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PRONE VENTILATION IN ARDS: WHAT DOES EVIDENCE SAY

Umesh Kumar Bylappa, Khair Muhammad Burki, Ali Hiis Jillal, Roman Romulo S Manrique JR, Albin Chacko

Respiratory Medicine/Therapy Department, Al Ain Hospital, Al Ain, UAE

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****Corresponding author:***
Umesh Kumar Bylappa

ABSTRACT

Prone position ventilation (PP) has been used since the 1970s to treat severe hypoxemia in patients with ARDS/ALI because of its effectiveness at improving gas exchange.Meta-analyses have suggested better survival in patients with an arterial oxygen tension (PaO2)/inspiratory oxygen fraction (FIO2) ratio, 100 mmHg. A recent randomized controlled PROSEVA study trial was performed in ARDS patients in 2013 after a stabilization period of 12–24 h and severity criteria (PaO2/FIO2-150 mmHg at a positive end-expiratory pressure >5 cmH2O). This randomized control study showed a significant reduction in mortality in prone group 32.8% versus in supine group 16% (P-0.001). The main goal of this article are to discuss about prone position ventilation which improves oxygenation in patients with ALI/ARDS; the evidence of its use based on trial analysis; and the limitations of its use as well as the current place of pronepositioning in the management of patients with ALI/ARDS. Since 2013 after proseva study trial proning has become more common in our ICUs. Although best clinical judgment to follow the PROSEVA trial's protocol as a guideline are used and remains inconsistency in the timing and duration of proning in ARDS patients.

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INTRODUCTION

Prone ventilation has been used for many years to improve oxygenation in the management of the critically ill patient with Acute Respiratory Distress Syndrome (ARDS). The physiological benefits of prone ventilation have been well described: with improved ventilation-perfusion mismatching, improve pulmonary mechanics, recruitment of dependent lung regions and enhanced drainage of tracheobronchial secretions. Available evidence suggests that prone positioning must be considered early in the disease process of ARDS and acute lung injury. The criteria were confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit. The optimal duration of prone ventilation has not been identified, however there is Proseva Study Group to suggest a fall in mortality in patients ventilated in the prone position for at least 16 consecutive hours. It is therefore recommended to prone patients for a period of 12-16 hours.

Physiological effects of prone positioning: The main physiological effects of prone position mechanical ventilation is improvement in oxygenation while improving the lung mechanics. During the prone position ventilation there will be uniform distribution of gases in the lung without over distention, which helps in homogeneous distribution of pleural pressure, alveolar ventilation. So prone ventilation opens up all the collapse alveoli and finally reduction in atelectasis of the lung and clearance of the secretion.

Distribution of alveolar inflation in the prone position: In supine position alveolar inflation is heterogeneous and there will be over distension of some of the alveolar and it is depending on transpulmonary pressure. As we discussed earlier in prone position there will be a homogeneous distribution of gases and transpulmonary pressure (Mutoh*et al.*, 1992). During the prone ventilation can also observe the movement of the chest wall and lung densities from dorsal region to ventral regions. Distributionof ventilation and alveolar recruitment can be seen in figure-1.There are many factors which are responsible for the changes of transpulmonary pressure during the prone ventilation. Which include weight of the heart will be on the sternum bone, reduces from 30 to 40 % of the weight, abdominal content moves downward so less effects of intraabdominal pressure on the diaphragm, mechanical properties and shape of the chest wall helps in homogeneous distribution of gases, transpulmonary pressure and alveolar inflation.

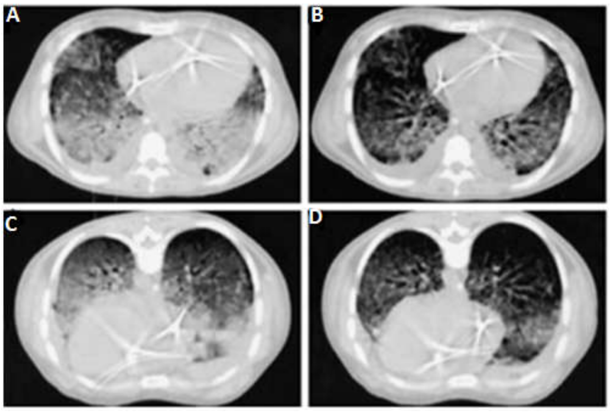

Figure1. A and B. Supine position C and D Prone position

Lung Weight: The increased lung weight, due to accumulated fluid increases edema, which raises hydrostatic pressure transmitted through the lung which called superimposed pressure in the lung which affects on the distribution of the intrapulmonary gases. Consequently, the gases in the dependent lung region squeezed out of the lungs causes decreased gas exchange and lungs to collapse.

