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*Original Article*

# Assessment and management of the failing heart in children

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Over the last 25 years, the diagnosis, assessment, and management of cardiac failure has changed dramatically. Diagnosis now depends on use of new modalities for imaging, and more recently, on the use of molecular techniques and biomarkers. The latter approaches help in prognosticating, and following the progression of, the failing heart. While the majority of new breakthroughs in the field have been in adults, with the data then extrapolated to the child with cardiac failure, therapies for the child with end-stage heart failure, such as mechanical circulatory support and cardiac transplantation, have also significantly advanced. The purpose of this review is to focus on these new modalities for diagnosis and treatment of cardiac failure as seen in children. It is beyond its scope to present a comprehensive description of the current state of the art in adults. The interested reader is referred to recent reviews and consensus statements on this topic[1–3].

## What's new in diagnosis and treatment of myocarditis?

Myocarditis is an inflammatory process affecting the heart and causing ventricular dysfunction. The inflammation may involve the myocytes, the supporting fibrous matrix, the vascular elements and neural elements, and/or pericardium. It may be an acute or chronic process.[4] In childhood, the most common cause of myocarditis is viral infection of the heart, which is predominantly an acute disorder.[5] These children typically present with cardiac failure of acute onset, cardiovascular collapse, or sudden death. A viral etiology, consistent with chronic myocarditis, can be identified in about one-fifth of cases of chronic dilated cardiomyopathy.

### *What's new in the diagnosis?*

The classic diagnostic criterions for myocarditis rely on the ability to analyze myocardial specimens, such as endomyocardial biopsies, explanted hearts or autopsied hearts, by histopathologic methods. The criterions known as the "Dallas Criteria" require inflammatory infiltrates with or without cellular necrosis, fibrosis and tissue oedema. Staining with haematoxylin-eosin, or Masson's trichrome stains, are standard in their evaluation.[6] In some centres, lymphocyte sub-typing is also used. None of these studies identify the underlying cause of disease, and other major issues with the basic concept are also in question. For instance, it is believed that viral infection is the major cause of myocarditis in children yet, when myocardium is obtained and cultured, it is extremely rare to identify an infectious agent. Hence, peripheral cultures are used as surrogates. These samples, including urine, stool, sputum, blood, and others, are taken to indicate cause-and-effect when culture-positive, although no correlation has ever been demonstrated. Another issue is the relationship of the histopathologic findings with the disease. Do all patients in whom inflammatory infiltrates are identified in myocardial specimens have myocarditis?

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Clearly not. Patients with genetic-based dilated cardiomyopathies commonly have inflammatory infiltrates focally in myocardial specimens. Indeed, many families in which cardiomyopathies occur are diagnosed with familial or inherited myocarditis. There is essentially no data supporting these views. And what about patients in whom a myocardial sample, particularly a biopsy, does not satisfy the Dallas criterions for myocarditis? Have they been excluded from this as a potential disease causing the clinical disorder? It is well appreciated that inflammatory infiltrates are patchy, and that myocarditis may be missed because of issues with sampling.[6] Another key issue, nonetheless, must also be kept in mind, namely the definition of myocarditis itself. The use of inflammatory infiltrates as the diagnostic sign of myocarditis is based on the belief that the disorder is primarily inflammatory, and that inflammatory disease must lead to infiltrates. Both of these assumptions have limited scientific basis. It is certainly possible, and in fact likely, that the infiltrates are nothing more than late responders to a primary insult, such as a viral infection of the myocardium. The central role that this finding has in the diagnosis, therefore, is problematic. There are other important issues. How do we know that inflammation in any way is a primary part of the disease? The use of cellular markers, such as cytokines, lymphocytic markers, and the like, are not definitive.[7] Many key inflammatory markers are down-regulated and are dependent on which virus is causative. Hence, the identification of the inciting virus or other factor becomes critical. Recently, criterions were published for performing endomyocardial biopsies.[8] In the case of suspected myocarditis, these criterions strongly suggested biopsy and the performance of polymerase chain reaction for known causes of myocarditis. These viruses, which include adenovirus, parvovirus B19, enteroviruses including coxsackievirus, cytomegalovirus, and Epstein-Barr virus, amongst others, can all be analyzed by the use of the polymerase chain reaction to identify the viral genome within the heart.[5,9] This reaction is a process of molecular amplification that enables the specific amplification of genomic nucleic acid. When added to a procedure for identification, this allows for identification in the reference specimen. In the current era, this method should be standard.

