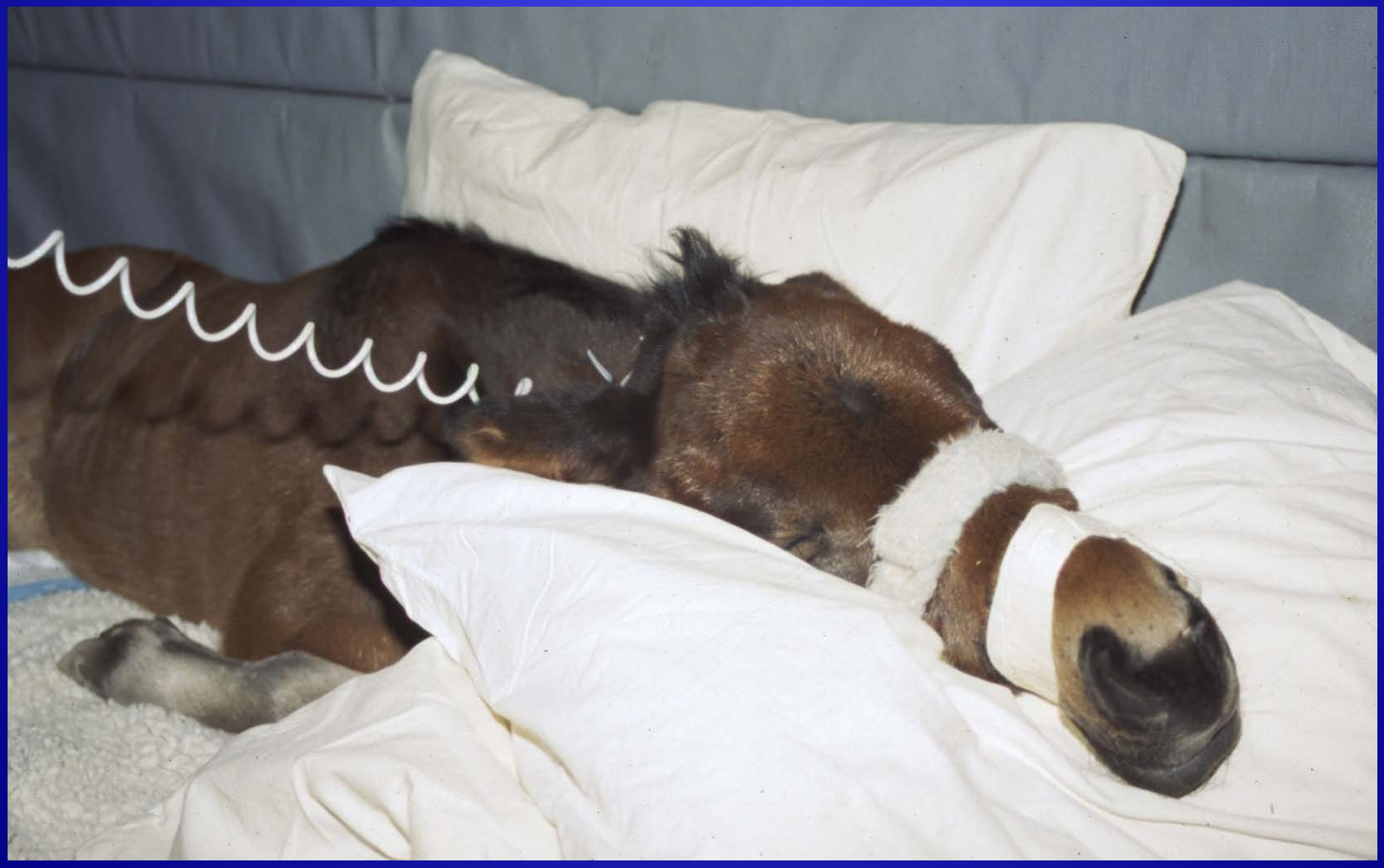
# When Fluids are Not Enough: Inopressor Therapy



# Problems in Neonatology

- Neonatal problem: hypoperfusion
  - Severe sepsis
  - Hallmark of septic shock
  - Secondary to neonatal encephalopathy
  - Vasoplegia Syndrome??
- First line therapy
  - Fluid loading – 20 ml/kg boluses
- Inopressor therapy
  - Inotropic therapy
  - Pressor therapy

# Treating Hypoperfusion

- GOAL: return of perfusion
  - Not to achieve a given set of blood pressure values
- Measure of perfusion
  - Flow is proportional to left ventricular output
  - Flow is inversely proportional to vascular resistance
  - BP is a measure of these
- But…
  - High blood pressure ≠ flow
  - Low blood pressure ≠ no flow

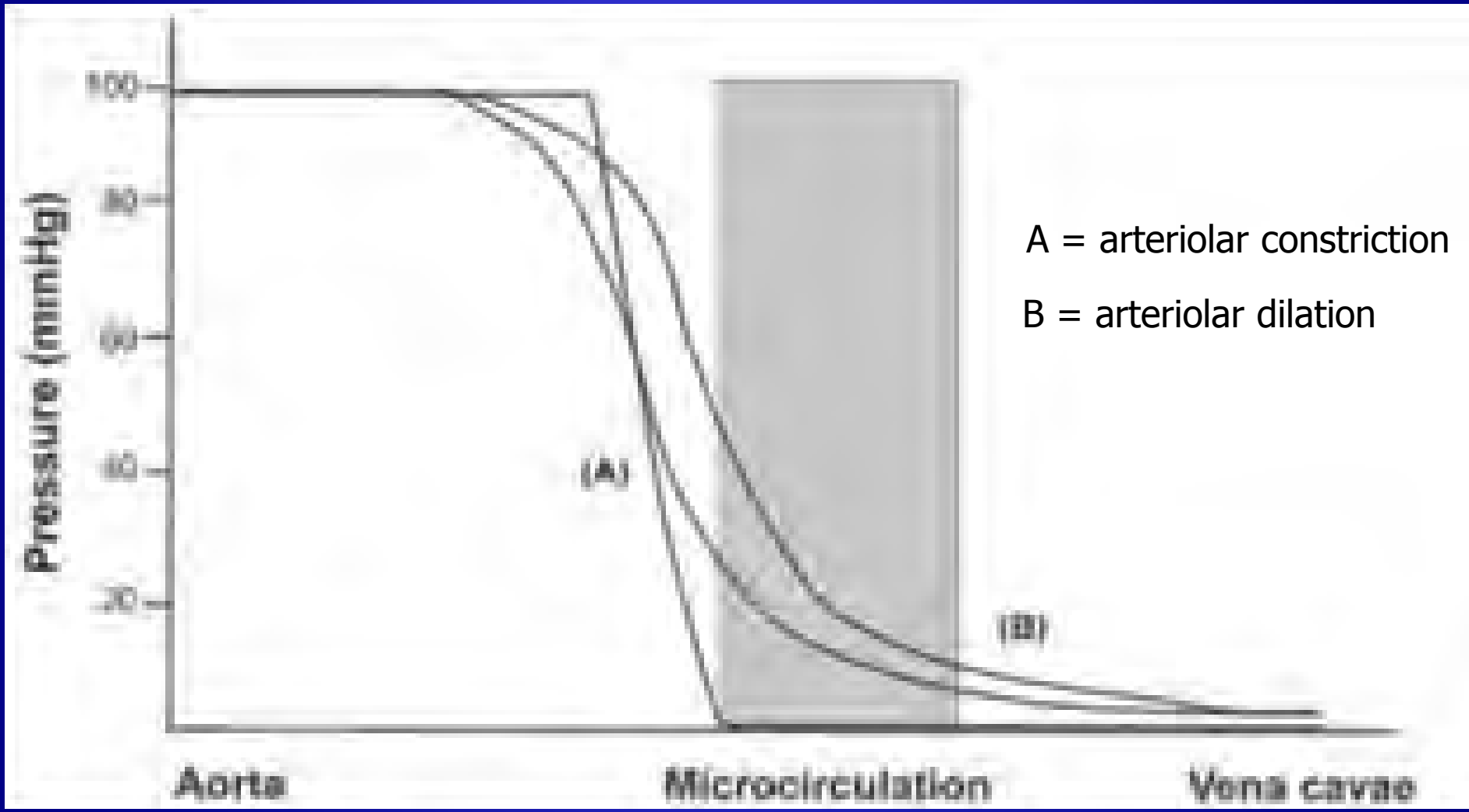
# BP and Capillary Perfusion Clinical Experience

- BP does not correlate with microcirculatory flow
- Increasing BP with noradrenaline
  - Unpredictable effects on capillary perfusion
- Normalizing BP with pure vasoconstrictor
  - Phenylephrine
  - Decrease microcirculatory perfusion
- Impaired cardiac function
  - Vasopressor increases afterload
  - Reduce cardiac output with increase BP
  - No benefit global perfusion

# Perfusion Physiology

- Normal foal
  - BP ≠ perfusion (tissue blood flow)
    - Microcirculation controlled by metabolic demand
    - ADP, K, $H^+$ or NO (shear stress), $O_2$ levels
- When decrease BP
  - Sympathetic control
    - Overrides tissue-driven blood flow regulation
    - Baroreceptors response
  - Peripheral vasoconstriction to preserve
    - Preserve heart and brain perfusion
    - At expense of global tissue hypoperfusion
- Shock

