When Fluids are Not Enough: Inopressor Therapy

Jon Palmer, VMD, DACVIM
Director of Neonatal/Perinatal Programs
Graham French Neonatal Section, Connelly Intensive Care Unit
New Bolton Center, University of Pennsylvania

Problems in Neonatology

- Neonatal problem: hypoperfusion
  - Severe sepsis
  - Hallmark of septic shock
  - Secondary to neonatal encephalopathy
- First line therapy
  - Fluid loading – 20 ml/kg over 10-20 min
- Inopressor therapy
  - Inotropic therapy
  - Pressor therapy

Hypoperfusion

Insure volume

Defend pressure

Achieve perfusion

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
  - Arterial blood pressure
    - Ventricular function
    - Arterial fill
    - Peripheral vascular resistance
- But…
  - High blood pressure ≠ flow
  - Low blood pressure ≠ no flow

Neonates
Low-pressure System

- Perfuses 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/nerous system

    Capable of maintaining higher pressures
  - Increase in precapillary tone

  Transition may not occur in unison in all tissues

Neonates
Low-pressure System

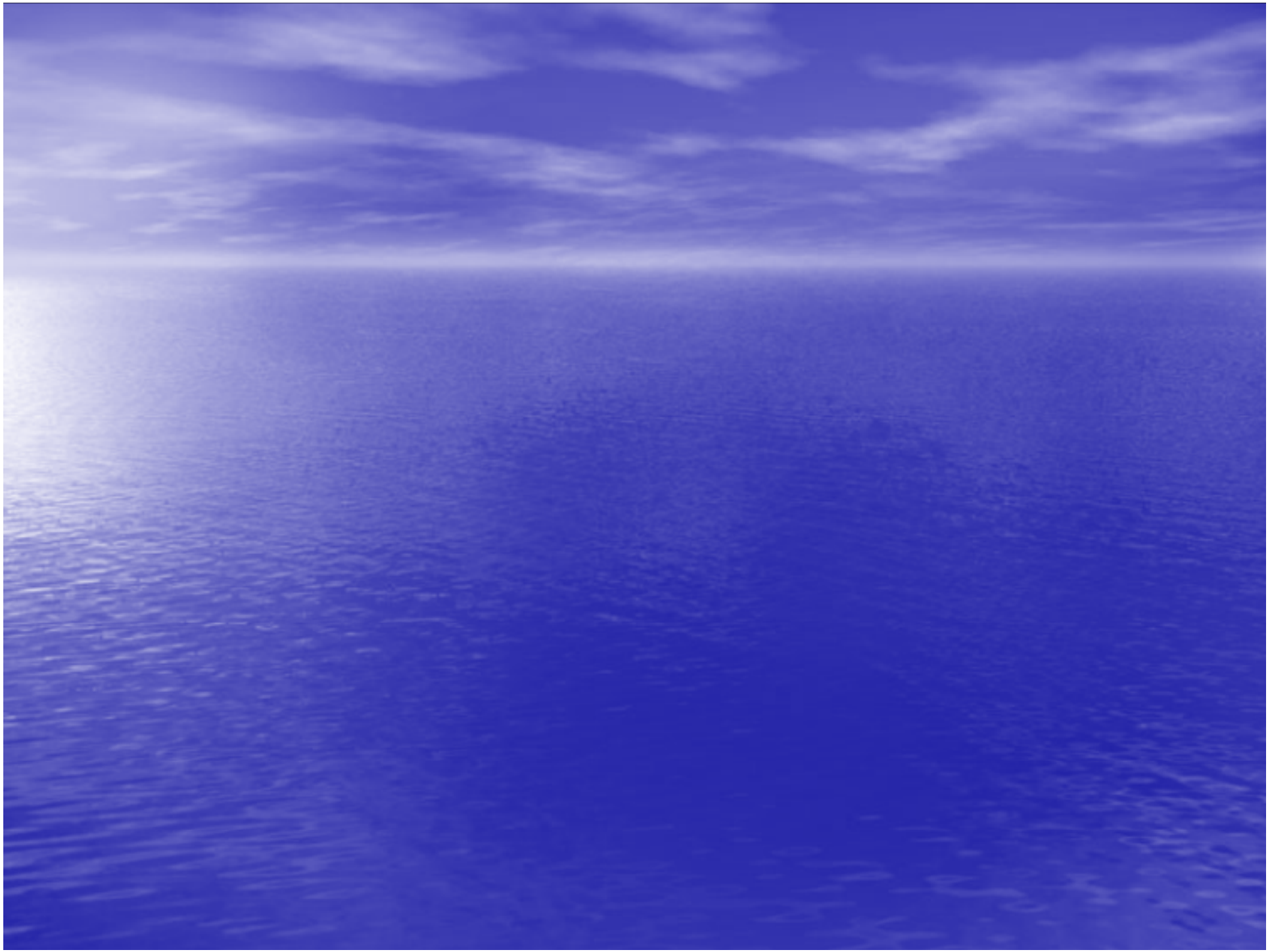
- Low systemic arterial pressures
  - Ensures capillary pressures remain low
  - Vital in maintaining fluid balance
    - Special capillary characteristics
    - Fluid and protein shifts
- Transition may be delayed
  - Neonates with perinatal disease
    - Hypoxic ischemic disease
    - Sepsis/SIRS/cytokine imbalance

Neonates
Low-pressure System

- Important pressure
  - Capillary pressure
  - Not arterial pressure
- When is arterial pressure transmitted to capillary?
  - Poor precapillary tone
  - Changes in venous tone
  - From arteial side
    - Many variables
    - Complicated picture

Neonates
Normal Arterial Blood Pressure

- Difficult to predict how much of the transition has occurred
- Human medicine - age and maturity adjusted values
  - For meaningful "normals" must be on resting, undisturbed neonate
  - Our normal neonates – no way to get reliable normal values
- Sense of normal
  - Experience based
  - Sick neonates with apparently normal perfusion
- Many neonatal foals adequate perfusion
  - MAP - in the 40s
  - SAP- in the 50s
  - DAP in the 30s
- Others require BP 15 mm Hg above these for adequate perfusion.



Neonates
Treating Hypotension

- Do not treat blood pressure numbers
- Treat hypoperfusion
- Constellation of signs of perfusion
  - SAP, DAP, MAP
  - Comparing central and peripheral pulse quality
  - Assessing arterial fill
  - Assessing arterial tone
  - Assessing leg warmth
  - Noting gradient between core and peripheral temperature
  - Observing signs of organ perfusion
    - Urine production
    - Borborygmi (enterokinesis)
    - Level of mental arousal

Neonates
Treating Hypoperfusion

- Initiation of pharmacologic cardiovascular support
  - Based on indications of poor perfusion
  - Not blood pressure numbers
- Modification of pharmacologic cardiovascular support
  - Based on signs of perfusion
    - One of which may be relative changes in BP
  - Not blood pressure goals

Inopressor Therapy Adrenergic Agonists

- Pharmacokinetics varies with each individual
  - Plasma half-life
  - Receptor density
  - Receptor affinity
  - Receptor reactivity
  - Plasma pH
- The dose used must be tailored to the individual
  - By monitoring for signs of improved perfusion
  - During CRI (continuous rate infusion)
  - Adjusting the dose accordingly
    - Short half-life
    - Effect of new dose evident within 10 to 15 minutes
  - Effective Dose may change with time
    - confounding factors
    - Need to adjust dose
- 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 amt 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
- Inotropes are almost always indicated
- Mixed inotropic and pressor support
  - Inopressor support
  - Selecting an inotrope
    - Dobutamine
    - Medium dose dopamine
  - If inotropic effect does not increase perfusion adequately
    - Add a pressor

Inopressor Therapy Adverse Effects

- Decreased cardiac output
- Arrhythmias
  - Tachycardia
    - Up to 20% with dobutamine
    - > 160 ↓ cardiac filling, ↓ CO
    - Discontinuing the offending adrenergic
  - Premature ventricular contractions
    - Usually secondary to pre-existing underlying cardiac damage
    - Withdrawing therapy - quickly identify role of adrenergic therapy
- Adrenergic drug
  - Discontinued
    - Adverse reaction
    - Lack of efficacy
  - Others adrenergics should be tried
  - Response
    - Varies between individuals
    - Cannot be predicted based on the response to other adrenergics

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 supranormal 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 - 5 µg/kg/min
  - Titrate to effective dose
- With severe sepsis, septic shock
  - Begin - 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 shocky
  - Begin - 5 µg/kg/min
  - Titrate to effective dose
- With severe sepsis, septic shock
  - Begin - 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 Norepinephrine

- Potent vasopressor
  - Strong $\alpha 1$ activity
  - Variable $\beta 2$ activity
- Both inotropic and chronotropic activities
  - $\beta 1$ activity
  - Chronotropic – usually blunted by vagal reflex
    - slowing the heart rate
    - induced by the rise in blood pressure
  - ↑ myocardial oxygen consumption
    - Cardiostimulation
    - ↑ afterload
- Thought of primarily as a pressor
  - Advocated in septic shock
  - Used in combination with either dopamine or dobutamine
    - to enhance the inotropic effect
- More maldistribution than the other adrenergic agonists

Inopressor Therapy Norepinephrine

- Initial dose
  - 0.3-0.5 µg/kg/min
  - Titration to effective dose
- Dose range
  - 0.1-3.0 µg /kg/min
- Difficult cases
  - 4 to 5 µg/kg/min
- Adverse reactions
  - Arrhythmias
    - Rare without pre-existing myocardial damage
      - Hypoxic ischemic 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

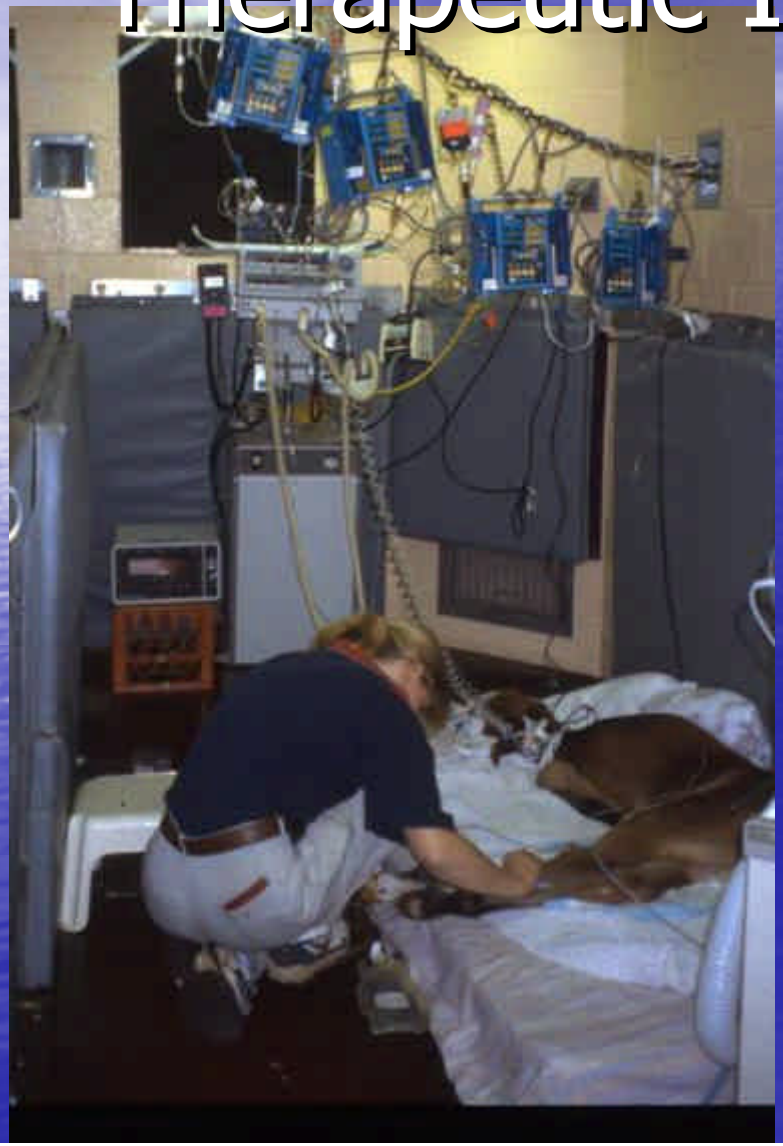
- Dobutamine – dopamine
  - Powerful combination
  - Most consistently useful therapy
- Dobutamine – norepinephrine
- Epinephrine – norepinephrine
- Dobutamine – dopamine – norepinephrine
- Dobutamins – vasopressin

