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: α and β
- Potency
  α: Norepi > Epi > Iso
  β: Iso > Epi > Norepi

Endogenous catecholamines

- 2003: 10 subtypes
- 4 Beta, 6 Alpha adrenoceptors
- β_1 : Cardiac
- β_2 : Smooth Muscle
- β_3 : Adipose tissue
- β_4 : Cardiac

Endogenous catecholamines

β_1 Receptor:

- Agonism → Gs protein activation → Adenyl cyclase activation → ↑ cAMP
- cAMP → PKA activation → L-type Ca channel opening → ↑ Ca influx

Endogenous catecholamines

β_2 Receptor:

- Agonism → Gs protein activation → Adenyl cyclase activation → ↑ cAMP
- cAMP → PKA activation → L-type Ca channel opening → ↑ Ca influx

Endogenous catecholamines

β_2 Receptor:

- Agonism → phosphorylation of myosin light chain kinase → smooth muscle relaxation
- Agonism → Gi protein activation → ↓ cAMP

Endogenous catecholamines

α_1 Receptor:

- Agonism → Gq protein activation → PLC activation
- PI → DAG + IP_3
- IP_3 → sequestered Ca influx

Desensitization

- Continuous stimulation leads to decreased response = DESENSITIZATION
- Mainly α_1 and β_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 $\rightarrow$ 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.
- *J Appl Phys 1994;76:1055-1059*

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

Hypoxia

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%

Hypoxia

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
- *Pediatr Res 1996;39:774-778*

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 β_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 monoiodination of T_4
- $T_4 \rightarrow T_3$ inhibited by:
  Surgery, CPB, hypothermia, catcholamines, glucocorticoids, propranolol and amiodarone

Triiodothyronine

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
- *Lancet 2000;356:529-534*

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

Insulin

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

Growth Hormone

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

Digoxin

- 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