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Effect of Prone Position Ventilation on Acute Respiratory Distress Syndrome: A Systematic Review

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Abstract:
Background:
Acute respiratory distress syndrome (ARDS) is a life-threatening disease with low survival rate and high mortality. However, it has been noted that changing position of the patients on ventilator has significant impact on respiratory mechanics. Prone positioning is supplementary strategy to enhance gas exchange in patients with ARDS and to lessen the lung damage due to mechanical ventilation. Several researches reported effects of prone positioning in ARDS patients and variable outcomes in different patients. Complex mechanisms are involved behind this changing position and lungs oxygenation. Our study aims to do a review on the demographic characteristics and clinical outcomes of prone positioning in ARDS patients as this has not been clearly described in literature.
Materials and Methods:
We searched PubMed, Google scholar, Medline, Scopus, CINAHL and Embase electronic databases from 2016 to 2020 and searched clinical trials. We included eight relevant studies reporting outcome measures including 362 patients.
Results:
This review suggests remarkable effect of prone positioning in ARDS patients as it accentuates PaO2/FiO2 ratio and alveolar ventilation. PP ventilation improves cardiac index, increases lung volumes and reduces dynamic lung strain.
Conclusion:
Reviewing effect of PP on respiratory mechanics and oxygenation based on current evidence helps to understand its role in the management of patients with moderate to severe ARDS on mechanical ventilation. It is an effective strategy in addition to positive end expiratory pressure (PEEP) and extracorporeal membrane oxygenation (ECMO) in improving hypoxemia in ARDS patients.
Keywords: *Acute respiratory distress syndrome, prone position, respiratory mechanics, mechanical ventilation, lung volume, positive end expiratory pressure (PEEP), extracorporeal membrane oxygenation (ECMO).*

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I. Introduction:

Acute respiratory distress syndrome (ARDS) is linked with high death rate in intensive care units. Various evidence is available that highlighted decrease in deaths of patients of ARDS by increasing positive end-expiratory pressure (PEEP) or by use of neuromuscular blockers. Prone posture is used in ARDS cases refractory to conventional therapy. Its use should be restricted to a specific stage of illness.[1] Prone positioning has been widely used in ARDS patients to reduce ventilator-associated pneumonia (VAP) that is thought to be responsible for high mortality in these patients. Prone positioning ventilation has significantly improved survival in ARDS patients.[2] A study demonstrated improvement in the effect of recruitment maneuvers such as "cyclical sighs" as a result of prone positioning ventilation.[3] Early management of severe ARDS with the prone position may improve patient survival and should not be used as a last resort.[4] It has been reported that maintaining severe ARDS patients on early prone position mechanical ventilation and for a prolonged period (for a mean of 17h/d for a mean of 10 days) may reduce mortality.[5] Another study demonstrated that how respiratory mechanics affect oxygenation.[6] More recently, the effect of semi-recumbent, lateral, and prone position on the respiratory mechanics in ARDS patients who are on mechanical ventilation has been studied.[7] Additionally, the etiology of ARDS determines the effect of prone posture. It also described pressure sores as a frequent complication of this maneuver.[8] Prone positioning ventilation does not affect respiratory function and quality of life of patients managed through prone vs. supine position.[9] Hydrostatic pulmonary edema (HPE) and ARDS patients benefit from prone posture but pulmonary fibrosis shows no improvement.[10]

For better understanding, this systematic review will evaluate the effect of prone positioning ventilation on respiratory mechanics, its effect on mortality, ventilator/ICU free days, impact on survival in these patients and associated complications based on recent evidence as little is known about prone positioning ventilation impact on respiratory mechanics and oxygenation.

II. Materials and Methods:

Eligibility criteria:

In this systematic review, we included studies that reported outcomes evaluating effect of prone positioning on respiratory mechanics, oxygenation and mortality. Clinical trials including randomized control trials, cohort studies and case series are included.

