VENTILATORY THERAPY AND ACUTE LUNG INJURY

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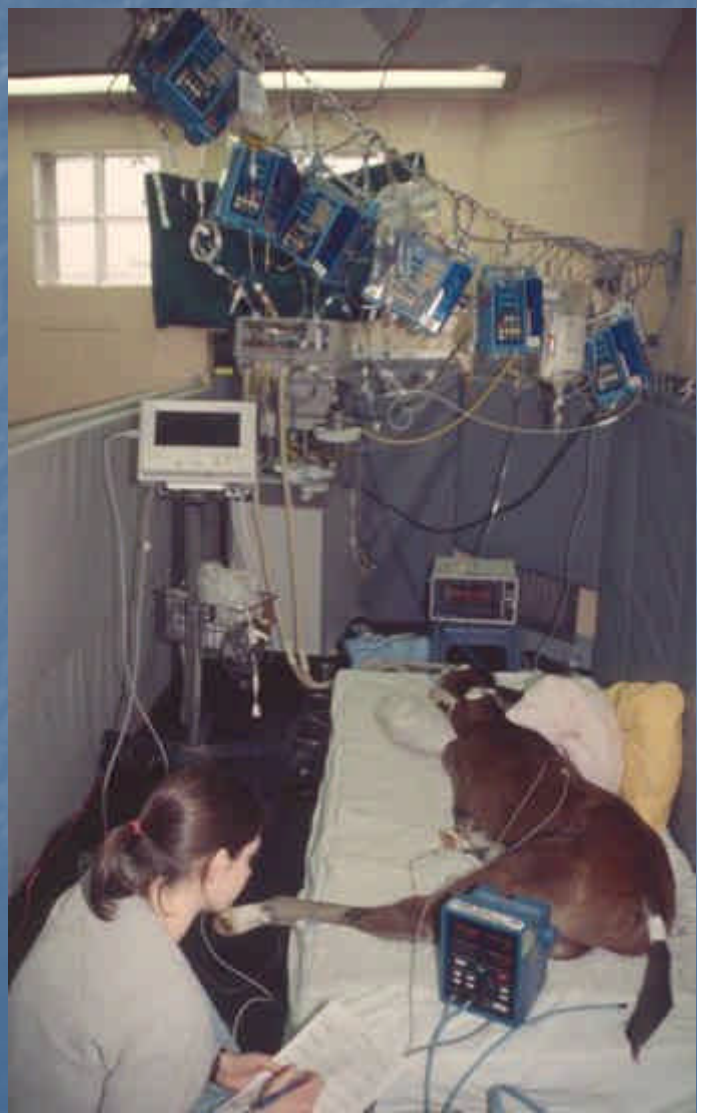
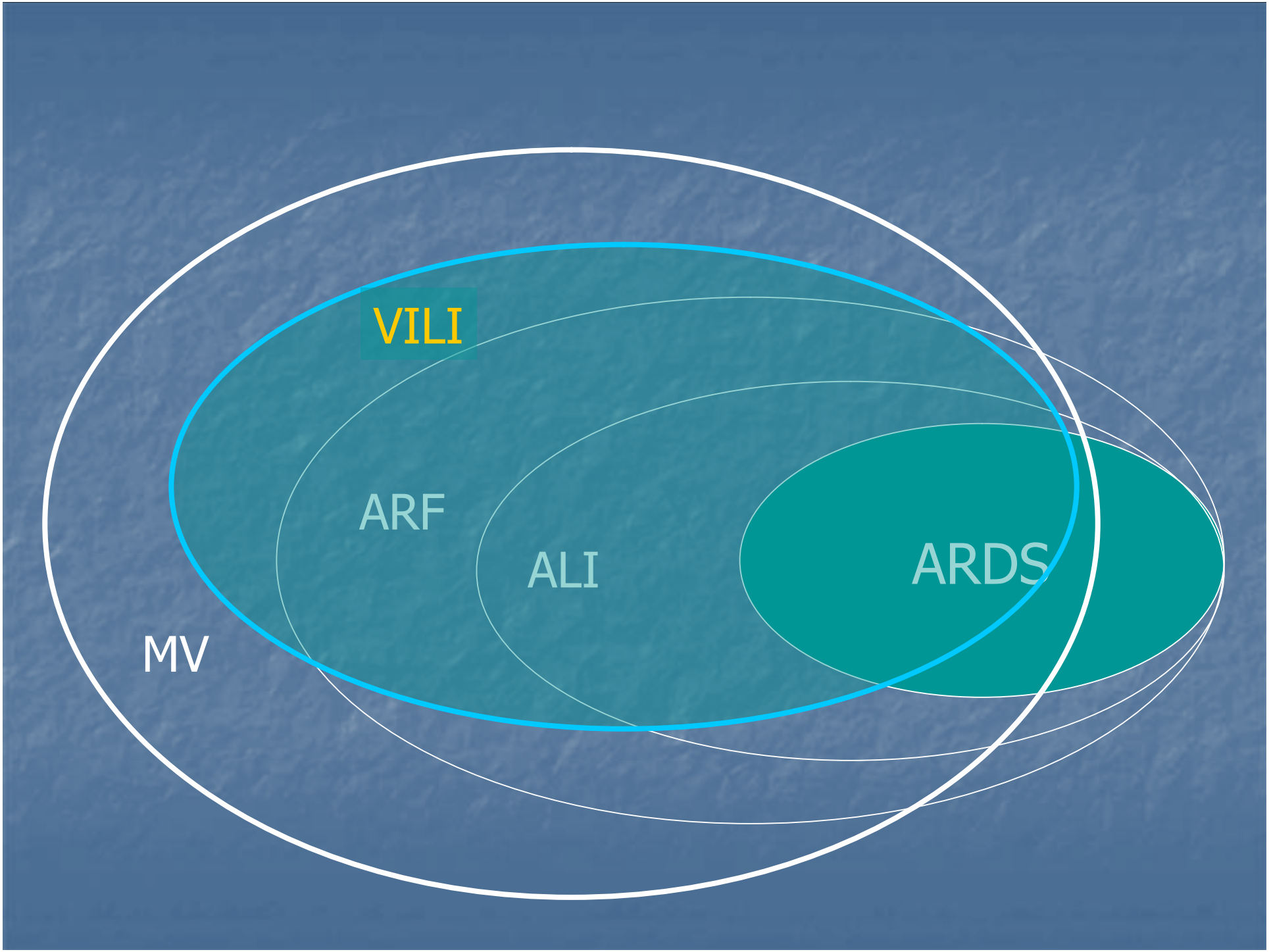
Acute Respiratory Failure

- Causes Acute Respiratory Failure
  - Many such as
    - Neurologic
    - Neuromuscular
    - Obstructive
  - Parenchymal disease most difficult to treat
- Causes of parenchymal disease
  - Organ dysfunction secondary to
    - Septic shock
    - Other shock - hemorrhagic, anemic, hypoxemic
  - Infectious pneumonia
    - Viral, bacterial, aspiration pneumonia
  - Non-infectious pneumonia
    - Meconium aspiration, interstitial pneumonia, aspiration pneumonia
  - Trauma secondary to fractures ribs

Acute Respiratory Failure

- Acute Lung Injury (ALI)
  - Acute onset
  - Pao2/Fio2 < 300
  - Radiographic evidence of pulmonary infiltrates
  - No evidence of cardiac failure
- Controversial expanded definitions
  - ALI
  - Distinction between ALI and ARDS
- ALI
  - Inflammation/remodeling
  - Alter lung structure and function
  - Respiratory failure – hypoxemia and hypercapnia
- Goal of therapy
  - Provide respiratory support
  - Treat underlying disease

