



Neonatal Physiology and the Stressed Neonate

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I have no disclosures related to this presentation.



Neonatal Period

- ▶ Physiologic transition period
 - ▶ Full dependence on maternal physiology
 - ▶ Adaptation to independent life
- ▶ Period transition all organ systems
 - ▶ First 3 to 4 weeks of life



Physiologic Transitions



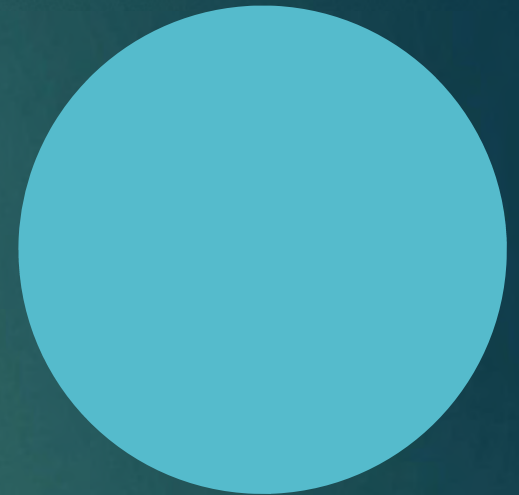
Counterintuitive Physiology

- ▶ Different from Adult Physiology
- ▶ Fetal Physiology



Renal Response to Hypovolemia

- ▶ Adult kidney
 - ▶ Producing concentrated urine
 - ▶ Maintain vascular volume
- ▶ Fetus
 - ▶ Concentrated urine
 - ▶ Increase fetal fluid osmolarity
 - ▶ Prevent reabsorption of the fluids
 - ▶ Draw fluid from the fetus
 - ▶ Negative effect on volemia



Renal Response to Hypovolemia

- ▶ Produces dilute urine
 - ▶ Decrease fetal fluid osmolarity
 - ▶ Enhance reabsorption of fetal fluids
 - ▶ Positive effect on volemia



Heart Rate Response To Hypoxemia

- ▶ Adult
 - ▶ Tachypnea and tachycardia
 - ▶ Deliver more oxygen to tissues
- ▶ Fetus
 - ▶ Bradycardia
 - ▶ Maximizing perfusion of fetal placenta
 - ▶ Increasing vascular tone - directing blood to vital organs
 - ▶ Increase in afterload
 - ▶ Increase cardiac work and thus oxygen demand
 - ▶ Decrease HR
 - ▶ New circulatory pattern
 - ▶ Requires no more oxygen



Species



Fluid Physiology



Fluid Physiology

Fetus/Neonate

- ▶ Unique characteristics of Fetal/ Neonatal
 - ▶ Interstitium
 - ▶ Lymph flow
 - ▶ Capillary endothelial permeability
- ▶ Interstitium
 - ▶ Heterogeneous space
 - ▶ Dynamically controls its fluid content
 - ▶ Compliance 10X adult (fetal lamb)



Fluid Physiology

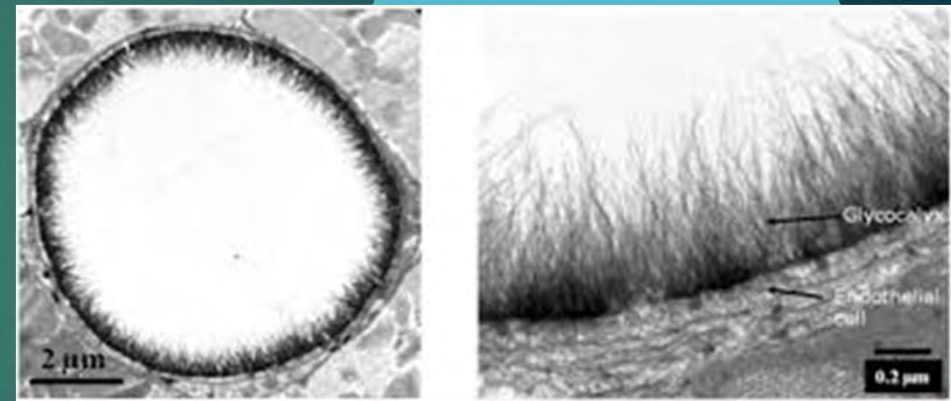
Fetus/Neonate

- ▶ Lymph flow
 - ▶ Volume of lymph 1 mL/kg in adult dogs
 - ▶ Thoracic duct lymph flow
 - ▶ Fetal lamb - 0.25 mL/minute/kg
 - ▶ 5x the adult rate
 - ▶ Lymph flow - subcutaneous
 - ▶ Puppies 2X adult dogs (per kg)
 - ▶ Pulmonary lymph flow
 - ▶ Newborn lambs and puppies > adults
 - ▶ Neonate – local/ whole body lymph flow > adult
 - ▶ Increased interstitial volume
 - ▶ Higher capillary permeability