Search strategy:

The systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We searched PubMed, Google scholar, Medline, Scopus, CINAHL and Embase electronic databases from 2016 to 2020. We searched the following key words: prone position AND Acute respiratory distress syndrome OR ARDS OR prone position AND ventilation OR acute lung injury AND Acute respiratory distress syndrome. We searched for MeSH terms on PubMed database. We included English language studies, conducted on humans and clinical trials reporting outcome measures. Time frame was chosen due to significant advances in mechanical ventilation.

Study selection:

For article to be included in our review, (1) Patients met Berlin definition criteria for ARDS (2) Application of at least one session of prone position (3) patients with PaO2/FIO2 < 150 mmHg, PEEP ≥ 5 cm H2O FiO2 of ≥ 0.6 (4) Intubated or tracheotomized and mechanically ventilated. All search results were screened based on title and abstracts. Full text articles were retrieved and relevant studies were included. Articles that did not fulfill our inclusion criteria were excluded. Eight studies were included in our systematic review.

Data collection:

Table 1 shows the study characteristics and extracted data from the relevant studies. Table 1 and 2 includes (1) Author (2) Study year (3) Study type (4) Sample size (5) Patients characteristics (6) Targeted disease (7) Outcomes

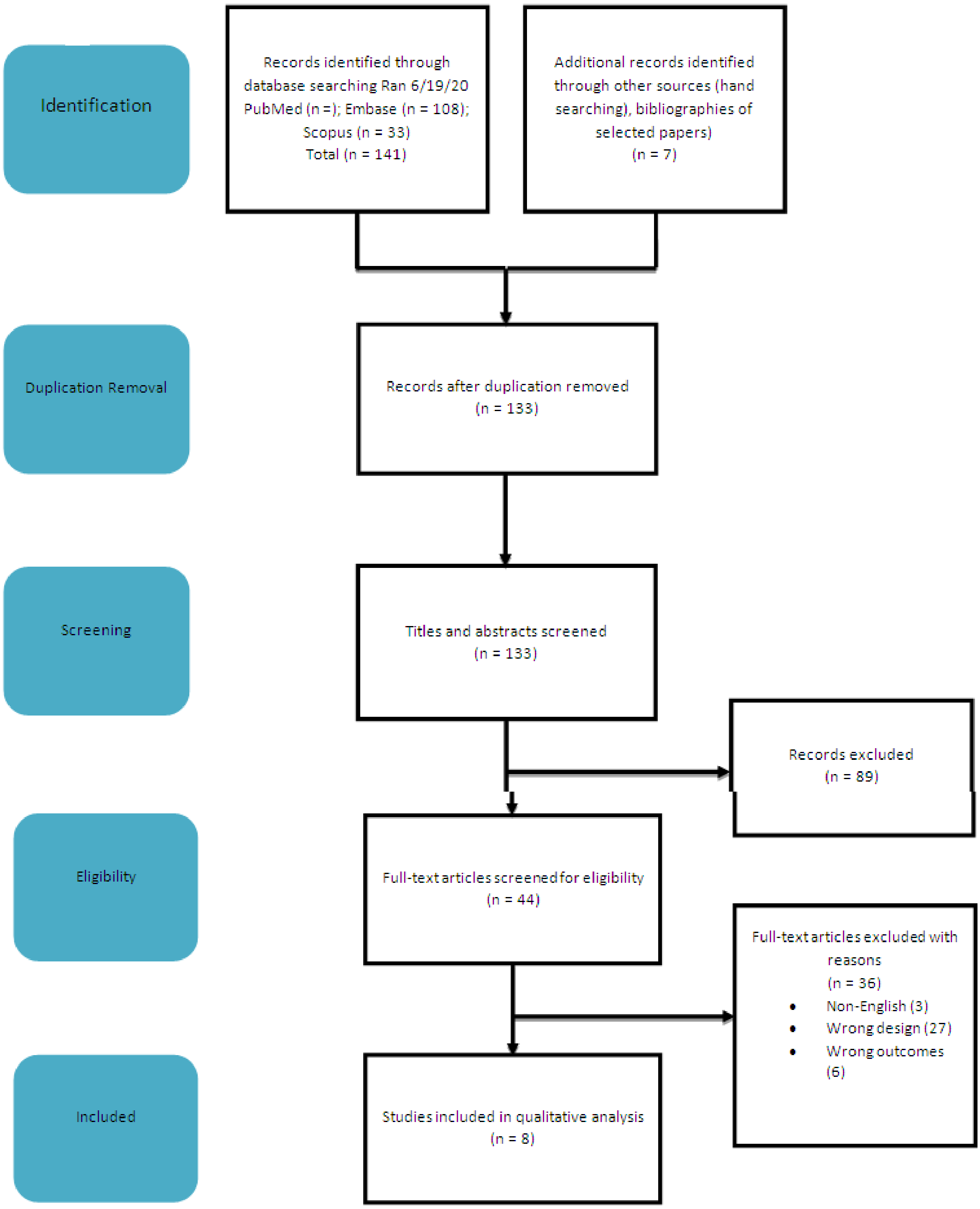
Quality assessment:

