation management worldwide.

Ventilation with a lower V_T comes with lower airway pressures. Consequently, the abovementioned trials compared ventilation at different airway pressures. The extent to which the airway pressure needs to be reduced to prevent injury remains a matter of debate. Animal studies showed that high plateau pressure (Pplat) can cause lung injury, and a posthoc analysis of the abovementioned ARMA study suggested ventilation with a Pplat < 30 cm H_2O to be safe [11].

Ventilation with a lower tidal volume is now considered standard of care, and V_T of up to 8 ml/kg can be accepted in cases of severe dyspnea, e.g. in patients with a metabolic acidosis. It remains uncertain whether a further reduction of the Pplat, e.g. by an additional reduction of V_T below 6 to 8 ml/kg PBW, can improve outcome of ARDS patients.

2.2. Fewer atelectasis and less overdistension

After its first use in clinical practice, positive end–expiratory pressure (PEEP) was mainly used to correct hypoxemia that was refractory to large increases in the fraction of inspired oxygen (FiO_2). Animal studies showed that ventilation with higher PEEP can prevent or reduce repeated opening and closing of lung tissue––a phenomenon frequently referred to as 'atelectrauma'. However, animal studies also showed that ventilation with higher PEEP can cause overdistension of healthy lung parts, which is increasingly recognized as harmful.

Three well–designed and sufficiently powered randomized clinical trials, named 'ALVEOLI', 'LOVES' and 'EXPRESS', failed to show benefit of ventilation with higher PEEP [13 to 15 cm H_2O] compared to ventilation with lower PEEP [7 to 10 cm H_2O] in patients with ARDS [12–14]. An individual patient data metaanalysis of these studies suggested benefit from ventilation with higher PEEP [15]––it was associated with a lower mortality in patients with moderate to severe ARDS. However, that same metaanalysis suggested harm from ventilation with higher PEEP in patients with mild ARDS, and one more recent randomized clinical trial, named 'ART', showed ventilation with higher PEEP combined with lung recruitment maneuvers to increase mortality in patients with severe ARDS, despite improvements in oxygenation and lung compliance [16]. One explanation for these findings could be that in some patients, benefit of ventilation with higher PEEP with respect to less atelectasis is nullified by coinciding overdistension.

Taken together, these findings suggest there is close balance between the positive and negative effects of ventilation with higher PEEP, and it remains debated whether PEEP should be titrated according to a higher PEEP–lower FiO_2 table or a lower PEEP–higher FiO_2 table in patients with ARDS.

2.3. Prone positioning

There are several reasons for why prone position can improve oxygenation, including a better match of ventilation with pulmonary blood flow, enhanced clearance of airway secretions, and recruitment of lung tissue due to a shifting weight of the mediastinum and the diaphragm. Experimental studies showed that prone positioning improves gas exchange, lung compliance and alveolar recruitment, and prevents lung injury.

Initial randomized clinical trials confirmed the improvement in oxygenation, but failed to show a better outcome with prone positioning [17–20]. Two metaanalyses, though, suggested an improved outcome with use of prone positioning in patients with severe ARDS [21,22]. One landmark randomized clinical trial from France, named 'PROSEVA', indisputably showed benefit from prone positioning, if applied early and for sufficiently long periods [23]––prone positioning improved survival in patients with ARDS.

Consequently, prone positioning is now part of standard care in patients with ARDS with severe hypoxemia refractory to high FiO_2.

2.4. Oxygen targets

ARDS patients are by definition hypoxemic, requiring higher FiO_2 than other ventilated critically ill patients. However, prolonged hyperoxia is also known to be toxic, causing pulmonary histopathological changes comparable to those seen in ARDS [24]. Two systematic reviews of retrospective studies performed in heterogenic cohorts of ventilated critically ill patients showed an association between hyperoxia and increased mortality [25,26]. A fairly large but nevertheless underpowered randomized clinical trial from Italy, named 'OXYGEN–ICU', showed a decreased mortality and a greater number of ventilator–free days in patients receiving conservative oxygenation therapy (arterial oxygen tension [PaO_2] 9.3 to 13.3 kPa), compared to a liberal approach (PaO_2 up to 20 kPa) [27]. These findings were supported by two metaanalyses of studies comparing various oxygenation strategies [28,29]. One randomized clinical trial from Australia, named 'ICU–ROX', comparing a strategy using a conservative oxygenation target (pulse oximetry [SpO_2] < 90%) to one that uses a conventional target (SpO_2 ≥ 97%) showed no difference in duration of ventilation or mortality [30]. It should be noted, though, that the conventional group was already treated with a low FiO_2, maybe explaining the lack of difference in outcomes in this study. A recent randomized clinical trial from France, named '$LOCO_2$' was prematurely aborted due a higher mortality in the conservative group [31]. In this study, the oxygen targets were SpO_2 88% to 92% versus > 96%.

Although the effects of an intermediate approach remain unclear, it seems justified to avoid liberal use of oxygen, i.e. to use conservative oxygenation targets during ventilation in patients with ARDS.

2.5. Additive rescue therapies

Muscle paralysis through continuous infusion of NMBAs can reduce oxygen consumption. This strategy may also prevent collapse of alveoli by improving patient–ventilator synchrony [32]. However, it may induce neuromuscular weakness [33] and requires deep sedation, which could also worsen outcome [34]. Of note, one recent RCT in patients with ARDS from another origin, named 'ROSE', failed to show benefit of early and continuous infusion of neuromuscular blockers [35].

The potent selective pulmonary vasodilator, iNO, can be used to improve oxygenation by redirecting blood flow toward well–aerated regions of the lungs, reducing ventilation–perfusion mismatch [36]. Additionally, this may also reduce pulmonary hypertension [37]. It should be noted, though, that one systematic review of 13 RCTs in patients with ARDS from another origin showed no survival benefit despite transient improvements in oxygenation [38].

ECMO provides oxygenation and CO_2 removal. Disadvantages include the risk of hemorrhage due to systemic anticoagulation and complexity of care, making it less available in non–specialized centers. In one RCT in patients with ARDS from another origin, named 'CESAR', referral to centers specialized in ECMO (not necessarily meaning that all patients continued with ECMO) compared to continuation of conventional ventilation in a non–specialized center resulted in lower mortality rates [39]. In one more recent RCT in patients with ARDS form another origin, named 'EOLIA', ECMO did not increase survival [40], albeit that this study was terminated early for futility, and a Bayesian analysis of this study showed ECMO to have a strong potential to increase survival [41].