Fluid Physiology Fetus/Neonate

- ▶ Capillary endothelial permeability
 - ▶ Filtration rate in fetal lambs vs adults
 - ▶ Fluid 5x more than adults
 - ▶ Proteins 15x more than adults
 - ▶ Why?
 - ▶ Poor precapillary tone
 - ▶ Higher capillary hydrostatic pressure
 - ▶ Higher filtration
 - ▶ The role of the glycocalyx?
 - ▶ Filtration related to hydrostatic pressure
 - ▶ Precapillary tone lambs – develops during 1st week
 - ▶ Doesn't develop in a uniform manner



From: <http://www.hubrecht.edu>

Fluid Physiology At Birth

- ▶ Blood pressure increases - lambs
 - ▶ Last weeks – increases 20%
 - ▶ During labor – increases another 18%
 - ▶ At birth – increases another 12%
- ▶ Transmitted to capillaries
- ▶ Increased transcapillary filtration
 - ▶ Poor precapillary tone



Fluid Physiology At Birth

- ▶ Other reasons for fluid shifts
 - ▶ Direct compression of the fetus
 - ▶ Increased venous pressure
 - ▶ Vasoactive hormones
 - ▶ Arginine vasopressin
 - ▶ Norepinephrine
 - ▶ Cortisol
 - ▶ Atrial natriuretic factor



Fluid Physiology

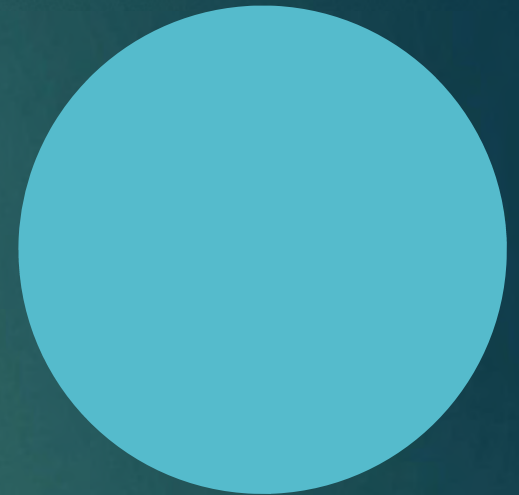
Neonates are Born Fluid Overloaded

- ▶ Fluid shifts
 - ▶ From fetal fluids / maternal circulation
 - ▶ Accumulating in the fetal interstitium
- ▶ ***All Neonates Are Born Fluid Overloaded***
- ▶ Rate of loss of this fluid - species variation
 - ▶ Foal – weeks
 - ▶ Other species
 - ▶ 10-15% body weight rapidly after birth
 - ▶ Important not to replace fluid loss
 - ▶ Poor outcomes with persistent fluid overload



Fluid Physiology Consequences

- ▶ Response to Hemorrhage
- ▶ Response to Volume Loading
- ▶ Response to Hypoxia



Fluid Physiology

Response to Hemorrhage

- ▶ Perinatal blood loss
 - ▶ Rupture of umbilical vessels
 - ▶ Internal bleeding
 - ▶ Premature placental separation
 - ▶ Fetofetal transfusion
 - ▶ Fetomaternal transfusion



Fluid Physiology

Response to Hemorrhage

- ▶ 30% loss of blood
 - ▶ Adult dogs, cats, and sheep
 - ▶ With out fluid therapy - 24 to 48 hours
 - ▶ Fetus or neonate is shorter
 - ▶ Fetal sheep
 - ▶ 2x adults within 30 minutes
 - ▶ 100% blood volume within 3 to 4 hours



Fluid Physiology

Response to Hemorrhage

- ▶ Neonatal kittens and rabbits
 - ▶ Greater blood loss /kg before BP decrease
 - ▶ Translocation fluid and protein
 - ▶ From the interstitial space
 - ▶ Tolerate blood loss better than adults