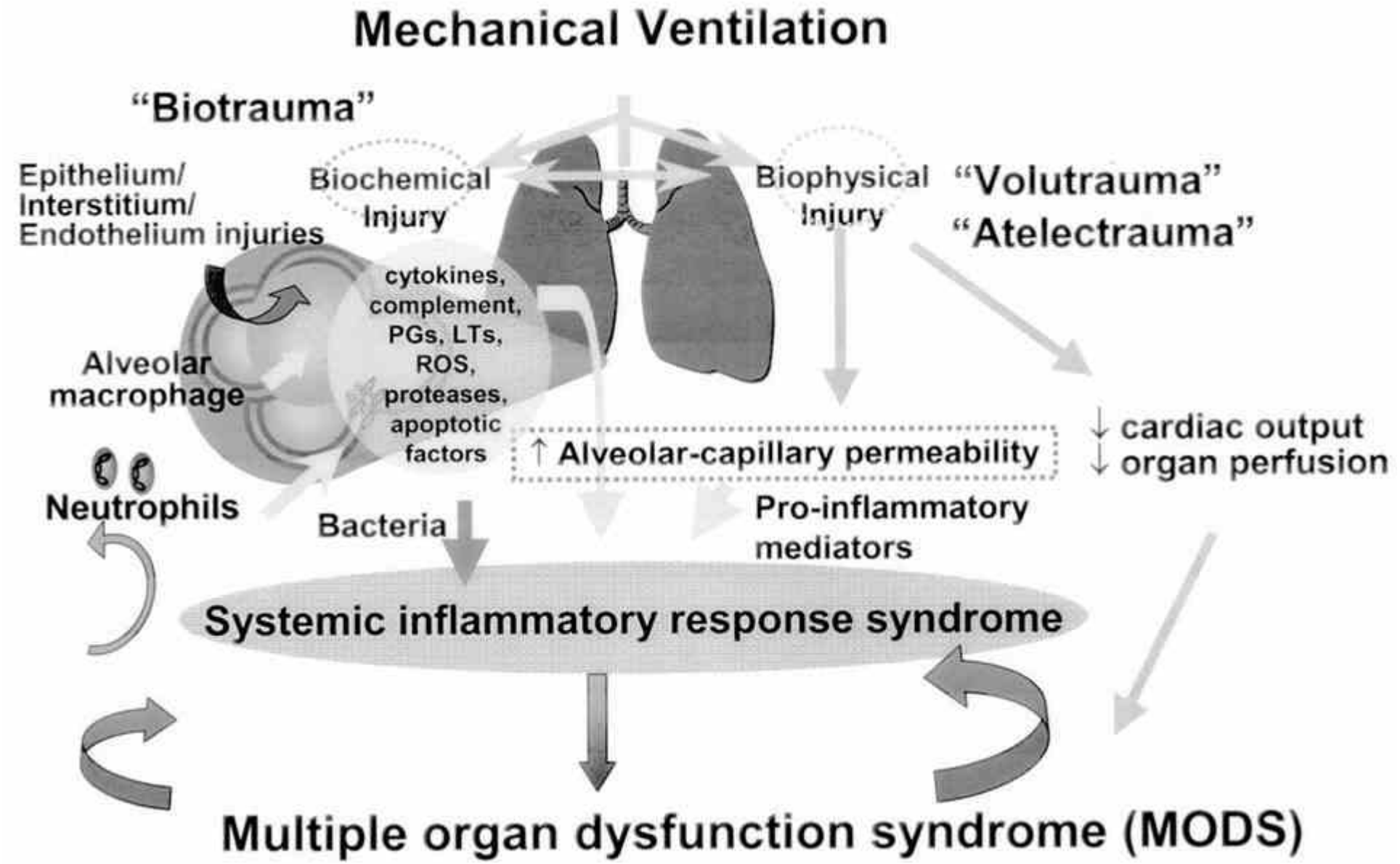



VILI
ARF
ALI
ARDS
MV

Ventilatory-Induced Lung Injury (VILI)

- Mechanical ventilation
  - Secondary lung injury – VILI
  - 3 mechanisms
    - Volutrauma
    - Atelectrauma
    - Biotrauma
- Volutrauma
  - Alveolar overexpansion
  - High lung volume (independent of pressure)
- Atelectrauma
  - Repetitive alveolar recruitment-derecruitment (R/D)
- Biotrauma
  - Cytokine induced injury
    - Released in response to mechanical injury

VILI


Mechanical Ventilation
"Biotrauma"
Epithelium/
Interstitium/
Endothelium injuries
Biochemical
Injury
Biophysical
Injury
"Volutrauma"
"Atelectrauma"
cytokines,
complement,
PGs, LTs,
ROS,
proteases,
apoptotic
factors
Alveolar
macrophage
↑ Alveolar-capillary permeability
↓ cardiac output
↓ organ perfusion
Neutrophils
Bacteria
Pro-inflammatory
mediators
Systemic inflammatory response syndrome
Multiple organ dysfunction syndrome (MODS)

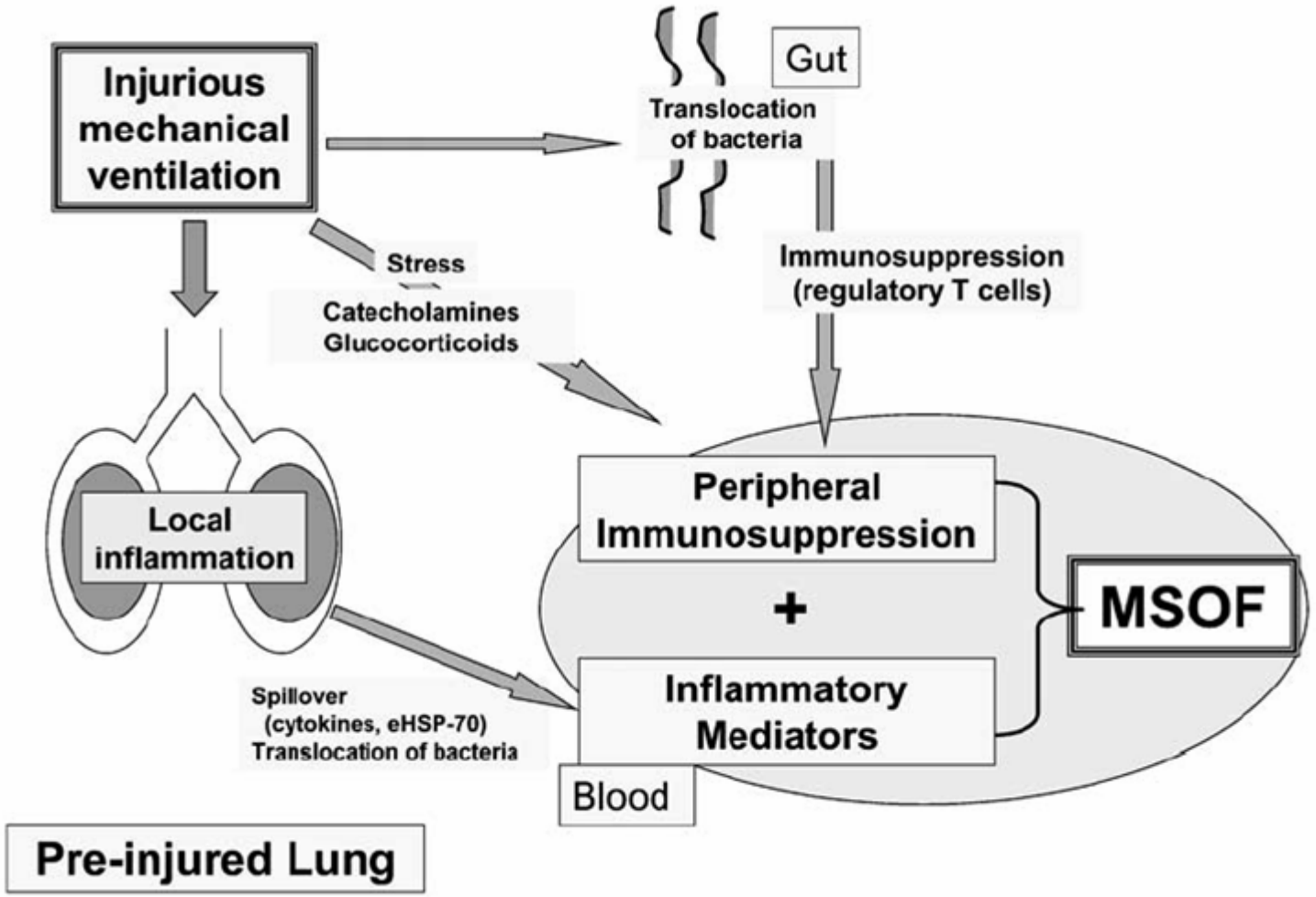
Ventilatory-Induced Lung Injury (VILI)

- Normal alveoli
  - Stable
  - Undergo small changes in size during ventilation
  - Unless they totally collapse or reexpand
  - Collapse and expansion
    - Folding/unfolding alveolar septa
- ALI
  - Large changes in alveolar size
  - Widespread alveolar recruitment-derecruitment R/D
    - Cause a significant shear stress-induced lung injury

Ventilatory-Induced Lung Injury (VILI)

- High PIP and low PEEP
  - Alveolar recruitment-derecruitment
  - Cause VILI in normal lungs
    - Abnormal mechanical forces - atelectrauma
      - Gross tearing of the alveolar walls
      - Destruction of epithelial cells
      - Denuded basement membrane
      - Gaps in capillary endothelium
    - Secondary biotrauma
      - Release of inflammatory mediators

Biotrauma and MSOF



From: Pltz et. al. Intensive Care Med (2004) 30:1865–1872

Strategies for ARDS Prevention and Therapy

Ventilation strategies
- 6 mL/kg tidal volume (67.9, 15.6, 6.4, 10.1)
- Pressure-regulated volume control (23.2, 35.2, 13.9, 27.8)
- PEEP at best lung compliance (21.5, 34.6, 20.6, 23.4)
- PEEP >15 cm H_2O (9.2, 39.5, 33, 18.4)
- Prone position (9.1, 52.7, 22.7, 15.5)
- Inverse ratio ventilation (5.546.4, 28.2, 20)
- CPAP lung recruitment maneuvers (8.4, 26.2, 22.4, 43)
- Airway pressure release ventilation (2.8, 7.3, 21.1, 68.8)
- High-frequency oscillation (0.9, 15.9, 19.1, 64.6)
- Jet ventilation (0, 14.6, 20.9, 64.6)
- Tracheal gas insufflation (0, 6.4, 11.9, 81.7)

Ventilator-delivered therapies
- Nitric oxide (2.8, 35.8, 14.7, 46.8)
- Surfactant therapy (0, 9.1, 12.7, 78.2)
- Prostaglandin therapy (0, 4.6, 11.8, 83.6)