Low-Dose Vasopressin Treatment for Septic Shock in Neonates

Septic shock

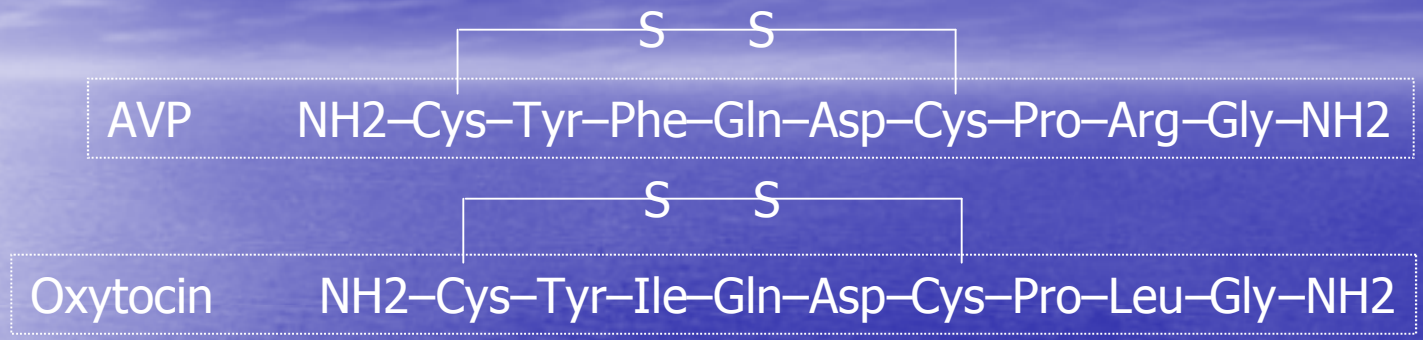
- Distributive shock
  - Progressive hypotension
  - Refractory to therapy
- Peripheral arterial vasodilation
  - Low vascular resistance
  - High cardiac output
- Inadequate tissue perfusion
  - Multiorgan dysfunction
  - Death

Septic Shock Therapeutic Interventions



- Fluid therapy
  - 20 ml/kg bolus
  - Crystalloids
  - Colloids
- Inotropics/Pressors
  - Dopamine
  - Dobutamine
  - Epinephrine
  - Norepinephrine
- Respiratory support
  - Oxygen therapy
  - Ventilation

Vasopressin



- Peptide hormone
- 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

Vasopressin Receptors

- Vascular V_1 receptors (V_{1a})
  - Increase intracellular Ca^{++}
  - Causes vasoconstriction
- Renal V_2 receptors (antidiuretic action)
  - Adenyl cyclase
  - Aquaporin 2 channels
- Anterior pituitary V_3 receptors (V_{1b})
  - Increase intracellular Ca^{++}
  - Stimulates the release of ACTH
  - Role in memory, emotion

Vasopressin Blood Pressure

- Pressor action
  - Large doses required
  - Traditionally thought pharmacologic effect
  - Under-estimates vasoconstrictor action
  - More potent than Angiotensin II, Norepinephrine
- Increases systemic vascular resistance
  - At low doses
  - V_1 receptors in the medulla oblongata
    - Reset the cardiac baroreflex
    - Slows heart rate – arterial pressure unchanged

Vasopressin as a Pressor

- For a given increase in blood pressure
  - More bradycardia than other vasoconstrictors
- 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

Infusion of Exogenous Vasopressin

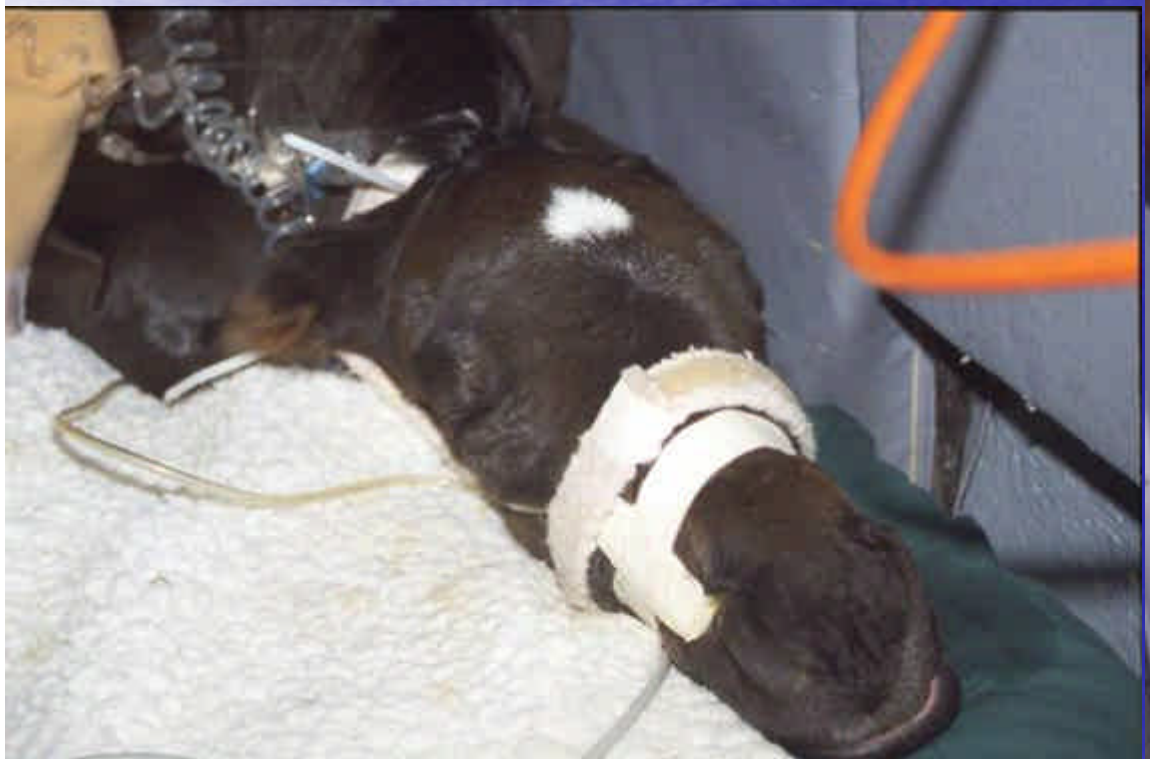
- Increase in systolic pressure
  - Patients in septic shock
  - Not occur in normal subjects
- Vasoconstrictor action low dose vasopressin
  - Blood pressure maintained without catecholamines
  - Result in plasma concentrations near normal levels
- Septic shock
  - Vasopressin secretion is inappropriately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

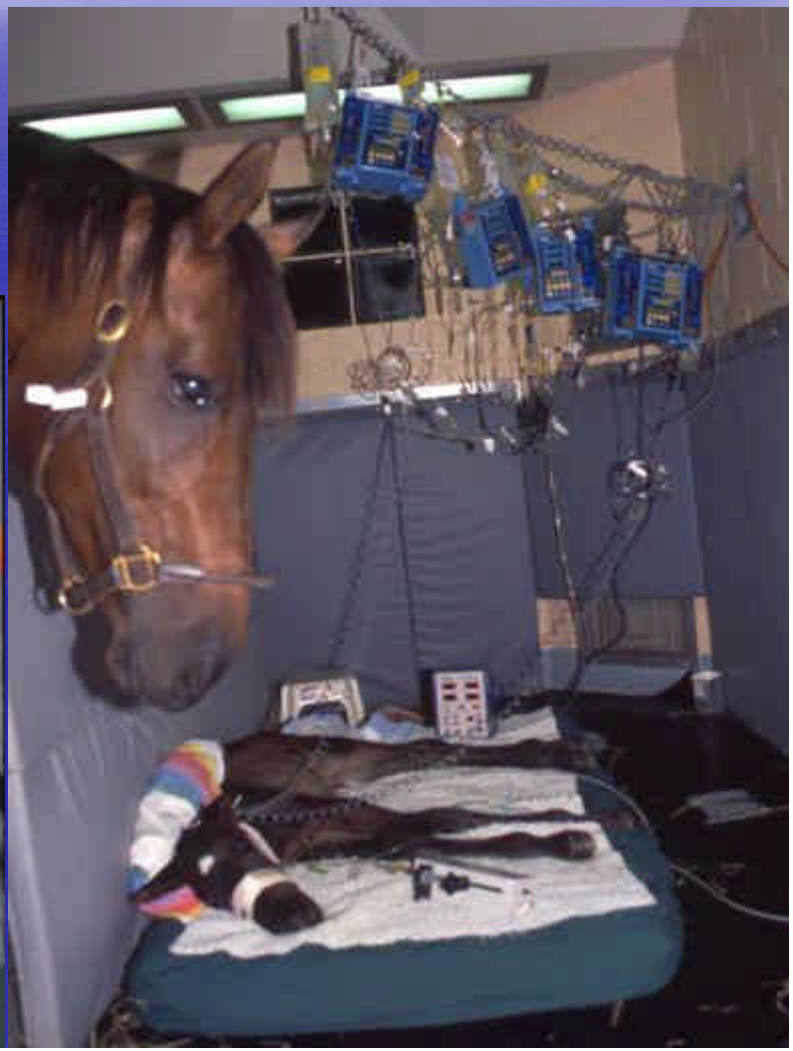
Urine flow rates

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

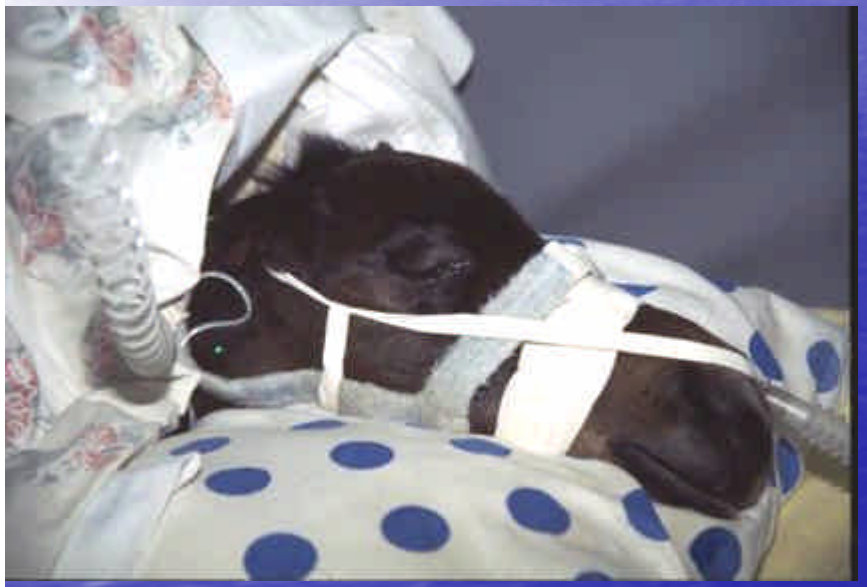
Hypoperfusion in Septic Shock

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

Refractory Hypotension

- Adrenergic pressors
  - ↓ vasoconstrictor effect
  - ↑ doses are required
    - Secondary to desensitization
    - Receptors down regulation
- Vasodilatory shock
  - Occurs in septic shock
  - Also occurs in
    - Late hemorrhagic shock
    - After cardiovascular surgery