Methodological quality is assessed independently by two researchers and their results were compared and analyzed. Third researcher was the tiebreaker and disagreements were resolved by consensus.

III. Results:

We identified 148 researches including 362 patients from different electronic databases and eight relevant clinical studies were included in qualitative analysis over the last 5 years. These studies reported different outcomes related to respiratory mechanics and hemodynamic stability. The characteristics of the included studies were described in Table 1.

Fig. 1 PRISMA Guidelines:



Aguirre-Bermeo et al.

This study published in 2018, was performed from 2010 to 2013 in the Intensive Care Department at a Hospital in Barcelona. They studied 23 patients of ARDS on mechanical ventilation in both supine and prone position.

The patients' mean VT (Tidal Volume) at study entry (with FiO2 0.8) was 6.9 ± 1.4 ml/kg and mean PEEP was 10 ± 1 cm H2O.

The PaO2/FiO2 ratio of patients in supine position was 210 ± 57 mm Hg. When patients were put in prone position, PaO2/FiO2 ratio increased to 281 ± 109 (p=0.021). Similarly, FRC (Functional Residual Capacity) of patients in supine position was 965 ± 397. This increased to 1140 ± 490 (p=0.021) in prone position.

This study also found that the Dynamic strain at zero end-expiratory pressure ZEEP (0.52 ± 0.23 in SP to 0.44 ± 0.18 in PP) and Dynamic strain at positive end expiratory pressure PEEP (0.38 ± 0.14 to 0.33 ± 0.13), both decreased dramatically when the patients were put in prone position from supine position.

Franchineau et al.

This monocentric study was conducted for a four-month period in ICU in 2020. It was published in the same year as well.

Those ARDS patients were selected for the study who were on veno venous extra corporeal membrane oxygenation (VV-ECMO), mechanical ventilation and sedated with a Richmond Agitation–Sedation Scale≤−2. Total number of patients in the study was 21. Static compliance (mL/cmH2O) before the proning session was 23(17–29) mL/cmH2O. this increased to 27 (20–37) mL/cmH2O (P<0.01) after the proning session. Similarly, VT (Tidal Volume) increased from 4.2 (3.3–5.4) to 5.6 (3.8–6.4) mL/kg after the proning session, and a corrected minute ventilation increased from 5.5 (4.3–6.8) to 6.2 (5.1–6.9) L/min (P=0.04). These beneficial effects remained for up to 6 hours after the return to supine position (P < 0.0001).

Ruste et al.

This study was published in 2018 and carried out between July 2012 and December 2016. This single-center retrospective observational study was performed mainly to find out if proning increases the cardiac index (CI) in patients of ARDS.

