Over the past 2 decades, there have been major advances in understanding the mechanisms by which the heart responds to stress, a process now referred to as either adaptive or maladaptive remodeling.\textsuperscript{1,4} Whereas cardiomyopathies were previously described predominantly by their physiological consequences, such as systolic dysfunction, diastolic dysfunction, dilation, or hypertrophy, we have now developed a detailed understanding of the alterations in cell signaling and cell and tissue remodeling underlying these basic physiological phenotypes.\textsuperscript{6–9} Powerful tools, such as whole genome sequencing and targeted genetic manipulation in the mouse, are rapidly advancing our understanding of the underlying genetic basis of these cellular events and provide further insight into the complex cross-talk between different signaling pathways regulating cardiac function and remodeling.\textsuperscript{10–14} However, even as we solve 1 layer of cellular regulation, new levels of complexity are being uncovered, eg, regulation of gene expression by non-coding RNAs and histone modification.\textsuperscript{15–19}

In a similar time frame, we have seen major advances in the clinical treatment of heart failure. Pharmacological therapies, in particular, the use of \(\beta\)-blockers and angiotensin-converting enzyme inhibitors, have revolutionized the care of adult patients with dilated cardiomyopathy.\textsuperscript{20–23} The addition of resynchronization pacing and the implantable cardioverter defibrillator have further improved transplant-free survival.\textsuperscript{24–26} And for those adult patients with intractable heart failure, the field has seen the equally rapid development of safer and more effective left ventricular assist devices and a total artificial heart, as well, either as a bridge to transplant or as destination therapy.\textsuperscript{27}

However, the cardiovascular challenges faced by infants and children with heart failure are substantially different from those in adults. Whereas ischemic cardiomyopathy comprises the majority of cases of adult heart failure,\textsuperscript{28} ischemia is a rare cause of heart failure in children, where cardiomyopathy is more likely to be of genetic or viral origin, or to develop as a consequence of repaired or palliated congenital heart disease.\textsuperscript{29,30}

Over the same 2 decades, there have been equally dramatic advances in the diagnosis and surgical treatment of congenital heart diseases. Children with even the most severe cardiac malformations, eg, hypoplastic left or right heart syndromes or tetralogy of Fallot with pulmonary atresia,\textsuperscript{31,32} now have an excellent chance of survival following staged palliative surgical procedures. However, despite these surgical successes, many patients with severe cardiac malformations eventually develop either ventricular failure (systolic or diastolic dysfunction) or circulatory failure (eg, complications related to the Fontan circulation)\textsuperscript{33,34} and will require some form of heart failure therapy and eventually cardiac transplantation.\textsuperscript{35} In infants, congenital heart disease currently represents 63\% of transplants, whereas among adolescents this percentage drops to 25\%, and is only 3\% in adults.\textsuperscript{36,37} However, as children with palliated complex congenital heart disease grow into adulthood, the number of older patients with congenital heart disease requiring transplantation will continue to grow. The unique aspects of transplantation in this patient population represent a major challenge to both the pediatric and the adult transplant community.\textsuperscript{38,39}

Unfortunately, research on the mechanisms and therapies for the types of heart failure experienced by children has lagged behind that of adults. Many of the models used to study cardiac failure, particularly ischemia, do not accurately recapitulate the cardiac stresses experienced by children with genetic cardiomyopathies or in patients with congenital heart disease.\textsuperscript{39} The signaling events regulating cardiac remodeling in ischemia may be quite different from those regulating a genetic dilated cardiomyopathy. One example has particular clinical relevance, given the widespread use of \(\beta\)-blocker therapy: whereas \(\beta_2\)-adrenergic receptor signaling has been shown to be cardioprotective in ischemic cardiomyopathy, leading to the suggestion that a combination of a \(\beta_2\)-blocker with a \(\beta_1\)-agonist would be more efficacious than a nonspecific \(\beta\)-blocker alone.\textsuperscript{40} \(\beta_2\)-adrenergic receptor signaling turns out to be detrimental in at least 1 form of genetic cardiomyopathy and also in pressure overload, both conditions more likely to be experienced in the pediatric population.\textsuperscript{41}