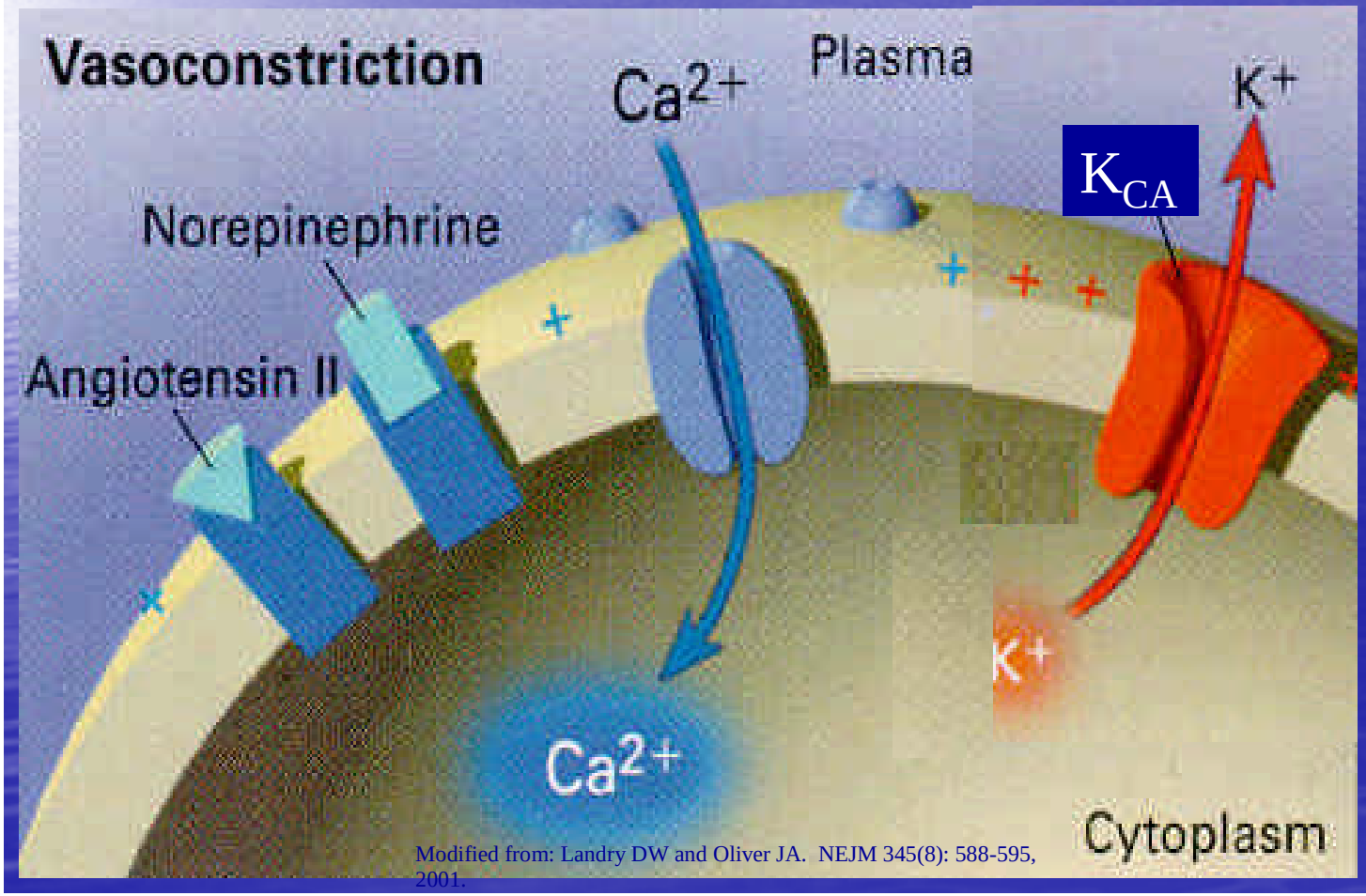
Vasodilatory Shock

- Resistance to adrenergic pressors
  - Vasopressin deficiency
- Low dose vasopressin infusion
  - Significantly increases arterial blood pressure
  - Permit withdrawal of adrenergic agents
  - Exogenous vasopressin
    - Provide a plasma concentration expected
    - Marked pressor response

Mechanisms of Active Vasodilation

- Nitric oxide induced
  - Accumulation of cGMP
  - Myosin relaxation
  - Open K_{CA} channels
- Activation of K_{ATP} channels
  - ATP sensitive K channels
  - Hyperpolarize myocyte

Normal Vasoconstriction

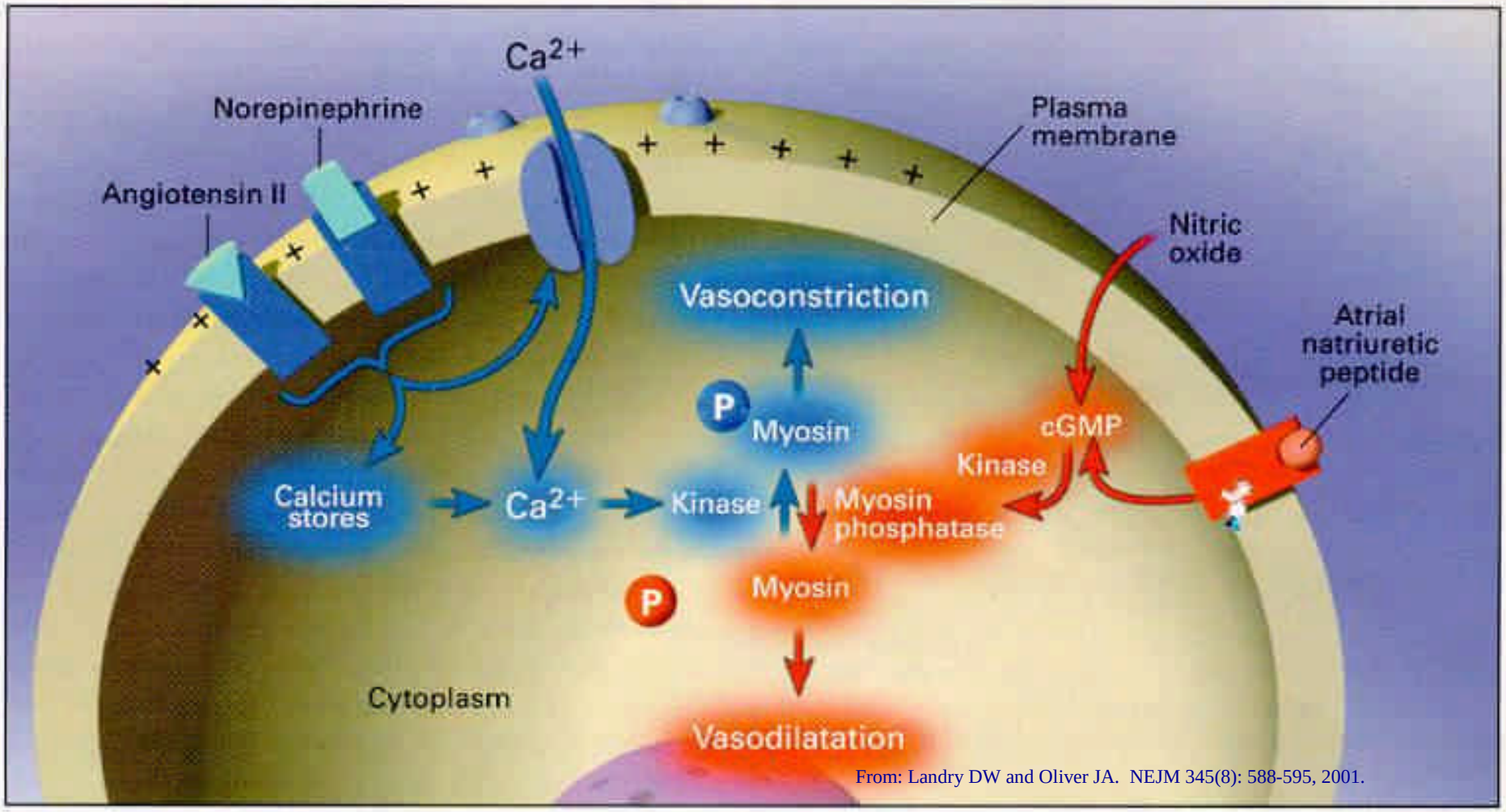


Modified from: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.

