Circulatory support in the Sick Child

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Circulatory support in the Sick Child

- Increased sympathetic drive
- Elevated catecholamines
- Continuing stimulation
- Exacerbated by exogenous agonist use
- Decreased effect
- Desensitization

Circulatory support in the Sick Child

- Endogenous catecholamines
- Mechanism of Desensitization
- Pathological causes
- Therapeutic Options

Endogenous catecholamines

- Stimulus: Sympathetic drive
- Origin: Adrenal medulla
- Delivery: Bloodstream
- Catecholamines: 80% epinephrine
  20%norepinephrine
- Action: via adrenergic receptors

Endogenous catecholamines

- 1913 Dale demonstrated epinephrine action
- 1948 Ahlquist defined two receptor subtypes: $\alpha$ and $\beta$
- Potency
  $\alpha$: Norepi > Epi > Iso
  $\beta$: Iso > Epi > Norepi
Endogenous catecholamines

- 2003: 10 subtypes
- 4 Beta, 6 Alpha adrenoceptors
- $\beta_1$: Cardiac
- $\beta_2$: Smooth Muscle
- $\beta_3$: Adipose tissue
- $\beta_4$: Cardiac

Endogenous catecholamines

$\beta_1$ Receptor:
- Agonism $\rightarrow$ Gs protein activation $\rightarrow$ Adenyl cyclase activation $\rightarrow$ $\uparrow$ cAMP
- cAMP $\rightarrow$ PKA activation $\rightarrow$ L-type Ca channel opening $\rightarrow$ $\uparrow$ Ca influx

Endogenous catecholamines

$\beta_2$ Receptor:
- Agonism $\rightarrow$ Gs protein activation $\rightarrow$ Adenyl cyclase activation $\rightarrow$ $\uparrow$ cAMP
- cAMP $\rightarrow$ PKA activation $\rightarrow$ L-type Ca channel opening $\rightarrow$ $\uparrow$ Ca influx

Endogenous catecholamines

$\beta_3$ Receptor:
- Agonism $\rightarrow$ phosphorylation of myosin light chain kinase $\rightarrow$ smooth muscle relaxation
- Agonism $\rightarrow$ Gi protein activation $\rightarrow$ $\downarrow$ cAMP

Endogenous catecholamines

$\alpha_1$ Receptor:
- Agonism $\rightarrow$ Gq protein activation $\rightarrow$ PLC activation
- PI $\rightarrow$ DAG + IP$_3$
- IP$_3$ $\rightarrow$ sequestered Ca influx

Desensitization

- Continuous stimulation leads to decreased response = DESENSITIZATION
- Mainly $\alpha_1$ and $\beta_1$
- Homologous - Agonist specific
- Heterologous - Not agonist specific

Desensitization

- Three distinct but interrelated processes
- Receptor/G protein uncoupling
- Receptor sequestration
- Downregulation
Desensitization

- Receptor/G protein uncoupling
- Rapid
- Receptor Phosphorylation
- β-arrestin complex formation
- Uncoupled state

Desensitization

- Sequestration
- Several Minutes
- β-arrestin complex binds to Clathrin
- Whole complex sequestrated
- Receptors recycled/degraded

Desensitization

- Downregulation
- Several hours and is irreversible
- Two processes
  1. Sequestered receptors degraded
  2. cAMP Response Element Binding protein activated

Desensitization

- Downregulation
- CREB protein inhibits RNA polymerase for receptor protein
- Recovery requires receptor synthesis

Desensitization

- In Summary
- Continuing receptor stimulation leads to an ever-decreasing response which ultimately causes irreversible destruction of receptors.

Desensitization

- Zeiders JL et al
- Agonist induced sensitization of beta-adrenoceptor signalling in neonatal rat heart:expression and catalytic activity of adenylyl cyclase
- *J Pharmacol Exp Ther* 1999;291:503-510
Desensitization

- Rats given isoproterenol daily for 4 days
- Rats aged 6, 15, 25 days and adult.
- Cardiac membrane evaluated day 5 to isoproterenol stimulation
- 6 day old rat exhibited sensitization and enhanced response.
- All others desensitized.

