The Pharmacology of Hypotension: Vasopressor Choices for HIE patients

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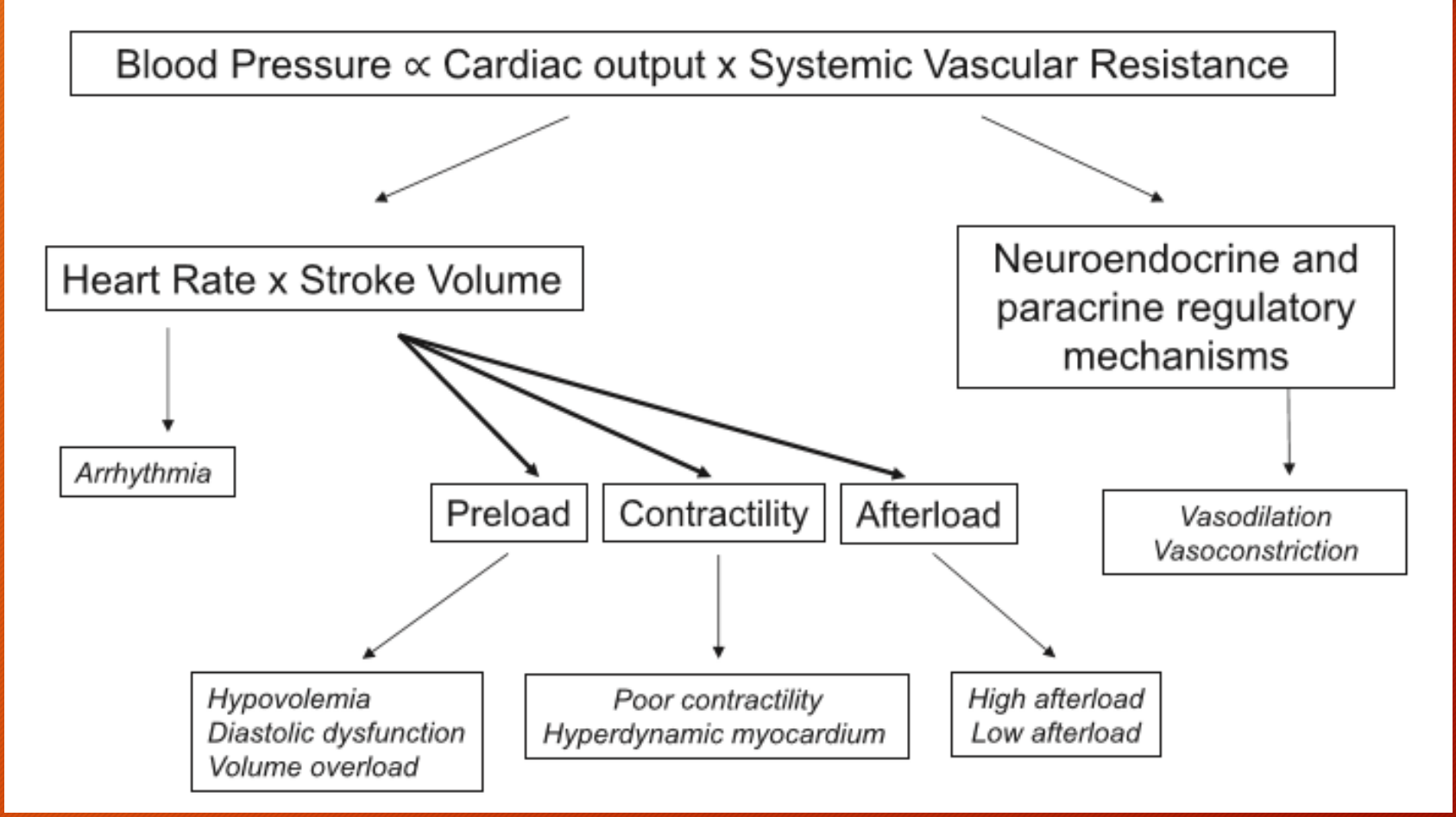
August 4, 2018

Objectives

- Review the pathophysiology of hypotension in neonates
- Discuss the role of vasopressors and inotropes in neonates with hypotension
- Compare vasopressor choices in neonates with HIE

Pathophysiology-Based Approach



Vascular Tone

- Vasodilation is one of the most frequent cases of shock in neonates
  - Sepsis, necrotizing enterocolitis
- Decrease in vascular tone most often due to dysregulated production of local nitric oxide and direct vascular cytokine effect
  - Decrease in perfusion pressure
  - Hypotension develops despite normal or elevated CO
- Preterm infants who do not survive shock only significantly dropped CO prior to death
- Gram-negative sepsis and late stages of septic shock also cause myocardial dysfunction

Impaired Contractility

- Systolic dysfunction also a common cause of circulatory failure in neonates

Etiologies:

