Basics of Mechanical Ventilation
C. Goals of Oxygenation

1. ***What are the general goals of oxygenation?*** As discussed in previous chapters, ventilator strategies that solely target normal arterial blood gas (ABG) results may cause ventilator associated lung injury (VALI) or hemodynamic compromise. Therefore, the goals of ventilation are to achieve acceptable PCO_2 and pH while keeping the Ppl <30 cm H_2O and minimizing autopeep in order to avoid patient harm. In addition, for patients with ARDS, the TV should also be restricted to 6 ml/kg of ideal body weight in order to improve survival. Analogous to these goals of ventilation, the goals of oxygenation are to achieve acceptable O_2 Sat while avoiding patient harm. Specifically, since prolonged exposure to high FIO_2 may cause oxygen toxicity, the FIO_2 should be reduced as soon as possible to 60% or less. Furthermore, since excessive PEEP can decrease cardiac output (CO), PEEP should be adjusted to avoid hemodynamic compromise. High PEEP, like excessive TV, can also contribute to the risk of volutrauma. This risk may be minimized by avoiding excessive levels of PEEP, using low tidal volumes when indicated, and maintaining Ppl <30 cm H_2O. These goals of ventilation, ARDS, and oxygenation are summarized in the table below. The goals of ventilation and ARDS were discussed in the previous chapter. The focus of this chapter is the goals of oxygenation.

General Goals of Ventilation	Additional Goal for ARDS	General Goals of Oxygenation
Acceptable PCO_2 and pH Ppl <30 cm H_2O Avoid Autopeep	TV = 6 ml/kg of Ideal Body Weight	O_2 Saturation >88-92% FIO_2 <60% Avoid Hemodynamic Compromise

   a. Goal #1: Oxygen Saturation >88-92% - In general, the O_2Sat should be maintained above 88-92%. Doing so will decrease the risk of adverse cardiac events (ischemia, arrhythmia, etc.) and avoid pulmonary vasoconstriction, while minimizing the risk of oxygen toxicity.
   b. Goal #2: FIO_2 <60%
      1) ***In terms of oxygen toxicity, what is a safe level of FIO_2?*** There is general consensus that prolonged exposure to high concentrations of oxygen can cause lung injury. However, there is no uniformly agreed upon "safe" level or duration of high FIO_2 exposure. Although there is no data to precisely guide this practice, FIO_2 should be decreased within 12 hours of intubation to 60% or lower.
      2) Consider a patient who is being mechanically ventilated as follows: FIO_2 50% / TV 0.5 L / rate 10 / PEEP 5 / AC mode; Cardiac Output (CO) 5; Hemoglobin (Hb) 10. ABG results are PO_2 60 / PCO_2 40 / pH 7.40.
         a) ***What is the expected O_2Sat?*** Assuming normal pH, temperature, and 2,3 diphosphoglycerate levels, PO_2 of 60 is associated with 90% saturation.
         b) ***The FIO_2 is increased to 100% and the ABG results are now: PO_2 300 / PCO_2 40 / pH 7.40. How beneficial is the increase in PO_2 for the patient?*** The O_2Sat will increase from 90% to 100%. Although the O_2Sat increased by 10%, this occurred at the price of potential oxygen toxicity.
         c) ***What should be done if the O_2Sat (>88-92%) and the FIO_2 (<60%) goals cannot be achieved simultaneously?*** Increasing PEEP may allow the FIO_2 to be decreased while maintaining acceptable O_2Sat. In general, PEEP decreases atelectasis, improves VQ matching, and thereby increases the O_2Sat.
   c. Goal #3: Avoid Hemodynamic Compromise
      1) ***What is the equation for Oxygen Delivery (DO_2)?*** Recall that, $DO_2 = CO(10)[(1.34)(Hb)(O_2Sat) + (0.003)(PO_2)]$. Normal DO_2 is approximately 1000 ml/min. Notice that the terms $(1.34)(Hb)(O_2Sat)$ and $(0.003)(PO_2)$ represent the oxygen bound to hemoglobin and that dissolved in plasma, respectively. The amount dissolved in plasma is typically small and thus often ignored. The equation then reduces to: $DO_2 = 13.4(CO)(Hb)(O_2Sat)$. Given this relationship, it is important to note that a patient may have 100% O_2Sat but the actual delivery of oxygen to the tissues may be inadequate if either the CO or the Hb is low.
      2) ***What is the relationship between PEEP and DO_2?*** By decreasing the amount of atelectasis, PEEP generally increases the O_2Sat, which would in turn increase the DO_2. However, if PEEP is excessive, it may decrease venous return to the point of reducing cardiac output and thereby cause hemodynamic compromise. If so, the DO_2 may paradoxically decrease even if the O_2Sat improves. In other words, when increasing PEEP to improve the O_2Sat, the effect of the increased PEEP on overall hemodynamic status and oxygen delivery must be considered. (See section below on PEEP for further discussion.)

