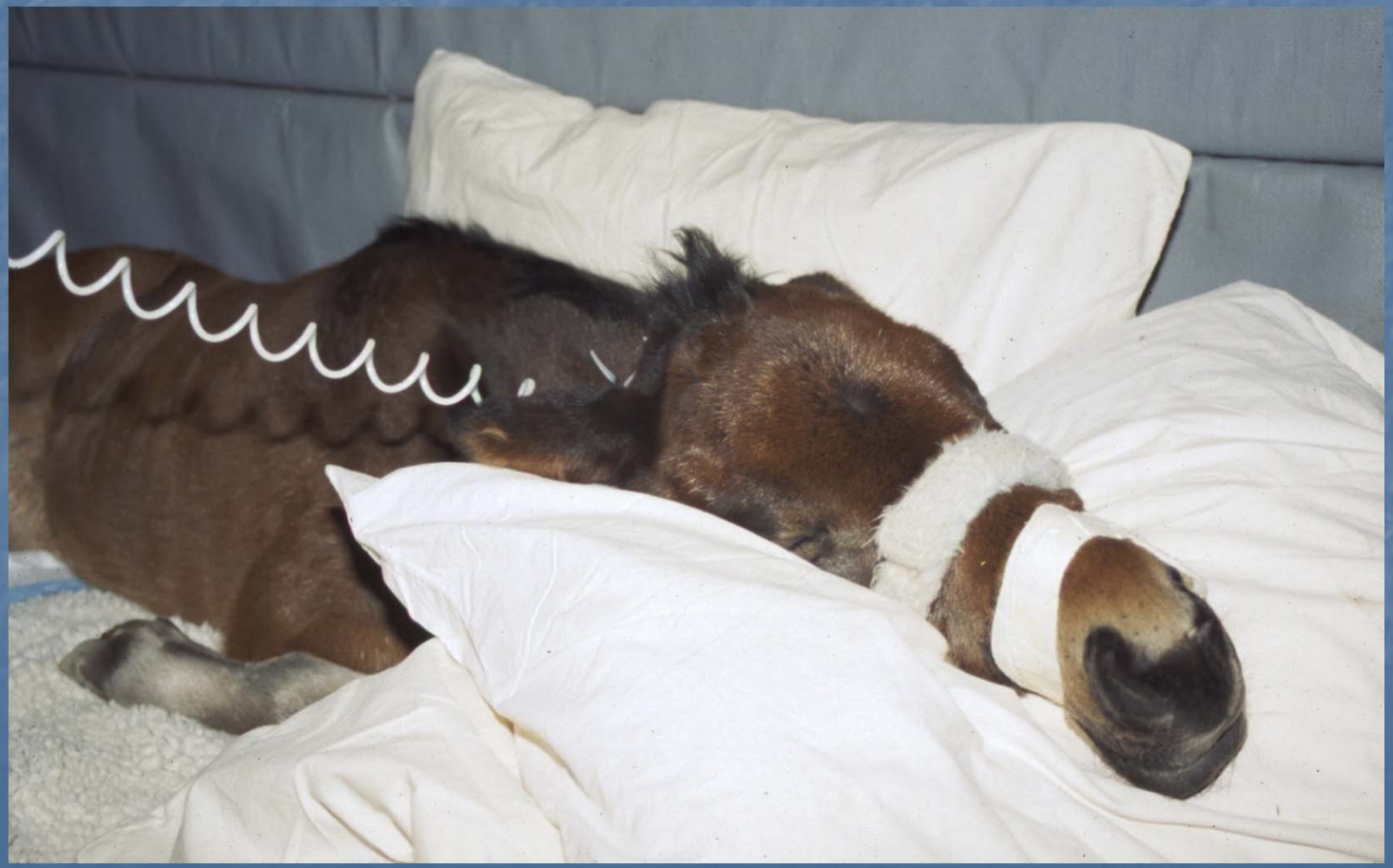
When Fluids are Not Enough: Inopressor Therapy



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

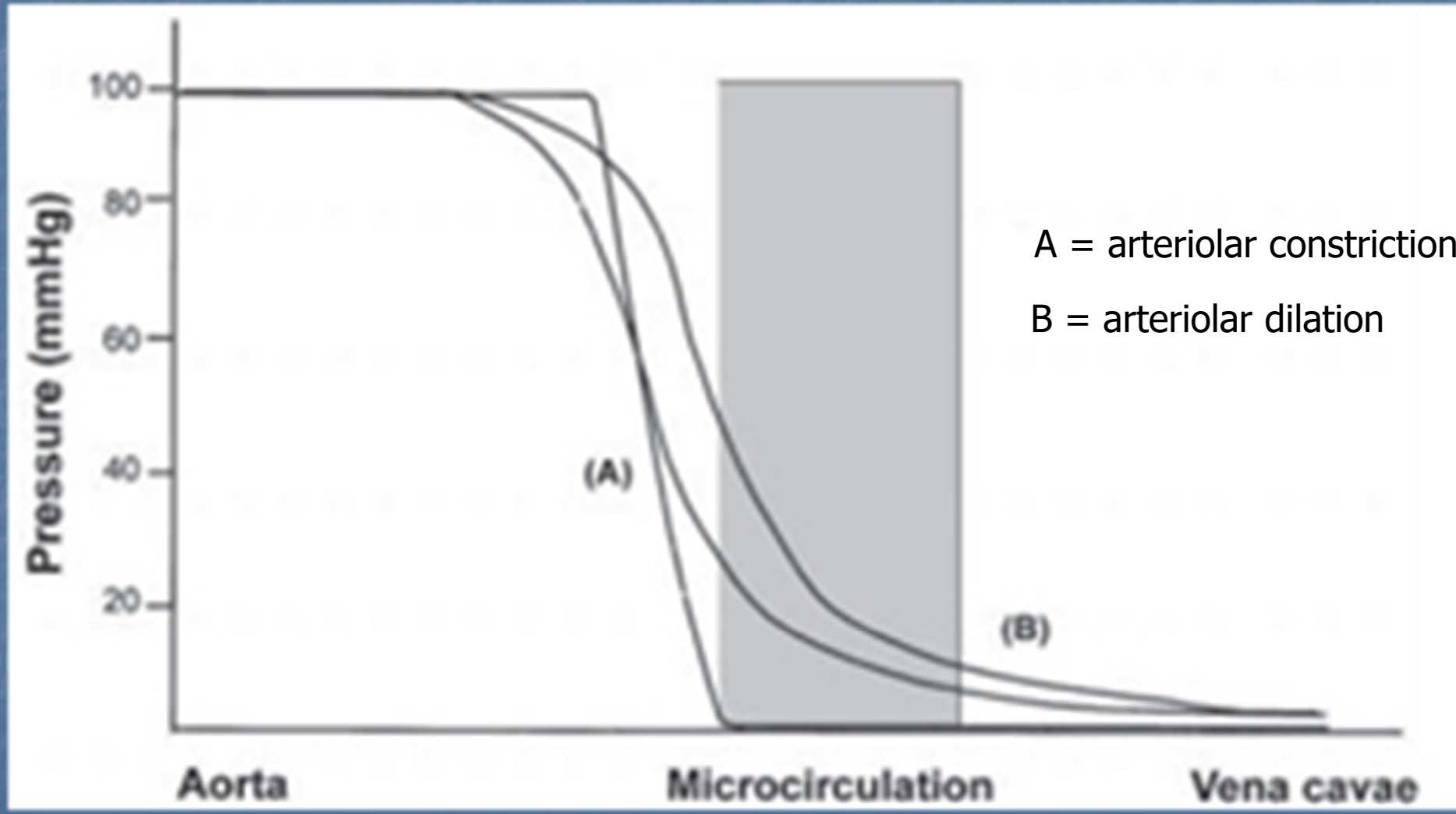
BP and Capillary Perfusion Clinical Experience