Voltage-gated Ca Channels

Ca-gated K channels

Vasoconstriction vs. Vasodilatation

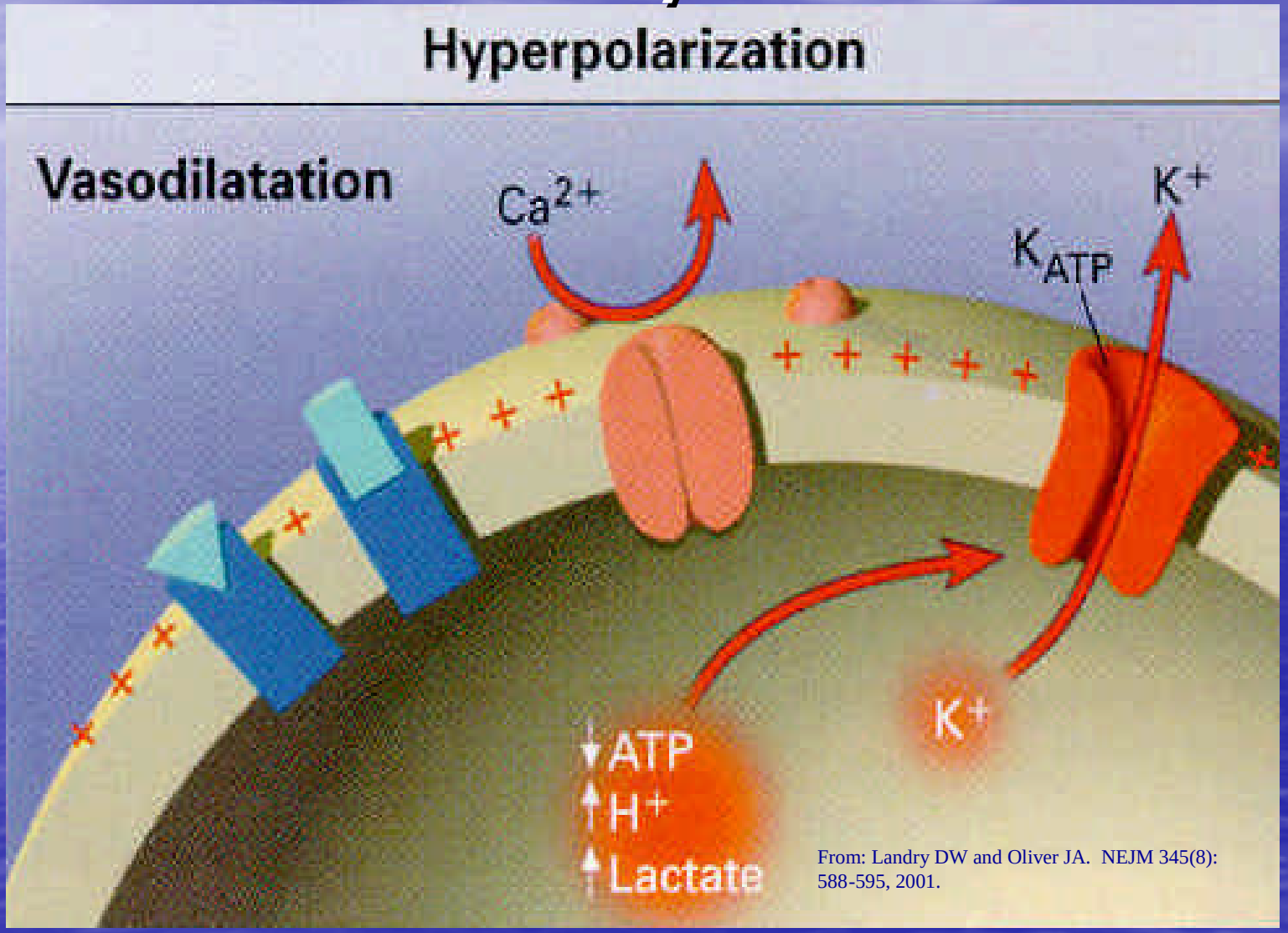


From: Landry DW and Oliver JA. NEJM 345(8): 588-595, 2001.

K_{ATP} channels

- Hypoperfusion $\rightarrow$ cellular acidosis
  - Open K_{ATP} channels
- Hyperpolarization of myocytes
  - Prevents calcium channels from opening
    - Voltage-gated Ca Channels
- Prevents catecholamine vasoconstriction
  - Refractory vasodilatory shock

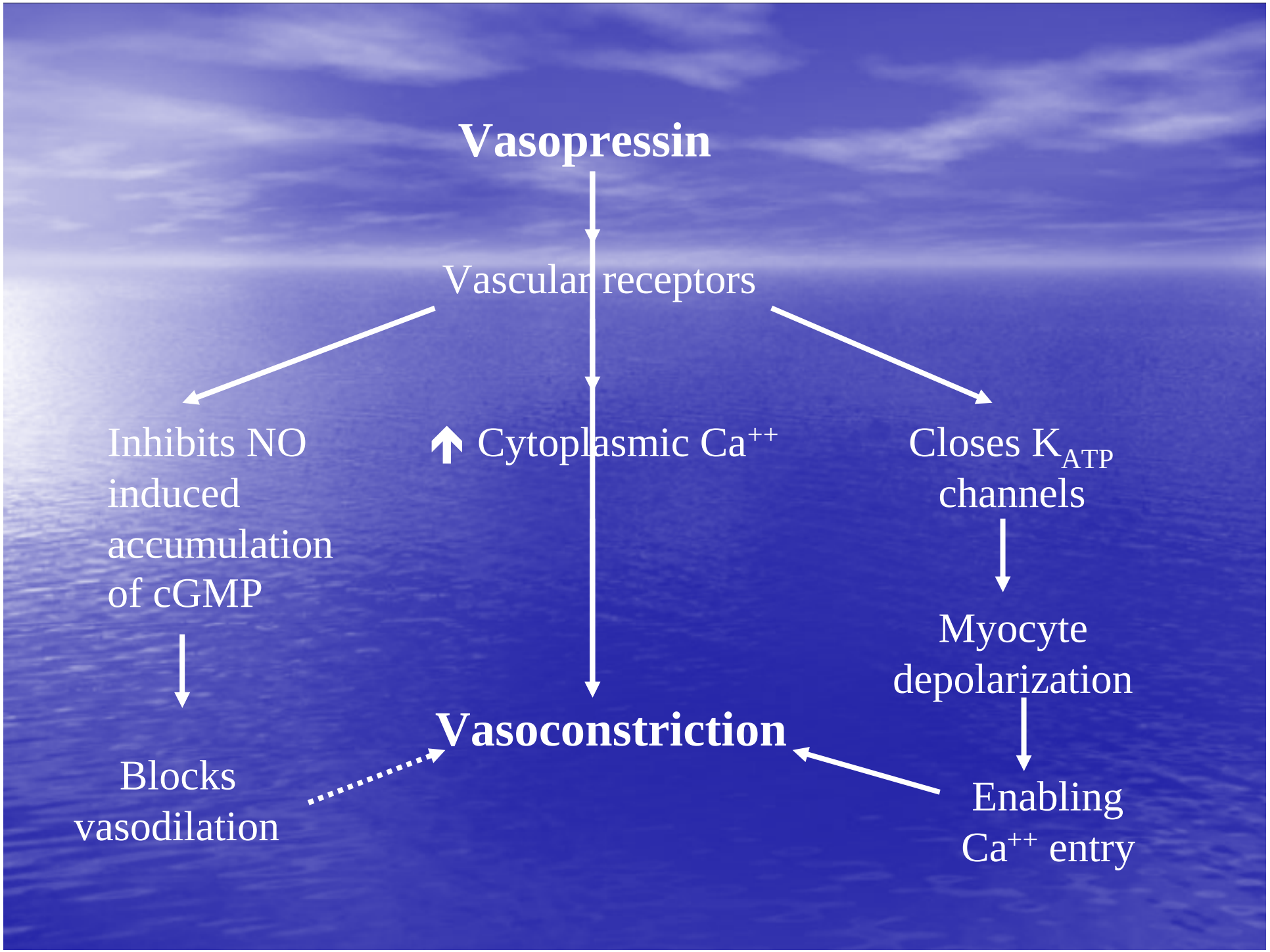
Vasodilatory Shock

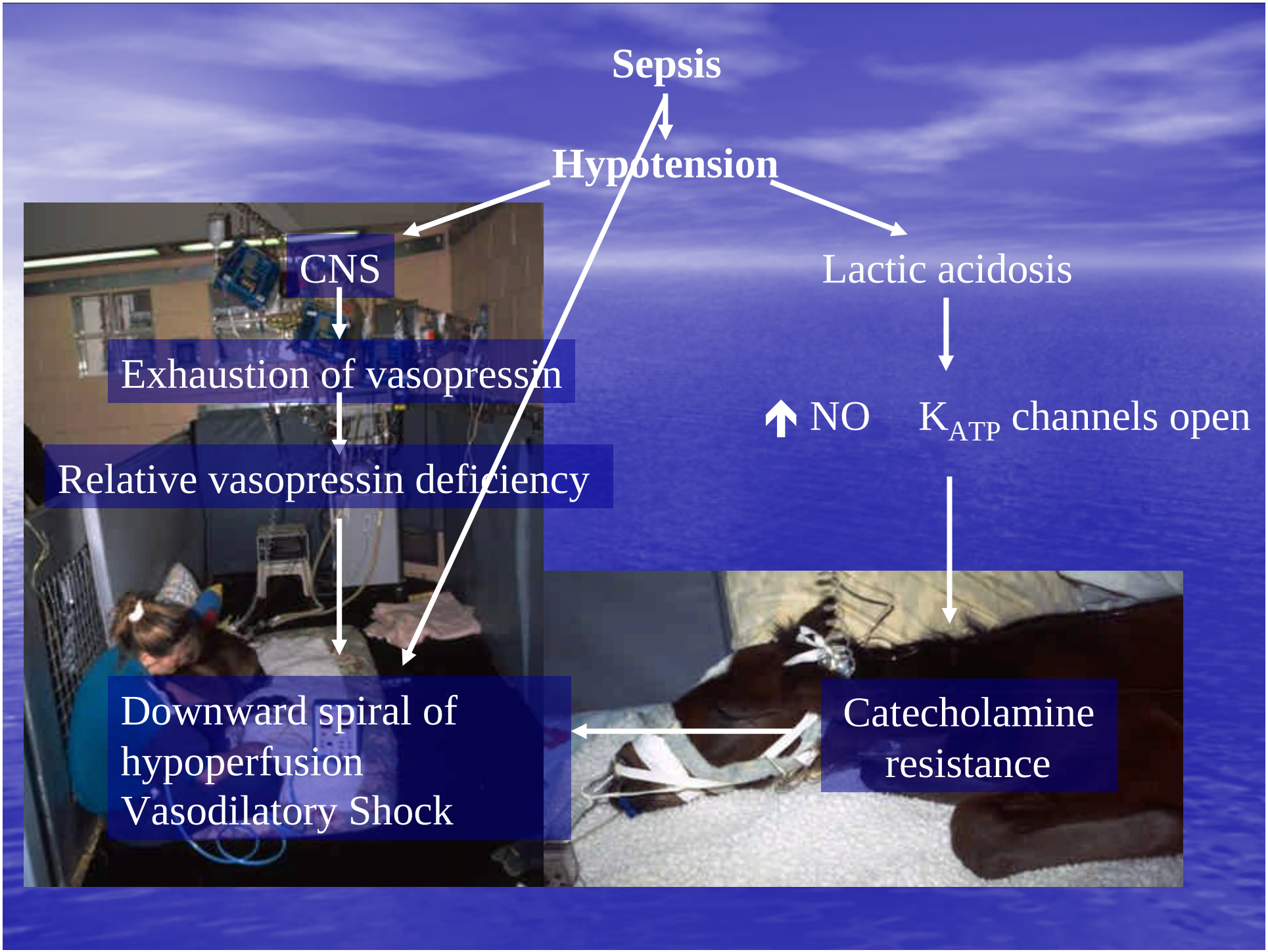


From: Landry DW and Oliver JA.
NEJM 345(8): 588-595, 2001.