2. Increasing Oxygen Saturation to Maximize Oxygen Delivery – In theory, DO_2 can be optimized by increasing any of the three major variables in the DO_2 equation: the O_2Sat, CO, or Hb. The variety of methods for increasing the O_2Sat will be treated first. For purposes of discussion, the options for increasing the O_2Sat is divided into "basic" methods vs. "rescue" methods that should be considered when the basic interventions fail. The rescue methods are further subdivided into "simple" rescue methods that are relatively inexpensive, are widely available, and do not require sophisticated equipment (i.e. proning, and recruitment maneuver, inverse ratio ventilation, sedation and paralysis,

treatment of fever) vs. more "complex" rescue methods that are more expensive, available only at limited number of hospitals, or require more sophisticated equipment or knowledge (i.e. extracorporeal membrane oxygenation, nitric oxide, high frequency oscillation, and airway pressure release ventilation). In this chapter, the discussion will be limited to the basic and simple rescue methods. The complex rescue methods will be discussed in the chapters on Modes of Mechanical Ventilation and ARDS.

Basic Methods	Simple Rescue Methods	Complex Rescue Methods
Treat Underlying Disease	Recruitment Maneuver	Extracorporeal Membrane Oxygenation
Increase FIO_2	Prone Position	Nitric Oxide
Increase PEEP	Inverse Ratio Ventilation	High Frequency Oscillation
	Treat Fever, Sedate, & Paralyze	Airway Pressure Release Ventilation

a. Basic Method: Treatment of Underlying Disease - The most important method of increasing oxygen saturation is to treat the underlying disease. For example, if a patient is hypoxic from CHF, treatment of the heart failure (i.e. diuresis, etc.) should be the first step. However, for many conditions, treatment of underlying disease may not be possible or may result in only slow improvement (i.e. ARDS).

b. Basic Method: FIO_2 - Besides treating the underlying disease, FIO_2 and PEEP have the most significant impact on the O_2Sat. However, as discussed earlier, the strategy of increasing the FIO_2 is limited by the risk of O_2 toxicity.

c. Basic Method: PEEP - PEEP applies pressure to the lung during exhalation, which minimizes atelectasis and thereby improves VQ matching. In general, patients are typically maintained at PEEP of 5 because this is thought to mimic physiologic conditions. However, if a patient requires high FIO_2, increasing the PEEP further can improve the O_2Sat and thereby allow the FIO_2 to be lowered to a "safer" level (i.e. <60%).

1) ***Does PEEP improve oxygenation in every hypoxic patient?*** In a study of 19 ARDS patients, increasing the PEEP from 0 to 9 then 16 resulted in a wide range of recruited lung volume: 25 to 850 ml. The investigators then grouped the subjects into "recruitable" (>150 ml of recruitment) vs. "nonrecruitable" (<150 ml of recruitment) patients. As summarized in the table below, increasing the PEEP from 0 to 9 significantly increased the PaO_2/FIO_2 ratio for both groups. When the PEEP was increased to 16, oxygenation further improved for the recruitable patients but not for the nonrecruitable patients. Instead, the nonrecruitable patients ended up with a much more positive fluid balance, which was required to preserve hemodynamic stability. This study demonstrates that PEEP will improve oxygenation in general but to widely varying degrees for different patients. PEEP presumably helps only if there are atelectatic lung units which can be recruited by PEEP. For many patients, beyond a certain level of PEEP, it may only reduce the cardiac output without improving oxygenation. (Grasso. AJRCCM 2005; 171: 1002-8.)

	Nonrecruiters, N = 10			Recruiters, N = 9		
PEEP	0	9	16	0	9	16
PaO_2/FIO_2	107	149	142	93	150	396

2) ***What is the optimal PEEP for a given patient?*** As discussed above, PEEP improves oxygenation in many, although not all, hypoxic patients. According to the PV curve model, by reducing atelectasis, PEEP can also theoretically minimize the risk of RACE injury. On the other hand, excessive PEEP can reduce cardiac output and increase the risk of volutrauma. Less importantly, PEEP can also increase the physiologic dead space since PEEP increases the VQ ratio by increasing ventilation and decreasing perfusion. Therefore, a conceptually useful definition of "optimal" PEEP is PEEP that maximizes potential benefit (better oxygenation and less RACE) while minimizing potential harm (hemodynamic compromise, volutrauma, and increased dead space).

a) Optimizing PEEP Based on Avoiding Hemodynamic Compromise - By decreasing venous return, excessive PEEP can reduce cardiac output and cause hypotension. Volume-depleted patients are particularly susceptible to PEEP-induced hypotension. ***Consider a patient who is mechanically ventilated as follows: FIO_2 100% / TV 0.6 L / rate 10 / PEEP 10; CO 5; Hb 10. ABG results are: PO_2 70 / PCO_2 40 / pH 7.40 / O_2Sat 94%. PEEP is increased in a step-wise fashion and ABG and hemodynamic parameters are recorded as shown in the table below. What is the optimal PEEP for this patient?***