- 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

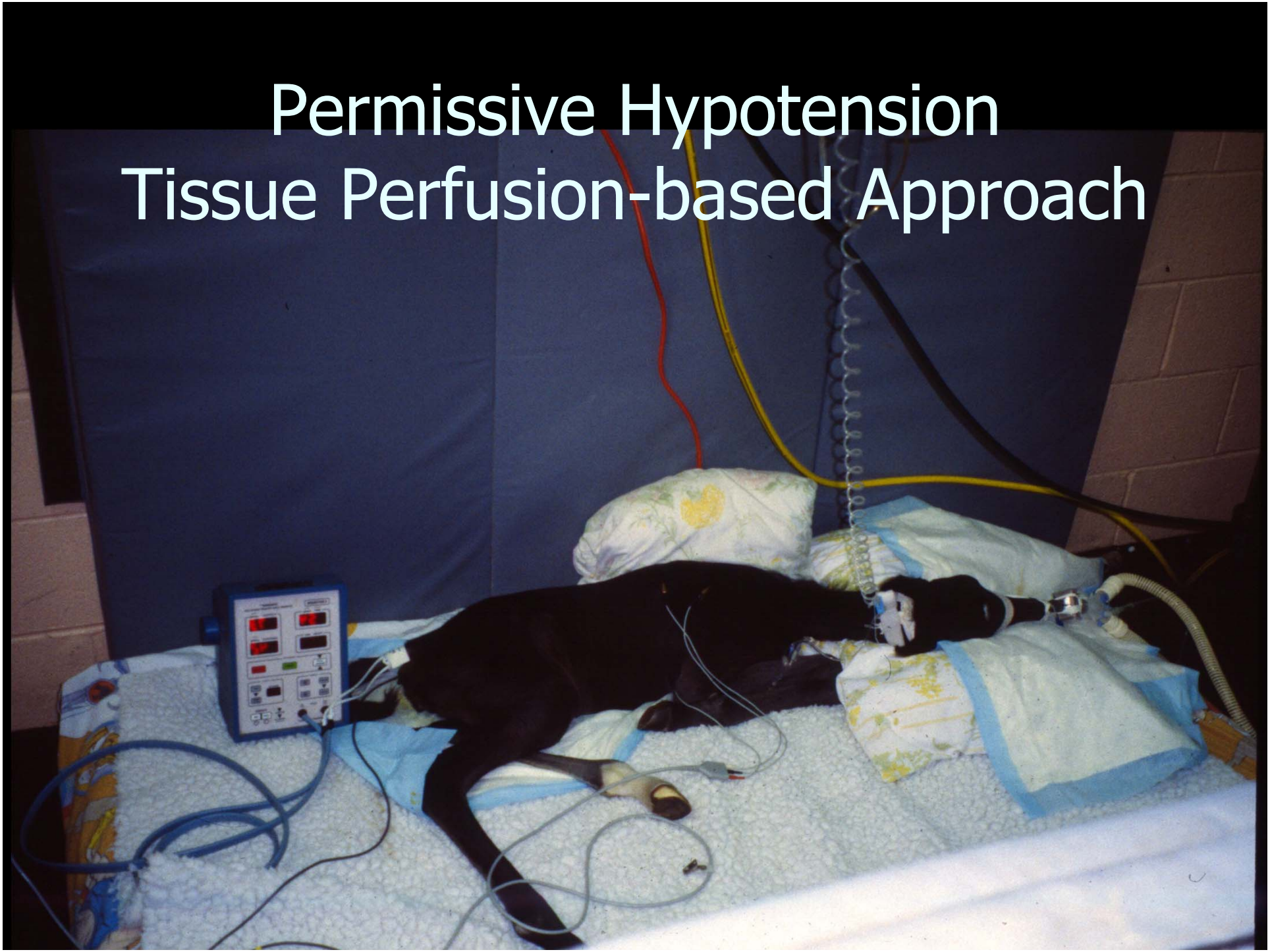


A = arteriolar constriction

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
MAP
45
SYSTOLIC
73
PULSE
97
DIASTOLIC
35
AUTO MANUAL
START
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 $\beta 1$ activity
    - at low to moderate doses
- In man
  - Mild vasodilation
    - Some $\alpha 2$ activity
  - Well balanced $\alpha 1$ and $\alpha 2$ stimulus
- In horses
  - At high doses
    - Significant vasoconstriction
    - $\alpha 1$ 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
  - $\uparrow$ 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 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
  - $\beta 1$, $\beta 2$ activity
  - ↑ cardiac output
  - ↓ peripheral resistance
- Inopressor activity as the dose increases
  - $\alpha 1$, $\alpha 2$ activity as well as $\beta 1$, $\beta 2$ 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***