# Hydrostatic Pressure

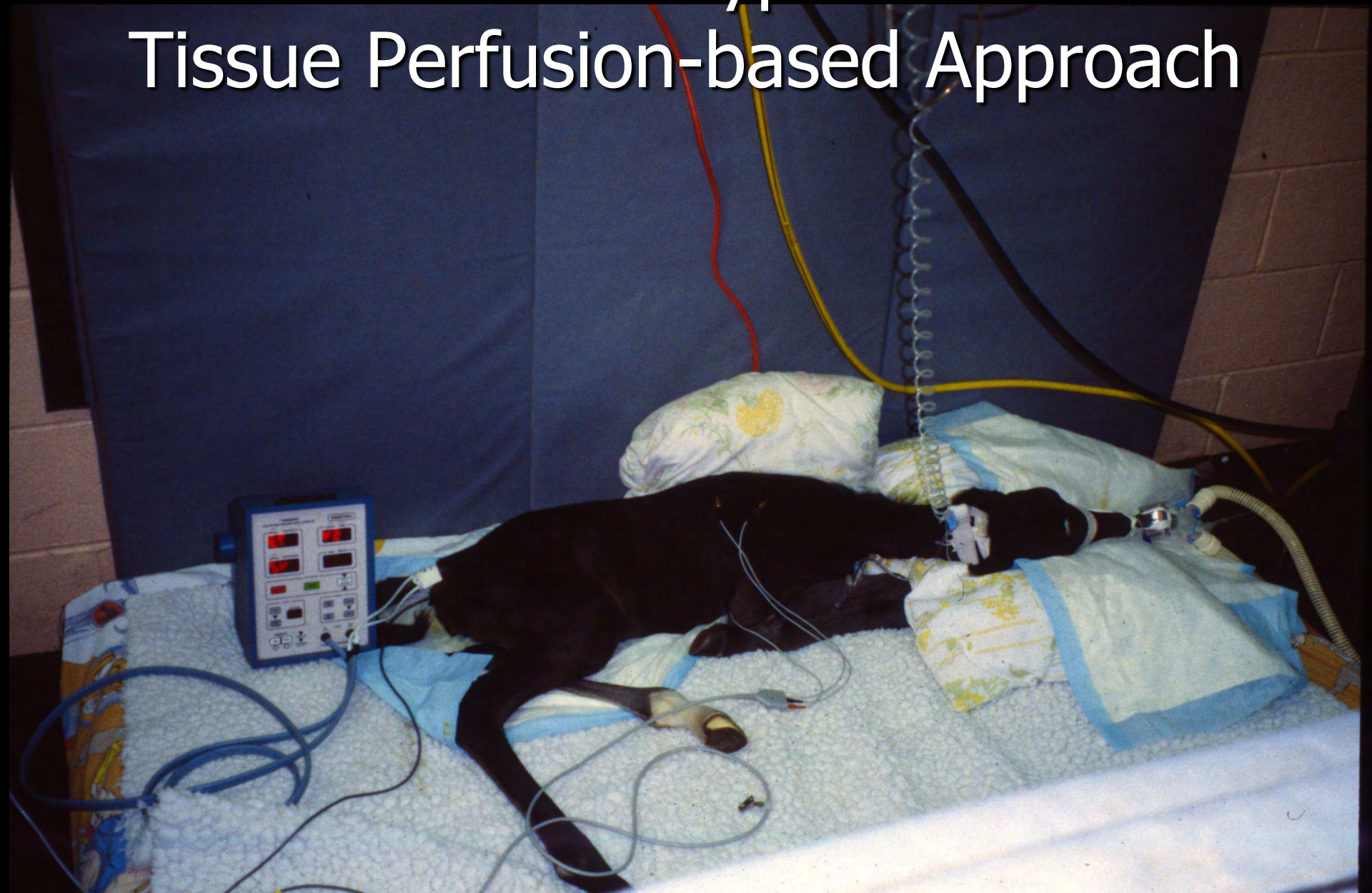



A = arteriolar constriction

B = arteriolar dilation

Dünser *et al*. *Critical Care* 2013, **17**:326

# Permissive Hypotension
# Tissue Perfusion-based Approach



# Resuscitation Endpoints
## Dünser et al

- Step one
  - Target BP to preserve heart and brain perfusion
  - Each individual will have a different target
- Step two
  - Target tissue perfusion-based endpoints
  - Currently no reliable microcirculatory perfusion markers
  - Indirect/Downstream markers of tissue perfusion
    - Arterial lactate, peripheral perfusion, urine output, central venous oxygen saturation
    - Macrohemodynamic variables minor importance (BP,CO)

# Resuscitation Endpoints
## Dünser et al

- Step three
  - Target markers of single-organ perfusion
  - Kidneys
    - Poorest capability to adjust to reductions in blood flow
    - Increasing noradrenaline doses
      - May augment kidney perfusion and urine output
      - Poor correlation of BP and renal perfusion
- Need to insure as move through steps
  - That previous target is not negated
- May need to decrease adrenergic support
  - To achieve the target
- Therapy must not be guided by BP alone


CRITIKON
DINAMAP
VETERINARY BLOOD PRESSURE MONITOR
MAP
45
SYSTOLIC
73
PULSE
97
DIASTOLIC
35
AUTO
MANUAL
START
CUFF
POWER
OFF
ON

# Inopressor Therapy Adrenergic Agonists

- Pharmacokinetics varies with individual
  - Plasma half-life
  - Receptor density
  - Receptor affinity
  - Receptor reactivity
  - Plasma pH
- Dose tailored to individual
  - CRI
    - Short half-life
    - Effect of new dose evident within 10 to 15 minutes
    - Effective Dose may change with time
- Goal: Withdraw therapy as soon as possible

# Inopressor Therapy
# "Rule of 6"

- Dopamine, dobutamine - 1 µg/kg/min

  6 X wt (kg) = # mg added to 100 ml

  1 ml/hr infusion = 1 µg/kg/min. drug delivery
- Adrenaline , noradrenaline – 0.1 µg/kg/min

  0.6 X wt (kg) = # mg added to 100 ml

  1 ml/hour infusion = 0.1 µg/kg/min. drug delivery
- Take out amount added

# Inopressor Therapy Adrenergic Agonists

- Ensure cardiac output
- Pressors without inotropic support
  - Cardiac output may fall
  - Perfusion may decrease
  - Despite rise in blood pressure numbers
- Inotropic support almost always indicated
- Mixed inotropic and pressor support
  - Inopressor support
  - Selecting an inotrope
    - Dobutamine
    - Medium dose dopamine
    - Low dose noradrenaline
    - Adrenaline
  - If inotropic effect does not increase perfusion adequately
    - Add a pressor

# Inopressor Therapy Adverse Effects

- Pharmacologic doses of adrenergic agonists
  - Increase in perfusion
  - Increase in maldistribution of that perfusion
  - Balanced between
    - Improved perfusion
    - Exaggerated maldistribution
- Aggressive support
  - "Industrial strength" agents
  - Goal: returning perfusion to minimally acceptable levels
  - Not to try to achieve normal perfusion
  - Not to try to achieve supernormal perfusion
    - Result in disastrous effects

# Inopressor Therapy Dobutamine

- Good inotrope
  - Primarily β1 activity
    - at low to moderate doses
- In man
  - Mild vasodilation
    - Some α2 activity
  - Well balanced α1 and α2 stimulus
- In horses
  - At high doses
    - Significant vasoconstriction
    - α1 activity appears
  - Inopressor at high doses

# Inopressor Therapy Dobutamine

- When support needed but not shocky
  - Begin 3-5 µg/kg/min
  - Titrate to effective dose
- With severe sepsis, septic shock
  - Begin 5-10 µg/kg/min
  - Titrate to effective dose
- Dose range is 2-20 µg/kg/min
  - Occasional cases - 50 µg/kg/min
- Adverse reactions
  - Tachycardia
  - Occasional arrhythmias

# Inopressor Therapy
# Dopamine

- Low doses - dopaminergic activity
- Moderate doses - $\beta$1 & $\beta$2 activity
- High doses - $\alpha$1 activity

  noradrenaline  release from nerve terminals

  Major mode of action at high doses??
  - Limitation with depletion in critical patients
- Inopressor
- Complex GI actions

  Dysmotility

# Inopressor Therapy Dopamine

- When support needed but not shocky
  - Begin 3-5 µg/kg/min
  - Titrate to effective dose
- With severe sepsis, septic shock
  - Begin 5-10 µg/kg/min
  - Titrate to effective dose
- Dose range is 2-20 µg/kg/min
- Adverse reactions
  - Doses > 20 µg/kg/min
    - Intrapulmonary shunting
  - Occasional arrhythmias

# Inopressor Therapy Noradrenaline

- Potent vasopressor
  - Strong $\alpha 1$ activity
  - Both inotropic and chronotropic activities
  - $\beta 1$ activity
  - Variable $\beta 2$ activity
  - Chronotropic – usually blunted by vagal reflex
  - $\uparrow$ myocardial oxygen consumption
- Thought of primarily as a pressor
  - Advocated in septic shock
  - Used in combination with either dopamine or dobutamine
- More maldistribution than the other adrenergics

# Inopressor Therapy Noradrenaline

- Initial dose
  - 0.3-0.5 µg/kg/min
  - Titration to effective dose
- Dose range
  - 0.1-3 µg /kg/min
- Difficult cases
  - 4 to 5 µg/kg/min
- Adverse reactions
  - Arrhythmias
    - Rare without pre-existing myocardial damage
      - Hypoxic ischemic or asphyxial disease
      - Sepsis