FIO_2	TV	Rate	PEEP	Hb	CO	PO_2	PCO_2	pH	O_2Sat	DO_2, ml/min
100	0.6	10	10	10	5	70	40	7.40	94%	630
100	0.6	10	12	10	5	80	40	7.40	96%	643
100	0.6	10	14	10	5	90	40	7.40	98%	657
100	0.6	10	16	10	3	100	40	7.40	100%	402

At first glance, PEEP of 16 appears best because it gives the best O_2Sat. However, recall that the more

important goal is to avoid hemodynamic compromise and to optimize the DO_2. Notice that the DO_2 increases with each PEEP change up to a PEEP of 14, but at a PEEP of 16, the CO decreases from 5 to 3 lpm. Consequently, the DO_2 paradoxically falls from 657 to 402 ml/min even though the O_2Sat increases from 98 to 100%. Thus, in this example, the optimal PEEP would be 14, because hemodynamic stability is preserved and the DO_2 is maximized.

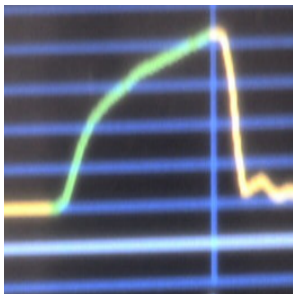
b) Optimizing PEEP Based on the PV Curve – Based on the PV curve model, insufficient PEEP can promote atelectasis and contribute to RACE injury. On the other hand, excessive PEEP can increase the risk of alveolar overdistention and contribute to the risk volutrauma, especially when large TV is used. Therefore, an alternative definition of "optimal" PEEP is one that allows a patient to be ventilated above the LIP to avoid RACE but below the UIP to avoid volutrauma. In practice, this explicit approach is seldom followed since PV curves are not routinely determined outside of research settings.

c) Optimizing PEEP Based on Respiratory System Compliance ("Poor Man's PV Curve") – In theory, the portion of the PV curve between the LIP and UIP is linear and the slope of this line is the compliance of the respiratory system (C_{RS}). Recall that $C_{RS} = \Delta V/\Delta P$, where ΔV is the tidal volume and ΔP is the difference between end-inspiratory and end-expiratory pressures (i.e. Ppl – PEEP). If ventilation is occurring on the linear portion of the PV curve, changing the PEEP by a set amount (without changing the TV) should change the Ppl by the same amount. However, if increasing the PEEP by a set amount increases the Ppl to a greater extent, it suggests that the C_{RS} has decreased and that UIP is being traversed. ***For example, consider a pharmacologically relaxed patient who is mechanically ventilated as follows: FIO_2 60% / TV 0.3 L / rate 30 / PEEP 12 / AC mode. PEEP is increased in a step-wise fashion and the Ppl is recorded as shown below. What is the optimal PEEP for this patient?***

FIO_2	TV, L	Rate	PEEP	PO_2	O_2Sat	Ppl	Compliance (C_{RS}, ml/cm H_2O)
60%	0.3	30	12	60	90%	28	C_{RS} = 300/(28-12) = 18.75
60%	0.3	30	14	70	94%	30	C_{RS} = 300/(30-14) = 18.75
60%	0.3	30	16	80	96%	32	C_{RS} = 300/(32-16) = 18.75
60%	0.3	30	18	90	98%	40	C_{RS} = 300/(40-18) = 13.64

Notice that for PEEP levels of 12-16, an increase in PEEP by 2 increases the Ppl also by 2 and the C_{RS} does not change. These observations are consistent with the patient being ventilated between the LIP and the UIP where the PV curve is linear. However, when PEEP increases by 2 from 16 to 18, the Ppl increases by 8 and the C_{RS} decreases substantially. This suggests that the UIP is being traversed at PEEP of 18. Therefore, for this patient, the "optimal" PEEP would be 16.

d) Optimizing PEEP Based on the Stress Index - A recently proposed concept known as the stress index may allow the clinician to set the PEEP at the bedside so as to theoretically avoid both the LIP and the UIP but without the need for a cumbersome PV curve. (See chapter on Ventilator Associated Lung Injury for background discussion.) Recall that stress index refers to the shape of the pressure-time curve in a pharmacologically relaxed patient who is receiving a fixed TV at a constant flow rate. Under these conditions, the airway pressure rises according the equation: $P_{aw} = m(V)^b + P_0$, where P_{aw} is the airway pressure, m is a constant equal to 1 / C_{RS}, V is the lung volume, P_0 is a constant equal to PEEP + Flow*Resistance, and b is the stress index. If the breath is being delivered between LIP and UIP, as is the theoretical goal, the compliance does not change during the breath so that the airway pressure rises linearly with time (i.e. b=1). On the other hand, if the breath is being delivered in such a way that it traverses the UIP, the compliance decreases during the breath so that the pressure-time curve becomes concave up (i.e. b>1). If the breath is being delivered in such a way that it traverses the LIP, the compliance increases during the breath so that the pressure-time curve becomes concave down (i.e. b<1). Pressure-time curves illustrating different types of stress indices are shown below.