Cardiac mass: The cardiac mass plays an important role in changes in densities of the lungs both in supine and prone position has been emphasized (Albert, 2000). The percentage of cardiac weight on the lungs is 7% to 42% (subcarinal to lower section) when in supine position. The percentage of cardiac weight on the lungs is 1% to 4% when in prone position.

Cephalic Displacement of the Abdomen: In supine position, intraabdominal pressure causes cephalic displacement of the abdominal content, which displaces the dome of the diaphragm into the pleural cavity. So motion of the diaphragm in supine position is uniform but in prone position motion will be in the nondependent areas (Krayer, 1989).In prone position, the intraabdominal pressure decreases and therefore unloading the weight of the abdominal content, it reduces cephalic displacement of the diaphragm in prone position compared to supine position (Mure, 1998).

Regional Mechanical Properties and Shape of the lung and Chest Wall: During the prone position ventilation modifies the regional mechanical properties and shape of the lung and chest wall. So distribution of the alveolar inflation is homogeneous compared to supine position which is heterogeneous alveolar inflation (Gattinoni, 1994). So,shape of the chest wall also contributes in distribution of alveolar inflation when the patient is in prone position ventilation and it is more homogeneous inflation.

Distribution of ventilation and perfusion in the prone position: The ventilation and perfusion distribution is gravity dependent and there will be good ventilation in ventral part of the lung region and good perfusion in dorsal part of the lungs (Cortney Henderson, 2013).So,in supine position, perfusion is greatest in the most diseased lung regions with an increase in shunt. In supine with ARDS patients because of collapse of the dorsal part, there won't be good ventilation but there will be good perfusion, as a result blood carries low oxygen and it is heterogeneous distribution of ventilation. When the patient is turned to prone position with ARDS patients the densities remain in the dorsal part, which is now ventral region of the lungs. As ventral region of the lung now dorsal region while perfusion following a gravitational gradient is increasedand there will be a homogeneous distribution of ventilation. Animprovement of V/Q correlating with increased oxygenation should be expected.The maximum perfusion will likely to remain in dorsal region, lung densities redistribute from dorsal to ventral regions.

Effects on respiratory mechanics: During the prone position ventilation, there may be decreased thoraco-abdominal compliance but there won't be any changes in respiratory system compliance.In supine position, the wall of the thorax is not free to move because it is dorsally supported and there will be decreased chest wall compliance. In prone position, the wall of the thorax dorsally unsupported and it is free to move as a result chest wall compliance will be increased. Some of the studies had shown an improvement in respiratory system compliance during the prone ventilation in ARDS patients (Blanch, 1997; Guerin, 1999).This structural benefit can occur on lung parenchyma to improve oxygenation and even total respiratory system mechanics improved after repositioning to supine position (Pelosi, 1998).

Mechanisms of improvement in oxygenation in the prone position: The physiological shunt present in the ARDS patients, is a combination of two factors which are reduction in ventilation/perfusion ratio(V/Q)and the shunt results when the alveoli of the lungs are perfused with blood as normal, but ventilation fails to supply the perfused region (V/Q=0). In prone position ventilation V/Q mismatch will improve with several mechanisms causes reduction in physiological shunt. These mechanisms include increased lung volume, recruitment of dorsal part of the lung regions, redistribution of perfusion and homogeneous distribution of ventilation all over the lung field.