Antiinflammatory medications
- Prophylactic systemic steroids (1.9, 8.4, 7.5, 82.2)
- Therapeutic, high-dose, early systemic steroids (3.7, 4.6, 9.2, 82.6)
- Steroids for refractory ARDS (5.5, 41.8, 20, 32.7)
- Prophylactic ketoconazole (5.6, 11.1, 17.6, 65.7)
- Therapeutic ketoconazole (1.8, 6.4, 8.2, 83.6)
- Indomethacin (0, 1.8, 10.9, 87.3)
- Prophylactic ibuprofen (0, 0.9, 10.4, 88.7)

Antioxidant medications
- Prophylactic *N*-acetyl-cysteine (0, 1.9, 2.8, 95.3)
- Therapeutic *N*-acetyl-cysteine (0, 1.8, 5.5, 92.7)
- Vitamin E (0, 0.9, 2.7, 96.4)
- Pentoxifylline (0, 0, 3.6, 96.4)

Fluid/hemodynamic management
- Daily negative fluid balance (40, 40, 10, 10)
- Pulmonary arterial catheter (24.1, 57.4, 13.9, 4.6)
- Intravenous colloid (8.2, 37.3, 30.9, 23.6)
- Continuous renal replacement therapy (2.8, 36.5, 18.7, 42.1)

Nutritional strategies
- Low-CHO, high-fat diet (1.9, 8.3, 16.7, 73.2)
- Medium chain lipid diet (0.9, 9.4, 16.8, 72.9)

Miscellaneous
- Therapeutic kinetic bed rotational (12.2, 30.8, 17.8, 39.3)
- Prophylactic kinetic bed rotation (1.9, 15.1, 20.8, 62.3)
- ECMO (0, 3.6, 14.6, 81.8)
- Aprotinin (0, 0, 2.7, 97.3)

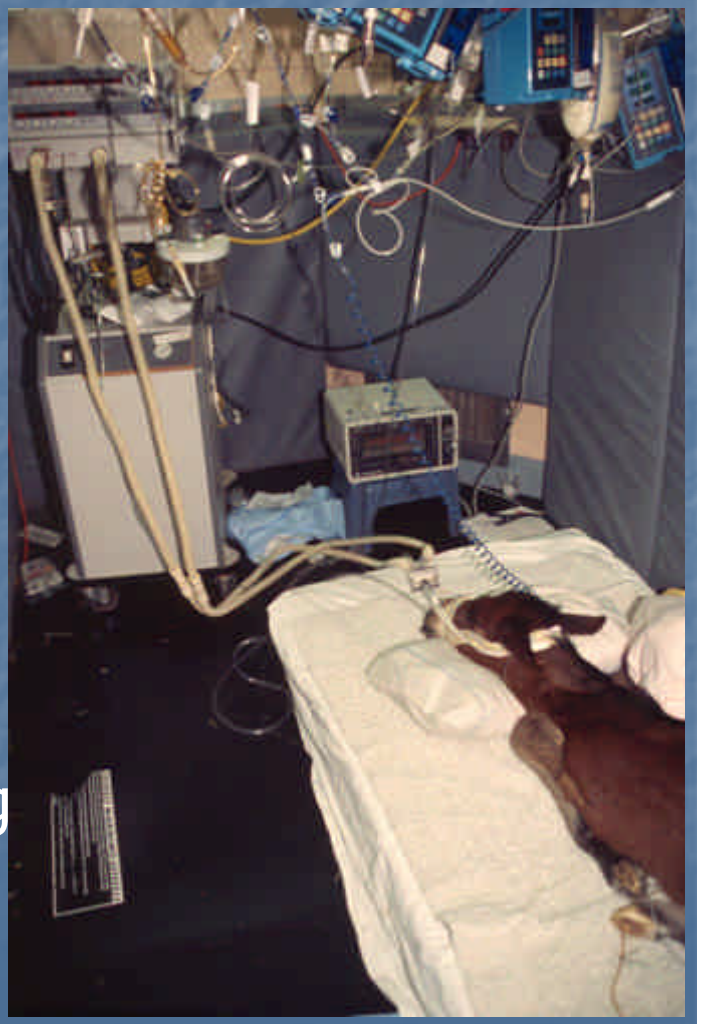
From: Meade: Crit Care Med, Volume 32(4).April 2004.946-954

Lung Protective Ventilation Techniques

- Small TV, relatively high PEEP
  - Stabilize alveoli
  - Protect lung from damage
  - Small TV proven beneficial
- Recruitment maneuver followed by PEEP
  - Unproven effect – commonly suggested
  - Alveoli recruited often recollapse
  - High PEEP after RM
    - Prevented alveolar recollapse
    - Stabilize recruited alveoli
    - Beneficial??

Tidal Volume

- Important in VILI
- Original recommendation
  - 10-15 ml/kg
  - Normalize pH, acceptable Pao_2
- ALI
  - Volume of aerated lung reduced
    - Edema
    - Atelectasis
    - Consolidation
  - Over distend normal aerated lung
    - Causes VILI



Tidal Volume

- Low volume/low pressure ventilation strategy
- ARDS Network trial
  - 6 ml/kg vs 12 ml/kg TV - lower fatality rate
  - Interpretation questioned
- 5 studies with low TV
  - 3 studies, not improved clinical outcomes
  - 4th study – small, also used high PEEP, recruitment maneuvers
  - 5th study ARDSNet
  - 3 studies were stopped early
    - 2 stopped because of futility - biased toward failure
    - 1 stopped because of benefit - biased toward success
- High TV normal lungs
  - Predispose to VILI

Tidal Volume

- Despite evidence
  - Physicians have not fully embraced
    - 5% of ARDS patients ventilated with recommended TV
    - Decrease in TV before study released – early 90s
  - Low TV have associated with systemic problems
    - Meta analysis showed lower survival rate with low TV
    - Greater incidence of renal failure with low TV
    - May be detrimental overall

Tidal Volume

- Species differences
  - Dangerous to extrapolate critical ml/kg TV from one species to another
- High TV detrimental because volutrauma
- What TV should be used in foals?
  - 6 – 9 ml/kg?
  - Use PIP as guide - < 30 cm H_2O
  - Approach needs to be individualized

Tidal Volume

- Stacking breaths
  - Conscious, non-sedated foals
  - Ventilated using 6 ml/kg
  - Stack 2 breaths
    - Effective tidal volume 12 ml/kg
  - Can go undetected
- Use of sedation
  - Associated complications
  - Not needed for ventilation

Permissive Hypercapnia

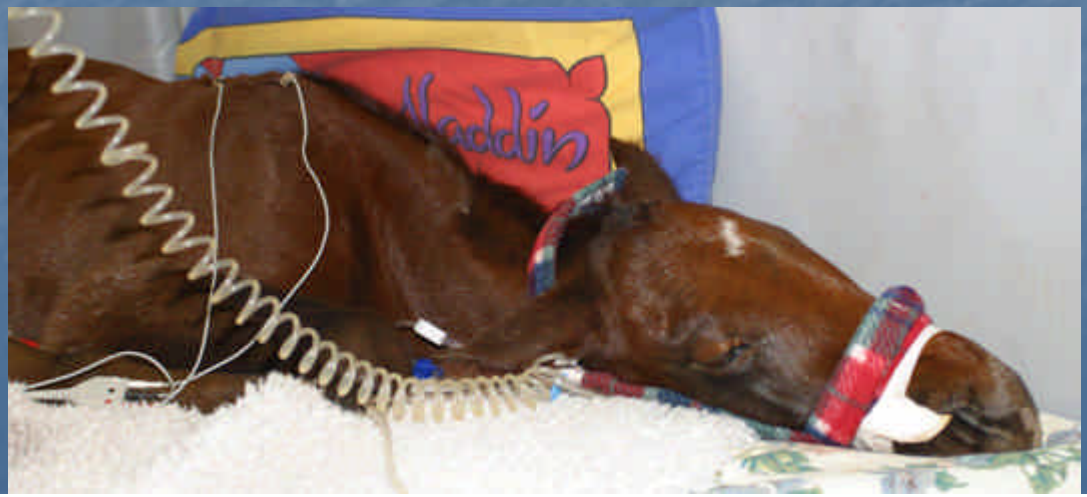
- Critically ill foals
  - Often have abnormal acid base balance
  - Significant metabolic alkalosis
  - $Paco_2$ often 55-60
    - Appropriate keeping pH > 7.35
    - Normal pH in foals 7.35-7.40
  - Target $Paco_2$ - returns the pH to the normal value
  - This is not permissive hypercapnia

Permissive Hypercapnia

- Permissive hypercapnia
  - Allowing high $Paco_2$ despite acid pH
  - Maintain pH > 7.20 but not necessarily > 7.35
  - Avoiding lung trauma
  - Higher priority than normal pH:
    - Low TV – avoid stretch
    - Optimal expiratory time – avoid auto-PEEP
    - High PEEP – "open lung"
  - Only needed if significant underlying lung injury

PEEP/CPAP

- Pulmonary mechanics
- Cardiovascular stability
- Pulmonary vascular resistance



PEEP/CPAP
FRC

- FRC in health - almost all alveoli open
- Weak/fatigued, FRC significantly reduced
  - Alveoli collapse during expiration
  - Must open on each breath
    - Alveoli repeatedly close
      - Shear stress injury
      - Breakdown surfactant
    - More difficult to open these alveoli
      - Atelectasis results
    - Further decreases the compliance
      - Collapse of more alveoli
    - **Progressive atelectasis**