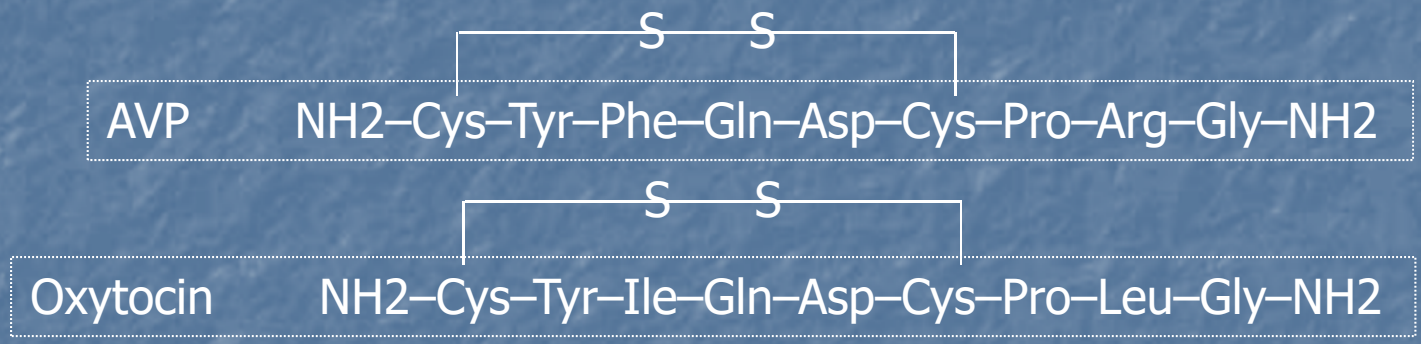

BD

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

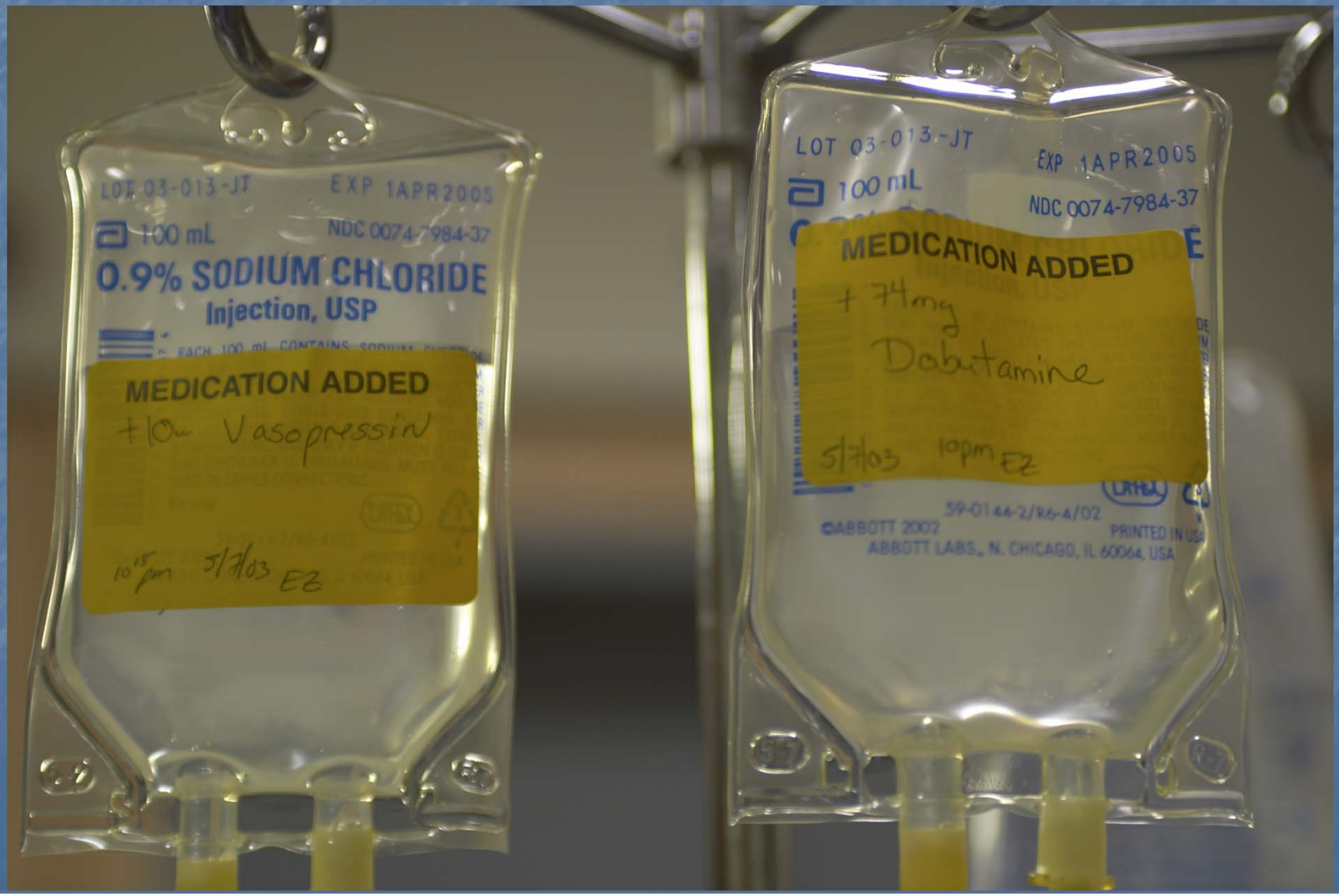
Vasopressin Vasoconstrictor Activity

- 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

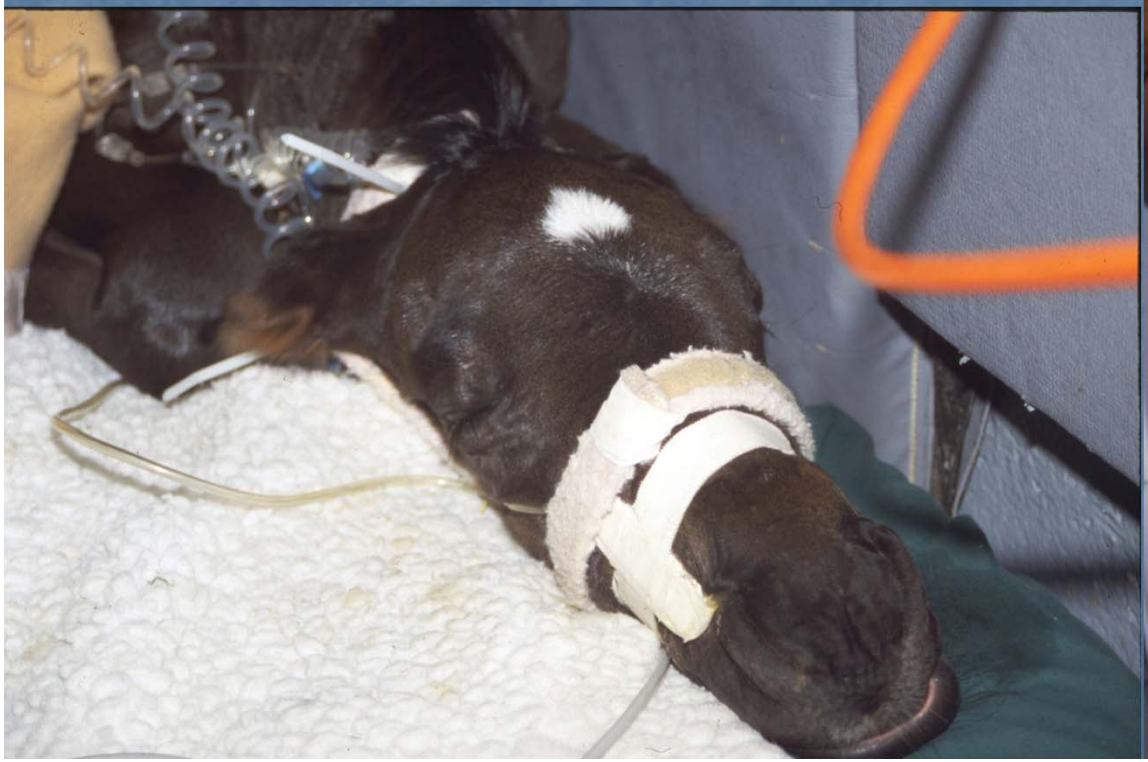
- Increase in systolic pressure
  - Patients in septic shock
  - Not occur in normal subjects
- Vasoconstrictor action low dose vasopressin
  - Blood pressure maintained without catecholamines
  - Result in plasma concentrations near normal levels
- Septic shock
  - Vasopressin secretion is inappropriately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

