Clinical and Molecular Comparison of Pediatric and Adult Reverse Remodeling with Ventricular Assist Devices

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Introduction

The last decade has witnessed great advancement in ventricular assist device (VAD) technology for adult patients with end-stage heart failure. Adult patients can now be supported with a variety of implantable, continuous-flow VADs (2nd and 3rd generation pumps) based on the individual need. The field of pediatric VAD, however, has lagged behind the adult counterpart.[1] The only VAD currently used in small children worldwide is an extracorporeal, pulsatile-flow VAD (1st generation), which is associated with a higher risk of device-related complications.[2] Although a miniaturized implantable VAD specifically designed for small children is on the horizon,[3] the 1st generation pulsatile VADs will continue to play an important role in children for the time being. While pulsatile VADs are inferior in terms of complication rates, they have several potential advantages over continuous-flow VADs – the most significant being a possible higher potential of cardiac recovery.[4] This potential is based on the anecdotal experience that cardiac recovery was seen more frequently in the old era when 1st generation pulsatile VADs were predominantly used in adult patients. While pediatric cardiomyopathy patients rely on pulsatile VADs, seeking treatment strategies to achieve cardiac recovery in children has significant clinical potential. This is particularly true considering the palliative nature of heart transplantation owing to inherent limitations from immunosuppression.

In reality, however, cardiac recovery through favorable myocardial alterations from mechanical unloading, termed ‘reverse remodeling,’ has gained much less attention in children than in adults. There has been a paucity of data in the pediatric population at both basic research and clinical levels, and a growing body of literature suggests that simply extrapolating adult therapies are ineffective.[5–8] With these considerations in mind, we conducted this literature review with two specific aims: 1) to summarize clinical cases of pediatric patients with end-stage heart failure who exhibited cardiac recovery following VAD support, and 2) to analyze genetic changes of pediatric myocardium induced by VAD support compared to those observed in adult patients.

Differences Between Pediatric and Adult Cardiomyopathy

VADs are implanted to provide mechanical circulatory support to heart failure that may have numerous causes including hypertension, ischemic heart disease, and valvular disease.[9] Among pediatric patients, the most common aetiology is cardiomyopathy, with one-third of cardiomyopathies requiring transplantation or progressing to death.[10] A high majority of pediatric cardiomyopathy cases are classified as primary cardiomyopathies (>80%) and the remainder as secondary cardiomyopathies that are associated with involvement of other organ systems.[11,12] Within primary cardiomyopathies, dilated cardiomyopathy (DCM) is the most common form (50%), followed by hypertrophic cardiomyopathy (HCM) (40%). [13–15] The incidence of DCM in the first year of life is tenfold higher than in older children and carries a worse prognosis,[2] consistent with the biphasic age distribution of patients in North America at either a median age of 1.5 years or between 20 and 50 years.[13,14,16] The Pediatric Cardiomyopathy Registry reports an annual incidence in infants and children of 1.13 cases per 100,000, which is less prevalent than the annual incidence in adults of 40 cases per

100,000.[12,13] DCM can be of familial, non-genetic, or idiopathic origins.[15] While there is evidence of bridge to recovery by VAD in non-DCM and ischemic cardiomyopathy patients,[9,17–21] a majority of the scientific and clinical pediatric VAD studies found in our review process report data almost solely from nonischemic DCM patients, so this review focuses on DCM pediatric and adult data to establish a consistent basis for comparison.

Two studies have found pathological differences between DCM in pediatric patients and DCM in adult patients that demonstrate disparate molecular responses to VAD support. On the molecular level, Hsia et al. provided the first evidence suggesting that the extracellular matrix phenotypes of pediatric DCM are unique from that of adult DCM.[22] Comparing ten pediatric (age 9 ± 5 years, range: 2-14 years) and 20 adult (age 62 ± 3 years, range: 57-68 years) idiopathic DCM patients, they found lower total myocardial collagen content in pediatric samples, consistent with higher levels of collagenase matrix metalloprotein-8 (MMP-8) and gelatinase MMP-9 alongside increased IL-1b, IL-2, and IL-8 interleukin levels. In contrast, levels of MMP-3 and MMP-7 were reduced in pediatric DCM compared to adult DCM, underscoring differential induction pathways.

