# Fluid Shifts and Renal Function

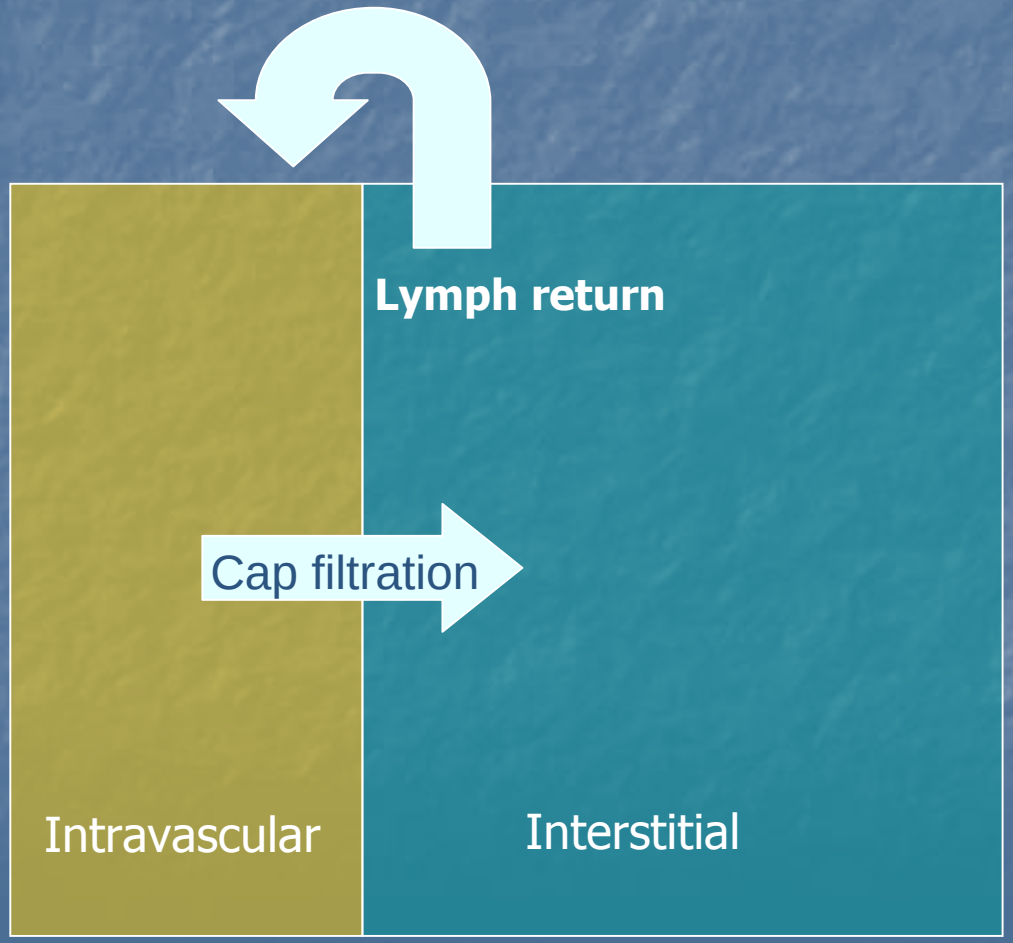
# in Neonatal Foals

# Edema Formation

- Oncotic pressure – hypoproteinemia
- BP/precapillary tone disharmony
- Venous pressure
- GFR/fluid intake balance
- Sodium balance
- Sepsis – direct and indirect factors
- Interstitial tone/compliance

# Fluid Balance In the Fetus

# Determinants of ECF distribution
# Intravascular : Interstitial




Capillary filtration

Lymph flow rates

Rates of fluid movement

- Fetal capillary endothelial barrier
- Lack of precapillary tone
- Plasma volume neg related to BP

# Fetal Fluid Balance
# Transcapillary Fluid Shifts

- Filtration coefficient body capillaries 5X adult
  - Filtration of plasma proteins 15X adult
- Interstitial compliance 10X adult
- Filtration coefficient fetal body 100X placenta
- Body transcapillary fluid movements
  - Dominant on short-term
- Transplacental shifts
  - More important long-term