- Asphyxia most common
  - 1/3 have clinical or electrographic evidence of cardiac involvement
- Premature infants after PDA ligation
  - 10-30% develop hypotension following surgery
  - Poor myocardial performance/contractility
  - Prophylactic milrinone shown to reduce post-ligation hypotension with CO<200 mL/kg/min

Decreased Preload

- Inappropriately high mean airway pressure, pneumothorax, pericardial effusion, pneumopericardium significantly reduce venous return
  - Reduced preload→reduced CO
- Insensible water losses through skin
- Capillary leak: sepsis, NEC, post-abdominal surgery
- Myocardial diastolic dysfunction from hypertrophic cardiomyopathy
  - 1/3 of poorly controlled IDMs

Increased Afterload

- High afterload worsens poor myocardial contractility in infants with dilated cardiomyopathy
  - Not as common

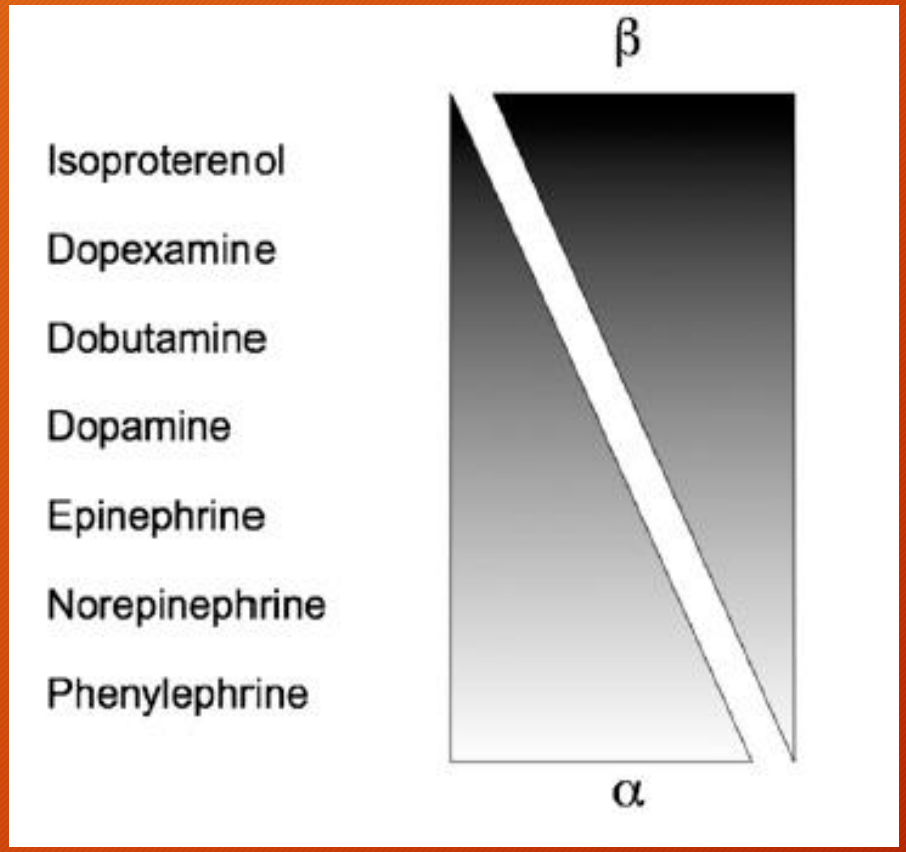
Heart Rate

- Neonates have higher dependence on HR to maintain CO compared to older children and adults
- Bradycardia tends to be transient, secondary to apnea and/or hypoxia
- Tachyarrythmia more common
  - SVT and atrial flutter
  - Circulatory failure

Pharmacology of Hypotension

- Vasopressor
  - Increases vascular tone
  - Peripheral action: vasoconstriction via alpha-1 adrenergic and vasopressin receptors
- Inotrope: dobutamine
  - Increases myocardial contractility
- Vasopressor-inotrope: dopamine, epinephrine
- Phosphodiesterase inhibitors: milrinone

Vasoactive Medications



Normal Saline Bolus

- Useful when hypovolemia is present
  - Increased intravascular volume, increased CO
- 10 mL/kg NS = 1.54 mEq/kg of normal saline
- Limited efficacy when pathophysiology is not related to hypovolemia

Isoproterenol

- Indications:
  - Improve cardiac output in patients with cardiovascular shock
  - Pulmonary vasodilator (older infants)
- Dosing: 0.05 to 0.5 mcg/kg/min (max = 2 mcg/kg/min)
- Monitoring: BP, blood glucose
- Toxicity: cardiac arrhythmia (tachycardia causing CHF), hypoglycemia, hypoxemia

Dobutamine

- Indications:
  - Hypotension/hypoperfusion related to myocardial dysfunction
  - Severe sepsis/shock in full term neonates unresponsive to fluid resuscitation
- Dosing: 2 to 20 mcg/kg/min (max 25 mcg/kg/min)
- Monitoring: heart rate, BP
- Toxicity: hypotension, tachycardia, vasodilation

