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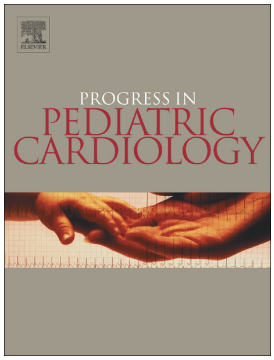

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Cardiac Rehabilitation in Pediatric Cardiomyopathy

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Abstract

Pediatric cardiomyopathies affect a small portion of the pediatric population, but the constellation of disorders encompasses a wide range of symptoms and disease severity. Medical and surgical therapies have continued to advance, and combined with increasing data from adult studies, cardiac rehabilitation likely has an important role in the care of these children as data shows benefits ranging from improved endothelial function to improved quality of life. While there are limited guidelines for exercise training and sports participation in children with cardiomyopathy, data to shape these guidelines remains sparse and the cardiomyopathy community is dependent upon expert opinions. Cardiac rehabilitation has been shown to be both feasible and safe although the studies are small and predominantly based on inpatient subjects with dilated cardiomyopathy which limits the applicability to other forms of cardiomyopathy and outpatient programs. Finally, multiple limitations exist to studying this area, but they are not insurmountable, and the evolution of technology may allow for innovative use of wearable technology to overcome some of these limitations.

Keywords: pediatric, cardiomyopathy, cardiac rehabilitation, exercise

Introduction

Pediatric cardiomyopathies are rare diseases affecting 1.1-1.5 per 100,000 children, [1, 2] and can be categorized as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (AVRC), and left ventricular non-compaction cardiomyopathy (LVNC). While the etiologies of these diseases can range from genetic to toxic exposures, the cause is idiopathic for nearly two-thirds of children with a form of cardiomyopathy.[2-4]

Current therapies for cardiomyopathies are targeted towards improving cardiac function, preventing or controlling arrhythmias, and minimizing cardiac symptoms, but heart transplantation remains the definitive therapy for progressive disease. Treatment of children with cardiomyopathy has followed adult heart failure trials as there has been only one pediatric heart failure medication trial.[5-8] Furthermore, as reported in a review from the Pediatric Cardiomyopathy Registry (PCMR), children with heart failure are frequently undertreated, with only 66% receiving angiotensin converting enzyme inhibitors and even fewer (4%) treated with beta blockers within the first month after diagnosis.[9] Nevertheless, recent data from this PCMR suggest that survival has improved in the current era, despite a persistently high rate of heart transplantation which has not decreased in the most recent era.[10]

The benefits of exercise training are well established for healthy adults. However, there is a paucity of data regarding the benefit and feasibility of exercise training in pediatric cardiomyopathy patients. This work looks to expand upon the discussion of cardiac

rehabilitation and exercise training in pediatric cardiomyopathy patients at the 4th International Conference on Cardiomyopathy in Children.

Current Recommendations

The goals of pediatric cardiac rehabilitation should be to improve the child's functional capacity, quality of life (QOL), increase lean mass compared to fat mass, increase overall physical activity, educate the child and family to adopt a healthy lifestyle, symptom recognition and management, and decrease risk of future cardiovascular disease.[11] In attempting to achieve these goals, cardiac rehabilitation should be tailored to each individual patient and is typically composed of 3 separate components—aerobic, resistance, and flexibility training. These categories of training have been previous described[11] as have the principles of an exercise prescription, including the F.I.T.T. Principle (Frequency, Intensity, Time, and Type).[12] Despite the limited amount of research, the International Society for Heart and Lung Transplantation has developed guidelines and recommendations for exercise training and activity in pediatric heart failure patients.[7] (Table 1) However, these recommendations are predominantly aimed at determining risk factors prior to participation and are based on expert opinion.