### *What's new in treatment?*

Very little has changed over the years in terms of treatment. Therapy to date focuses on the clinical signs and symptoms of cardiac failure, cardiovascular collapse, and arrhythmias. Supportive care is provided with inotropic agents and anti-arrhythmics, and, when necessary, devices such as those providing ventricular assistance and extracorporeal mechanical oxygenation. Targeted therapy with antiviral agents or vaccines has not become common place. Some centers continue to use steroids despite the lack of supportive data.[10] The use of intravenous gamma globulin is not universally agreed upon, as limited supportive data currently exists. More recently, particularly in Europe, the use of interferon therapy has been studied. While this option is supported by the enthusiasts, it has yet to become commonplace. Hence, a trial is needed to test these various agents in children.

Thus, while the diagnosis of myocarditis in childhood has moved into the molecular era, therapy has remained stagnant. The outcomes of treatment in children rely, to some extent, on early diagnosis and therapeutic intervention. When necessary, devices should be considered for use prior to the occurrence of life-threatening events. Novel diagnostic and therapeutic options require the community of paediatric cardiologists to work to develop trials in order to make progress with this important problem.

## Tachycardia-mediated and pacemaker-mediated cardiomyopathies

There are two important causes of dilated cardiomyopathy induced by an abnormal cardiac rhythm, namely tachycardia-mediated cardiomyopathy and pacemaker-mediated cardiomyopathy.

### *Tachycardia-mediated cardiomyopathy*

The concept of a cardiomyopathy resulting from a tachyarrhythmia was recognized several decades ago through observations that induced tachycardias, as well as chronic clinical tachycardias, could result in ventricular dysfunction which could be reversed when the arrhythmia was controlled.[11–13] Although the mechanism of tachycardia-mediated cardiomyopathy is not completely understood, experimental studies have demonstrated disturbed cellular anatomy and physiology.[14] Clinically, the absolute heart rate and duration of tachycardia are thought to be important determinants of the development of signs and symptoms of congestive cardiac failure. An arrhythmia with an average rate greater than 140 beats per minute is thought to have an increased association with the development of cardiomyopathy. Automatic ectopic atrial tachycardia, and orthodromic reciprocating tachycardia due to a slowly conducting accessory pathway, are the most common causes of tachycardia-mediated cardiomyopathy in children. Chronic atrial fibrillation and ventricular tachycardia are less common causes in this age group.

In the experience at The Children's Hospital of Philadelphia, we identified 23 children who

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presented with congestive cardiac failure, left ventricular dysfunction, or fetal hydrops due to supraventricular tachycardia over the period 1989 through 2004. Almost four-fifths of these children presented at less than 6 months of age, including 5 who presented prenatally. In two-thirds, there was a delay in diagnosis. Most of the young patients had orthodromic reciprocating tachycardia in association with Wolff-Parkinson-White syndrome, while the most common arrhythmic mechanism for the older children was an automatic ectopic atrial tachycardia. All but one patient had complete resolution of ventricular dysfunction.

Overall, full recovery of ventricular function is the rule with good control of the abnormal rhythm. This may be accomplished with medications or catheter ablation therapy. The time course to full resolution is variable, with more severe and long-standing cases needing longer. If complete resolution of the cardiomyopathy does not occur, a secondary arrhythmia related to an end-stage cardiomyopathy should be considered.

### *Pacemaker-mediated cardiomyopathy*

This cardiomyopathy can be defined as left ventricular or systemic ventricular dysfunction secondary to nonphysiologic ventricular activation and contraction due to repetitive, artificial pacing stimulation. Due to accessibility, for decades the heart has been paced from the right ventricular apex as the standard technique. The studies proposing potential mechanisms for pacemaker-mediated cardiomyopathy are summarized in Figure 1.

Abnormalities of echocardiographic indexes of cardiac function and performance have been found in studies of children. In one study measuring echocardiographic parameters of function in children with structurally normal hearts who had been paced for an average of 9.5 years, and comparing them to age-matched controls,[15] a significant decrease was noted in left ventricular fractional area of change, as well as an abnormal left ventricular index of myocardial performance. Another study compared patients with congenital complete heart block with chronic right ventricular pacing to age-matched controls.[16] Based upon echocardiographic and exercise data, patients who were paced had increased measures of dyssynchrony, abnormal morphologic changes, increased left ventricular end diastolic diameter, and lower exercise capacity.