A more recent study from Miyamoto *et al.* in 2012 was the first to show that beta-adrenergic receptor and adrenergic signaling pathways adapt differently in pediatric heart failure compared to adults.[8] The study analyzed explanted left ventricular tissue from failing hearts with nonischemic idiopathic DCM (22 adult samples of mean age 48 ± 2 years, 31 pediatric samples of mean age 4 ± 1 years) in comparison to unused organ donors as controls (25 adult samples of age 49 ± 3 years, 12 pediatric samples age 6 ± 1 years). Based on mRNA and protein analyses, key results unique to the pediatric LV samples were down-regulation of both β_1 -adrenergic receptor and β_2 -adrenergic receptor expression, an attenuated decrease in cAMP, and no increase in protein phosphatase 2A (PP2A) and PP1 β expression. Overall, these observations indicate that pathological gene regulatory responses to DCM in pediatric hearts are different from those in adult hearts.

Clinical Series of Pediatric Ventricular Assist Device

We identified ten clinical articles reporting on long-term pediatric VAD support (Table 1). All series had a small proportion of patients (ranging from 5% to 73%) who were weaned off from support following cardiac recovery. For instance, Hetzer and colleagues reported their experience with pediatric VAD at the German Heart Institute between 1990 and 2004, during which they saw sufficient cardiac recovery in 15% of pediatric VAD patients (9 out of 62) to wean them device support.[23] In another article, Blume and associates examined the Pediatric Heart Transplant Study database that contained data from 23 pediatric heart transplantation centers in North America to report that 5% of pediatric VAD patients (5 out of 99) were explanted following VAD implantation.[24]

Table 1. Prospective and retrospective clinical reviews of pediatric LVAD support reporting outcomes of bridge to recovery (BTR) and bridge to transplantation (BTT). Days, months, and years are abbreviated as d, m, and y.

Year	Authors (<i>et al.</i>)	Date of Cases	Pediatric Patients (#)	BTR (%)	BTR (#)	BTT (#)	Mean Age at Implant	Mean Support Duration	Most Common VAD Type
2001	Reinhartz[25]	1999 to 2001	58* (12)	10%	6	35	13.8y (7-17y)	47d (0-434d)	Thoratec VAD
2006	Blume[24]	1993 to 2003	99* (22)	5%	5	77	13.3 y* (2d-7.9y)	Long term: 70d (1-465d) Short term: 9.4d (0-80d)	Thoratec VAD
2006	Hetzer[23]	1999 to 2004	28	21%	6	13	3y (2m-17.5y)	53.2 ± 83.9d	Berlin EXCOR
2009	Imamura[26]	2001 to 2008	21* (5)	10%	2	16	4.1 ± 4.1y	42.2 ± 41.6d	Berlin EXCOR
2010	Zimmerman[6]	2004 to 2009	11	73%	8	0	1.7y (0.08-6y)	12.7d (6-22d)	Berlin EXCOR
2011	Fan[27]	1999 to 2009	56* (14)	21%	12* (8)	24* (23)	3.6y (12d-14y)	55d (1-432d)	Berlin EXCOR
2011	Morales[28]	2000 to 2007	73* (19)	7%	5	51	2.1y (12d-17.8y)	BTT: 1.6m (1d-7.7m). BTR: 3.1m (19d-5.5m)	Berlin EXCOR
2011	Ihnat[29]	2004 to 2009	13	62%	8	1	19.2m (1m-6y)	12.5d (2-23d)	Medos, Berlin EXCOR, Jostra
2012	Valeske[30]	1997 to 2001	11* (6)	18%	2	3	2y (20d-11y)	9d [§] (0.5-30d)	Medos EXCOR
2012	Valeske[30]	2006 to 2011	17* (3)	24%	4	7	8y (95d-19y)	30d [§] (8-283d)	Berlin EXCOR

*Number includes cardiomyopathies other than dilated cardiomyopathy, which are quantified in parentheses.

[§]Number is a median because mean was not reported.

Out of the ten reports, only three articles, from Zimmerman *et al.*, [6] Ihnat *et al.*, [29] and Morales *et al.*, [28] provide information about etiology and support duration specific to the patients who are weaned off VAD support. For the other seven reports, it is uncertain whether the functional cardiac recovery seen in these recovered patients represents myocardial recovery truly from reverse remodeling, in other words myocardial recovery from alteration in

myocardial structure. Additionally, some pediatric heart centers use long-term VADs even for acute etiologies of heart failure such as acute myocarditis that are often recoverable processes. Recovery from acute etiologies of heart failure should not be confused with reverse remodeling since the purpose of VAD support in those settings is to stabilize the circulation until the inflammatory storm subsides, which typically occurs within 2 weeks, and not to alter myocardial structure, which should take months.