A total of 107 patients fulfilled the inclusion criteria. In those patients, the CI (L min m−2) at T1, T2, T3 and T4 of proning sessions were 3.5±1.3, 3.4±1.2, 3.4±1.1 and 3.2±1.1 respectively. These results showed that proning did not have any significant impact on CI of ARDS patients.

The Global end-diastolic volume index (GEDVI) (mL m−2) values were: T1= 719±193, T2= 738±185, T3 = 757±209 and T4 = 714±200. Thus, the study found a small but significant increase in GEDVI at the end of proning session, but this increase was reversed after the patients were put in supine position.

This study also measured some respiratory parameters during PP sessions and found that PP was associated with a significant increase in PaO2/FiO2 ratio in patients of ARDS.

Guérin et al.

This prevalence study was carried out four times during 2016 and 2017. This study included ICUs from 20 different countries.

6723 patients were screened, out of these 735 patients had ARDS. 13.7% (101 patients) of 735 underwent one or more sessions of proning in four days. 634 patients were not put in prone position because of various reasons (Hypoxemia not severe enough, tracheostomy etc.).

The prone positioning sessions were done for 18 (16–23) hours without interruption, during the four days.

PaO2/FIO2 ratio before the proning was 101 (76–136) mm Hg and the driving pressure and Pplat (Plateau pressure) was 14 (11–17) cm H2O and 26 (23–29) cm H2O respectively. After the proning session, PaO2/FIO2 ratio increased to 171 (118–220) mmHg (P=0.0001), and the driving pressure and Pplat both decreased to 13 (10–16) cm H2O (P = 0.001) and 25 (23–28) cm H2O (P=0.04), respectively.

Sun et al.

This prospective study was conducted in 2015-16 and was published in 2019. It was done to investigate the feasibility and effectivity of electromyography of the diaphragm (EMGdi) in monitoring respiratory drive in ARDS patients during PP.

14 patients with severe ARDS in ICU were studied. 9 healthy volunteers were enrolled as a control group. After taking proper consent, an esophageal electrode was placed in all patients before PP session.

EMGdi (μV) for healthy individuals in supine position was 6.9±3.1. This increased to 10.5±6.9 (p=0.372) in prone position. While EMGdi (μV) values in ARDS patients Pre-PPV, 2 hours after starting PPV and 2 hours after return to SPV were 15.2 (12.6-20.1), 14.9 (12.4-17.3) and 16.0 (12.3-20.2) respectively. Thus, the EMGdi levels in ARDS patients were higher in supine ventilation and lower during the early, middle, and late stages of prone position ventilation. This study also found that PaO2/FiO2 ratio increased significantly during PP, while PEEP and Plat remained unchanged in prone or supine position.

Haddam et al.

This prospective multicenter study was conducted in 6 ICUs from March 2014 to January 2015 and from December 2015 to January 2016. The study was published in 2016.

Patients of ARDS who had PaO2/FiO2 ratio less than 150 mmHg and positive end-expiratory pressure (PEEP) at least 5 cmH2O were included in the study. 426 patients in the ICUs developed ARDS, 98 underwent proning and the data of only 51 patients was included in the final study. The lung ultrasound (LUS) data of these patients was measured 4 times: one hour before and one hour after proning session, one hour before and one hour after returning to the supine position.

This study concluded that there was no noteworthy association between lung ultrasound scores and the oxygenation response both after the start and end of prone positioning sessions.

Electrical impedance tomography (EIT) monitoring of ARDS patients on ECMO during prone position showed positive effects of PP on regional and global ventilation: during proning, VT and EELI (End-Expiratory Lung Impedance) redistributed from ventral to dorsal regions.

Gaudry et al.

This multicenter retrospective study was primarily designed to compare the occurrence of complications in prone versus supine position in patients of ARDS after undergoing an abdominal surgery. This study was carried out from 2009 to 2014 in intensive care units of three different hospitals.