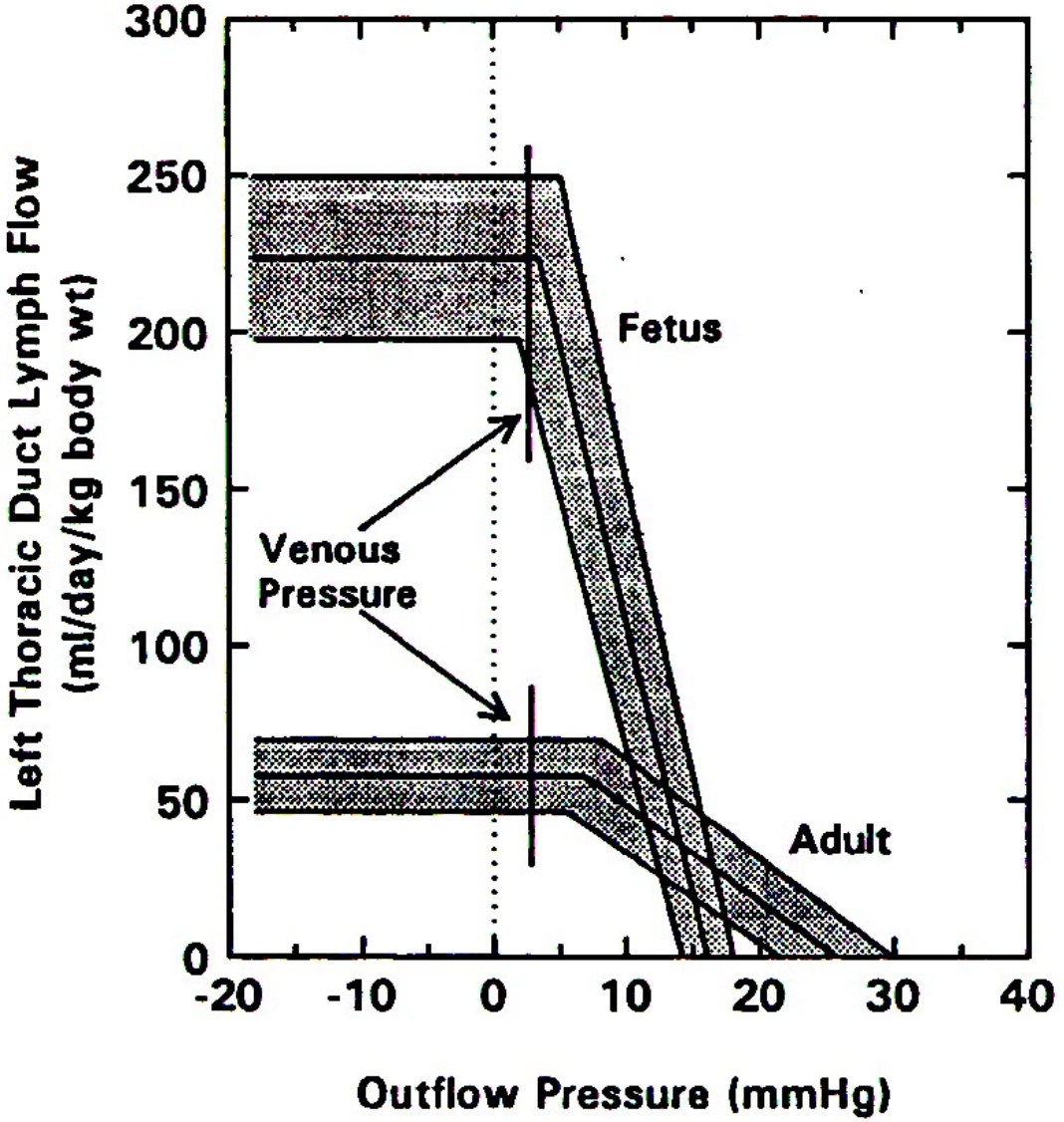
# Fetal Fluid Balance
# Transcapillary Shifts - Blood Loss

Acute hemorrhage

5-25% - 5 min or 30% - 2 hrs

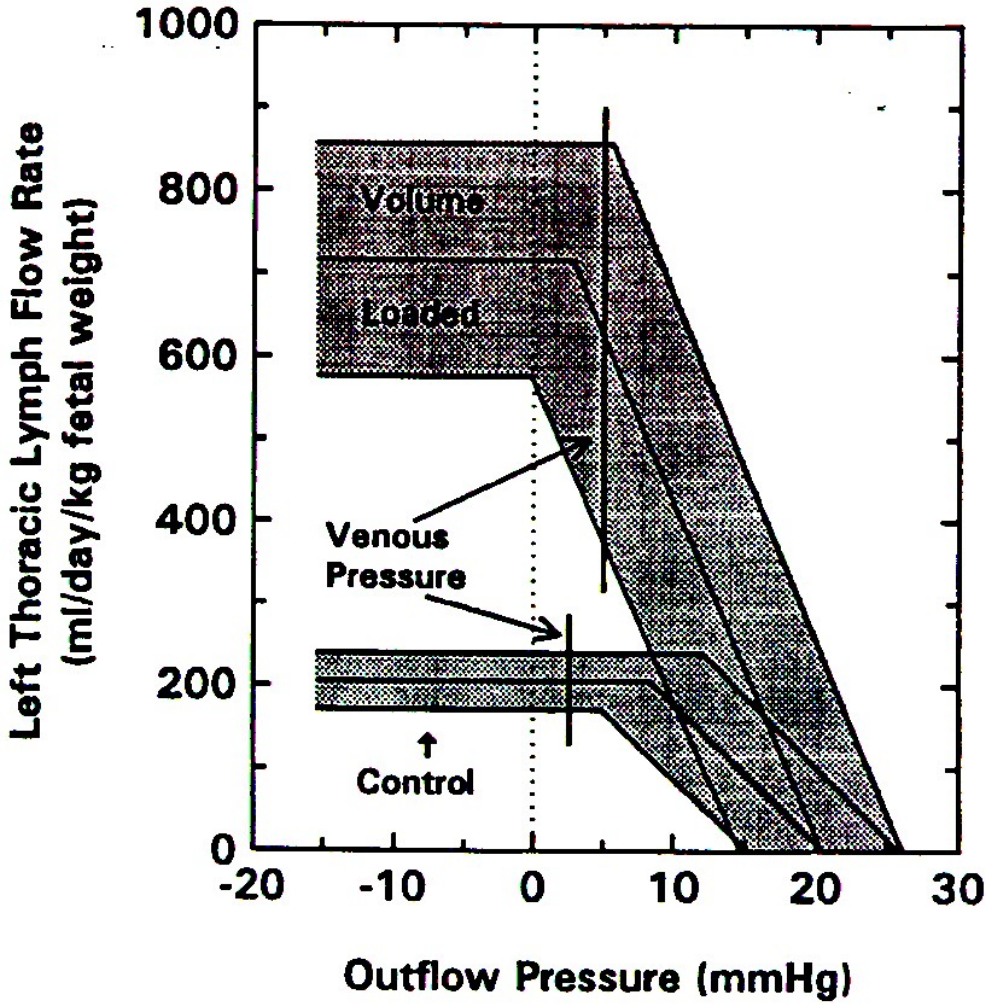
- 50-60% loss volume replaced in 30 min
  - 2X to 3X volume replaced by adult
- Blood volume returns to normal
  - Fetus - within 3-4 hrs of the end of the bleed
  - Adult requires 24-48 hours
- Translocation fluid and protein
  - From fetal interstitial space