Dopamine

- Most commonly used cardiovascular medication in the NICU
- Dose-dependent stimulation of alpha, beta, and dopaminergic receptors
  - Low (≤0.5 mcg/kg/min)
    - Vascular dopaminergic receptors selectively expressed
    - Renal, mesenteric, coronary circulations
  - Moderate (2-4 mcg/kg/min)
    - Alpha receptor activation-vasoconstriction, inotropy
  - High (≥ 4 – 8 mcg/kg/min)
    - Beta receptor activation-inotropy, chronotropy, peripheral vasodilation

Dopamine-Clinical Considerations

- At least 50% of positive inotropic effects caused by inducing release of norepinephrine (NE) stores in the peripheral sympathetic nerve endings in the myocardium
  - Myocardial NE depletes within 8-12 hours
- Dopamine in the premature neonates
  - Decreased NE stores
  - Immature expression of alpha, beta receptors→ alpha receptors likely to be activated at low-to-medium doses
  - Cardiovascular adrenergic receptor expression regulated by corticosteroids, higher risk of vasopressor-dependence with adrenal insufficiency

Dopamine-Systemic Blood Pressure

- Dopamine consistently increases blood pressure in neonates
  - Normal saline
  - Hydrocortisone
  - Dobutamine

Dopamine-Cardiac Output

- Increased cardiac output caused by drug-induced increases in myocardial contractility, increased ejection fraction
- Premature infants
  - May cause excessive increases in SVR
  - Decreased cardiac output

Dopamine-Pulmonary Vasculature

- In premature infants on dopamine, 50% will experience an increase in pulmonary vascular resistance (PVR)
- PDA with left-to-right shunt
  - Increased PVR may be helpful to improve systemic circulation
- PDA with right-to-left shunt
  - Increased PVR may be harmful because additional blood would flow away from the lungs

Dopamine Dosing Information

- Usual dosing range: 5-20 mcg/kg/min
  - Titration: 2.5-5 mcg/kg/min every 5-10 minutes
- Monitoring:
  - MAPs, oxygen saturations, urine output
- Concerns:
  - worsening pulmonary status when used in patients with pulmonary hypertension (i.e. PDA with right-to-left flow)
- Administration:
  - NEVER through arterial line, central venous access preferred

Epinephrine

- Dose-dependent stimulation of alpha and beta adrenergic receptors
- Low dose (0.01 to 0.1 mcg/kg/min)
  - Stimulates cardiac and vascular beta 1 and 2 receptors
  - Increased inotropy, chronotrophy, peripheral vasodilation
- Higher dose (>0.1 mcg/kg/min)
  - Stimulates vascular and cardiac alpha 1 receptors
  - Vasoconstriction, increased inotropy
- Net effect: increased blood pressure, systemic blood flow via drug-induced increases in SVR and cardiac output

Epinephrine

- Compared to dopamine
  - Similar efficacy in improving blood pressure and increasing cerebral blood flow
  - Epi group more likely to develop increased serum lactate levels, hyperglycemia requiring insulin
- Clinical considerations
  - Beta-2 stimulation in liver and muscle causes decreased insulin release and increased glycogenolysis (elevates lactate)
  - May be unable to use serum lactate as clinically useful marker of overall perfusion
  - Insulin infusion may be necessary
  - Most useful with low vascular resistance with or without myocardial contractility impairment

Epinephrine Dosing Information

- “Low-dose”: 0.01-0.1 mcg/kg/min
- “High dose”: >0.1 mcg/kg/min
  - No documented true maximum dose
  - Dose-limiting side effects: tachycardia, peripheral ischemia, lactic acidosis, hyperglycemia
- Titration: 0.01-0.02 mcg/kg/min every 3 to 5 minutes
- Monitoring:
  - MAP, heart rate, glucose, lactates
- Administration:
  - NEVER through arterial access, central venous access preferred

Vasopressin

- Primary physiologic role is extracellular osmolarity
- Vascular effects mediated by stimulation of vasopressin 1A and 2 receptors in the cardiovascular system
  - V1A: vasoconstriction
  - V2: vasodilation
- Most useful with vasodilatory shock, deficiency of endogenous vasopressin production with septic shock, infants after cardiac surgery

Vasopressin Clinical Considerations

- Increases
  - MAP, SVR
- Decreases
  - PVR, oxygenation index, iNO requirement, vasopressor requirement
- At high doses, increased SVR may impair cardiac contractility

Vasopressin Dosing Information

- “Low dose”: 0.17 -0.7 milli-units/kg/min
  - Decreased in catecholamine requirement
- “High dose”: 1-20 milli-units/kg/min
  - Effective for reducing catecholamine requirement, but more side effects
- Titration: 0.05-0.1 milli-units/kg/min every 15-30 minutes
- Monitoring:
  - Blood pressure, serum sodium (hyponatremia), weight gain, urine output (decreases), liver enzymes