The reports from Zimmerman *et al.* and Ihnat *et al.* are exceptional in a sense that the incidences of recovery are substantially high compared to other reports at 72% (8 out of 11 patients) and 62% (8 out of 13 patients) respectively.[6,29] It must be noted that the mean support duration in these studies are short: 12.7 and 12.5 days for Zimmerman and Ihnat *et al.* respectively. In this regard, careful interpretation is necessary to determine if their series represent true myocardial recovery because the support durations are too short for significant structural changes.

In contrast, the other seven articles in Table 1 report smaller incidences of VAD support bridging to recovery: from 5% to 24%. Despite the lack of detailed information on the patients who were weaned from the VAD support, the articles in Table 1 as a whole demonstrate that most of pediatric heart centers utilizing a VAD have seen some “recovered” patients in their series. An important but unsolved question is whether or not these recovered patients represent cardiac recovery truly from reverse remodeling.

Clinical Cases Describing Cardiac Recovery from Reverse Modeling in Children

We also conducted a literature review of case reports that describe successful weaning from VAD support in children to identify clinical cases that represent cardiac recovery truly from reverse remodeling. Compared to aggregate studies, case reports provide more detailed clinical information about etiology and support duration. In an attempt to exclude cases of recovery from acute illnesses, we used search criteria requiring the application of a long-term device for support durations longer than one month. Surprisingly, even with an extensive literature search, we identified only 4 case reports that met our criteria.

The first report is by Hoashi and colleagues from Osaka, Japan where there has been a severe shortage of donor organ supply.[31] Under these circumstances, Osaka University Hospital developed a protocol for VAD weaning,[32] and all patients on VAD at their institution were routinely screened for possible recovery of cardiac function. The patient reported was an eleven-year old male with DCM implanted with the Toyobo left ventricular assist device (LVAD) (Toyobo, Osaka, Japan), which is a device for adult patients. Histology of the left ventricle (LV) apical core showed moderate interstitial fibrosis and no inflammatory cell infiltration, consistent with a diagnosis of chronic cardiomyopathy. Within the first month of LVAD support, the patient showed LV functional improvement. It must be noted, however, that even after functional improvement, the LV ejection fraction remained low. LV ejection fraction during and after VAD support was in the range of mid to high 30's. The LVAD was explanted after 118 days of support, and this report was written at four months of follow up during which the patient had been clinically stable. Approximately a year after explantation, however, this patient deteriorated again (personal communication). He was placed on LVAD support once more and eventually bridged to transplantation. The observations of this case

demonstrate that the use of LVAD can improve the function of a severely dysfunctional heart to the extent of discontinuing LVAD support. Such functional recovery, however, does not necessarily guarantee sustained cardiac function.

The second report is from our own institution by Lowry *et al.*[7] A fourteen-year-old, previously healthy male with a history of septic arthritis with *methicillin-resistant Staphylococcus aureus* developed multisystem organ failure. The organs involved included the heart, lungs, kidneys and liver. After a prolonged period of intensive care, his end-organ functions recovered except for the heart. He remained inotrope- and ventilator- dependent due to persistently depressed cardiac function with an LV ejection fraction around 15%. Despite maximal medical therapy, he was unable to be weaned from inotropic and ventilator support. He was implanted with the HeartMate II (Thoratec) 5 months into his hospitalization. The LV histology showed only mild interstitial edema and minimal, patchy interstitial fibrosis, along with no evidence of an inflammatory process. After LVAD placement, his LV ejection fraction improved significantly and continued to improve (49% at 3 months post LVAD, 50% at 4 months, and 59% at 5 months). BNP was decreased from 4,735 (pg/mL) preoperatively to less than 100 postoperatively. After 176 days of device support, he was successfully explanted. His cardiac function remained normal during the follow up period of 30 months, and he has yet to have recurrence of heart failure symptoms.

The other 2 reports from Jones *et al.*[33] and George *et al.*[34] are similar. Both of these cases described infants suffering from severe heart failure due to acute myocarditis. The two patients were initially supported with ECMO as rescue therapy and subsequently transitioned to long-term VAD support using the Berlin Heart EXCOR. Histological investigations of the LV core showed severe inflammation with myocardial loss or injury. During prolonged periods of support, cardiac function significantly improved until reaching a normal range. At 120 and 152 days of support respectively, the VADs were removed. Although long-term follow-up information is not available for these cases, a difference between these cases and the first case reported by Hoashi *et al.* is that full functional recovery was achieved, whereas the case by Hoashi exhibited only partial recovery as evidenced by a persistently low LV ejection fraction (<40%).

