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

Neonates
Low-pressure System

- Perfuse tissues quite well
- Low systemic blood pressures
  - Vital for intrauterine survival
  - Neonate - transition from low pressure system
    - Decreasing activity and synthesis of vasodilators
    - Intrinsic changes in vascular smooth muscle function
      - Responsive to mediators/nervous system
      - Capable of maintaining higher pressures
    - Increase in sympathetic responsiveness
    - Reset baroreceptor response level
    - Increase in precapillary tone
  - Transition may not occur in unison in all tissues

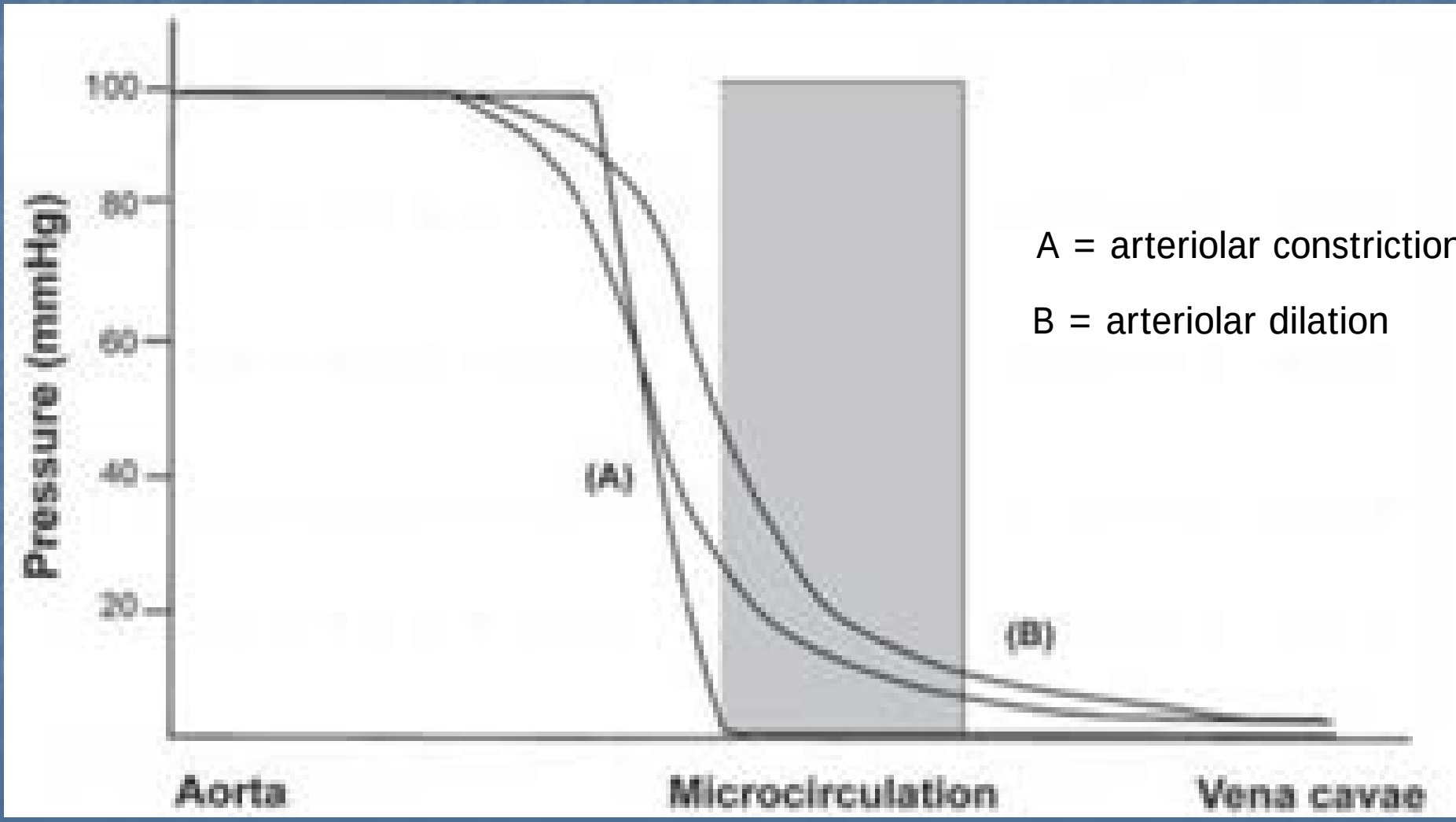
BP and Capillary Perfusion Clinical Experience

- BP does not correlate with microcirculatory flow
- Increasing BP with norepinephrine
  - 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
    - Preserve heart and brain perfusion
    - At expense of global tissue hypoperfusion
- Shock

Hydrostatic Pressure

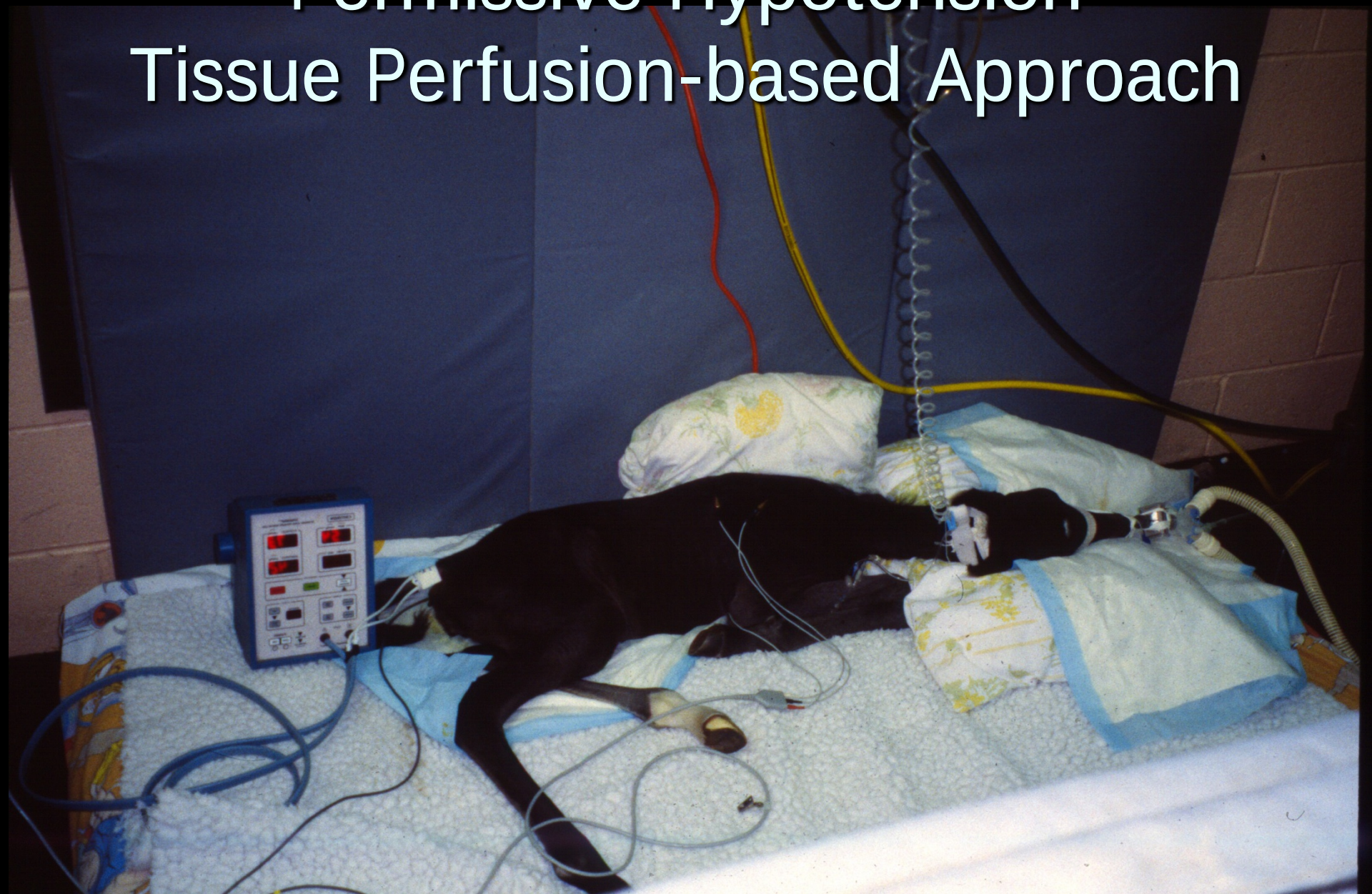


A = arteriolar constriction

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 norepinephrine 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
STOP
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
- Epinephrine , norepinephrine – 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 norepinephrine
    - Epinephrine
  - 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 - β1 & β2 activity
- High doses - α1 activity
  - Norepinephrine 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 shock
  - 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
  - GI effects