3. Methods

3.1. Search strategy

To compile evidence on current ventilation management in patients with acute respiratory failure related to COVID-19, and in patients with ARDS from another origin, we performed two comprehensive literature searches in PubMed.

For the search focusing on ventilation in patients with ARDS from another origin, we used keywords and MeSH terms for 'epidemiology' AND 'intensive care' AND 'mechanical ventilation' AND 'acute respiratory distress syndrome' AND 'tidal volume' OR 'plateau pressure' OR 'positive end expiratory pressure' OR 'prone positioning' OR 'oxygenation' OR 'neuromuscular blockage' OR 'inhaled nitric oxide' OR 'ECMO'––selection of articles was restricted to those published after 2012, as the Berlin definition for ARDS had not been defined before then [42]. For the search focusing on ventilation in patients with acute respiratory failure related to COVID-19, keywords and MeSH terms for 'acute respiratory distress syndrome' were interchanged with those for 'coronavirus disease 2019'––selection of articles of this search was restricted to those published after March 2020.

Screening of abstracts and titles identified by our search methods were performed independently by two authors. If a study was considered potentially eligible, full text was obtained. The full text was reviewed for selection according to inclusion and exclusion criteria. Inclusion criteria for both searches were: (1) reporting on invasively ventilated critically ill patients with ARDS, or acute respiratory failure related to COVID-19; (2) reporting on at least one of the four key components of lung-protective ventilation, i.e. V_T or Pplat, PEEP, prone positioning or FiO_2, or additive rescue therapies, i.e. use of NMBA, iNO or ECMO.

We excluded randomized clinical trials, reviews, research letters, and case reports. In addition, studies not using the Berlin definition, and reports on highly specific populations, such as pediatric patients, one–lung ventilation, etc. were excluded. We restricted this review to studies with at least 500 invasively ventilated ARDS patients, and to studies with at least 100 invasively ventilated patients with acute respiratory failure related to COVID-19.

3.2. Reporting

Data on key components of lung-protective ventilation and additive rescue therapies were extracted per study. Findings were reported for each study and, depending on reporting and completeness, existing of proportions of patients receiving the lung-protective intervention, defined as ventilation using lower V_T or airway pressures, and median or mean V_T and Pplat, the median or mean PEEP, the proportion of patients receiving prone positioning, the median or mean

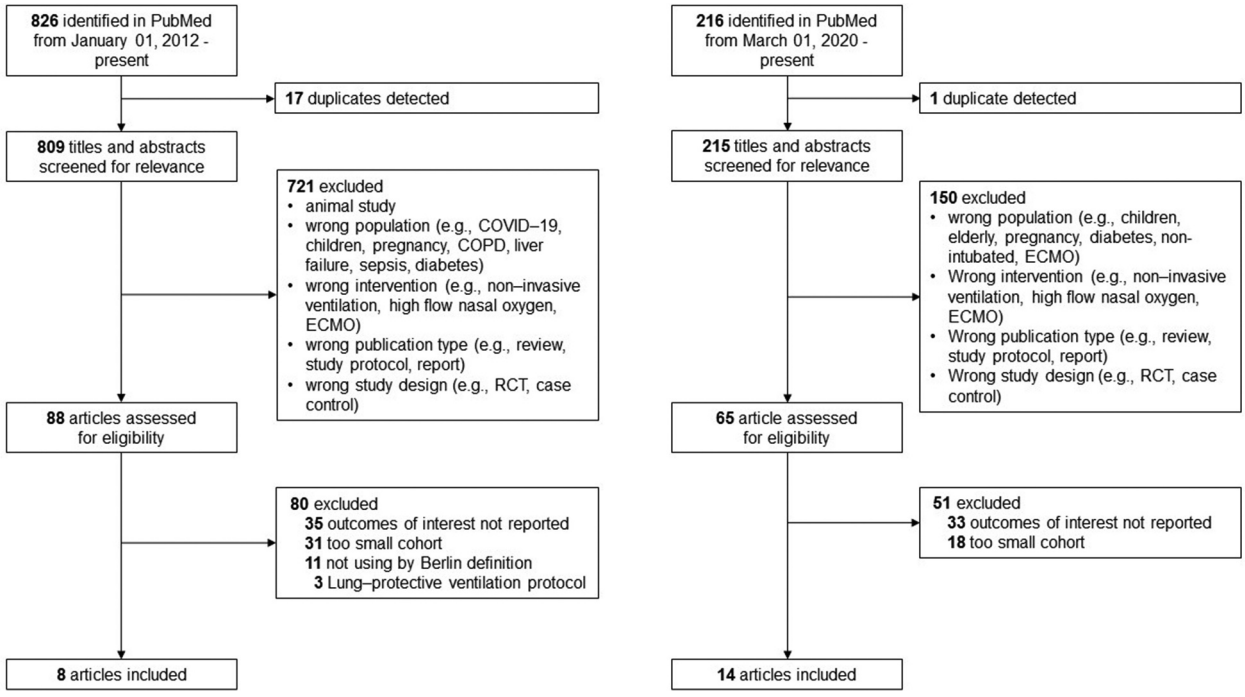

Figure 1. Search results.

FiO_2, and the proportion of patients receiving NMBAs, iNO or ECMO, if reported.

Medians were reported with interquartile ranges, means with 95%–confidence intervals or standard deviations in the tables; in the text we reported medians or means where appropriate. We neither metaanalysed the data nor did we use statistical tests to compare ventilation management in patients with acute respiratory failure related to COVID-19 versus in patients with ARDS from another origin.

4. Results

4.1. Search results

The two searches identified 826 articles on ventilation management in patients with ARDS from another origin, and 216 articles on ventilation management in patients with acute respiratory failure related to COVID-19. Reasons for exclusion of articles are shown in Figure 1. We included 8 articles of ventilation in patients with ARDS from another origin [43–50], and 14 articles of ventilation in patients with acute respiratory failure related to COVID-19 [51–64]. Characteristics of the reported studies and the described cohorts are provided in Table 1 and Table 2. Articles of patients with ARDS from another origin were comprised of cohorts from > 50 countries––articles of patients with acute respiratory failure related to COVID-19 included national cohorts from 8 different countries.

