Cardiovascular Pharmacology

Jennifer Owensby MD
Pediatric Critical Care
Medical Director, Pediatric Sedation Services
Bristol Myers Squibb Children’s Hospital
Definitions

• inotropes: improve myocardial contractility and enhance stroke volume
• pressors: increase systemic vascular resistance and, hopefully, blood pressure
• chronotropes: increase heart rate
Important Relationships

- \( BP = CO \times SVR \)
- \( CO = HR \times SV \)
- MVO2 determined by
  - contractility
  - myocardial wall tension
  - heart rate
  - external workload (afterload)
Determinants of Cardiac Output

- **Contractility**
- **Heart Rate**
- ** preload**
- **Afterload**

**Cardiac Output**

\( CI = \frac{CO}{m^2} \)

L/min
Cardiovascular Pharmacology

- main effects of the catecholamines usually determined by the adrenergic properties
  - alpha-adrenergic
  - beta-adrenergic
  - dopaminergic
Alpha-Adrenergic Agents

- can be divided into:
  - $\alpha_1$-adrenergic effects:
    - vascular smooth muscle contraction
  - $\alpha_2$-adrenergic effects:
    - vascular smooth muscle relaxation-
      - very mild effect; seen at low doses of an alpha-adrenergic agent
Beta-Adrenergic Agents

- can be divided into:
  - beta$_1$-adrenergic effects:
    - direct cardiac effects
      - increased inotropy
      - increased chronotropy
  - beta$_2$-adrenergic effects:
    - vasodilation
    - bronchodilation
Continuous Infusion

- epinephrine
- norepinephrine
- dopamine
- dobutamine
- milrinone/amrinone
- sodium nitroprusside
- isoproterenol
Epinephrine

• route – IV, IO, SQ, IM, ET (cardiac arrest without vascular access)
  – alpha- and beta-adrenergic properties
    • alpha- increase in SVR
    • beta- increased inotropy, chronotropy
Epinephrine

• actions dose dependent (mcg/kg/min):
  – 0.02-0.08 = mostly beta_1 and beta_2 stimulation
    • increased cardiac output
    • mild vasodilation
  – 0.1-2.0 = mix of beta_1 and alpha_1
    • increase cardiac output
    • increase SVR
  – > 2.0 = mostly alpha_1
    • increase SVR, and may decrease CO by increasing afterload
Epinephrine

- anxiety, tremors, palpitations
- tachycardia, tachyarrhythmias
- increased myocardial oxygen requirement, decreased perfusion; potential ischemia
- decreased splanchnic and hepatic circulation (elevation of AST and ALT)
- anti-insulin effects: lactic acidosis, hyperglycemia
Norepinephrine

- primarily alpha agonist - increases SVR without significant increase in C.O.
- useful in hypotension due to low SVR with a normal or high C.O. state - “warm shock”
- increases myocardial work secondary to increased afterload
- starting infusion rates 0.05 mcg/kg/min titratable to 3 mcg/kg/min
Norepinephrine

- side effect profile similar to that of epinephrine
- may compromise perfusion in extremities due to intense vasoconstriction
- severe sloughing with extravasation
- more profound effect on splanchnic and renal circulation
Dopamine

- intermediate product in the enzymatic pathway leading to the production of norepinephrine; thus acts indirectly by releasing norepinephrine.
- has direct alpha, beta and dopaminergic actions which are dose-dependent.
- dosage based on adrenergic actions desired.
Dopamine

- renal vasodilation: 2-5 mcg/kg/min
- inotropy: 5-10mcg/kg/min
- vasoconstriction: 10-20mcg/kg/min
Dobutamine

• synthetic catecholamine with inotropic effect (increases stroke volume) and peripheral vasodilation (decreases afterload)
• positive chronotrope
• net improvement in cardiac output
Dobutamine