There has also been a very left ventricular-centric bias in heart failure research,\textsuperscript{39} whereas many patients who have congenital heart disease experience failure of their right ventricle, either in a normal pulmonary position (eg, tetralogy of Fallot) or in a systemic position (eg, I-transposition of the great arteries, hypoplastic left heart syndrome). Developing a better understanding...
of the similarities and differences between left and right ventricular remodeling and failure is critically important. This point is emphasized by clinical studies that show that many standard left ventricular heart failure therapies (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) fail to improve exercise capacity or cardiac function in right ventricular (RV) failure.42,43 In the largest pediatric clinical trial of a heart failure drug to date, Shaddy et al44 actually found a possible detrimental effect of the β-blocker carvedilol when used in patients with systemic RVs in comparison with those with systemic left ventricles. In another study, the angiotensin-converting enzyme inhibitor enalapril failed to improve ventricular function or somatic growth (a sign of heart failure in children) in patients with single ventricles, the majority of whom had a single RV.45 Thus, the characterization of models of RV failure that more accurately recapitulate the ventricular stresses experienced in patients with congenital heart disease46,47 will be important to advance our understanding of the molecular mechanisms unique to RV remodeling, as similar models have done for the left ventricle. The results of these studies will hopefully lead to new therapies for patients with a vulnerable RV.

The development of nonpharmacological treatments for heart failure in children has also shown unique challenges in comparison with adults. Resynchronization pacing, most useful in adults with left ventricular dysfunction and left bundle-branch block, may have different indications in children, where left bundle-branch block is rare and right or single ventricular dysfunction may be more attractive targets.48,49 Finally, perhaps nowhere else are the challenges of treating children versus adults more evident than in the field of ventricular assist devices. One of the largest challenges to device development for children is the size constraint inherent in using a mechanical device in a small infant. However, the solution to these problems is not limited to just building a smaller version of adult devices, because the risks for complications like thrombosis and stroke appear to increase with miniaturization.50,51 For those patients with a univentricular heart, the complications associated with mechanical assist support are even more daunting. Even if all of these challenges are overcome, implantation of a destination device that can provide an extra 5 to 10 years of quality life for a 65-year-old adult is, at best, a temporizing option for the pediatric population.

The articles making up this series will address, in 3 major areas, several pressing challenges and opportunities facing pediatric cardiologists who care for children with heart failure and after transplantation. Focusing on mechanisms of heart failure, Drs Mark Friedberg and Andrew Reddington will review the physiology of right versus left ventricular failure, suggesting that not all ventricles are built the same. Dr Sushima Reddy will detail several novel models of right ventricular failure that are uncovering differences in gene and microRNA expression and cell signaling between the stressed right and left ventricles. Dr Jeff Towbin will then provide a guide to the testing for genetic cardiomyopathies in the age of rapid and increasingly inexpensive genome sequencing.

Focusing on therapeutics, Drs Joseph Rossano and Robert Shaddy will provide an update on pharmacological heart failure therapies in children, reviewing whether adult medications work in the pediatric population and the potential mechanisms for any differences. Drs Charles Canter and Kathleen Simpson will review the current status of diagnosis and treatment of myocarditis in children. Drs Kara Motonaga and Anne Dubin will summarize the outcomes of cardiac resynchronization therapy for pediatric heart failure and congenital heart disease patients. Finally, Dr Betsy Blume will summarize the experience with pediatric mechanical support devices and review the engineering and regulatory challenges of developing these orphan devices.

A third focus of this series is on transplantation, where Dr Daphne Hsu will review the changing indications for pediatric heart transplantation with a particular emphasis on complex congenital heart disease. Dr Clifford Chin will review transplantation in the highly sensitized pediatric patient, Dr Lori West will review her pioneering work with transplantation across the ABO barrier, and Dr Steven Webber will provide insight into a pharmacogenomic approach to personalized health care for the pediatric patient undergoing heart transplant. Finally, the series will conclude with my review of the current status of stem cell–induced cardiomyocytes and their potential as both diagnostic and therapeutic tools in pediatric cardiology.

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Disclosures

None.

References


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