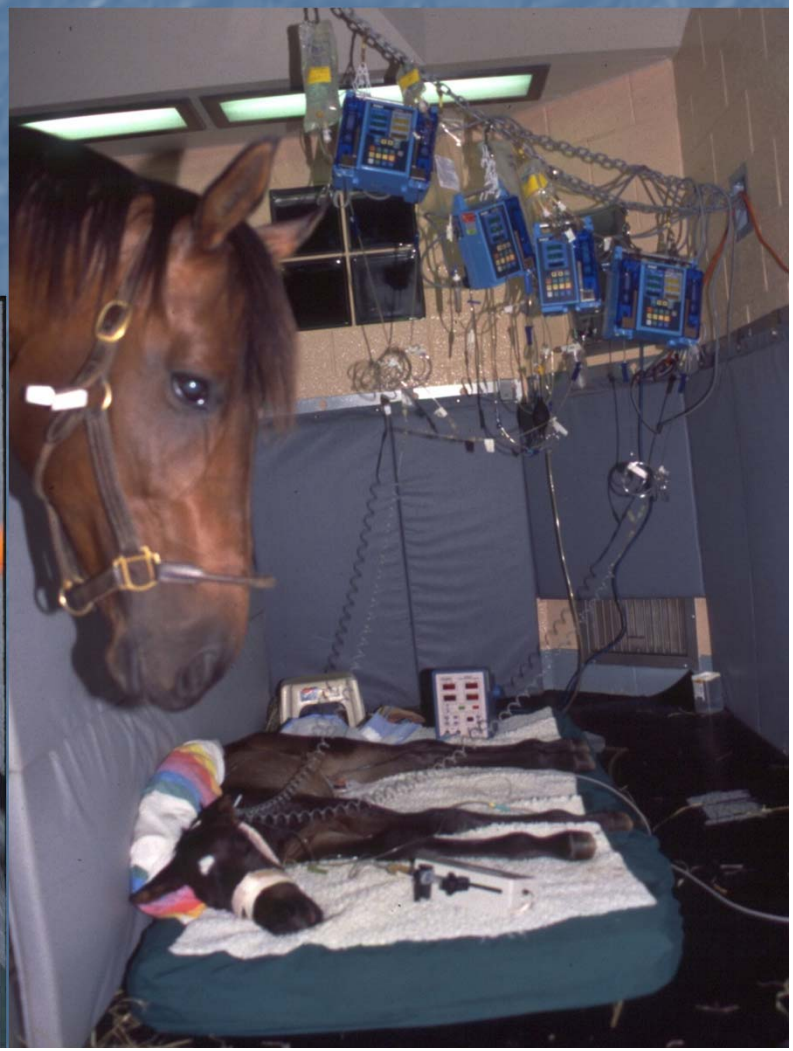
Urine flow rates

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

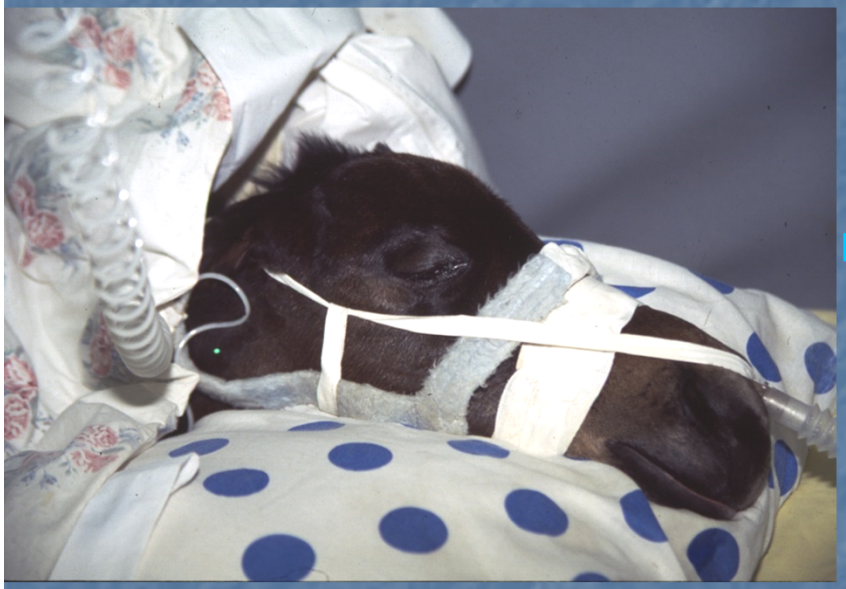
Hypoperfusion in Septic Shock

Initially responsive
Becomes refractory



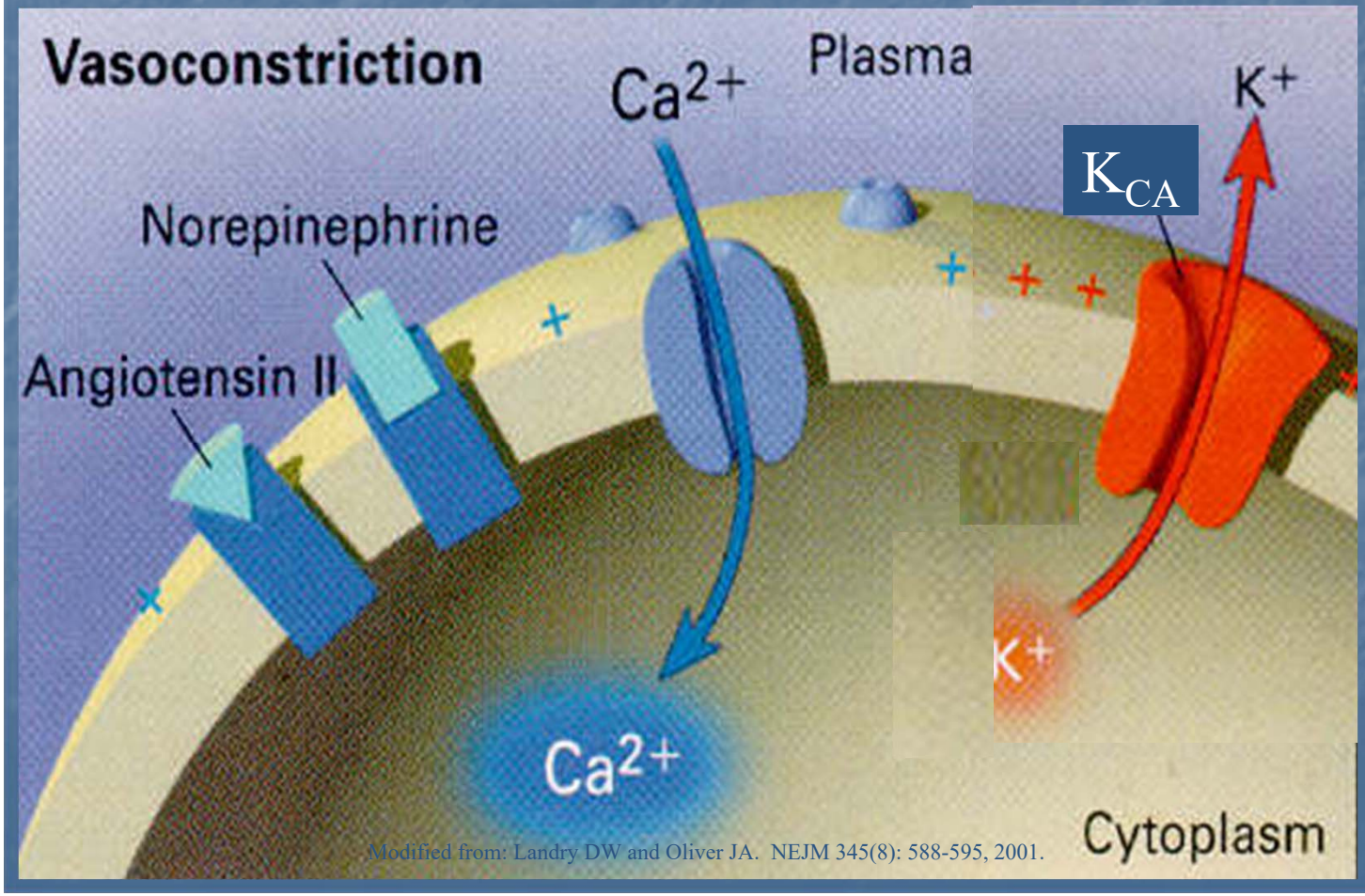


Septic Shock
Mechanism of Hypotension



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