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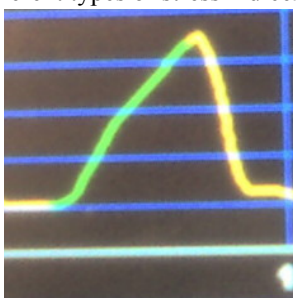

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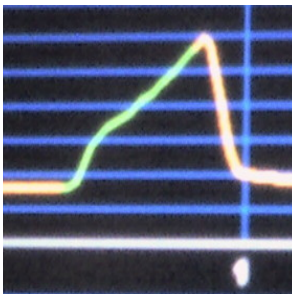


b>1

(1) ***How does the PEEP set by the stress index compare to that set by a more conventional approach?*** Grasso. AJRCCM 2007; 176: 761-7. A study of 15 ARDS patients compared strategies of setting PEEP per the stress index (i.e. b=1) vs. setting PEEP per the ARDS-NET protocol x 12 hours in the same patient in random order. ARDS-NET protocol included the strategy of low TV, Ppl <30, and predetermined PEEP based on the FIO_2 requirement. PEEP set per the ARDS-NET approach was significantly higher than that set by the stress index (13 vs. 7, $P < 0.01$) but there was no difference in the TV used between the two groups (420 vs. 440 ml, P=NS). Interestingly, the mean stress index in the ARDS-NET approach was significantly higher ($b = 1.15$ vs. 1.01, $P < 0.01$), suggesting that patients were subject to risk of volutrauma with this approach. As predicted by the stress indices, the plasma levels of IL-6, IL-8, and sTNF-α-RI were all higher with the ARDS-NET strategy compared to the stress index strategy. These observations suggest that significant ventilator associated lung injury may occur despite the use of low TV and low Ppl.

(2) ***Should PEEP be set according to the stress index?*** The concept of stress index is rather attractive because it is a relatively simple technique that can be performed in almost any ICU without special equipment, cumbersome protocols, or undue risk to the patient. However, studies demonstrating improvement in major clinical outcomes (rather than surrogate markers) are still needed for validation. Thus, it is premature to recommend that it be used routinely to optimize the PEEP.

3) ***Does PEEP improve clinical outcome?*** PEEP improves oxygenation in many patients and may theoretically decrease the risk of RACE injury by reducing atelectasis and ventilating the patient above the LIP. However, evidence for survival advantage of PEEP is still lacking in humans. The table below summarizes the results of the three major randomized clinical trials that have explicitly tested the role of PEEP in ARDS patients. In brief, all of the studies demonstrated improved oxygenation with higher PEEP but no study has demonstrated a survival benefit. (ALVEOLI. NEJM 2004; 351:327-36. Meade. JAMA 2008; 299: 637-45. Mercat. JAMA 2008; 299: 646-55.) As a representation of these trials, the EXPRESS Study is described further.

	ALVEOLI, N=549			LOV, N=983			EXPRESS, N=768		
PEEP	Low	High		Low	High		Low	High	
TV, Day 1 ml/kg	6.1	6.0	NS	6.8	6.8	NS	6.1	6.1	NS
TV, Day 7 ml/kg	6.2	5.8	NS	7.0	6.9	NS	6.4	6.8	<0.001
PEEP, Day 1	9	15	<0.01	10	16	<0.001	7	15	<0.001
PEEP, Day 7	8	13	<0.01	8	10	<0.001	6	9	<0.001
Ppl, Day 1	24	27	<0.05	25	30	<0.001	21	28	<0.001
Ppl, Day 7	26	26	NS	25	29	<0.001	21	24	<0.001
Mortality	25%	28%	NS	40%	36%	NS	31%	28%	NS
PaO_2/FIO_2, Day 1	168	220	<0.01	149	187	<0.001	150	218	<0.001
PaO_2/FIO_2, Day 7	181	218	<0.05	181	213	<0.001	184	206	<0.001
Ventilator Free Days	14.5	13.8	NS	-	-	-	3	7	0.04
Organ Failure Free Days	16	16	NS	-	-	-	2	6	0.04
Need for Rescue Therapies	-	-	-	12%	8%	0.045	35%	19%	<0.001

a) EXPRESS Study - Mercat. JAMA 2008; 299: 646-55. Among 768 ARDS/ALI patients, this PRCT compared "minimal distention" strategy (TV 6 ml/kg, PEEP and Ppl were kept as low as possible) vs. "increased recruitment" strategy (TV 6 ml/kg, PEEP was kept as high as possible irrespective of the oxygenation status but the Ppl was kept <30). Recruitment maneuvers were allowed but discouraged. Oxygenation was better (206 vs. 184 for PaO_2/FIO_2 on Day 7, $P<0.001$) and fewer rescue therapies were required (19% vs. 35%, $P<0.001$) with the increased recruitment strategy but there was no significant difference in survival at 28 days (28% vs. 35%, P=NS). Increased recruitment strategy was also associated with more ventilator free days (7 vs. 3, P=0.04) and organ failure free days (6 vs. 2, P=0.04).