Molecular Mechanisms of Reverse Remodeling in Children is Different from Adults

Since pathological genetic mechanisms of DCM are different between pediatric and adult patients, the genetic changes of reverse remodeling by VAD in children and adults may also be different. We examined the gene expression analysis of VAD implantation in pediatric nonischemic DCM patients from Mohapatra *et al.*,[5] which was the only pediatric data we could find, and compared its limited data against corresponding adult results.

Mohapatra *et al.* analyzed the pre- and post-LVAD expression profiles of 326 genes that have been reported to be differentially expressed in cardiomyopathy and after long-term LVAD support in adult myocardium such as dystrophin and the pro-apoptotic cytokines TNF- α and caspase-3.[5] Pre- and post-LVAD LV myocardial biopsies were obtained from 4 end-stage DCM patients (Table 2) , in which LVAD implantation lasted from 8 to 16 days before transplantation. As controls, normal myocardial tissue was also obtained from 5 infants aged 1

to 3 years who died of non-cardiac disease. The mRNA levels of all samples were analyzed by quantitative real-time polymerase chain reaction (QT-PCR), and total proteins were isolated by Western blot. Protein remodeling was also assessed by immunohistochemistry.

Table 2. Demographics of Mohapatra *et al.* pediatric samples.[5]

Patient No.	Age (mo.)	Gender	Diagnosis	Duration of Heart Failure	Duration of LVAD
1	54	M	Idiopathic DCM – Chronic myocarditis	6 wks	8 d
2	10	M	LV non-compaction	2 wks	8 d
3	4	F	Familial DCM	4 mo	16 d
4	25	F	Idiopathic DCM	3 mo	10 d

Between the pre- and post-LVAD hearts, 109 out of the 326 genes were differentially expressed, with 59 changing more than two-fold. However, the changes were not consistent between genes of related functions, and a portion of gene expression levels changed towards disease-associated states rather than healthy states. While multiple cytoskeletal genes were upregulated, desmosomal proteins were downregulated. The heart failure marker neuro peptide Y was downregulated even though secretogranin II associated also with heart failure was upregulated. Calcium-binding proteins and second signaling pathway proteins, cell growth and differentiation genes, and extracellular matrix remodeling proteins were all upregulated. These differential gene regulations indicate that remodeling by LVAD is not a uniform reversal of molecular disease traits.

Mohapatra *et al.* examined dystrophin's protein levels in addition to its mRNA levels and found a discrepancy. Microarray analysis detected no changes in dystrophin gene expression while immunostaining and western blot analysis indicated an upregulation of dystrophin protein amount. Similar discrepancies between gene and protein levels have been observed in molecular studies of adult myocardial reverse remodeling, suggesting that intermediary factors of mRNA localization, translation efficiency, and posttranslational protein modifications prevent direct correlation of gene expression data to phenotypes.[35,36]

In addition, a significant decrease in B-type Natriuretic Peptide (BNP) levels was measured between pre- and post-LVAD placement in two of the patients for whom the measurement was available. As a biomarker indicating mechanical loading stress,[37] decreasing BNP levels support the clinical observation of decreasing intracavitary dimensions along with symmetrical wall thickening.[6,38] The decrease in BNP levels was consistent with the periodic BNP decrease reported by Hoashi *et al.*[31] in an eleven-year-old male during LVAD support. While clinical data clearly show functional myocardial recovery, the underlying molecular changes are discrepant and require more study to understand how they relate to reverse remodeling.

Comparison of Current Pediatric and Adult Reverse Remodeling Data

Adult Studies of Remodeling after VAD are Abundant Relative to Pediatric Studies

In contrast to the lack of studies on LVAD-induced reverse remodeling in children, there are numerous studies examining the myocardial reverse remodeling process in adult heart failure patients. The findings are summarized in numerous recent reviews,[9,39–41] and the normalizing impact of LVAD support in partially reversing the remodeling of a failing heart has been found to be a complex process with molecular, structural, functional, and electrical aspects.[9] Observing the differences between As molecular aspects of DCM are different from those of adults, knowledge of reverse remodeling in adults should not be applied to children. To better understand the difference between pediatric and adult reverse remodeling, we compared existing LVAD gene expression data from children and adults.