Affects of right ventricular pacing on clinical outcome have been studied in large, prospective trials in adults.[17,18] As the frequency of right ventricular pacing increased, endpoints of death or congestive heart failure increased. Relevant studies in children have looked at the incidence of late onset dilated cardiomyopathy in patients with congenital

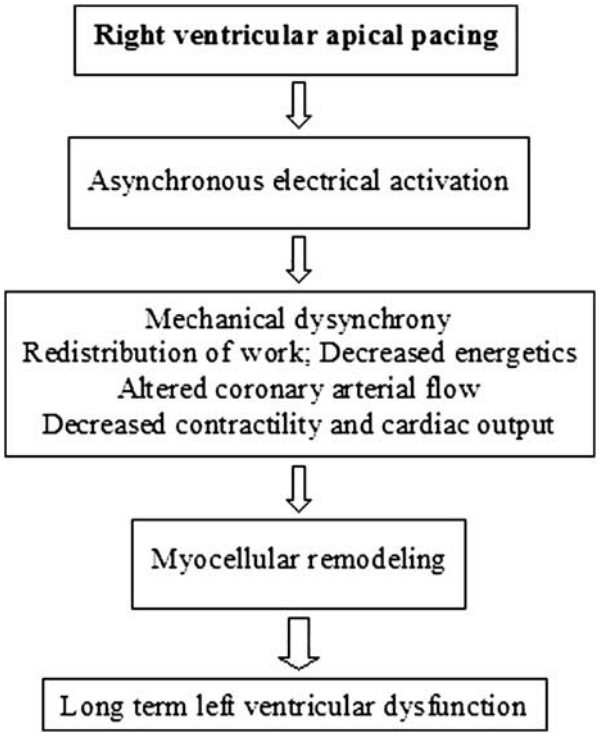


**Figure 1.**
*The proposed mechanisms for pacemaker-induced cardiomyopathy.*

complete heart block.[19–22] In these patients, cardiac structure and function are generally normal, with long term pacing required. Dilated cardiomyopathy was noted in about five percent of the children over the first two decades. Potential risk factors for the development of late onset cardiomyopathy, however, were not evaluated.

At The Children's Hospital of Philadelphia, we are following 70 patients undergoing pacing for congenitally complete heart block. After a mean pacing duration of 6.5 years, one-tenths have developed a dilated cardiomyopathy, with one going on to cardiac transplantation, and two receiving upgrades to biventricular devices. The remaining patients are treated medically. Only pre-existing cardiac failure was a risk factor for late onset of dilated cardiomyopathy. The incidence of a dilated cardiomyopathy developing in patients without pre-existing heart failure was approximately 5%. Thus, the incidence of clinically relevant pacemaker-induced cardiomyopathy is relatively low in the first and second decades of pacing. In addition, the interaction of pacing with pre-existing myocardial dysfunction may accelerate the potential development of an induced cardiomyopathy.

## Imaging in children with cardiac failure

Echocardiography is a tool widely used to quantify ventricular function. Systolic dysfunction is a powerful

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predictor of cardiac symptoms and outcomes in both adults and children with congestive cardiac failure and dilated cardiomyopathy. Important considerations for the systematic evaluation of the many tools available for measuring ventricular function are:

- Accuracy, in that the measurement should be validated in comparison to a gold standard
- Reproducibility, in that the measurement should have acceptable reproducibility between studies, different observers, and the same observer
- Load independence, in that changes in the measurement should reflect changes in contractility rather than changes in loading conditions
- Geometry independence, in that the measurement should be valid regardless of ventricular morphology, size or shape and
- Prognostic capability, in that the measurement should be predictive of outcomes.

Measurements may be grouped into two broad categories. The first depends on indexes for the phase of ejection. These measurements are dependent on assumptions regarding ventricular geometry, and are inherently load-dependent.