Vasopressin Vascular Receptors

- Vasoconstriction
  - Causes rise in cytoplasmic Ca^{++}
- Inhibits NO induced accumulation of cGMP
  - Inhibits NO induced vasodilation
- Closes K_{ATP} channels if open
  - Promoting myocyte depolarization
  - Enabling Ca^{++} entry into the cells
    - Voltage-gated channels
  - Vasoconstriction


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

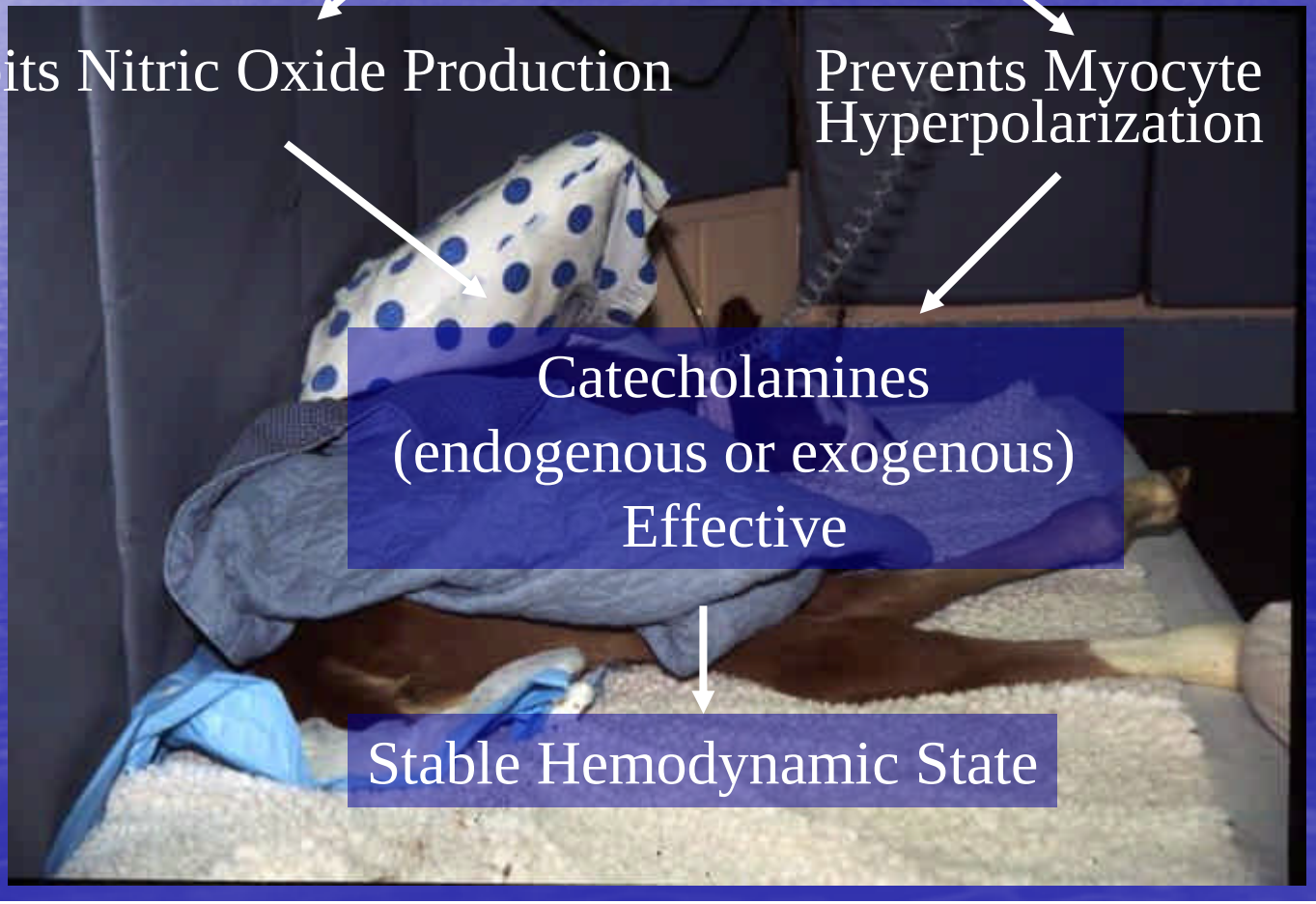

Sepsis
Hypotension
CNS
Exhaustion of vasopressin
Relative vasopressin deficiency
Downward spiral of hypoperfusion Vasodilatory Shock
Lactic acidosis
NO
K_{ATP} channels open
Catecholamine resistance

Exogenous Vasopressin

Physiologic Levels

Inhibits Nitric Oxide Production

Prevents Myocyte Hyperpolarization

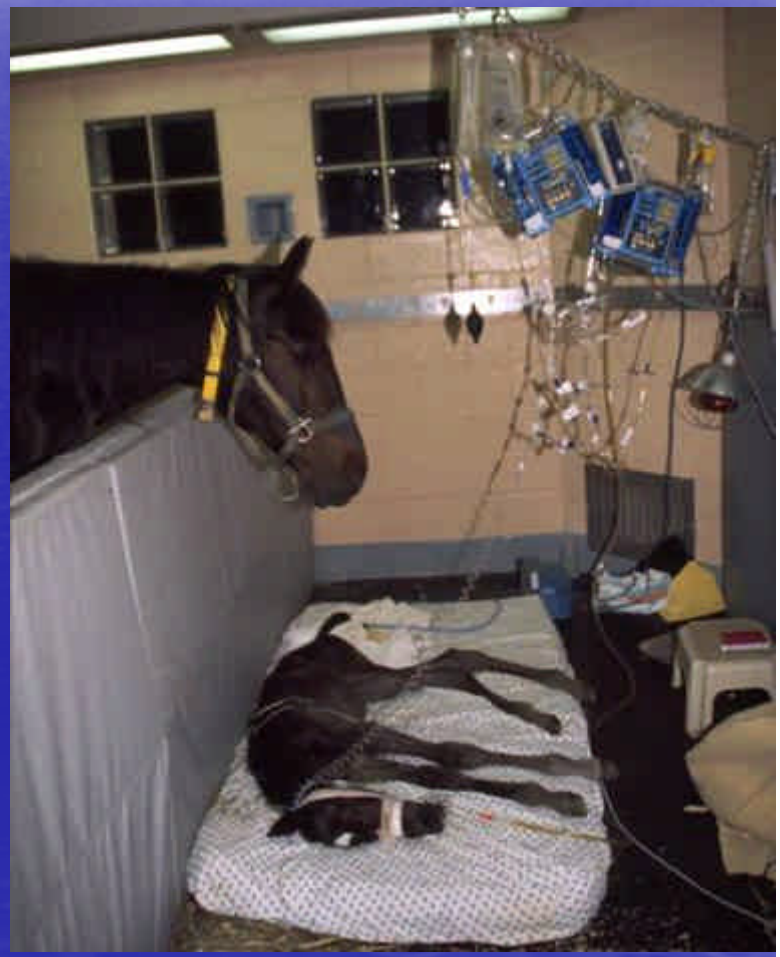


Catecholamines
(endogenous or exogenous)
Effective

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

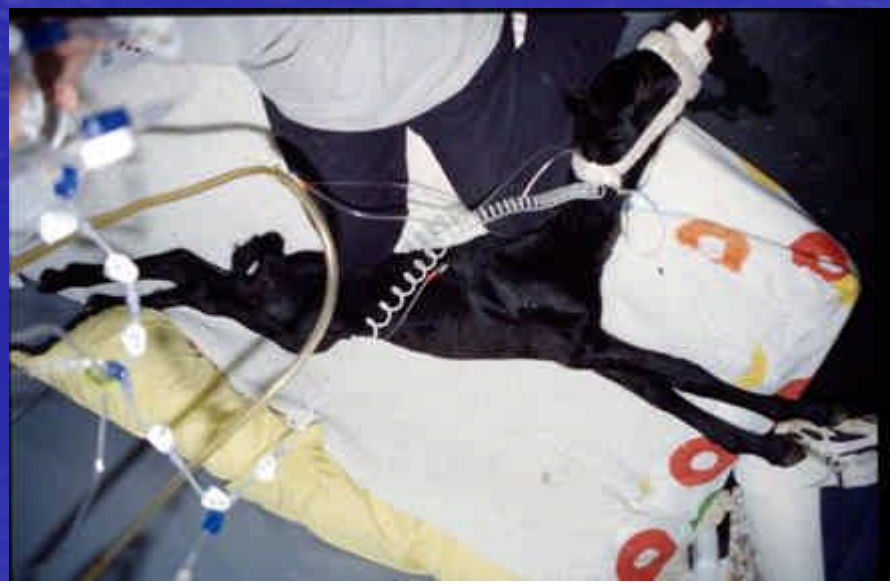


Premature Friesian Foal

- 280 - 300 days gestation
  - Small- 56 lbs
- 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



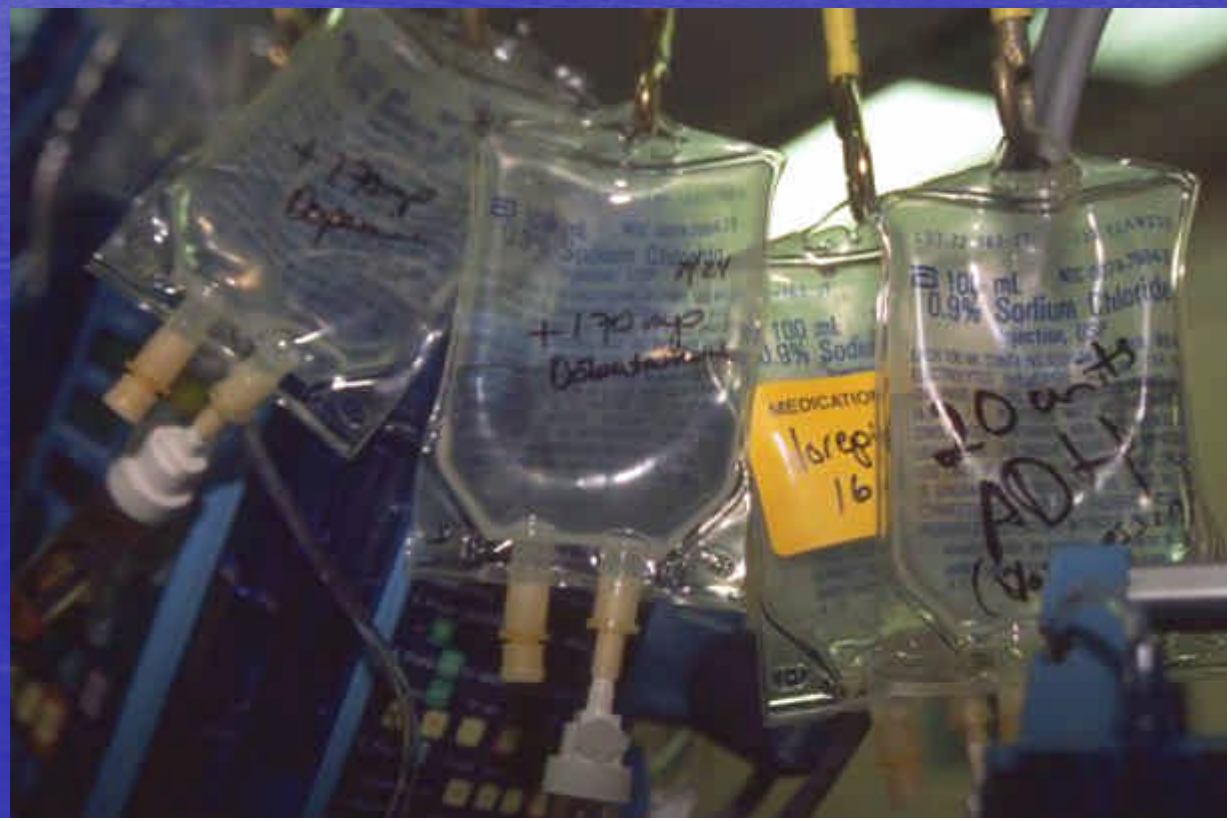
Premature Friesian Foal

- 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

Defend Pressure



Vasopressin Adverse Reactions

- Experience with more than 30 neonates
  - Has been positive
- Caution should be exercised
  - Metabolic ramifications not clearly defined
  - Several cases of severe refractory hypotension
    - Development of hyponatremia
    - High risk of hyponatremia
      - Difficulty handling water loads
      - Predilection for sodium losing nephropathies
      - Development of depletional hyponatremia
      - Development of redistribution hyponatremia
    - Unlikely that hyponatremia is secondary to inappropriate antidiuresis
      - since the urine is not concentrated
    - Unclear whether vasopressin has played a role
  - Similar cases
    - Hyponatremia has occurred
    - Vasopressin not been given