Inopressor Therapy Norepinephrine

- Potent vasopressor
  - Strong $\alpha 1$ activity
  - Both inotropic and chronotropic activities
  - $\beta 1$ activity
  - Variable $\beta 2$ activity
  - Chronotropic – usually blunted by vagal reflex
  - ↑ 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 Norepinephrine

- 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
Epinephrine

- 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

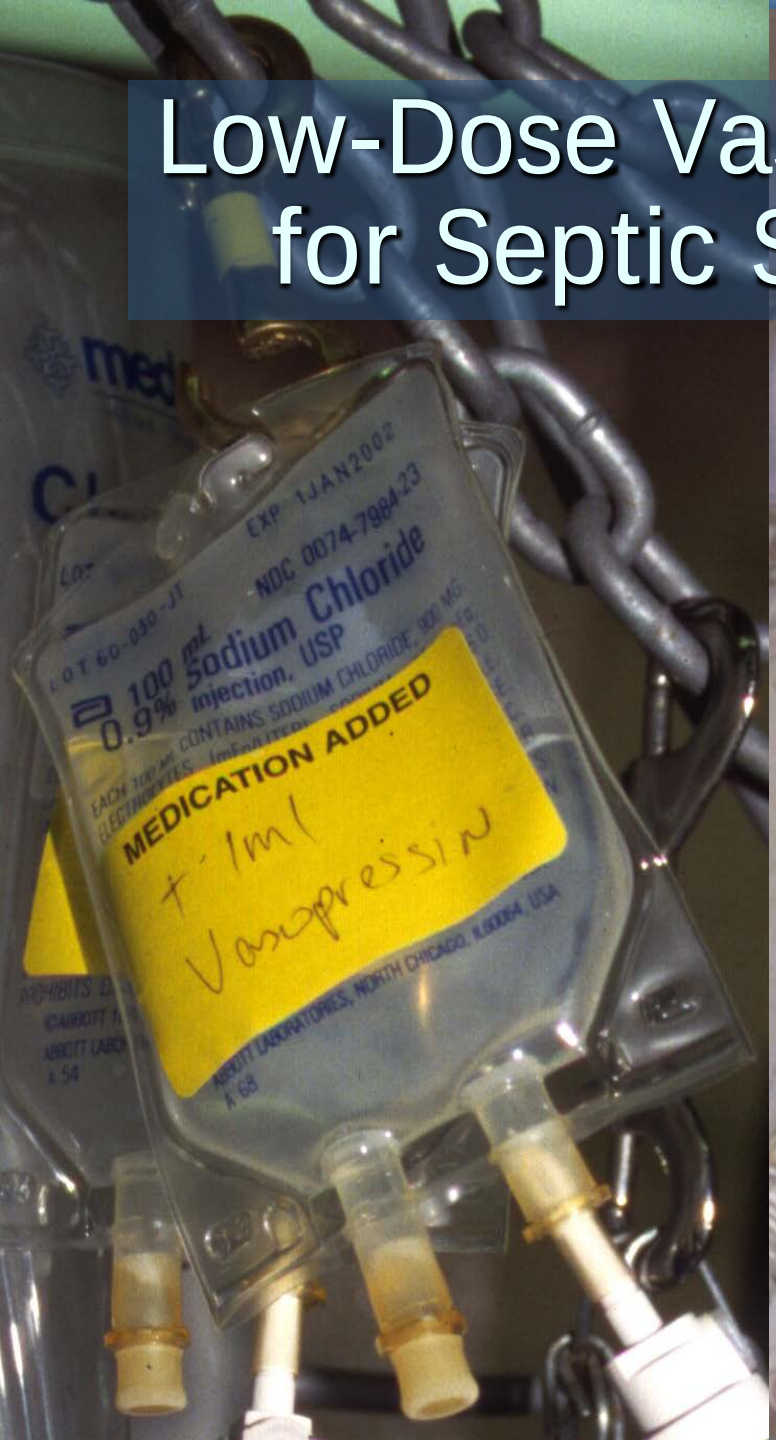
Inopressor Therapy Epinephrine

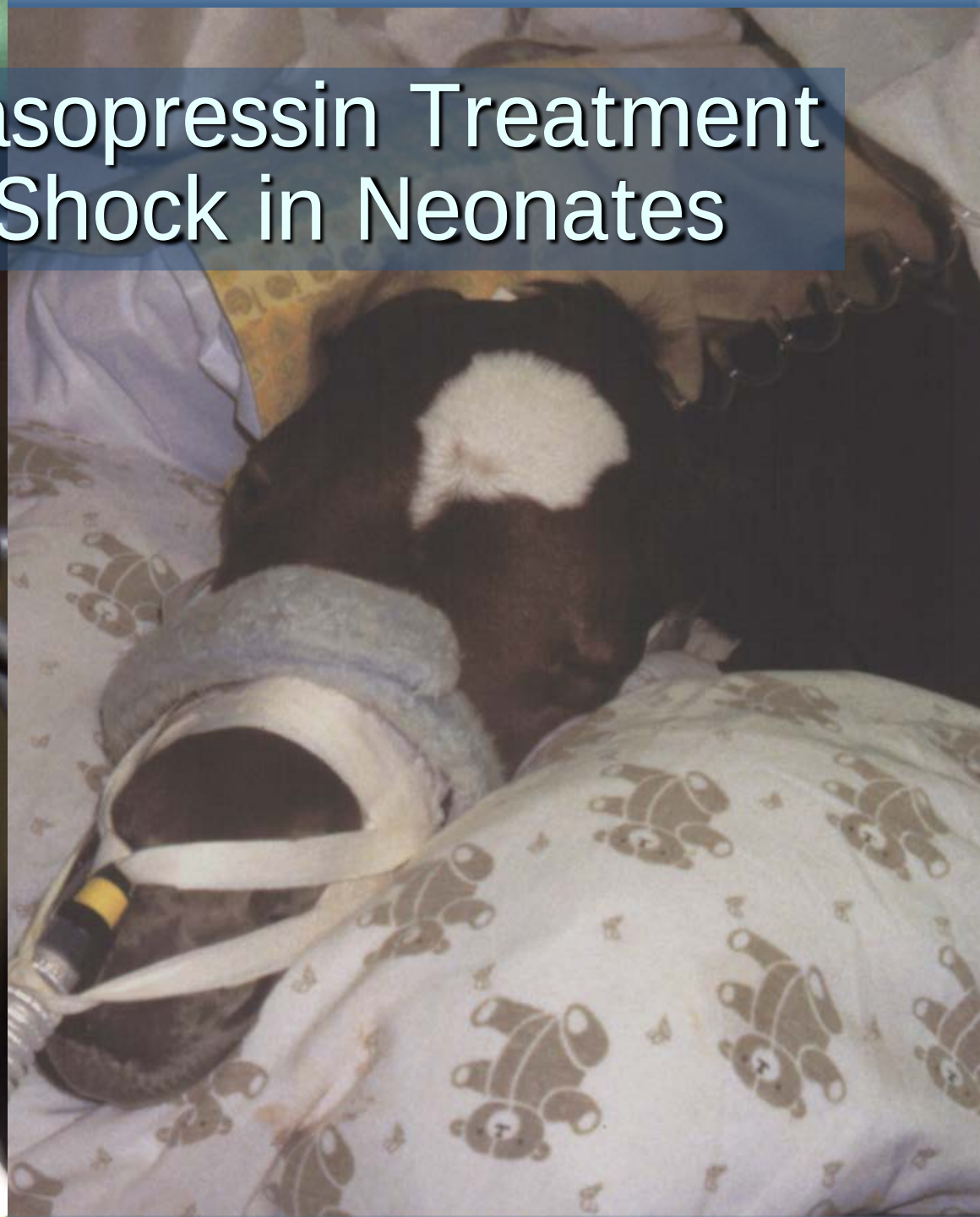
- For its inotropic effect
  - Start 0.3-0.5 µg/kg/min
  - Titrate to an effective dose
- Dose range
  - 0.1-2.0 µg /kg/min
  - Difficult cases – 3 to 4 µg/kg/min
- Adverse reaction
  - Metabolic derangements
  - Occasional arrhythmias
    - With pre-existing myocardial damage
      - Hypoxic ischemic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