Fluid Physiology

Response to Volume Loading

- ▶ Rapid intravascular infusions crystalloids
 - ▶ Fetal lambs - 6 to 7% retained at 30-60 min
 - ▶ Adults – 20% to 50% retained at 30-60 min
- ▶ Rapid transfer into the interstitial space
 - ▶ High interstitial compliance
 - ▶ High capillary filtration coefficient



Fluid Physiology

Response to Volume Loading

- ▶ Fluid Overload – lack of intravascular retention
 - ▶ Adults (dogs, sheep)
 - ▶ The adult clears the fluid load hours
 - ▶ Renin
 - ▶ Vasopressin
 - ▶ Atrial natriuretic factor



Fluid Physiology

Response to Volume Loading

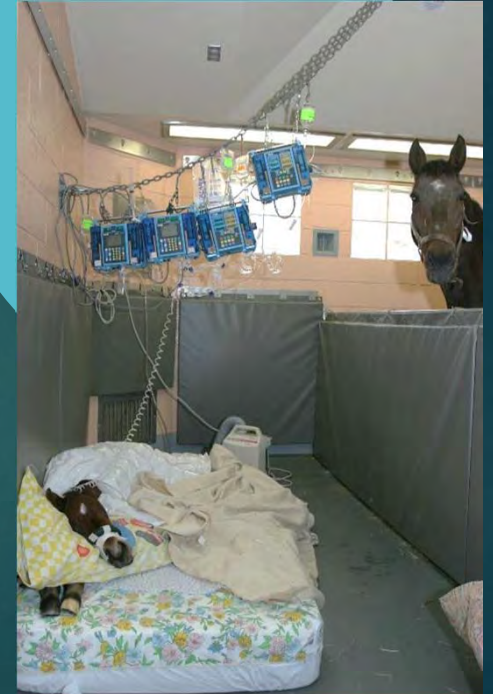
- ▶ Fluid Overload – lack of intravascular retention
 - ▶ Neonates (puppies, lambs)
 - ▶ 24 to 36 hr to clear fluid load
 - ▶ Volume load escapes vasculature space quickly
 - ▶ Escape volume sensors detection
 - ▶ No diuretic response
 - ▶ Urine flow rapidly returns to normal
 - ▶ Before clearing volume load