Pathological Causes

- Exogenous Catecholamines
- Heart Failure
- Hypoxia
- Hypertrophy and Outflow Obstruction
- Sepsis

Low Cardiac Output/Heart Failure

- Inadequate Preload: Haemorrhage, Dehydration
- Increased Afterload: Hypertension, Severe polycythaemia
- Decreased Contractility: Cardiomyopathy

Low Cardiac Output/Heart Failure

- Wu JR et al
- Circulating Noradrenaline and beta-adrenergic receptors in children with congestive heart failure
- *Acta paediatr* 1996;85:923-927

Low Cardiac Output/Heart Failure

- 94 non cyanotic children with heart disease
- 43 with CHF
- 52 without CHF
- Increased Norepi levels and decreased beta receptor density in CHF group
- Both returned to baseline post repair
Low Cardiac Output/Heart Failure

- Wu JR
- Reduction in lymphocyte beta adrenergic receptor density in infants and children with heart failure secondary to congenital heart disease
- *Am J Cardiol 1996;77:170-174*

Low Cardiac Output/Heart Failure

- 91 children with non cyanotic heart disease
- Degree of L → R shunt and PA pressure correlated closely with plasma Norepi levels
- and inversely with beta receptor density

**Conclusion**
- Congestive heart failure causes norepinephrine induced homologous desensitization

Hypoxia

- Antezana et al
- Adrenergic status of humans during prolonged exposure to the altitude of 6542m.

Hypoxia

- 10 subjects
- Studied at sea level, 1 and 3 weeks at altitude
- Measurements taken:
- Plasma Norepinephrine
- Response to Isoproterenol
- Density of lymphocyte beta receptors

**Conclusion**
- Increasing plasma norepinephrine levels
- Decreasing response to isoproterenol
- Response did not improve with acclimatization
- Density of beta receptors reduced by 45%
Hypoxia

• Mardon K et al
• Effects of 5-day hypoxia on cardiac adrenergic neurotransmission in rats
• *J Appl Physiol* 1998;85:890-897

Hypoxia

• 32 Male Wistar rats
• 5 days in hypobaric chamber
• Comparison with normoxic rats

**Results**

• Plasma Norepi levels increased
• Norepi reuptake reduced 35%
• Response to isoproterenol reduced by 35%

**Conclusion**

• Chronic hypoxia leads to a loss of specific uptake 1 carrier protein for Norepinephrine
• This leads to catecholamine induced desensitization

Hypoxia

• Contrary Findings
• Sun LS et al
• Right ventricular infundibular beta adrenoceptor complex in tetralogy of fallot patients
• *Pediatr Res* 1997;42:12-16

Hypoxia

• Compared symptomatic vs asymptomatic children with TOF preoperatively

**Results**

• Symptomatic children had increased receptor density and enhanced agonist response compared with asymptomatic
• Therapy with beta blockers validates this
Outflow Obstruction

- Galal O et al
- Sympathetic activity in children undergoing balloon valvuloplasty of pulmonary stenosis

Outflow Obstruction

- Determined density of lymphocyte beta adrenoceptors pre and post dilation
- Children having PDA occlusion as controls
- Pre: 23% decreased receptor density
- 10 Minutes post: Equal density to controls

Mechanism of desensitization:
- Wall stress without receptor agonism

Sepsis

- 5 per 1,000 children < 1 require in-patient therapy for sepsis per year
- Cost to the nation: $1.1 billion/year
- Cardiac failure predominant cause of death

Sepsis

- Joe EK et al
- Regulation of cardiac myocyte contractile function by inducible nitric oxide synthase:Mechanisms of contractile depression by nitric oxide
- *J Mol Cell Cardiol* 1998;30:303-315

Sepsis

- Study conducted at the B and W
- Incubated cardiac myocytes
- Added LPS-activated macrophages
- Examined after 20 hours

Results

- Inducible NO synthase activity increased
- Increased NO production
Sepsis

Results
• Reduced response to isoproterenol
• NOS activity did not affect receptor density or adenylyl cyclase activity

Conclusion
• NO inhibited cAMP via cGMP
• NO synthase inhibitor reversed the trend

Desensitization
• Thus numerous pathological conditions result in desensitization.
• How to proceed?
  • 1. Mechanical Support?
  • 2. Non adrenergic receptor mediated inotropic support

Therapeutic Options
• Phosphodiesterase Inhibitors
• Tri-iodothyronine
• Insulin
• Growth Hormone
• Digoxin

Phosphodiesterase Inhibitors
• Non catecholaminergic inotropic agents
• Amrinone, Milrinone and Enoximone
• Mechanism of action
• Phosphodiesterases degrade cAMP to 5AMP
• Inhibition leads to increased cAMP
• Increased Ca and increased contractility

