Mechanical Ventilation of the Neonatal Foal



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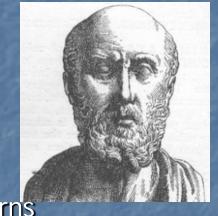






History of Pediatric Ventilation

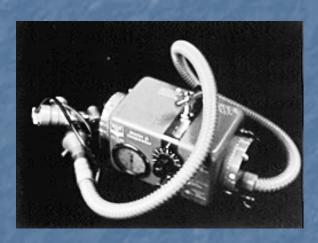
- 10th Century BC Hebrew doctors
- 4th Century BC Hippocrates
- 1667 Hooke bellows inflate dog's lungs
- 1806 Chaussier
 - O₂ Rx, Intubation/ventilation premature/newborns
- 1845 1st ventilator manufacture
- 1887 Case series 50 children ventilated
- 1904 Negative pressure ventilator
- 1905 CPAP
- 1907 Positive pressure mechanical ventilator
- 1960-1970 Birth of neonatology
- 1963 First baby successfully ventilated



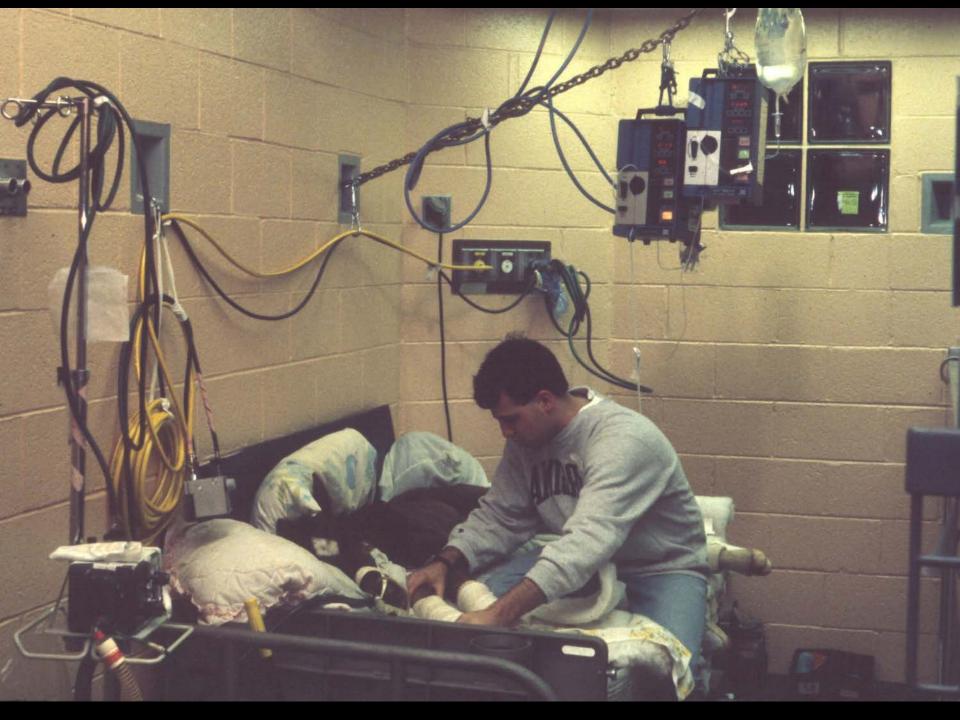


First Successfully Ventilated Infant 1963













Ventilation of NICU Patients

- Equine Neonatal Intensive Care Unit
 - First foals ventilated 35 years
 - Ventilating foals with secondary respiratory failure
 - Botulism or neonatal encephalopathy
 - 80% of such patients survive to discharged
 - Many become productive athletes
 - Most challenging cases
 - Viral pneumonia
 - ARDS
 - Sepsis MODS



Positive Pressure Ventilation Goals

- Pulmonary gas exchange
 - Support exchange
 - Allow manipulation V/Q matching
- Manipulate lung volume
 - Returning normal FRC
- Decrease work of breathing
 - Allow fatigued muscles to rest
 - Decrease O₂ and energy utilization
 - Redirect perfusion



Positive Pressure Ventilation Clinical Indications

- Neonatal Encephalopathy
- Weakness
- Persistent pulmonary hypertension
- Acute respiratory failure
 - ARDS
 - Infectious pneumonia
 - Non-infectious pneumonia
- Upper airway obstruction
- Septic shock
- Neuromuscular disorders



Goal of Ventilation

Provide respiratory support while therapies for underlying cause of the acute event are initiated and allow time for recovery



Case 1

- 50-day-old Morgan colt
- June 13
 - Normal in the morning
 - Evening found down in the field
 - Weak
- Rx
 - Intravenous fluids
 - Antibiotics
 - Tube fed milk
- June 14 6:00 a.m.
 - Respiratory distress
 - Cyanotic