Inopressor Combinations

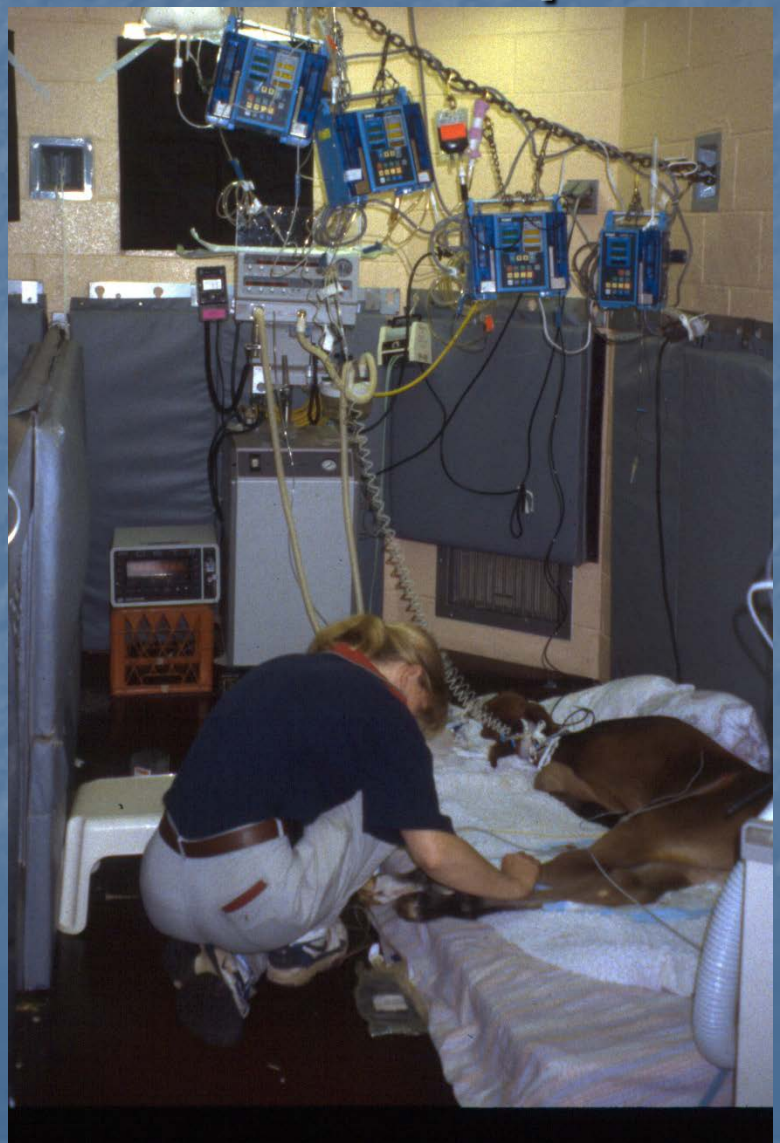
- Dobutamine – Dopamine
- Dobutamine – Norepinephrine
- Epinephrine – Norepinephrine
- Dobutamine – Dopamine – Norepinephrine
- Dobutamine – Vasopressin***

Low-Dose Vasopressin Treatment for Septic Shock in Neonates



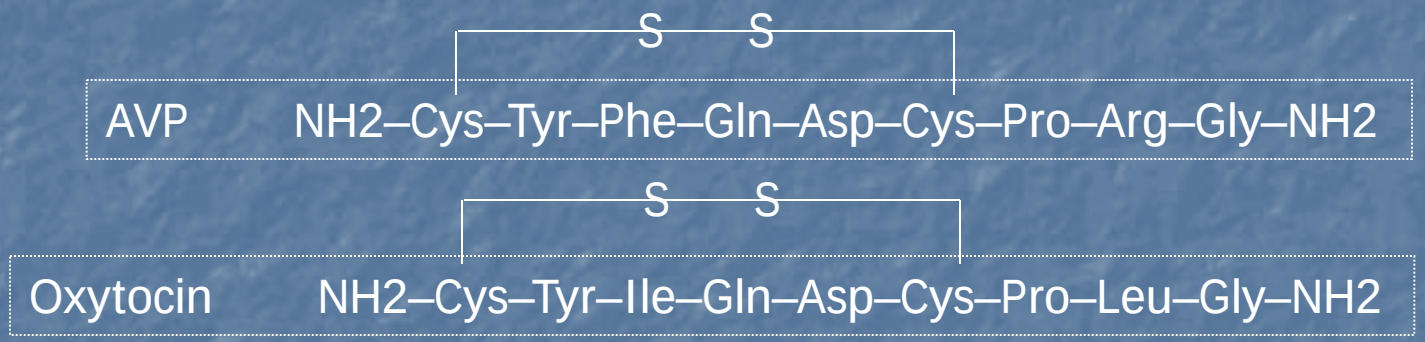


Septic Shock Therapeutic Interventions



- Fluid therapy
  - Fluid bolus
  - Crystalloids
  - Plasma
- Inotropes/Pressors
  - Dopamine
  - Dobutamine
  - Epinephrine
  - Norepinephrine
- Respiratory support
  - Oxygen therapy
  - Ventilation

Vasopressin



- Peptide hormone
  - Arg vasopressin – most mammals
  - Lys vasopressin – pigs, hippos, warthogs, some marsupials
- Synthesized in the hypothalamus
- Transported to the posterior pituitary

Vasopressin Release

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

Vasopressin Blood Pressure

- Pressor action
  - Traditionally thought pharmacologic effect
  - More potent than Angiotensin II, norepinephrine
- 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