# Inopressor Therapy
# Adrenaline

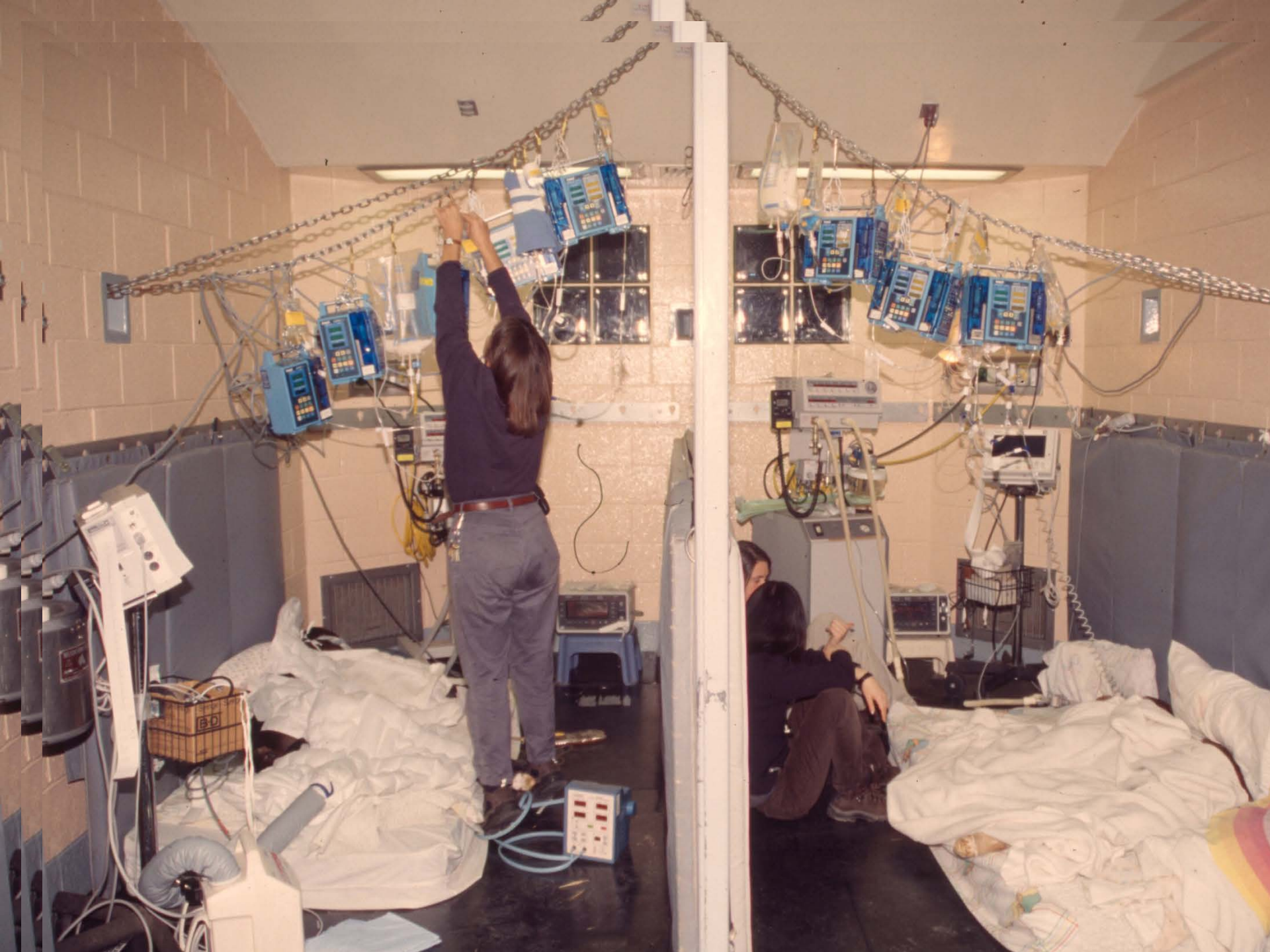
- Primarily beta activity at low doses - inotropic
  - β1, β2 activity
  - ↑ cardiac output
  - ↓ peripheral resistance
- Inopressor activity as the dose increases
  - α1, α2 activity as well as β1, β2 activity
- Metabolic affects
  - Hyperglycemia
  - ↑ lactate production
    - Rapid and may be dramatic
    - Easily reversible

# Inopressor Therapy Adrenaline

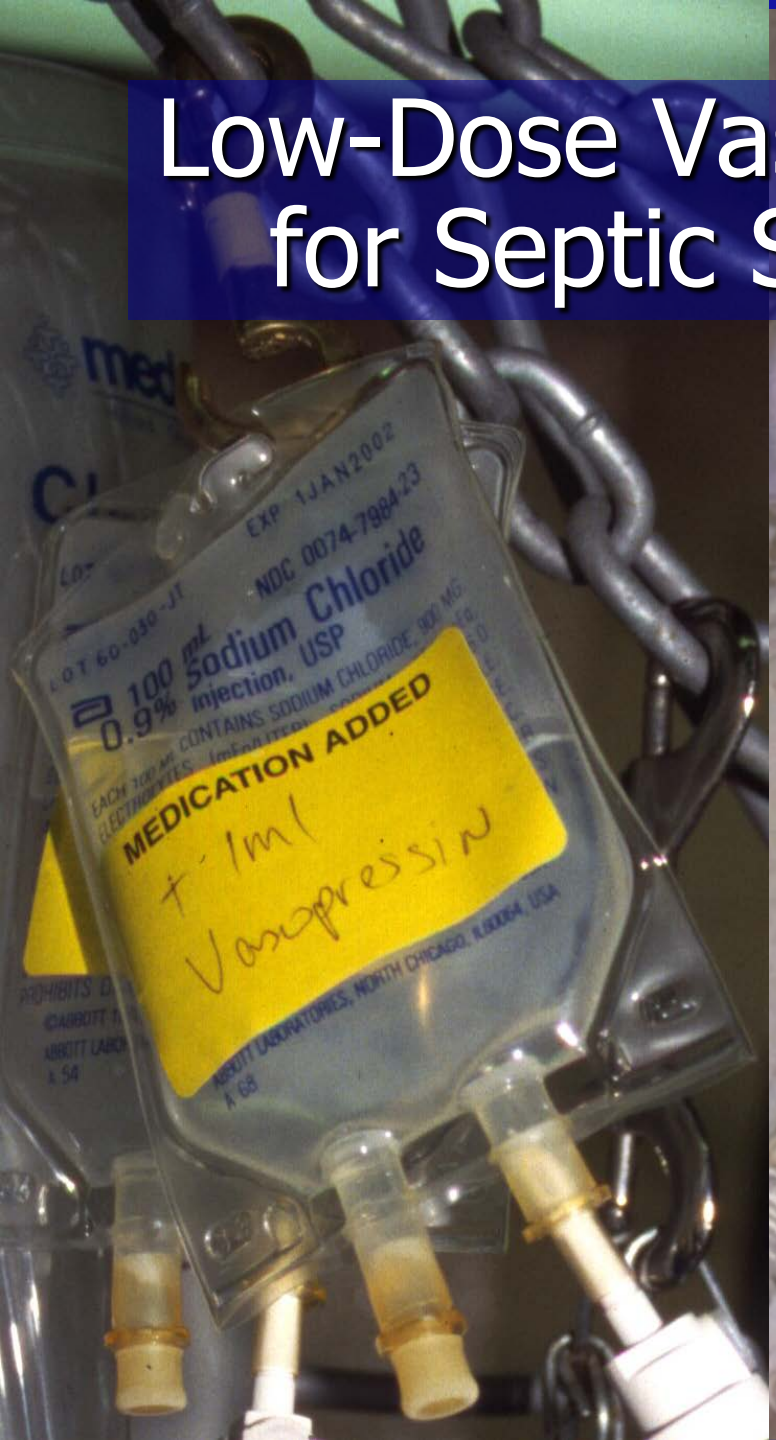
- For its inotropic effect
  - Start 0.3-0.5 µg/kg/min
  - Titrate to an effective dose
- Dose range
  - 0.1-2.0 µg /kg/min
  - Difficult cases – 3 to 4 µg/kg/min
- Adverse reaction
  - Metabolic derangements
  - Occasional arrhythmias
    - With pre-existing myocardial damage
      - Hypoxic ischemic asphyxial disease
      - Sepsis

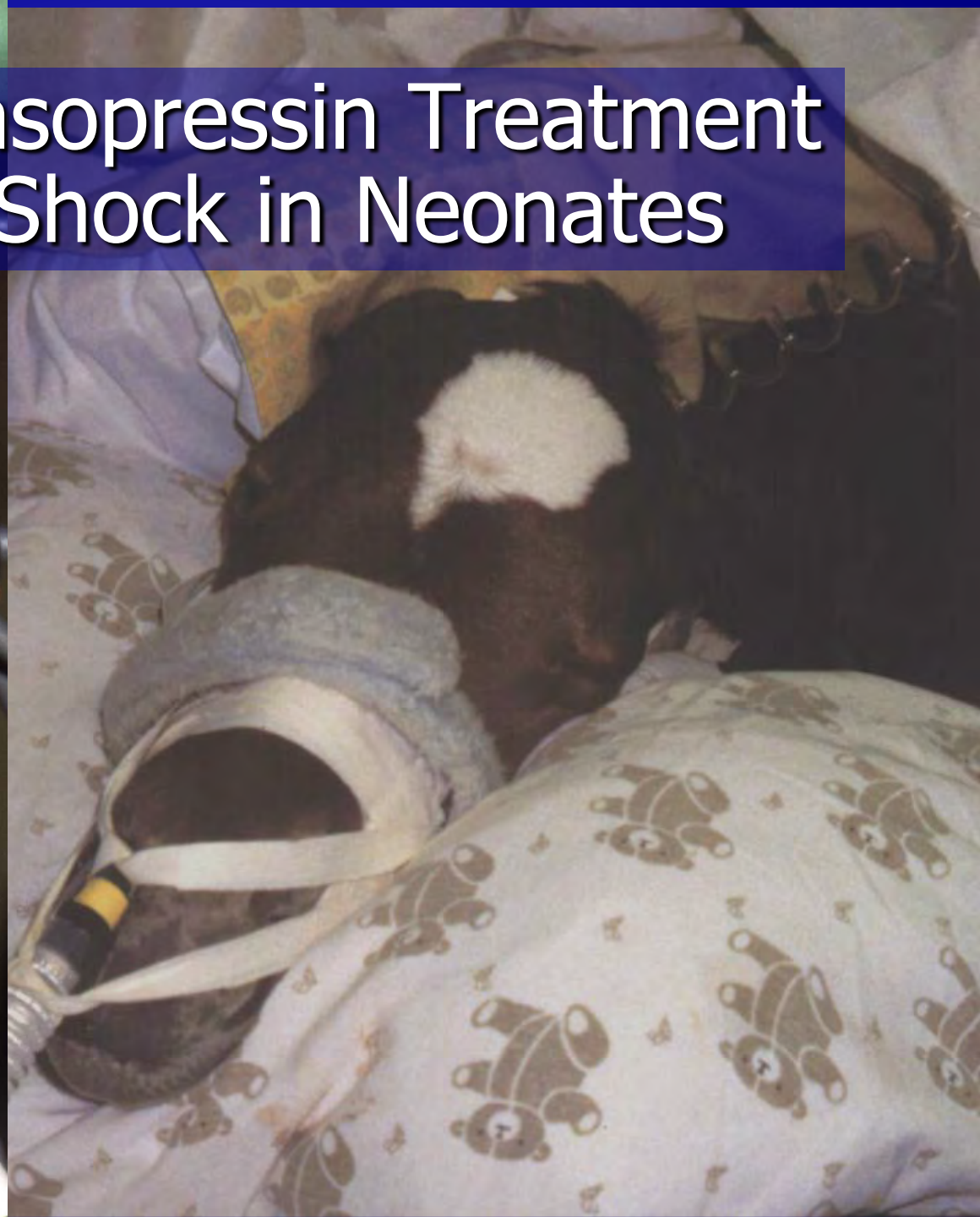
# Inopressor Combinations

- Dobutamine – Dopamine
- Dobutamine – Noradrenaline
- Adrenaline – Noradrenaline
- Dobutamine – Dopamine – Noradrenaline
- Dobutamine – Vasopressin***