### *M-mode: fractional shortening*

*Accuracy:* While M-mode fractional shortening is performed almost universally as a measurement of left ventricular function, its accuracy cannot be validated because there is no gold standard which would permit calculation of this value, which is fundamentally a derived number.
*Reproducibility:* In a large study, the agreement found between local and core laboratories was marginal.[23] For example, a measurement of 32% measured by the core laboratory could be reported as low as 22% and as high as 40% in the local laboratory. This reflects a high degree of inter-observer variability.
*Prognostic capability:* The technique passes this test in that a recent large study of children with dilated cardiomyopathy demonstrated it to be an independent predictor of subsequent death or the need for transplantion.[24]

### *Ejection fraction measured by cross-sectional echocardiography*

*Accuracy:* This technique is fair at best in adults, and has not been validated in children.[25,26]
*Reproducibility:* No data is available for use in children
*Prognostic capability:* In keeping with data from adult studies, the technique has been shown to be an independent predictor of hospitalization, death or transplantation for children with dilated cardiomyopathy.[27]

The other broad category is made up of the Doppler indexes. These measurements examine time intervals and velocities of the flow of blood and movement of myocardium as a means of evaluating ventricular performance. These methods are inherently independent of ventricular geometry.

### *The myocardial performance, or Tei index*

Ventricles perform two types of work, namely the work involved in isovolumic contraction and relaxation, and the work needed for ejection. A healthy ventricle expends proportionately less time doing isovolumic work, and more time doing ejection work. As the ventricle begins to fail, it expends increasingly more time doing isovolumic work and less time doing ejection work. The Tei index is the ratio of isovolumic to ejection times, which increases as the ventricle fails.
*Validation, accuracy and reliability:* No data is yet available for children.
*Load-independence:* It has been shown[26] that the index does not change following relief of right ventricular pressure or volume overload, thus suggesting that it is load-independent.
*Prognostic capability:* In a controlled study of children with dilated cardiomyopathy,[27] it was found that the Tei index for neither the right or left ventricle was predictive of the need for hospitalization or transplantation, or a predictor of death.

### *The mitral valvar dP/dT*

This is a measurement made using continuous wave Doppler of the maximum rate of increase in left ventricular pressure during ventricular systole. It is an attractive measurement because most patients with congestive cardiac failure have quantifiable mitral regurgitation. As the ventricle fails, this number should decrease.
*Validation:* The index has been validated in adults by comparison to measurements obtained during cardiac catheterization.[28]
*Reproducibility:* No data is available for children.
*Prognostic capability:* While dP/dT has been shown to be predictive of hospitalizations and mortality in adults with dilated cardiomyopathy and congestive cardiac failure,[29,30] there is no data available concerning its prognostic capability in children.

### *Myocardial velocities*

The concept underlying the measurement of tissue Doppler velocities is that the movement of the atrioventricular junction reflects global ventricular function. Validation of these measurements would be difficult. These measurements have been shown to be reproducible.[26] There is conflicting data on

the load-dependence of tissue Doppler parameters in adults, and little to no data in children.[26,31–34] The technique is inherently independent of ventricular geometry, and has been shown to have prognostic capability in children not only with dilated and hypertrophic cardiomyopathy,[27,35] but also for left ventricular non-compaction.[36]

*Recent advances*

Over the past three years, three dimensional echocardiography has evolved into a practical bedside tool for quantifying left ventricular volume and ejection fractions. Early data on the validation of this method, in children as well as adults, and in functionally univentricular as well as biventricular hearts, is encouraging.[37–39] The technique has also been proven to be feasible in a clinical environment, and shown to have excellent reproducibility.[40] The application of quantitative three-dimensional echocardiographic techniques has revealed a strong association between left ventricular dysfunction and intra-left ventricular dyssynchrony.[41] It is conceivable that the application of this technique could improve our ability to customize pacing strategies for children who have dysfunction and dyssynchrony.

## What's new in diagnosis and treatment of the failing heart in children?

The search for biomarkers that correlate with imaging assessments of ventricular function and clinical outcomes of heart failure is a recent focus of the field. Natriuretic peptides have become standard-of-care for the diagnosis and prognostication of heart failure in adults and in children. Both b-type natriuretic peptide and N terminal pro-brain natriueretic protein have been extensively studied, with the most recent work being done to determine their predictive value. A recent study randomized adults who presented to an emergency room with dyspnoea to have the levels of the N terminal protein measured in the serum in addition to routine diagnosis and treatment.[42] The addition of this biomarker resulted in a significant reduction in duration and cost of the visits to the emergency department, and the number of recurrent hospitalizations. When reviewing the experience in a single centre with measuring levels of brain natriuretic peptide in children with cardiac failure due to left ventricular dysfunction seen as outpatients, the levels of the protein were shown to be predictive of adverse events.[43]