Dorsal lung recruitmentand homogeneous distribution of ventilation/perfusion: The homogeneous distribution of ventilation and perfusion is the most probable causes of increased oxygenation in the prone position. When the patient is turned to prone position the densities which was present earlier in dorsal lung region causing more homogeneous distribution of alveolar inflation and ventilation, but perfusion remains greatest in the dorsal lung region. Prone position ventilation also decreasesthoraco-abdominal compliancewhich reflects improvement in oxygenation and ventilation.In Prone ventilation the improvement in oxygenation probably results from a redistribution of blood flow away from unventilated areas to regions with normal V′/Q′, most probably resulting from alveolar recruitment in previously atelectatic, but healthy and well-perfused alveoli (Lamm, 1994). In some of the researches, the improvement in oxygenation was partially maintained even when the patients were repositioned supine (Langer, 1988; Gattinoni, 1997).The improvement of oxygenation seen in the prone position, it's because of homogeneous redistribution of ventilation in the dorsal region and also uniform distribution of perfusion.

Lung protection from Ventilator Induced Lung Injury in Prone Ventilation: The mechanisms by which mechanical ventilation may induce lung injury involve increased alveolar wall stress (stretch) by high tidal volume (Volutrauma) and cyclic closing and reopening of atelectatic lung regions (Atelectrauma). There will be volutrauma induced parenchymal injury due to gross physical disruption and because of stretch-responsive inflammatory pathways. Theincreased alveolar wall stretches by high tidal volumelead to high transpulmonary pressures with consequent stretch of the pulmonary tissues (Dreyfuss, 1985).Alveolar shear stress-related injury and heterogeneous nature of lung aeration in ALI/ARDS commonly seen. During the ventilation in supine position, there is physical damage to lung tissue caused by a difference in pressure between a gas space inside, or in contact with the body, and the surrounding fluid (Barotrauma). The greater attention should be focused on cyclic closing and reopening of atelectatic lung regions, which can generate shear forces that increases capillary permeability and induces activation of inflammatory factors, releasing cytokines leading to local and systemic inflammatory responses (Biotrauma) (Ranieri, 1999).Protecting the lung from VILI (Ventilator induced lung injury) is the main goal of mechanical ventilation. There are several lines of evidence to support that prone position can achieve this objective. The prone position could promote lung recruitment but also reduce hyperinflation (Galiatsou, 2006; Cornejo, 2013).However, only higher PEEP (Positive end-expiratory pressure) used in the prone position was able to minimize cycling opening and closure during tidal breath, the so-called atelectrauma (Cornejo, 2013). The lung concentration of pro-inflammatory cytokines was found reduced in prone as compared to supine position in ARDS patients (Papazian*et al*., 2005). The overall stress and strain is reduced in prone position in ARDS patients (Mentzelopoulos, 2005). Experimental studies found that prone position reduced VILI due to high tidal volume and made it more homogeneously distributed throughout the lung in dogs(Broccard, 2009), increased the time required to double elastance of the respiratory system as compared to supine position in rats (Valenza, 2005), modulated the expression of a kinase strongly involved in VILI in rats and attenuated VILI due to injurious ventilation in mice deficient for this kinase (Park, 2012). Therefore, there isa strong background for VILI prevention by using prone position. The likely mechanism for this to occur is by making the lung distribution of tidal volume, and hence the strain more homogenous, and by minimizing the compression of the lung by its own weight and also that of the heart. This means that the mechanics by which prone position improves survival in ARDS patients should stem from these beneficial physiological effects.

Recruitment maneuvers: The prone position ventilation not only contributes to the success of recruitment maneuvers, but also itself be considered as a recruitment maneuver.In the prone position ventilation, the transpulmonary pressure in dorsal lung region increases, opening alveoli and improving gas-exchange (Mutoh, 1992). Some of the researches have reported that in healthy (Nakos*et al*., 2006), as well as in lung-injured animals (Broccard, 1997), mechanical ventilation leading to lung overdistension and cyclic collapse/reopening was associated with less change in dorsal regions in the prone position, as compared to the supine position. The development of VILI due to high V_T seems to be reduced during prone position compared to supine positioning (Valenza, 2005).