Ventilation Case 1

- Admission Physical Exam
 - Weak, no eyelid tone
 - No tongue tone, weak tail tone
 - Shallow, rapid respiratory pattern
 - Mark nostril flare
- Therapy
 - Botulism antitoxin
 - Intravenous fluids
 - Intravenous ceftiofur sodium
 - Indwelling nasogastric tube
 - Ventilation



Case 1

	Adm	40 min	2 hr
рН	7.325	7.265	7.289
Pco ₂	56	68	70
Po ₂	40	229	243
SAT	64.5	99.7	99.7
HCO ₃	29.6	31.1	33.5
BE	+2.7	+2.6	+5.5
	RA	10 lpm	10 lpm



Ventilator Modes

- Continuous mandatory ventilation (CMV)
 - Volume controlled (VC-CMV)
 - Pressure controlled (PC-CMV)
- Intermittent mandatory ventilation (IMV)
 - Volume controlled (VC-IMV)
 - Pressure controlled (PC-IMV)
- Continuous Spontaneous Ventilation (CSV)
 - Pressure support ventilation (PSV)
 - Continuous positive airway pressure (CPAP)
- Proprietary modes



Intermittent Mandatory Ventilation (IMV)

- Combination of spontaneous and CMV
- Mechanical breath is synchronized with spontaneous breaths
- Mandatory set rate
- Spontaneous efforts
 - Can trip mandatory breaths

Intermittent Mandatory Ventilation (IMV)

- If spontaneous breathing occurs faster
 - Extra breaths
 - Warmed, Humidified, Oxygen-enriched gas
 - No preset volume or pressure
- IMV is better tolerated than CMV
 - Extra breaths completely patient controlled
 - Timing, depth, duration
 - Pressure Support Ventilation (PSV)
 - Preset breaths
 - Unforgiving



Pressure Support Ventilation (PSV)

- Partial ventilatory support
 - Assist flow-cycled mode
 - Support spontaneous breathing effort
 - Providing satisfactory oxygenation
 - Decreased the work of breathing
- Breathing controlled by foal
 - Inspiratory time
 - Inspiratory flow rate
 - Tidal volume
- Reduced work of breathing
- "Off-switch" value
 - 25% of the peak flow
 - Fixed low inspiratory flow rate



Pressure Support Ventilation Detrimental

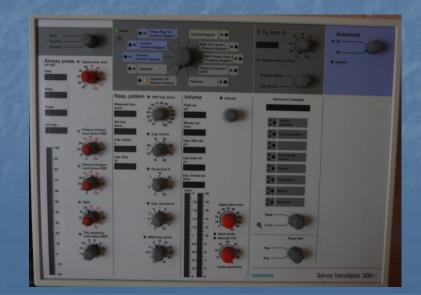
- Dyspneic despite ventilation
 - Risk of alveolar collapse
- High initial flow rate
 - Early termination of PS
 - Not provide sufficient minute ventilation
- Low initial flow rate
 - Late termination
 - Deliver large TV
- Ventilator-patient dyssynchrony

Pressure Support Ventilation New Ventilators

- Pressure targeted, time-cycled breath
 - Control inspiratory time
- Control of the pressure slope
 - Rapid peak resulting in a higher peak flow and thus a shorter inspiratory time
 - Slow peak initial flow resulting in a longer inspiratory time
- Allow adjustment of the "off-switch"
 - Flow criteria

Pressure Support Ventilation New Ventilators

- Volume Support Ventilation
 - Pressure support
 - Target volume
 - Breath to breath changes in parameters
 - Adjust Pressure Support to a volume goal





Positive End-Expiratory Pressure (PEEP) Continuous Positive Airway Pressure (CPAP)

PEEP

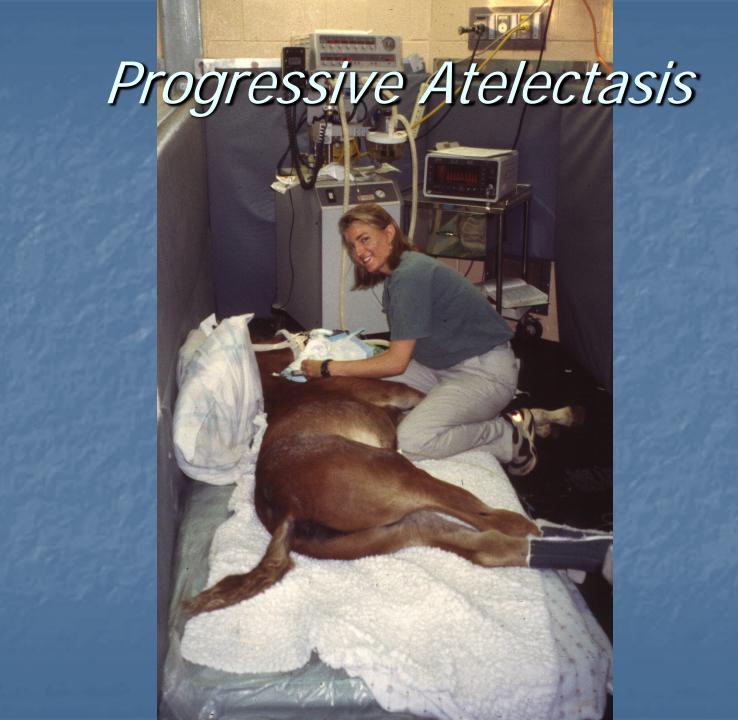
Positive pressure between ventilator breaths