Fluid Physiology

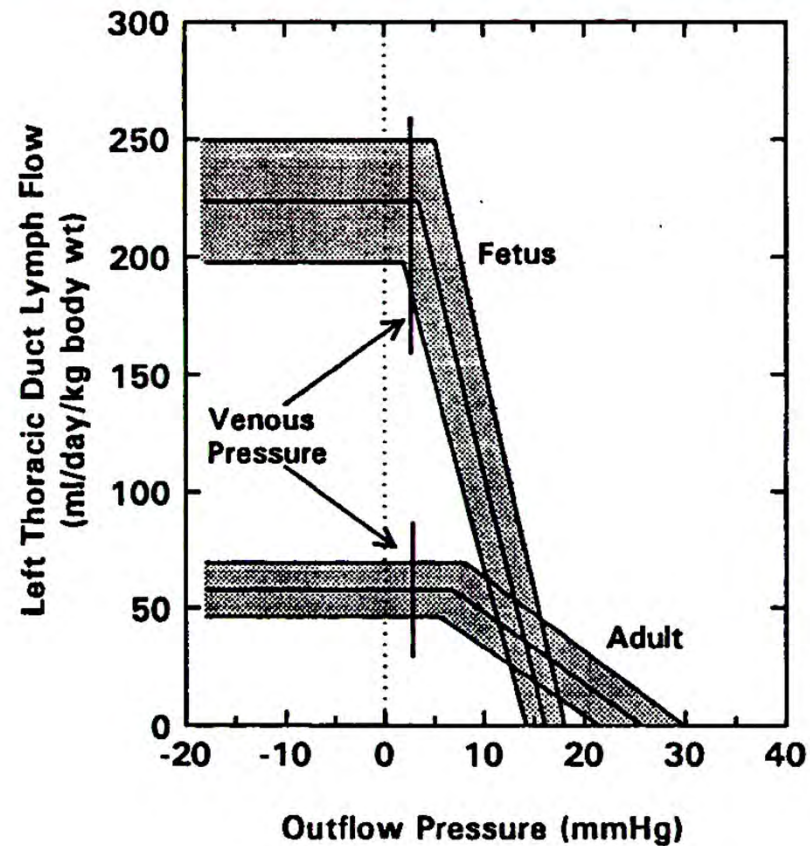
Response to Volume Loading

- ▶ After fluid loading (fetal lambs, neonatal lambs)
 - ▶ Increase thoracic duct lymph flow
 - ▶ Increase by 3.5 times (max flow rate)
 - ▶ Angiotensin II augments lymph flow
 - ▶ Fluid therapy – rapid infusion
 - ▶ Increases CVP
 - ▶ Dramatic decrease in lymphatic flow
 - ▶ Result in edema



Thoracic Lymph Flow

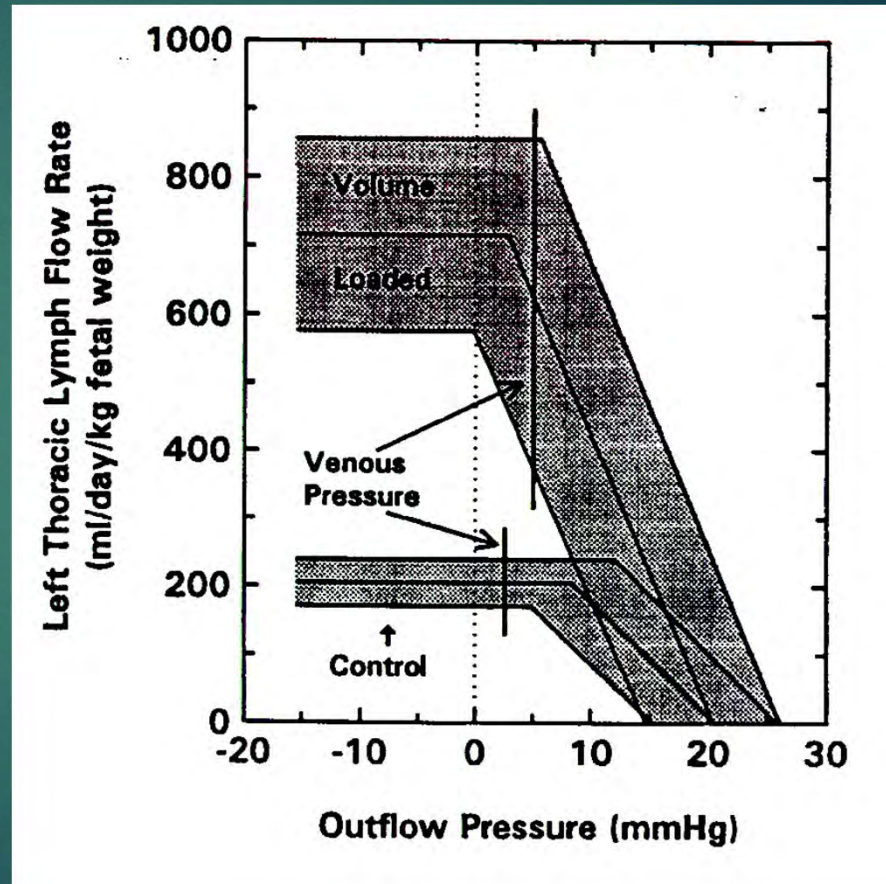
- ▶ Fetal lamb
- ▶ Adult sheep



From: Brace RA et.al.

Thoracic Lymph Flow

- ▶ Fetal lamb
- ▶ With large volume intravenous infusion
 - ▶ ↑↑ Lymph flow as much as 340%
- ▶ Limited by CVP



From: Brace RA et.al.