# Fetal Fluid Balance
## Lymph Flow



# Fetal Fluid Balance
# Lymph Fluid Shifts

- Lymph flow maintains interstitial volume
- With large volume intravenous infusion
  - ↑↑ Lymph flow as much as 340%
  - Limited by CVP




Fetus, birth, neonate
Fluid Balance Changes

# Perinatal Fluid Shifts
# Plasma Loss - Increase BP

- Days before delivery (fetal sheep)
  - Increased arterial pressure
  - Results in increase capillary pressure
  - Plasma volume shift to interstitium
- During labor
  - Increased vasoactive hormones
    - Vasopressin, norepinephrine, cortisol
  - Plasma volume shift to interstitium

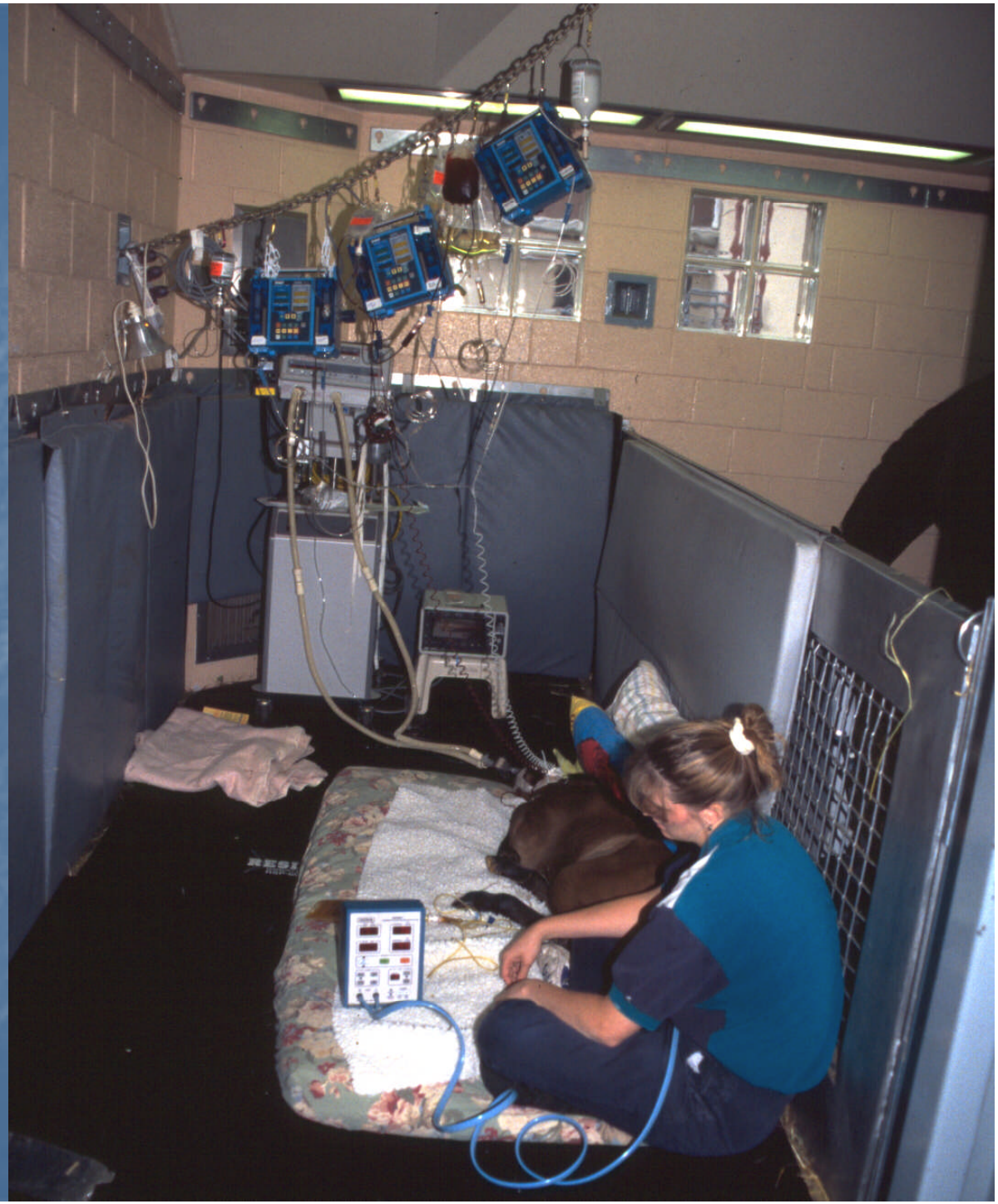
# Perinatal Fluid Shifts
# Hypoxia Associated Plasma Loss