CPAP

- Positive pressure throughout spontaneous respiration
- Physiologic effect
 - Increase functional residual capacity (FRC)
 - Decreases intrapulmonary shunting
 - Increase V/Q mismatch

PEEP/CPAP

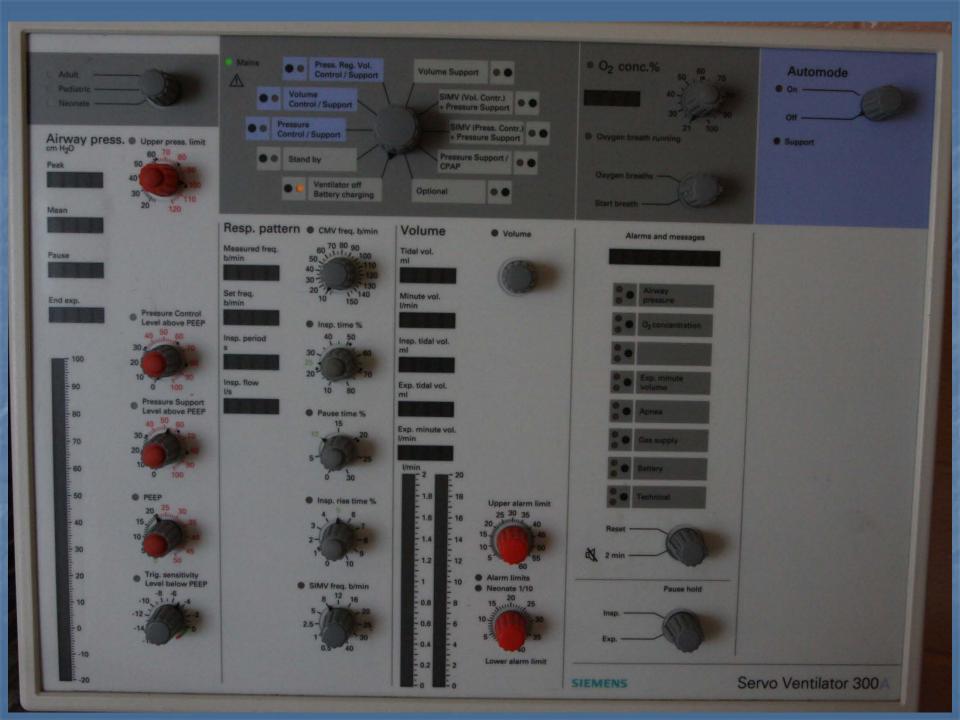
- Ideal FRC best compliance
- Ideal FRC least airway resistance
 - Less atelectasis
- Cardiovascular effects
 - Excessive PEEP
 - Decrease cardiac return
 - Increase pulmonary Resistance
 - Depends on the lung compliance
 - Low compliance less transmitted to vessels
 - Hypovolemia increase negative effect
- V/Q matching



PEEP

- Full recruitment
 - Requires 15 to 20 minutes
 - PEEP does not recruit but stabilizes lung
 - Break in circuit begin again
- Optimal PEEP
 - Maximum improvement pulmonary function
 - Minimal hemodynamic compromise
 - Inflection points on PV curves
 - PEEP/CPAP grid
 - Pao₂
 - Static Compliance
- Optimal PEEP is a balance
 - Holding open recruitable alveoli diseased regions
 - Not overdistending alveoli healthier lung

VENTILATOR SETTINGS VENTILATOR PATIENT DATA 1cmH₂O-1mbar 40 60 80 LOW INSPIRATORY LOW EXHALED TIDAL VOLUME LOW EXHALED MINUTE VOLUME HIGH RESPIRATORY APNEA LOW PRESSURE O2 INLET LOW PRESSURE AIR INLET EXHALATION VALVE LEAK MEAN PEAK AIRWAY AIRWAY LOW BATTERY PRESSURE PRESSURE PEAK TIDAL RESPIRATORY INSPIRATORY VOLUME RATE PEEP/ PLATEAU FLOW CPAP PRESSURE 6 PLATEAU ASSIST SENSITIVITY 02% SPONTANEOUS HIGH LOW LOW PRESSURE INSPIRATION PEEP/CPAP LIMIT PRESSURE PRESSURE 0 SIGH LOW LOW HIGH EXHALED EXHALED RESPIRATORY RATE I:E CLEAR PLATEAU TIDAL VOL MINUTE VOL RATE bpm RATIO LAMP ++ SIMV CMV CPAP TEST 100% O2 ALARM SUCTION SILENCE TIDAL SPONT. MINUTE MANUAL MANUAL AUTOMATIC ALARM **NEBULIZER** VOLUME MINUTE VOLUME INSPIRATION SIGH SIGH RESET VOLUME