In contrast to these goals and recommendations, physicians and exercise physiologists often have to weigh the benefits of cardiac rehabilitation versus the risks associated with the underlying disease process. To this end, the 36th Bethesda Conference Reports (Task Forces 1 and 4) and the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for the diagnosis and treatment of HCM may provide helpful reference in

determining not only who can and cannot participate in an exercise program, but also to what degree of physical activity children can participate in.[13-15] While HCM and ARVC have specific recommendations to help guide care teams, the guidelines for disease including DCM, LVNC, and RCM are much vaguer given the lack of research to impact the recommendations. While the risk profile for these latter diseases is likely variable, data does not exist to guide clinicians regarding who can safely participate in the most strenuous activities. This lack of guidance, combined with perceived risks of arrhythmia, exertional syncope, and sudden death, can lead to variability in degree of exercise restriction as shown by Christian *et al.*[16] This study surveyed 45 cardiologists and found considerable variation in exercise restrictions for patients with inherited arrhythmogenic conditions (including HCM and ARVC). They found that factors influencing provider recommendations included phenotype, type of exercise, the chosen guideline, and the physician level of activity.

Furthermore, with changes in the Centers for Medicare and Medicaid services coverage of cardiac rehabilitation for patients with chronic heart failure with reduced ejection fraction, there are practical recommendations regarding exercise for adult patients with heart failure[17] although it is unclear that these will extend into the pediatric population.

Utility of Exercise Testing

While not studied in all cardiomyopathy populations, cardiopulmonary exercise testing has been shown to predict risk for death and heart transplantation in children with DCM. Giardini *et al.* studied 82 children with DCM and found that peak heart rate, peak VO_2, and peak blood pressure

were all associated with increased risk for death or transplant, but on multivariate analysis, the study found that only peak $VO_2 \leq 62\%$ of predicted had a higher rate of death or heart transplant at 24 months (50.6% vs. 4.4%, hazard ratio of 10.8).[18] Chen *et al*, demonstrated similar outcome predictions in children with DCM, but expanded their outcomes to also include heart failure hospitalization and initiation of mechanical circulatory support as well. They found lower peak predicted heart rate, lower blood pressure response, lower predicted peak oxygen consumption, and higher minute ventilation/carbon dioxide production slope were associated with adverse outcomes in children with DCM.[19]

While cardiopulmonary exercise testing has been shown to be predictive of outcomes, it is also more difficult to perform in certain populations. However, a 6 minute walk test is a less sophisticated test but can easily be administered and performed in wide population of patients, including those that may not be able to participate in a formal cardiopulmonary exercise test. A recent study in children with DCM demonstrated that a higher % 6 minute walk test resulted in lower risk of death or transplantation and a 6 minute walk test <63% predicted for age- and gender-specific normal values had a lower 2 year transplant-free survival (73% vs. 92%, p=0.003).[20] Given the ability to easily administer this test, it may serve as a useful test in the serial follow-up for patients with cardiomyopathy, but these results have not been validated in other pediatric cardiomyopathy populations.

Feasibility

Cardiopulmonary exercise testing has been shown to be feasible in children with cardiomyopathy and heart failure.[18, 19] However, there are only limited reports of feasibility of cardiac rehabilitation or exercise training in pediatric cardiomyopathy populations. McBride *et al.* demonstrated that inpatient low-intensity aerobic training was both safe and feasible in pediatric patients with cardiomyopathy was possible while waiting for transplantation.[21] Of note, sixteen cardiomyopathy patients were included and the majority (n=15) had DCM. In this study, 83% of the participant sessions were completed and they experienced no episodes of hypotension or significant arrhythmias. In addition, as ventricular assist devices take on an increasing role in the management of pediatric heart failure patients awaiting heart transplantation, two studies have been able to show that cardiac rehabilitation is not only feasible in this population, but also beneficial.[22, 23] Neither of these studies, and no studies to date, have demonstrated the impact on long-term outcomes or post-heart transplant outcomes.

Potential Benefits of Exercise

The benefits of exercise training have been demonstrated in healthy adults, as well as for patients recovering from ischemic injury, cardiac surgery, and following heart transplantation.[24-29] Cardiac rehabilitation and physical activity has also been shown to impact cardiac biomarkers. Asymmetric dimethylarginine (ADMA) has been linked to impairment in endothelial function and nitric oxide production.[30] Elevated ADMA levels have been shown to correlate with cardiac decompensation in congestive heart failure patients, major cardiac events, and all-cause mortality.[31] Tsarouhas *et al.* demonstrated that a 12 week walking program (40 minutes, 5 days per week) resulted in a decrease in ADMA, in addition to improved heart rate recovery and perceived QOL in patients with congestive heart failure.[32] In addition, Legallois *et al.*

demonstrated significantly improved coronary endothelial function in adults with non-ischemic DCM when 12 weeks of cardiac rehab was combined with medication optimization.[33] Adult studies have also demonstrated improved N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, which are correlated with ventricular function, as a result of aerobic training.[34]