Gene Expression Changes in Pediatric Heart Oppose Changes in Adult Heart.

Referencing reported data, we compared the changes in mRNA levels post-LVAD relative to pre-LVAD of 24 genes in pediatric and adult DCM patients to find that there are changes in pediatric gene expression that oppose those in the adult heart (Table 3). Adult data for 30 of the 54 (55.5%) differentially expressed genes reported by Mohapatra *et al.*[5] could not be found,[1,36,42–48] owing to either papers not reporting examined genes that show insignificant pre- and post-LVAD changes or a lack of examination. The pediatric data of Mohapatra *et al.* does not report genes found to be unchanged in their pediatric patients.

Out of the 24 genes compared, 9 (37.5%) are oppositely regulated between children and adults, 7 are regulated in the same direction, and 2 are not regulated in adults. Opposite regulation of multiple genes support that pediatric and adult failing hearts respond differently to LVAD support. Furthermore, 8 out of those 9 (88.9%) oppositely regulated genes are upregulated in the pediatric heart. Examining the functions of the oppositely regulated genes in relation to DCM does not reveal any pattern in this upregulation. Contrary to the expectation of reverse remodeling, half of the upregulated genes (4 out of the 8) are positively associated with heart failure (Table 4).

Table 3. Comparison of fold changes in gene expression between pediatric and adult heart.

Official Gene Symbol ^a	Gene Name	Pediatric Fold Change ^b	Comparison	Adult Fold Change ^b	Reference
<i>Cytoskeletal Proteins</i>					
ACTC1	Actin alpha, cardiac muscle	2	Opposite	-1.12	[36]
LMCD1	LIM and cystein-rich domain 1	2.03	Opposite	-5.14	[36]
OBSCN	Obscurin	3.6	Same	1.57	[36]
ITGB1	Integrin B1	-2.18	Same	-1.27	[36]
ANKD2	Ankyrin repeat domain 2	2.44	Same	1.52	[36]
LMO1	LIM domain only 1	3.25	Same	1.7	[49]
CAV3	Caveolin 3	-2	Pediatric Only	None	[1]
<i>Desmosomal proteins</i>					
DSG2	Desmoglein 2	-2.55	Opposite	1.49	[36]
DMN	Desmuslin	2	Same	1.44	[36]
DLL1	Delta-like 1	2.51	Same	1.39	[36]
<i>Calcium homeostasis</i>					
CALR	Calreticulin	37.7	Opposite	-1.4	[36]
CNN1	Calpoinin, basic, smooth muscle	4.27	Opposite	-3.72	[36]
<i>Second signaling pathways</i>					
DUSP1	Dual-specificity phosphatase 1	2.2	Same	1.52	[36]
<i>Cell growth and differentiation</i>					
FOS	V-fos oncogene	4.66	Same	2.37	[36]
JUNB	JunB protooncogene	24.2	Same	1.61	[36]
<i>Inflammatory cytokines</i>					
IL3	Interleukin-3	3.42	Same	1.6	[36,42]
ANGPT1	Angiopoietin	3.12	Same	1.31	[42]
IL6	Interleukin-6	-4.96	Opposite	1.62	[36]
CCL2	Chemokine motive 2	2.1	Opposite	-6.1	[36]
NPPB	Natriuretic peptide precursor B	9.7	Opposite	-3.76	[36]
FASLG	Fas ligand	2.16	Pediatric Only	Variable	[50]
<i>Extracellular remodeling</i>					
MMP9	Matrix metalloproteinase 9	2.64	Same	1.18	[36]
CYR61	Cystein-rich, angiogenic inducer, 61	2.64	Same	1.82	[36]
FN1	Fibronectin	3.5	Opposite	-2.28	[36]

^a Official gene symbols are provided by the HUGO Gene Nomenclature Committee (HGNC).

^b Fold change of mRNA level in post-LVAD sample relative to pre-LVAD sample. All pediatric gene expression fold changes are referenced from Mohapatra et al. while adult data is from referenced studies.

Table 4. Functions of genes oppositely regulated upon LVAD support between pediatric and adult heart and their relation to dilated cardiomyopathy (DCM). Gene expression changes are from Table 3.