The reduction in the development of VILI in the prone position can be explained by different mechanisms: (a) A more homogeneous distribution of transpulmonary pressure gradient due to changes in the lung-thorax interactions and direct transmission of the weight of the abdominal contents and heart (Mutoh, 1992), results in a re-distribution of ventilation, (b) increased end-expiratory lung volume resulting in a reduction in stress and strain (Valenza*et al*., 2005), and (c) changes in regional perfusion and/or blood volume (Richter, 2005). In a ALI, the prone position was associated with a better perfusion in ventral and dorsal regions, a more homogeneous distribution of alveolar aeration which reduced lung mechanical changes and increased end expiratory lung volume and oxygenation (Santana, 2009). These findings suggest that the prone position may protect the lungs against VILI, and recruitment maneuvers can be more effective in the prone position compared to the supine position.

Types of recruitment maneuvers: There are wide variety of recruitment maneuvers has been described. The most relevant are represented by: Sustained inflation maneuvers, high pressure-controlledventilation, incremental PEEP, and intermittent sighs. The best way of recruitment maneuver technique is currently unknown and may vary according to the specific circumstances.The most commonly used recruitment maneuver is the sustained inflation technique, in which a continuous pressure of 40 cmH_2O is applied to the airways for up to 40 sec (Fan, 2008). Sustained inflation has been shown to be effective in reducing lung atelectasis (Farias, 2005), improving oxygenation and respiratory mechanics (Farias, 2005; Riva, 2009), and preventing endotracheal suctioning-induced alveolar de-recruitment (Maggiore, 2003). However, the efficacy of sustained inflation has been questioned and showed some side effects associated with circulatory impairment (Odenstedt, 2005), an increased risk of barotraumas (Meade, 2008), a reduced n*et al*veolar fluid clearance (Constantin, 2007), or even worsened oxygenation (Musch*et al*., 2004). In order to avoid such side effects, other types of recruitment maneuver have been developed and evaluated. The most important are: 1) incrementally increased PEEP limiting the maximum inspiratory pressure (Rzezinski*et al*., 2009),2) pressure-controlled ventilation applied with escalating PEEP and constant driving pressure(Villagr2002, ,), 3) intermittent sighs to reach a specific plateau pressure in volume or pressure control mode (Shu Ling, 2014), and 4) long slow increase in inspiratory pressure up to 40 cmH_2O (Riva, 2009).

Evidences: Hu *et al*. (2014) Randomized controlled trials (RCTs) that compared prone and supine ventilation were retrieved by searching the following electronic databases: PubMed/MEDLINE, the Cochrane Library, the Web of Science, and Elsevier Science. Two investigators independently selected RCTs and assessed their quality. The data extracted from the RCTs were combined in a cumulative meta-analysis and were analyzed using the methods recommended by the Cochrane Collaboration. He concluded PP reduced mortality among severe ARDS patients and patients receiving relatively high PEEP levels. Moreover, long-term PP improved the survival of ARDS patients.

Claude Guérin*et al*. (2013) Conducted a multicenter, prospective, randomized, controlled trial, we randomly assigned 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position. He concluded that patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality.Jordi M *et al*. (2005) Conducted a study in that he enrolled 136 patients within 48 h of tracheal intubation for severe ARDS, 60 randomized to supine and 76 to prone ventilation. Guidelines were established for ventilator settings and weaning. The prone group was targeted to receive continuous prone ventilation treatment for 20 hrs per day. He concluded that prone ventilation is feasible and safe and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day.Jolliet P *et al*. (1998) Conducted a research on Nineteen consecutive, mechanically ventilated patients (age 45+/-20 yrs, mean+/-SD) with ARDS and severe hypoxemia, defined as PaO2/FiO2 of < or = 150 with FiO2 of > or = 0.6 persisting for < or =24 hrs, and a pulmonary artery occlusion pressure of <18 mm Hg. Patients were turned prone for 2 hrs. Non-responders were returned supine, but responders were maintained prone for 12 hrs before being returned to the supine position. The procedure was repeated on a daily basis in all patients, until inclusion criteria were no longer met or the patients died. He concluded the prone position can improve oxygenation in severely hypoxemic ARDS patients without deleterious effects on hemodynamics. This beneficial effect does not immediately disappear on return to the supine position.Evgeni B *et al*. (2014) conductedan observational, retrospective study provided in university teaching hospital from January 2006 and June 2012. In this study, we retrospectively examined clinical data of 33 trauma and 56 non-trauma critically ill adult patients suffering from severe ARDS and managed by application of prone positioning (PP) during General Intensive Care Unit (GICU) stay. He concluded that study showed clinical benefit by application of PP in the treatment of severe ARDS in posttrauma critically ill patients.