Hypotension
Other Therapeutic Interventions

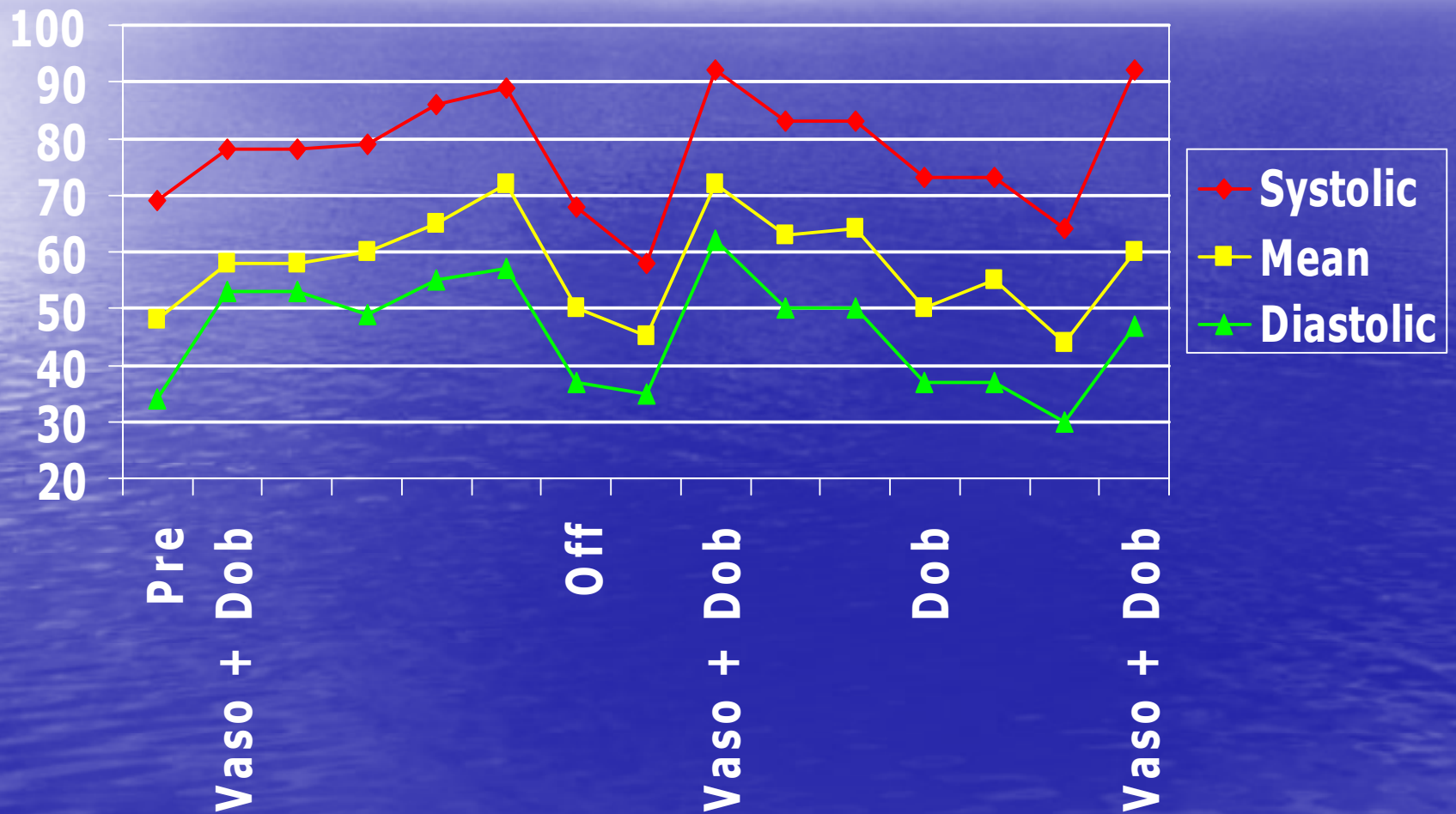
- Low dose steroid therapy
  - Hypotensive secondary to adrenal insufficiency
    - Premature neonates
  - Dexamethasone – 0.02 to 0.03 mg/kg
  - May result in a dramatic increase in blood pressure
  - Adverse reaction
    - Refractory hyperglycemia
    - In human neonates, a poorer long-term outcome
- Methylene blue
  - NO blocker
  - Refractory hypotension – septic shock
  - Dramatic resolution of hypotension
    - Concurrent maldistribution of perfusion
    - Resulting in negative outcomes
  - Recent publications success in human neonatal critical care
- Naloxone therapy
  - Enhancement of adrenergic inotropic effects in sepsis
  - Correct maldistribution of perfusion
  - Anecdotal experience not encouraging

Response to Low-dose Vasopressin

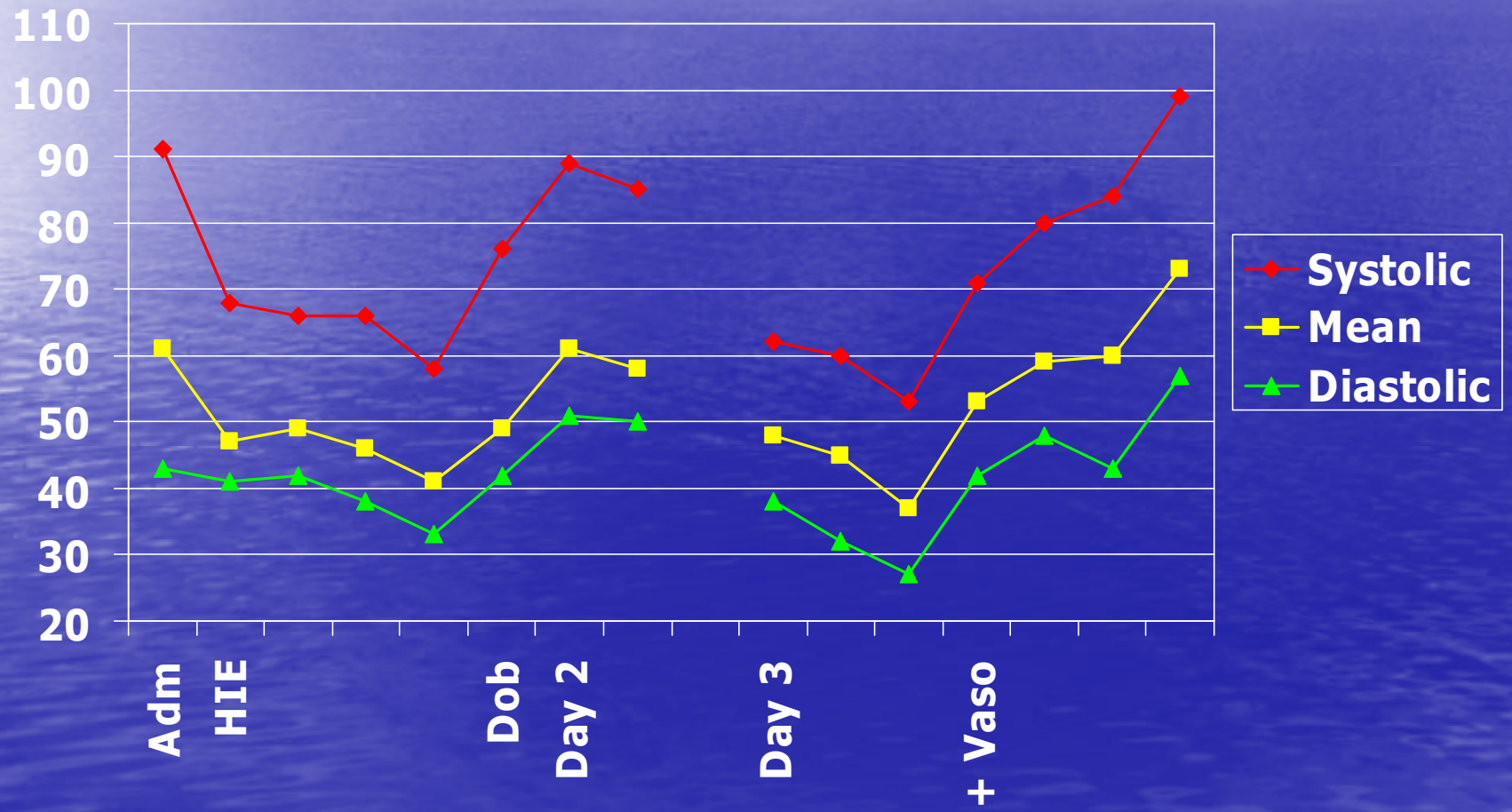
Blood Pressure Response of Hypotensive Foals* to Vasopressin and Dobutamine CRI Therapy					
Case	Base line BP	Therapy	Result	Modification	Result
#1	38/24 (29) 72**	Vasopressin, 0.5***	100/52 (60) 66		
#2	60/39 (47) 102	Vasopressin 0.5	100/63 (81) 70		
#3	68/26 (38) 120	Vasopressin 0.5	73/37 (55) 120	Vasopressin 1.0	96/61 (84) 70
#3	63/32 (45) 90	Vasopressin 0.5	89/52 (61) 88	Off	64/34 (49) 82
#4	67/34 (45) 84	Dobutamine, 5 ****	93/49 (65) 72	Off	69/35 (45) 84
#5	66/33 (40) 84	Dobutamine, 10	64/31 (43) 74	Added vasopressin 0.5	78/42 (60) 64
#6	59/34 (41) 60	Vasopressin, 0.5 dobutamine, 5	90/55 (70) 60 120/73 (87) 56	Off both	58/29 (37) 72 38/24 (29) 72

* 6 selected clinical cases; **arterial BP - systolic/diastolic (mean) HR; *** infusion rate – mU/kg/min; **** infusion rate – µg /kg/min

