Neonatal Physiology and the Stressed Neonate

JON PALMER, VMD, DACVIM
NEW BOLTON CENTER, KENNETT SQUARE, PENNSYLVANIA
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

- Fetus
- Neonate
- Pediatric
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 Hypovolemic

- 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)
**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
    - Without 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 of 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
    - Increases 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 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 decrease 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
    - Usg < 1.004

- Foal
  - First urine
    - 12 hours, Usg > 1.035
    - 24 hours Usg < 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
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?