Normal Vasoconstriction

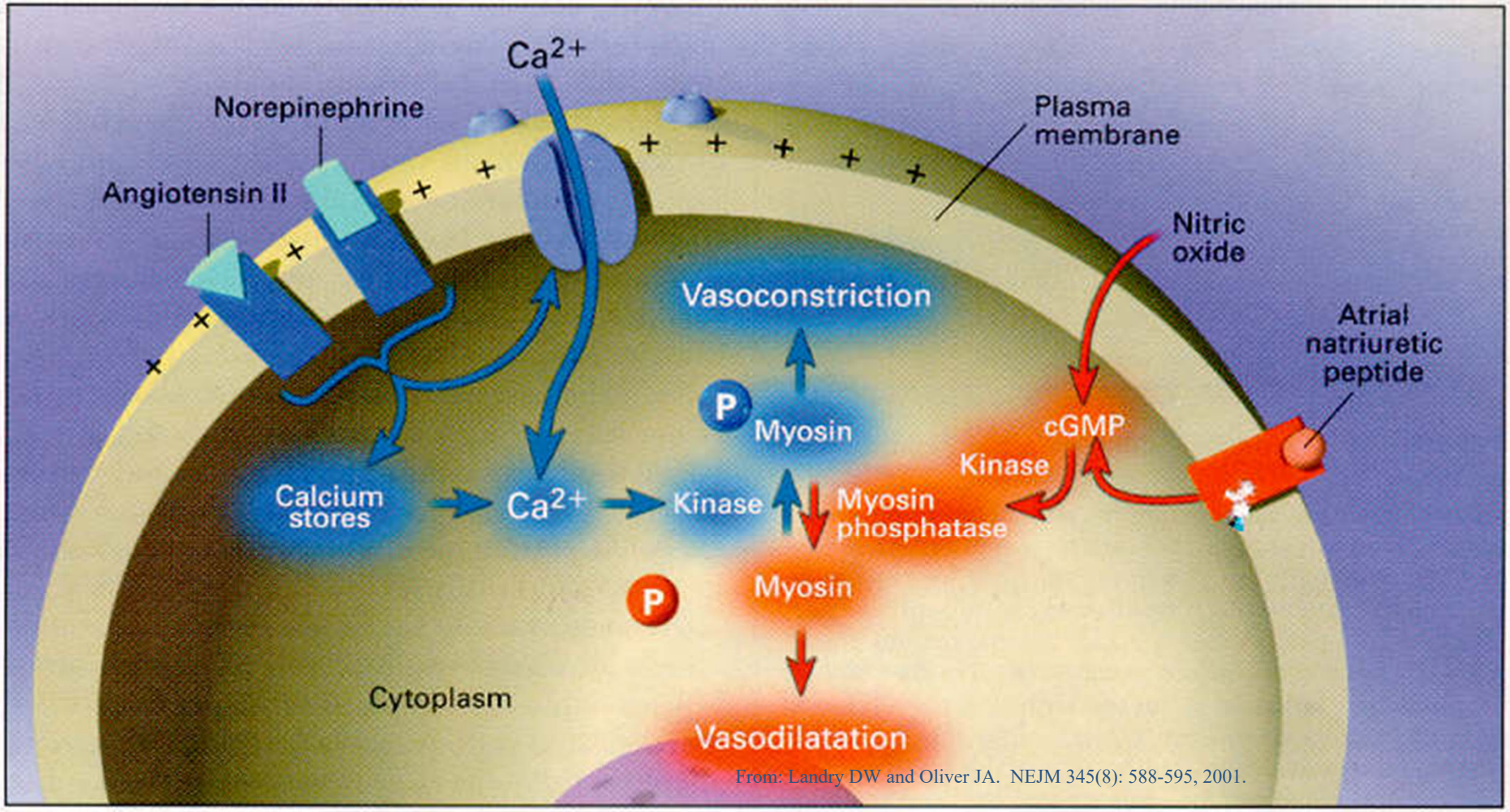


Modified from: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.

Voltage-gated Ca Channels

Ca-gated K channels

Vasoconstriction vs. Vasodilatation



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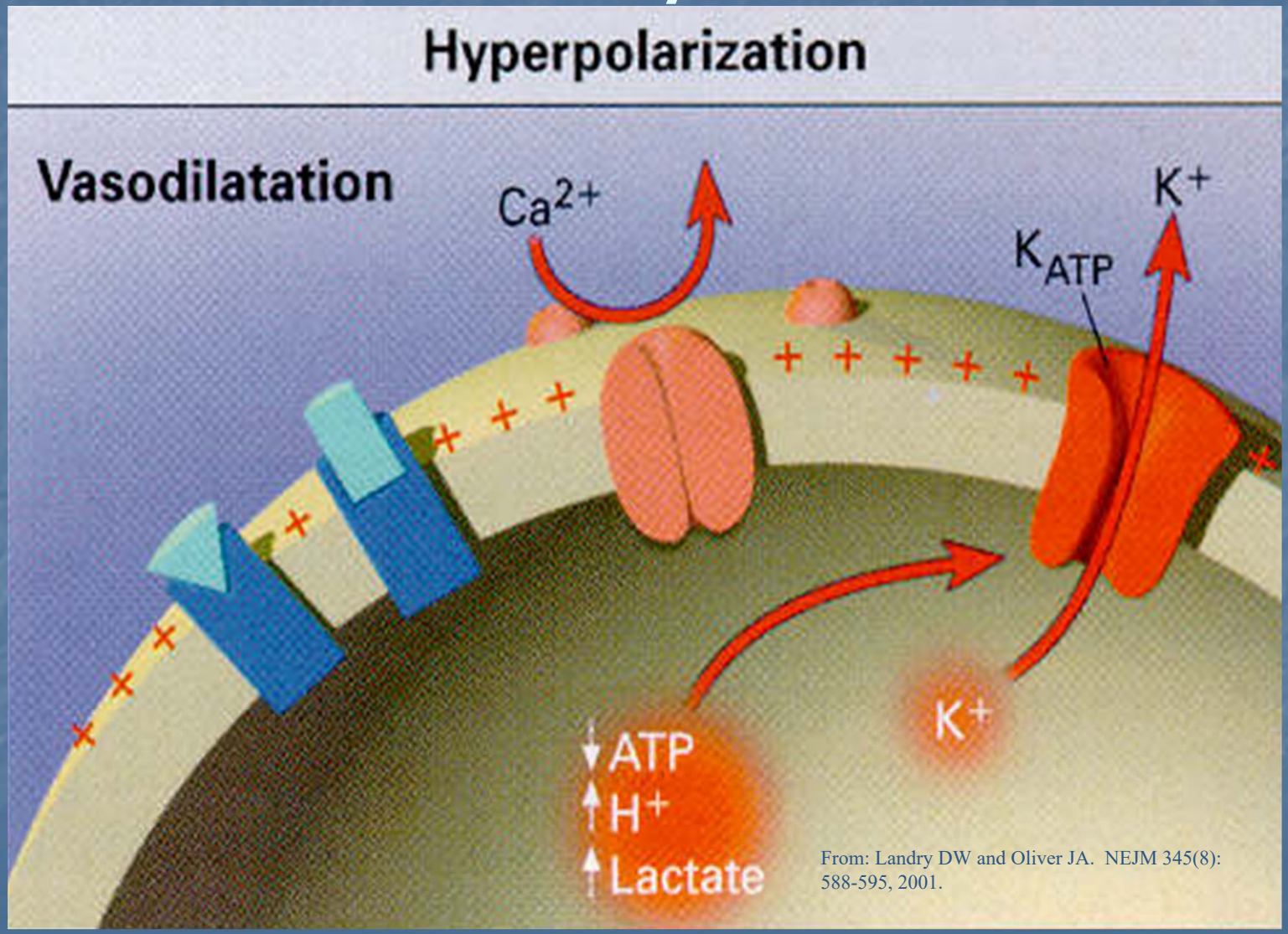
Vasodilatory Shock



