Determinants of Neonatal Cardiac Output

F. Jay Fricker MD
Neonatology basic core curriculum
Determinants of cardiac output in the Neonate

Differences between Fetal and adult Myocardium

Organization and the number of myofibrils undergo changes during development.

- Orientation of myofibrils
- Non-contractile elements
Determinants of Neonatal Cardiac Output

Fetal vs Adult Myocardium

- Active Tension lower than adult at same fiber length (Systolic Function)
- Resting tension greater in Fetus than adult (Diastolic function)
- Sarcomeral length not different
- Cannot be explained by greater proportion of non contractile elements
- ?Different sensitivity of fetal contractile proteins to cytosolic Calcium
Determinant of Cardiac Output
Fetus Vs adult
Afterload
Starling Curve Concept of Descending Limb
Determinants of Cardiac Output
The Sarcomere
Determinants of Cardiac Output
The Sarcomere
Determinants of Fetal Cardiac output

Major factors determining Cardiac Output

• Heart Rate
• Preload
• Afterload
• Contractility
Heart Rate and Stroke Volume

Heart Rate Neonate: Cardiac output more dependent on Heart Rate 80-180 bpm
Pressure Volume Loop
The Model
Pressure Volume Loop

Interpretation

The Pressure-Volume Loop

- End Systolic Volume (ESV)
  Closure of the aortic valve

- Beginning of systole
  Opening of aortic valve

- Isovolumic contraction

- End Diastolic Volume (EDV)
  Closure of mitral valve

This slope represents the relationship between ESV and afterload and reflects inotropy.

Opening of the mitral valve and beginning of ventricular filling.

The width of this area represents Stroke Volume.

Pressure (mmHg) vs. Volume (mL)
Pressure Volume loop

Fig. 9-3. The effect of varying afterload, preload, and contractility on the pressure-volume loop. A. When the preload (EDV) and contractility are held constant, sequential increases (points 1, 2, 3) in arterial pressure (afterload) are associated with loops that have progressively lower stroke volumes and higher end-systolic volumes. B. When the arterial pressure (afterload) and contractility are held constant, sequential increases (points 1, 2, 3) in preload (measured as end-diastolic volume) are associated with loops that have progressively higher stroke volumes but a constant end-systolic volume (ESV). C. A positive inotropic intervention shifts the end-systolic pressure-volume relation upward and leftward from ESPVR-1 to ESPVR-2, resulting in loop 2, which has a larger stroke volume and smaller end-systolic volume than the original loop 1.

D. Burtt, MD
Normal Circ & CHF
9/3/97
Determinants of Cardiac Output

Increase in AfterLoad
The Staircase Effect (*Bowditch effect*; *Treppe*; *Frequency-dependent inotropy*)

Increases in heart rate cause an automatic increase in the tension generated by contracting myocardial cells, even when all neural and hormonal influences are eliminated.

This phenomenon is called the Bowditch effect after the physiologist (Henry Bowditch) that discovered it.
Determinants of Neonatal cardiac Output

Anrep Effect

Sudden increase in afterload on the heart causes an increase in ventricular inotropy. This Phenomenon is observed in denervated hearts, isolated muscle and in intact hearts. Significance is that the increased inotropy compensates for the increased endd-systolic volume and decreased stroke volume casused by increase in afterload.
Heart Failure
Definition

• “..Heart failure is a clinical syndrome in which heart disease reduces cardiac output, increases venus pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death”  ARNOLD KATTZ

• Or

• “The Heart is unable to meet the metabolic demands of the body”
Heart Failure

- Effective Arterial Blood Volume
  - Renal Vasoconstriction
  - Renin
  - Angiotension Axis

- Na and $\text{H}_2\text{O}$ Retension
- Renin release
- Angiotension II
Heart Failure
Concept of forward or backward failure

Increased intravascular volume

Increase in the End-Diastolic Pressure LV and RV

Increase in Systemic and Pulmonary Venous Pressure

Hepatomegaly, Pulmonary edema and edema
Heart Failure

Regional Circulation

Sympathetic Nervous system

Angiotension II

Vasoconstriction

NA and H₂O content of Blood vessels
Heart Failure

Concept
“Backward or Forward Failure”