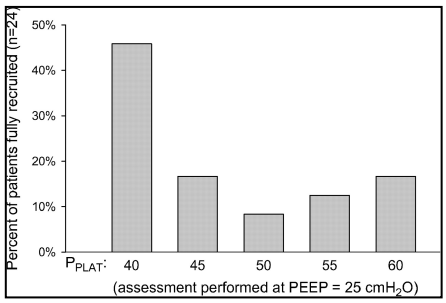
b) ***Does PEEP improve oxygenation but not survival?*** - Although PEEP appears to improve oxygenation, none of the major studies have demonstrated a survival advantage with high PEEP. Therefore, one potential conclusion is that PEEP improves oxygenation but not survival. However, an alternative view is that all of these studies failed to demonstrate a survival advantage because the PEEP was not set according to the PV curve model as described earlier in this chapter. Recall that according the PV curve model, optimal PEEP ventilates the patient between the two inflection points. Since none of these studies set the PEEP with LIP and UIP in mind, it is possible that the PEEP may have been too low for some patients but too high for others. The mean PEEP used in the three studies were 15-16 on day 1 but had decreased to 9-13 by day 7. Since the mean LIP for ARDS patients varies from 15-17 in the literature, it is likely that the PEEP level was insufficient to avoid RACE injury in many situations. (Albaiceta.

AJRCCM 2004; 170: 1066-72. Borges. AJRCCM 2006; 174: 268-278.) If this is true, despite so called "high" PEEP, many patients may have experienced RACE injury because the PEEP was not high enough to be above the LIP. On the other hand, as discussed above, PEEP set without consideration for the UIP may be associated with more pulmonary and systemic inflammation. (Grasso. AJRCCM 2007; 176: 761-7.) Thus, PEEP may have been too high for other patients, subjecting them to the risk of volutrauma. These observations also emphasize the fact that ARDS is not a uniform condition and that some patients may benefit from higher PEEP while others may actually be harmed by it. Therefore, future studies should move away from a "one-size-fits-all" approach to PEEP but rather try to individualize PEEP based on the PV curve, the stress index, or in other meaningful ways.

c) As discussed earlier, a conceptually useful definition of "optimal" PEEP is PEEP that maximizes potential benefit (improved oxygenation, reduced risk of RACE) while minimizing potential harm (hemodynamic compromise, risk of volutrauma, increased dead space). Although none of the three studies tried to balance the benefit and harm in these explicit terms, the EXPRESS study came closest by choosing the highest possible PEEP irrespective of oxygenation status as long as the Ppl did not exceed 30. Thus, it is interesting that the EXPRESS study was the only study to demonstrate significant improvements in terms of ventilator free and organ failure free days.

d. Simple Rescue Method: Recruitment Maneuver

1) ***What is a recruitment maneuver?*** Recruitment maneuver describes a variety of methods that apply high pressure (i.e. 35-60 cm H_2O) for a prolonged period of time (i.e. 30-120 seconds) in order to recruit atelectatic lung units. For example, one popular method is to apply pressure of 40 cm H_2O for 40 seconds. Another method advocates an incremental approach starting with a pressure of 40 cm H_2O (PEEP 25 + pressure control 15) but increasing to 60 cm H_2O in a step wise fashion if needed (PEEP 45 + pressure control 15). (Borges. AJRCCM 2006; 174: 268-278.) As shown in the figure to the right, more than half of the ARDS patients required pressure greater 40 cm H_2O for maximal recruitment.



2) ***Why is it theoretically important to minimize atelectasis?*** Atelectasis may be harmful for ARDS patients in several ways. Perfusion of atelectatic lung units leads to VQ mismatching and hypoxia. If this results in use of high FIO_2 or excessive PEEP, the potential consequences include oxygen toxicity, decreased cardiac output, and excessive airway pressures leading to volutrauma. Secondly, if the atelectatic lung units undergo repeated cycles of opening and collapse with each tidal breath, RACE injury may occur. Furthermore, atelectatic lung units cause much of the delivered TV to be shunted to more distensible regions of the lung, exposing that part of the lung to risks of overdistention and volutrauma. Thus, by minimizing atelectasis, recruitment maneuver has the potential to improve oxygenation while decreasing the risks of oxygen toxicity, RACE injury, and volutrauma.