- Mild hypoxia
  - Loss of plasma volume into interstitium
- Severe hypoxia
  - Greater shift in plasma volume
  - Associated with ↑ arterial/venous pressure
    - Causes increased capillary leak

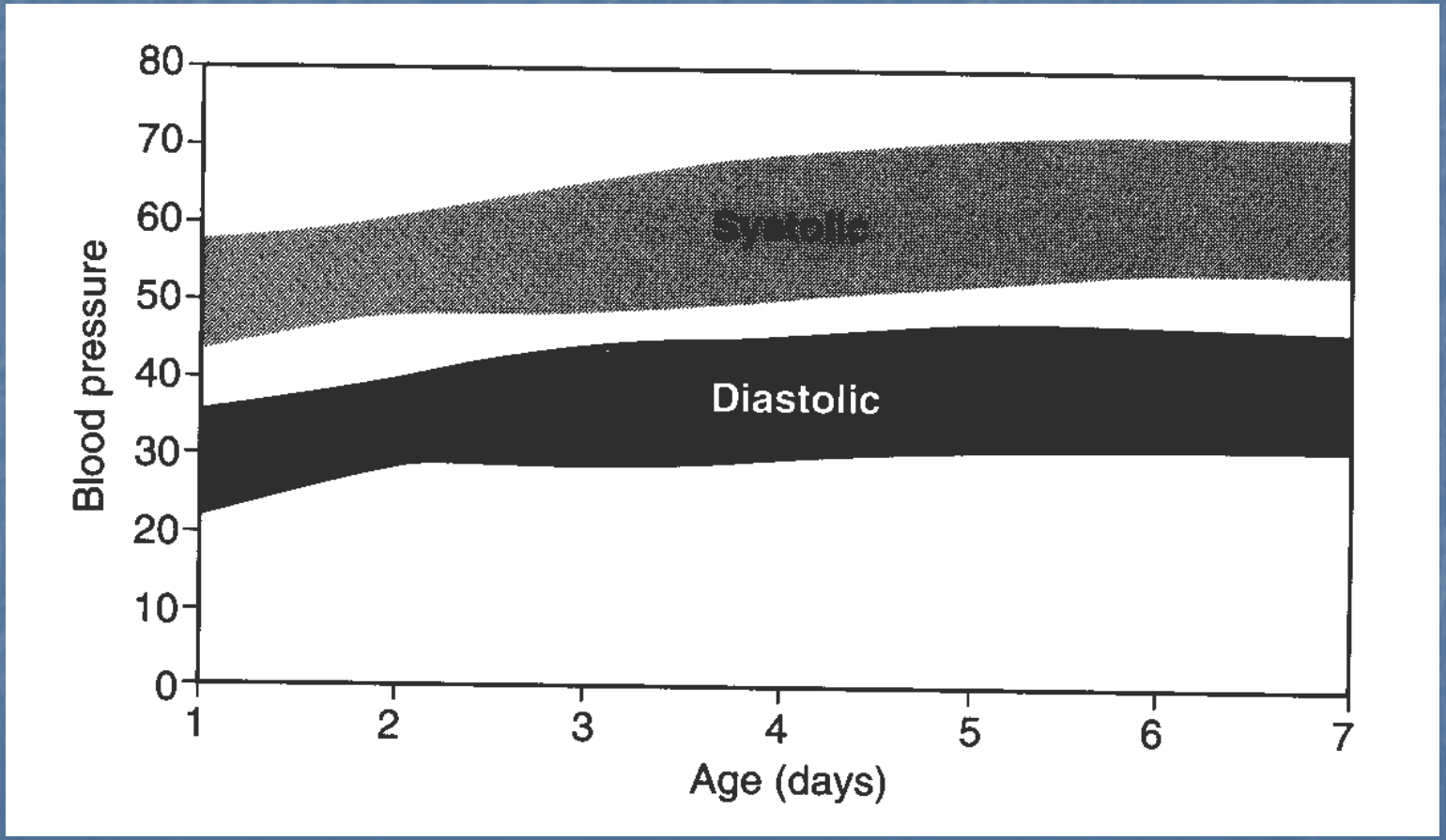
# Perinatal Fluid Shifts
# Adaptive Advantages

- Rapid recovery from acute hemorrhage
- More blood loss is required before BP↓
  - Rapid mobilization of interstitial fluid
- Blood volume restored
  - 1/10 the time of adult
- Protect against neonatal hemorrhage
- Persist for the first week of life
- Same mechanism protects against hypovolemia