In a recent randomized control study, Saberi *et al* examined the impact of an unsupervised cardiac rehabilitation program on adult patients with hypertrophic cardiomyopathy. Aerobic exercise training was initiated at a frequency of three times per week, 20 minutes per session, with a moderate intensity of 60% heart rate reserve and was carried out over 16 weeks. This program was shown to increase peak VO_2 by 1.27 mL/kg/min among participants, reduce the burden of premature ventricular contraction, and improve physical function QOL scores.[35] Furthermore, no major adverse events occurred in this study and exercise training was not associated with increased rates of nonfatal arrhythmias. Limitations to this study include relatively normal left ventricular ejection fraction inclusion criteria, >55%, potentially limiting the translation of moderate-intensity exercise training to broader populations from a safety perspective. No home-based studies have been expanded to the pediatric cardiomyopathy population.

It has also been shown that exercise and cardiac rehab impact QOL, particularly in children. Children followed in a cardiomyopathy clinic were found to have lower QOL scores, including total QOL score, physical summary score, and psychosocial summary score.[36] In addition, activity restrictions also result in decreased health-related QOL in children with congenital heart

disease.[37] This can likely be extrapolated to children with cardiomyopathy who have activity restrictions implemented for the reasons previously discussed. There is extremely limited data to assess the impact of exercise on QOL in pediatric cardiomyopathy patients. A small case series demonstrated improved QOL in two patients, both 7 years old, undergoing a 12 week cardiac rehabilitation program.[11] Larger studies have shown that exercise training not only resulted in improved cardiopulmonary status, but also QOL in pediatric patients with congenital heart disease, including Fontan palliation.[38-40]

These findings are in addition to the known benefits of improved strength, flexibility, and decreased risk of future cardiovascular/metabolic diseases. Given these constellation of benefits, it is reasonable to think that cardiac rehabilitation programs may be an important part of the medical therapy for patients with various forms of cardiomyopathy—not just for the physical benefits, but also for the emotional benefits.

Challenges and Innovation

Successful implementation of a cardiac rehabilitation program poses several challenges. First, these are often small populations at individual institutions. Combined with the fact that cardiac rehabilitation programs require infrastructure support, dedicated and committed staff (including exercise physiologists, physical therapists, and cardiologists with an interest and experience in both pediatrics and cardiac rehabilitation), dedicated facility space, and the ability to track outcomes, the development of such a program can prove to be a costly endeavor for a small patient population. This limitation could be somewhat mitigated by expanding the program to

include not only patients with congenital heart disease, but also other patient populations that suffer from cardiopulmonary diseases, such as neuromuscular disorders or chronic respiratory illnesses. In addition, multicenter collaboration could not only help pool limited resources, but would help in the study of outcomes and impact of cardiac rehabilitation in these populations. Development of basic exercise protocols that could be implemented based on pre-participation baseline cardiopulmonary exercise testing could also benefit smaller programs that may not be able to invest in a full inpatient and outpatient cardiac rehabilitation program. Finally, partnering with adult facilities that have a significantly more experience with cardiac rehabilitation may be beneficial for adolescent patients if feasible based on age, diagnosis, and comfort level of providers.

Even in the outpatient setting, this often requires patients and families to travel to a tertiary care center several times per week, resulting in increased stress to the family, potential lost school days, and potential lost work days for caregivers. Adult studies have demonstrated that home-based cardiac rehabilitation programs can be as successful as center-based programs in short-term follow-up, although the choice to participate in these home-based programs may be limited by patient choice and availability.[41] Two relatively recent studies report safe and feasible home-based programs in the pediatric Fontan population and successfully utilized data from accelerometer and Fitbit® technology to track activity. A pilot study by Jacobsen *et al*. demonstrated improved exercise capacity at 12 weeks in patients 8-12 years old and improved parent-proxy report health-related QOL scores.[42] Longmuir *et al*. followed patients over a 2 year period and reported both improved gross motor skills and physical activity following either education or exercise prescription intervention groups.[43] Perhaps as our experience grows with

center-based programs and expansion of successful templates from other congenital heart disease populations occurs, home-based pediatric cardiomyopathy rehabilitation programs may become a possibility.