BD

# Low-Dose Vasopressin Treatment for Septic Shock in Neonates



# Vasopressin Release

- Increase plasma osmolarity
- Baroreflex response
  - Decrease blood volume
  - Decrease blood pressure
- Other stimuli
  - Adrenergic agents
  - Pain, Stress
  - SIRS – Cytokines, Prostaglandin
  - Hypoxia, Hypercapnia

# Vasopressin Receptors

- Vascular $V_1$ receptors ($V_{1a}$)
  - Causes vasoconstriction
- Renal $V_2$ receptors (antidiuretic action)
  - Aquaporin 2 channels
- Anterior pituitary $V_3$ receptors ($V_{1b}$)
  - Stimulates the release of ACTH
  - Role in memory, emotion
- Oxytocin receptors
  - Mixed vasodilatation/constriction

# Vasopressin Blood Pressure

- Pressor action
  - Traditionally thought pharmacologic effect
  - More potent than Angiotensin II, noradrenaline
- Increases systemic vascular resistance
  - $V_1$ receptors in the medulla oblongata
    - Reset the cardiac baroreflex
    - Slows heart rate – arterial pressure unchanged
- Baroreceptor dysfunction
  - Sympathetic nerve impairment
  - Autonomic failure
  - Enhanced pressor activity of vasopressin

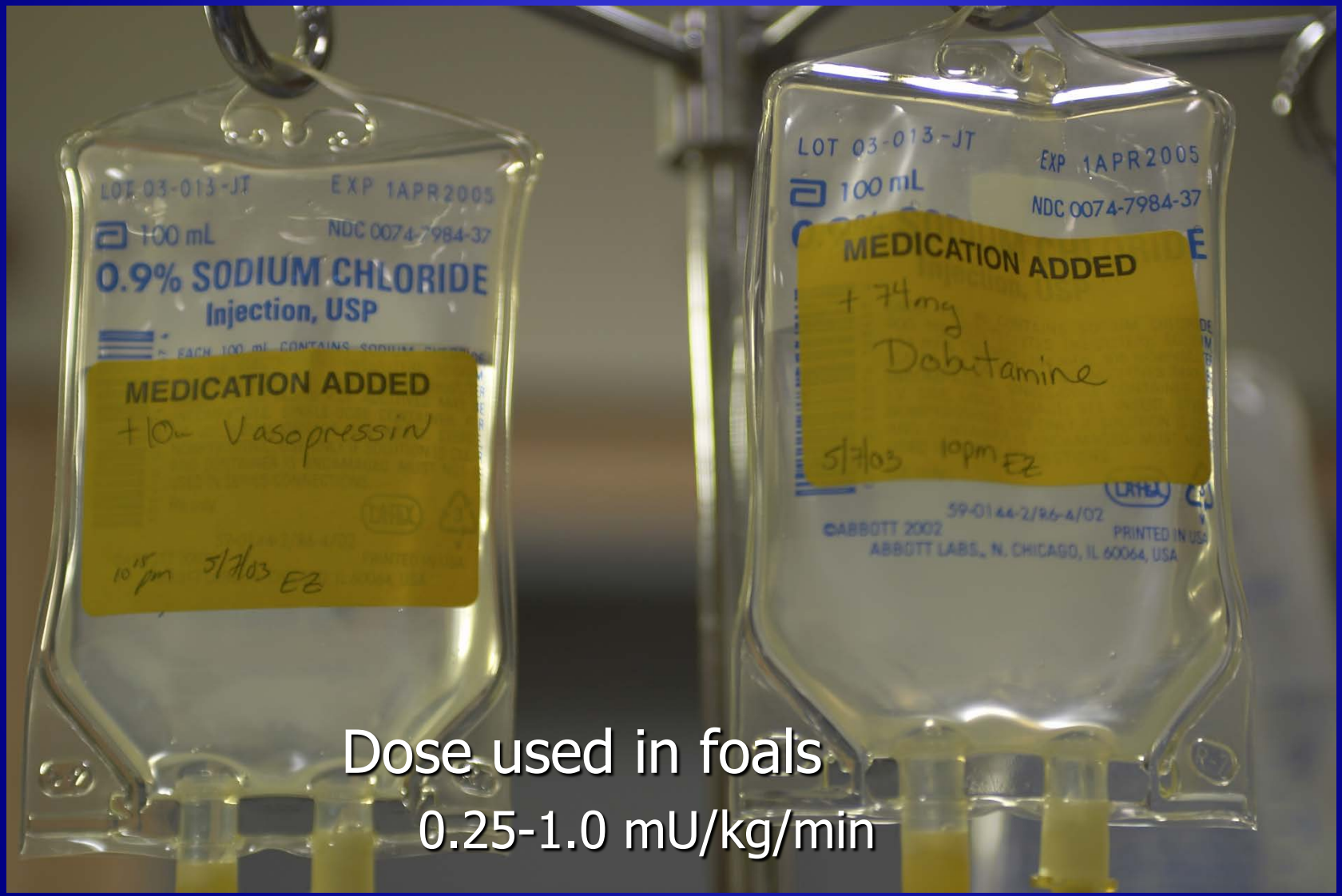
# Vasopressin Vasoconstrictor Activity

- Role in the regulation of arterial pressure
- Hypovolemic states
  - Water deprivation
  - Hemorrhage
  - Fluid loss
- Septic shock
  - Very sensitive to the pressor action
  - Vasopressin blood level very low
  - Cytokine levels should stimulate vasopressin release

# Inappropriately Low Levels in Septic Shock

- Impaired baroreflex-mediated secretion
- Secondary to autonomic failure
- Depleted pituitary vasopressin stores
  - Excessive secretion in early stages of septic shock
  - Exhaustion of stores of vasopressin

# Resuscitation of the Critical Foal
# Vasopressin




Dose used in foals

0.25-1.0 mU/kg/min

# Infusion of Exogenous Vasopressin

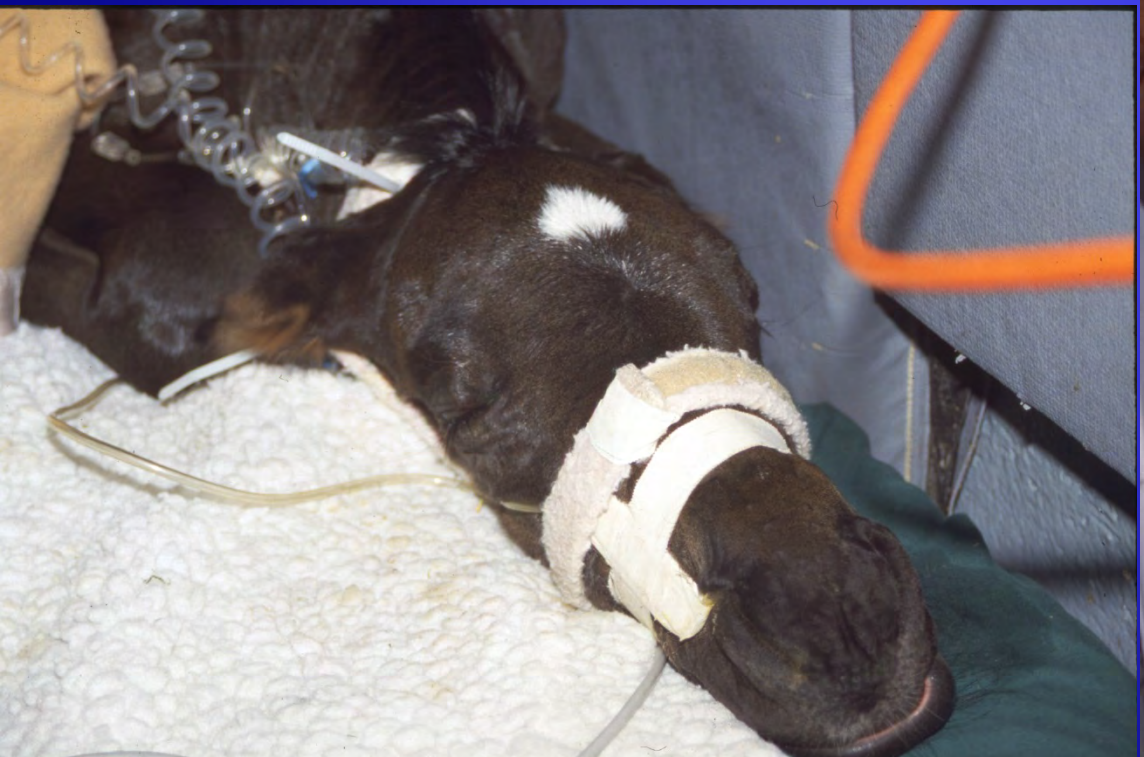
- Increase in systolic pressure
  - Patients in septic shock
  - Not occur in normal subjects
- Vasoconstrictor action low dose vasopressin
  - Blood pressure maintained without catecholamines
  - Result in plasma concentrations near normal levels
- Septic shock
  - Vasopressin secretion is inappropriately low
  - Pressors sensitivity to vasopressin is enhanced
  - Autonomic failure