Liver Congestion/Pulmonary edema

Renal Perfusion

Na and H2O

Intravascular Volume → RVEDP → LVEDP → Liver enlargement

Pulmonary edema
Inotropes in Neonates
**Inotropes**

- Chosen according to physiology and titrated to a goal to be achieved
- Combination of drugs is more often used to prevent side effects
- Other factors affecting CO:
  - Acid-base and electrolyte balance (ex: acidosis, hypoCa)
  - Cardiopulmonary interactions (ex: ventilation)
  - Hypoxemia (ex: HIE, PH)
  - Presence of intra or extracardiac shunts (ex: ASD, PDA)
  - Neuro-humoral response (ex: adrenal, thyroid, glucose)
  - Oxygen carrying capacity (CaO2), Oxygen Consumption (VO2 = metabolic demands)
  - Dysrhythmias and lost of AV synchrony
  - Patophysiology (Biventricular vs. SV)

Nicholz, *Heart Disease in Infants and Children*
# Table 1. Mechanism of Action and Dosages of Inotropes

<table>
<thead>
<tr>
<th>Drug Dosage</th>
<th>Vascular</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peripheral Vasoconstriction</td>
<td>Peripheral Vasodilation</td>
</tr>
<tr>
<td></td>
<td>$\alpha_1$</td>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>Dopamine, $\mu g/kg/min$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5–2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2–6</td>
<td>0/+</td>
<td>0</td>
</tr>
<tr>
<td>&gt;6–10</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine, $\mu g/kg/min$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–10</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>1–20</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Epinephrine, $\mu g/kg/min$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01–0.1</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>&gt;0.1</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Norepinephrine, $\mu g/kg/min$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05–0.5</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

*Specific dose responses are based on data in children and adults.*
Dopamine

• Endogenous catecholamine precursor of norepinephrine and epinephrine
• Receptors: alpha, beta, dopamine
• Dose dependent:
  – 0.5-2mcg/kg/min: dopaminergic recept (no benefit)
  – 2-10mcg/kg/min: Beta1 recept (↑CO and SBP)
  – >10mcg/kg/min: alpha recept (vasoconstr, ↑SBP and DBP)
• Undesired CV effects:
  – ↑ oxygen consumption of myocardium
  – ↑ automaticity (arrhythmias), tachycardia
  – 1 pediatric study: associated with increased mortality– Ventura et al, PCCM 2015
• Non-CV effects:
  – Prolactin, thyrotropin and growth-hormone secretion suppression
  – Extravazation

Osborn, Evans, Kluckow, Neoreviews 2004
Ruoss, McPherson and DiNardo, Neoreviews, 2015
Dobutamine

• Synthetic catecholamine: does not release NE
• Receptors: beta1 myocardium (↑ contractility) and B2 peripheral (vasodil)
• Used in many HIE studies (↓ contractility-LCOS)
• Doses:
  – >10mcg/kg/min: ↑CO and HR
    -Devictor et al., Arch Fr Ped, 1988
  – 5-7.5mcg/kg/min: ↑CO but not HR and BP
    -Martinez et al., Pediatrics, 1992

• Undesired effect:
  – Arrhythmia
  – Vasodilation

Osborn, Evans, Kluckow, Neoreviews 2004
Ruoss, McPherson and DiNardo, Neoreviews, 2015
Epinephrine

- Endogenous catecholamine
- Receptors: alpha, beta
- Predictable dose-dependent response (not in preterms)
  - 0.01-0.1 mcg/kg/min: beta receptors (b1>b2)
  - >0.1 mcg/kg/min: alpha receptors (alpha1)
- NICU: often used for refractory hypotension
- Undesired CV effects:
  - ↑ oxygen consumption of myocardium
  - ↑ automaticity (arrhythmias)
  - Down-regulates receptors
- Non-CV effects:
  - HypoK: B2 mediated K influx to muscle cells
  - Hyperglycemia: ↑ glycolysis and suppresses insulin release
  - Intestinal hypoperfusion
  - Extravazation injury

Cheung et al., 1997
Osborn, Evans, Kluckow, Neoreviews 2004
Ruoss, McPherson and DiNardo, Neoreviews, 2015
Norepinephrine

- Endogenous catecholamine
- Doses: 0.01-0.4mcg/kg/min
- Undesired effects:
  - ↑ afterload to the heart (workload)
  - Poor end-organ perfusion (kidneys and gut)- tissue ischemia
  - Extravazation injury
- Usual indications: low SVR (vasodilated-septic shock), hypertrophic cardiomyopathies with hypotension

Osborn, Evans, Kluckow, Neoreviews 2004
Ruoss, McPherson and DiNardo, Neoreviews, 2015
Dopamine or dobutamine?