- Fio₂
 - Dictate by
 - Pre-ventilation Pao₂
 - Response to INO₂
 - Usually 0.3-0.5
- TV
 - Depends on lung pathology
 - Goal maintain low airway pressures
 - Usually 6 10 ml/kg
 - Species differences stacking breaths
- Respiratory rate
 - Often set by patient
 - Machine rate minimal rate
 - Set with TV to achieve a minute volume (Paco2)
 - Usually 20 30 and adjusted with ETCO2
 - Target pH not Paco2
 - Permissive hypercapnia vs appropriate hypercapnia



- Peak Flow (insp time; insp rise time)
 - Determines inspiratory time of machine breath
 - Setting depends on
 - Pulmonary mechanics
 - Airway resistance
 - Time constants
 - Airway pressure gradients
 - No clear formula
 - Initially set
 - Inspiratory time is similar to unventilated patient
 - I/E ratio of approximately 1:2 (⅓ resp cycle)
 - Dynamically adjusted
 - Prevent negative airway pressures
 - Improperly set peak flow
 - Source of patient-ventilator dyssynchrony

- Inspiratory pause
 - Depends on airway resistance
- Trigger sensitivity
 - Pressure based or flow based
 - Flow based smoother transition
 - Pressure 2-3 cm H₂O
 - Non-respiratory triggering
 - High pressure used in weaning

PEEP/CPAP

- Usually $4 9 \text{ cm H}_2\text{O}$
- Initially 4 5 cm H_2O
- Once the foal is stable adjust by aid of
 - Flow loops
 - Compliance grid
 - Pao₂ grid



- Pressure Support
 - Level dependent on
 - Resistance and compliance of ventilator
 - Airway resistance
 - Lung compliance
 - Inspiratory effort
 - Absence of lung disease 8 12 cmH₂O
 - Low compliance as high as 20 25 cm H2O
 - Higher PS helpful in patient-ventilator dyssynchrony
 - When inspiratory effort exceeds rate of gas delivery

No Sedation



Case 1 Ventilator Set Up

- Goals
 - Decrease work of breathing
 - Maintain FRC
- Mode: Pressure Support with CPAP
 - PS initially set at 9
 - Normal lungs
 - CPAP initially set at 4
 - Normal lungs
- Parameters set by foal
 - Tidal Volume = 5.6 6.2 ml/kg (7 ml/kg)
 - RR 32
 - $PIP = 18-20 \text{ mmH}_2O$

	7 hr	HD 2	HD 2	HD 7	Cas	se 1
рН	7.393	7.385	7.396	7.414		
Pco ₂	53	51	51	48	mode	PS
Po ₂	97	74	127	114	mode	
SAT	96.7	92.8	98.4	98.4	TV	550-680
Cont		17	17.4	17.1	RR	32 – 26
HCO_3	32	31	31	31	PIP	20 – 18
BE	+6.5	+5.2	+6.0	+6.0		
FIO ₂	0.3	0.3	0.4	0.3	P _{Plat}	24 – 18
PEEP	4	4	5	5		
ETCO ₂	53	48	49	48		
PS	9	11	11	11		



Ventilator Settings

- All ventilator settings
 - Adjusted dynamically
 - Success dependent on tailoring to the individual
 - Monitor
 - Pulmonary mechanics
 - ETCO₂
 - Airway pressures
 - Clinical status
 - ABG determinations





