APPROACH TO REFRACTORY HYPOXEMIA: VENTILATOR AND ADJUNCT THERAPY

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ABSTRACT

- Refractory hypoxemia is never missed.
- All patients with ALI should be on lung protective ventilation.
- None of the treatments that improve oxygenation have been shown to affect mortality.
- Some of the treatments for refractory hypoxemia can be harmful particularly if you use them rarely
  1. Paralysis
  2. Recruitment
  3. Inhaled prostacyclin
  4. Prone
- There is no evidence that one is better than others – have several in your bag of tricks.
- The choice of rescue therapy is based on the equipment and clinician expertise.

INTRODUCTION

Hypoxia is a pathological condition in which reduction of oxygen supply to a tissue below physiological levels despite adequate perfusion of the tissue by blood.

WHAT IS REFRACTORY HYPOXEMIA?

No official definition
\[ \text{PaO}_2 < 50 \text{ on an FIO}_2 = >70 \]
Persisten for > 12-24 hrs
Despite PEEP trial of up to 20 - 25 cm H\textsubscript{2}O
Despite ruling out readily reversible causes
- Mucus plugging/lobar or greater collapse
- Pneumothorax
- Systemic vasodilators enhancing shunt
- Pulmonary embolism
- Intra-cardiac R > L shunt
- Circulatory collapse (low S\textsubscript{vO}_2)

REFRACTORY HYPOXIA – CAUSES

- Hypoventilation- machine failure, leak, calibration error
• V/Q mismatch - pulmonary oedema, infiltrates lung, atelectasis, pulmonary embolism
• Increase R>L shunt - ARDS, Pulmonary oedema
• Low $PvO_2$ = anemia, increase demand, decrease cardiac output
• Severe alkalosis

CLINICAL SITUATIONS
1. Sepsis
2. Pneumonia
3. Major trauma
4. Pulmonary aspiration and near drowning
5. Burns
6. Fumes
7. Fat embolism
8. Massive blood transfusion
9. Amniotic fluid embolism
10. Air embolism
11. Eclampsia
12. Poisoning
13. Radiation.

BY FAR THE COMMONEST CAUSE OF REFRACTORY HYPOXEMIA IS SEVERE ALI

HOW TO CORRECT REFRACTORY HYPOXEMIA?

GOAL
1. Decrease further damage to alveoli
2. Increase recruitment of remaining alveoli

A. Ventilatory Strategies
   • PEEP - open lung approach
   • Pressure controlled ventilation (PCV)
   • Inverse ratio ventilation (IRV)
   • Recruitment maneuvers
   • High frequency oscillatory ventilation (HFOV)
   • High frequency percussive ventilation (HFPV)
   • Airway pressure release ventilation (APRV)

B. Non-Ventilator Strategies
   • Inhaled vasodilators INO, PGE1
   • Prone position
   • Neuromuscular blockade

• Conservative fluid management
• Corticosteroids
• Nutritional support
• Extracorporeal life support

None of these always improve oxygenation

Evidence lacking that any one of these is better than another

Evidence lacking that any of these improves survival.

C. Lung Transplant

A. Ventilatory Strategies
   1. Lung Recruitment Strategy
   2. PEEP
   3. PCV
   4. Prone ventilation
   5. Pressure Control Inverse Ratio Ventilation (PCIRV)
   6. Airway Pressure Release Ventilator (APRV)
   7. HFOV
   8. HFPV

1. Lung Recruitment Maneuvers

Recruitment maneuvers aim to open collapsed lung unit and increase functional residual capacity by increasing transpulmonary pressure. To recruit lung, airway pressure must be greater than the critical or threshold opening pressure at end inspiration.

A recruitment maneuver is a transient increase in transpulmonary pressure intended to promote reopening of collapsed alveoli and has been shown to open collapsed alveoli, thereby improving gas exchange.