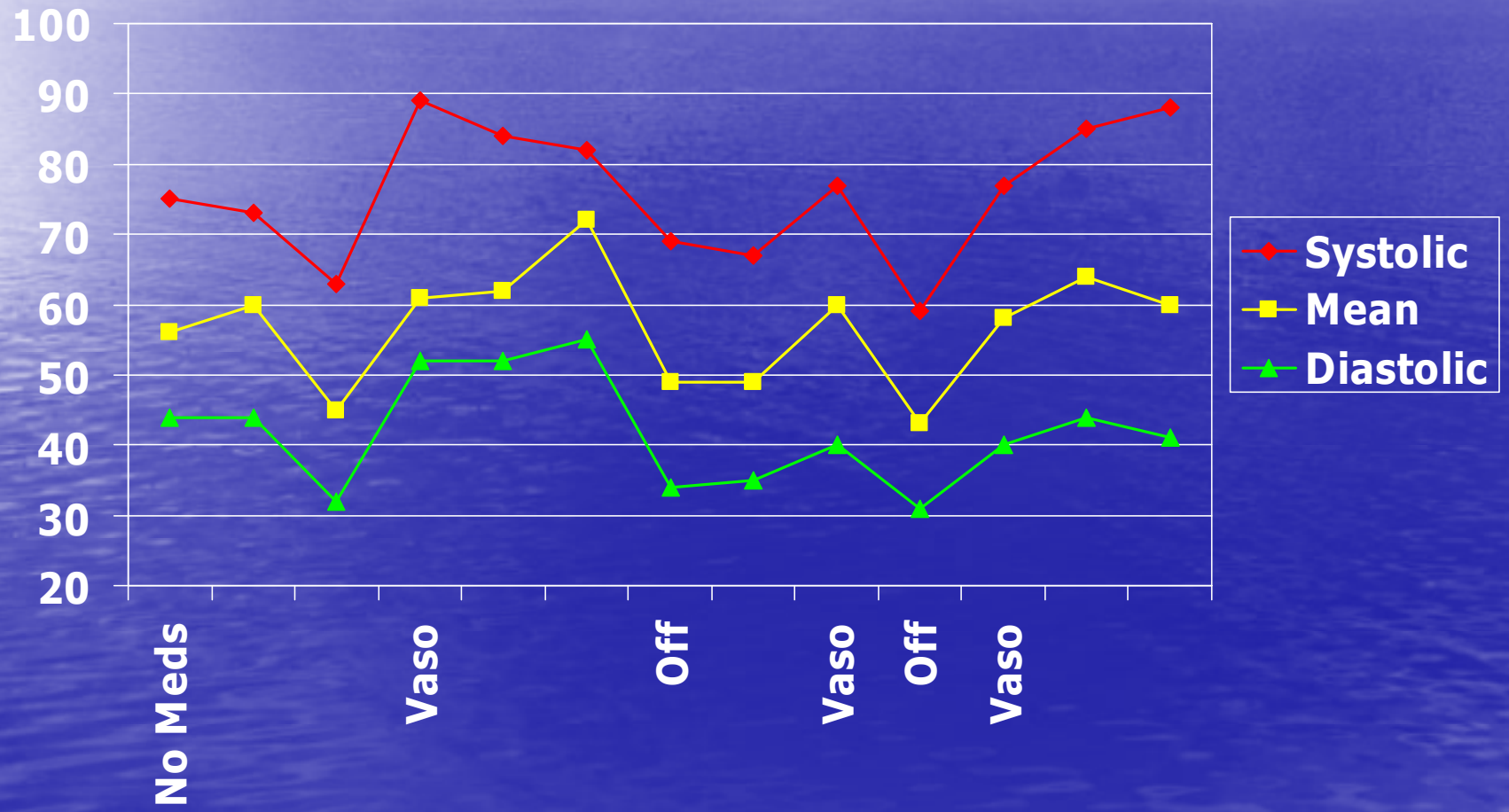
Dobutamine and vasopressin BP Response



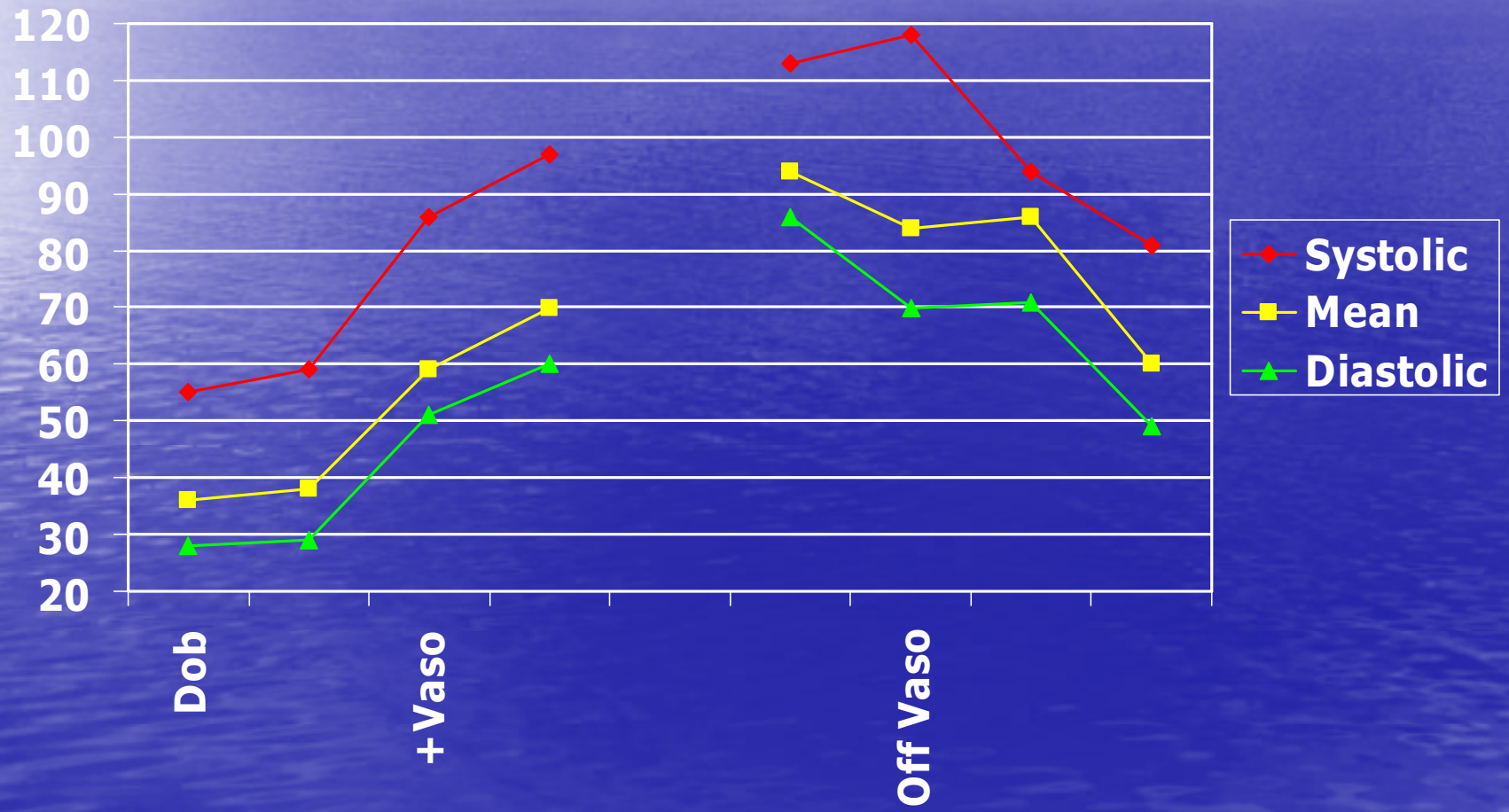
Dobutamine and Vasopressin BP Response



Vasopressin BP Response



Dobutamine and Vasopressin BP Response



When Fluids are Not Enough: Inopressor Therapy

Jon Palmer, VMD, DACVIM
Director of Neonatal/Perinatal Programs
Graham French Neonatal Section, Connelly Intensive Care Unit
New Bolton Center, University of Pennsylvania

One of the most difficult problems in neonatal medicine is managing severe hypoperfusion. Severe hypoperfusion accompanies severe sepsis, is the hallmark of septic shock, and can occur secondary to neonatal encephalopathy. The first line of treatment is fluid loading. If fluid loading does not return perfusion, inopressor therapy (combination of inotropic and pressor therapy) can be very helpful, despite possible pitfalls. Above all insure volume and defend pressure to achieve perfusion.

The goal is return of perfusion and not to achieve a given set of blood pressure values. Flow resulting in tissue perfusion is proportional to left ventricular output and inversely proportional to vascular resistance. Arterial blood pressure is also determined by ventricular function, arterial fill and peripheral vascular resistance. But, high blood pressure does not equate to flow and low blood pressure does not necessarily mean there is no flow. In fact, neonates initially have a low-pressure system which perfuses tissues quite well. Low systemic blood pressures are vital for intrauterine survival and the neonate is involved in the transition from this low pressure system. This transition is probably associated with decreasing activity and synthesis of vasodilators as well as intrinsic changes in vascular smooth muscle function which makes them more responsive and capable of maintaining higher pressures. Low systemic arterial pressures in the neonate may be important in ensuring capillary pressures remain low, which is vital in maintaining the neonate's fluid balance because of the special capillary characteristics. The transition from a low-pressure system may be delayed in neonates with perinatal disease.

In any particular patient it is difficult to predict how much of the transition has occurred. Many foals will have adequate perfusion with mean blood pressures in the 40s, systolic pressures in the 50s and diastolic pressures in the 30s. Others will require blood pressures 15 mm Hg above these for adequate perfusion. It is very important for the clinician not to treat blood pressure numbers but to treat hypoperfusion. The blood pressure numbers are one of a constellation of signs of perfusion and should be taken as a relative gauge in individual cases. It is much more important to judge perfusion by comparing central and peripheral pulses, feeling arterial fill, arterial tone and leg warmth, noting the gradient between core and peripheral temperature and observing signs of organ perfusion such as urine production, borborygmi (enterokinesis) and level of mental arousal. The decision to deliver pharmacologic cardiovascular support should be based on indications of poor perfusion and not blood pressure numbers. Cardiovascular support should be modified based on signs of perfusion and not blood pressure goals.

Adrenergic Agonists

When adrenergic agonists are used for pharmacologic support of perfusion, each patient is a pharmacokinetic experiment. This is because of the variation in plasma half-life, receptor density, receptor affinity, receptor reactivity and the effect of plasma pH on all of these factors. Because of this variation, the dose used must be tailored to the individual. This is easily accomplished by monitoring for signs of improved perfusion during CRI (continuous rate infusion) and adjusting the

does accordingly. Because of the short half-life the effect of new doses is readily evident within 10 to 15 minutes. The individual may change with time depending on many confounding factors so the deliver dose may also need to be adjusted. The goal is to withdraw therapy as soon as possible.

When preparing infusions, it is convenient to use the "**rule of 6**:"

6 X body wt in kg = # mg to add to 100 ml so that 1 ml/hr infusion = 1 µg/kg/min. drug delivery (dopamine, dobutamine, other drugs delivered in this dose range).

Alternately: 0.6 X body wt in kg = # mg to add to 100 ml so that 1 ml/hour infusion = 0.1 µg/kg/min. drug delivery (epinephrine, norepinephrine, other drugs delivered in this dose range)

When choosing drugs to support the cardiovascular system, it is important to ensure cardiac output. If pressors are used without inotropic support, there's a danger that cardiac output will fall and perfusion will decrease (despite a rise in blood pressure numbers). For that reason, inotropes are almost always indicated when pressers are used. Mixed inotropic and pressor support or inopressor support can best be achieved by selecting an inotrope, such as dobutamine or medium dose dopamine as part of the initial therapy. Besides decreased cardiac output, other adverse effects occasionally seen with adrenergic agonists include arrhythmias and tachycardia. Occasional premature ventricular contractions may be seen in critically ill neonates receiving any adrenergic. Many times the arrhythmia is secondary to pre-existing underlying cardiac damage, but withdrawing therapy will quickly identify if adrenergic therapy is playing a role. Tachycardia will occasionally occur, especially secondary to dobutamine. The tachycardia can result in decreased cardiac filling and diminished cardiac output, especially when heart rates consistently increased above 160 beats per minute. In this case, discontinuing the offending adrenergic is the only option. When an adrenergic drug has to be discontinued because of an adverse reaction or just appears not to be effective in increasing perfusion others in the same class should be tried. The response to these drugs varies between individuals and cannot be predicted based on the response of other drugs in their class.