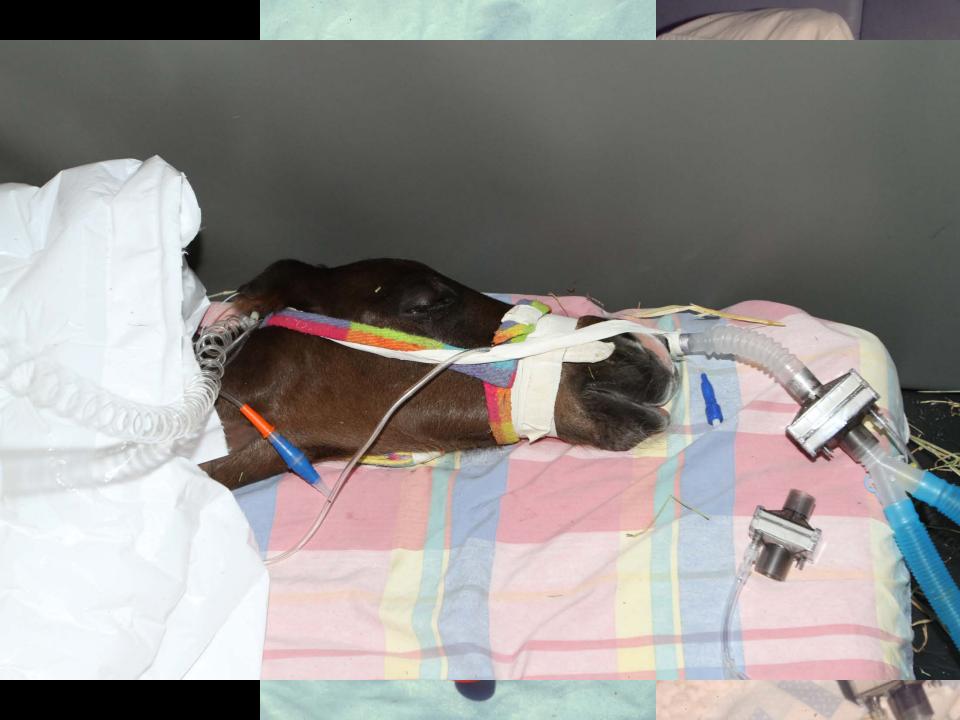
Preconditioning Ventilator Gases

- Heat and moisture must be added
 - Drying and cooling causes mucosal injury
 - Response of the trachea
 - Proliferation of goblet cells
 - Production of discharge
 - Becomes desiccated, tenacious
 - Obstruct airway/endotracheal tube
- Active humidifiers
 - External water source
 - Electrical powered heating elements
 - Intratracheal temperature > 35C
 - Water content > 40 mg/L



Preconditioning Ventilator Gases

- Passive Humidifiers HME filters
 - Trap heat and moisture from exhaled breath
 - Effective with average foal
 - Antimicrobial filter
- Limitations of HME filters
 - Large foals (>70 kg)
 - Large minute volumes
 - Add a cold active humidifier
 - Hypothermic patients
 - Airway discharge
 - Obstruct the filter dangerous situation





Cold Cascade Humidifier in line

Monitoring During Ventilation

- Arterial blood gas (ABG)
- Capnography
- FIO₂
- Tidal Volume/Minute Volume
- Airway pressure
- Compliance/Resistance
- Endotracheal tube





Capnography

- Endotracheal cuff integrity
- Ventilator leaks
- ETCO₂ depends on
 - PaCO₂
 - Cardiac output
 - Alveolar dead space ventilation
 - Pulmonary perfusion
 - Airway time constants (Rz)
 - CO2 production (metabolic rate)
 - Bicarbonate therapy
- Changing V/Q relations
- Other valuable information



Case 1 Problems

- \blacksquare ETCO₂ = 0
- Long inspiration
- Flow meter shows a dramatic ↓TV
- Common problem
 - Have foal sitter monitor cuff
 - Often slow leak
 - Bad valve use hemostat or clamp
 - Leaking cuff replace endotracheal tube



HD 9	HD 9
------	------

pH 7.304 7.443

Pco₂ 76 52

Po₂ 115 111

SAT 97.5 98

Cont 16.0 16.3

 HCO_3 38 36

BE +9.6 +10.8

FIO₂ 0.35 0.35

ETCO₂ 72 52

Mode PS PS

PS 20 12





Weaning from Ventilation

When?

- Consider as soon as begin ventilation
- Goal: keep ventilation period short

Indications

- Cardiovascular stability
- Metabolic stability
- Sepsis Controlled
- Original problem has resolved/improved
- No reliable predictor foal is ready



Case 1 Weaning

- 1st weaning challenge HD 6
 - Off the ventilator
 - Good breathing efforts
 - ETCO2 increased
 - Foal became cyanotic (on INO2)
 - Aerophagia increased abdominal size
 - 10 minute trial
- 2nd weaning trial HD 8
 - After 22 minutes Paco₂ 48 → 60

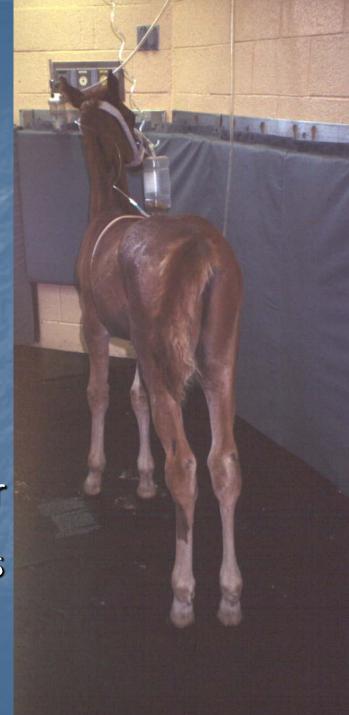


3rd Weaning Attempt

	HD 10	3 pm	6 pm	3 am	6 am	HD 14
рН	7.443	7.365	7.394	7.338	7.031	7.420
Pco ₂	52	55	50	64	129	49
Po ₂	111	72	184	79	49	120
SAT	98	91	99	92	60	98
HCO ₃	36	32	31	34	34	32
BE	+10.8	+5.4	+5.5	+6.7	-1.3	+7.0
FIO ₂	0.35	8 lpm	10 lpm	8 lpm	0.5	4 lpm
ETCO ₂	52				84	
Mode	PS	off	off	off	PS	off