3) ***Has RM been shown to improve clinical outcome?*** Recruitment maneuver appears to increase oxygenation in many but not all people. However, it is unknown whether it improves mortality or other clinically important outcome. Furthermore, as is the case with PEEP, the amount of atelectasis recruited by a recruitment maneuver varies highly from person to person. (Gattinoni. NEJM 2006; 354:1775-86.) Studies demonstrating improvement in major clinical outcomes (rather than just oxygenation) are still lacking and it is premature to recommend that it be used routinely.

e. Simple Rescue Method: Prone Positioning

1) ***How is proning performed?*** Proning simply involves turning a supine patient to a face-down position. This has to be done safely without dislodging the endotracheal tube, venous catheters, or other important tubes and lines. One method is to have a clinician take charge of the patient's head and the endotracheal tube and four other people attend to each limb and the associated tubes and lines. The patient is turned at the command of the clinician in charge the endotracheal tube. Patient is then positioned and appropriately padded to minimize development of pressure sores. A kinetic rotational bed can be used to facilitate the proning process but in most cases, it can be performed manually just as easily.

2) ***How does proning improve the O_2Sat?*** Proning increases the O_2Sat in many patients but the exact mechanisms are still debated. With this in mind, the following discussion highlights only some of the mechanisms. The distribution of lung disease is often not uniform in respiratory failure patients. For example, in ARDS patients, the dorsal lung units tend to be more involved, with relative sparing of the ventral lung units. Due to gravity, perfusion tends to be higher in the dorsal, less ventilated lung units. The end-results are severe VQ mismatching and hypoxia. Proning redistributes the blood flow toward the better-ventilated,

ventral lung units. At the same time, proning improves ventilation in the dorsal areas since these regions are no longer dependent, allowing edema and atelectasis to improve. Both of these factors improve VQ matching and thereby the PO_2. For some patients, this increase in PO_2 can be significant although the benefit tends to fade with time. In addition, because of the anatomic configuration of the chest, proning may promote better drainage of secretions. (Guerin. Intensive Care Medicine 1999; 25: 1222-30. Mutoh. American Review of Respiratory Diseases 1992; 146: 300-6. Richard. Journal of Applied Physiology 2002; 93: 2181-91. Pelosi. AJRCCM 1998; 157: 387-93. Albert. AJRCCM 2000; 161: 1660-5.)

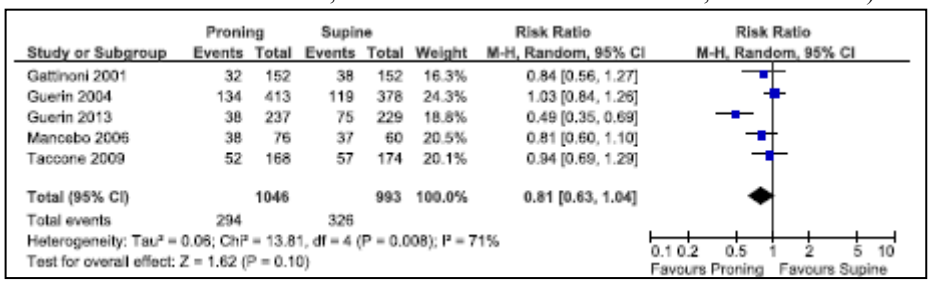
3) ***What are the adverse effects of proning?*** The potential adverse effects of proning include accidental removal of tubes and catheters, difficult access for CPR, pressure necrosis, and facial edema. In some patients, hemodynamic instability or oxygen desaturation may occur. In general, patients may require more sedative or paralytic agents. The risk of adverse events will likely vary depending on the experience of the ICU team caring for the patient.

4) ***Does prone positioning improve clinical outcome?***

a) Several randomized controlled trials have compared supine vs. prone position among patients with various types of respiratory failure. The table below summarizes the results of the five major trials (>100 patients) that have explicitly tested the role of proning in adult ARDS patients. In brief, all of the studies demonstrated improved oxygenation with proning but only one study demonstrated a survival benefit. (Prone-Supine I Study. Gattinoni. NEJM 2001; 345(8): 568-73. Guerin. JAMA 2004; 292: 2379-87. Mancebo. AJRCCM 2006; 173: 1233-9. Prone-Supine II Study. Taccone. JAMA 2009; 302: 1977-84. PROSEVA Study. Guerin. NEJM 2013; 368: 2159-68.)