Norepinephrine

- Endogenous catecholamine that activates alpha 1,2 and beta 1 receptors
  - Increases systemic vascular resistance>>pulmonary vascular resistance
  - Increases cardiac output by increasing contractility via beta 1 receptors
- First-line treatment for septic shock in adult patients
- Neonatal data
  - Sepsis: increased MAP, decreased oxygen requirement, improved tissue perfusion
  - PPHN: produced pulmonary vasodilation, decreased oxygen requirement, increased cardiac output, improved blood flow to lungs without evidence of peripheral ischemia

Norepinephrine Dosing Information

- Dosing range: 0.05-0.7 mcg/kg/min
  - Max: 3.3 mcg/kg/min
  - Titration: 0.05-0.1 mcg/kg/min every 5-10 minutes
- Monitoring:
  - MAP, oxygen saturations, tissue perfusion
- Administration:
  - NEVER through arterial line, central venous access preferred

Milrinone

- Selective phosphodiesterase-III inhibitor
  - Exerts cardiovascular effects through preventing breakdown of cAMP
  - Enhances myocardial contractility, promotes myocardial relaxation, decreases vascular tone in systemic and pulmonary vascular beds
- Disease states
  - Post-operative cardiac repair, PPHN as an adjunct to iNO
  - Post PDA-ligation to prevent hemodynamic instability in 24 hours after procedure

Milrinone-PPHN

- In cases unresponsive to iNO, oxygenation may be improved with addition of milrinone
- Exogenous NO upregulates PDE-III in smooth muscle cells of pulmonary vasculature
  - Decrease or loss of cAMP-dependent vasodilation
- Addition of milrinone to iNO restores pulmonary vasodilation mechanisms dependent of cAMP
  - Increased pulmonary vasodilation, improved oxygenation

Milrinone Dosing Information

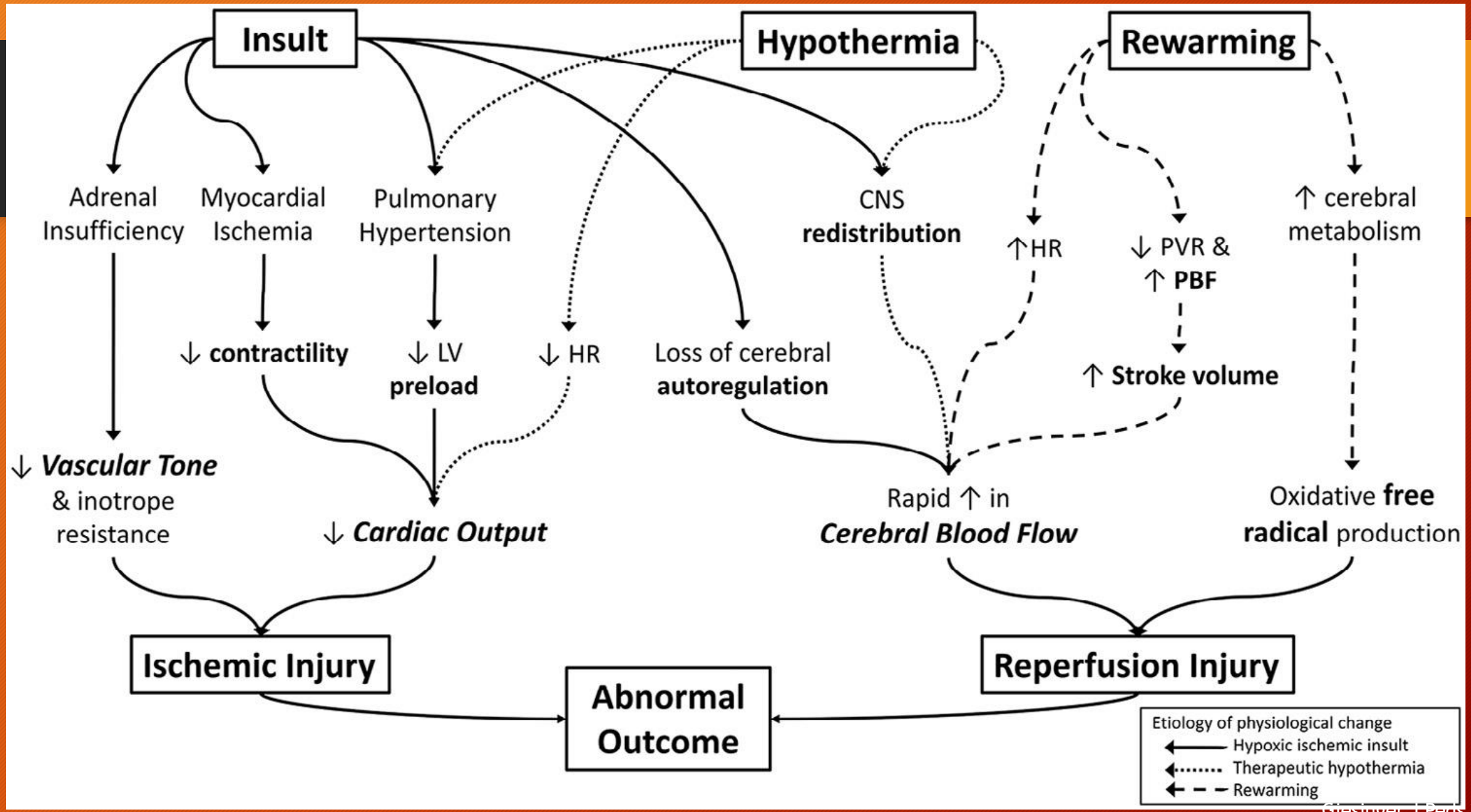
- Dosing range: 0.25-0.99 mcg/kg/min
  - Dose reduce for renal impairment
- Titration: 0.2-0.4 mcg/kg/min every 2-4 hours
- Monitoring:
  - MAP: can initially decrease, usually returns to baseline within 1-2 hours
  - Heart rate: can initially decrease, may increase if bolus used (not recommended)
  - UOP: improved
  - Oxygen saturations: improved