Patients were included in the study only if they had ARDS according to the Berlin definition. Characteristics of abdominal surgery and postoperative surgical complications were clearly defined before the start of study. A total of 10,039 patients were admitted in the ICUs during study period. From these, only 98 patients had both ARDS and undergone abdominal surgery. 36 of these underwent PPV and 62 remained supine.

This study found no significant correlation between prone position ventilation and occurrence of complications after abdominal surgery. The rate of occurrence of postsurgical complications remained fairly consistent in both prone and supine position.

Like the studies before, this study also found the patients' oxygenation increased during PPV. This was reflected in an increase in PaO2/FiO2 ratio of >100 mmHg. However, in patients that had undergone sessions of prone position ventilation, mortality rate did not decrease, neither did the ICU length of stay.

Akatsuka et al.

This single site retrospective study was carried out over a span of 14 years from 2004 to 2018 and was published in 2020. The aim of this study was to evaluate the CT scan lung findings in patients of abdominal surgery that developed ARDS as a complication of surgery and underwent prone position ventilation sessions.

Only those (51) patients in the ICU were included in the study that developed ARDS as a complication of abdominal surgery. The diagnosis of ARDS was made following the criteria of Berlin definition. The included patients were divided into two groups: group A (24 patients) that underwent PPV and group B (27 patients) that did not.

This study found that PaO2/FiO2 ratio in group A increased from 157 ± 41 mm Hg at O hrs. to 290 ± 75 mm Hg at 72 hrs. after the start of mechanical ventilation in prone position. CT scan findings in group A were as follows: Ground glass appearance (GGO) in 5 patients, dorsal lung atelectasis (DLA) in 17patients, GGO and DLA both were present in 2 patients. Similarly, CT scan findings in group B were: GGO in 9 patients, DLA in 9, and both GGO and DLA in 9 patients as well. Another significant finding was that the 28 days mortality rate was lower in group A patients (16.7%) with DLA as compared to group B patients (37%) with DLA.

Table 1 Study characteristics:

ID	Author	Study year	Study type	Number of subjects	PEEP at enrollment	PaO2/FiO2 baseline (mm Hg)	Time in prone position (Hours)	SAPS II	SOFA score	VT delivered (mL/kg at inclusion)	Targeted disease	Average prone positioning sessions	Days from diagnosis of ARDS to study inclusion
1	Aguirre Bermeo et al. [11]	2018	Observational Study	20	10 ± 1	210 ± 57	NA	78 ± 14	NA	6.9 ± 1.4	ARDS with pneumonia and septic shock	NA	4 ± 3
2	Franchineau et al. [12]	2020	Monocentric observational study	21	NA	NA	16	68 (55–79)	13 (11–16)	4.2 (3.3–5.4)	ARDS subject on VV-ECMO, pressure-controlled mechanical ventilation mode and sedated with a Richmond Agitation–Sedation	2	NA
3	Ruste et al. [13]	2018	Single-center retrospective observational study	107	10±3	112±28	16±3	62±18	15±4	6.2±0.7	Moderate and severe ARDS	2±2	3±3
4	Guérin et al. [14]	2018	Prospective international 1-day prevalence study	734 (101 proned, 634 not proned)	12 (9–14)	101 (76–136)	NA	47 (37–58)	NA	6.1 (5.5–7.0)	All ARDS stages	1	NA
5	Sun et al. [15]	2019	Observational Study	14	8 (7, 10)	133 (105-168)	52±48	NA	NA	401 (349-447) in ml	Severe ARDS	4±4 (range 1–15 times)	8±12
6	Haddam et al. [16]	2016	Prospective multicenter study	51	11 ± 3	95 ± 27	17 ± 3	55 ± 18	NA	6 ± 1	Severe and moderate ARDS	1	4 ± 7