Outcome

- Successful weaning HD 14
- Standing day 15
- Dysphagia
 - HD 22 able to swallow water
 - HD 23 able to swallow solids
- Hospital Discharge HD 30





Case 2 Clinical Problems

- Septic Shock
- Bacteremia/Sepsis
 - Pantoea agglomerans
- Neonatal Encephalopathy
 - Somnolent, facial nerve paresis
 - Seizure-like activity
- Neonatal Enteropathy
 - Fetal diarrhea, dysmotility
- Neonatal Nephropathy
- Other problems
 - Urachitis, hepatomegaly
 - Linear dermal necrosis, patent urachus
 - Angular limb deformity



	Adm	1 hr
рН	7.339	7.349
Pco ₂	60	58
Po ₂	44	144
SAT	77	100
Cont	13	15
HCO_3	32	32
BE	+5.6	+5.9
INO ₂	RA	10 lpm



Neonatal Encephalopathy

- 4 hours
 - Respiratory effort decreased
 - Apneustic breathing (breath holding)



	Adm	1 hr	4 hr	5 hr
рН	7.339	7.349	7.284	7.354
Pco ₂	60	58	82	62
Po ₂	44	144	80	250
SAT	77%	100	97	100
Cont	13.3	14.9	15.4	16.4
HCO ₃	32	32	34	35
BE	+5.6	+5.9	+10.5	+8.2
INO ₂	RA	10 lpm	10 lpm	15 lpm



Caffeine for Central Hypoventilation

- Naturally occurring methylxanthine
 - Theophylline, aminophylline
- Mechanism of action
 - Mild, direct general CNS stimulant
 - Increases respiratory center output
 - Increases chemoreceptor sensitivity to CO₂
 - Cardiac stimulate increases cardiac output
 - Increases renal blood flow
 - Mild diuretic

Caffeine for Central Hypoventilation

- Pharmacokinetics
 - Well absorbed from the GI tract



- Metabolized in the liver, excreted in urine
- Plasma half-life is long in neonates (40 230 hr)
- Dosage caffeine base PO or PR
 - Loading 10 mg/kg may repeat 2-3X
 - (Maintenance 2.5 mg/kg SID)
 - 2 mg caffeine citrate = 1 mg caffeine base

Caffeine for Central Hypoventilation

- Response monitored through ABG
- High therapeutic index
 - Effective blood levels 5-20 μg/ml
 - Toxic levels > 40 50 μg/ml in humans
 - Safer than aminophylline
- Adverse effects
 - Hyperactive more difficult to manage
 - Tachycardia have not seen

Case 2 *Neonatal Encephalopathy*

- 10 hours
 - Apneic respiratory pattern
 - 40 second apneic period
 - Cluster breathing in-between



	Adm	1 hr	4 hr	5 hr	10 hr	12 hr
рН	7.339	7.349	7.284	7.354	7.276	7.451
Pco ₂	60	58	82	62	85	45
Po ₂	44	144	80	250	105	141
SAT	77%	100	97	100	100	100
Cont	13.3	14.9	15.4	16.4	16.1	15.5
HCO ₃	32	32	34	35	40	32
BE	+5.6	+5.9	+10.5	+8.2	+11	+7.4
INO ₂	RA	10 lpm	10 lpm	15 lpm	10 lpm	10 lpm

Case 2 *Neonatal Encephalopathy*

- 12 hours
 - Periods of somnolence and nonresponsiveness
 - Apneic respiratory pattern with cluster breathing
 - Facial nerve paresis
 - Right ear lower and slower to respond
 - Ears are not synchronized
- 21 hours
 - Seizure-like activity
 - Opisthotonus
 - Tonic/Clonic marching activity
 - Treated with intravenous phenobarbital

27 hr 29 hr

pH 7.313 7.269

Pco₂ 75 85

Po₂ 118 119

SAT 100 100

Cont 14.5 14.7

 HCO_3 38 39

BE +10.4 + 10.3

INO₂ 10 lpm 10 lpm





Ventilate

- Goals
 - Increase alveolar ventilation
 - Maintain FRC
- Mode: IMV/PS with PEEP/CPAP
 - TV = 460 ml (8.5 ml/kg)
 - PIP = $18 \text{ cmH}_2\text{O}$
 - PS initially set at 9 cmH₂O
 - Normal lungs
 - PEEP/CPAP = $4 \text{ cmH}_2\text{O}$
 - Normal lungs
 - Peak flow = 60 lpm
 - RR = 24
 - Foal's rate 33