Hydrocortisone

- Decreases breakdown of catecholamines, increases calcium in myocardial cells, upregulate adrenergic receptors
- Delayed onset of action for hypotension
  - Inferior as first-line treatment to dopamine
- Relative adrenal insufficiency in premature infants may play a role in need for supplementation
- Timing
  - Prophylactic: prevents adrenal insufficiency, subsequent complications of uninhibited inflammation
  - Refractory hypotension: effectively increases BP and reduces catecholamine requirement

Biophysical Effects of Asphyxia

- Direct cardiovascular effects
- Cardiovascular and CNS injury interaction
- Cerebral blood flow
- Impact of therapeutic hypothermia



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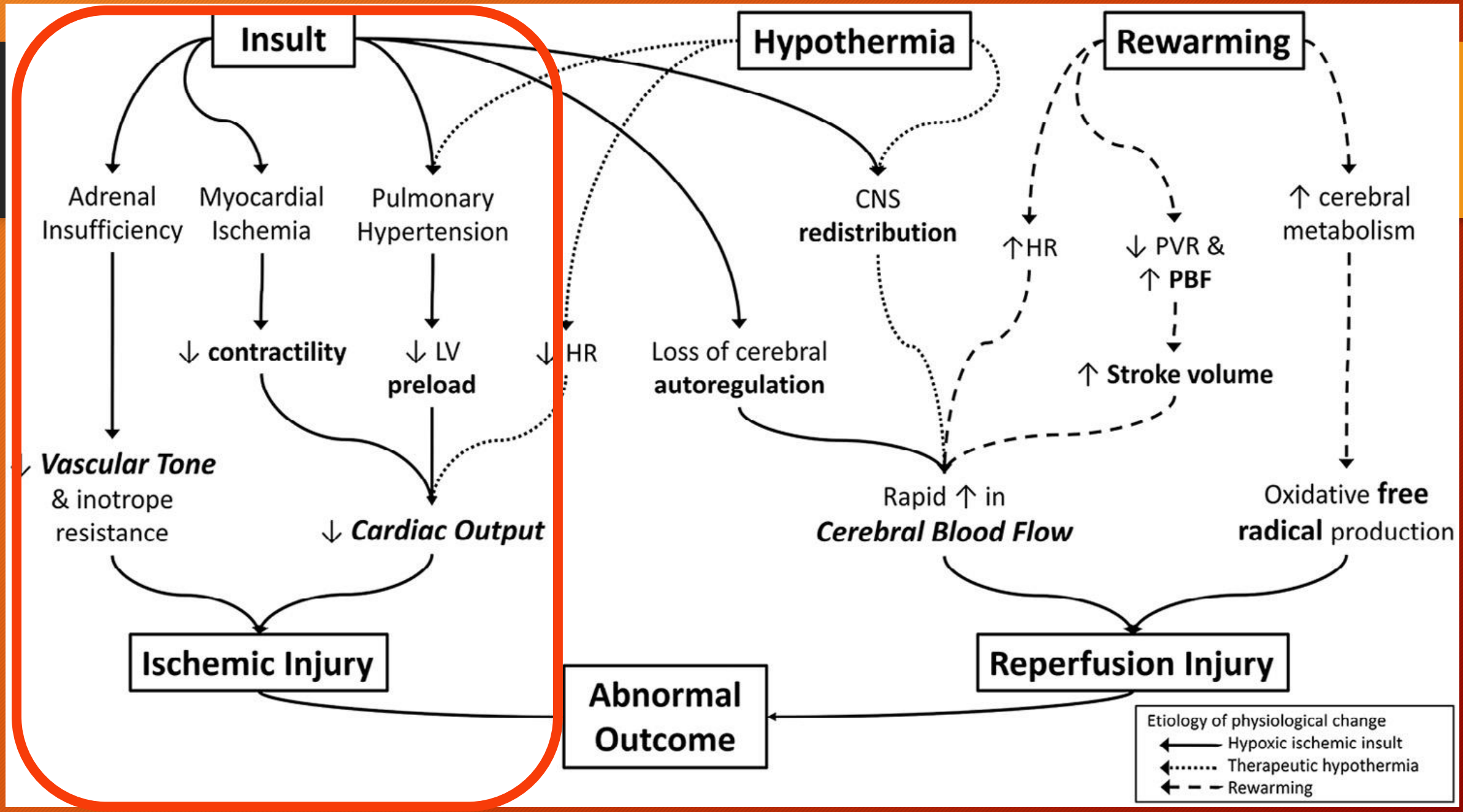
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Rewarming
Adrenal Insufficiency
Myocardial Ischemia
Pulmonary Hypertension
CNS redistribution
↑HR
↓ PVR & ↑ PBF
↑ cerebral metabolism
↓ contractility
↓ LV preload
↓ HR
Loss of cerebral autoregulation
↑ Stroke volume
↓ Vascular Tone & inotrope resistance
↓ Cardiac Output
Rapid ↑ in Cerebral Blood Flow
Oxidative free radical production
Ischemic Injury
Reperfusion Injury
Abnormal Outcome
Etiology of physiological change
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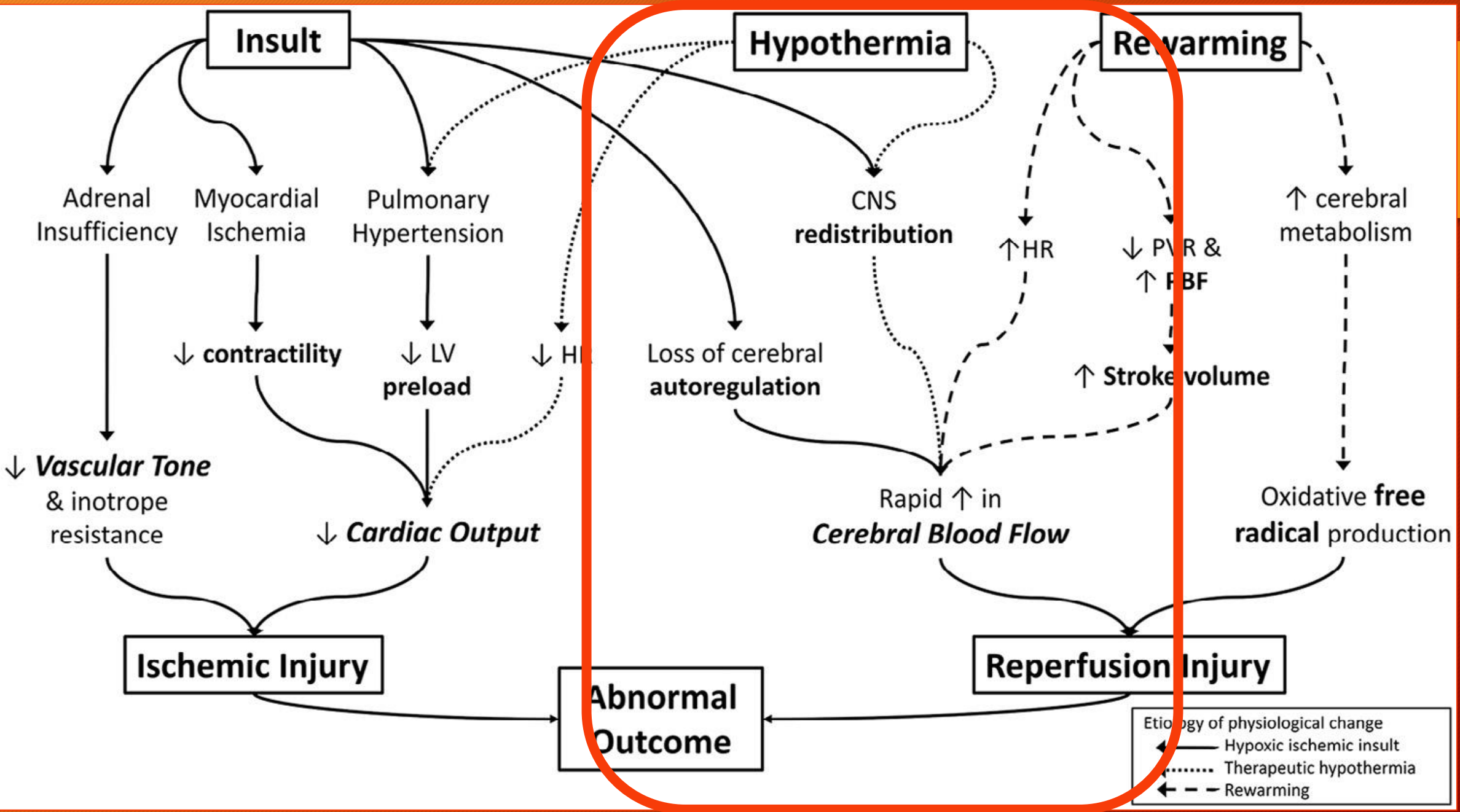
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Hypothermia Cardiovascular Effects

