Beta-adrenergic adaptation in idiopathic dilated cardiomyopathy: differences between children and adults

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This editorial refers to ‘Beta-adrenergic adaptation in paediatric idiopathic dilated cardiomyopathy’†, by S.D. Miyamoto et al., on page 33–41

The study of Miyamoto et al.¹ found differences in beta-adrenergic adaptation to heart failure (HF) in explanted heart tissue between children and adults with symptomatic dilated cardiomyopathy (DCM). Differences included: (i) down-regulation of beta-1- and beta-2-adrenergic receptors in children but maintained beta-2-adrenergic receptor expression in adults; and (ii), in children, uncoupling of the beta-1-adrenergic receptors and stimulatory G-proteins, among others.¹

An important family of cell surface protein receptors, the G-protein-coupled receptors (GPCRs), enable cells to sense and respond to outside signals. For children with cardiomyopathy and heart failure, we need a better understanding of the structure–function relationships and the detailed regulation of GPCRs, as well as the drugs that stimulate or inhibit these relationships. Understanding beta-adrenergic adaptation in children with HF should indicate how cardiomyocytes interact with their extracellular environment and adapt to new situations, such as when epinephrine acts on cells to increase blood pressure and heart rate.

Miyamoto and colleagues observed that the GPCR signalling system has become the target of prescription drugs, including beta-blockers, to relieve HF.¹ In fact, about half of all medications act on these receptors, so learning about them is key to developing better drugs.

The GPCR initiates a cascade of signals into the cell, prompting it to respond appropriately, as well as a secondary cascade in which a feedback signal leads to desensitization. A molecule called beta-arrestin binds to the GPCR and reduces or temporarily stops GPCR’s sensitivity.

Beta-arrestin, in addition to receptor desensitization, is involved in receptor endocytosis and activating extracellular signal-regulated kinase (ERK) and other mitogen-activated protein (MAP) kinases. GPCRs use two major signalling mechanisms—one mediated through the classical activation of G-proteins and the other through activation of beta-arrestins. The observation that GPCRs signal through G-protein and beta-arrestin pathways has profound implications for understanding cell biology and drug development.

Here, we review differences between children and adults with DCM and emphasize the need to better understand the genetic causes, clinical course, and biomarkers of cardiovascular disease, including beta-adrenergic adaptation (Figure 1).

The course of paediatric cardiomyopathy, regardless of aetiology, is usually progressive; its prevention should occur in children at risk of or with ventricular dysfunction (Figure 1). The identification of cardiomyopathy risk factors helps to identify high-risk populations that through screening may lead to: (i) early diagnosis, institution of disease-specific therapies, and alteration of disease course; and (ii) primary prevention of disease by targeted strategies (Figure 1). Further understanding of adrenergic adaptation in this population will determine its role in defining risk and aetiology.

The developmentally regulated assembly of the ternary complex model of receptor interactions with a GTP-binding G-protein to form a high-affinity receptor–G-protein complex that activates adenylate cyclase is a dynamic process during early cardiac development. This development is characterized by high densities of beta-adrenergic receptors on cardiomyocytes, high levels of adenylate cyclase activity, and high intracellular cyclic AMP concentrations.² In the developing heart, the rate-limiting step for functional beta-adrenergic sensitivity and agonist responsiveness is functional coupling of the G-protein to the GPCR. Before functional coupling, the embryonic heart is insensitive to beta-adrenergic agonist chronotropic and inotropic stimulation.² Therefore, when considering the responses of children and adults with adult HF, normal developmental changes in beta-adrenergic adaptation in children must be considered, in addition to HF changes.

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We have addressed the issue of recommending treatments in the absence of data from clinical trials specifically designed for children with DCM. Miyamoto et al. suggest, ‘that age-related differences in adaptation could influence response to therapy’, which, if true, would shift the paradigm of managing HF in children. Further, the authors state in their letter to the editor in response to reviewer comments that accompanied this accepted manuscript that: ‘The influence of non-selective beta-blockade in the setting of down-regulated beta-2-adrenergic receptors as is uniquely seen in paediatric HF is unknown. Based on the current studies demonstrating multiple differences in cardiac remodelling it is impossible for us to ignore the possibility that the down-regulation of this pro-survival and anti-apoptotic pathway in children with HF might be of pathophysiologic significance. We have attempted to indicate the speculative nature of this hypothesis.’

Although this study should not determine whether beta-blockers or related therapies should be used in clinical care, this new hypothesis is welcome.