While some may view the lack of research involving cardiac rehabilitation in pediatric cardiomyopathy patients as a limitation, given the ever-expanding era of technology, this is a field that may lend itself to innovative research opportunities, such as wearable technology. Wearable activity trackers, such as those manufactured by Garmin®, Fitbit®, and Jawbone®, may have a role in cardiac rehabilitation. These devices use accelerometers to track activity levels, and many are now able to monitor heart rates and estimate energy expenditure. While some devices have displays that allow the user to monitor their activity parameters, others may only be able to display the information when downloaded to a computer or paired to a smartphone, and most have the potential to upload data to a web-based interface that could be utilized to monitor compliance and participation. Studies have compared these devices to research-grade accelerometers, and while there is correlation, the accuracy is variable.[44, 45] Correlations have also been shown in healthy children[46] as well as those with congenital heart disease.[47] Again, there have not been studies to validate their use in the pediatric cardiomyopathy population, but there is an adult trial currently enrolling subjects to evaluate the use of a personal activity tracker to assess exercise capacity in adults following acute coronary syndrome,[48] and they have been shown to have potential research interest in coronary microvascular dysfunction.[49] Other adult studies have called into the question the validity of these devices, particularly for use exercise prescriptions.[50] At this time, the role of these devices in the study of the pediatric cardiomyopathy population is unclear, but given the potential

challenges and limitations in performing cardiac rehabilitation in these children, combined with the technological savvy skills of today's youth, it warrants further consideration and ongoing investigation.

Conclusion

Pediatric cardiomyopathies are a heterogeneous group of diseases but affect a small portion of the population. As such, data guiding the implementation and impact of cardiac rehabilitation on this population is strikingly limited. Despite this, few guidelines do exist, and they are based on expert opinion. There are likely multiple benefits of cardiac rehabilitation in this population, ranging from microscopic to psychological, although ongoing research is necessary to fully define these benefits. However, the benefits have to be weighed against the potential risks for each patient. Finally, the limited research provides an opportunity for multicenter collaboration, as well as the implementation of evolving technology to try to overcome the limitations identified.

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Table 1. Exercise training and activity recommendations for children with heart failure (adapted from ISHLT guidelines for management of pediatric heart failure)[7]

Recommendation	*Class*	*Level of Evidence*
Pre-participation health screening and risk stratification should be performed before initiating a program of exercise training to identify children at risk for adverse events during exercise.	I	C
Pediatric patients with HF should undergo cardiopulmonary exercise testing (age ≥6–8 years) before initiating exercise training to determine exercise capacity, assess risk for adverse events, and determine suitability for exercise training.	I	C
If deemed safe, exercise training in a supervised setting should be prescribed as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF.	I	C
An exercise-training program should be individualized to the patient's ability and the patient's response to exercise, with an emphasis on safety. Recommendations for a supervised exercise program should include the frequency, intensity, time, and type of exercise.	IIa	C
Medical contraindications to an exercise-training program should be assessed. Detection of children at risk for sudden death and appropriate recommendations for a defibrillator as a primary or secondary intervention is essential before initiating an exercise program or increasing the frequency, intensity, or duration of a current program.	IIa	C
Informed consent from parents and/or assent from the child should be obtained at each session for exercise training.	IIa	C
Exercise training for children with HF should be performed by personnel with expertise in pediatric exercise physiology and in a facility with the ability to monitor vital signs and perform cardiopulmonary resuscitation.	IIa	C

HF – heart failure

Highlights: Cardiac Rehabilitation in Pediatric Cardiomyopathy

- Pediatric cardiomyopathies are rare but have a wide range of disease severity
- There is limited data to guide both exercise and cardiac rehab in these pediatric patients
- Cardiac rehabilitation has been showed to be feasible and safe in very small case series
- Evolving wearable technology may help facilitate home rehabilitation in these children