	Gattinoni 2001 Prone Supine I N = 304		Guerin 2004 N = 791		Mancebo 2006 N = 136		Taccone 2009 Prone Supine II N = 342		Guerin 2013 PROSEVA N = 466	
PaO_2/FIO_2 Ratio	Inclusion: < 200 Mean: 127		Inclusion: < 300 Mean: 152		Inclusion: < 200 Mean: 105		Inclusion: < 200 Mean: 113		Inclusion: < 150 Mean: 100	
Duration of Proning	Planned: 6 h/d Actual: 7 h x 4.7 d		Planned: > 8 h/d Actual: 9 h x 4.1 d		Planned: 20 h/d Actual: 17 h x 10 d		Planned: 20 h/d Actual: 18 h x 8.3 d		Planned: > 16 h/d Actual: 17 h x 4 d	
Mean TV	10.3 ml/kg		8.1 ml/kg		8.4 ml/kg		8.1 ml/kg		6.1 ml/kg	
Allocation	Central Randomization		Sealed Opaque Envelopes		Sealed Opaque Envelopes		Central Randomization		Central Randomization	
Mortality Assessed	At 10 Days		At 28 Days		At Hospital Discharge		At 28 Days		At 28 Days	
Oxygenation	Improved with Proning		Improved with Proning		Improved with Proning		Improved with Proning		Improved with Proning	
	Prone	Supine	Prone	Supine	Prone	Supine	Prone	Supine	Prone	Supine
Mortality	21%	25%	32%	32%	50%	62%	31%	33%	16%	33%
P	NS		NS		NS		NS		<0.001	

b) As shown in the figure below, a pooled random effects analysis of these five trials does not demonstrate mortality reduction (RR and 95% CI 0.81 (0.63-1.04), P = 0.10), but there was substantial statistical heterogeneity (I^2 71%, P = 0.008). Some have argued that only those with severe hypoxemia (PaO_2/FIO_2 ratio < 100) may benefit in terms of mortality, an argument that is supported by the Guerin study. (Sud. Intensive Care Medicine 2010; 36: 585-99. Guerin. NEJM 2013; 368: 2159-68.)



c) In summary, although proning undoubtedly improves oxygenation, it does not convincingly improve survival. Nevertheless, it is an inexpensive intervention that can be performed in almost any ICU. Since other more complex or expensive modalities (i.e. ECMO, high frequency oscillation, etc.) have not demonstrated a survival benefit, proning should be considered in ARDS patients with refractory hypoxemia, provided that an experienced ICU team can perform it safely.

f. ***What are some other methods for increasing the O_2Sat?*** Other simple methods include inverse ratio ventilation, sedation and paralysis, and treating fever. In general, these techniques have only a minor impact on the O_2Sat.
   1) Lengthening the inspiratory time increases the mean airway pressure and may allow for better gas exchange. If the inspiratory time is purposefully set longer than the expiratory time, this pattern is termed inverse ratio ventilation (IRV). In general, the increase in PO_2 is small, if any. Since IRV decreases the expiratory time by definition, air trapping (i.e. autopeep) may occur. Higher mean airway pressure associated with IRV may also reduce the blood pressure or the cardiac output by mechanisms similar to excessive PEEP. Finally, because IRV tends to be uncomfortable, a heavier level of sedation is often necessary.
   2) Some advocate purposefully decreasing oxygen consumption in setting of hypoxia in order to improve the balance between oxygen delivery and consumption. These strategies include heavy sedation, pharmacologic paralysis, and treatment of fever. However, the benefit or harm of these maneuvers is largely unknown. Regardless, the increase in PO_2 is generally small, if any.
   3) More complex rescue methods for improving oxygenation include extracorporeal membrane oxygenation, nitric oxide, high frequency oscillation, and airway pressure release ventilation. These are more sophisticated interventions that are expensive, available only at a limited number of hospitals, or require more specialized equipment or knowledge. The complex rescue methods will be discussed in the chapters on Modes of Mechanical Ventilation and ARDS.

3. Increasing Hemoglobin to Increase Oxygen Delivery
   a. ***On the surface, blood transfusion is a simple way to increase oxygen delivery. If so, why not transfuse everyone in the ICU?*** Hebert. NEJM 1999 340(6), 409-17. This PRCT compared the effects of restrictive (Hb goal 7-9) vs. liberal (Hb goal 10-12) transfusion strategies among 838 ICU patients with Hb <9.0. Patients were euvolemic and not actively bleeding. At the time of enrollment, 81% of the patients were on mechanical ventilation and 37% were receiving vasopressor medications. Overall, there was no significant benefit of maintaining the Hb above 10 in terms of the primary outcome which was mortality at 30 days. In fact, the risks of hospital mortality, myocardial infarction, CHF, or multiple organ failure were all higher with the liberal transfusion strategy.

	Restrictive	Liberal	P
30-day Mortality	18.7%	23.3%	0.11
Hospital Mortality	22.2%	28.1%	0.05
MI	0.7%	2.9%	0.02
CHF	5.3%	10.7%	<0.01
Multiorgan Dysfunction Score	10.7	11.8	0.03