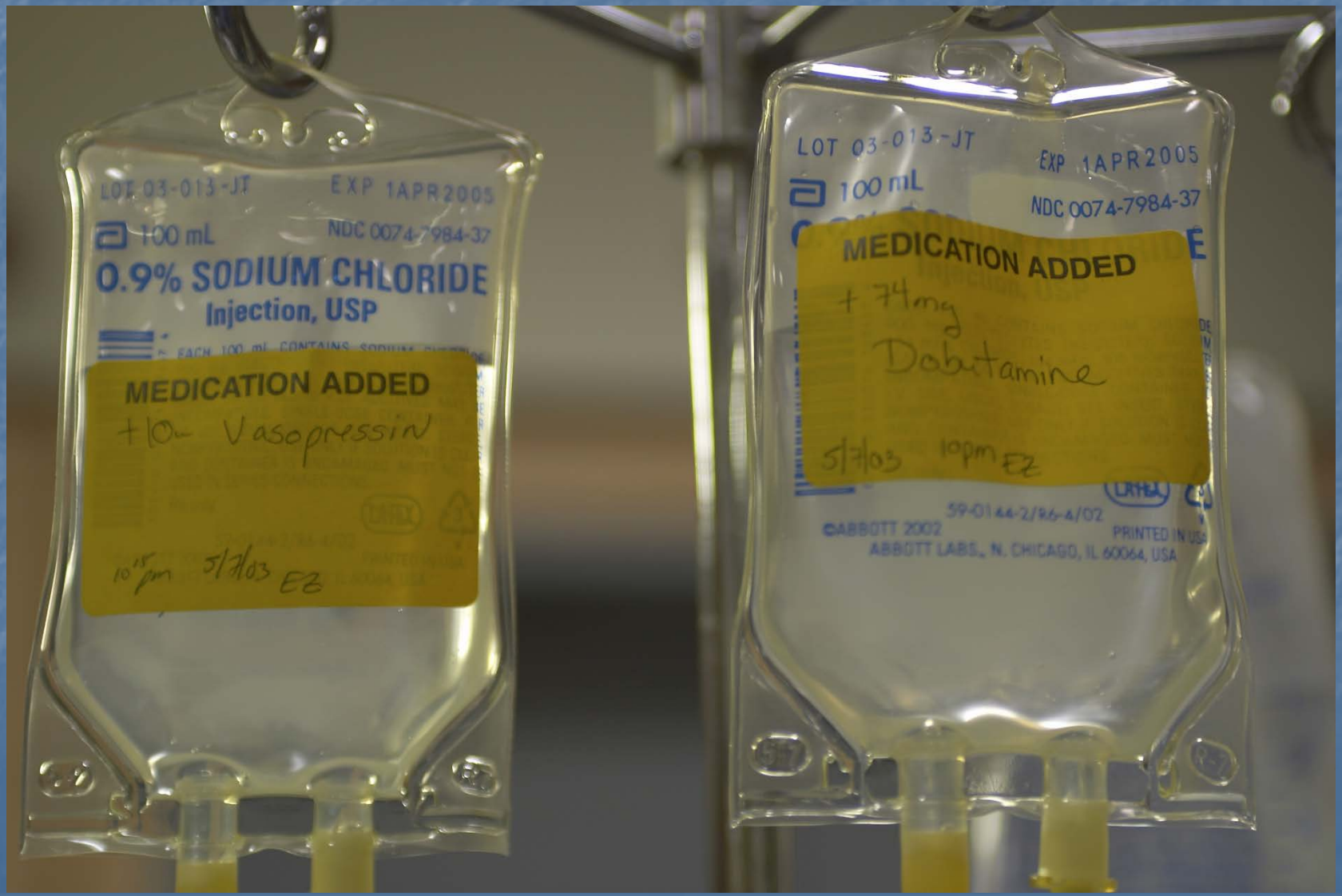
Vasopressin Vasoconstrictor Activity

- 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 – why?
  - 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



Infusion of Exogenous Vasopressin

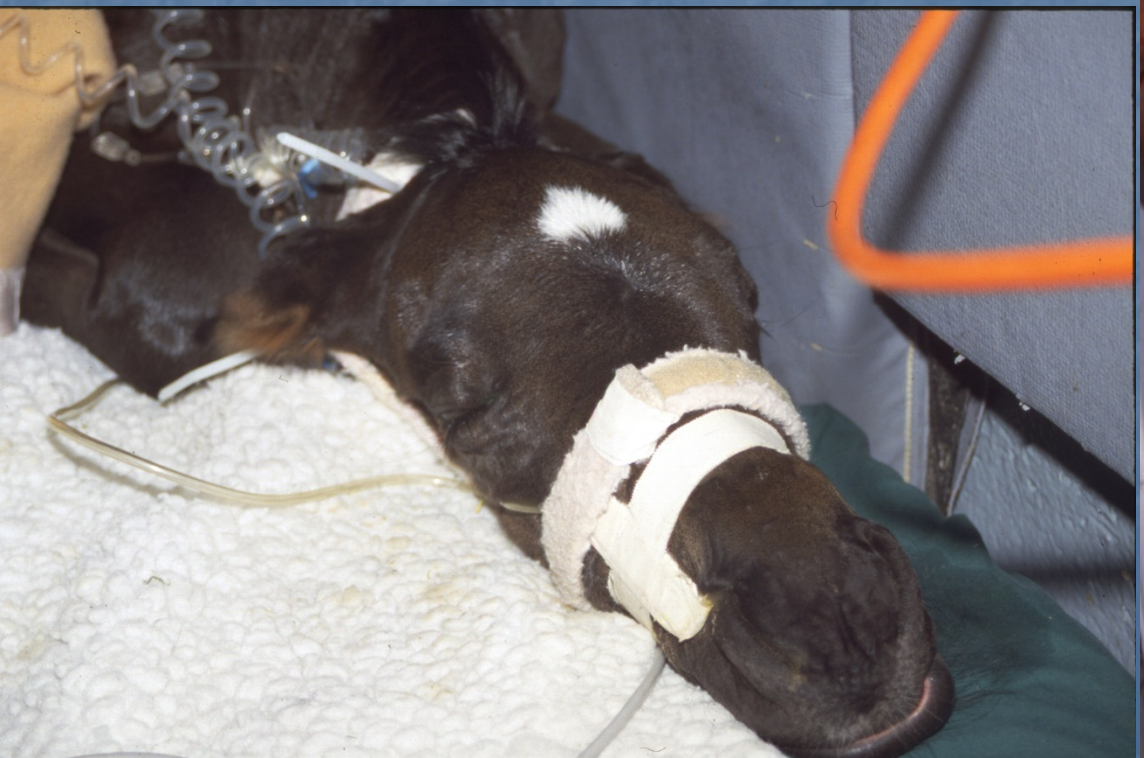
- Increase in systolic pressure
  - Patients in septic shock
  - Not occur in normal subjects
- Vasoconstrictor action low dose vasopressin
  - Blood pressure maintained without catecholamines
  - Result in plasma concentrations near normal levels
- Septic shock
  - Vasopressin secretion is inappropriately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

Urine flow rates

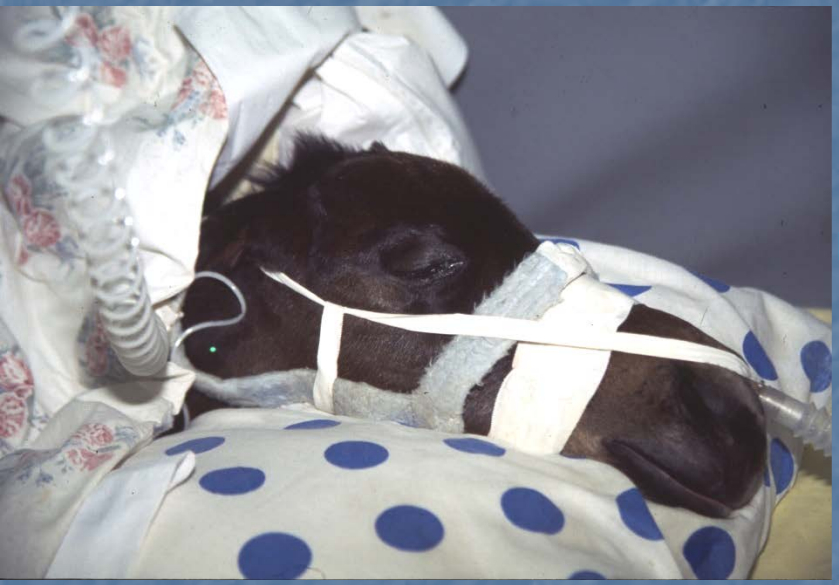
- Increase significantly
  - Improve renal perfusion
  - Constrict only the efferent arterial
    Maintaining glomerular filtration rate
- Tubular effect (V_2)
  - Not present
  - Why?