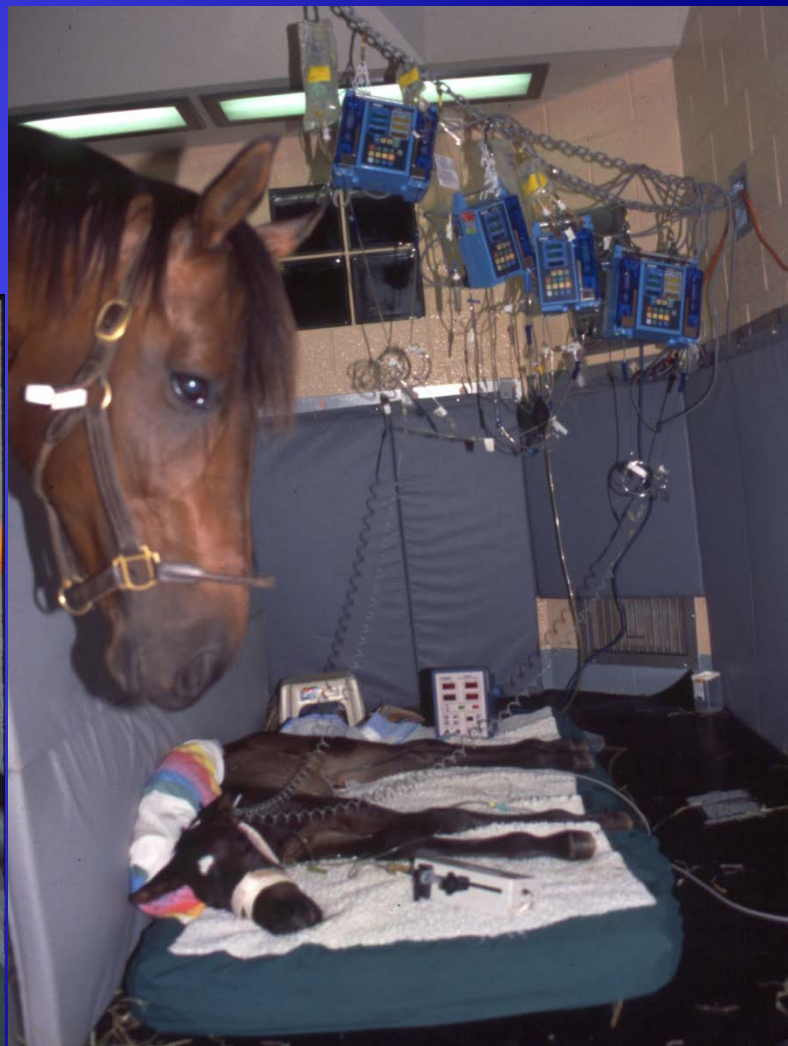
# Urine flow rates

- Increase significantly
  - Improve renal perfusion
  - Constrict only the efferent arterial
    - Maintaining glomerular filtration rate
- Tubular effect ($V_2$)
  - Not present
  - Why?

# Hypoperfusion in Septic Shock

Initially responsive
Becomes refractory

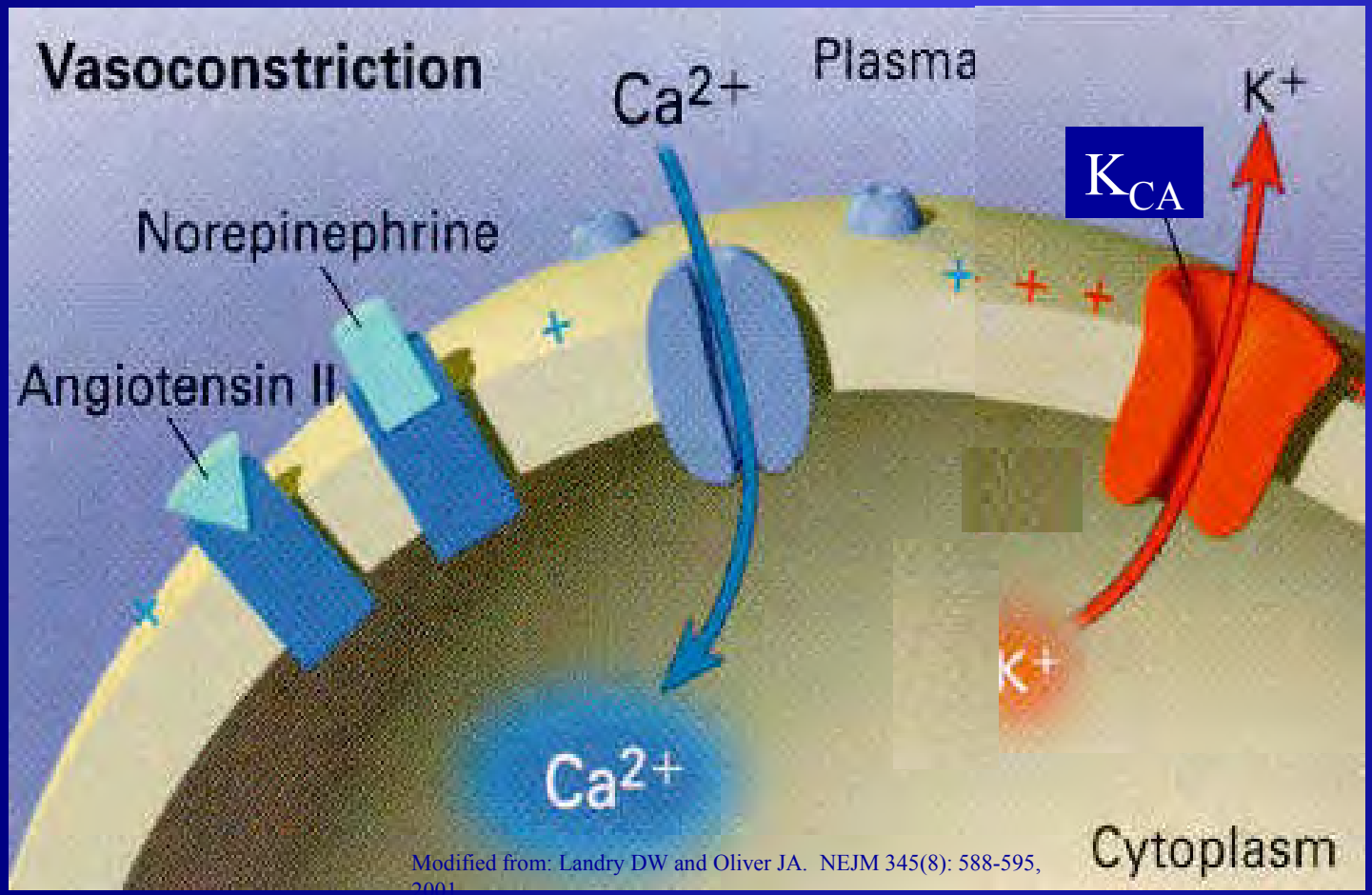




# Septic Shock
# Mechanism of Hypotension

- Active vasodilation
  - Initiators of SIRS
    - TNF, IL-1, other cytokines
  - Increase generation of local NO
- Abnormalities in vasoconstriction
  - Adrenergic down-regulation