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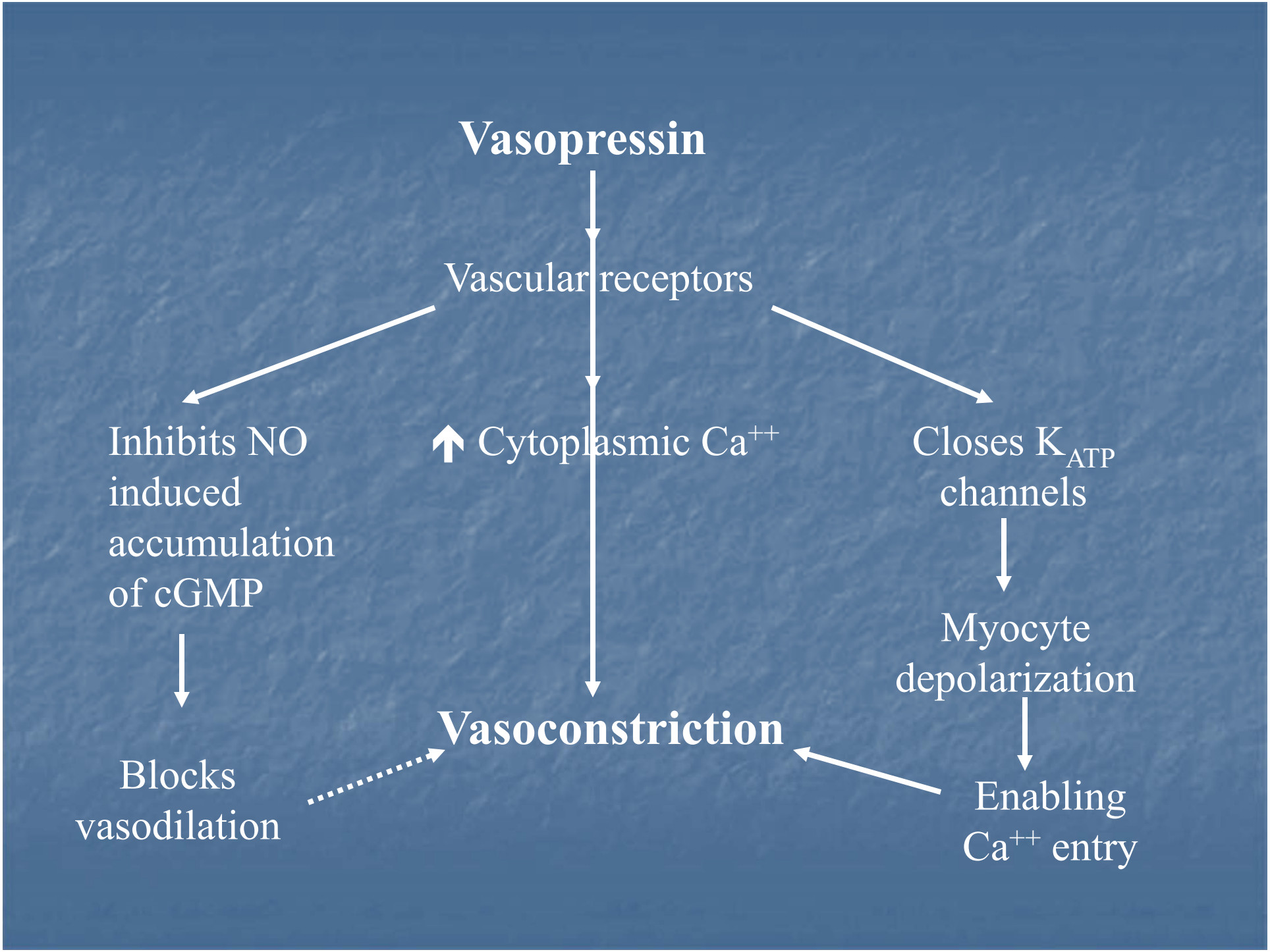
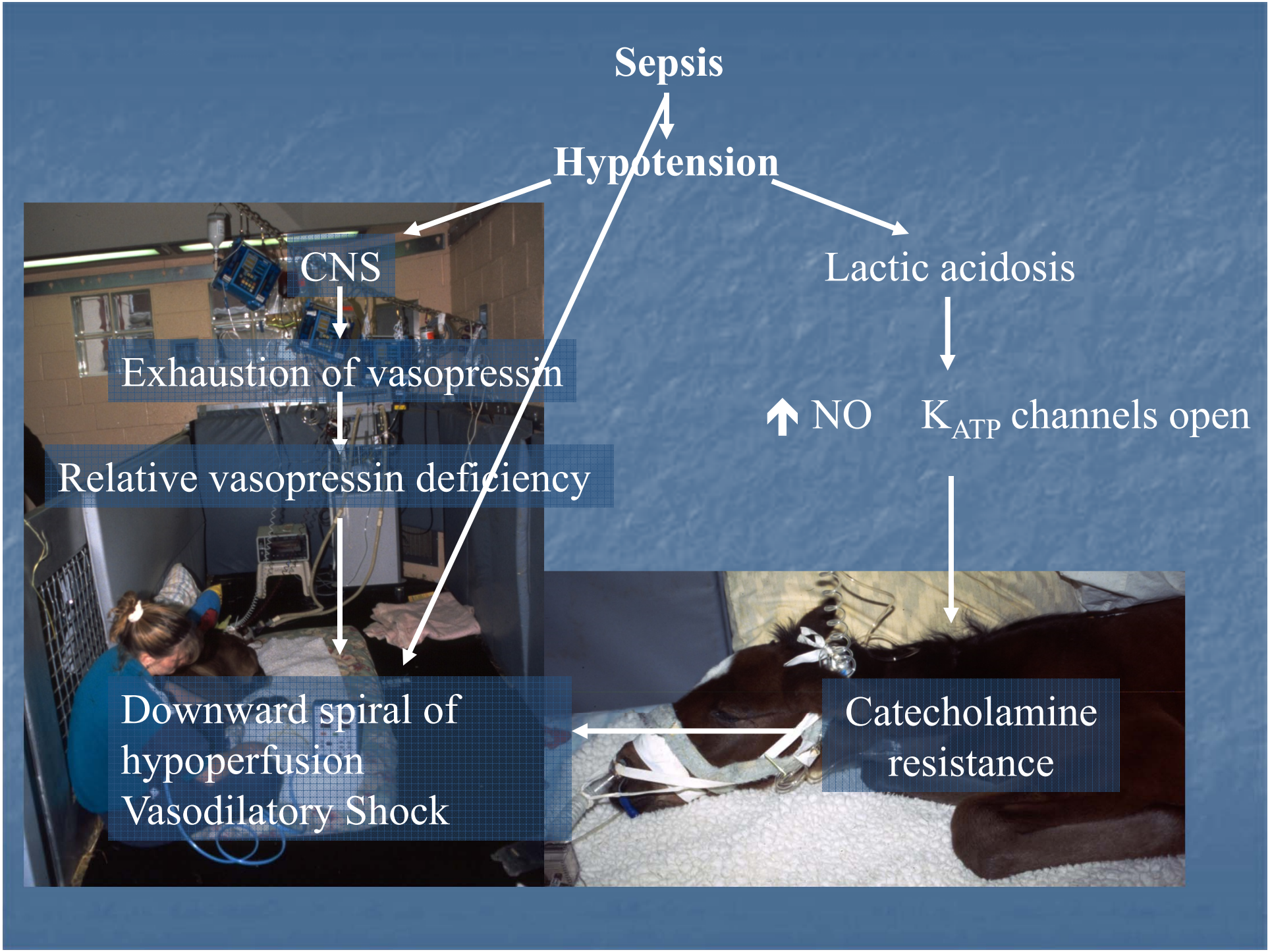

Vasopressin
Vascular receptors
Inhibits NO induced accumulation of cGMP
↑ Cytoplasmic Ca++
Closes K ATP channels
Myocyte depolarization
Vasoconstriction
Blocks vasodilation
Enabling Ca++ entry