# Effect of Blood Pressure



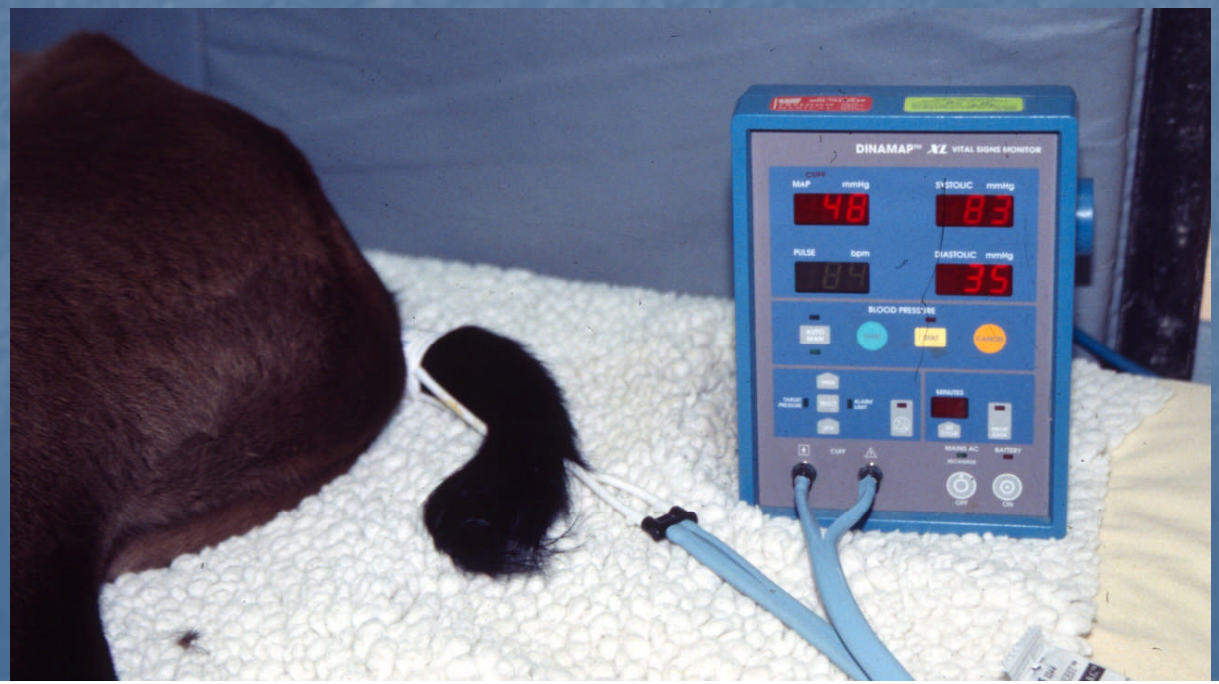
# Normal Term Baby Blood Pressure




Human Neonate – sleeping

# Implications for Intervention

- Fetal existence depends on low systemic BP
- Neonate
  - Also has a low pressure vascular system
  - Important in maintaining plasma volume



# Implications for Intervention

- Neonate is in a transitional state for BP
  - Precapillary tone is the key
  - Once established
    - Systemic BP not transmitted to capillary
    - Increase in peripheral resistance
    - Increase in baroreceptor set point
    - Increase in resting BP
  - Maturation of precapillary tone
    - Occurs regionally
    - Not globally
- Attempts to increase pressure
  - Before the transition
  - May decrease intravascular fluid volume
    - Cause protein leak

# Implications for Intervention

- Method used to raise BP may be important
  - Fluid loading transmitted to the capillaries
  - Adrenergics ?
    - May depend on drug
    - Neonate's receptor maturation
    - Complex physiologic responses
- Lymph Flow
  - Slowed by increased central venous pressure
    - May occur with high fluid infusion rates
    - Advantage of periodic boluses

# Fluid Shifts
# Volume Loading

- Adult
  - Volume load excreted via kidneys within hours
- Neonate
  - Low intravascular retention
  - Little change in vasopressin or rennin levels
  - Atrial natriuretic factor only transient increase
  - Urine flow only very transiently increases
  - Retained fluid load long term
  - Not handle fluid loads well
- Once fluid overloaded
  - Prolonged retention

# Edema Formation

- BP - precapillary tone disharmony
  - Lack precapillary tone
    - Fluids rapidly redistribute to interstitium
    - BP increases before tone develops
      - Fluid loading
      - Increased adrenergic tone
      - Pharmacologic adrenergic effect

# Edema Formation

- Venous pressure
  - Impede lymphatic return
  - Can be secondary to intravenous fluids
    - Pausing fluids after a bolus – second bolus
    - CRI – constant interference

# Edema Formation

- Venous pressure
  - Adrenergic tone – stress/sepsis
    - Venous system stores 70% blood volume
    - Most in splanchnic / skin – side stream of circulation
      - Splanchnic 25% of CO, 20% blood volume
    - "Stressed" & "unstressed" volume
    - Increased adrenergic tone
      - Will mobilize the reserve volume
      - Respond to low level of stimulation
      - Increased simulation – increase SVR
    - Septic mediators do the opposite
      - Increased unstressed volume