4.2. Tidal volumes and plateau pressures

In studies in patients with ARDS from another origin, median V_T varied from 6.7 to 8.4 ml/kg PBW––mean V_T from 7.1 to

Table 1. Characteristics of 'ARDS of another origin' studies.

Name/study acronym	Ref.	Design	Location	N	Berlin classification	Ventilation characteristics	Reported as
APRONET	43	Pro	Belgium, France and Switzerland	735	25.4%, 54.3% and 20.3% with mild, moderate or severe ARDS	V_T, Pplat, PEEP, FiO_2, prone positioning, duration	median (IQR), %
Gupta *et al.*	44	Pro	Peru	514	not reported	V_T, Pplat, PEEP, FiO_2	mean (SD), proportions ≤ 6 ml/kg PBW
Lanspa *et al.*	45	Retro	US	1385	24.5%, 48.7% and 26.8% with mild, moderate or severe ARDS	V_T, Pplat, PEEP, FiO_2	median (IQR)
Leite *et al.*	46	Retro	US	1142	not reported	V_T, Pplat, PEEP	median (IQR), mean (SD)
LOTUS–FRUIT	47	Pro	US	895	not reported	V_T	mean (95%CI), proportions ≤ 8 ml/kg PBW
LUNG–SAFE	48	Pro	worldwide study	2377	30.0%, 46.6% and 23.4% with mild, moderate or severe ARDS	V_T, Pplat, PEEP, FiO_2, prone positioning	mean (95%CI), proportions ≤ 8 ml/kg PBW
Parhar *et al.*	49	Pro	Canada	633	31.6%, 54.2% and 14.2% with mild, moderate or severe ARDS	V_T, Pplat, PEEP	median (IQR), proportions ≤ 8 ml/kg PBW
Schmidt *et al.*	50	Retro	US	543	not reported	V_T, Pplat, PEEP	median (IQR)

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CI = confidence interval; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; PBW = predicted body weight; Pplat = Plateau pressure; PEEP = Positive end-expiratory pressure; Pro = prospective; Retro = retrospective, SD = standard deviation; UK = United Kingdom; US = United States; V_T = Tidal volume

Table 2. Characteristics of 'acute respiratory failure in COVID-19' studies.

Name/study acronym	Ref.	Design	Location	N	Berlin classification	Ventilation characteristics	Reported as
Camporota *et al.*	51	Retro	UK	213	10.8%, 57.3% and 31.9% with mild, moderate or severe ARDS	V_T, PEEP	mean (95%CI)
Chand *et al.*	52	NA	US	274	4.3%, 35.3% and 52.0% with mild, moderate or severe ARDS	prone positioning	%
COVID–ICU Network	53	Pro	France	2635	24%, 52% and 24% with mild, moderate or severe ARDS	V_T, Pplat, PEEP, prone positioning	median (IQR), %
Cummings *et al.*	54	Pro	US	203	Berlin definition not used	V_T, Pplat, PEEP, FiO_2, prone positioning	median (IQR), %
Ferrando *et al.*	55	Pro	Spain	742	17.1%, 44.6% and 38.1% with mild, moderate or severe ARDS	V_T, Pplat, PEEP, FiO_2, prone positioning	median (IQR), proportions ≤ 6 ml/kg PBW, %
Fusina *et al.*	56	Retro	Italy	187	not reported	V_T, PEEP, FiO_2	median (IQR), mean (SD)
Grasselli *et al.*	57	Retro	Italy	1150	Berlin definition not used	PEEP, FiO_2, prone positioning	median (IQR), %
Grasselli *et al.*	58	Retro	Italy	2929	Berlin definition not used	PEEP, FiO_2	median (IQR)
McWilliams *et al.*	59	Pro	UK	110	Berlin definition not used	prone positioning	%
Primmaz *et al.*	60	Pro	Switzerland	124	Berlin definition not used	PEEP, FiO_2, prone positioning	median (IQR), %
PRoVENT–COVID	61	Retro	Netherlands	553	24.9%, 66.5% and 8.6% with mild, moderate or severe ARDS	V_T, PEEP, FiO_2, prone positioning, duration	median (IQR), proportion ≤ 6 ml/kg PBW, %
Roedl *et al.*	62	Retro	Germany	167	4%, 42% and 49% with mild, moderate or severe ARDS	PEEP, prone positioning	median (IQR), %
Schenck *et al.*	63	NA	US	267	not reported	V_T, Pplat, PEEP, prone positioning	median (IQR), %
Thomson *et al.*	64	Pro	UK	136	Berlin definition not used	PEEP, prone positioning	median (IQR), %

Abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CI = confidence interval; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; PBW = predicted body weight; Pplat = Plateau pressure; PEEP = Positive end-expiratory pressure; Pro = prospective; Retro = retrospective, SD = standard deviation; UK = United Kingdom; US = United States; V_T = Tidal volume

8.7 ml/kg PBW (Table 1 and Figure 2). In the worldwide 'LUNG SAFE' study, almost two–thirds of patients received lung-protective ventilation with V_T of ≤ 8 ml/kg PBW [48]. In one study from the United States, a vast majority of patients received lung-protective ventilation with a V_T ≤ 8 ml/kg PBW [47]. In one study from Canada, less than half of patients received a V_T ≤ 8 ml/kg PBW [49]. In one study from Peru, only a fraction of patients received ventilation with a V_T of ≤