PEEP/CPAP

- Positive airway pressure during expiration
  - Alveoli stay open
  - On each new inspiration
    - Alveoli recruited
    - Full recruitment requires 15-20 min
- Optimal PEEP/CPAP
  - Ideal volume
    - Optimum compliance
    - Low airway resistance

PEEP/CPAP

- Injury is heterogeneous
  - Optimizing PEEP is a balance
    - Open recruitable alveoli in diseased regions
    - Without over distending healthier regions
- Another potential detrimental effect of PEEP
  - Raises mean and peak airway pressure
  - Contributes to volutrauma

PEEP/CPAP Cardiovascular Stability

- High PEEP/CPAP
  - Compress right sided vessels
  - Decreasing cardiac return
  - Decreased cardiac output
- PEEP/CPAP level needed
  - Depends on the lung compliance
  - Depends on the state of volemia

PEEP/CPAP
Pulmonary Vascular Resistance

- Pulmonary perfusion
  - Modified by alveolar fill (PEEP/CPAP)
  - Collapsed/poorly distended
    - Increased pulmonary resistance
  - Ideally distended
    - Less pulmonary resistance
  - Over distended
    - Increased pulmonary resistance
- Optimal PEEP/CPAP will optimize the V/Q ratio

High PEEP Protocols

- Experimental studies
- Ventilation strategies
  - Included high PEEP levels
  - Better survival
  - Lower levels of inflammatory mediators
- Clinical protocols
  - Low TV
  - Low PIP
- PEEP or low volume/pressure

High PEEP Protocols
ARDS Cases

- PEEP – ARDS Net trial (549 patients)
  - Keeping TV low (6 ml/kg), PIP < 30
  - PEEP levels
    - Low level initially 9 dropping to 8
    - High level initially 16 dropping to 13
    - PEEP set by arterial-oxygenation response (PEEP–FiO2 settings)
- No difference
  - Survival rate
  - Duration of ventilation
  - Duration of ICU care
  - Duration of organ failure
  - Level of inflammatory mediators

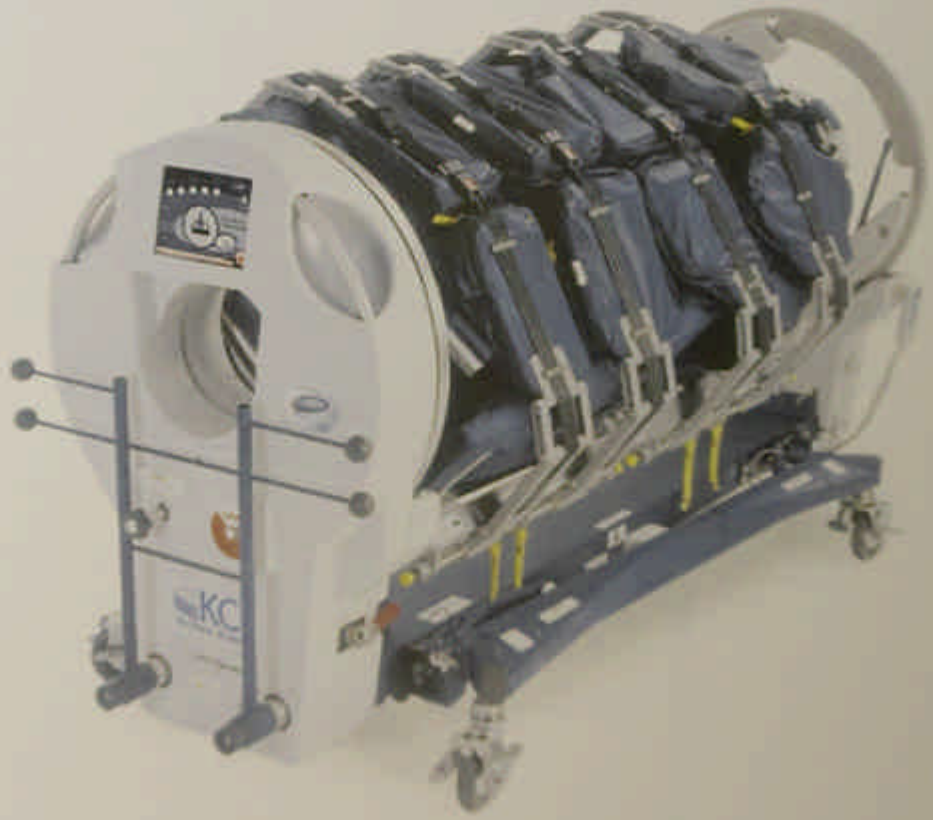
Recruitment Maneuvers

- CPAP 40 cm H_2O for 40 sec
- Intermittent Sighs
  - P_{plat} = 45 cm H_2O
  - PIP = 40 cm H_2O for 6 sec
  - PEEP = 35 cm H_2O
- Stepwise increase PEEP
- ARDS Net Trial
  - 80 patients higher-PEEP group
  - Recruitment maneuver
    - Single sustained inflation high airway pressure and volume
    - Airway pressure of 35 - 40 cm H_2O for 30 sec
  - Increase in Pao_2 - small and transient

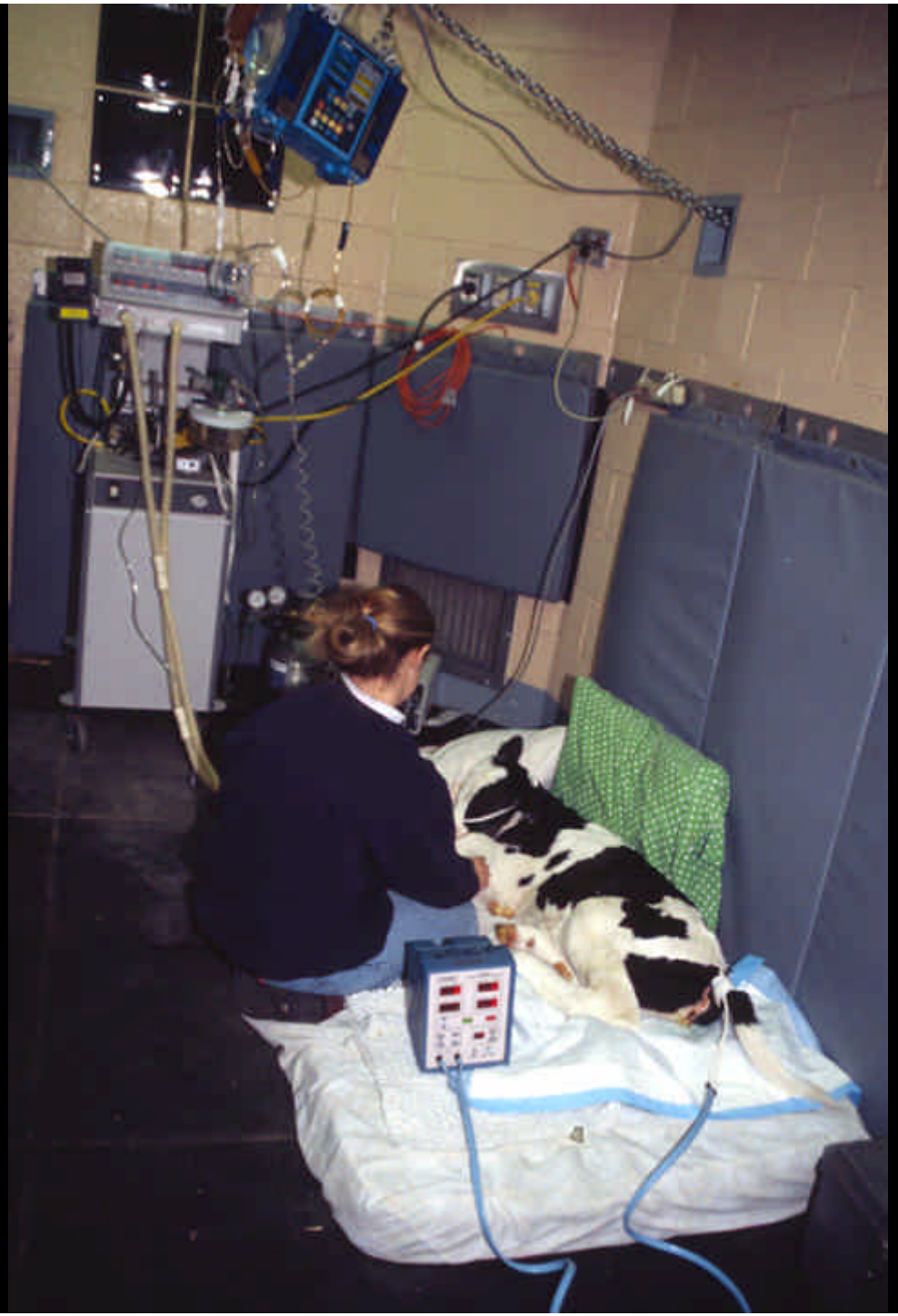
Other Ventilator Associated Therapies

- NO therapy
  - Low NO (5 ppm)
  - Transient improvement in $Pa0_2/FIO_2$
  - No change in outcome
- Surfactant
  - Transient improvement in $Pa0_2/FIO_2$
  - No change in outcome
- Use of prone positioning
  - Initial improvement in $Pa0_2/FIO_2$
  - Controversial
  - Not much help in survival

PRONE THERAPY IS NOW ALMOST AS EASY AS PUSHING A BUTTON.