# Edema Formation

- GFR/fluid intake balance
  - Fluid overload
  - Cr = 120 µmol/l (1.4 mg/dl) - low GFR
    - Real baseline Cr = 60 µmol/l (0.7 mg/dl)
- Sodium balance
  - Neonate conserves Na
  - Iatrogenic Na overload from fluid therapy
    - Na containing fluids/plasma
    - Nursing foal 1.9 meq/kg/day
    - Fluid therapy – 6 – 10 meq/kg/day

# Edema Formation

- Sepsis
  - Increased adrenergic tone
    - Increase venous tone = edema
    - Increase BP = edema
    - Increased unstressed volume – venous pooling
  - Loss of precapillary tone
  - Endothelial damage – septic shock
- Interstitial tone/compliance
  - Neonate compliance 10X adult
  - Complex control
    - Lymphatic motility – pumping
    - Contractile fibers – vary compliance
  - Adrenergic tone – change characteristics

# Edema Formation

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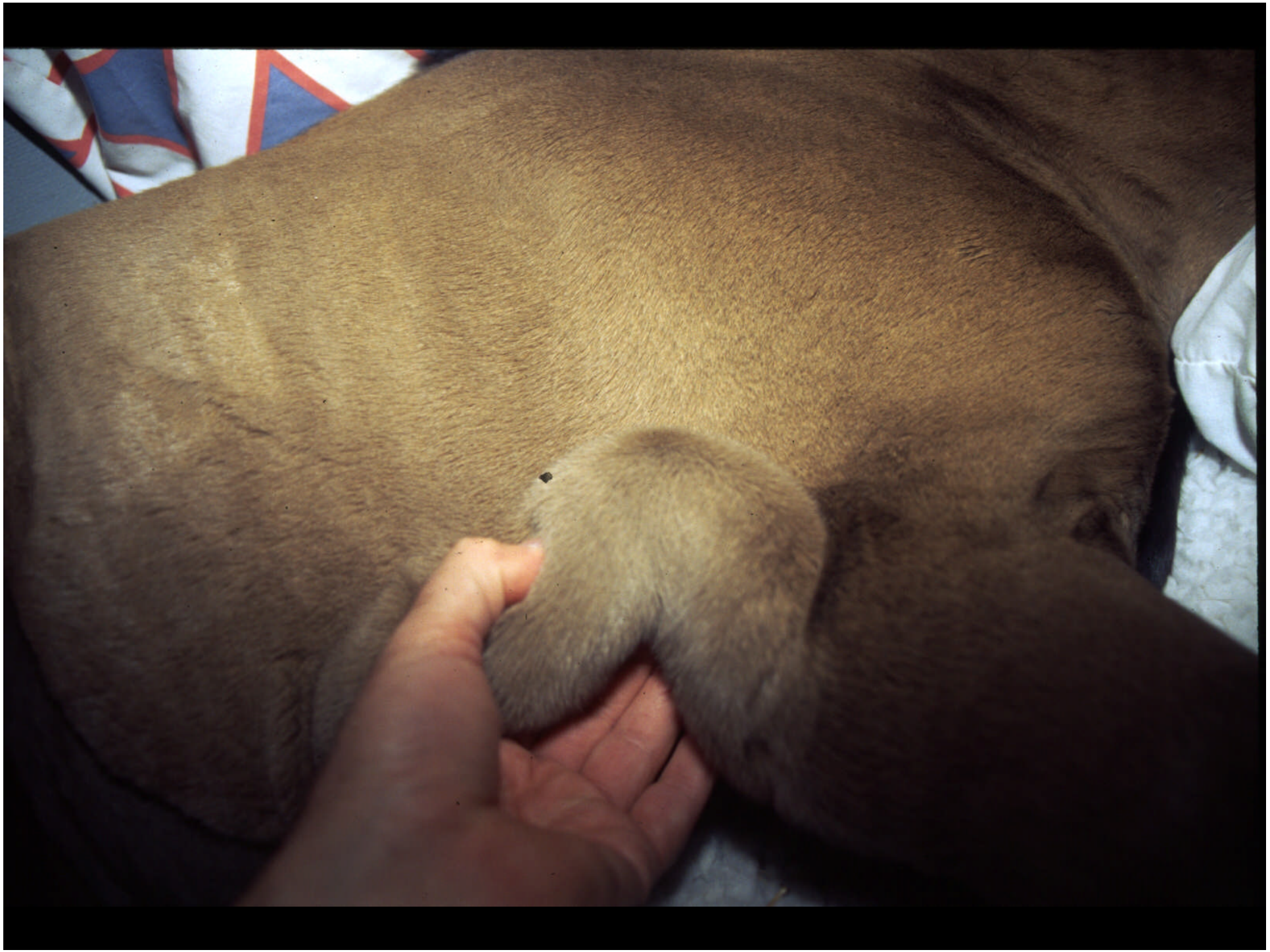


# Renal Function

# in Neonatal Foals

# Fetal-Neonatal Transition

- Fetal kidneys - 3% CO
  - High renal vascular resistance
  - Low GFR
- Newborn about 15% (lambs)
  - At moment of birth immediate increase renal blood flow
    - 86% decrease renal vascular resistance (piglets)
  - Redistribution from the inner cortex to outer superficial cortex
- Weeks after birth
  - Rise in arterial blood pressure
    - Less important
  - Further decrease in vascular resistance
- Both anatomic and vasoactive effect