Gene Symbol	Gene Name	Encoded Protein Function	Relation to DCM	Pediatric Change	Adult Change
ACTC1	Actin alpha	Sarcomere component, with mutations affecting sarcomere contraction [51]	Mutations of the gene associated with familial DCM [52]	Up	Down
LMCD1	LIM and cystein-rich domain 1	Regulates calcineurin/nuclear factor of activated T cells signaling pathway [53]	Increased LMCD1 expression augments cardiac fibrosis and promotes expression of fibrotic mediators [53]	Up	Down
DSG2	Desmoglein 2	Cadherin that mediates desmosomal adhesion [54]	DSG2 polymorphism associated with shortened desmosomes of cardiac intercalated disk is a risk variant for DCM [55]	Down	Up
CALR	Calreticulin	Calcium binding protein [56]	Levels of calreticulin not different in nonfailing and failing human myocardium [56,57]	Up	Down
CNN1	Calponin	Binds to thin filament proteins calmodulin and actin [58]	Increased expression female heart failure patients but not in male heart failure patients [59]	Up	Down
IL6	Interleukin-6	Cytokine exerting negative inotropic influence on myocardium [60]	Plasma levels of IL6 elevated in DCM [60]	Down	Up
CCL2	Chemokine motive 2	Chemoattractant for mononuclear cells, eosinophils, basophils, natural killer inflammatory cells [61]	Downregulated in DCM [60]	Up	Down
NPPB	Natriuretic peptide precursor B	Precursor to B-type natriuretic peptide released in response to myocyte stretch, relaxing vascular smooth muscle [62]	Elevated in DCM [63]	Up	Down
FN1	Fibronectin	Composes extracellular matrix and cellular basement membrane, with increase indicating progressive fibrosis [64]	Increased by 5-fold in DCM [64]	Up	Down

Pediatric Cardiomyopathy Patients May Have Greater Potential Than Adult Patients for LVAD-induced Reverse Remodeling

We propose that the pediatric heart may have a greater capacity for reverse remodeling than the adult heart. Three reasons for this expectation proposed by Zimmerman *et al.* are that pediatric hearts have: a smaller size for decreased mechanical load, shorter time from onset of heart failure and LVAD implantation, and reestablishment of the collagen skeleton once ventricular size normalizes.[6] Compared to pediatric cardiomyopathy patients, adult patients have mature hearts with less plasticity, and they often present with advanced heart failure from multiple years of DCM.[16] An additional factor that could influence increased reverse remodeling capacity in the pediatric heart is a higher percentage of human cardiac progenitor cells or stem cell types such as mesenchymal stem cells that promote myocardial regeneration.[65] Resident human cardiac progenitor cells have been demonstrated to be most abundant in the neonatal period, decreasing three-fold by two-years of age.[65] Two more possibly advantageous mechanisms of the pediatric heart include decreased apoptosis,[66] which is consistent with the observed decrease in pro-apoptosis cytokines,[5,50] and the potential for hibernating myocardium that recovers from chronic contractile dysfunction upon reperfusion.[67]

Conclusion

Fundamental molecular differences have been demonstrated between pediatric and adult cardiomyopathy, specifically in the myocardial extracellular degradation pathway[22] and adrenergic receptor signaling pathways of nonischemic DCM[8] that may explain the tendency for reverse remodeling in the LV to be more accelerated in pediatric patients.[22] From the comparison of Mohapatra *et al.*'s pilot study to adult studies, we observed that changes in gene expression from VAD support are significantly different between pediatric and adult nonischemic DCM patients.

Overall, the exact alterations in VAD-unloaded pediatric hearts are still poorly understood, and future studies should target the pediatric heart's molecular responses to LVAD unloading, covering changes in gene regulation, protein levels and possibly mRNA localization, translation efficiency, and posttranslational protein modifications or interactions.[36] Comparison of molecular traits in pediatric patient populations that undergo successful bridge-to-recovery to those in unsuccessful cases, following the example of adult studies,[21,68] would provide insight into improving bridge-to-recovery management of pediatric cardiomyopathy. Biomarkers identified for pediatric heart failure provide a starting point for pathophysiological pathways to analyze.[69] Studies on adult cardiomyopathy populations highlight the difficulty of collecting myocardial sample sizes large enough to make statistically significant conclusions,[70] so multi-center studies would help provide the statistical power needed to make conclusive observations of the vast molecular changes in reverse remodeling. A further understanding of the specific mechanisms and time frames involved in pediatric remodeling on VAD support would lead to improved therapeutic strategies, increased use of VADs as a bridge to recovery, and a decreased need for pediatric heart transplants.

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Conflict of Interest

None declared.

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