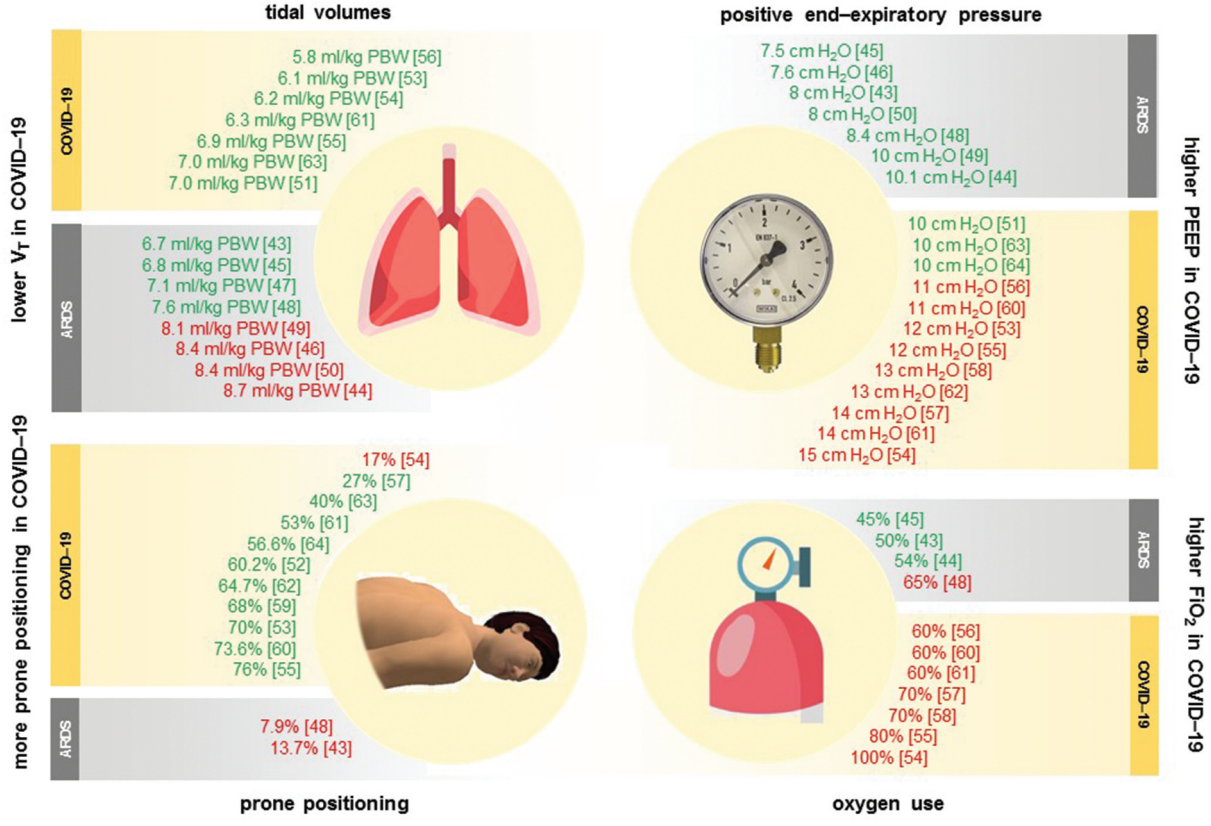

Figure 2. Summary of ventilation settings in patients with acute respiratory failure related to COVID-19 versus in patients with ARDS from another origin. references are provided between square brackets. green fonts: median or mean VT ≤ 8 ml/kg PBW, PEEP ≤ 10 cm H2O, FiO2 ≤ 60%, and prone ventilation use ≥ 15% – red fonts: median or mean VT > 8 ml/kg PBW, PEEP > 10 cm H2O, FiO2 > 60%, and prone ventilation use < 15% (cutoffs are arbitrarily chosen).

6 ml/kg PBW [44]. In studies in patients with acute respiratory failure related to COVID-19, median V_T varied from 5.8 to 7.0 ml/kg PBW––mean V_T was ~7 ml/kg PBW in one study from the United Kingdom [51] (Table 2 and Figure 2). In one study from the Netherlands, named 'PRoVENT–COVID', more than half of patients received ventilation with a V_T of ≤ 8 ml/kg PBW [61]. In the study from Spain, more than three–quarters of patients received ventilation with a V_T of ≤ 8 ml/kg PBW [55].

In studies in patients with ARDS from another origin, median Pplat varied from 19 to 26 cm H_2O––mean Pplat from 23 to 27 cm H_2O (Table 1). In the worldwide 'LUNG SAFE' study, two–thirds of patients received ventilation with Pplat ≤ 30 cm H_2O in combination with a lower V_T [48]. In another study, four–fifths of patients received ventilation with Pplat ≤ 30 cm H_2O [49]. In studies in patients with acute respiratory failure related to COVID-19, median Pplat varied from 24 to 27 cm H_2O (Table 2). In one study that reported Pplat per oxygenation category, Pplat was slightly higher in patients with the most severe oxygenation problems [53].

4.3. Positive end–expiratory pressure

In studies in patients with ARDS from another origin, median PEEP varied from 7.5 to 10.0 cm H_2O––mean PEEP from 7.6 to 10.1 cm H_2O (Table 1 and Figure 2). In the 'LUNG SAFE' study, a vast majority of patients received a PEEP < 12 cm H_2O [48]. In studies in patients with acute respiratory failure related to COVID-19, median PEEP was from 10 to 15 cm H_2O, mean from 10 to 11 cm H_2O (Table 2 and Figure 2). In one study from Spain, 6.4% of patients received ventilated with PEEP > 12 cm H_2O [55], while in one study from France, this proportion was 54% [53]. In the 'PRoVENT–COVID' study from the Netherlands [61] and one study from Italy [57], PEEP was reported to vary substantially between patients––from 5 and 20 cm H_2O, and from 4 and 22 cm H_2O, respectively.

4.4. Prone positioning

In studies in patients with ARDS from another origin, prone positioning was used from 7.9% to 13.7% (Table 1 and Figure 2). In the 'LUNG SAFE' study, prone positioning was used in 1%, 5.5% and 16.3%, in patients with mild, moderate and severe ARDS, respectively, [48]. Duration of proning in patients with ARDS, thus far only reported in one study, named 'APRONET', was median 8 hours [43]. In studies in patients with acute respiratory failure related to COVID-19, prone positioning was used much more often, in up to three–quarters of patients (Table 2 and Figure 2). Clear differences in use of prone positioning between ARDS severity groups was seen in studies from Spain and from France [53,55], with five in every six patients receiving this intervention when oxygenation problems were severe [55]. In one study that reported on duration of prone positioning, sessions lasted median 13 hours [61].