# Fetal-Neonatal Transition Renal Hemodynamics

- Vasoconstrictors and vasodilators
  - Balance produces renal vascular resistance
  - Differ from adults
    - Different effects
    - Different intrarenal levels
    - Different sites of action
- Balance major determinate of GFR

# Renal Hemodynamics Summary

- Increase renal vascular resistance
  - Angiotensin II
  - Adrenergic tone (circulating/innervation)
- Critical vasodilators counterbalance
  - NO
  - PG
- Increase in renal blood flow
  - Decrease vasoconstrictors

# Fetal-Neonatal Transition Renal Hemodynamics

- PG
  - Intrinsic PG are involved
    - COX 2 (and COX 1)
  - NSAIDs in fetus, neonate
    - Decrease urine output
    - Significant decrease blood flow
    - Increase in renal vascular resistance
    - Fetus - oligohydramnios
  - Vasodilatory
    - Counteract vasoconstricted state

# Fetal-Neonatal Transition Tubular Function

- Fractional Na absorption
  - Less in proximal tubule in neonate
  - More distal tubule
  - Overall lower $FxNa$
- Enhanced distal tubule reabsorb Na
- Blunted Na excretion
  - In the face of a Na load
- Increase transport
  - Maturation of the Na-K-ATPase
  - Increases density

# Autoregulation

- Autoregulation
  - Range of autoregulation set to lower perfusion pressure
    - MAP 40-60
    - Renal pressure-flow relationship changes with renal maturation
  - Mediated by PG dependent rennin release
    - Causing vasoconstriction at lower levels of perfusion pressure
    - NSAID therapy may disrupt

# Tubuloglomerular Feedback

- Tubuloglomerular feedback
  - Macula densa cells
    - ↓ NaCl  delivery distal tubules
    - Inverse relationship NaCl absorption, PG production
    - Stimulate angiotensin II form juxtaglomerular cells
    - Constrict efferent arterioles
    - Increase GFR
  - Matures with growth
    - Maximally sensitive at normal tubular flow range
    - As GFR increases, maximum response and flow range also increases
    - Relative sensitivity unaltered during growth

# Consequences of Renal Failure

- Failure to
  - Regulate fluid balance – water overload
  - Regulate electrolyte balance
    - Na
    - K
    - Ca, PO4, Mg
  - Regulate acid-base balance
    - Cl
    - SID

# Pathogenesis Abnormal GFR

- Vasomotor nephropathy

  Decrease renal blood flow

  - Hypovolemia
    - Release vasoconstrictors
      - Angiotensin II, vasopressin, catecholamines
  - Sepsis
    - Inflammatory mediators
    - Hypovolemia
    - Release of vasoactive mediators
  - Hypoxia/asphyxia
    - Overactivation of the rennin-angiotensin system, intrarenal adenosine, vasopressin, catecholamines
- Extrarenal and intrarenal – difficult to separate