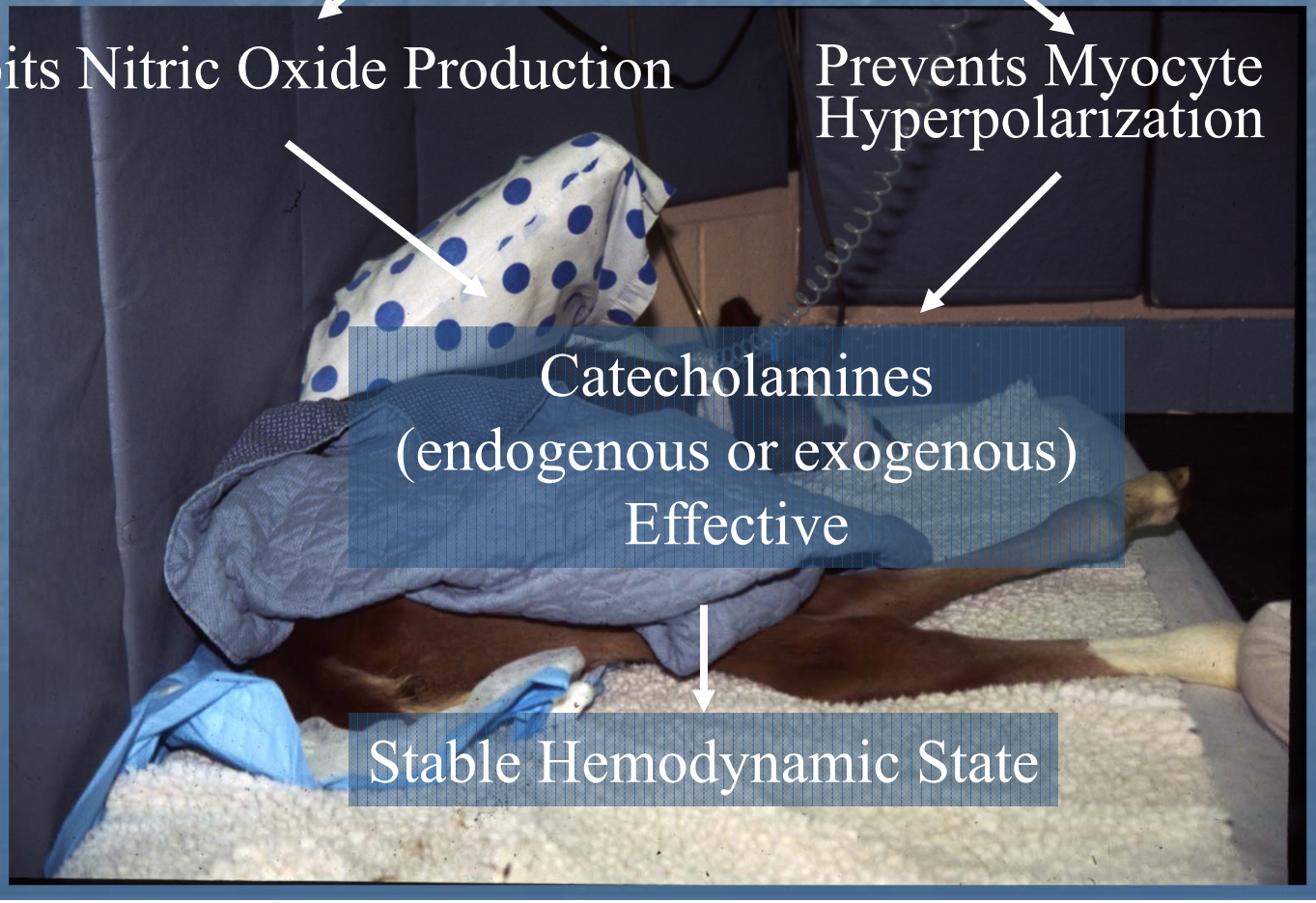

Sepsis
Hypotension
CNS
Exhaustion of vasopressin
Relative vasopressin deficiency
Lactic acidosis
NO
K_{ATP} channels open
Catecholamine resistance
Downward spiral of hypoperfusion Vasodilatory Shock

Exogenous Vasopressin

Physiologic Levels

Inhibits Nitric Oxide Production

Prevents Myocyte Hyperpolarization

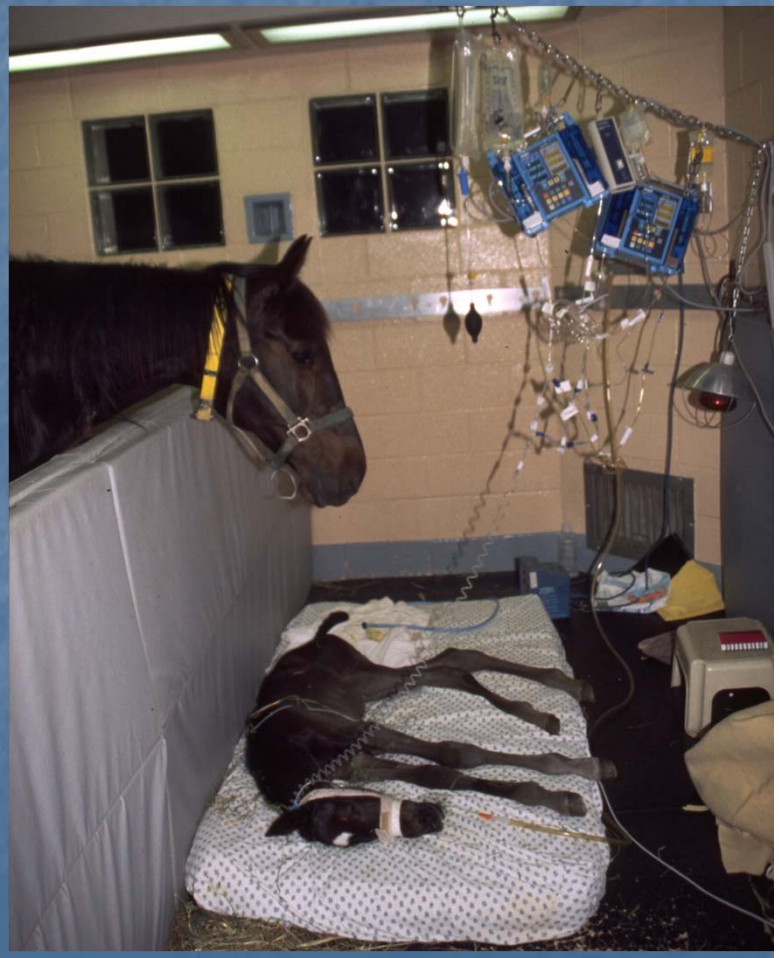


Catecholamines
(endogenous or exogenous)
Effective

Stable Hemodynamic State

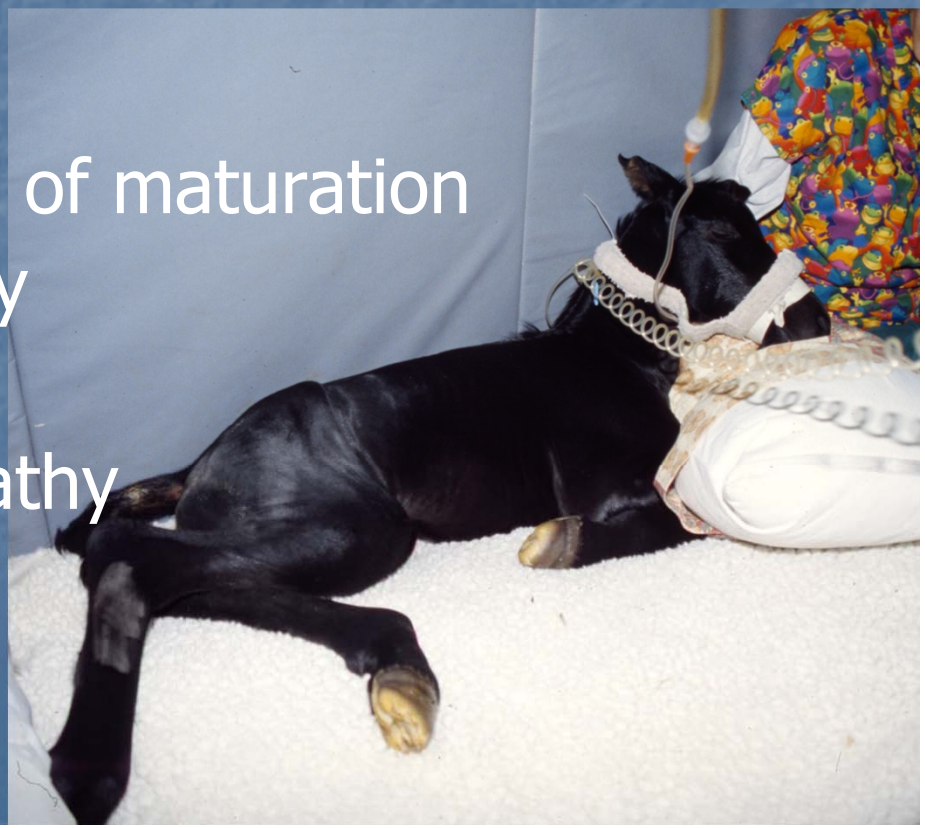
Low-dose Arginine Vasopressin Pressor Therapy Foals

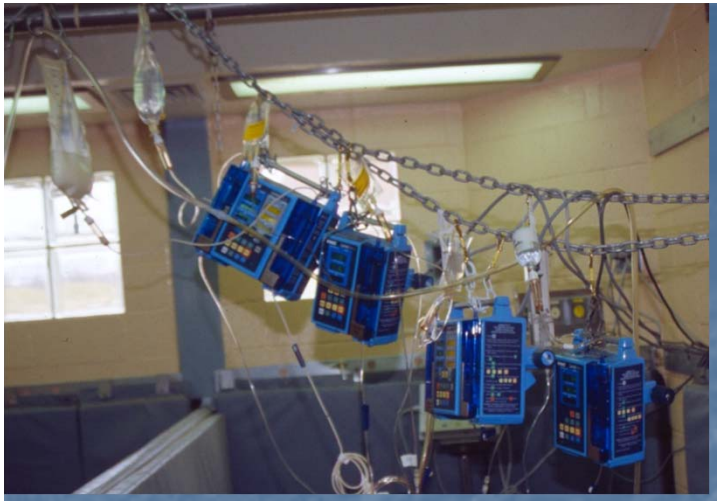
- Dose
  - 0.25-0.5 mU/kg/min
- Constant infusion
- Response within minutes
  - Inotrope/Pressor Score 20 – 60
  - BP increase ~ 20 mmHg
  - Signs of perfusion improve
- Cost – was ¢, now $$