-Dopamine: more effective in the short term treatment of hypotension in preterm infant
-No evidence of adverse neurological sequelae (severe P/IVH and/or PVL)

“in the absence of data confirming long term benefit… dopamine compared to dobutamine, no firm recommendations can be made regarding the choice of drug to treat hypotension.”

Subhedar and Shaw, Cochrane 2003
Milrinone

- Bipyridine group: selective phosphodiesterase-3 inhibitor.
- Increases cytosolic cAMP w/o receptor mechanism: positive inotropic and lowers SVR (Inodilator) as perpetuates influx of Calcium= \( \uparrow \) CO
- Pulmonary hypertension: weak vasodilator
- Drug of choice to balance QP:QS and prevent LCOS after cardiac surgery
- Doses: 0.25-1mcg/kg/min
- Undesired CV effects:
  - Hypotension
  - Tachycardia/arrhythmia
- Non-CV effects:
  - Thrombocytopenia
  - Careful administration when renal dysfunction

Osborn, Evans, Kluckow, Neoreviews 2004
Ruoss, McPherson and DiNardo, Neoreviews, 2015
Dopamine or Epinephrine?

**DOPAMINE (D) VERSUS EPINEPHRINE (E) FOR INOTROPIC SUPPORT IN THE NEONATE: A RANDOMIZED DOUBLE BLINDED CONTROLLED TRIAL.**

Ernest Z Phillipos, Keith J Barrington and Murray A Robertson

1NICU, University of Alberta Hospital, Edmonton, Alberta, CANADA.

- D causes 10% decrease LV output secondary to drop in LV stroke volume; E increases LV output by 10% due to increase in LVS
- Conclusion: “Epinephrine has better effect on contractility”

**Dopamine Versus Epinephrine for Cardiovascular Support in Low Birth Weight Infants: Analysis of Systemic Effects and Neonatal Clinical Outcomes**

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*Department of Neonatology and Biostatistics Unit, La Paz University Hospital, Madrid, Spain  

Pediatrics, 2006

- No differences found rate treatment failure
- Conclusion: “Low/mod-dose E is as effective as low/mod dose D for treatment hypotension in low birth weight infants, although is associated with more transitory adverse effects”

MORE STUDIES NEEDED!
Steroids

- **Mechanism of action:**
  - Decreases the breakdown of catecholamines
  - Increases calcium levels in myocardial cells
  - Upregulates adrenergic receptors
  - Inappropiate cortisol secretion during sickness (relative adrenal insufficiency)

- **Dose:** 50mg/m^2/day

- **Adverse effects:**
  - Hyperglycemia
  - Gastric irritation
  - Fluid retention
  - Long-term: osteopenia, immunossupression, decreased somatic growth, asseptic acetabular necrosis

Ruoss, McPherson and DiNardo, *Neoreviews, 2015*
Frank-Starling Curve

The heart has an intrinsic capability to increase its force of contraction and therefore stroke volume (SV) in response to an increase in venous return. This is called the Frank-Starling law (Fig 2). The raise of venous return increases the ventricular filling (end-diastolic volume) and therefore preload, which extends the myocyte sarcomere length, causing an increase in force generation. The underlying mechanism is found in the length-tension and force-velocity relationships for cardiac myocytes. Briefly, increase of sarcomere length enhances troponin C calcium sensitivity, which upregualtes the rate of myosin-actin attachment and detachment, and the amount of tension developed by the muscle fiber.

Is there a descending limb of the starling curve?
Heart Failure

Contractility

Figure 3-8. Frank-Starling relationship and the effect of positive and negative inotropic agents.
Isoproterenol

- Synthetic catecholamine structurally related to adrenaline
- Receptor: almost exclusively Beta (HR)
- Doses: 0.01-0.1mcg/kg/min
- Undesired effects:
  - ↑ oxygen consumption of myocardium
  - ↑ automaticity (arrhythmias)
  - Extravazation injury
- Usual indications: congenital heart block, PPHN, post heart transplant (denervated heart)

Osborn, Evans, Kluckow, Neoreviews 2004
Vasopressin

- Neuropeptide acting on V1 and V2 receptors on smooth muscle cells and NO selective vasodilation of cerebral and pulmonary circulations
- Possible synergistic action to cathecolamines
- Peripheral vasoconstr (except CNS, coronary, gut, lungs)
- Uses:
  - Septic shock
  - Post-CPB
- Doses: 0.0001-0.002 Units/kg/min
- Adverse effects: vasoconstriction, tissue necrosis and hyponatremia

Maffei, Pediatric Critical Care Study Guide, 2012
Ruoss, McPherson and DiNardo, Neoreviews, 2015