Whenever the cardiovascular system is supported by pharmacologic doses of adrenergic agonists, there may be both an increase in perfusion and, simultaneously, an increase in the maldistribution of that perfusion. There is a balanced between improved perfusion and exaggerated maldistribution of perfusion. When we begin aggressive support, we need to keep in mind that the goal is returning perfusion to minimally acceptable levels and not to try to achieve normal or supranormal perfusion. Doing so will usually result in disastrous effects.

Dobutamine has primarily β1 activity at low to moderate doses and thus is a good inotrope. In man some α2 activity may result in mild vasodilation but in general α1and α2 stimulus is well balanced so that clinically they are not important. In horses α1 activity appears as the dose increases causing significant vasoconstriction. Thus dobutamine could be classified as an inopressor at high doses. When cases need support but are not shocky, I usually begin by giving 5 ug/kg/min. and then titrate to the effective dose. In cases where the neonate is suffering from shock, my starting point is 10 µg/kg/min. and then titrate to the effective dose. The dose range is 2-20 µg/kg/min. with occasional cases needing as high doses as 50 µg/kg/min. Adverse reactions include tachycardia and occasional arrhythmias.

Dopamine has dopaminergic activity at low doses, β1 & β2 activity at moderate doses, and α1 activity at high doses. It causes norepinephrine release from nerve terminals which has lead to the suggestion that this is its major mode of action at high doses and the suggested limitation in critical patients who become depleted. Dopamine can be classified as an inopressor. When cases need support but are not shocky, I usually begin by giving 5 µg/kg/min. and then titrate to the effective dose. In cases where the neonate is suffering from shock, my starting point is 10 µg/kg/min. and titrate to the effective dose. The dose range is 2-20 µg/kg/min. At doses over 20 µg/kg/min intrapulmonary shunting may occur which limits the high end of the dose range. Adverse reactions include occasional arrhythmias.

Norepinephrine has α1 and β1 activity but variable β2 activity resulting in potent vasopressor activity; it as both inotropic and chronotropic activities but its chronotropic affect is usually blunted by vagal reflex slowing the heart rate induced by the rise in blood pressure. There is an increase in myocardial oxygen consumption due to cardiostimulation and increased afterload. It has been thought of primarily as a pressor and its use has been advocated in septic shock.. It is frequently used in combination with either dopamine or dobutamine to enhance the inotropic effect because of the strong pressor effect. Although frequently used, it appears to suffer more from maldistribution of blood flow than the other adrenergic agonists. A good starting place for dose is 0.3-0.5 µg/kg/min. with further titration to an effective dose. The dose range is from 0.1-3.0 µg /kg/min. with a few difficult cases requiring 4 to 5 µg/kg/min. The major adverse reactions are occasional arrhythmias. These are rare unless there is pre-existing myocardial damage such as in hypoxic ischemic asphyxial disease or secondary to sepsis.

Epinephrine has α1, α2, β1, β2 activity; Beta activity is predominant resulting in increased cardiac output and decreased peripheral resistance at low doses, making it an attractive inotrope at low doses with inopressor activity as the dose increases. It has been associated with hyperglycemia and increased lactate production. The increase in lactate is rapid and may be dramatic but is easily reversible. When given for its inotropic effect, a good starting point is 0.3-0.5 µg/kg/min. with further titration to an effective dose. The dose range is from 0.1-2.0 µg /kg/min. with a few difficult cases requiring 3 to 4 µg/kg/min. The major adverse reaction (in addition to the metabolic derangements) are occasional arrhythmias. These generally occur when there is pre-existing myocardial damage such as in hypoxic ischemic asphyxial disease or secondary to sepsis.

Vasopressin

Use of low-dose vasopressin treatment for septic shock has become a hot topic in the past five years with primarily positive reports being published monthly. Recent studies have suggested a deficiency in vasopressin levels in patients who succumb to septic shock. Current approach to therapy has been suggested to be in essence replacement therapy and not pharmacologic therapy.

Vasopressin is a peptide hormones synthesized in the supraoptic and periventricular nuclei of the hypothalamus and transported to the posterior pituitary where it is stored. Increase plasma osmolarity or baroreflex response to decrease blood volume or blood pressure will result in release of vasopressin. Nausea, pain, endotoxemia, cytokines and other stimuli will also increase vasopressin release.

Since in normal individuals it is evident that larger doses of vasopressin are required to increase blood pressure than to cause maximal antidiuresis, it has been traditionally thought that the pressor action was pharmacologic rather than physiologic. However it is now appreciated that the pressor action of vasopressin significantly under estimates its vasoconstrictor action. Vasopressin is a more potent vasoconstrictor than angiotensin II or norepinephrine and is capable of increasing systemic vascular resistance with doses less than those required to produce maximum urine concentration. The reason for the relatively weak pressor activity is the vasopressin resets the cardiac baroreflex to a lower pressure. For a given increase in blood pressure, vasopressin causes more bradycardia than other vasoconstrictors. So little pressor effect is seen in normal subjects when given vasopressin exogenously, but the heart rate slows preventing an increase in blood pressure. If this buffering mechanism is removed (e.g. baroreceptor dysfunction such as occurs in sympathetic nerve impairment, sepsis), there's greatly enhanced pressor activity of vasopressin. Pressors sensitivity is also increased in patients with autonomic insufficiency.

Inappropriately low levels of vasopressin are found in septic shock due to low secretion rate secondary to impaired baroreflex-mediated vasopressin secretion. The impaired baroreflex-mediated vasopressin secretion appears to be a result of autonomic failure secondary to septic shock. Alternately, excessive secretion of vasopressin in early stages of septic shock may deplete pituitary vasopressin stores. Endotoxin is a very potent stimulus of vasopressin secretion it and in animal models of acute septic shock, a dramatic rise in plasma vasopressin during the first hours after endotoxin/bacterial administration is followed by a rapid decline over the next few hours implying that there may be exhaustion of stores of vasopressin in the neurohypophysis. The critically ill neonate with hypoxic ischemic asphyxial disease may also have decreased vasopressin output secondary to autonomic imbalance or exhausted stores secondary to prolonged stress.

Vasopressin has been found to be effective in situations where severe refractory hypotension has developed which is no longer responsive to adrenergic agonist therapy. In this setting, besides its direct effect on vascular tone, vasopressin has been found to have two additional important mechanisms of action. First, it appears to block the vasodilatory effect of nitric oxide on vascular smooth muscle. Second, vasopressin returns adrenergic sensitivity through its affect on myocyte polarization. This latter effect not only returns sensitivity to exogenous adrenergic therapy, but will increase the effectiveness of endogenous catecholamines. The end result is that not only will the hypotension be reversed, the perfusion may be maintained allowing withdrawal of exogenous adrenergic support.

Infusion of exogenous vasopressin had a rate of 0.25-1.0 mU/kg/min causes an increase in arterial pressure in many of our hypotensive patients. There may even be a modest increase in our normotensive neonates. In some patients blood pressure may be maintained with vasopressin alone without the administration of exogenous adrenergic agonists. The clinically apparent positive effect of vasopressin on perfusion has become consistent enough that I have begun to use vasopressin has a first-line therapy, rather than just a rescue intervention. My feeling is that at the very low doses being used, this is primarily a replacement therapy and we are treating a vasopressin deficiency. Returning vasopressin to its physiologic levels allows endogenous blood pressure regulation mechanisms to cope with the challenges facing the neonate.

Urine flow rates increase significantly during administration of vasopressin in patients in septic shock. This may be due to improve renal perfusion has arterial pressure increases. Increased pressure with catecholamines rarely increases urine output because the glomerular afferent arterial is constricted and filtration decreases. In contrast, vasopressin appears to constrict only glomerular efferent arterial, thus maintaining glomerular filtration rate despite a decrease in real blood flow. The tubular effect of vasopressin does not seem to be present in these situations, although the reason is not readily apparent. The urine produced is not concentrated. Rather large amounts of dilute urine are usually produced.

Although our experience with more than 30 neonates has been positive for the most part, caution should be exercised in treating neonates with vasopressin, since all of the metabolic ramifications of this intervention are not clearly understood. In several cases of severe refractory hypotension that have responded to vasopressin treatment, we have seen development of hyponatremia. These cases are at high risk of hyponatremia for many reasons including their difficulty handling water loads, their predilection for sodium losing nephropathies, development of depletional or redistribution hyponatremia. In these cases, it is unlikely that hyponatremia is secondary to inappropriate antidiuresis since the urine is not concentrated. It is unclear whether vasopressin has played a role in the development of the hyponatremia or whether the hyponatremia is secondary to other therapeutic interventions and confounding pathologic influences. In similar cases, hyponatremia has occurred when vasopressin has not been part of the therapeutic regime.

Other Therapeutic Interventions

Some neonates, especially if premature, are hypotensive secondary to adrenal insufficiency. In such cases low doses of dexamethasone (0.02-0.03 mg/kg) may result in a dramatic increase in blood pressure. This therapy may result in refractory hyperglycemia and in human neonates, a poorer long-term outcome. For more than a decade, I have occasionally used methylene blue for its nitric oxide blocking ability in cases of refractory hypotension secondary to septic shock. I have had the impression that in most cases, although there may be a dramatic resolution of hypotension, there's concurrent maldistribution of perfusion resulting and negative outcomes. In the past year, there has been renewed interest in this therapy in human neonatal critical care with modification of therapeutic regime which may improve the likelihood of a successful outcome. Like methylene blue, I have also occasionally tried naloxone therapy in hypotension, trying to take advantage of its enhancement of adrenergic inotropic effects in sepsis and its tendency to correct maldistribution of perfusion. However my anecdotal experience has not been encouraging.

Blood Pressure Response of Hypotensive Foals* to Vasopressin and Dobutamine CRI Therapy

Case	Base line BP	Therapy	Result	Modification	Result
#1	38/24 (29) 72**	Vasopressin, 0.5***	100/52 (60) 66		
#2	60/39 (47) 102	Vasopressin 0.5	100/63 (81) 70		
#3	68/26 (38) 120	Vasopressin 0.5	73/37 (55) 120	Vasopressin 1.0	96/61 (84) 70
#3	63/32 (45) 90	Vasopressin 0.5	89/52 (61) 88	Off	64/34 (49) 82
#4	67/34 (45) 84	Dobutamine, 5 ****	93/49 (65) 72	Off	69/35 (45) 84
#5	66/33 (40) 84	Dobutamine, 10	64/31 (43) 74	Added vasopressin 0.5	78/42 (60) 64
#6	59/34 (41) 60	Vasopressin, 0.5 dobutamine, 5	90/55 (70) 60 120/73 (87) 56	Off both	58/29 (37) 72 38/24 (29) 72

* 6 selected clinical cases; **arterial BP - systolic/diastolic (mean) HR; *** infusion rate – mU/kg/min; **** infusion rate – µg /kg/min