   b. ***What if the patient has been actively bleeding?*** By tradition, patients who had been actively bleeding would be transfused to Hb > 10-12 mg/dl to create a "reserve" in case of future bleeding. However, a recent PRCT compared restrictive (Hb target >7.0) vs. liberal transfusion (Hb target >9.0) strategies in 921 patients with severe upper gastrointestinal bleeding and found significantly worse 45-day mortality with higher hemoglobin targets (9% vs. 5%, P = 0.02). The risk of further bleeding was also higher in the liberal transfusion group (16% vs. 10%, P = 0.01). Patients with massive exsanguinating bleeding were excluded from the study. (Villenueva. NEJM 2013; 368: 11-21.)
   c. ***Should "restrictive" transfusion strategy be used for all ICU patients?*** In general, critically ill ICU patients with anemia who are not actively bleeding (including those on mechanical ventilation and vasopressors) do not appear to benefit from routine PRBC transfusions if the Hb is >7 mg/dl. Contrary to popular belief, the risk of MI was not decreased with PRBC transfusions. Findings were similar in high risk patients with risk factors for coronary artery disease who were undergoing hip surgery. (Carson. NEJM 2011; 365: 2453-62.) However, some exceptions to the "restrictive transfusion rule" should be considered. The most obvious are the actively bleeding patients who were excluded from this study. Intuitively, it makes sense to transfuse people who are actively loosing blood. A second possible exception is the patients with active coronary artery disease. By tradition, most clinicians prefer to keep the Hb > 10-12 mg/dl in patients with acute coronary disease because of the theoretical risk of worsening myocardial ischemia. However, two large observational studies offer exactly opposite conclusions: a study of 78,974 elderly patients admitted for myocardial infarction suggests a survival advantage with transfusions while another study of 24,112 patients with acute coronary syndrome suggests worse survival with transfusions. (Wu. NEJM 2001; 345:1230-1236. Rao. JAMA 2004; 292:1555-62.) Therefore, more studies are clearly needed in this area.
   d. ***What about erythropoietin?*** Hebert's study has prompted some to advocate for routine use of erythropoietin. In theory, erythropoietin-stimulated endogenous RBCs are better carriers of oxygen than transfused cells and without the latter's potential adverse effects. However, recent PRCT of 1460 critically ill patients comparing recombinant erythropoietin vs. placebo found no significant difference in transfusion requirements. Furthermore, there was no

difference in mortality but there was a higher risk of venous thromboembolism, stroke, and myocardial infarction with erythropoietin. (Corwin. NEJM 2007; 357: 965-76.)

4. Increasing Cardiac Index to Increase Oxygen Delivery
   a. ***In theory, increasing the cardiac output is yet another way to improve oxygen delivery. Then why not boost everyone's cardiac index (CI) in the ICU?*** Unfortunately, the well-designed randomized controlled trials that have investigated this strategy found no significant benefit. (Hayes. NEJM 1994; 330: 1717-22. Gattinoni. NEJM 1995; 333: 1025-32.) The larger of these studies is discussed below.
   b. ***Does routine use of inotropic agents improve outcome in critically ill patients?*** Gattinoni. NEJM 1995; 333:1025-32. This PRCT of 762 critically ill patients compared three strategies: (1) control (CI target 2.5-3.5), (2) supranormal CI (CI goal >4.5), and (3) normal SvO_2 (SVO_2 goal >70%). A combination of volume expanders, vasopressors, inotropic agents, and vasodilators were used as needed to achieve these goals. Patients were otherwise treated similarly with goals of MAP >60, PCWP <18, CVP 8-12, UO >0.5 cc/kg/h, and pH 7.3-7.5. It was not possible to achieve the physiologic target in 55% of patients assigned to the supranormal CI group and 33% of the normal SvO_2 group. There was no significant difference in the rates of organ failures or survival among the groups.

	Control Group	CI>4.5 Group	SvO_2>70%	P
% Reaching Target Goal	94.3	44.9	66.7	<0.001
ICU Mortality	48.4	48.6	52.1	NS
Respiratory Failure	94.4%	93.3%	96.5%	NS
Renal Failure	54.8%	53.0%	52.1%	NS

   c. Oxygen Delivery vs. Oxygen Extraction - Although PO_2, O_2Sat, and DO_2 are all related, it is ultimately the DO_2 that measures the amount of O_2 available to the cells. Thus the goals of mechanical ventilation include not only keeping O_2Sat >88-92% but also optimizing DO_2. Given the risk of O_2 toxicity, both of these goals should be achieved with FIO_2 <60%, if possible. However, optimizing DO_2 is still not the ultimate goal of oxygenation. This is evidenced by numerous well-designed studies that demonstrate the lack of benefit (and possible harm) of strategies that increase CO or Hb as means of increasing DO_2. In other words, simply increasing the supply of O_2 to the cells does not translate into increased utilization of the O_2 or into a survival advantage.

SUGGESTED READING

Key Original Articles

Grasso. ARDSnet ventilatory protocol and alveolar hyperinflation – role of PEEP. American Journal of Respiratory & Critical Care Medicine 2007; 176: 761-7.

EXPRESS Study. Mercat. PEEP setting in adults with ALI and ARDS. JAMA 2008; 299: 646-55.

Guerin. Prone positioning in severe acute respiratory distress syndrome. New England Journal of Medicine 2013; 368: 2159-68.

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