• Designed to open collapsed alveoli and shift the volume-pressure curve up and to the right
• Most common methodology
  - 40 cm $H_2O$ CPAP
  - 40 seconds
• Often possible to reverse hypoxemia and completely recruit the lung in early ARDS
  - 24/26 patients; transient ↓ BP and ↑ $PaCO_2$
• A decremental PEEP trial can then identify the PEEP level needed to maintain oxygenation after a recruitment maneuver
• Sustained high-pressure: CPAP 30-50 cm H₂O for 20-40 s
• Pressure control + PEEP: pressure control ventilation of 10 – 15 cm H₂O with PEEP of 25-30 cm H₂O to reach a peak inspiratory pressure of 40-45 cm H₂O for 2 min
• Intermittent sigh: Three consecutive sighs/min at Plat 45 cm H₂O
• Extended sigh: stepwise increase in PEEP with a simultaneous stepwise decrease in VT over 2 min leading to a CPAP of 30 cm H₂O for 30 s
• Intermittent PEEP increase: increase in PEEP from baseline to set level for 2 consecutive breaths/min

Best Approach Unknown

2. PEEP

Setting PEEP for ALI/ARDS
- 0 cm H₂O: likely harmful
- 8 – 16 cm H₂O: appropriate in most patients
- Higher PEEP for ARDS; lower PEEP for ALI
- >20 cm H₂O: seldom necessary
- High PEEP should be reserved for cases where recruitment can be demonstrated
- PEEP should be selected in the context of prevention of ventilator-induced lung injury
- The benefit of precise PEEP is unproven

• Incremental PEEP: PEEP/FIO₂ combinations to achieve the desired level of oxygenation or highest compliance.
- Decremental PEEP: high level of PEEP (e.g., 20 cm H₂O), after which PEEP is decreased in a stepwise fashion until a decrease in PaO₂ and decrease in compliance
- Optimal PEEP by Tidal Compliance
- 15 normovolemic patients requiring mechanical ventilation for ARF
- PEEP resulting in maximum oxygen transport and the lowest dead-space fraction resulted in highest compliance
- Optimal PEEP varied from 0 to 15 cm H₂O
- Mixed venous PO₂ increased from 0 PEEP to the PEEP resulting in maximum oxygen transport, but then decreased at higher PEEP

• Conclusion: compliance may be used to indicate the PEEP likely to result in optimum cardiopulmonary function ↑ PEEP

3. Pressure Controlled Ventilation (PCV)

In patients with severe ARDS, PCV as an alternative to volume-controlled ventilation (VCV), the peak inspiratory pressure is lower on PCV; patient-ventilator synchrony is believed to be better with PCV.
- Higher mean airway pressure and lower end inspiratory flow should improve gas exchange
- With attention to tidal volume, plateau pressure, PEEP, and inspiratory time, the differences between PCV and VCV are minor and neither is clearly superior to the other
- ARDSnet trial was conducted with VCV

4. Prone Ventilation:

Prone ventilation – takes the heart off the lungs

• Implications of observations
  - Less overinflation of non-dependent lung
  - Less airspace opening/closing of dependent lung
• Speculation
  - Less ventilator-induced lung injury

5. Pressure Control Inverse Ratio Ventilation (PCIRV)

ARDS and severe hypoxemia

Prolonged inspiratory time (3:1) leads to better gas distribution with lower PIP
Elevated pressure improves alveolar recruitment
No statistical advantage over PEEP, and does not prevent repetitive collapse and reinflation
PCIRV: improvement in oxygenation is small; risk of auto-PEEP and hemodynamic compromise is great
Often Used With PCV/ VCV
6. **Airway Pressure Release Ventilator (APRV)**

APRV is a mode of ventilation designed to allow patients to breathe spontaneously while receiving high airway pressure with an intermittent pressure release. The high airway pressure maintains adequate alveolar recruitment. Oxygenation is determined by high airway pressure and FIO2. The timing and duration of the pressure release (low airway pressure) as well as the patient’s spontaneous breathing determine alveolar ventilation (PaCO2). The ventilator-determined tidal volume depends on lung compliance, airway resistance, and the duration and timing of the pressure-release maneuver.

