PHARMACOLOGICAL SUPPORT FOR THE IMMATURE MYOCARDIUM

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Differences between immature & mature myocardium that affect use of vasoactive drugs:
1. **Physiological**: differences in autonomic nervous system activity, force-frequency response, cardiomyocyte calcium regulation, & response to changes in preload & afterload.
2. **Pathological**: myocardial ischaemia less of a problem, pulmonary hypertension & chronic hypoxia more of a problem.
3. **Pharmacological**: differences in drug pharmacokinetics &/or pharmacodynamics.

**Autonomic nervous system activity:**
Premature & small for gestational age neonates exhibit higher sympathetic tone & reduced vagal activity compared to term infants. Parasympathetic-mediated fluctuations in R-R interval spectral power & baroreflex sensitivity increase progressively with postmenstrual age.

**Force-frequency response:**
Rate-related changes in intracellular calcium cycling are particularly important in the immature myocardium

**Cardiomyocyte calcium regulation:**
Cardiomyocytes taken from infants have 25-50% less sarcoplasmic reticulum calcium ATPase (SERCA2a) activity than those taken from older children, significantly reducing the cell’s ability to sequestrate cytosolic Ca++. As Ca++ release from the sarcoplasmic reticulum (SR) is proportional to SR uptake, reduced SR Ca++ uptake can result in reduced contractility.
Low SERCA activity also results in deceleration of relaxation, i.e. poor diastolic function.
To complicate matters further, expression of phospholamban, an important regulator of SERCA2a activity, is affected by the dynamic demands on the cell. Calcium influx into the immature cardiomyocyte through L-type calcium channels is about 33% less than in mature cardiomyocytes, though this decrease is somewhat compensated for by a 44% increase in reverse mode sodium-calcium exchanger activity. Ryanodine receptor (the primary Ca\(^{++}\) release channel in the SR) activity in the human neonate is 23% less than in the adult. These major differences in intracellular Ca\(^{++}\) ion regulation in the immature myocardium have significant implications for neonatal cardiac function & treatment.

**Response to changes in preload:**
Cardiac muscle normally responds to a change in length in two distinct phases: an immediate change in twitch force & a slower phase that develops over the course of several minutes. The latter phase is due to myocyte stretch inducing release of preformed angiotensin II, which through a complex cascade of intracellular mediators results in phosphorylation of the sodium-hydrogen exchanger (NHE). NHE activation leads to an increase in intracellular Na\(^{+}\) & subsequently, intracellular Ca\(^{++}\), from resulting stimulation of the sodium-calcium exchanger. Animal studies suggest that NHE activity is relatively high during myocardial growth & early infancy.

**Response to changes in afterload:**
Neonates have a low baseline afterload, which contributes to their high resting contractile state. Neonates & infants respond relatively poorly to increases in afterload & do not increase their contractility in response, unlike the older child & adult. Lowering afterload below a critical point results in a disproportionate increase in contractility.

**Conclusions:**
The optimum choice of drugs used to support an immature myocardium can be made only by appreciating the pathophysiological milieu. Most neonates will benefit from a heart rate kept between 140 & 170, low afterload for both right & left ventricles, only moderate preload (LAP: 5-9 mm Hg) & normal blood concentrations of ionized calcium & electrolytes. Drug therapy should include catecholamines such as dobutamine & inodilators such as milrinone. In addition, adjuvant drugs such as triiodothyronine, insulin & inhaled nitric oxide may be considered. Preliminary studies examining the role of levosimendan in paediatric patients are encouraging.
Key references:
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Caldiz CI et al. J Physiol 2007; 584: 895-905