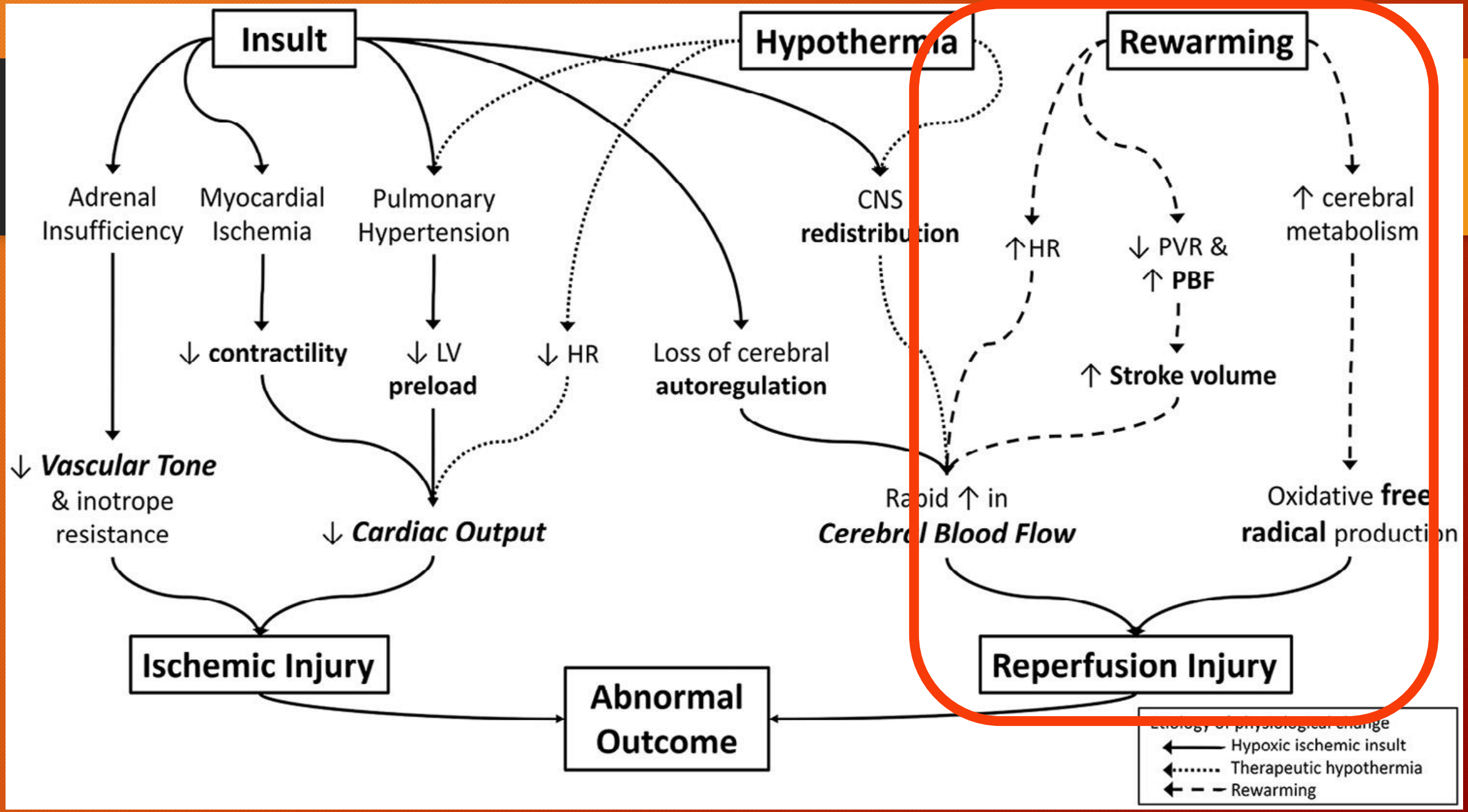
- TH alone is not associated with increased risk of hypotension
  - Normal or slightly increased BP related to hypothermia-induced vasoconstriction
- Reduction in heart rate after TH leads to 60-70% decrease in LV output compared to normothermic controls
  - Often sufficient because of decreased metabolic activity
- Sinus bradycardia
  - Slowed diastolic repolarization in SA node
  - Diminished influence of sympathetic autonomous nervous system on heart rate
- Normal heart rate despite low temperature may reflect subclinical systemic hypoperfusion and contribute to ongoing brain injury