THE ROTOPRONE® THERAPY SYSTEM.



Monitoring During Ventilation Capnography

- Used continuously during ventilation
- $ETCO_2$ depends on
  - $Paco_2$
  - CO_2 production
    - Metabolic rate
    - Bicarbonate therapy
  - Cardiac output
  - Alveolar dead space ventilation
    - Pulmonary perfusion
  - Airway time constants

Monitoring During Ventilation Capnography

- Capnography can be used to determine
  - Adequacy of alveolar ventilation
  - Cardiac output
  - Pulmonary blood flow
    - During CPR
  - Proper functioning of the ventilator
    - Rebreathing of CO_2
  - Patency and placement of endotracheal tube
  - Endotracheal cuff integrity

Monitoring During Ventilation Capnography

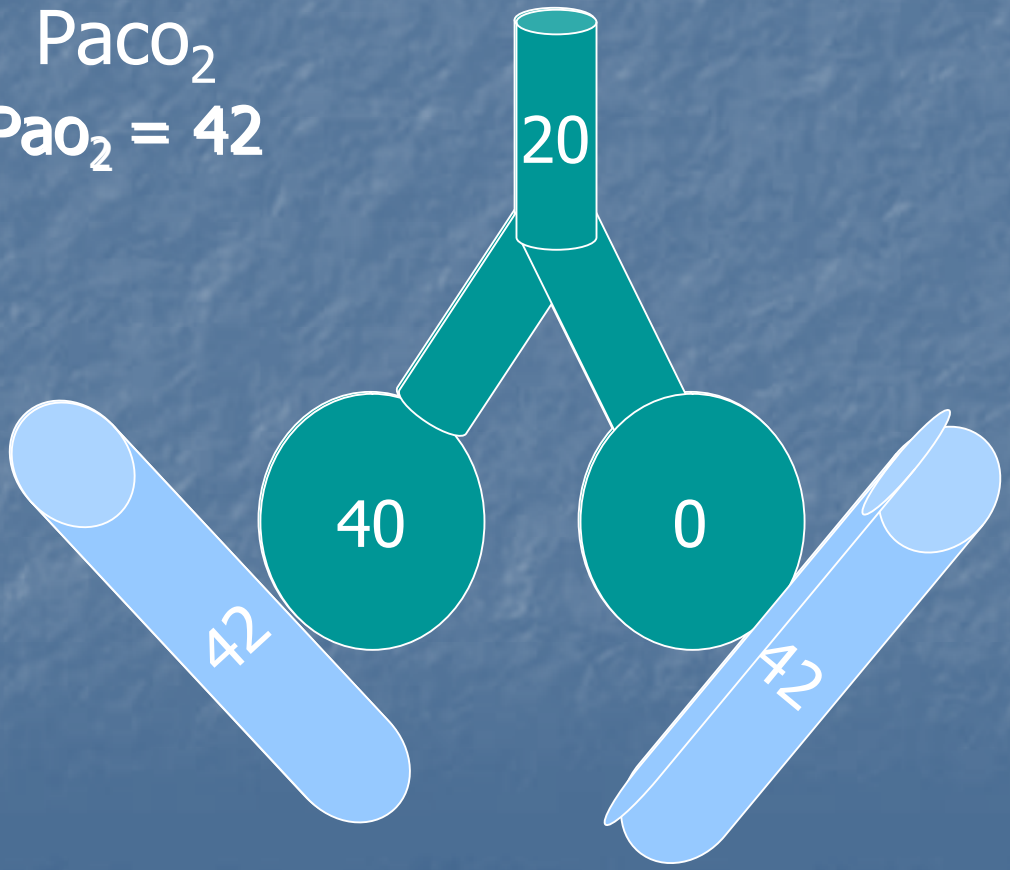
- $Paco_2$ is determined by
  - Pco_2 of all perfused alveoli
- $ETCO_2$ represents the
  - Pco_2 of all ventilated alveoli
- $Paco_2$ - $ETCO_2$ gradient
  - V/Q abnormalities
- Alveolar dead space ventilation
  - Volume of alveoli that are ventilated but not perfused
  - Failure of pulmonary perfusion
    - Secondary to decreased CO
    - Secondary increased pulmonary vascular resistance

Alveolar Dead Space

$$ADV = \frac{Paco_2 - ETCO_2}{Paco_2}$$

$ETCO_2 = 40$

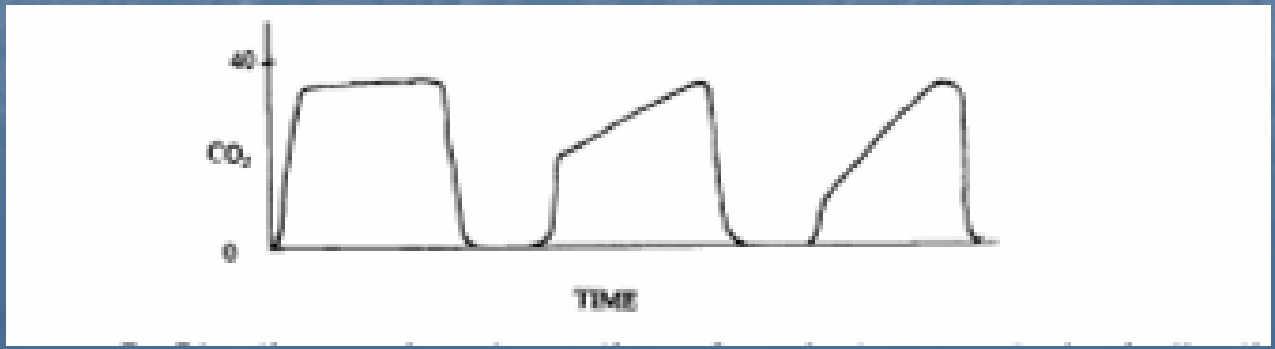
$Pao_2 = 42$



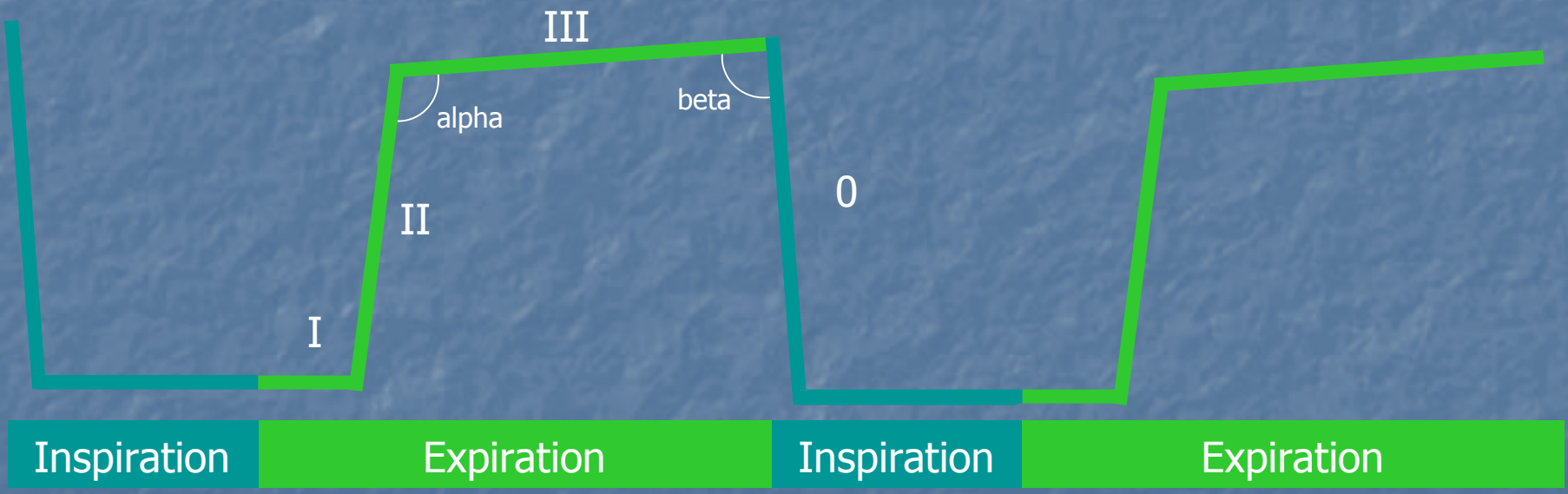
Monitoring During Ventilation Capnography

- $Paco_2$ - $ETCO_2$ gradient – not ADV
  - Long time constants
    - $ETCO_2$ is CO_2 in last alveoli to empty
    - Less ventilation
    - $ETCO_2 > Paco_2$
    - $Paco_2$-$ETCO_2$ gradient < ADV
    - Slope of phase III