Conclusion

In these modern days prone position ventilation is a challenge and several studies supporting prone ventilation improves oxygenation and decreases mortality in patients with severe ARDS. Many data suggests to start early prone ventilation not less than 12-16 hrs. Prone position ventilation duration also plays very important role in the survival benefits of ARDS patients.

Abbreviations

ARDS: Acute respiratory distress syndrome, VILI: Ventilator induced lung injury, PEEP: Positive end-expiratory pressure,V_T: Tidal volume.PP: Prone positioning, ALI: Acute lung injury, V/Q: Ventilation perfusion ratio, RCTs: Randomized controlled trials.

References

Albert RK, Hubmayr RD. The prone position eliminates compression of the lung by the heart.Am J RespirCrit Care Med 2000; 161: 1660–1665.

Blanch L, Mancebo J, Perez M, *et al*. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. Intensive Care Med 1997; 23: 1033–1039.

Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ (2000) Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. Crit Care Med 28:295–303

Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ: Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit Care Med* 1997, 25:16–27.

Constantin JM, Cayot-Constantin S, Roszyk L, *et al*.: Response to recruitment maneuver infl uenc.es n*et al*.:veolarfluid clearance in acute respiratory distress syndrome. *Anesthesiology* 2007 106:944–951.

Cornejo RA, Diaz JC, Tobar EA, Bruhn AR, Ramos CA, Gonzalez RA, Repetto CA, Romero CM, Galvez LR, Llanos O, Arellano DH, Neira WR, Diaz GA, Zamorano AJ, Pereira GL (2013) Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J RespirCrit Care Med 188:440–448.

Cortney Henderson, Rui Carlos, The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung:Journal of Applied Physiology Published 1 August 2013 Vol. 115 no. 3, 313-324 DOI: 10.1152 / japplphysiol.01531.2012.

Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985; 132: 880–884.

Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome.Jolliet P, Bulpa P, Chevrolet JC. Critical Care Medicine. 26(12):1977-85, DEC 1998.

Fan E, Wilcox ME, Brower RG, *et al*.: Recruitment maneuvers for acute lung injury: a systematic review. *Am J RespirCrit Care Med* 2008,178:1156–1163.

Farias LL, Faff e DS, Xisto DG, *et al*.: Positive end-expiratory pressure prevents lung mechanical stress caused by recruitment/derecruitment. *J ApplPhysiol*, 2005 98:53–61.

Galiatsou E, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G (2006) Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. Am J RespirCrit Care Med 174:187–197

Gattinoni L, Pelosi P, Valenza F, MascheroniD.Patient positioning in acute respiratory failure. In:Tobin M, ed. Principles and Practice of Mechanical Ventilation. New York, McGraw-Hill, 1994; pp.1067–1076.

Gattinoni L, Tognoni L, Brazzi L, *et al*. Ventilation in the prone position. The prone-supine study collaborative group. Lancet 1997; 350: 815.

Guerin C, Badet M, Rosselli S, *et al*. Effects of prone position on alveolar recruitment and oxygenation in acute lung injury. Intensive Care Med 1999; 25: 1222–1230.

Krayer S, Rehder K, Vettermann J, Didier P, Ritman EL. Position and motion of the human diaphragm during anesthesia-paralysis. Anesthesiology 1989; 70:891–898.

Lamm WJE, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury.Am J RespirCrit Care Med 1994; 150: 184–193.

Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients: a clinical study. Chest 1988; 94: 103–107.

Maggiore SM, Lellouche F, Pigeot J. Prevention of endotracheal suctioning-induced alveolar rerecruitment in acute lung injury. Am J RespirCrit Care Med. 2003;167:1215–1224. doi: 10.1164/rccm.200203-195OC.

Meade MO, Cook DJ, Griffith LE, *et al*.: A study of the physiologic responses to a lung recruitment maneuver in acute lung injury and acute respiratory distress syndrome. *Respir Care* 2008 53:1441–1449.