If APRV is used, auto-PEEP and tidal volume must be closely monitored.

7. **HFOV**

High-frequency ventilation is any application of mechanical ventilation with a respiratory rate of >100 breaths/min. This can be achieved with a small tidal volume and rapid respiratory rate with conventional mechanical ventilation, various forms of external chest wall oscillation, HFPV, high-frequency jet ventilation, or HFOV, which currently is the form of high-frequency ventilation most widely used in adult critical care. It delivers a small tidal volume by oscillating a bias gas flow in the airway. The oscillator has an active inspiratory and expiratory phase. A frequency of 3 to 15 Hz can be used, although lower rates (3-6 Hz) are used in adults. Nevertheless, higher rates are feasible and may result in smaller tidal volumes and decreased risk for lung injury. The use of HFOV may improve oxygenation in patients with refractory hypoxemia. However, there is not sufficient evidence to conclude that HFOV reduces mortality or long-term morbidity in patients with ALI or ARDS.

8. **HFPV**

HFPV is a flow-regulated, pressure-limited, and time-cycled ventilator that delivers a series of high-frequency (200-900 cycles/min) small volumes in a successive stepwise stacking pattern, resulting in the formation of low-frequency (upper limit, 40-60 cycles/min) convective pressure-limited breathing cycles. Compared with HFOV, only a few studies have investigated the use of HFPV in adult patients with ARDS.
h resulted in sustained improvements in oxygenation. Although possible explanations for better oxygenation include improved chest wall compliance and reduced oxygen consumption, the investigators also reported lower concentrations of pulmonary and systemic proinflammatory cytokines and postulated that NMBAs may blunt the pulmonary inflammation associated with ARDS e.g. atracurium 0.3-0.6 mg/kg

2. Inhaled nitric oxide

   By using an inhaled vasodilator, such as inhaled nitric oxide (iNO), selective vasodilation of the pulmonary blood vessels in ventilated lung units may occur, often resulting in improved ventilation-perfusion mismatch, better oxygenation, and lower pulmonary arterial pressure (PAP). iNO redistributed pulmonary blood flow away from non-ventilated lung zones to ventilated lung regions, thus decreasing intrapulmonary shunting and thereby improving arterial oxygenation, while selectively reducing PAP without causing systemic vasodilation.

3. IV phenylephrine

   Phenylephrine is a nonselective α-receptor agonist, which produces both pulmonary and systemic vasconstriction. In a study of 12 patients with PaO2/ FiO2 > 180 mm Hg, phenylephrine was combined with iNO, this improvement was further accentuated. More work is needed before IV phenylephrine can be endorsed as adjunctive therapy with or without iNO for refractory hypoxemia

4. Inhaled prostacyclins PGE1

   Inhalation of prostacyclins produces selective pulmonary vasodilation, which might improve oxygenation. Aerosol delivery systems for epoprostenol include various pneumatic and ultrasonic nebulizers. Inhaled treprostinil and iloprost have been shown to produce comparable decreases in pulmonary vascular resistance; the type of nebulizer used may also affect the tidal volume delivered. Continuous nebulization of prostacyclin may result in occlusion of the expiratory filters and malfunction of the expiratory valves.

5. Almitrine

   Almitrine bismesylate is a selective pulmonary vasconstrictor that promotes hypoxic vasconstriction when administered intravenously and has been demonstrated to improve oxygenation, particularly in combination with iNO. Almitrine was used infrequently as rescue therapy for refractory hypoxemia in a large European ARDS RCT.

