The role of epigenetics in the origin of congenital heart disease

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The past decade has seen a remarkable explosion of insights into the control of heart development. This has come about as a consequence of the temporal confluence of several research domains: the better delineation of syndromic congenital heart disease (see article in this issue), the completion of the Human Genome Project in 2003, the remarkable advances in molecular embryology and a deeper understanding of genetic evolution. It is against this background, and by combining data from anatomical embryology, early fetal myocardial function, and fetal blood flow with a new understanding of the genetically modular development of cardiac chambers (the independent, regional development of cardiac chambers under distinct genetic control) that the ballooning model of heart development has revolutionised our understanding of normal heart development.

The evolution of endothermic physiology required the efficiency of a four-chambered heart, with two parallel but separate circulations: systemic and pulmonary. The complexity of its development from a single heart tube in the very early fetus allows for little redundancy, and relatively small lesions may compromise metabolic efficiency severely, leading to heart disease and early death. It seems reasonable to assume that most, if not all, congenital heart disease (CHD) stems from errors in the genetic control of heart development, and that the understanding of these controlling molecular mechanisms may allow us to understand the origins of CHD. And with understanding comes the potential of prevention and possibly even early repair.

Some questions arise, however

• If all cells have essentially exactly the same DNA, how is differentiation during development controlled? A nerve cell is fundamentally different from a right ventricular myocyte, which differs markedly from a cell in the sino-atrial node!
• The birth incidence of CHD is approximately 8/1 000, of which 80% is sporadic (non-syndromic): if sporadic CHD is usually not associated with known DNA changes (and is therefore rarely familial) then why do some developmental processes result in CHD?
  • How do teratogens cause the genetic mistakes that lead to CHD?
  • In contrast, how does folate decrease the incidence of CHDs? In Fig. 1 the significant decrease in the incidence of severe CHD followed the introduction of mandatory folate fortification of all flour and pasta in Quebec in 1998.²

The startling decrease in CHD incidence in Quebec, possibly due to folate supplementation, hints at an environmental factor which has an immediate and direct effect on the control of cardiac development without altering the DNA sequence: this is epigenetics. It smacks of witchcraft, but how is it possible?

Epigenetics: a fresh look at developmental control

A recent definition: epigenetics is ‘the molecular factors and processes around DNA that regulate genome activity independent of the DNA sequence and that are mitotically and meiotically stable.’ In other words, the controlling process of DNA transcription and replication may be as important as the actual base pair sequence per se. If the mechanism of control is altered or defective, it may result in serious developmental errors such as CHD. Skinner comments: “The paradigm that genetics is the primary factor to regulate developmental biology is limited and ignores the plasticity to respond rapidly to environment, nor does it explain abnormal development and disease etiology in the absence of genetic alterations.”³

The control of heart development is primarily the function of the T-box transcription factors. These factors directly control gene transcription, but in addition are intimately linked to developmental processes through interactions with epigenetic control complexes. The complexes alter chromatin and histones in a dizzying symphony of modifying and remodelling factors that in turn activate and repress DNA transcription. Teratogenic or other modifications of these (epigenetic) controlling mechanisms can lead to CHD without causing any changes of the DNA sequence. Epigenetic modification may therefore result in a non-mutagenic alteration of the phenotype, potentially causing a heart lesion.

Evidence of the direct links between these gene transcription controls and environmental factors such as teratogens (ethanol, lithium, homocysteine, etc.) is now rapidly accumulating. Simultaneously, the role and mechanism of folate protection against CHD by the epigenetic manipulation and control of developmental pathways is coming to light.

Should it become clear that a significant number of congenital heart lesions are indeed due to altered epigenetic control

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Fig. 1. The significant decrease in the incidence of severe CHD in Quebec after mandatory fortification of grain products in 1998.²
Defibrillation and cardioversion in children: demystifying the shock of shocking

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Health care practitioners looking after children are often uncomfortable about using direct current (DC) shock treatment on a child. This article emphasises practical points when using electrical shock therapy in children, but does not replace the value of attending an APLS course to gain hands-on experience.

The most common life-threatening dysrythmias in children are non-shockable rhythms, mostly due to hypoxia. However, childhood shockable dysrythmias cannot be considered as rare. These include ventricular fibrillation (VF), pulseless ventricular tachycardia (VT) and supraventricular tachycardia (SVT).