Hypoperfusion in Septic Shock

Initially responsive
Becomes refractory

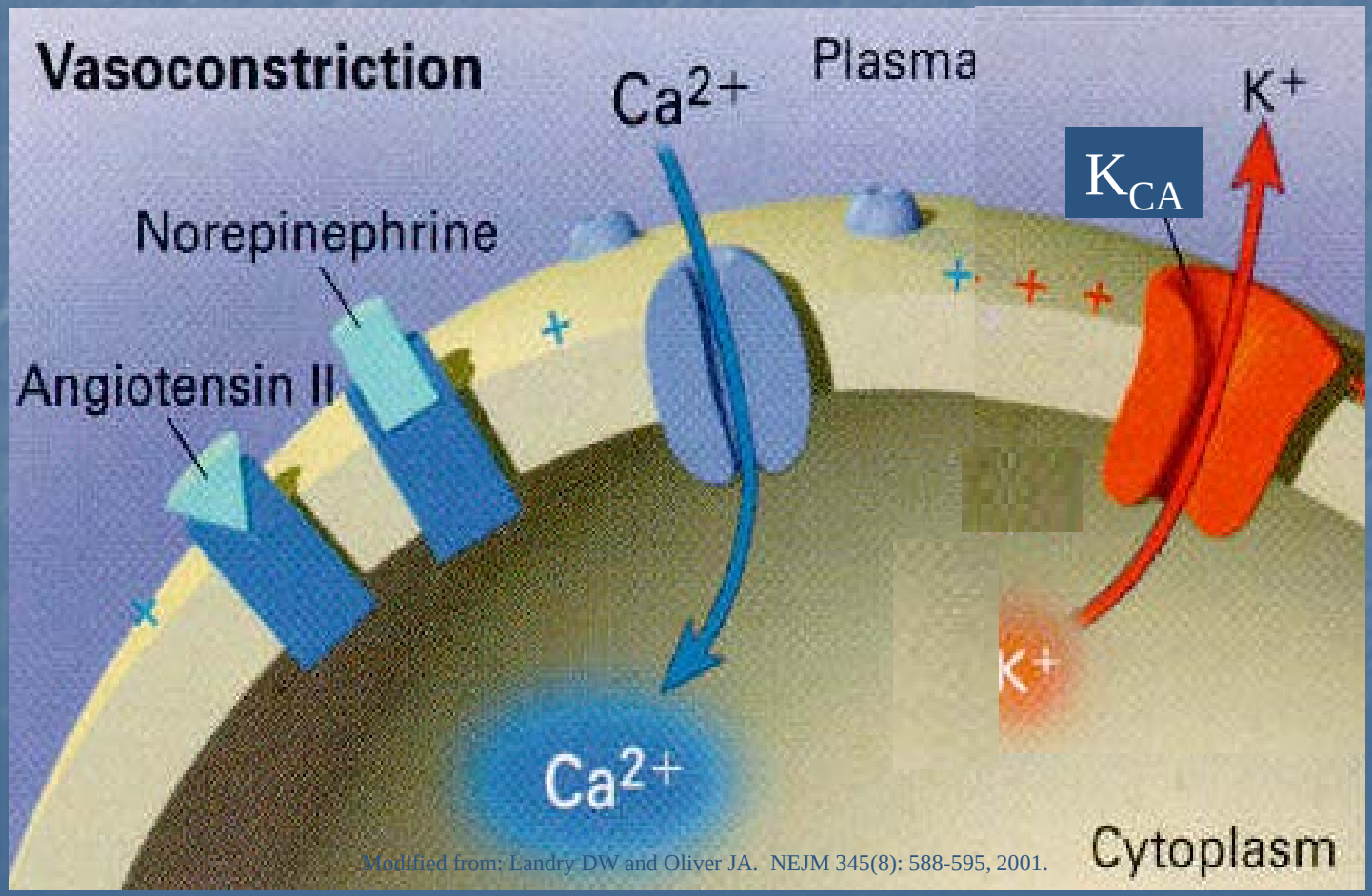


Septic Shock
Mechanism of Hypotension



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

Normal Vasoconstriction

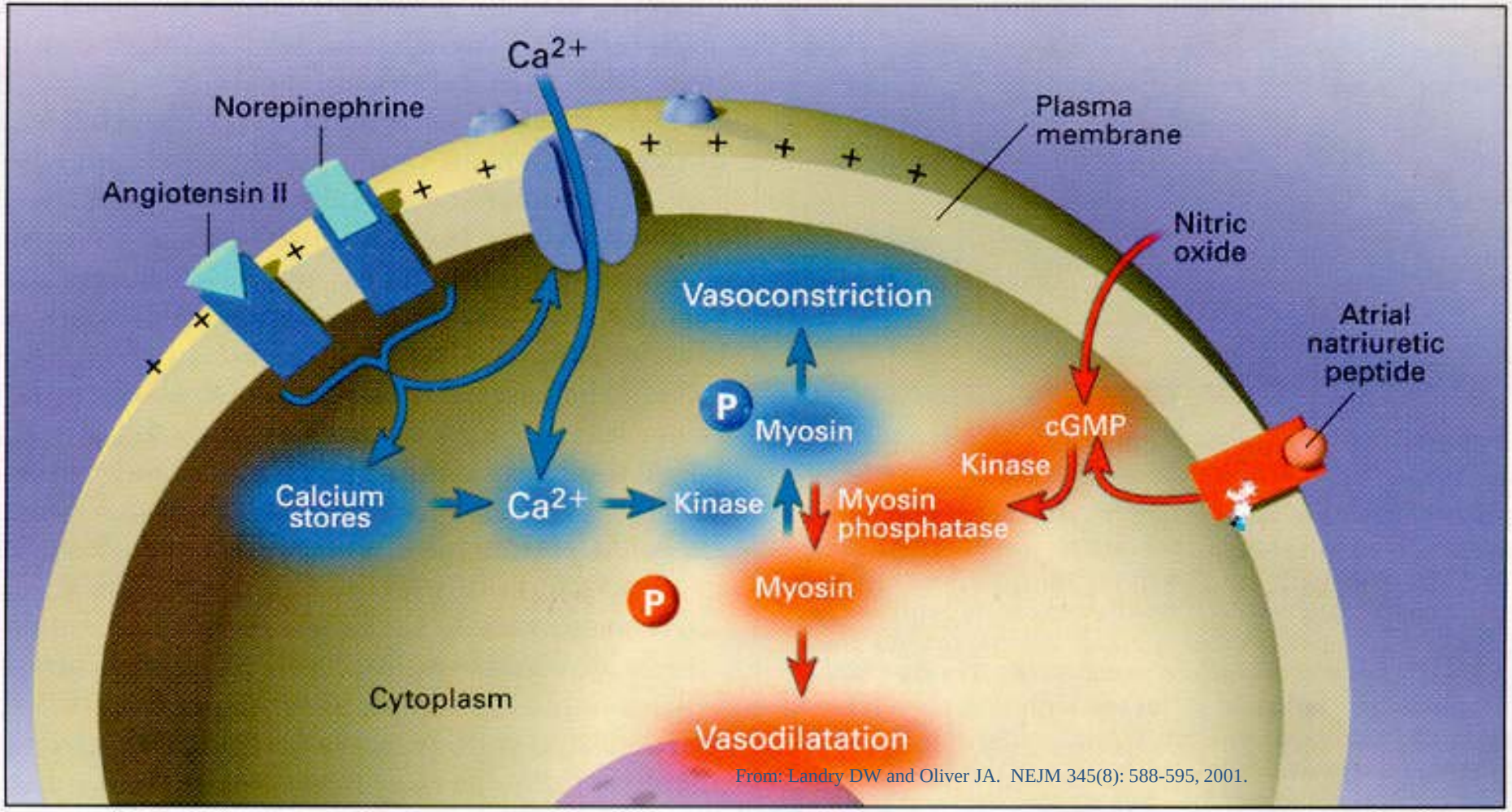


Modified from: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.

Voltage-gated Ca Channels

Ca-gated K channels

Vasoconstriction vs. Vasodilatation



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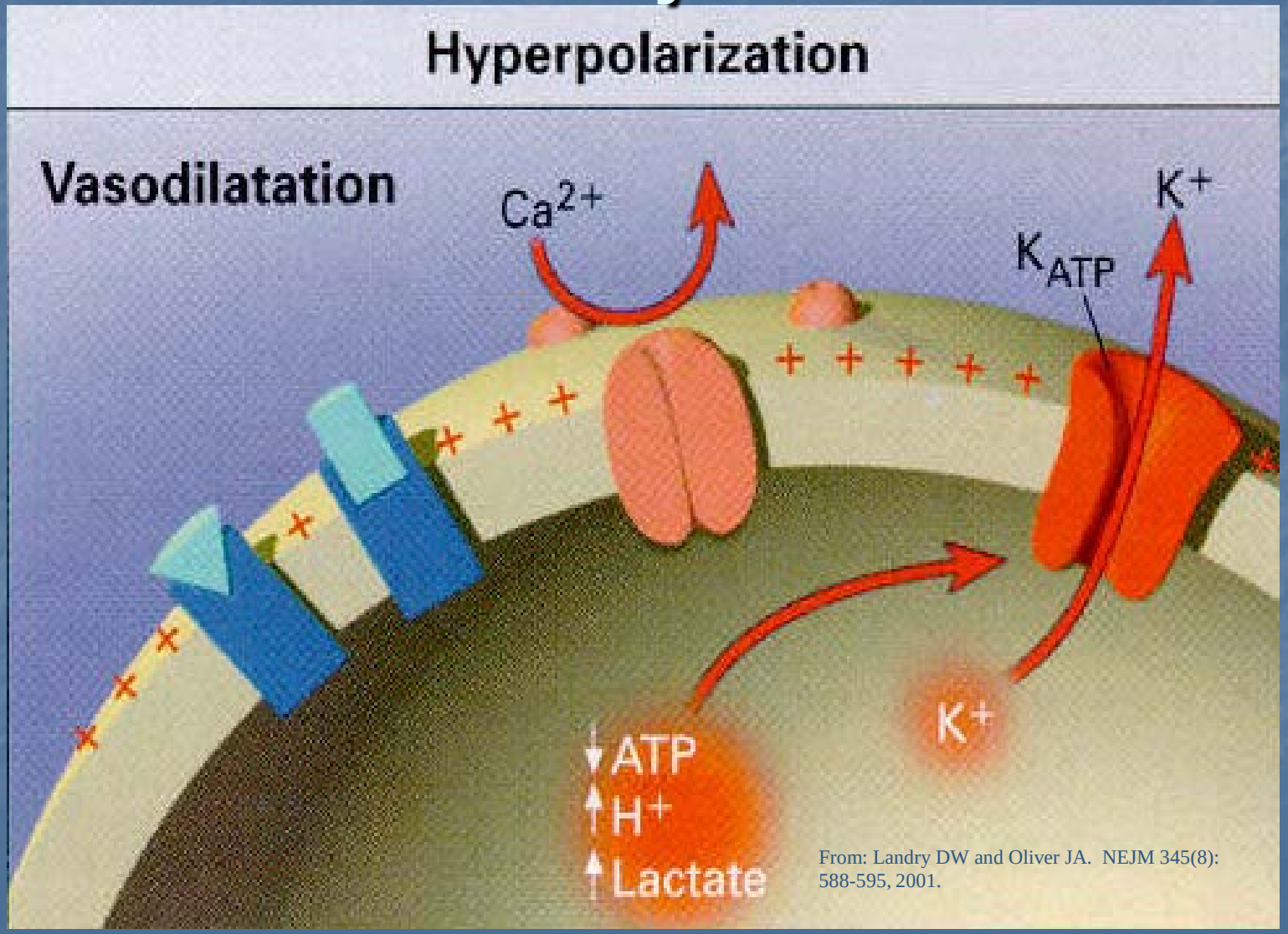
Vasodilatory Shock