Fluid Physiology

Response to Hypoxia

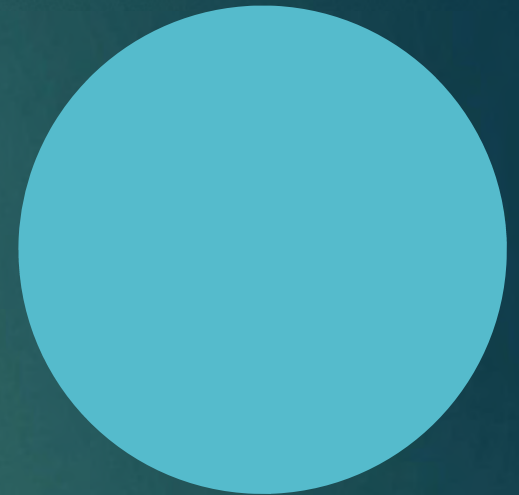
- ▶ Moderate/severe hypoxemia (fetal lambs)
 - ▶ Increases arterial and venous pressures
 - ▶ Poor precapillary tone
 - ▶ Increase capillary pressure
 - ▶ Greater fluid shift interstitial space
 - ▶ Leading to excessive fluid overload



Fluid Physiology

Response to Hypoxia

- ▶ All neonates
 - ▶ Fluid overloaded at birth
- ▶ With hypoxia/asphyxia
 - ▶ Greater degree of fluid overload
- ▶ *Hypovolemic with concurrent fluid overload*



Renal Physiology



Renal Physiology

Renal Maturation At Birth

- ▶ Nephrogenesis is complete, GFR adult levels in days
 - ▶ Lambs
 - ▶ Foals
 - ▶ Calves
- ▶ Nephrogenesis continues 2 + weeks
 - ▶ Puppies
- ▶ ??
 - ▶ Kitten
 - ▶ Kid
 - ▶ Cria



Renal Physiology

Neonatal Puppy Renal Function

- ▶ Low GFR
- ▶ Low renal plasma flow (RPF)
- ▶ Low filtration fraction (FF)
- ▶ Decreased tubular reabsorption
 - ▶ Amino acids
 - ▶ Phosphate
- ▶ Exaggerated proximal tubule natriuresis
 - ▶ Balanced by increased distal tubule Na reabsorption
- ▶ Low concentrating ability



Renal Physiology

Neonatal Cr & BUN Levels

- ▶ BUN
 - ▶ Lower than adults
 - ▶ Dependent on nutrition
- ▶ Cr level at birth
 - ▶ Cr lower than adult
 - ▶ Puppy
 - ▶ Adult level at birth
 - ▶ Infant - increase first 48 hr then decreases
 - ▶ Higher Cr than adult at birth but rapid drop
 - ▶ Foals
 - ▶ Calves