- major metabolite is 3-O-methyldobutamine, a potent inhibitor of alpha-adrenoceptors; vasodilation possible secondary to this metabolite
- starting infusion rate 5 mcg/kg/minute; titrate to effect (20 mcg/kg/min)
Dobutamine

- low C.O. states and CHF - myocarditis, cardiomyopathy, myocardial infarction
- if BP adequate, can be combined with afterload reduction (milrinone, ACE inhibitor)
- in combination with vasopressor in profound shock states to improve cardiac output and provide some peripheral vasodilatation
Milrinone / Amrinone

- new class of agents- bipyridines
- non-receptor mediated activity based on selective inhibition of phosphodiesterase type III enzyme resulting in cAMP accumulation in myocardium
- cAMP increases force of contraction and rate, and increases EDV
- inotropy, chronotropy, vasodilation
Milrinone / Amrinone
Advantages

• overall reduces myocardial work and oxygen demand
• not receptor mediated; no tachyphylaxis
• minimal chronotropism - improved diastolic filling, coronary artery perfusion
Amrinone

- first generation agent - limited use now
- long half-life (4.4 hours) with potential for prolonged hypotension after loading dose
- associated with thrombocytopenia
- dosage: Load 0.75 mg/kg then infusion 5-10 mcg/kg/min
Milrinone

• increases CO by improving contractility, decreasing SVR, ?PVR, lusotropy; decreased preload due to vasodilatation
• unique in beneficial effects on RV function
• half-life 1-2 hours
• load 50 mcg/kg over 30 mins then 0.3 to 0.75 mcg/kg/min
• Minimal increase in myocardial O2 consumption
Vasodilators

- classified by site of action
- venodilators: reduce preload - nitroglycerin
- arteriolar dilators: reduce afterload - minoxidil and hydralazine
- combined: act on both arterial and venous beds and reduce both pre- and afterload - sodium nitroprusside (Nipride)
Nitroprusside

- acts directly on arterial and venous vascular smooth muscle.
- indicated in hypertension and low cardiac output states with increased SVR.
- also used in post-operative cardiac surgery to decrease afterload on an injured heart.
- immediate onset, short half life; titratable
Nitroprusside

- cyanide one of the metabolites; may reduce toxicity by adding thiosulfate
- severe, unexplained metabolic acidosis suggests cyanide toxicity
- dosing: start at 0.5 mcg/kg/min and titrate to 5 mcg/kg/min to desired effect; may go higher (up to 10 mcg/kg/min) for short periods of time.
Nitroglycerin

- arteriolar vasodilator, but major effect is as a venodilator
- not as effective as nitroprusside in lowering blood pressure
- relaxes coronary arteries – improves myocardial regional blood flow and myocardial oxygen demand
Nitroglycerin

• improves myocardial perfusion following cardiac surgery
• dose ranges from 0.5 to 8 mcg/kg/min; typical dose 2 mcg/kg/min for 24 to 48 hours post-operatively
• methemoglobinemia
Isoproterenol

• synthetic catecholamine
• non-specific beta agonist with minimal alpha-adrenergic effects
• inotropy, chronotropy, systemic and pulmonary vasodilatation
• indications: bradycardia, decreased cardiac output, bronchospasm (bronchodilator)
• occasionally used to maintain heart rate following heart transplantation
• no longer widely used
Inhaled Nitric Oxide

• selective pulmonary vasodilator
• dilates pulmonary capillaries only in alveoli participating in gas exchange
• decreases intrapulmonary shunt and improves V/Q matching
• rapidly inactivated by Hgb in capillary so no systemic side effects
Inhaled Nitric Oxide

- currently only FDA approved for use in neonatal pulmonary hypertension
- use in ARDS controversial
- expensive
- special monitoring/scavenging equipment required
- methemoglobinemia
- dose: concentration of 5-60 ppm in inhaled gas
Resuscitation

- epinephrine
- atropine
- sodium bicarbonate
- calcium (chloride or gluconate)
- lidocaine
- amiodarone
Epinephrine