# Pathogenesis Abnormal GFR

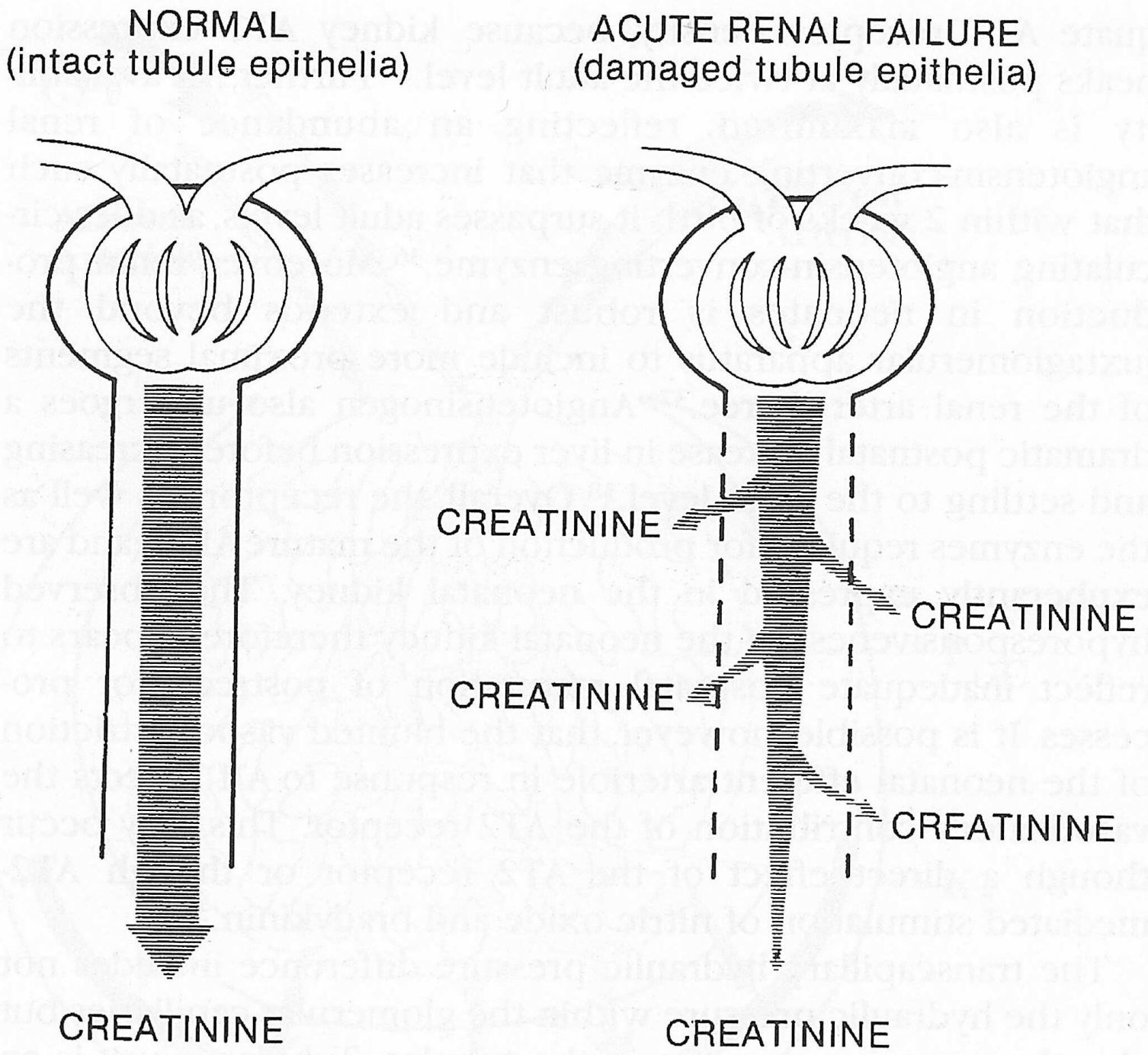
- Other causes - NSAIDs
  - High PG levels
    - Needed to maintain perfusion neonatal kidney
  - Hypotension/hypovolemia
    - High PG levels
  - NSAIDs
    - Reduce GFR
    - Reduce renal blood flow
    - Effect transient
    - Nonselective and COX-2 selective inhibitors
      - Same effect
    - Also may affect
      - Autoregulation
      - Tubuloglomerular feedback

# Acute Renal Failure Autoregulation

- Autoregulation impaired in Acute Renal Failure
  - Decreasing renal blood flow
  - Decrease GFR
  - Cause additional renal ischemia
- Neonates
  - Autoregulate with low BP
  - Low set point
  - But with volume depletion
    - Higher renal vascular resistance
    - Lower GFR
    - Potentially more injury

# ARF

- Tubular injury
  - Interrupts structural integrity
  - Loss of tight junctions
  - Backleak of Cr
  - High plasma Cr
    - How much is decrease GFR
    - How much is back leak


NORMAL
(intact tubule epithelia)
ACUTE RENAL FAILURE
(damaged tubule epithelia)
CREATININE
CREATININE
CREATININE
CREATININE
CREATININE
CREATININE

# Causes Acute Renal Failure

- Decrease GFR
  - Prerenal azotemia
  - Neonatal Vasogenic Nephropathy
  - Glomerulonephritis
- Tubular dysfunction
  - Acute Tubular Necrosis
  - Osmotic Nephrosis
  - Renal Tubular Acidosis

# Causes Acute Renal Failure

- Interstitial Nephritis
  - Idiosyncratic Drug Reactions
  - Sepsis
  - Immune Mediated Interstitial Disease
- Infections
  - Systemic sepsis
  - Interstitial
  - Abscesses Pyelonephritis

# Causes Acute Renal Failure

- Toxic Nephropathies
  - NSAID
    - Flunixin, Phenylbutazone, COX 2 inhibitors
  - Antimicrobials
    - Aminoglycosides
    - Beta-lactams: cephalosporins, penicillins, carbapenems
    - Trimethoprim-sulfa drugs
    - Macrolides
    - Fluoroquinolones
    - Tetracyclines
  - Other drugs
    - Furosemide

# Neonatal Vasomotor Nephropathy

# Neonatal Vasomotor Nephropathy

- GFR and RBF
  - Balance afferent/efferent tone
  - Vasoconstrictors
    - Angiotensin II
    - Adrenergics
      - Circulating – epi/norepi
      - Renal derived
      - Renal sympathetic tone
    - Vasodilators
      - PG
      - NO

# Neonatal Vasomotor Nephropathy

- Risk
  - Hypovolemia/hypoperfusion
  - Stress
  - Hypertension
  - Autonomic dysfunction
  - Pressor therapy
  - NSAID therapy
  - Failure birth transition
- Signs
  - Oliguria
  - Concentrated urine
  - Normal/high/low Fxna
  - Slow Cr decrease or increase

# Neonatal Vasomotor Nephropathy

- Therapy
  - Volume trial
  - Inotrope/pressor trial
    - Dopamine?
  - Furosemide trial
    - Increase PG – vasodilate
    - 1-4 mg/kg trial doses
  - Time
- Consequences
  - Usually no parenchymal damage
    - Can occur rare cases
    - Increase/failure to decrease Cr
    - Sodium waisting
  - Fluid/water overload
  - Na overload
  - Impaired acid/base correction?