7	Gaudry et al. [17]	2017	multicenter retrospective cohort study	98	11 (4)	95 ± 47	15.8 (±10.4) 19.2 (±10.3)	53 (17)	NA	446 [400–497]	Severe ARDS	1	2 [1–4]
8	Akatsuka et al. [18]	2020	single site, retrospective observational study	51(24 subjects prone)	10.3 ± 2.3	118 ± 41	16.1 ± 0.8	NA	7.3 ± 3.1	NA	ARDS	1.5 ± 0.5 times	1

PEEP = Positive End-Expiratory Pressure
SAPS = Simplified Acute Physiology Score
SOFA score = Sequential Organ Failure Assessment score
VT = Tidal Volume
ARDS = Acute Respiratory Distress Syndrome
ECMO = Extracorporeal membrane oxygenation

Table 2 Subjects' characteristics and outcomes:

ID	Author	Mean age	Gender	Height (cm)	Weight (kg)	BMI (kg/m2)	Risk factors for ARDS	Co morbidities	Mean increase in PaO2/FiO2 on Proning (mm Hg)	Tidal volume after prone position ml/kg	*p* value
1	Aguirre Bermeo et al. [11]	58 ± 18	NA	NA	NA	NA	Pneumonia Septic shock Pancreatitis Trauma	NA	281 ± 109	NA	p = 0.008
2	Franchineau et al. [12]	56 (46–61)	Male (62%)	NA	NA	29 (27–39)	Viral pneumonia Bacterial pneumonia Aspiration pneumonia	NA	NA	5.6 (3.8–6.4) mL/kg	P < 0.01
3	Ruste et al. [13]	65±12	Male (68%)	NA	86±19	29±7	Pneumonia Aspiration Extra pulmonary sepsis	NA	153±60	No change	p < 0.001
4	Guérin et al. [14]	64 (52–73)	Male (66%)	170 (164–176)	77 (65–87)	26 (23–30)	Pneumonia Aspiration Smoke inhalation Near drowning Burns Systemic diseases Chest trauma Sepsis Pancreatitis Multiple trauma TRALI	Chronic respiratory failure CKD Chronic heart disease Diabetes Immunodeficiency Chronic liver failure	171 (118–220)	No change	P = 0.0001
5	Sun et al. [15]	60±14	Male (11/14) Female (3/14)	165±9	60±12	22±3	NA	Severe pneumonia, septic shock and acute renal injury	169 (120, 221)	391 (341-437) in ml	P < 0.001
6	Haddam et al. [16]	58 ± 15	Male (69%)	169 ± 9	78 ± 17	NA	NA	Primary lung disease (38)	20% increase in 71% subjects	NA	NA

7	Gaudry et al. [17]	64(18)	Male (60%)	NA	83(24)	31 (9)	Abdominal surgery	COPD Ischemic heart disease Systemic hypertension Diabetes	189 ± 92	NA	$p < 0.0001$
8	Akatsuka et al. [18]	71.0 ± 11.2	17 / 7(male/female)	NA	NA	NA	Abdominal surgery	NA	290 ± 75	NA	0.002

BMI = Body Mass Index
CKD = Chronic Kidney Disease
TRALI = Transfusion Related Acute Lung Injury
COPD = Chronic Obstructive Pulmonary Disease