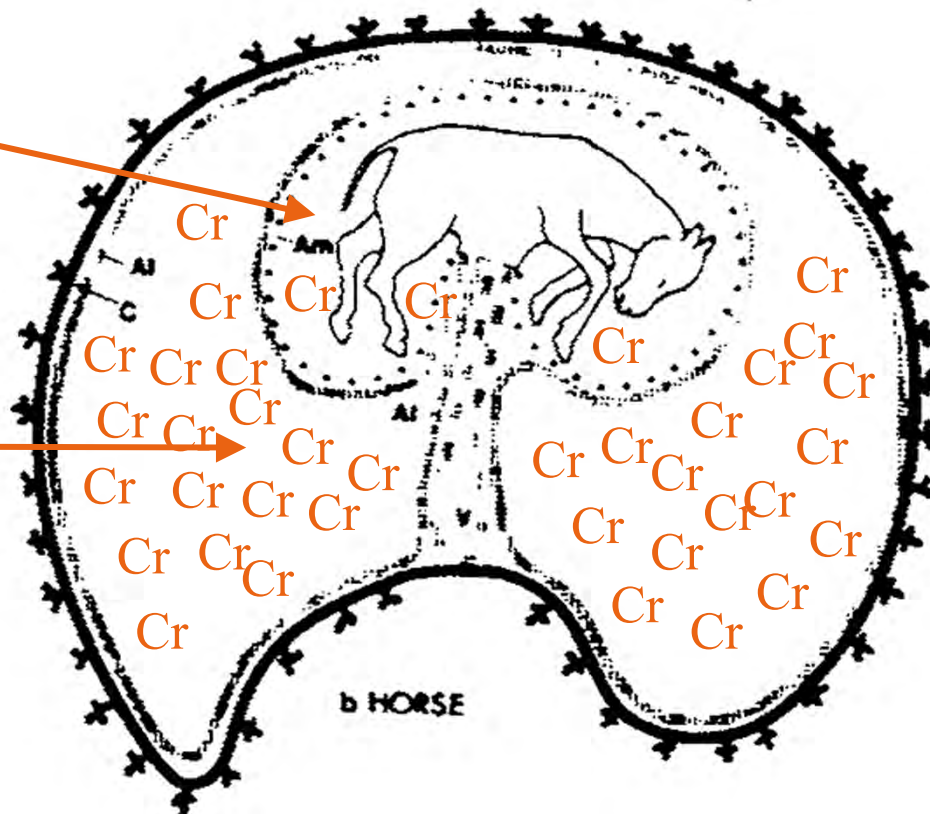


Renal Physiology

Sea of Cr – Fetal Foal

Amnionic Cr
9 – 12 mg/dl

Allantoic Cr
120 – 180 mg/dl



Renal Physiology

Renal Perfusion

- ▶ Fetus - 3-5% of cardiac output
- ▶ Birth rapid increases to 15%
 - ▶ Increase in BP
 - ▶ Renal vascular resistance
 - ▶ Increases modestly
 - ▶ But less relative to other vascular beds



Renal Physiology

Renal Perfusion

- ▶ Autoregulation
 - ▶ Normal range for age
 - ▶ “Autoregulatory range” increases as BP increases
- ▶ Puppies
 - ▶ GFR/RPF increase in parallel with
 - ▶ Increases in BP
 - ▶ Decreased in VR
 - ▶ Not changed by inhibition of angiotensin
 - ▶ Until 6 weeks old
- ▶ Foal, calf and lamb
 - ▶ GRF becomes adult-like
 - ▶ Independent of increases in arterial BP



Renal Physiology

Neonatal Vasogenic Nephropathy

- ▶ Balancing BP and renal VR
 - ▶ Vital for proper renal function
- ▶ Neonatal Vasogenic Nephropathy (NVN)
 - ▶ Abnormal levels of vasoactive substances
 - ▶ Increased sympathetic tone
- ▶ Prostaglandins in neonates
 - ▶ Afferent arteriolar vasodilation
 - ▶ Counterbalancing endogenous vasoconstrictors
 - ▶ High PG activity is physiologically necessary
 - ▶ Maintain renal perfusion



Renal Physiology

NSAID

- ▶ Greater potential for adverse renal effects
 - ▶ Reduce GFR and RBF
 - ▶ Neonatal Vasogenic Nephropathy
 - ▶ Oliguria
 - ▶ Fluid overload
- ▶ Both COX 1 and COX 2 inhibition equal effect



Renal Physiology

Hypothermia

- ▶ Rabbits decreases temperature 2 C
 - ▶ Induce renal vasoconstriction
 - ▶ Decrease GFR
- ▶ Hypothermic neonates at risk
 - ▶ Environmental temperature at birth
 - ▶ Sympathoexcitatory response
 - ▶ Response occurs before a decrease in core temperature
 - ▶ Reversible with rewarming
 - ▶ Mediated by cutaneous cold-sensitive thermoreceptors
 - ▶ Not core temperature



Renal Physiology

Nephron Development

- ▶ Number of nephrons
 - ▶ Great variation in normal individuals
 - ▶ Linear relation with body weight
- ▶ Normal and compensatory renal growth
 - ▶ Primarily proximal tubular mass



Renal Physiology

Nephron Development

- ▶ Decrease nephron numbers
 - ▶ Intrauterine growth restriction
 - ▶ Perinatal asphyxia
 - ▶ Shock
 - ▶ Exposure of the fetus to maternal administration
 - ▶ NSAIDs
 - ▶ Glucocorticoids
 - ▶ Aminoglycosides
 - ▶ Beta lactam antibiotics



Renal Physiology

Tubular Function

- ▶ Immature at birth
 - ▶ Low carrier density
 - ▶ Short tubules
- ▶ Puppies
 - ▶ Urine specific gravity
 - ▶ Birth is limited (1.006 to 1.017)
 - ▶ Adult levels 12 weeks (8 weeks kittens)
 - ▶ Protein, glucose, amino acids in the urine
 - ▶ Neonate
 - ▶ Adult levels by 3 weeks



Renal Physiology

Tubular Function

- ▶ Large animal neonates urine specific gravity
 - ▶ Broad range within 24 hours
 - ▶ 1.001 to > 1.035
 - ▶ Herbivore Milk diet
 - ▶ $U_{sg} < 1.004$
- ▶ Foal
 - ▶ First urine
 - ▶ 12 hours, $U_{sg} > 1.035$
 - ▶ 24 hours $U_{sg} < 1.004$