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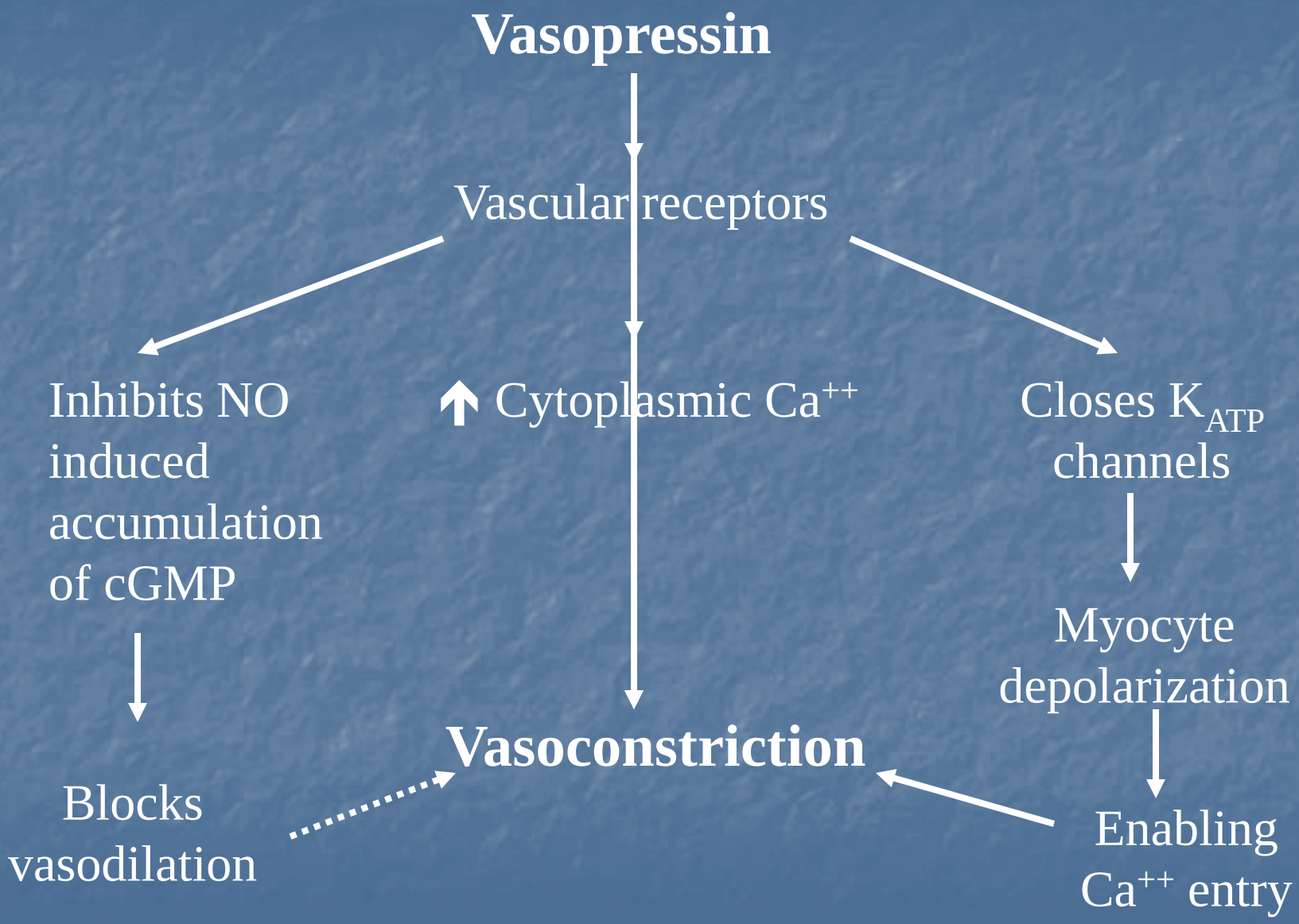

Vasopressin
Vascular receptors
Inhibits NO induced accumulation of cGMP
↑ Cytoplasmic Ca++
Closes KATP channels
Myocyte depolarization
Vasoconstriction
Blocks vasodilation
Enabling Ca++ entry