Monitoring During Ventilation
Time Capnography



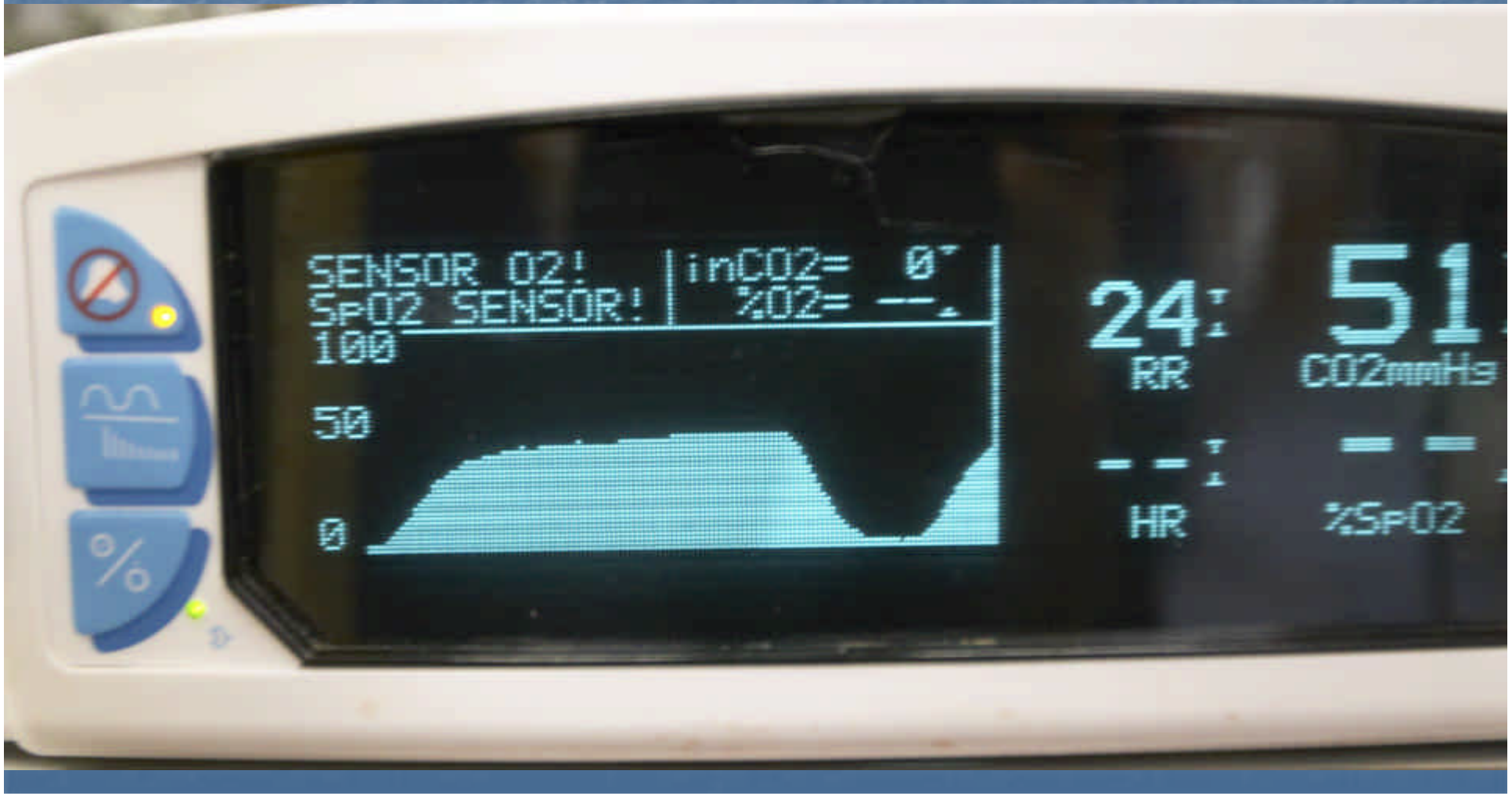
Monitoring During Ventilation
Time Capnography



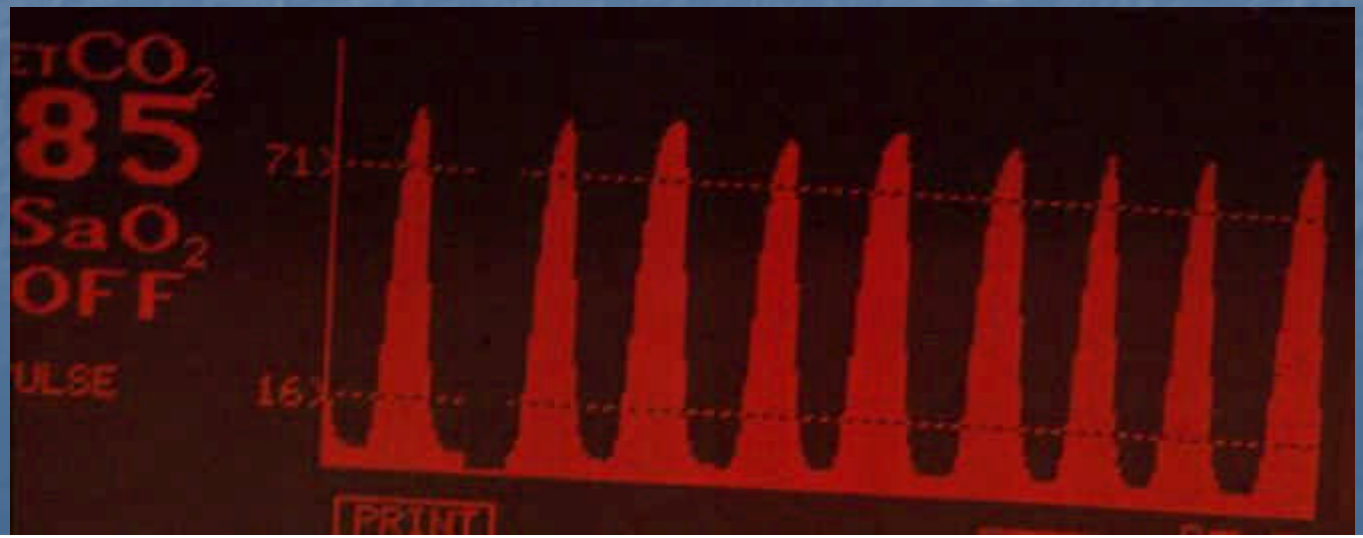
Monitoring During Ventilation Capnography

- Prolonged, sloped upstroke (II), no plateau
  - Bronchospasm
  - Obstructive pulmonary disease
  - Kinked endotracheal tube
  - Leaks in breathing circuit
- Slope to plateau (III)
  - All cases
    - CO2 excreted, alveoli progressively smaller
    - Range of V/Q ratios, variation of time constants
  - Changes which can change regional V/Q
    - Changes in CO
    - Changes in CO2 production
    - Changes in airway resistance
    - Changes in FRC
  - Steep slope indicates abnormalities V/Q mismatch
    - If extreme – $ETCO_2 > Paco_2$