• dosage:
  - initial (low) dose: 0.01 mg/kg
    = 0.1 cc/kg of 1:10,000
  - subsequent doses SAME: 0.01 mg/kg
    = 0.1 cc/kg of 1:10,000
  - endotracheal route still HIGH DOSE: 0.1 mg/kg = 0.1 cc/kg of 1:1000
Atropine

• parasympathetic (NOT alpha- or beta-adrenergic) agent--acts by blocking cholinergic stimulation of the muscarinic receptors of the heart.
• results in an increase in the sinus rate of the heart.
• little effect on systemic vascular resistance or myocardial contractility.
Atropine

• indications:
  – bradycardia
  – second or third degree heart block
  – asystole
  – pulseless electrical activity (electrical-mechanical dissociation)

• Route IV, IO, ET
Atropine

• dosage:
  - 10 to 20 mcg/kg; maximum (adult) dose 2 mg
  - minimum dose 0.1 mg--smaller doses may cause reflex bradycardia (central stimulatory effect on the medullary vagal nuclei)
Adverse Effects of Acidosis

Cardiac

- Decreases contractility
- Lowers threshold for ventricular fibrillation
- Decreases responsiveness to catecholamines

Vascular

- Decreases systemic vascular resistance
- Decreases systemic vascular responsiveness to catecholamines
- Increases pulmonary vascular resistance
Sodium Bicarbonate

- use during CPR remains controversial
- raises blood pH by binding with hydrogen to form water and CO₂
- may play role in prolonged resuscitation
- must have adequate ventilation to remove CO₂. THAM good alternative in hypercarbic states
Sodium Bicarbonate

• indications:
  - pre-existing acidosis
  - prolonged CPR ( > 10 minutes)
  - pulmonary hypertensive crisis
  - hyperkalemia
  - tricyclic anti-depressant overdose

• route
  - IV, IO

• dosage
  - 1-5 meq/kg/dose
Calcium

- current recommendations for calcium during CPR are restricted to a few specific situations.
- intracellular calcium plays an important role in the process of cell death, but no studies have shown that transient hypercalcemia worsens outcome after cardiac arrest.
Calcium

• hypocalcemia
  – decreases myocardial contractility
  – decreases systemic vascular resistance
  – decreases catecholamine release
  – decreases cardiovascular response to catecholamines
Calcium

• indications:
  – hypocalcemia
    • ionized hypocalcemia may result from severe alkalosis or after large transfusions of citrated blood products.
  – hyperkalemia
  – hypermagnesemia
  – calcium channel blocker overdose
Calcium

• route - IV, IO
  - calcium chloride – rapidly bioavailable; slough with extravasation - central venous line
  - calcium gluconate – needs enzymatic rxn; less caustic - peripheral venous line

• dosage:
  - calcium chloride = 10-20 mg/kg
  - calcium gluconate = 100-200 mg/kg
Lidocaine

• class 1B antiarrhythmic
• raises automaticity threshold and ventricular fibrillation threshold
• effective in terminating PVCs
• ventricular arrhythmias uncommon but not unknown in children
• useful in conjunction with electrocardioversion/defibrillation
Lidocaine

• indications:
  – ventricular tachycardia
  – ventricular fibrillation in conjunction with cardioversion
  – frequent PVCs

• route - IV, IO, ET

• dosage:
  – 1 mg/kg/dose (may need up to 2.5 mg/kg ET)
Amiodarone

- Class III anti-arrhythmic
- ventricular arrhythmias
- prolongs refractory phase in myocardium
- alternative / adjunct to lidocaine
- dosage: 5 mg/kg IV/IO over 20 minutes
Don’t Forget the Basics

- oxygen and mechanical ventilation
- analgesia, anxiolysis, paralysis
- minimize unnecessary energy expenditure – fever, seizures
- electrolyte homeostasis – Ca++ and Mg
- nutrition - hypoglycemia, starvation
- correct anemia to maximize oxygen delivery
- maintain appropriate intravascular volume