IV. Discussion:

Our updated systematic review included eight clinical trials conducted over 5 years in patients with ARDS. The objective of our systematic review is to study available evidence of prone positioning on respiratory mechanics and hemodynamics in ARDS patients. Of the selected studies, four studies assessed mortality in ARDS patients subjected to prone positioning ventilation. Trials varied with regards to time spent in a prone position, the number of sessions of the prone position, and days from diagnosis of ARDS to study inclusion. The treatment group is on mechanical ventilation along with some other co-interventions, such as ECMO, prone position, and increased PEEP. The major finding of our systematic review is that prone positioning in ARDS patients improves respiratory mechanics, oxygenation, hemodynamics, and alveolar ventilation when the PaO2/FiO2 ratio is no greater than 150 mmHg. It has a beneficial effect in patients with severe hypoxemia. Lung volumes are affected in ARDS at positive end-expiratory pressure (PEEP) and zero end-expiratory pressure (ZEEP). A significant increase after PP is observed in end-expiratory lung volume (EELV) and functional residual capacity (FRC) (18% in FRC and 17% in EELV). It also reported a decrease in the dynamic strain at PEEP as well as at ZEEP as an increase in dynamic lung strain is associated with lung injuries.[11] The prone position helps in reducing dynamic lung strain in patients with moderate to severe ARDS. Another study suggested to prone all ECMO supported ARDS patients as this influences redistribution of EELI and VT. 16 hr. prone positioning session increases VT dorsal/VT global ratio. PEEP studies through Electrical impedance tomography (EIT) after prone positioning shows a decrease in optimal PEEP values.[12] Decrease in EMGdi was observed after prone positioning ventilation as compared to healthy normal volunteers and this explains why ARDS patients tolerate long term PPV despite a decrease in static lung compliance. VT changes according to this study were insignificant due to a decrease in Ccw-stat, static compliance of chest. The lung is protected during long term PPV due to insignificant change in ΔPL, the difference between end-inspiratory and end-expiratory transpulmonary pressure. This study proved that regular monitoring of EMGdi can be done for the evaluation of respiratory drive-in patients of ARDS during prone position ventilation.[15] Guérin et al. study showed the prevalence of PP in ARDS patients, effects, and reasons for not using it. The use of PP is more prevalent in severely hypoxemic patients. PaO2/FIO2 < 150 mmHg + PEEP ≥ 10 cmH2O and FIO2 ≥ 60% is widely used criteria to determine indication for prone position. The study observed low airway related complications and pressure sores. Moreover, it shows improvement in lung oxygenation by an increase in tidal volume.[14] PP has no effect on global aeration in focal and non-focal ARDS patients.[16] The available evidence in our review suggested that cardiovascular status may improve during PP sessions and they are reversible when the subject is returned to the supine position. Both CI and oxygenation is significantly decreased in the supine position. Therefore, hemodynamic instability should not be an obstacle to PP.[13] Gaudry et al. conducted the first retrospective multicenter study to determine complications associated with the prone position in abdominal postoperative ARDS patients. There was no increase in complications after proning postoperative ARDS patients compared to patients in the supine position. Moreover, there was an increase in oxygenation in these hypoxemic patients. Hence abdominal surgery is not a contraindication to the prone position in patients having ARDS but the number of prone sessions should be considered.[17] Akatsuka et al. also studied prone positioning ventilation in patients after abdominal surgery developing ARDS as a result of postoperative infection. After doing CT scans of these patients, those having dorsal infiltrates and dorsal lung atelectasis showed marked improvement compared to those having diffuse infiltrates having growing glass opacities (GCO). Prone positioning also reduces mechanical ventilation days and patients are weaned off early having dorsal infiltration. Keeping in view the CT scan lung findings, this study concluded that PPV is beneficial for treatment of ARDS especially in patients with DLA.[18]

Our systematic review is unique as we have discussed outcome measures of prone positioning ventilation in ARDS patients considering both duration of PP, session of PP and time between ARDS and start of session. We discussed importance of PP in improving oxygenation and how it affects lung mechanics. We included recent data that takes into account recent advances in mechanical ventilation and treatment strategies for ARDS.

Our study has several limitations. The included patients in our review are not similar. Most of the included studies have not described mortality data and long-term survival benefits in patients.

V. Conclusion:

Prone positioning ventilation in ARDS patients significantly improves oxygenation in severely hypoxemic patients. Also, prone positioning ventilation causes no severe complications and helps in improving subject survival. Although the impact of PP on mortality is inconclusive, intensivists should not refrain from using prone posture in severe ARDS patients having PaO_2/FiO_2 <150 mmHg as it can help improve subject lung volumes and gas exchange. .

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