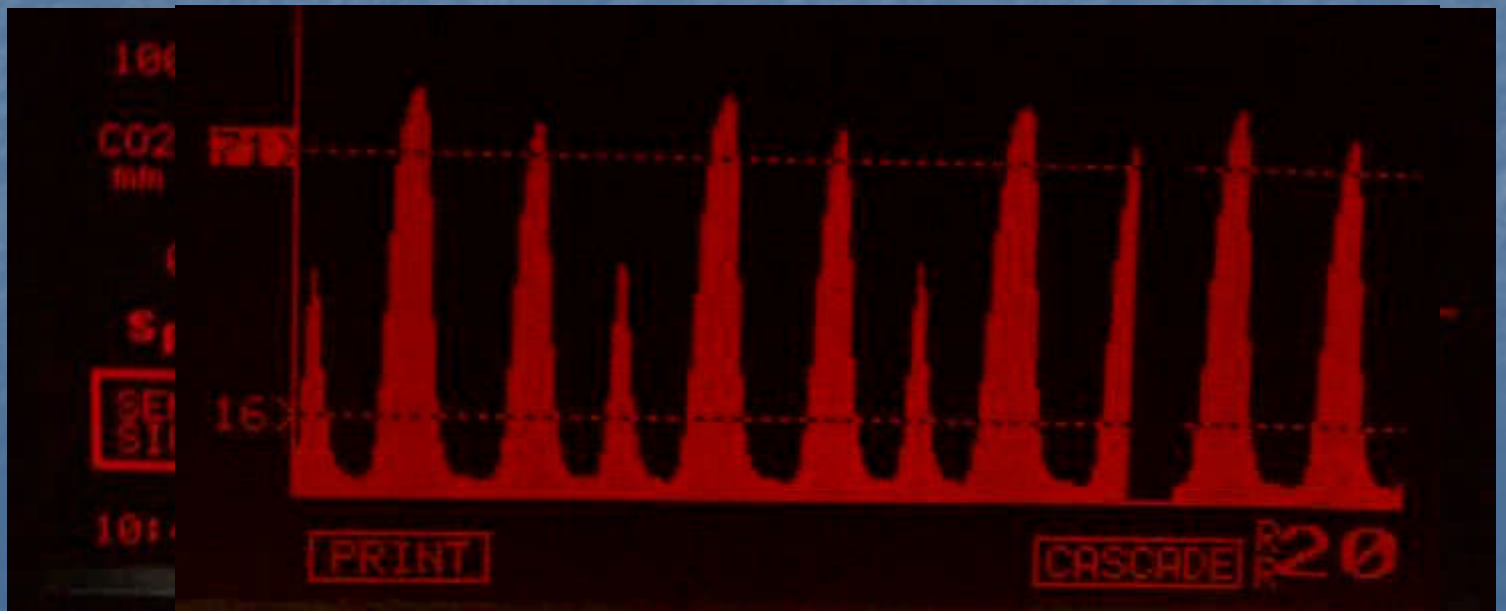
Capnography
Slope Phase III



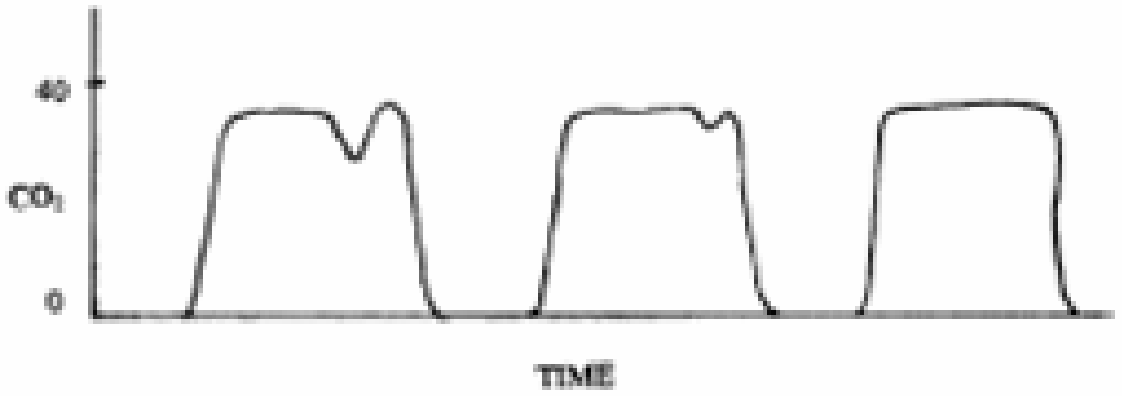
Capnography
No Plateau



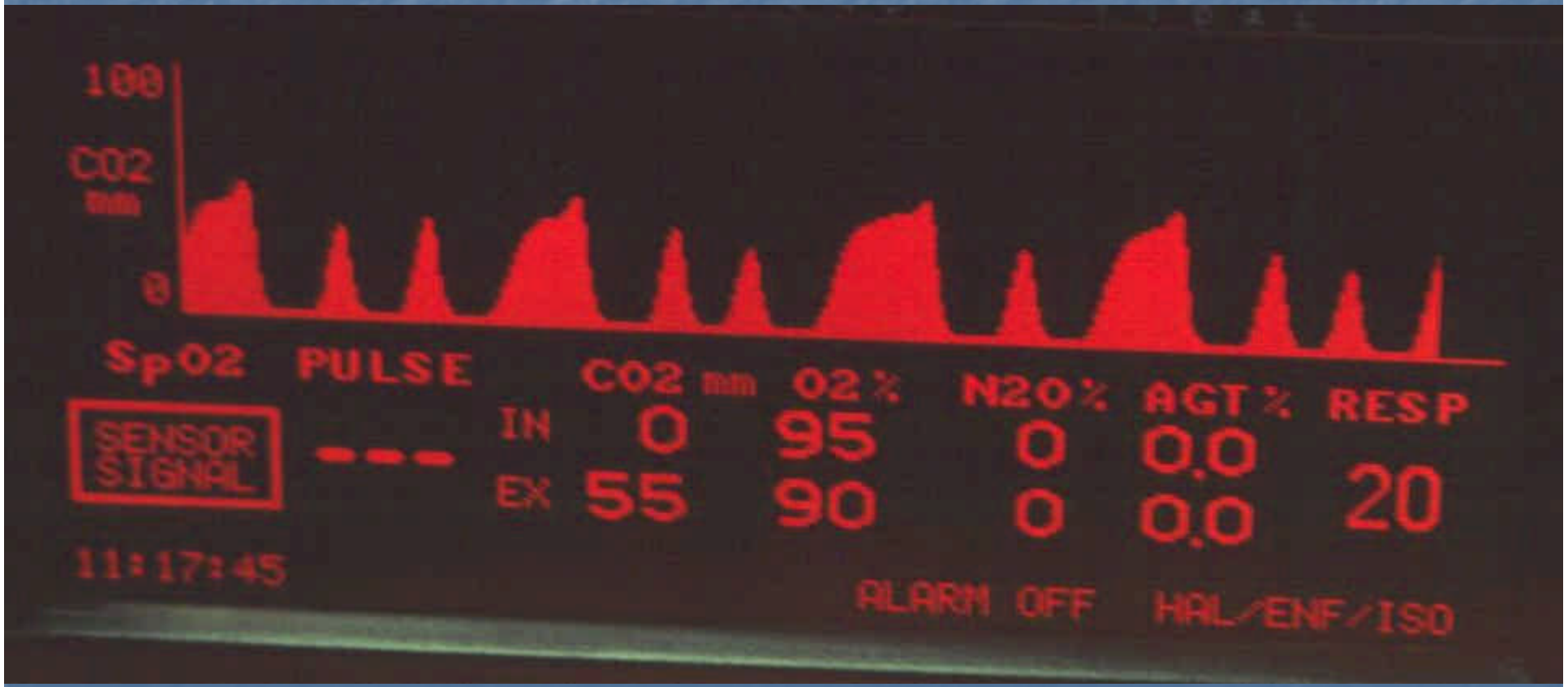
Capnography
Wave Variation



Capnography
Curare Notch



Capnography
Uneven V/Q



VENTILATORY THERAPY AND ACUTE LUNG INJURY

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Acute respiratory failure as the result of parenchymal disease is the most difficult to successfully treat. There may be many causes of severe pulmonary parenchymal damage such as organ dysfunction secondary to septic shock or other shock (hemorrhagic, anemic, hypoxemic, etc.), infectious pneumonia (viral, bacterial, aspiration pneumonia), non-infectious pneumonia (meconium aspiration, interstitial pneumonia, aspiration pneumonia) and trauma secondary to fractures ribs. The resulting pulmonary failure can be classified as Acute Lung Injury (ALI) if it has an acute onset, $Pao_2/F_{IO2} < 300$, radiographic evidence of pulmonary infiltrates and no evidence of cardiac failure. There are expanded definitions of ALI and the distinction between ALI and its most severe form, Acute Respiratory Distress Syndrome (ARDS), remains controversial and are beyond the scope of this discussion. No matter what the cause of ALI, typically the goal is to provide respiratory support while therapies for underlying causes of the acute event are initiated.

The benefits of mechanical ventilation include improvement of gas exchange by increasing ventilation, improvement of ventilation-perfusion (V/Q) matching and decrease of intrapulmonary shunt fraction. Less well appreciated are the benefits of decreasing the work of breathing in cases of pulmonary failure especially secondary to septic shock. With normal quiet breathing, inhalation is an active process requiring energy, utilizing 3% to 5% of the oxygen the patient consumes. Exhalation is a passive process that requires no energy. When patients experience respiratory distress, as occurs with primary lung disease or septic shock, oxygen consumption required for the work of breathing increases up to 50% of the available oxygen and diverts perfusion resources as accessory muscles are recruited. Relieving this work of breathing will allow redistribution of these oxygen and perfusion resources to support vital organ function. Respiratory support through mechanical ventilation is an important therapeutic modality in treating septic shock.

Pulmonary hypertension is an important sequela to many cases of ALI. Increased pulmonary vascular resistance can be mediated by inflammatory mediators as well as severe hypoxemia common with ALI. Pulmonary hypertension has added significance in the neonate since often as pulmonary pressure rises, right to left shunting will occur through the foramen ovale and ductus arteriosus as these structures are not permanently close for up to 3 weeks or more after birth. Thus reversion to fetal circulation will further complicate the hypoxemia and must be addressed to achieve successful correction of the respiratory failure. Actually, there is an adaptive advantage in the ability of the neonate to regress to the fetal circulatory pattern. If pulmonary hypertension is excessive, the only way to achieve adequate systemic cardiac output is shunted blood. The neonate's unique ability to exist in a hypoxemic state and its ability to regain cardiac output with pulmonary hypertension by shunting, allows compensation and the ability to survive pulmonary hypertension without generalize systemic ischemic episodes.

In cases with very low P_{ao_2} values despite high intranasal oxygen flows, a trial with a F_{Io_2} of 1.0 can be useful diagnostically in identifying the source of the hypoxemic response. If the P_{ao_2} is less than 100 torr after 15 to 20 minutes of ventilation with a F_{Io_2} of 1.0 then it is very likely that the cause of the hypoxemia is a large cardiac shunt rather than an intrapulmonary problem. In most of these cases, the P_{ao_2} is often between 20 and 45 torr and only increases 2 or 3. This clinical rule of thumb has been very accurate in my hands predicting the presents of either persistent fetal

circulation with pulmonary hypertension and a large fraction of right to left shunting or a significant cardiac malformation resulting in the same. Also, reversion to fetal circulation can easily be detected by this method.