# Normal Vasoconstriction

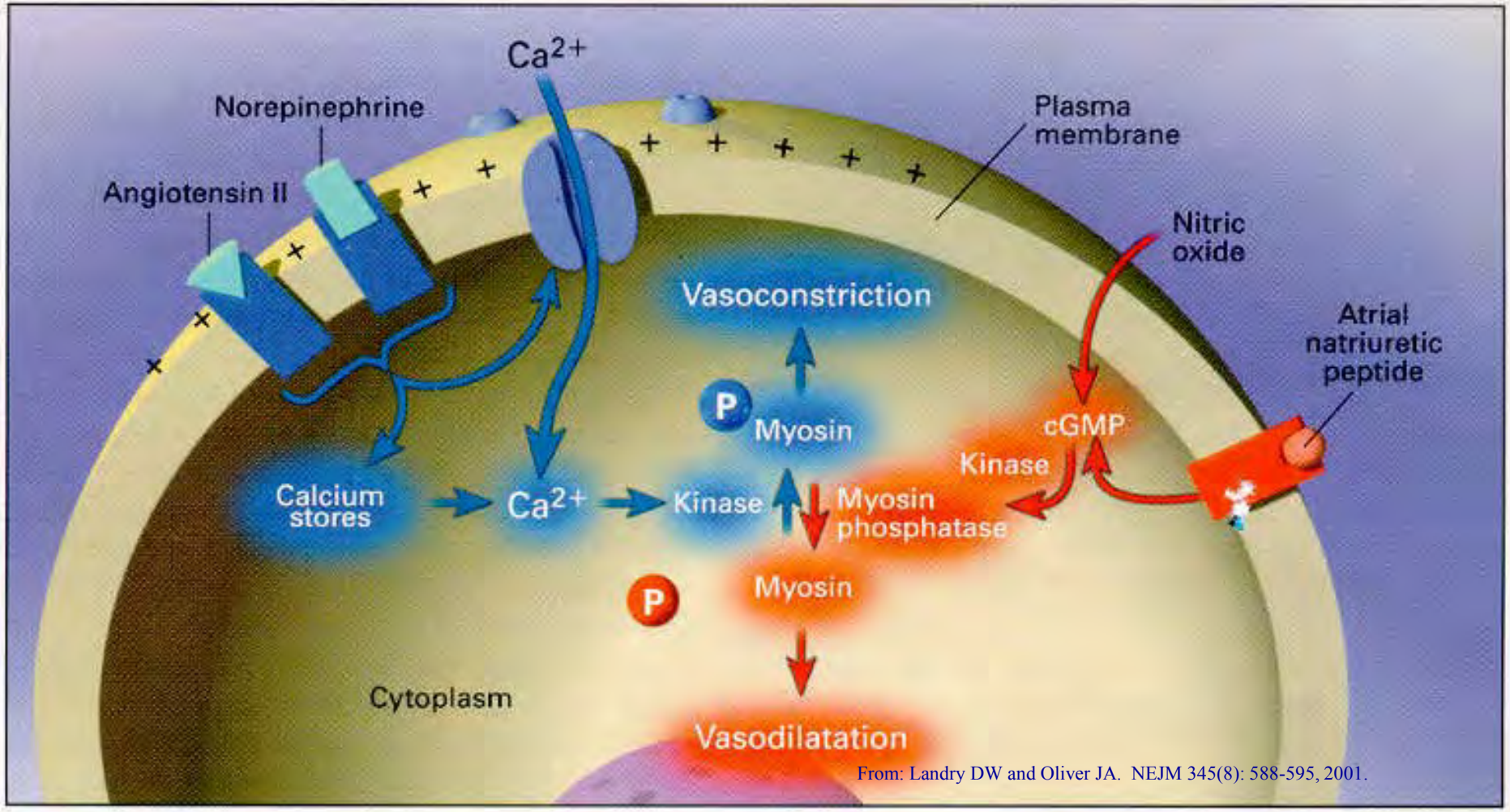



Modified from: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001

**Voltage-gated Ca Channels**

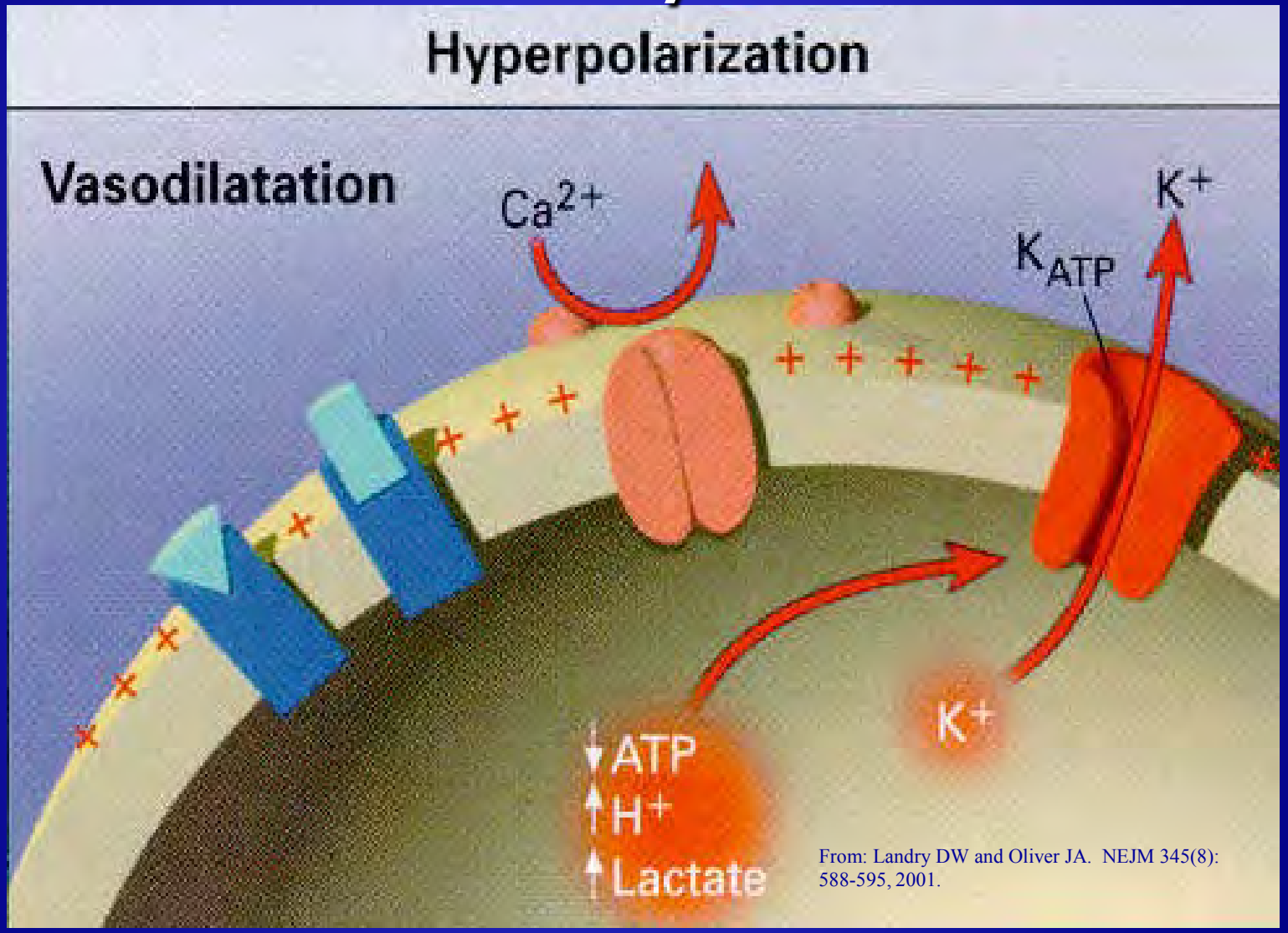
**Ca-gated K channels**

# Vasoconstriction vs. Vasodilatation

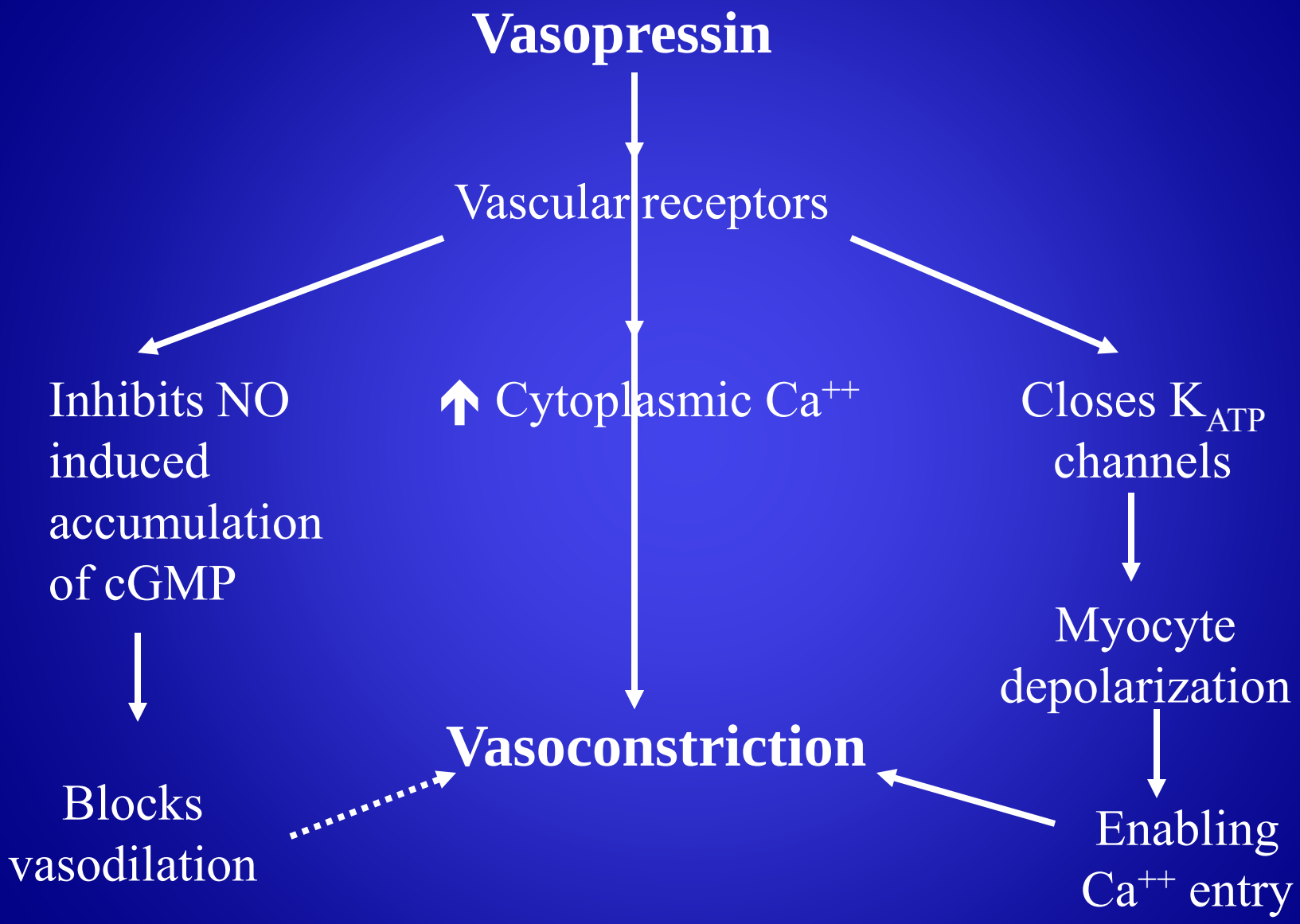



From: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.

# Vasodilatory Shock




From: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.