Hypothermia Pulmonary Vascular Effects

- Severity of brain injury may be associated with dysregulation of vascular tone in pulmonary vascular bed
- Concurrent HIE and pulmonary hypertension more likely to have abnormal brain MRI despite TH
  - Greater disease severity-severe/prolonged hypoxia increases risk of impaired transition, persistent pulmonary hypertension

Hypothermia Pulmonary Vascular Effects

- Reduced pulmonary blood flow
  - Lower preductal cardiac aoutput + systemic hypotension = worsened ischemic insult
- Use of rapidly-acting pulmonary vasodilators (iNO)
  - Increased pulmonary venous return + augmentation of preductal cardiac output = reperfusion injury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Effects of Rewarming

- Augmentation of cardiac output and systolic blood pressure + concurrent decrease in systemic vascular resistance and DBP
  - Overall reduction in mean BP by ~8 mmHg
- Changes in drug volume of distribution, metabolism, and clearance
  - High Vd medications mobilized from sequestered tissue and can have exaggerated effects during rewarming
- Adjustment of cardiovascular medications
  - CNS hemorrhage during rewarming associated with greater degree of hemodynamic instability
  - Avoid iatrogenic hypertension and excessive unregulated cerebral blood flow

Clinical Considerations/Confounders

Variables	Change Seen	Pathophysiology
Heart rate	Sinus bradycardia	Decreased SA node repolarization
Blood pressure	Increased DBP	Systemic vasoconstriction
	Decreased SBP	Decreased cardiac output
Color	Pallor	Decreased skin perfusion
Capillary refill time	Prolongation	Decreased skin perfusion
Lactate	Lactic acidosis	Lactate washout after initiation insult, sequestering
Blood gas	Metabolic acidosis	Residual perinatal acidosis
Urinary output	Oliguria or Anuria	Acute renal injury

Approach to Cardiovascular Care

- Consider pathophysiology, phase of intervention, and impact of concomitant treatments
  - Isolated transient myocardial ischemia may not require intervention
- Weigh impact of treatment for impaired function/low cardiac output against consequences of reperfusion injury

Treatment of Hypotension with HIE

Table V. Echocardiography findings, pathophysiology, and suggested therapy in neonates with HIE and hemodynamic instability[39]

Clinical presentation	Echocardiography findings	Management principles	Suggested management
Low SAP, normal oxygenation	LV/RV systolic dysfunction	(+) Inotropy	1st line: dobutamine 2nd line: epinephrine - Hydrocortisone (if refractory)
Low SAP, impaired oxygenation	PPHN	Pulmonary vasodilation and ↑SBF	1st line: iNO, optimum ventilation 2nd line: vasopressin or norepinephrine - PGE_1 (if restrictive DA) - Hydrocortisone (if refractory)
	LV dysfunction + PPHN	(+) inotropy, maintain R → L ductal shunt to support SBF	1st line: dobutamine, PGE_1 (if restrictive DA) 2nd line: epinephrine (caution if severe oxygenation failure) - Hydrocortisone (if refractory)
	RV dysfunction + PPHN	(+) Inotropy, reduce RV afterload, maintain adequate RV preload	1st line: dobutamine, iNO 2nd line: PGE_1 (if restrictive DA) 3rd line: vasopressin or norepinephrine - Hydrocortisone (if refractory)

Hypovolemia Hypotension

- Aggressive volume resuscitation should be avoided
  - Association between increased cerebral blood flow and poor outcome
  - Exception: direct evidence of acute hypovolemia
- Blood transfusions for anemia + pulmonary hypertension
  - Increased oxygen carrying capacity

Isolated Hypotension

- Presentation
  - Low systolic BP and evidence of end organ hypoperfusion
- Treatment goals
  - Increase stroke volume and cardiac output
- Treatment options
  - Epinephrine
  - Dobutamine

Hypotension + Increased Afterload

- Presentation
  - Low pulmonary blood flow, impaired oxygenation, low cardiac output
- Treatment goals
  - Sedation, +/- muscle relaxation, ventilation, iNO
  - Avoid excessive mean airway pressure—further impairment of pulmonary venous return
- Treatment options
  - Dobutamine
  - Milrinone
  - Vasopressin
  - Norepinephrine

Refractory Hypotension

- Adrenal insufficiency can occur independently or in combination with other causes of hypotension
- Refractory
  - Persistent hypotension despite catecholamine therapy
  - Hypoglycemia, hyponatremia
  - Adrenal injury
- Treatment
  - Hydrocortisone

Summary

- Pathophysiology of hypotension in neonate is diverse
  - Gestational age, patient factors
- Treatment for hypotension should consider pathophysiology
- HIE/TH represents unique treatment considerations

Questions