Premature Friesian Foal

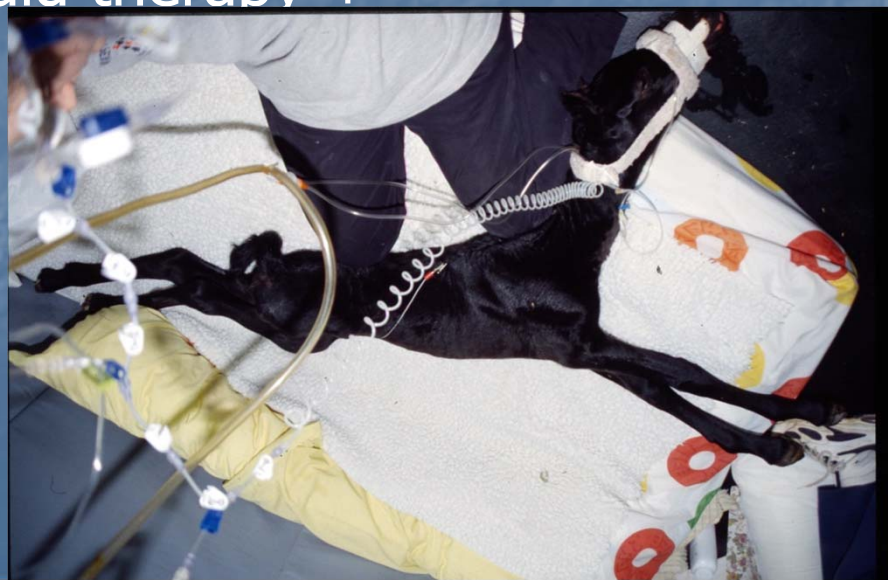
- 280 - 300 days gestation
  - Small- 25 kg
- Clinical Problems
  - Intrauterine acceleration of maturation
  - Neonatal Encephalopathy
  - Neonatal Nephropathy
  - Neonatal Gastroenteropathy
  - Incomplete ossification
  - SIRS





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

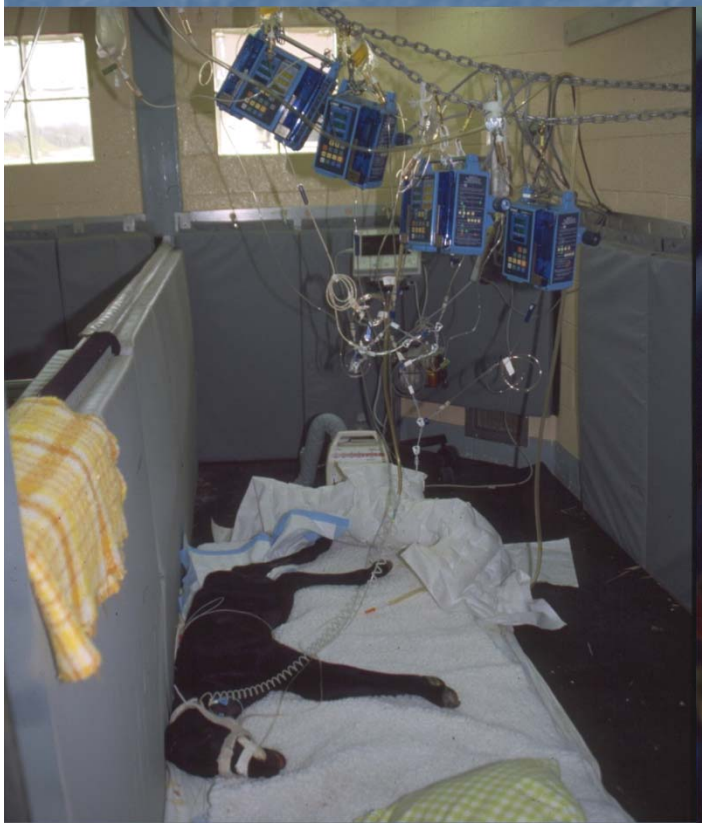
- At 48 hrs on Dobutamine (10 µg/kg/min)
  - BP – 50/28 (36) 88 and deteriorating perfusion
- Dobutamine (20 µg/kg/min)
  - → BP 43/32 (38) 88
- Dobut + Dopamine (10 µg/kg/min)
  - → 43/26 (32) 100
  - Inotrope/Pressor Score = 60 with no improvement
- Dobut + Dop + Vasopressin (0.25 mU/kg/min)
  - →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

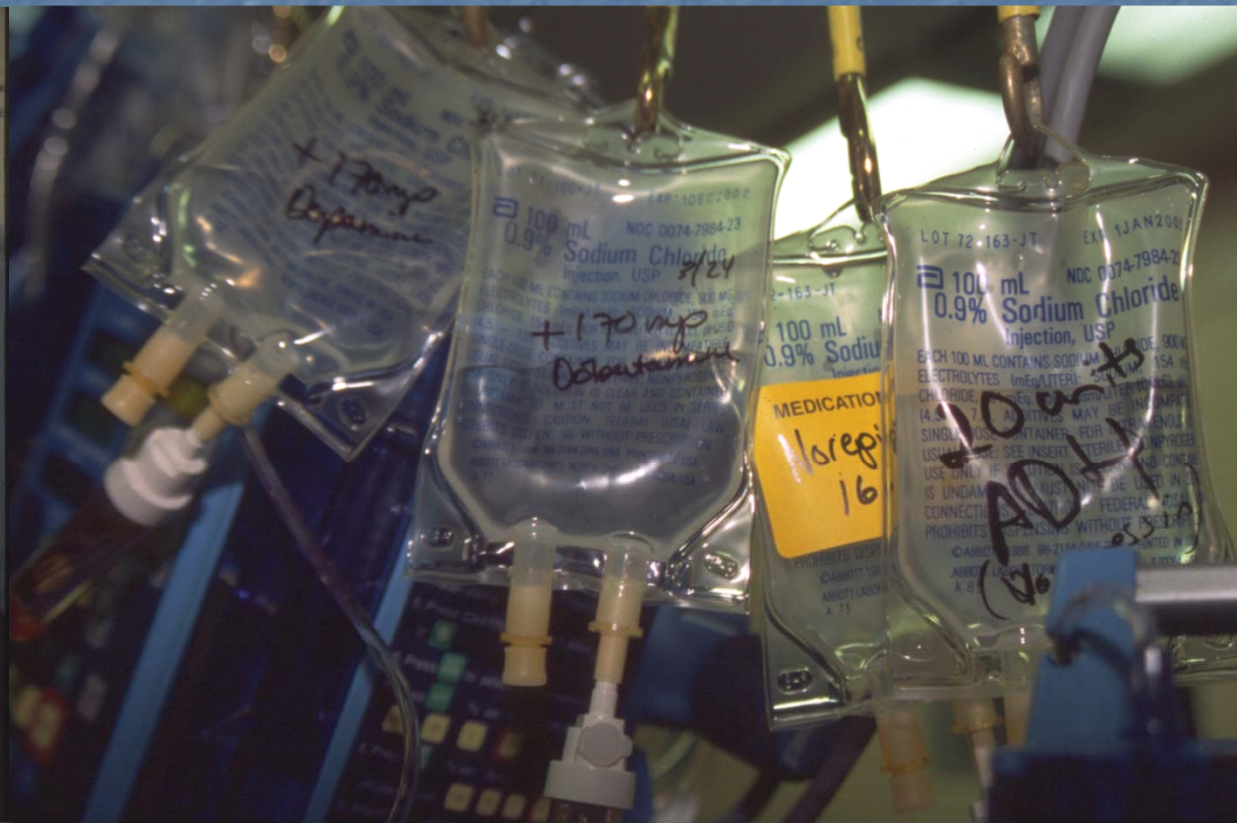
Basic Principles of Cardiovascular Support

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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