Recent reports indicate that as many as 25% of in-hospital cardiac arrests in children and 5 - 22% of out-of-hospital paediatric cardiac arrests are due to VF or pulseless VT. Shockable dysrythmias are more likely to present in children with an underlying cardiac disease, or present as a sudden collapse.

Defibrillation

Defibrillation indicates a DC shock treatment aimed at depolarising a myocardium that is not generating a co-ordinated, perfusing rhythm. Organised QRS complexes cannot be identified and the electrical current is delivered without synchronising with the patient’s native rhythm. DC shock should not be delayed once a shockable rhythm is recognised. The longer the time delay the worse the outcome. CPR should continue while preparing the defibrillator. Care should be taken to clear all involved, and the oxygen should be cleared before discharging the current. CPR should resume (starting with compressions) immediately after the DC shock and continued for five cycles (2 minutes) before the next rhythm check.

Defibrillation energy dose

The optimal and safe defibrillation energy dose in children is unknown. The risk of myocardial damage when using higher electrical currents should be considered against using lower energy but wasting time before achieving a stable rhythm. The International Liaison Committee on Resuscitation recommends an initial dose of 2 J/kg, thereafter 4 J/kg. Evidence suggests that more than 4 J/kg (biphasic defibrillator) is effective and safe. Some defibrillators provide limited manual joule options. When dialling in the weight-based energy on the defibrillator, round the number down to the lower joule setting.

Modern defibrillators deliver biphasic shocks as opposed to monophasic shocks. Biphasic shocks are more effective and cause less myocardial damage. Biphasic currents are delivered in two phases: first a positive current in one direction and then a negative current from the opposite direction. Evidence in adults suggests a survival benefit in single shock versus stacked shocks.

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Transthoracic impedance is the primary determinant of effective energy delivery. Measures to reduce the transthoracic impedance include: firm contact between the paddle and the chest, larger paddle size and electrolyte-containing gel.

Paddles and positions

Paediatric-sized paddles should be used in children under 1 year of age (<10 kg) and adult-sized paddles in those older than 1 year (>10 kg). One paddle should be below the right clavicle parallel to the sternum and the other parallel to the first paddle in the left axilla to optimise the energy transfer. Paddles should be applied firmly, parallel to each other, with at least a 3 kg force applied onto paddles for infants and a 5 kg force for children.

Defibrillation gel reduces the transthoracic impedance. KY jelly, sonar gel, alcohol- or saline-soaked gauze should not be used as alternatives. Take care that the gel does not smear over the chest wall and cause potential arcing (i.e. the current flows over the chest between the paddles and not into the chest). DC shock should ideally be discharged on end-expiration to minimise impedance.

Larger paddles reduce impedance but risk arcing of the current if the paddles are too close. There should be at least 3 cm between the paddles. In the case of a small chest and large paddles, use the anterior-posterior paddle position to prevent arcing: one paddle is placed below the left scapula and the other parallel to the left of the sternum. It does not matter which paddle is placed in which position.

Cardioversion

The terms defibrillation and cardioversion are often wrongly used interchangeably. Cardioversion is applied to a myocardium with an abnormal rhythm that is able to generate a pulse, but insufficient for adequate perfusion. Defibrillation is used when there is no pulse or no perfusing rhythm. Cardioversion is used for patients with haemodynamically unstable SVT, VT (with a pulse), atrial fibrillation and atrial flutter.

The energy dose in cardioversion is less (0.5 - 2 J/kg) than in defibrillation (2 - 4 J/kg). In cardioversion the shock is discharged synchronously with the native R wave of the patient. Without synchronisation, VF can be induced if a shock is delivered during the refractory period of the cardiac cycle. The majority of defibrillators default to unsynchronised mode. It is therefore imperative to reset the synchronisation button before each discharge. Synchronisation with a broad complex VT can be difficult. Choose the lead with the best identifiable R waves. Synchronisation problems must be suspected when the defibrillator fails to discharge after pressing the shock button. In this case use unsynchronised cardioversion.

Children with congenital heart disease are now surviving into adulthood. Unfortunately cardiac surgery leaves atrial scars that may predispose the patient to dysrythmias. Therefore life-threatening shockable dysrythmias will be seen more often in the emergency setting. Healthcare practitioners should aim to deliver the first DC shock within 3 minutes after recognising the shockable arrhythmia.

Suggested reading available at www.cmej.org.za

References and further reading available at www.cmej.org.za

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