The causes and clinical course of cardiomyopathies differ greatly between adults and children. Nearly 40% of children with symptomatic cardiomyopathy undergo heart transplantation or die within 2 years. Outcomes have not improved during the past 35 years, and cardiomyopathy remains the leading cause of cardiac transplantation for children >1 year of age. Cardiomyopathy-related HF mortality in children exceeds the combined mortality rate of all childhood cancers.

Using biomarkers of cardiac signalling to differentiate cardiac health from disease requires that they are validated surrogates for the cardiac endpoints of interest. The lack of a validated biomarker is a limitation of the Miyamoto study, which focuses on end-stage disease.

Serological biomarkers, along with cardiac imaging, are critical in diagnosing heart disease before cardiac remodelling and functional impairment become irreversible. Currently underinvestigated in children with cardiomyopathy are the newer classes of cardiac biomarkers, including some of the markers of adrenergic adaptation used by Miyamoto et al. The matrix metalloproteases, protein ST2, and galectin-3, among others; and other neurohormones and inflammatory biomarkers. Multiple biomarker panels may be more informative than a single biomarker, but all biomarkers must be validated.
Certainly, validated biomarkers of adrenergic adaptation would be relevant to children with cardiomyopathy. In pre-clinical and clinical studies, beta-adrenergic agonist stimulation has resulted in cardiomyocyte injury or death, in addition to tachyphylaxis, receptor down-regulation, and negative inotropic effects, all of which may be harmful.11–13 Further, more than half of children with idiopathic DCM and HF who failed medical management had mitochondrial DNA mutations, deletions, or functional abnormalities, suggesting that common anticongestive therapy with beta-adrenergic agonists may have actually worsened their condition.14–15 This result illustrates the importance of not treating a phenotype but instead emphasizing causal investigations. We took this approach, using pre-clinical models followed by randomized trials in children at risk for DCM, to develop a targeted therapy currently used clinically that minimizes anthracycline cardiotoxicity.9

In contrast to the nearly 20 000 articles on cardiac biomarkers in adults, searches for children with cardiomyopathy found only 44 articles published in the past two decades, mostly single-institution retrospective studies. Much is unknown about cardiac biomarker validity and utility in children with cardiomyopathy. Therefore, the molecular basis of these disorders must be identified.

A primary myocardial disease characterized by ventricular dilation and dysfunction, DCM is one of the most common causes of HF in children, as well as being a leading indication for cardiac transplantation. Current treatment is limited to supportive management or transplantation, with a 5-year mortality of ~50%. More than 30 genes, many of which encode sarcomeric or cytoskeletal proteins, can cause DCM in adults. The prevalence of gene mutations in children with DCM has not been investigated, although some genetic causes are shared.

A high percentage of causative genes in children with cardiomyopathy remain unidentified; the mechanisms underlying the phenotypes, uncertain; and the modifiers of disease severity, poorly understood. Because paediatric cardiomyopathy is a rare and heterogeneous disease, the Pediatric Cardiomyopathy Registry was created to collect longitudinal data on >3500 children with cardiomyopathy in North America.4–8 Despite this robust data set, 60–70% of the diagnoses are ‘idiopathic’. The clinical features predicting death or heart transplant are poorly characterized, although the cause of cardiomyopathy is a factor.4–8 Genetic syndromes, neuromuscular disease, inborn errors of metabolism, mitochondrial disorders, and mutations in genes encoding structural components of the cardiomyocyte all contribute to the genetic heterogeneity.

The use of sarcomeric and cytoskeletal gene testing for clinical evaluation has been productive. The Heart Failure Society of America Practice Guideline recommends cardiac surveillance and genetic testing for possible familial or genetic causes of cardiomyopathy, establishing genetic testing as standard of care. With further genetic evaluation or testing, the phenotypic variability resulting from mutations in genes encoding sarcomeric or cytoskeletal proteins is increasingly recognized. However, most genetic studies on cardiomyopathy in children are case reports or small case series. Classifying mutation pathogenicity, integrating genotype and phenotype information, and identifying susceptibility alleles or modifier genes can only be accomplished with information from large studies with standardized clinical evaluation. Such studies could produce algorithms incorporating genetic information into disease management. Identifying the disease-causing and disease-associated genetic risk factors for paediatric cardiomyopathy would greatly improve prevention, surveillance, early management, and disease course.

Understanding complex inheritance patterns and gene—environment interactions will provide additional information about disease susceptibility and identify children at risk for progression to HF.

In summary, understanding paediatric HF adrenergic adaptation, as well as across the lifespan in health and disease, is essential to determining the function and importance of these pathways and to validate them as biomarkers of subsequent cardiovascular disease. Understanding their function in disease, will enable biomarker use to test the efficacy of primordial, primary, and secondary prevention and to minimize the morbidity and mortality of childhood cardiomyopathy (Figure 1).

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References