Renal Physiology

Sodium Story

- ▶ Positive sodium balance needed for growth
 - ▶ Increase interstitium
 - ▶ Bone growth
- ▶ Fresh milk is sodium poor
 - ▶ Mare's milk – 9 to 14 mEq/L
 - ▶ 20% milk diet – 1.9mEq/kg/day
 - ▶ Growth requirement 1 mEq/kg/day



Renal Physiology

Sodium Story

- ▶ Immature kidney Na reabsorption
 - ▶ With sodium loading in dogs
 - ▶ Proximal tubule – 64% adult dog: 48% puppy
 - ▶ Distal tubule – 26% adult dog: 51% puppy
 - ▶ Total – 91% adult dog: 98% puppy
 - ▶ Upregulation distal tubular Na transporters



Renal Physiology

Sodium Story

- ▶ Slow to respond to Na load
 - ▶ Species dependent
 - ▶ Predisposes to Na overload
 - ▶ Problem in critically ill neonatal foals
- ▶ Crystalloid fluid therapy
 - ▶ Na overload
 - ▶ Fluid overload
 - ▶ Limited urine dilution
 - ▶ Neonatal Vasogenic Nephropathy



Cardiovascular Physiology



Cardiovascular Physiology At Birth

- ▶ Increase in
 - ▶ Arterial blood pressure
 - ▶ Heart rate
 - ▶ Cardiac output
 - ▶ 4X higher than adult (lamb)
- ▶ Regional changes blood flow
 - ▶ Initially retains low-resistance–high-flow system
 - ▶ Renal 3% to 15% at birth



Cardiovascular Physiology

Neonatal Changes

- ▶ Puppies
 - ▶ SBP 61 ± 5 birth to 139 ± 4 at 4 wk
 - ▶ HR 204 ± 3 at birth to 123 ± 6 at 4 wk
- ▶ Large animal neonates
 - ▶ Studies confounded by restrain artifacts
 - ▶ Clinical experience – low BP/VR to high BP/VR
 - ▶ Most make a rapid transition
 - ▶ A few neonates retain the low BP/VR maintain excellent perfusion
 - ▶ Critically ill neonates more likely delay transition



Cardiovascular Physiology

Neonates

- ▶ BP cannot be used as surrogate for perfusion
- ▶ Absolute BP numbers - Dangerous therapeutic goals



Cardiovascular Physiology

Autonomic influence heart rate

- ▶ Puppies, kittens
 - ▶ Sympathetic innervation functionally incomplete
 - ▶ Puppies – less chronotropic response
 - ▶ Lack of vagal tone - minimal response to atropine
 - ▶ Puppies < 14 days
 - ▶ Kittens < 11 days
 - ▶ Atropine not effective in neonatal resuscitation
- ▶ Clinical observations in foals, calves, crias, lambs and kids
 - ▶ Autonomic cardiac control at birth
 - ▶ Calves, crias
 - ▶ Intubation may induce dangerous bradycardia



Cardiovascular Physiology

Resetting baroreflex

- Baroreflex sensitivity changes with maturation
 - Resets - shifts toward higher pressures
 - Shifts during fetal life
 - Shifts immediately after birth
 - Shifts during postnatal period
 - Paralleling BP increases
- Resetting complex
 - Peripheral resetting
 - Level of the baroreceptor
 - Central resetting
 - Sympathetic or parasympathetic activity



Cardiovascular Physiology

Resetting baroreflex

- Puppies
 - Baroreceptor reflex absent until 4 days of age
- Large animal neonates
 - Most make rapid transition
 - Some critically ill neonates
 - Retain the fetal baroreceptor set point
 - Apparent inappropriate bradycardia
 - Low BP
 - But good perfusion



Cardiovascular Physiology

Ductus Arteriosus, Foramen Ovale

- Functional closure
 - 50% by 24 hr
 - 90% by 48 hr
- Anatomic closure
 - Within weeks
 - Until then – powerful survival tool



Cardiovascular Physiology

Ductus Arteriosus, Foramen Ovale

- Pulmonary hypertension
 - Hypoxemia
 - Sepsis
- Consequences of Pulmonary hypertension
 - Adult – Hypoxia Ischemia
 - Neonate – Hypoxia without ischemia



Confused?