Pulmonary hypertension may be present before ALI because of failure to make the birth transition associated with an imbalance of pulmonary vasodilators and vasoconstrictors such as nitric oxide and endothelin, or arise from regression to fetal circulation due to perinatal hypoxemia or cytokine showers or it can be secondary to pulmonary disease, septic shock or development of ALI. The usual approach to treating pulmonary hypertension is to maximize pulmonary exposure to oxygen through ventilation with 100% oxygen, alkalinize the arterial pH with mild hyperventilation or treatment with bases and maintaining systemic blood pressure to counterbalance the increasing pulmonary pressure. The existence of ALI will frustrate many of these approaches. The advent of inhaled nitric oxide (NO) therapy has revolutionized the treatment of neonatal pulmonary hypertension, appears to be effective in the large animal species and can be an important adjuvant in the treatment of ALI. Inhaled nitric oxide at rates as low as 5 to 10 ppm can result in a dramatic reversal of pulmonary hypertension in some cases. One problem with NO is that it can cause significant pulmonary toxicity through the production of free radicals in the presents of high oxygen concentrations, but at low concentrations this appears to be a rare complication. Nitric oxide causes pulmonary vasodilation by increasing cGMP levels which causes relaxation the smooth muscle of the pulmonary vasculature. Recently, type V phosphodiesterase inhibitors which selectively prevent cGMP destruction have been developed. Thus, either endogenous nitric oxide or pulses of exogenous nitric oxide can be utilized to increase cGMP levels resulting in vasodilation and the phosphodiesterase inhibitors can be utilized to maintain vasodilation for a prolonged period of time. This results in a decrease in exposure to nitric oxide and simplification of therapy since continuous NO delivery is no longer necessary. Although there are a number of phosphodiesterase inhibitors available with more or less pulmonary selectivity, we have had some success using sildenafil using a dose of 0.5-2.5 mg/kg. Although it is too early to predict the success or anticipate the complications of this therapy, limited anecdotal experience is promising.

Ventilatory-Induced Lung Injury (VILI)

Although mechanical ventilation can be critical in surviving acute respiratory failure secondary to conditions such as ALI, improper use of mechanical ventilation can cause secondary ventilatory-induced lung injury (VILI). There are 3 mechanisms for VILI: volutrauma, atelectrauma, and biotrauma. Volutrauma is caused by alveolar overexpansion secondary to high lung volume (with or without high pressure). Atelectrauma is caused by alveolar shear-stress that occurs with repetitive alveolar recruitment-derecruitment (R/D). Biotrauma is alveolar injury secondary to cytokines released in response to mechanical injury sustained by the alveolus. Normal alveoli are very stable and undergo relatively small changes in size during ventilation unless they totally collapse or reexpand. This collapse and expansion likely occurs by the folding and unfolding of alveolar septa. In contrast, large changes in alveolar size and widespread alveolar R/D appear predominant in acute lung injury with each breath. The unstable alveoli that open and collapse with each breath can cause a significant shear stress-induced lung injury. Ventilator settings that are associated with alveolar R/D (high peak inspiratory pressure and low PEEP) can cause VILI even in normal lungs. Abnormal mechanical forces are the initial mechanism of VILI followed by secondary biotrauma. Atelectrauma appears to be a critical component of VILI leading to gross tearing of the alveolar walls and widespread destruction of epithelial cells leading to denudation of

the basement membrane and multiple gaps in the capillary endothelium. These changes stimulate the release of inflammatory mediators leading to further biotrauma.

There is evidence that ventilation techniques which stabilize alveoli are protective. These include the use of small tidal volumes which significantly improved alveolar stability and relatively high PEEP which stabilize open alveoli. Less is known about the combined effects of a recruitment maneuver (RM) followed by PEEP. Alveoli recruited with an accepted RM will often recollapse if subsequently ventilated with "minimal" PEEP but, increasing PEEP after the RM prevented alveolar recollapse and stabilized newly recruited alveoli. Ventilator maneuvers that promote alveolar stability such as the use of small tidal volume, appropriate PEEP or HFOV may reduce VILI, especially if used early in the course of the disease.

Setting an appropriate tidal volume is important for successful mechanical ventilation with avoiding VILI. The recently published NIH ARDS Network study showed that the use of 6 ml/kg tidal volume resulted in a significantly lower fatality rate than 12 ml/kg. The interpretation of these results, that a tidal volume of 6 ml/kg is ideal in ARDS patients, has been debated. Rather, the study shows that 12 ml/kg tidal volumes are not as successful as 6 ml/kg, but the ideal tidal volume may depend on the individual patient and could be 7, 8 or 9 ml/kg or it might be less than 6 ml/kg. Indeed, physicians have not fully embraced the use of these low tidal volumes in ARDS. Recently, the use of high tidal volumes in ventilated patients with no evidence of lung disease at the onset of ventilation has been shown to predispose to VILI. We should also be careful not to over interpret this data when choosing a tidal volume in ventilated foals. It could be dangerous to extrapolate the critical volume based on body weight from one species to another when the ratio of lung volume to body weight differs. High tidal volumes appear to be detrimental because of resulting volutrauma/barotrauma. This is compounded in situations where damaged lung results in a smaller ventilated lung volume as in ALI. The lesson from this landmark study is that the tidal volume should be set as low as practical with the goal of keeping the plateau airway pressure less than 30 cmH_2O even at the expense of mild hypercapnia. Thus the tidal volume should be set between 6 and 10 ml/kg depending on the plateau airway pressure. Conscious, non-sedated foals ventilated using a low tidal volume (e.g. 6 ml/kg) will frequently stack breaths so that the effective tidal volume is higher (e.g.12 ml/kg). The breath stacking can go undetected unless the clinician is very observant. Sedation, with its associated complications, in order to achieve a low tidal volume may be more detrimental than a slightly higher tidal volume. Indeed, in human studies, low tidal volumes have been associated with systemic problems suggesting that although this approach may be beneficial for the lungs, it may be detrimental overall.

Setting an appropriate PEEP is also very important in avoiding VILI. Low PEEP levels (4-6 cmH_2O) which are often successful in ventilating healthy lungs where the goal is to return FRC to normal, often are not sufficient in these cases. PEEP can be titrated to a few centimeters of H_2O above the lower inflection point on the pressure–volume curve or, if the ventilator does not produce such curves by producing a PEEP/CPAP grid. By adjusting PEEP/CPAP to 1 cm above and 1 cm below current levels and then, after 10-15 minutes to allow maximal recruitment, obtaining either a Pao_2 or measuring effective compliance the optimum PEEP/CPAP can be identified. Because alveolar injury is often quite heterogeneous, PEEP that is appropriate in one region may not be appropriate in another being either suboptimal or excessive. Optimizing PEEP is thus a balance between enrolling the recruitable alveoli in diseased regions without over distending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it also raises mean and peak airway pressure potentially contributing to barotrauma/volutrauma, so it is

important to combine low tidal volumes with the higher PEEP settings. The PEEP required is often in the range of 8 to 14 cmH_2O.

Protective ventilator strategies used to avoid VILI and effectively treat ALI include the use of low tidal volumes (in the range of 6-9 ml/kg) with the goal of minimizing average airway pressure or peak airway pressure to avoid repetitive R/D and PEEP levels which stabilize open alveoli. It is less clear if combining recruitment maneuvers, using brief periods of high PEEP levels (e.g. 30 cmH_2O for 40 seconds), with protective ventilator strategies is beneficial in neonates suffering from ALI.

Evolving Therapies

Newer modes of ventilatory therapy are gaining acceptance in human intensive care but few have had more than very small clinical studies. Most of these modes have a firm basis in theoretical pathophysiology of lung injury and have been added to modern ventilators but largely remain unproven in human medicine and rarely tried in foal ventilation. Some of these therapies may have an important place in evolving therapy but recommendation for adaptation requires further studies.

Inverse ratio ventilation (IRV) is mechanical ventilation with an extended inspiratory time greater than expiration. It has been used in infants and adults suffering from ARDS. The purpose is to maintain oxygenation at lower levels of PEEP and airway pressures, thereby minimizing volutrauma. Airway pressure release ventilation (APRV) augments spontaneous breathing with CPAP. The patient's inspiration is aided by CPAP and then expiration is allowed by periodically releasing the CPAP to a lower level. This modality was designed specifically for patients with severe restrictive lung disease, who poorly tolerate PPV because of their susceptibility to barotrauma and cardiac depression. High-frequency ventilation (HFV) is a generic term for any mode of mechanical ventilation that supplies small tidal volumes at rates of more than 60 breaths/min. HFV is administrated by a jet of gas in the endotracheal tube that entrains additional airway gases, delivering 2 to 5 ml/kg tidal volumes at 60 to 80 breaths/min. Large studies supporting the use of HFV in clinical critical care are lacking. Proportional assist ventilation (PAV) is an approach to ventilatory support in which the ventilator responds to each spontaneous breath in an independent manner. This modality augments patient effort but leaves the patient completely in control of all aspects of breathing. For a given breath, the pressures, volumes, times, and flows may differ from previous and subsequent breaths. The use of PAV may allow for assisted ventilation with relatively low peak airway pressures and therefore less risk of barotrauma or cardiac depression. Liquid ventilation has also enjoyed some popularity but successful large scale studies are not yet available.

Use of noninvasive positive pressure ventilation and noninvasive CPAP has become very popular in human medicine. The major stumbling block to this methodology is that successful maintenance is more labor intensive and requires experienced staff. Adapting this technique for foals will require the development of an effective noninvasive nasal delivery apparatus.