6. Prone position

   Implications of observations
   a. Less overinflation of non-dependent lung
   b. Less airspace opening/closing of dependent lung
   c. Speculation
   d. Less ventilator-induced lung injury

   Placing a patient in the prone position is an adjunctive strategy that has been used to improve oxygenation in patients with severe ARDS, particularly those with refractory hypoxemia. Mechanisms, which include alveolar recruitment, redistribution of ventilation toward the dorsal regions resulting in enhanced ventilation-perfusion matching and the elimination of compression of the lungs by the heart. Another mechanism that has been reported for prone positioning is a decrease in shunt, as a result of better perfusion of previously atelectasis lung regions that are recruited. Both occur as a result of the redistribution of the gravitational forces and the reduction in the pleural pressure gradient in these regions. Prone positioning has been associated with complications that include pressure sores, endotracheal tube obstruction, unplanned extubation, loss of central venous access, and increased use of sedation. Despite these limitations, prone positioning may be considered a reasonable short-term therapy for patients with ARDS requiring high FiO2 (> 60) or elevated plateau pressure (> 30 cm H₂O).

7. Extra-corporeal Life Support

   - Extra-corporeal membrane oxygenation (ECMO)
   - Veno-arterial ECMO (VA-ECMO)
   - Veno-venous ECMO (VV-ECMO)
   - Extra-corpooreal CO₂ Removal (ECCO2R)
   - IVOX (intra-venous oxygenator)

   Extracorporeal Life Support (ECLS)
   - Patients randomized to ECLS transferred to a single center to receive treatment.
   - No standardized management of patients in the control group.
   - Survival in ECLS group 57/90 (63%) vs. 45/90 (50%); P = .11.
Procedure:

An ECMO machine is similar to a heart-lung machine. To initiate ECMO, cannulae are placed in large blood vessels to provide access to the patient’s blood. Anticoagulant drugs, usually heparin, are given to prevent blood clotting. The ECMO machine continuously pumps blood from the patient through a membrane oxygenator that imitates the gas exchange process of the lungs, i.e. it removes carbon dioxide and adds oxygen. Oxygenated blood is then returned to the patient.

ECMO – Problems

• VA-ECMO has adverse cardiopulmonary effects
• Bleeding is excessive
  - 1.76 - 2 L/day of blood loss

ECOM can provide sufficient oxygenation for several weeks, allowing diseased lungs to heal while the potential additional injury of aggressive mechanical ventilation is avoided. It may therefore be life-saving for some patients. However, due to the high technical demands, cost, and risk of complications, such as bleeding under anticoagulant medication, ECMO is usually only considered as a last resort.

8. Conservative fluid management:

Fluid administration increases hydrostatic pressure in the lungs and promotes fluid filtration and edema formation, particularly in states of increased microvascular permeability, such as ARDS. Additionally, the administration of blood products can contribute to circulatory overload or pulmonary edema as a result of ALI (i.e., transfusion-related ALI). Worsening pulmonary edema is associated with progressive hypoxemia. Patients with ARDS generally accumulate about 1 L of fluid per day with conventional management. In RCTs, a conservative fluid management strategy for patients with ARDS or ALI resulted in lower intravascular pressures and higher oncotic pressure, less extravascular lung water, shorter duration of mechanical ventilation, and shorter ICU LOS.

9. Corticosteroid therapy

• Controversial
• Useful in fibrosing alveolitis phase of ARDS
• Is considered in patients with severe disease with resistance prolonged course. Methyl prednisone 2.5 mg/kg/day

10. Nutritional supplementation therapy

There has been accumulating evidence that the use of a nutritional product rich in antioxidants and supplemented with omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and γ-linoleic acid (GLA), can modulate proinflammatory properties in patients with ARDS and septic shock, resulting in improved oxygenation and favorable outcomes.