	27 hr	29 hr	31 hr	36 hr		
рН	7.313	7.269	7.353	7.428	mode	SIMV
Pco ₂	75	85	67	50	TV	460 ml
Po ₂	118	119	96	164	PF	60
SAT	100	100	99	100	RR	38
Cont	14.5	14.7	13.9	14.4	PEEP	4
HCO ₃	38	39	38	33	PS	9
BE	+10.4	+10.3	+10.9	+8.3	P _{peak}	24
	10 lpm	10 lpm	0.4	0.5	P _{plat}	18
ETCO ₂			54	46		

Weaning

Began asking when? within 12 hours

After 21 hours – PS trial

	48 hr	52 hr	57 HR	60 hr	48 hr	52 hr
рН	7.447	7.473	7.392	møde	SIMV	PS/CPAP
Pco ₂	45	40	54	20	460 ml	520-75
Po ₂	242	91	252	9 5	60	
SAT	100	100	100	RR .7	36	22
Cont	14.5	14.1	14.3	PEEP	4	4
HCO ₃	31	29	33	B8	9	6
BE	+7.2	+6.0	+7.7	P _p Z _a A	21	
F110 ₂	0.5	0.35	10 lpm	P _p lam	16	
ETCO ₂	42	38				











- Admission 8 hr old
- Septic shock Streptococcus bacteremia
 - Minimally responsive
 - Hypothermic (36.8 C)
 - Hypotonia
 - Pupils were pinpoint, iris edema
 - Inappropriately low heart rate
 - Cold legs, and poor peripheral perfusion
- Admission lab work
 - Leukopenic (WBC = 528 cells/ul)
 - Hypoglycemia required 20 mg/kg/min to get > LO

Case 3 Therapy

- Intranasal oxygen
- Shock doses of fluids
- Plasma
- Antimicrobials
- Ventilation
- Dobutamine
- Norepinephrine



Benefits of Mechanical Ventilation

- Traditional
 - Improve gas exchange
 - Improve V/Q matching
 - Decrease shunt fraction
- Benefit of decreasing work of breathing
 - Normal quiet breathing
 - Inhalation active process
 - Requires energy
 - 3% 5% O₂ consumed
 - Exhalation is a passive
 - Requires no energy, O₂

Benefits of Mechanical Ventilation

- Pulmonary failure 2ndary to septic shock
 - Respiratory distress
 - Work of breathing
 - O₂ required up to 50% of available O₂
 - Diverts perfusion resources
 - Accessory muscles recruited
- Relieving work of breathing
 - Redistribution of O₂
 - Redistribution of perfusion
 - Sparing energy resources
- Ventilation foals with septic shock
 - Improve perfusion, increase BP
 - Improved glucose balance



Ventilate

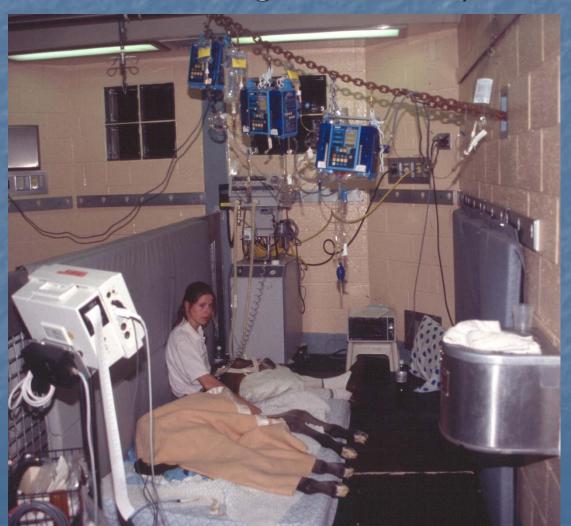
- Goals
 - Decrease the work of breathing
 - Correct pulmonary hypertension
 - Maintain FRC
- Initial settings
 - Mode: PS with CPAP
 - PS initially set at 18 cmH₂O
 - Based on easy of breathing and resulting TV
 - PEEP/CPAP = $8 \text{ cmH}_2\text{O}$
 - FIO₂ = 1.0
- Set by foal
 - TV = 180 ml (7 ml/kg)
 - PIP = 32 cmH₂O
 - RR = 48



	Adm	1 hr	1.5 hr	Mode	PS
рН	7.220	7.072	7.073	TV	180
Pco ₂	65	70	62	RR	48
Po ₂	22	20	248	PEEP	8
SAT	27.7	21.2	99.6	PS	18
Cont	5.1	3.4	14.9	P _{peak}	32
HCO ₃	27	20	18		
BE	-1.7	-9.6	-11.3	NO	20 ppm
FIO ₂	0.21	1.0	1.0		