4.5. Oxygen

In studies in patients with ARDS from another origin, median FiO_2 varied from 45% to 50%, mean from 54% to 65% (Table 1 and Figure 2). Much higher FiO_2 was used in studies in patients with acute respiratory failure related to COVID-19, median varying from 60 to 80%, mean 60% (Table 2 and Figure 2). In one study from France, up to three–quarters of patients needed FiO_2 ≥ 50% [53]. In one Italian study, a vast majority of patients received ventilation with FiO_2 ≥ 50% [57] and in one study for the United States, reported median of highest FiO_2 was even 100% in the first day of ventilation [54].

4.6. Additive rescue therapies

In studies in patients with ARDS from another origin, the proportion of patients receiving continuous infusion of NMBAs ranged from 21.7% to 31.8%, use of iNO ranged from 4.7% to 7.8%, and the incidence of ECMO was between 0.5% and 4.8%. In studies in patients with acute respiratory failure related to COVID-19, the proportion of patients receiving NMBAs varied between 22.2% and 90%, the use of iNO ranged from 10.8% to 19.1%, and the incidence of ECMO was between 0.6% and 16.1%.

5. Discussion

5.1. Summary of findings

The findings of this review can be summarized as follows: (1) lower V_T are more rigorously used in patients with acute respiratory failure related to COVID-19 than in patients with ARDS from another origin; (2) PEEP is higher in patients with acute respiratory failure related to COVID-19, and there is substantial variation in PEEP between patients within studies; (3) patients with acute respiratory failure related to COVID-19 receive prone positioning much more often than patients with ARDS from another origin; and (4) FiO_2 is higher in patients with acute respiratory failure related to COVID-19 than in patients with ARDS from another origin.

5.2. Strengths of this review

This review has several strengths. It used two systematic searches to identify articles reporting on ventilation management. The searches identified articles originating in various countries worldwide, were all of sufficient size. The cohorts reporting on COVID-19 patients covered practice over a relative short period of time. Studies reporting on ventilation management in patients with ARDS from another origin were only included if the Berlin definition for ARDS [42] was used, increasing homogeneity of those cohorts. All studies were rich in detail, especially with regard to the four key components of lung-protective ventilation.

5.3. Ventilation with a lower tidal volume

Ventilation with a lower V_T is applied more frequent in patients with acute respiratory failure related to COVID-19

than in patients with ARDS from another origin. This could have several reasons. First, it is possible that this component of lung-protective ventilation is more easily applied in acute respiratory failure related to COVID-19. This may not be the most obvious reason, however, since acute respiratory failure related to COVID-19 has much in common with ARDS of another origin [65,66]. Second, it could be that ICUs were well prepared, using local guidelines designed especially for the COVID-19 outbreak. Unfortunately, we had no access to the local guidelines, neither from centers that participated in the various studies of ventilation management in patients with ARDS from another origin, nor from those in studies of ventilation management in acute respiratory failure related to COVID-19. Third, it could be that compliance with existing guidelines was much better in patients with acute respiratory failure related to COVID-19, which can be explained in two ways. It is possible that because care for a surge of patients with COVID-19 had to be provided by hospital personnel who had less experience or confidence with setting a ventilator, the compliance with existing guidelines for the ventilation of patients with ARDS increased; it is also possible that use of ventilation with lower V_T improved overall over recent years––new service reviews in patients with ARDS from another origin may reveal a better overall compliance with recommendations on use of a lower V_T.

5.4. Use of PEEP

The debate on what PEEP to use in patients with ARDS is ongoing, even after publication of studies that failed to show benefit [12–14], or even demonstrated harm from ventilation with higher PEEP [16]. Consequently, it is also uncertain how much PEEP to use in COVID-19 patients. In absence of randomized clinical trial evidence, it has been recommended to use 'higher' PEEP, following the higher PEEP/lower FiO_2 table of the ARDS Network [67–69]. The substantial variation in PEEP between patients with acute respiratory failure related to COVID-19 within the studies could reflect the uncertainty of physicians in titration of PEEP. Of note, how PEEP was titrated, and whether caregivers indeed used a higher PEEP–lower FiO_2 table or a lower PEEP–higher FiO_2 table was not collected in the studies. Although it has been suggested that there could be two different phenotypes of acute respiratory failure related to COVID-19 [3], possibly needing different levels of PEEP, several studies failed to confirm this [66,70–72]. The use of high PEEP could also have been caused by a desperate attempt to normalize the at times severe hypoxemia, in a time when mortality from severe COVID-19 was reported to be as high as 80% [73] .

5.5. Use of prone positioning

In patients with respiratory failure due to COVID-19, use of prone positioning was remarkably higher than in patients with ARDS from another origin. Alike the better use of a lower V_T, this could reflect an improvement in ventilation care over the recent years. Interestingly enough, limited staffing and resources during the pandemic did not have an effect on use of prone positioning, although this was reported as the reason for the somewhat lower use in one study [54]. Probably, the common use of prone positioning is due to the high incidence of severe hypoxemia in patients with COVID-19 [51,57]. Not only has prone positioning been indisputably shown to improve oxygenation and mortality in ARDS [23], it has been suggested to be a safer method of improving oxygenation than use of PEEP [74]. The posthoc analysis of one recent randomized clinical trial from France, named 'LIVE', that compared standard of care to personalized ventilation consisting of either lower PEEP and early prone positioning in non–recruitable ARDS to higher PEEP and prone positioning as a rescue intervention in recruitable ARDS, showed that if patients received the 'wrong' treatment, i.e. higher PEEP and prone positioning in non–recruitable ARDS or lower PEEP and early prone positioning in recruitable ARDS, outcome worsened. If COVID-19 behaves like non–recruitable ARDS, prone ventilation could be much more effective than use of higher PEEP [75].

5.6. Titration of FiO_2

Not surprisingly, FiO_2 was higher in patients with acute respiratory failure related to COVID-19, most likely reflecting the higher incidence of severe hypoxemia in these patients. The use of high FiO_2 supports the idea that COVID-19 patients do not respond well to increases in PEEP and could thus be classified as having non–recruitable ARDS. However, lung infiltrates are not the only contributor to hypoxemia in COVID-19 patients––coagulopathy is frequently observed in these patients [61,64] and could be a major determinant of the severity of hypoxemia. In a study comparing computed tomography pulmonary angiography between non–ventilated and ventilated COVID-19 patients, both with clinical suspicion of pulmonary embolism, ventilated patients showed much larger areas of scattered perfusion defects bilaterally [76]. The pattern in ventilated patients was independent of pulmonary embolism, suggestive of microcirculation dysfunction. Impeded perfusion in normally aerated lung tissue leads to increased dead space ventilation and shunting to diseased areas of the lung, which has deleterious effects. The matter of recruitability may be less relevant in these patients.