Vasopressin
Vascular receptors
Inhibits NO induced accumulation of cGMP
↑ Cytoplasmic Ca++
Closes KATP channels
Myocyte depolarization
Vasoconstriction
Blocks vasodilation
Enabling Ca++ entry

**Sepsis**

**Hypotension**

CNS

Exhaustion of vasopressin

Relative vasopressin deficiency

Downward spiral of hypoperfusion
Vasodilatory Shock

Lactic acidosis

↑ NO  $K_{ATP}$ channels open

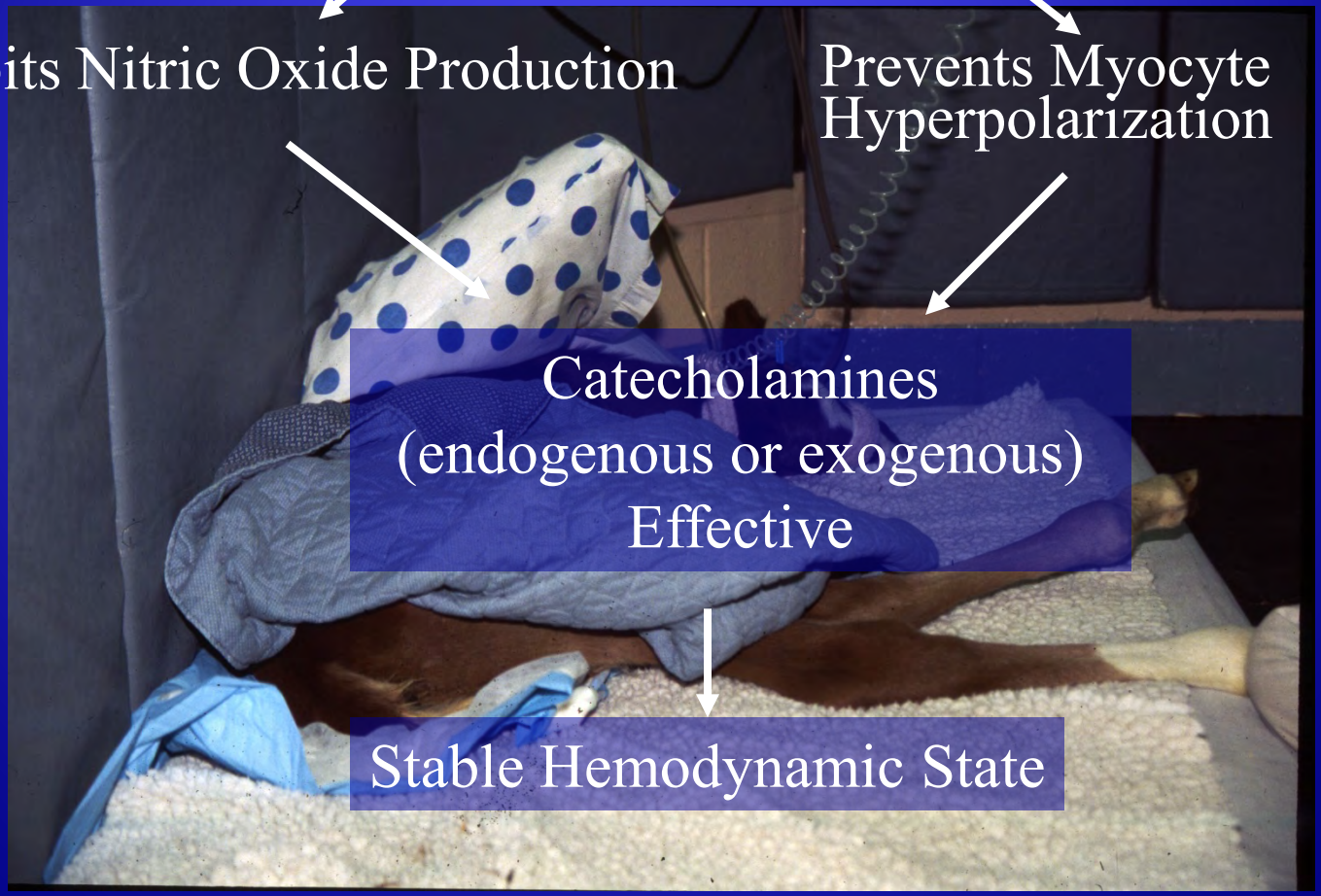
Catecholamine resistance

**Exogenous Vasopressin**

Physiologic Levels

Inhibits Nitric Oxide Production

Prevents Myocyte Hyperpolarization

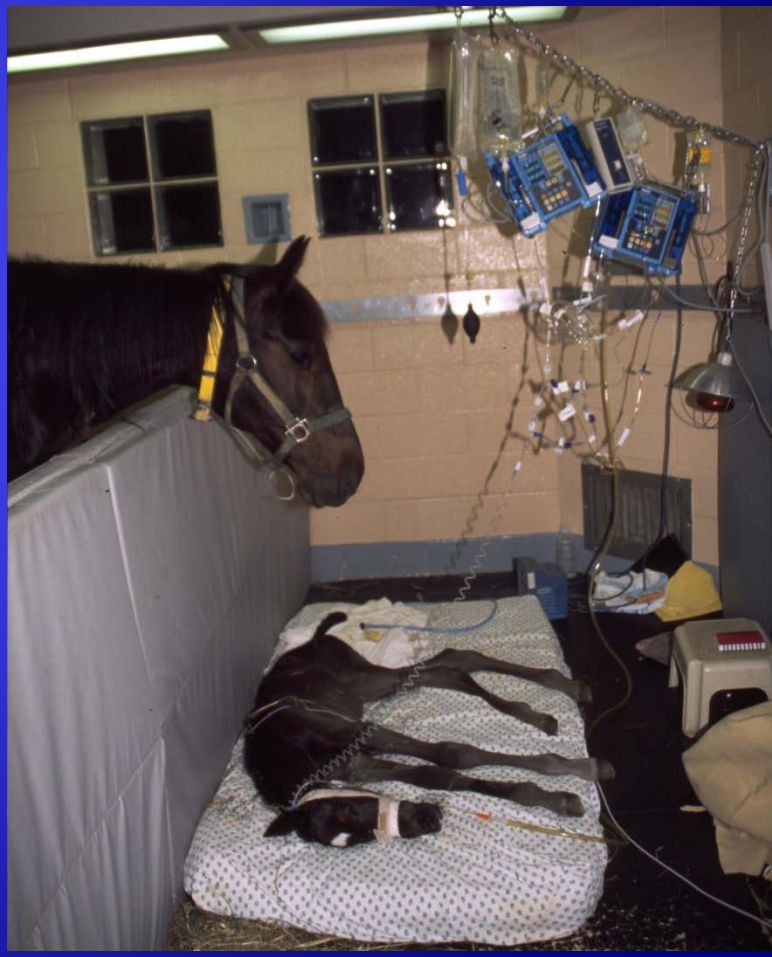


Catecholamines (endogenous or exogenous) Effective

Stable Hemodynamic State

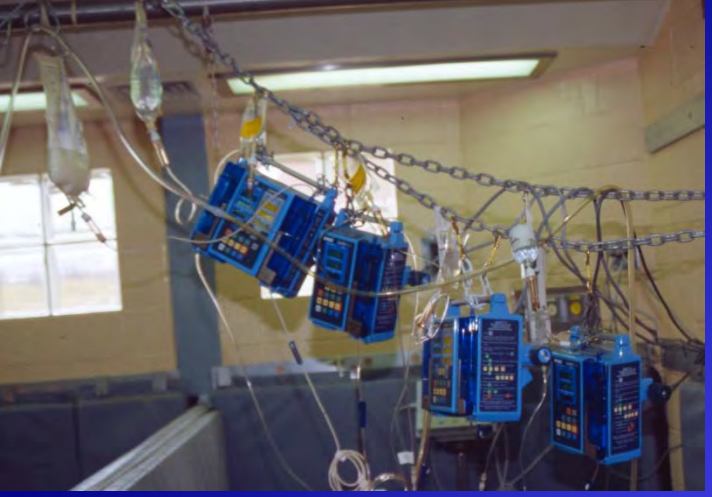
# Low-dose Arginine Vasopressin Pressor Therapy Foals

- Dose
  - 0.25-0.5 mU/kg/min
- Constant infusion
- Response within minutes
  - Inotrope/Pressor Score 20 – 60
  - BP increase ~ 20 mmHg
  - Signs of perfusion improve
- Cost



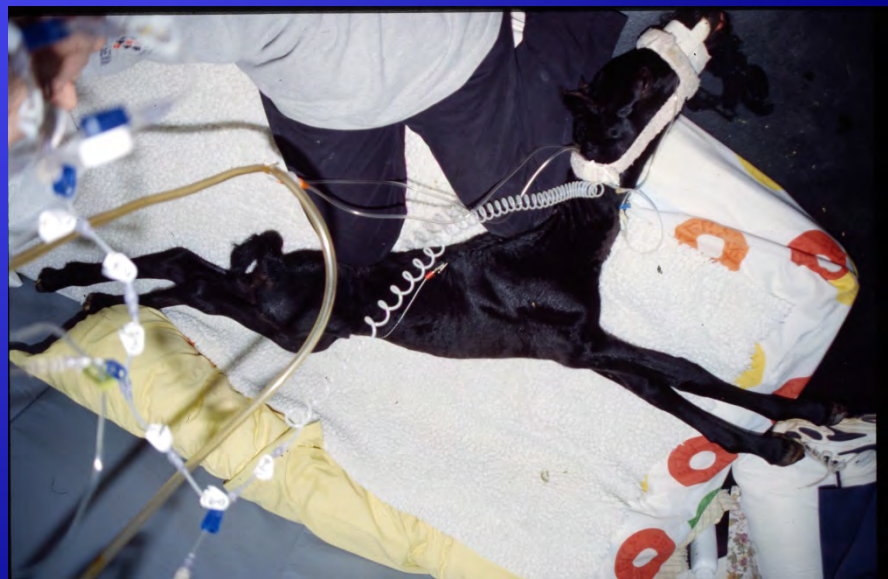
# Premature Friesian Foal

- 280 - 300 days gestation
  Small- 25 kg
- Clinical Problems
  Intrauterine acceleration of maturation
  Neonatal Encephalopathy
  Neonatal Nephropathy
  Neonatal Gastroenteropathy
  Incomplete ossification
  SIRS



# Premature Friesian Foal

- Admission
  - Poor perfusion – fully compensated shock
    - BP - 77/47 (57) 92
  - Respond well to fluid therapy + dobutamine
    - BP - 105/67 (80) 90
- At 12 hrs
  - On dobutamine
    - BP – 86/62 (67) 104
  - Off dobutamine
    - BP – 67/44 (51) 99