	3.75 hr	4 hr	5 hr	6 hr	Mode	PS
рН	7.000	7.062	7.089	7.061	TV	220
Pco ₂	96	92	84	98	RR	46
Po ₂	73	25	146	96	PEEP	10
SAT	86.3	29.4	97.8	92.3	PS	20
Cont	11.4	4.1	14.1	13.2	P _{peak}	35
HCO ₃	24	26	26	28		
BE	-7.5	- 4.6	- 4.6	- 3.1	NO	20 ppm
FIO_2	1.0	1.0	1.0	0.50		

Multifocal necrotizing interstitial pneumonia



- Sequela to many cases of ALI
- Increased pulmonary vascular resistance
 - Inflammatory mediators
 - Severe hypoxemia

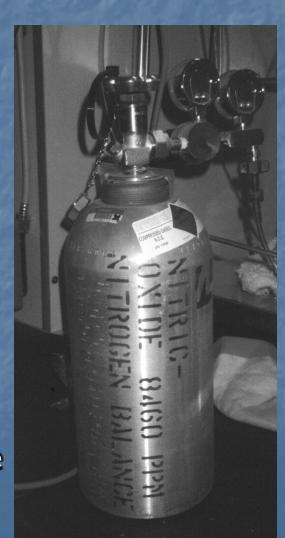
- Neonate
 - Right to left shunting
 - Foramen ovale
 - Ductus arteriosus
 - Reversion to fetal circulation
 - Adaptive advantage
 - Achieve adequate systemic cardiac output
 - Neonate's unique ability
 - Exist in a hypoxemic state
 - Regain CO by shunting
 - Survive pulmonary hypertension without systemic ischemia

- 1.0 F_{IO2} trial
 - Pao₂ < 100 torr after 15-20 min
 - Shunt fraction > 30%
 - Cause of the hypoxemia extrapulmonary
 - Large cardiac shunt
 - PPHN

- Pulmonary hypertension
 - Failure to make the birth transition PPHN
 - Imbalance of vasodilators and vasoconstrictors
 - Nitric oxide and endothelin
 - Regression to fetal circulation PPHN
 - Perinatal hypoxemia
 - Cytokine showers
 - Secondary
 - Pulmonary disease
 - Septic shock
 - _ ALI

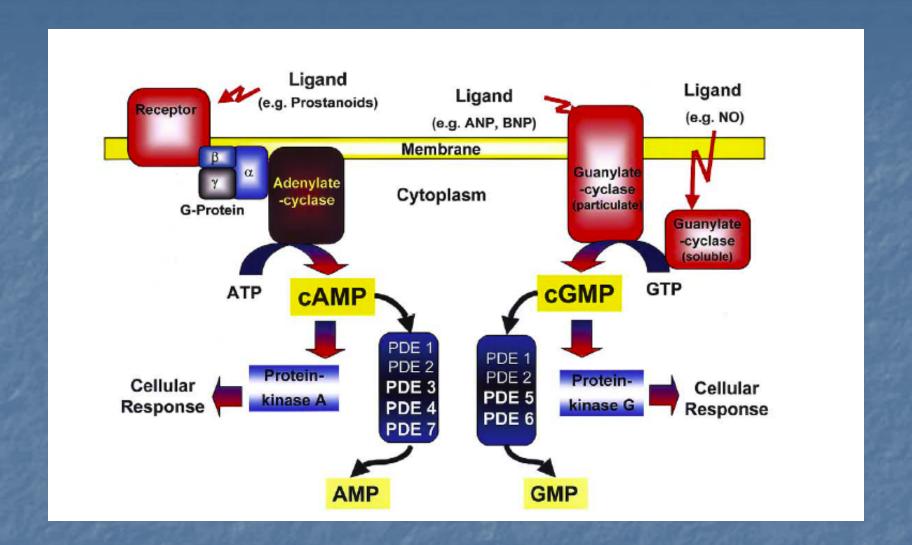
Pulmonary Hypertension Therapy

- Traditional therapy
 - Maximize exposure to O₂
 - Ventilation with 100% oxygen
 - Alkalinize arterial pH
 - Mild hyperventilation
 - Treatment with bases
 - Maintain systemic blood pressure
 - Counterbalance the pulmonary pressure
 - ALI will counteract these approaches
- Inhaled NO therapy
 - 5 to 20 ppm
 - Immediate effect
 - Significant pulmonary toxicity possible
 - Free radicals



Pulmonary Hypertension Therapy

- NO Mechanism of action
 - Vasodilation
 - Increasing cGMP levels
 - Relaxation of the pulmonary vasculature
- Type V phosphodiesterase inhibitors
 - Selectively prevent cGMP destruction
 - Endogenous nitric oxide
 - Pulses of exogenous nitric oxide
 - Currently available
 - Sildenafil
 - Vardenafil
 - Tadalafil



From: Ghofrani HA, et. al. J Am Coll Cardio 44(7):1488-96, 2004