5.7. Additive rescue therapies

The incidence of continuous infusion of NMBAs in the cohorts of COVID-19 patients was up to threefold higher than in cohorts of patients with ARDS from another origin. This could have multiple reasons. First, it is not uncommon for physicians to consider muscle paralyses to be mandatory in patients that are positioned prone, and often this is continued until a patient is turned back to supine––since prone positioning is applied often in COVID-19 patients due to severe hypoxemia, it is not surprising that with this increase, use of muscle paralysis increased as well. Second, NMBAs might have been used to combat the fits of coughing, frequently seen in COVID-19 patients, and at times resulting in deep desaturations. Third, the high incidence of severe hypoxemia could have triggered the use of NMBAs in an attempt to lower

oxygen consumption. The severity of hypoxemia, and the urge to act on it, probably also clarifies the high use of iNO and ECMO in COVID-19 patients, which was up to fourfold higher than in patients with ARDS of another origin.

Also, there was remarkable variability in the use of additive therapies in the cohorts of COVID-19 patients. This is not surprising, as recommendations for use of NMBAs and iNO were at best contradictory before the COVID-19 pandemic. Use of these additive rescue therapies is probably at the discretion of attending physicians, and less dictated by local guidelines than the key components of lung-protective ventilation. Indication for use of ECMO before the COVID-19 pandemic may have been better defined, but use of ECMO could depend on available resources, workloads, admission capacities and also transfer possibilities.

5.8. Respiratory mechanics in acute respiratory failure in COVID-19 vs. ARDS of another origin

Although respiratory failure in COVID-19 was recognized as, and even named 'ARDS' fairly early in the pandemic, it was suggested that ARDS in COVID-19 patients had different characteristics than ARDS from another origin. There is increasing evidence against this. For instance, one study reported on lung physiology and recruitability in 30 invasively ventilated COVID-19 patients compared to 30 matched ARDS patients from an existing database [77]. Although compliance was slightly higher in COVID-19 patients compared to patients with ARDS from another origin, heterogeneity of respiratory mechanics was comparable. COVID-19 patients showed a varied, but overall greater response in oxygenation and respiratory mechanics in response to increase of PEEP than ARDS from another origin, but the response was independent of recruitability, which was similar in the two groups. Although the sample of this study was limited, these results coincide with other studies showing large variability in respiratory mechanics and responses to PEEP [66,78]. These findings support the idea that ventilation management in COVID-19 patients should follow the recommendations for patients with ARDS from another origin.

5.9. Limitations

This narrative review has limitations. First, despite the observational character of the included studies, it could be that daily practice was affected by knowledge of data collection in some studies. Second, the studies reporting on ventilation management in patients with acute respiratory failure related to COVID-19 originated in only 8 countries––all of which included centers with no limitations in resources. It remains uncertain if ventilation management in resource-limited settings differs from that in centers in high-income countries. Third, we excluded studies reporting only on 'special' cohorts, like patients with previous lung conditions, children, and pregnant patients, and special treatments, like ECMO. Fourth, while use of the Berlin definition for ARDS increased homogeneity in cohorts of patients with ARDS from another origin, we could not use this definition for selection of studies of ventilation management in COVID-19 patients––in fact, most studies reported on patients receiving ventilation for 'severe COVID-19' or 'COVID-19 pneumonia'. Nevertheless, in those reports that explicitly mentioned the proportions of COVID-19 patients with ARDS according to the Berlin definition, nearly all patients fulfilled the Berlin definition for ARDS. Fifth, heart–lung interactions, if present, were not reported in the studies identified by the two literature searches. Heart–lung interactions, however, do exist and may affect ventilation management. Absence of information in study reports may reflect how difficult it is to collect data on heart–lung interactions, or worse, that heart–lung interactions are inadequately used in ventilator management. Sixth, in the studies identified by the literature searches, occurrence of barotrauma was not routinely collected and may thus have been underreported. The incidence of barotrauma, including pneumothorax and pneumomediastinum, has declined after the implementation of lung-protective ventilation strategies. If it happens, however, it is an important adverse event of invasive ventilation in ARDS patients [79]. Seventh, the data extracted from the studies was heterogeneous and therefore difficult to compare. We did not perform any analysis for this reason and only described the data, making the findings in this review only suggestive.

6. Conclusion

In patients with acute respiratory failure related to COVID-19, ventilation with a lower V_T and prone positioning is applied more rigorously than in patients with ARDS from another origin. Applied positive end–expiratory pressures and oxygen fractions are higher in patients with acute respiratory failure related to COVID-19. It is likely that lung protection is of equal importance in COVID-19 patients as it is in patients with ARDS from another origin.

7. Expert opinion

Mechanical ventilation has moved from a 'simple concept of "in goes the good air, out goes the bad air" into a sophisticated life support system in common use today', and from a 'technology to "normalize" physiology as much as possible with little regard for harm beyond overt barotrauma and cardiac compromise' to one that follows the 'principles of lung-protective ventilation management as a cornerstone of management'––well described in a recent historic overview of ventilation from the 1970 to 2020 [80]. Indeed, the targets in ventilation in ARDS patients have shifted––oxygenation and decarboxylation are now secondary to preventing ventilation–induced injury. A large number of studies have been dedicated to perfecting lung-protective ventilation, or even bypassing the need for oxygenation from ventilation by techniques such as ECMO. In the end, the ultimate goal is to minimize the intensity of the treatment, i.e. the additional harm caused by ventilation. It is not yet clear how to achieve this exactly and individually, as every patient presents with their own clinical and biological characteristics, making generalization of treatment at times challenging.