Phosphodiesterase Inhibitors
• Response related to increased cAMP not phosphodiesterase inhibition per se.
• Greatest effect if increased endogenous or exogenous catecholamine present.
• Synergy with $\beta_1$ agonists
• Greatest synergy in neonates
• Significant positive effect on their own
Phosphodiesterase Inhibitors

**Advantages**
- Increased contractility
- Myocardial oxygen consumption unchanged
- Afterload reduction from RV and LV
- Improved coronary perfusion

**Disadvantages**
- Inhibition of platelet aggregation

Phosphodiesterase Inhibitors

- Enoximone
  - Loading Dose: 0.5mg/kg over 1 hour
  - Infusion: 10 mic/kg/min

- Milrinone
  - Loading Dose: 0.05mg/kg over 1 hour
  - Infusion: 0.5-1.5 mic/kg/min

Triiodothyronine

- T$_3$ essential for maturation of sarcolemmal Ca channels, myosin, actin and troponin
- Hypothyroid rats show:
  - Decreased beta receptor
  - Decreased Gs protein density
  - Increased Gi receptor density

Triiodothyronine

- 80% produced by monoiiodination of T$_4$
- T$_4$ → T$_3$ inhibited by:
  - Surgery, CPB, hypothermia, catcholamines, glucocorticoids, propranolol and amiodarone

Nucleus Mediated Effects

- Increase in mitochondrial density
- Increase in mitochondrial respiration
- Increase in contractile protein synthesis
- Upregulation of beta adrenoceptors
**Triiodothyronine**

*Extranuclear Effects*

- Increase in sarcolemmal glucose transport
- Stimulation of L-type calcium channels
- Increase in SRCaATpase activity → improved calcium reuptake → improved diastolic relaxation

**Triiodothyronine**

*Advantages*

- Increased contractility
- Myocardial oxygen consumption unchanged
- Synergy with beta agonists
- Upregulation of beta receptors
- Reversal of depressed contractility secondary to desensitization

**Triiodothyronine**

- Bettendorf M et al
- Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study

**Triiodothyronine**

- 40 Children
- T$_3$ group - 2mic/kg day 1, 1mic/kg to day 12
- Simple and complex cardiac surgery

*Results*

- Better myocardial function and decreased ITU requirement in T$_3$ group
- No delay in recovery of thyroid function

**Insulin**

*normal resting cardiac metabolism*

- 60-70% Free fatty acids, 30-40% Glucose
- Glucose – less ATP, more efficient
- FFA – more ATP, less efficient
- Substrate utilised determined by relative plasma levels overall
- Glucose preferential if myocardium stressed
**Insulin**

- Use of insulin based on two principles:
  1. Insulin stimulates myocardial Na/K ATPase, increasing K reuptake thus stabilising membrane.
  2. ATP produced from glucose metabolism preferentially used to support ion pumps.
- This improves calcium homeostasis and functional recovery

**Results of adult studies**

- Decreased myocyte excitability
- Improved systolic and diastolic function with little increase in oxygen consumption
- Synergy with beta agonists
- Decrease in systemic vascular resistance
- Studies in children awaited

**Growth Hormone**

- Probably acts via insulin-like growth factors I and II.
- IGF I crucial for development of neonatal myocardium

**Probable mechanism**

- Increase in contractile protein synthesis
- Increase in calcium channel activity
- Increase in myocardial calcium sensitivity

**Overall**

- Beneficial short term effects seen in adult heart failure
- Increased longer term mortality seen secondary to derangement of immune function in adults

**Digoxin**

**Mechanism of action**

- Beta stimulation increases PKA activity
- Resultant increase in Na/K ATPase activity
- Digoxin inhibits pump action
- Decreased need to use Na/Ca pump
- Increased intracellular calcium
- Improved contractility

**Advantages**

- Children with dysrhythmia induced ventricular dysfunction
- Less evidence for beneficial effect if patient in sinus rhythm
New Agents

- Vasopressin
- Nesiritide
- Levosimendan
- Fenoldopam

Conclusion

*Treatment of the sick child*

1. Correction of metabolic abnormalities
2. Treatment of any underlying cause
3. Optimisation of heart rate, preload and afterload
4. Use of combination pharmacological therapy
5. Mechanical support