Treatment of cardiac failure in adults and children can be divided into pharmacologic as opposed to electrophysiologic therapies. The current class I recommendations for the pharmacologic treatment of cardiac failure in adults include diuretics for fluid overload, inhibitors of angiotensin converting enzyme, blockers of beta-adrenergic receptors, antagonists of aldosterone, and blockers of the angiotensin receptors for those intolerant to the inhibitors themselves.[1] Almost all guidelines are based on the results of large clinical trials of adults. Such a recent study in adults demonstrated that inhibitors of angiotensin converting enzyme cause a significant reduction in cardiac events, including arrhythmias, cardiac failure and death, in those who developed cardiotoxicity after administration of anthracyclines.[44] Spironolactone, and more recently eplerenone, have been shown to improve survival in adults with moderate-to-severe cardiac failure.[45,46] Another recent study suggested that the addition of spironolactone to candesartan improves left ventricular remodeling in adults with mild-to-moderate failure.[47] In contrast, a recent update on a clinical trial of eplerenone showed no effect on left ventricular remodeling.[46] Nesiritide, a recombinant form of human brain natriuretic peptide, promotes natriuresis and diuresis, acts as a vasodilator, and antagonizes the renin-angiotensin-aldosterone system. Initial studies with this agent showed that it reduced cardiac preload and dyspnoea in adults.[47] Subsequent metanalysis raised concern of increased renal dysfunction and mortality in adults who received nesiritide.[48] A more recent trial reported no benefit of nesiritide compared to placebo on a composite of all-cause mortality and cardio-renal hospitalization in adults.[49] When used in children, however, there was no evidence of increased renal dysfunction or mortality, but a marked improvement in the acute clinical condition of those in cardiac failure when receiving the drug.[50] More recently, results were published of the prospective, randomized trial of carvedilol in children with cardiac failure. Although the study showed no benefit of carvedilol compared with placebo on a composite endpoint of clinical outcomes, analysis of subgroups suggested a possible differential effect on those with a systemic left ventricle compared with those whose systemic ventricle was not morphologically left.[51]

Electrophysiologic therapy with cardiac resynchronization and implantation of cardioverter-defibrillators have both gained widespread popularity in adults, and are both now class I recommendations for the treatment of selected patients with symptomatic cardiac failure.[1] A new area of intense investigation is the definition of dyssynchrony, in order to be able to identify those that could benefit from resynchronization. Dyssynchrony has become an increasingly complex concept, requiring definition of electrical as opposed to mechanical dyssynchrony, and systolic

versus diastolic dyssynchrony.[52] A recent study showed that adults without electrical dyssynchrony, having narrow QRS complexes on their electrocardiographic traces, but with echocardiographic evidence of mechanical dyssynchrony, failed to benefit from resynchronization.[53] Although resynchronization is currently a class I recommendation for selected adults with mild-to-moderate heart failure, adults with severe failure have also been shown to benefit both from resynchronization and implantation of cardioverter defibrillators.[54] The indications for both of these therapies in children, however, remain speculative.

## What's new in cardiac transplantation

The year 2007 marked the 25th anniversary of transplantation of the heart for children. The era began in 1982, with the discovery of cyclosporine as an effective immunosuppressive agent. Survival of children subsequent to transplantation has been steadily improving by era during this period of 25 years, most significantly in the early postoperative period (Fig. 2).[55] Survival at 6 months after transplantation has improved from 74% to 90% from the earliest era, 1982 to 1989, to the most recently reported era, 2000 to 2005. Experience with selection of patients and postoperative management in the intensive care unit are likely the major contributors to this decrease in early mortality.[56,57]

This year also marked the publication of the tenth annual report of the Registry of the International Society of Heart and Lung Transplant for cardiac transplant in children, which includes data on almost 5,000 recipients worldwide from 1982 to the present.[58] Access to the full report is publically available at www.ishlt.org. New in the analysis this year is the report of complications observed in paediatric recipients with 10 or more years of follow-up. Hypertension is common, reported in almost three-quarters of those surviving 10 years, with hyperlipidemia also having a significant prevalence of almost two-fifths. While renal dysfunction is certainly a concern in long-term survivors, the prevalence of severe renal dysfunction in long-term follow-up was less than 2%. The risk of coronary vasculopathy, which is the most common reason for retransplantation and the cause of many deaths, was 16.7% at 10 years, significantly less than that observed in adults.