11. Furosemide Plus Albumin

• Randomized controlled trial
• N = 37 adults with acute lung injury and total protein < 5 g/dL
• Treatment (N = 19)
  - 25 g human serum albumin q8h
  - Continuous IVI furosemide
• Placebo (N = 18)
  - Placebo + placebo

12. Clearance of Alveolar Edema:

• β - agonists
  - Inhaled
  - Intravenous
• Lasix plus albumin
• Atrial natriuretic peptide

13. **Beta-Agonists**
- Clearance of alveolar edema
  - Stimulates Na+-K+-ATPase activity
- Increases secretion of surfactant from Type II pneumocytes
- Anti-inflammatory?
- Appealing
  - No serious side effects
  - Easy to use
  - Inexpensive

14. **Avoid Vasodilators:**
Systemically administered vasodilators can produce hypoxemia for a number of reasons, including altered distribution of pulmonary blood flow due to increases in cardiac output, impairment of hypoxic vasoconstriction as a direct drug effect or as a result of higher mixed venous PO₂, changes in intracardiac pressure or PAP leading to redistribution of pulmonary blood flow, and direct action on pulmonary vascular tone. Nitroprusside, hydralazine, nitroglycerine, nifedipine, dopamine, dobutamine, and other vasodilators can produce this effect.

**Flow chart Non-Ventilatory strategies**

C: **LUNG TRANSPLANT**
In the setting of end-stage lung disease, lung transplantation may be considered in the appropriate patient. In the vast majority of cases, transplantation occurs in patients with progressive chronic lung disease, such as interstitial pulmonary fibrosis or emphysema. Given the time required for candidate evaluation and limited availability of donor organs, lung transplantation is rarely possible in the setting of acute respiratory failure (e.g., severe ARDS). Furthermore, these patients are often critically ill, with other concomitant organ failures precluding their candidacy for transplantation.

Clinical Approach to Refractory Hypoxemia:
- Safety first
- Use things in order of
  - Local experience, cost, and availability
  - Likelihood of worsening other organ failure or complications
  - Experimental trials with fixed endpoints
- Finally, and most importantly,
  - If you are routinely using lung protective ventilation targeting tidal volumes of < 6 ml/kg PBW and Pplat-30 and diuresis

Do not feel like your patients are missing state-of-the-art care if you cannot provide ECMO, iNO, HFO, prone, etc

**The P’s of Refractory Hypoxemia:**
1. PEEP
2. Pee (diuresis)
3. Prone
4. Paralysis
5. Pleural evacuation
6. Prostacyclin (or iNO)
7. More Peep

**Author’s Experience and Strategy Recommendations**
**Therapeutic Strategy for Severe Acute Respiratory Distress Syndrome (ARDS) With Refractory Hypoxemia**

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<thead>
<tr>
<th>Intervention</th>
<th>Special Considerations</th>
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<tbody>
<tr>
<td>Heavy sedation and neuromuscular blockade</td>
<td>Consider for patient-ventilator asynchrony</td>
</tr>
<tr>
<td></td>
<td>Low cost and widely available</td>
</tr>
<tr>
<td>Risk of delirium from heavy sedation</td>
<td>Risk of prolonged weakness from neuromuscular blockade</td>
</tr>
</tbody>
</table>

<p>| Higher positive end-expiratory pressure or recruitment maneuvers | Easily done with conventional mechanical ventilators |
| Low cost and widely available |
| Risk of barotrauma and hypotension |</p>
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Special Considerations</th>
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</table>
| 3 Prone positioning                  | No special equipment required  
Low cost and widely available  
Risk of local complications (e.g., pressure sores, facial edema)  
Difficulty performing routine nursing care while patient is prone |
| 4 High-frequency oscillatory ventilation | Consider early application if oxygenation improves with higher positive end-expiratory pressure or recruitment maneuvers  
Requires special ventilator and expertise |
| 5 Inhaled nitric oxide               | Consider if associated pulmonary hypertension  
Change in dose-response curve over time  
May not be widely available  
Expensive |
| 6 Extracorporeal membrane oxygenation | Ability to use lower tidal volumes and airway pressures for lung recovery  
Requires systemic anticoagulation  
Expensive  
Highly invasive  
Requires expertise |

REFERENCES