When the world was overcome by the COVID-19 pandemic, COVID-19 was initially perceived as a 'new disease'. This

perception could have caused us to abandon current evidence–based ventilation strategies for other approaches, including strategies that have been shown not to benefit patients with ARDS from another origin. The findings of this review suggest, at least in part, that acute respiratory failure related to COVID-19 may not be too different from ARDS from another origin with respect to ventilation management. In addition, this summary suggest there are many similarities in respiratory mechanics between acute respiratory failure related to COVID-19 and ARDS from another origin. The actual question is now––are more studies needed, or do we accept that ventilation management in COVID-19 patients should be as that in patients with other forms of ARDS?

Probably, added information could come from research dedicated to the effects of 'personalized' ventilation, in all patients with ARDS, i.e. irrespective of its cause, thus ARDS from another origin or COVID-19. Research points to the implications of certain differences between individual patients for ventilation management, for instance whether or not ARDS has a 'focal' or a 'non–focal' appearance. The recent seminal randomized clinical trial, named 'LIVE', attempted to compare a strategy considered beneficial in patients with 'focal' ARDS with one that could be preferred in patients with 'non–focal' ARDS. Classification of patients was a challenge, but the study results suggest that if an incorrect strategy was chosen, i.e. a 'focal' approach in patients with 'non–focal' ARDS, or a 'non–focal' approach in patients with 'focal' ARDS, outcomes worsened dramatically. The findings of this study guide the way we could go. From a 'one size fits all' approach to one that uses certain information to individualize, and thereby improve ventilation management.

One important lesson remains that physiological improvements, like a better oxygenation, do not automatically translate in better outcomes, like duration of ventilation or death. Certainly, this also applies also for any personalized approach.

Declaration of interest

A. Serpa Neto has received personal fees from Drager, outside of the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005 Oct 20;353 (16):1685–1693.
2. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012 Aug;122(8):2731–2740.
3. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020 Jun;46(6):1099–1102.
4. Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med. 2020 8;Aug(8):816–821.

•• **In this review the management of acute respiratory failure related to COVID–19 is compared to that in patients with ARDS from another origin.**

5. Briegel J, Mohnle P, Surviving Sepsis C. [International guidelines of the Surviving Sepsis Campaign: update 2012]. Anaesthesist. 2013 Apr;62(4):304–309.
6. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999 Aug;27(8):1492–1498.
7. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med. 1998 Dec;158(6):1831–1838.
8. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med. 1998 Feb 5;338(6):355–361.
9. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000 May 4; 342(18): 1301–1308.

•• **This study showed that a ventilation strategy with a lower V_T benefits survival in ARDS patients.**

10. Putensen C, Theuerkauf N, Zinserling J, et al. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med. 2009 Oct 20;151(8):566–576.
11. Hager DN, Krishnan JA, Hayden DL, et al. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005 Nov 15;172 (10):1241–1245.
12. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004 Jul 22;351(4):327–336.
13. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008 Feb 13;299(6):637–645.
14. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008 Feb 13;299(6):646–655.
15. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010 Mar 3;303(9):865–873.
16. Cavalcanti AB, Suzumura EA, Laranjeira LN, et al.; Effect of lung recruitment and titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: a Randomized Clinical Trial. JAMA. 2017 Oct 10;318(14):1335–1345.

•• **This study showed ventilation with higher PEEP and recruitment maneuvers to increase mortality, despite improving lung compliance and oxygenation.**

17. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med. 2001 Aug 23;345(8):568–573.
18. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA. 2004 Nov 17;292(19):2379–2387.

19. Mancebo J, Fernandez R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006 Jun 1;173 (11):1233–1239.
20. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2009 Nov 11;302 (18):1977–1984.
21. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010 Apr;36(4):585–599.
22. Gattinoni L, Carlesso E, Taccone P, et al. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol. 2010 Jun;76 (6):448–454.
23. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013 Jun 6;368 (23):2159–2168.

•• **This study showed prone positioning to improve survival.**

24. Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care. 2007 Feb;13 (1):73–78.
25. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014 Dec 23;18(6):711.
26. Helmerhorst HJ, Roos-Blom MJ, Van Westerloo DJ, et al. Association between Arterial Hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of Cohort Studies. Crit Care Med. 2015 Jul;43 (7):1508–1519.
27. 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 Oct 18;316(15):1583–1589.

•• **This study showed a conservative oxygen strategy to improve survival.**

28. Barbateskovic M, Schjorring OL, Russo Krauss S, et al. Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. Cochrane Database Syst Rev. 2019 Nov 27;2019(11):11.
29. 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 Apr 28;391(10131):1693–1705.
30. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with sepsis: a post hoc analysis of data from the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). Intensive Care Med. 2020 Jan;46(1):17–26.
31. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for Acute Respiratory Distress Syndrome. N Engl J Med. 2020 Mar 12;382(11):999–1008.
32. Torbic H, Duggal A. Neuromuscular blocking agents for acute respiratory distress syndrome. J Crit Care. 2019 Feb;49:179–184.
33. Price DR, Mikkelsen ME, Umscheid CA, et al. Neuromuscular blocking agents and Neuromuscular Dysfunction acquired in critical Illness: a systematic review and meta-analysis. Crit Care Med. 2016 Nov;44(11):2070–2078.
34. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med. 2012 Oct 15;186(8):724–731.
35. National Heart L, Blood Institute PCTN, Moss M, et al. Early neuromuscular blockade in the Acute Respiratory Distress Syndrome. N Engl J Med. 2019 May 23;380(21): 1997–2008.
36. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS study group. Crit Care Med. 1998 Jan;26 (1):15–23.
37. Fierobe L, Brunet F, Dhainaut JF, et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. Am J Respir Crit Care Med. 1995 May;151(5):1414–1419.
38. Karam O, Gebistorf F, Wetterslev J, et al. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane systematic review with trial sequential analysis. Anaesthesia. 2017 Jan;72(1):106–117.
39. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351–1363.
40. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. 2018 May 24;378(21):1965–1975.
41. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. JAMA. 2018 Dec 4;320 (21):2251–2259.
42. Adt F, Vm R, Gd R, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012 Jun 20;307(23):2526–2533.
43. Guerin C, Beuret P, Constantin JM, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med. 2018 Jan;44(1):22–37.
44. Gupta E, Hossen S, Grigsby MR, et al. Risk factors for the development of acute respiratory distress syndrome in mechanically ventilated adults in Peru: a multicenter observational study. Crit Care. 2019 Dec 6;23(1):398.
45. Lanspa MJ, Peltan ID, Jacobs JR, et al. Driving pressure is not associated with mortality in mechanically ventilated patients without ARDS. Crit Care. 2019 Dec 27;23(1):424.
46. Leite TT, Gomes CAM, Valdivia JMC, et al. Respiratory parameters and acute kidney injury in acute respiratory distress syndrome: a causal inference study. Ann Transl Med. 2019 Dec;7(23):742.
47. Lanspa MJ, Gong MN, Schoenfeld DA, et al. Prospective assessment of the feasibility of a trial of low-tidal volume ventilation for patients with Acute Respiratory Failure. Ann Am Thorac Soc. 2019 Mar;16(3):356–362.
48. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 countries. JAMA. 2016 Feb 23;315(8):788–800.
49. Parhar KKS, Zjadewicz K, Soo A, et al. Epidemiology, mechanical power, and 3-year outcomes in Acute Respiratory Distress Syndrome patients using standardized screening. an observational cohort study. Ann Am Thorac Soc. 2019 Oct;16(10):1263–1272.
50. Schmidt MFS, Amaral A, Fan E, et al. Driving pressure and hospital mortality in patients without ARDS: a cohort study. Chest. 2018 Jan;153(1):46–54.
51. Camporota L, Sanderson B, Dixon A, et al. Outcomes in mechanically ventilated patients with hypoxaemic respiratory failure caused by COVID-19. Br J Anaesth. 2020 Dec;125(6):e480–e483.
52. Chand S, Kapoor S, Orsi D, et al. COVID-19-associated critical Illness-report of the first 300 patients admitted to Intensive Care Units at a New York City Medical Center. J Intensive Care Med. 2020 Oct;35(10):963–970.
53. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 29Oct 2020;47:60–73.
54. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020 Jun 6;395(10239):1763–1770.
55. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020 Jul;46(12):2200–2211.