Significant differences in terms of survival have been observed based on age at time of transplantation.[59,60] The median survival of the graft, or the so-called half-life, was 15.8 years for those transplanted during infancy, 14.2 years for children,

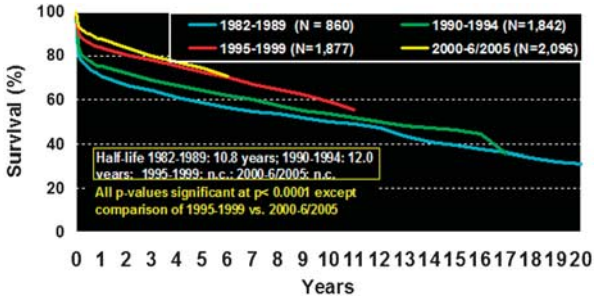


**Figure 2.**
*Kaplan-Meier Survival by Era for cardiac transplantation in children as revealed by the data from the pediatric heart transplantation registry of the International Society for Heart and Lung Transplantation (J Heart Lung Transplant 2007; 26: 796–798).*

and 11.4 years for adolescents across all eras. Those transplanted during infancy showed a bimodal curve for survival, with higher early mortality but seemingly lower late mortality than the older cohorts. The increased early mortality may be related to the increased incidence of congenital cardiac disease, which is an independent risk factor for death at 1 and 5 years. Whether the differential long term survival represents a true form of tolerance of the graft for infants versus the insurmountable problem of nonadherance in the teens, or some combination of these effects, is unknown.

The identification of populations shown to be at high risk for potentially modifiable risk factors that affect long-term survival is now the focus of many recent investigations. Examples of this are an increased focus on the presensitized recipient, and immune-mediated effects on the graft. Exposure to nonself human lymphocytic antigens occurs via homograft materials used during surgical procedures for congenitally malformed hearts, multiple exposures to blood products, ventricular assist devices, and previous transplantations, all of which are increasing in frequency among children being referred for transplantation. At the time of transplantation, a mismatch between donor and recipient for human lymphocytic antigens can result in a reaction between pre formed antibodies and the donor graft, resulting in a positive donor specific cross-match. A positive cross-match has been associated with damage to the transplanted heart via a cascade mediated by complement, the effects of which are not limited to the early postoperative period. Increased risks of rejection, graft vasculopathy, graft dysfunction, and mortality have been associated with presence of alloantibodies and positive cross-match in large studies of adults. In the past year, there has been at least 6 reports from single centres concerning outcomes of the sensitized

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child undergoing cardiac transplantation.[55–57,61] Decreased survival of sensitized as opposed to nonsensitized candidates was reported by 4 of the 6 centres. Increased rejection was observed in half the studies. In one centre, an increased incidence of graft vasculopathy was noted in the presensitized population. A multicentric clinical trial sponsored by the National Institutes of Health to study further the influence of immunologic factors on outcomes in children subsequent to cardiac transplantation is currently being formulated.

A noteworthy event on the theme of sponsored clinical trials in children is the trial of the Berlin Heart EXCOR® Pediatric Ventricular Assist Device. This device is a miniaturized pneumatic paracorporeal implant now available in sizes suitable for infants and small children. There have been 96 devices implanted in the United States of America between July 2000 and May of 2007 under regulations for emergency compassionate use. The multicentric prospective single arm trial is to determine the risk-benefit profile of the device as a potential alternative to extracorporeal oxygenation for infants and small children requiring long-term mechanical circulatory support.[62] Comparison is to a historical control group of children bridged to transplant with extracorporeal oxygenation. Included in the approval granted by the Food and Drug Administration for this trial is the provision of a relatively streamlined procedure for providing the device under the regulations for compassionate use in centres not actively participating in the trial.

Another exciting advancement is being made worldwide with increasing experience of transplantation of incompatible hearts in terms of ABO blood groups. The strategy depends on transplantation of hearts from incompatible donors successfully into infants who have yet to develop isohaemagglutinins, which typically occurs at about 1 year of age.[63] The pioneers of this approach recently reported follow up data from their initial cohort of infants, who underwent transplantation from 1995 through 2006,[64] showing a reduced mortality whilst awaiting transplantation, with comparable outcomes up to 4 years subsequent to transplantation. Similar findings have been reported in the experience of such transplantation in the United Kingdom.[65] Again there was reduced mortality whilst awaiting transplantation, without any adverse events noted for transplantation across blood groups. This ongoing work of transplantation between apparently incompatible donors and recipients, in the realms of both clinical practice and research, is not only providing insight into the unique nature of the infant immune system, but also into the mechanisms of graft tolerance, which represents the leading edge of transplantation medicine.

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