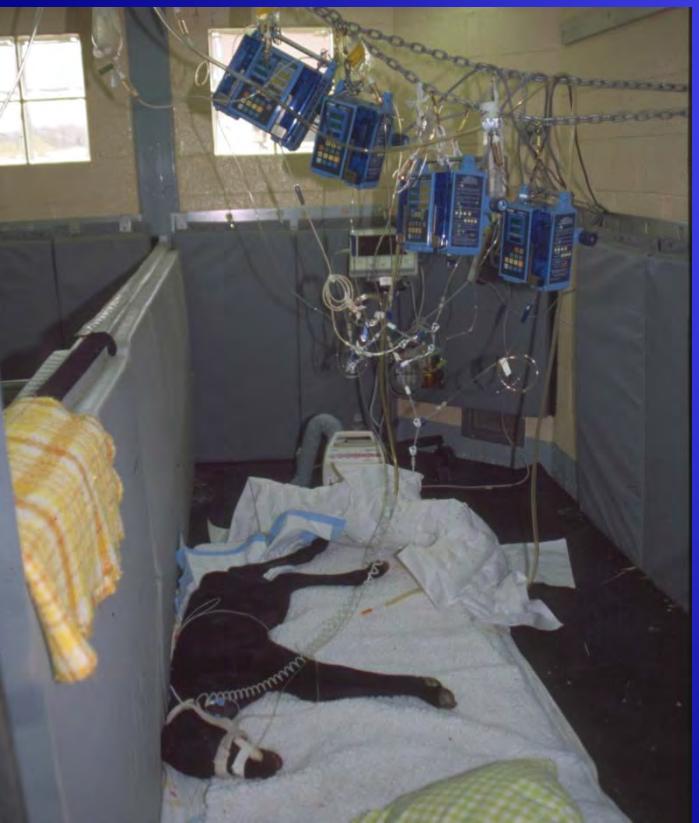


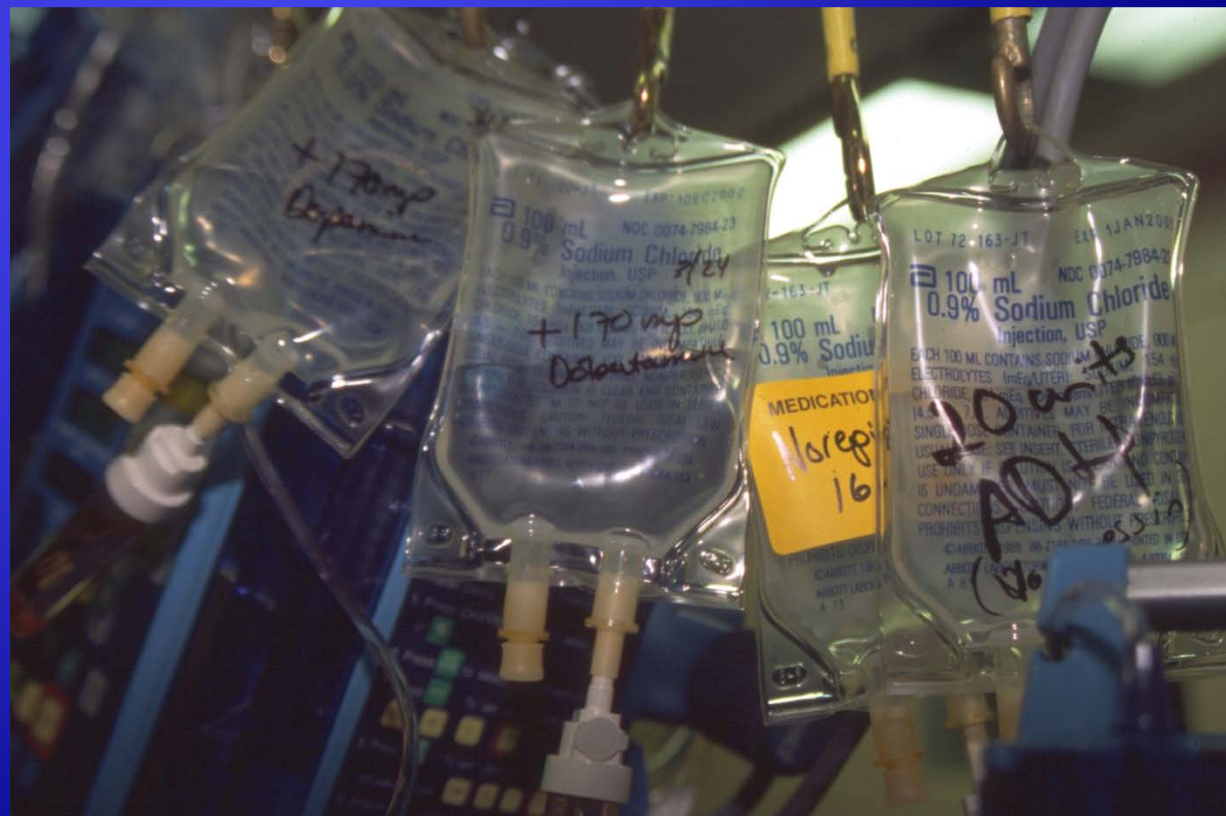
# Premature Friesian Foal

- At 48 hrs on Dobutamine (10 µg/kg/min)
  BP – 50/28 (36) 88 and deteriorating perfusion
- Dobutamine (20 µg/kg/min)
  → BP 43/32 (38) 88
- Dobut + Dopamine (10 µg/kg/min)
  → 43/26 (32) 100
  Inotrope/Pressor Score = 60 with no improvement
- Dobut + Dop + Vasopressin (0.25 mU/kg/min)
  → 69/41 (57) 100 and perfusion improved
- Cardiovascular stability until day 7
  adrenaline , noradrenaline
  Cardiovascular failure

# Basic Principles of Cardiovascular Support

Insure Volume  Insure Tissue Perfusion  Defend Pressure



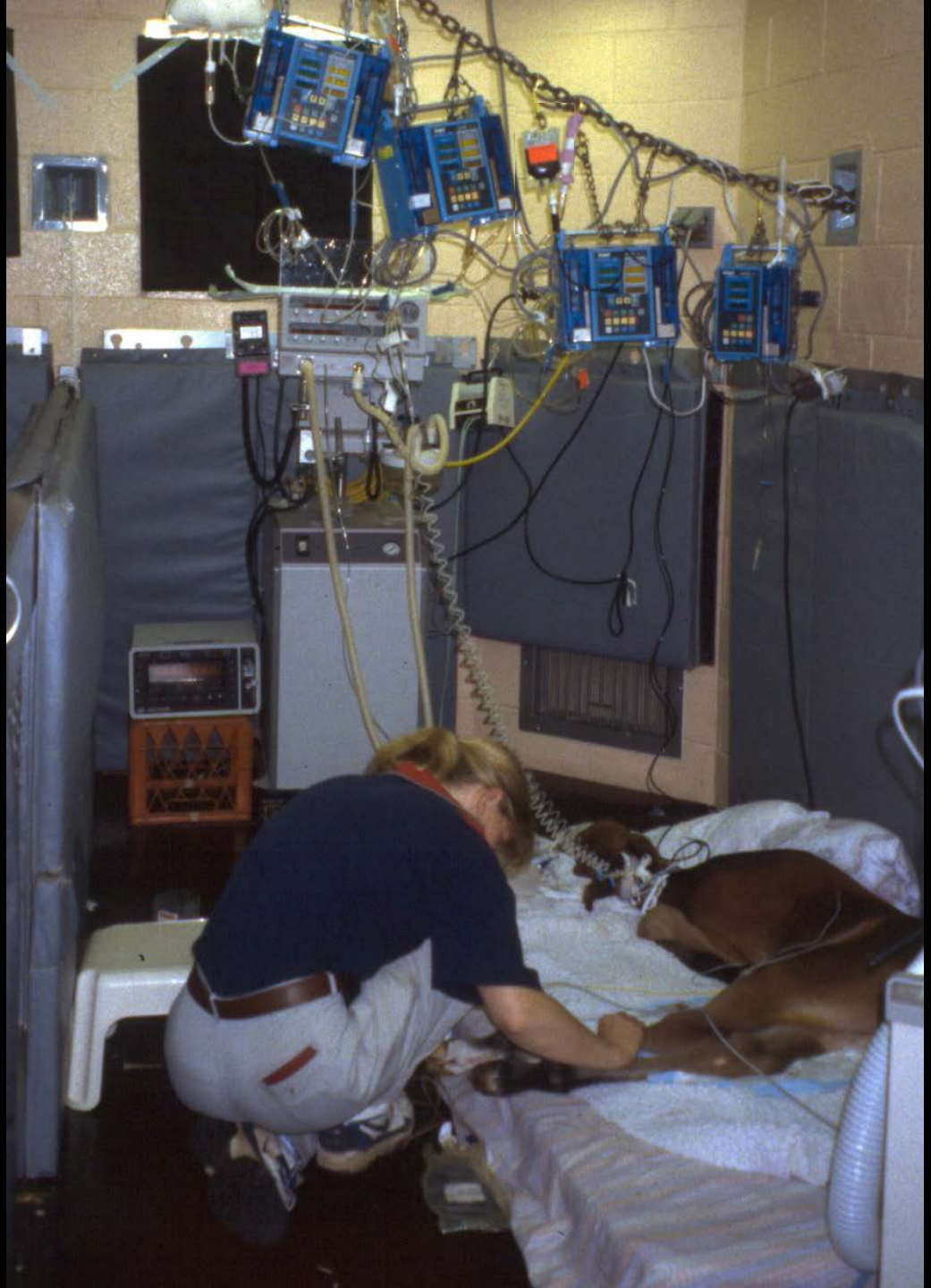


# Hypotension
# Other Therapeutic Interventions

- Low dose steroid therapy
  - Hypotensive secondary to adrenal insufficiency
    - Premature neonates
  - Dexamethasone – 0.02 to 0.03 mg/kg
  - Cortisol – 1 mg/kg QID
    - Solu-cortef®
  - May result in a dramatic increase in BP
  - Adverse reaction
    - Refractory hyperglycemia
    - In human neonates, a poorer long-term outcome

# Hypotension
# Other Therapeutic Interventions

- Methylene blue
  - NO blocker
  - Refractory hypotension – septic shock
  - Dramatic resolution of hypotension
    - Concurrent maldistribution of perfusion
    - Resulting in negative outcomes
  - Recent publications in human critical care
    - vasoplegic syndrome – cardiac surgery
- Naloxone therapy
  - Enhancement of adrenergic inotropic effects in sepsis
  - Correct maldistribution of perfusion
  - Anecdotal experience not encouraging




Do NOT Touch VENT
KCL