56. Fusina F, Albani F, Bertelli M, et al. Corrected minute ventilation is associated with Mortality in ARDS Caused by COVID-19. Respir Care. 2020 Dec;66(4):8.
57. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 Apr;323(16):1574–1581.
58. Grasselli G, Greco M, Zanella A, et al. risk factors associated with mortality among patients with COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020 Jul;180(10):15.
59. McWilliams D, Weblin J, Hodson J, et al. Rehabilitation Levels in COVID-19 patients admitted to Intensive Care Requiring Invasive Ventilation: an observational study. Ann Am Thorac Soc. 2020 Sep;18(1):122–129.
60. Primmaz S, Le Terrier C, Suh N, et al. Preparedness and reorganization of care for coronavirus disease 2019 patients in a Swiss ICU: characteristics and outcomes of 129 patients. Crit Care Explor. 2020 Aug;2(8):e0173.
61. Botta M, Tsonas AM, Pillay J, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. Lancet Respir Med. 2020 Oct;9(2):23.
62. Roedl K, Jarczak D, Thasler L, et al. Mechanical ventilation and mortality among 223 critically ill patients with coronavirus disease 2019: a multicentric study in Germany. Aust Crit Care. 2020 Oct;34(2):27.
63. Schenck EJ, Hoffman K, Goyal P, et al. Respiratory mechanics and gas exchange in COVID-19-associated respiratory failure. Ann Am Thorac Soc. 2020 Sep;17(9):1158–1161.
64. Thomson RJ, Hunter J, Dutton J, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 admitted to an intensive care unit in London: a prospective observational cohort study. PLoS One. 2020;15(12):e0243710.
65. Bos LD, Paulus F, Vlaar APJ, et al. Subphenotyping ARDS in COVID-19 patients: consequences for Ventilator Management. Ann Am Thorac Soc. 2020 May;17(9):12.
66. Haudebourg AF, Perier F, Tuffet S, et al. Respiratory mechanics of COVID-19- versus Non-COVID-19-associated Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020 Jul 15;202(2):287–290.
67. Alhazzani W, Moller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020 Jun;48(6):e440–e469.
68. Tsolaki V, Siempos I, Magira E, et al. PEEP levels in COVID-19 pneumonia. Crit Care. 2020 Jun 6;24(1):303.
69. Rello J, Storti E, Belliato M, et al. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. Eur Respir J. 2020 May;55(5):5.
70. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020 Jun 15;201(12):1560–1564.
71. Barbeta E, Motos A, Torres A, et al. SARS-CoV-2-induced Acute Respiratory Distress Syndrome: pulmonary mechanics and gas-exchange abnormalities. Ann Am Thorac Soc. 2020 Sep;17(9):1164–1168.
72. Mauri T, Spinelli E, Scotti E, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the Acute Respiratory Distress Syndrome From Coronavirus Disease 2019. Crit Care Med. 2020 Aug;48(8):1129–1134.
73. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Feb;8(5):24.
74. Constantin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med. 2019 Oct;7(10):870–880.

•• **A posthoc analysis of this study suggests that higher PEEP worsens outcomes in patients with non–recruitable ARDS.**

75. Schultz MJ. High versus low PEEP in non-recruitable collapsed lung tissue: possible implications for patients with COVID-19. Lancet Respir Med. 2020 Jun;8(6):e44.
76. Beenen LFM, Bos LD, Scheerder MJ, et al. Extensive pulmonary perfusion defects compatible with microthrombosis and thromboembolic disease in severe Covid-19 pneumonia. Thromb Res. 2020 Aug 22;196:135–137.

•• **This study suggests that impeded perfusion plays a large role in the severe hypoxemia seen in patients with acute respiratory failure related to COVID–19.**

77. Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care. 2020 Aug 28;24(1):529.

•• **This study suggests that respiratory physiology of COVID-19 induced respiratory failure is similar to ARDS of other etiologies.**

78. Pan C, Chen L, Lu C, et al. Lung recruitability in COVID-19-associated Acute Respiratory Distress Syndrome: a single-center observational study. Am J Respir Crit Care Med. 2020 May 15;201(10):1294–1297.
79. Anzueto A, Frutos-Vivar F, Esteban A, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med. 2004 Apr;30(4):612–619.
80. MacIntyre N, Rackley C, Khusid F. Fifty Years of Mechanical Ventilation-1970s to 2020. Crit Care Med. 2021 Feb;49(4):12.