Mentzelopoulos SD, Roussos C, Zakynthinos SG (2005) Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. EurRespir J 25:534–544

Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome: Jordi Mancebo, Rafael Fernа´ndez, Lluis Blanch, Gemma Rialp, Federico Gordo, Miquel Ferrer, Fernando Rodrı´guez, Pau Garro, PilarRicart, ImmaculadaVallverdu´, IgnasiGich: https://doi.org/10.1164/rccm.200503-353OC

Mure M, Glenny RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. Am J RespirCrit Care Med 1998; 157: 1785–1790.

Musch G, Harris RS, Vidal Melo MF, *et al.*: Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. *Anesthesiology* 2004, 100:323–330.

Mutoh T, Guest RJ, Lamm WJE, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. Am Rev Respir Dis 1992; 146: 300–306.

Mutoh T, Guest RJ, Lamm WJE, Albert RK: Prone position alters the eff ect of volume overload on regional pleural pressures and improves hypoxemia in pigs invivo. *Am Rev Respir Dis* 1992,146:300–306.

Nakos G, Batistatou A, Galiatsou E, *et al.*: Lung and 'end organ' injury due to mechanical ventilation in animals: comparison between the prone and supine positions.*Crit Care* 2006, 10:R38.

Odenstedt H, Aneman A, KЈrason S, Stenqvist O, Lundin S: Acute hemodynamic changes during lung recruitment in lavage and endotoxininduced ALI. *Intensive Care Med* 2005, 31:112–120.

Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, Roch A, Forel JM, Bongrand P, Bregeon F, Sainty JM (2005) Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 33:2162–2171

Park MS, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS (2012) Mitogen-activated protein kinase phosphatase-1 modulates regional effects of injurious mechanical ventilation in rodent lungs. Am J RespirCrit Care Med 186:72–81

Pelosi P, Tubiolo D, Mascheroni D, *et al*. Effects of 1026 P. Pelosi *et al*. Effects of prone position on respiratory mechanics and gas exchange during acute lung injury. Am J RespirCrit Care Med 1998; 157: 387–393.

Prone Positioning Improves Oxygenation and Outcome of Trauma Patients with Severe Acute Respiratory Distress Syndrome (ARDS): Evgeni Brotfain, Netzah Ben Hur , Nancy Bonie, Amit Frenkel, Leonid Koyfman, Alexander Zlotnik, Moti Klein : Brotfain, *et al*., J Trauma Treat 2014, 4:1, http://dx.doi.org/10.4172/2167-1222.1000228

Prone Positioning in Severe Acute Respiratory Distress Syndrome: Claude Guérin, Jean Reignier, Jean-Christophe Richard, Pascal Beuret, Arnaud Gacouin: N Engl J Med 2013;368:2159-68. DOI: 10.1056/NEJMoa1214103.

Ranieri VM, Suter PM, Tortorella C, *et al*. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. JAMA 1999; 282: 54–61.

Richter T, Bellami G, Scott Harris R, *et al*.: Eff ect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. *Am J RespirCrit Care Med* 2005, 172:480–487.

Riva DR, Oliveira MB, Rzezinski AF, *et al*.: Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury. *Crit Care Med* 2009, 36:1900–1908.

Rzezinski AF, Oliveira GP, Santiago VR, *et al*.: Prolonged recruitment manoeuvre improves lung function with less utrastructural damage in experimental mild acute lung injury. *RespirPhysiolNeurobiol*2009, 169:271–281.

Santana MC, Garcia CS, Xisto DG, *et al*.: Prone position prevents regional alveolar hyperinflation and mechanical stress and strain in mild experimental acute lung injury. *RespirPhysiolNeurobiol*2009,167:181–188.

The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. Shu Ling Hu, Hong Li He, Chun Pan, Ai Ran Liu, Song Qiao Liu, Ling Liu, Ying Zi Huang, Feng Mei Guo, Yi Yang, Hai Bo Qiu Critical Care 2014 18:R109.

Valenza F, Guglielmi M, Maffioletti M, *et al*.: Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005 33:361–367.

Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, Aletti G, Porro GA, Irace M, Carlesso E, Carboni N, Lazzerini M, Gattinoni L (2005) Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role?Crit Care Med 33:361–367

VillagrЈ A, Ochagavيa A, Vatua S, *et al*.: Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J RespirCrit Care Med* 2002 165:165–170.

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