Sepsis

Hypotension

CNS

Exhaustion of vasopressin

Relative vasopressin deficiency

Downward spiral of hypoperfusion
Vasodilatory Shock

Lactic acidosis

↑ NO

K_{ATP} channels open

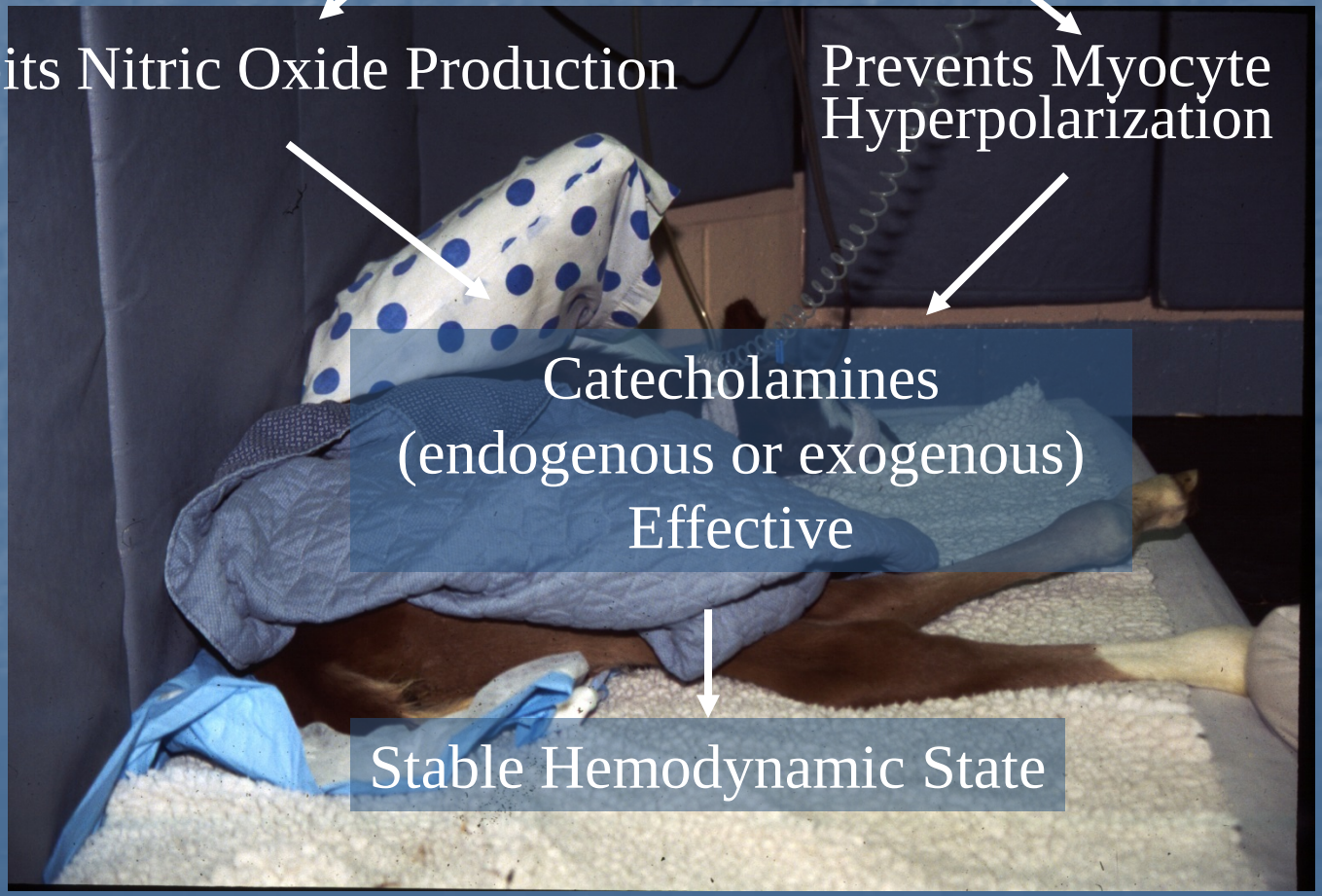
Catecholamine resistance

Exogenous Vasopressin

Physiologic Levels

Inhibits Nitric Oxide Production

Prevents Myocyte Hyperpolarization

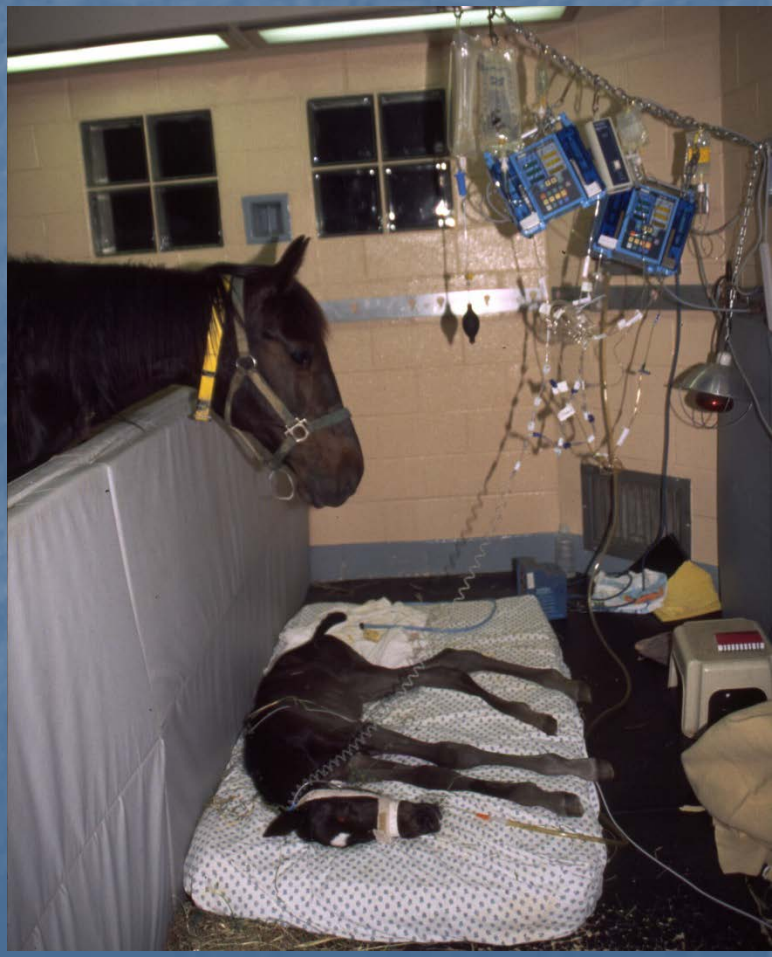


Catecholamines
(endogenous or exogenous)
Effective

Stable Hemodynamic State

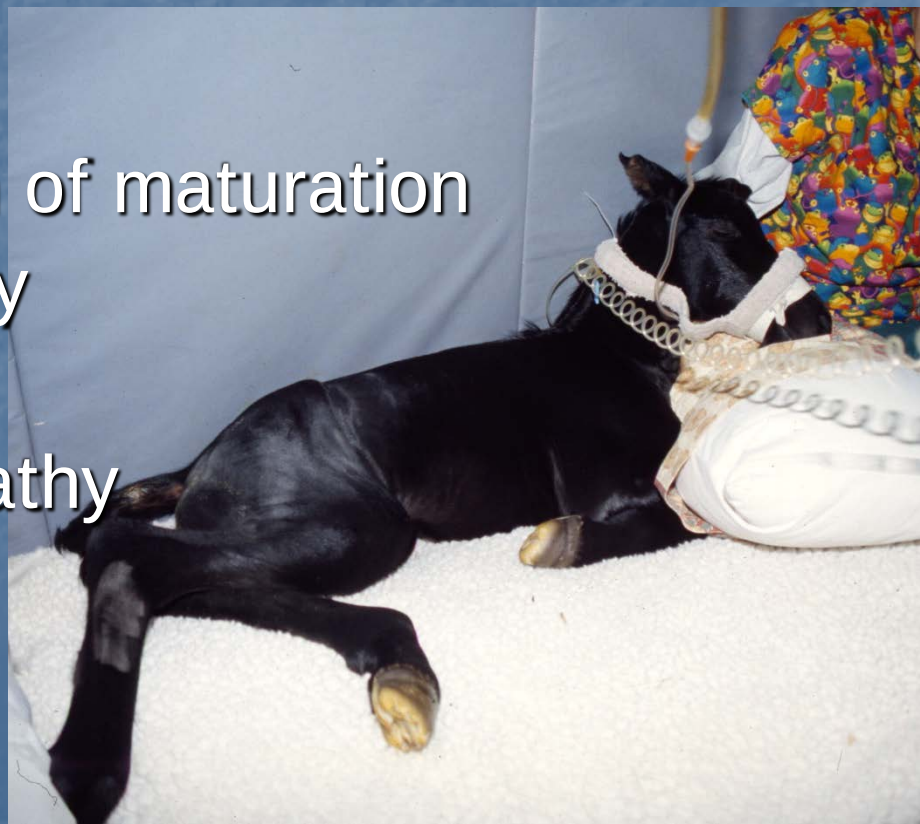
Low-dose Arginine Vasopressin Pressor Therapy Foals

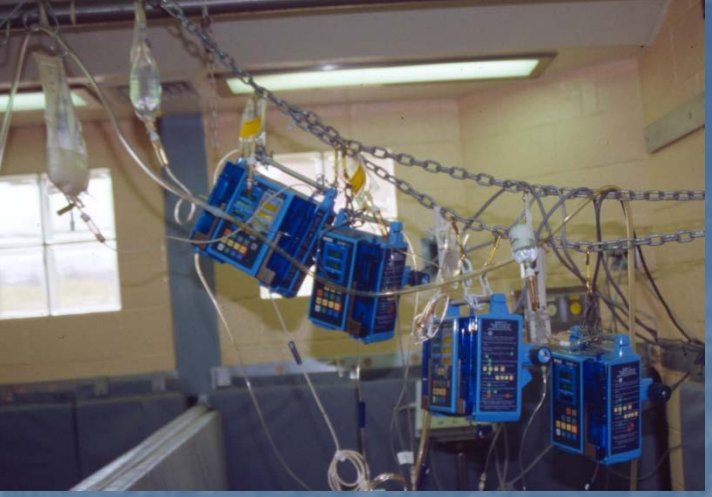
- Dose
  - 0.25-0.5 mU/kg/min
- Constant infusion
- Response within minutes
  - Inotrope/Pressor Score 20 – 60
  - BP increase ~ 20 mmHg
  - Signs of perfusion improve
- Cost – was ¢, now $$



Premature Friesian Foal

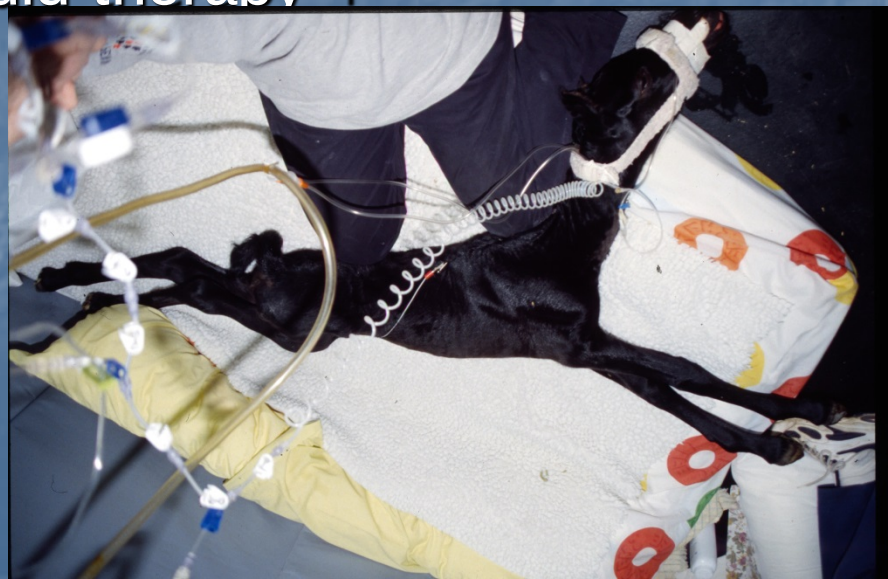
- 280 - 300 days gestation
  - Small- 25 kg
- Clinical Problems
  - Intrauterine acceleration of maturation
  - Neonatal Encephalopathy
  - Neonatal Nephropathy
  - Neonatal Gastroenteropathy
  - Incomplete ossification
  - SIRS





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

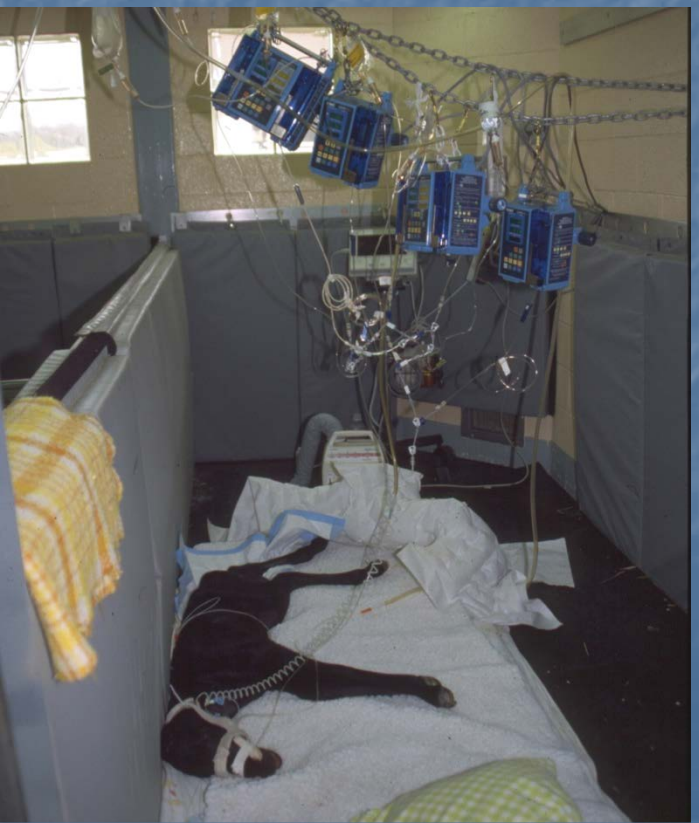


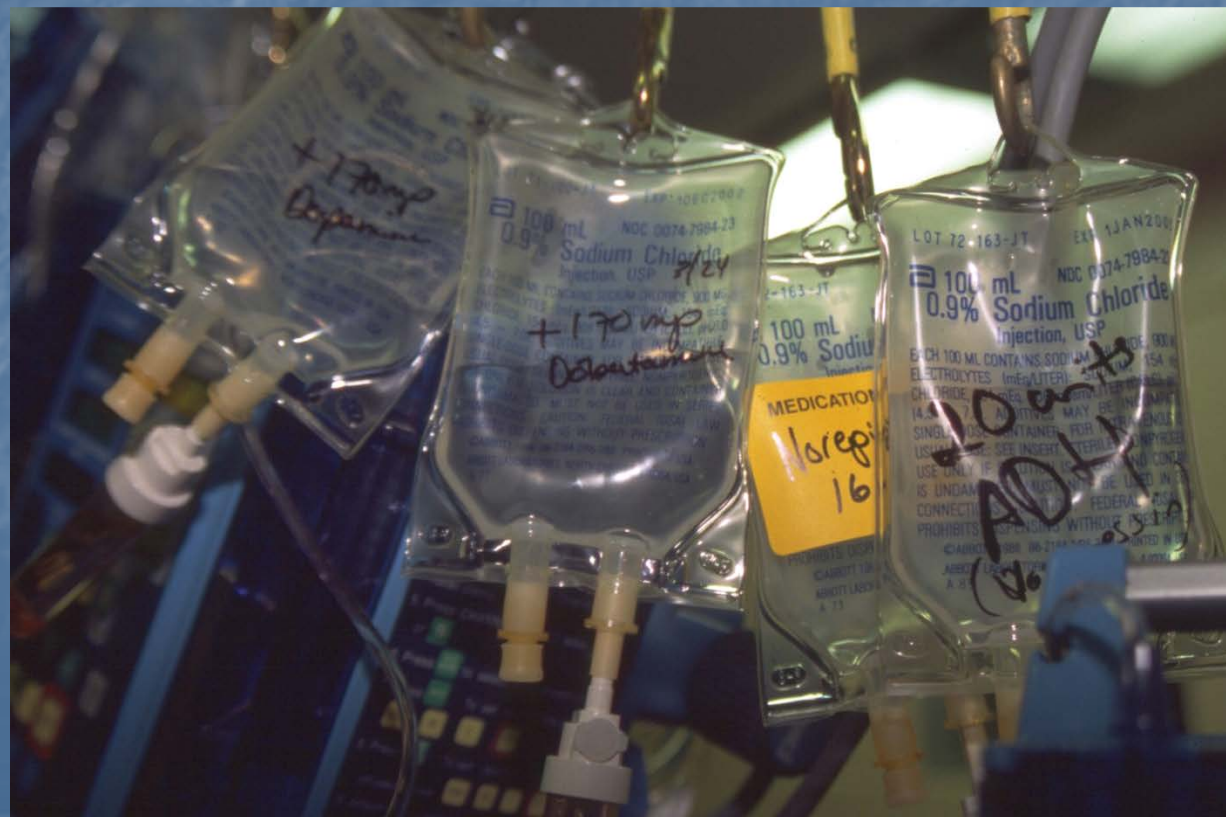
Premature Friesian Foal

- 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
  - epinephrine , norepinephrine
  - 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
    - Critical illness–related corticosteroid insufficiency (CIRCI)
  - Solu-cortef®
    - Hydrocortisone sodium succinate
    - Not Solu-delta cortef
      - Prednisolone sodium succinate
    - Dose in neonattes – 1 mg/kg QID
    - Adults CRI 200 mg/kg/day
  - Dexamethasone – 0.02 to 0.03 mg/kg

Low-dose Hydrocortisone

- Low dose steroid therapy (LDH)
  - May result in a dramatic increase in BP
  - Adverse reaction
    - Refractory hyperglycemia
    - In human neonates, a poorer long-term outcome
- Adult Patients - unresponsive septic shock
  - Not respond to fluid therapy
  - Not responsive to vasopressor therapy
- Improve morbidity but mortality??
  - Specific target groups of critically ill patients?
  - Beneficial mortality not yet demonstrated

Low-dose Hydrocortisone

- Critical illness–related corticosteroid insufficiency (CIRCI)
  - Replacement
    - Rx relative deficiency of cortisol
      - But same effect if no deficiency
    - Rx decreased tissue sensitivity to corticosteroids
  - Septic shock predisposes for CIRCI
- LDH reduces duration of vasopressor therapy
  - Included in human sepsis treatment protocols
  - BUT hemodynamic response independent of adrenocortical function
  - Inconsistent results - 28-day mortality

Low-dose Hydrocortisone

- Studies in man
  - PROWESS-Shock (2015)
    - Mortality did not differ in response to Rx
  - HYPRESS (2016)
    - Hydrocortisone for prevention of septic shock
    - BP effect of steroids not prevent septic shock
    - LDH only helped in septic shock
      - Unresponsive to fluids and vasopressor therapy

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

Methylene blue: The drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass?

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