Neuromuscular-Associated Cardiomyopathy: Assessment and Management in the Modern Era

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This is to acknowledge that Pradeep Mammen, MD has disclosed that he does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mammen will not be discussing off-label use of FDA-approved drugs.

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Scientific Expertise: In keeping with Dr. Mammen's clinical interest in the treatment and management of patients with heart failure, he is keenly interested in the molecular mechanisms underlying skeletal and cardiac myopathies. Dr. Mammen runs a NIH R01-funded molecular laboratory with a long term goal of enhancing our understanding of how regulation of the metabolic and redox states of myocytes can be modulated to serve as potential therapeutic targets for various skeletal and cardiac myopathies. He also serves as the Co-Director with Dr. Eric Olson of the UT Southwestern Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, one of six NIH funded centers in the country.

Purpose & Overview

The muscular dystrophies represent an array of inherited myogenic disorders involving mutations and dysregulations of a variety of cytoskeleton or nuclear proteins. Many muscular dystrophy patients also develop a concomitant cardiomyopathy. Due to an enhanced understanding of the underlying pathogenesis of many of the muscular dystrophies and advances in neurological and pulmonary care, the primary mode of death today in many of these patients is cardiovascular in nature. However, despite the high incidence of cardiomyopathy in many muscular dystrophy patients there is limited data regarding optimal management of the underlying cardiomyopathy. Therefore, the objective of this Medical Grand Rounds is to enhance ones understanding of the assessment and management of neuromuscular-associated cardiomyopathy.

Educational Objectives

1. Recognize the high prevalence of cardiomyopathy in neuromuscular patients.
2. Recognize emerging clinical data supporting the management of DMD-associated cardiomyopathy.
3. Assess and manage neuromuscular-associated cardiomyopathy.

Introduction

The neuromuscular disorders represent an array of inherited myogenic disorders involving mutations and dysregulations of a variety of cytoskeleton, mitochondrial or nuclear proteins. Skeletal muscle is particularly susceptible to injury due to genetic mutations in one of these proteins[1, 2]. Thus, these mutations result in progressive muscle degeneration/regeneration which ultimately leads to loss of muscle fibers and subsequent replacement with fatty tissue and fibrosis. Similarly, many of these inherited myogenic disorders also effect the respiratory as well cardiac muscles resulting in restrictive lung disease as well as cardiomyopathy. Unfortunately to date, there is no definitive therapy to reverse or cure neuromuscular disorders. Thus, the associated morbidity and mortality in patients with neuromuscular disorders is very high.

Due to an enhanced understanding of the underlying pathogenesis of many of the neuromuscular disorders and advances in neurological and pulmonary care over the past 2 decades, the primary mode of death today in many of these patients is cardiovascular in nature. However, despite the high incidence of cardiomyopathy in many neuromuscular patients there is limited data regarding optimal management of the underlying cardiomyopathy.

Neuromuscular Disorders

Neuromuscular disorders represent a heterogeneous group of genetic diseases due to mutations in an array of genes resulting in variable age of onset and clinical presentations. Advances in molecular genetics have enabled the medical community to make definitive diagnoses, which has enhanced our understanding of the underlying pathophysiology of these disorders. The particular genetic mutation drives the clinical phenotype of patients with neuromuscular disorders. Listed below are examples of various neuromuscular disorders grouped by the location of the genetic defect:

1. Mutations within the dystrophin–glycoprotein complex: Duchenne/Becker muscular dystrophy, limb-girdle muscular dystrophy, and X-linked dilated cardiomyopathy.
2. Mutations within the nuclear lamina: Emery Dreifuss muscular dystrophy.
3. Unstable repeat expansion within introns: myotonic dystrophy.
4. Mutations within mitochondrial proteins: mitochondrial myopathies.
5. Glycogen storage disorders: Pompe Disease.
6. Mutations within the extracellular matrix: Bethlem myopathy, collagen VI-associated myopathies, congenital muscular dystrophy, and Ullrich congenital muscular dystrophy.
7. Miscellaneous mutations: Facioscapulohumeral muscular dystrophy and Friedreich ataxia.

The frequency of cardiac involvement in patients with neuromuscular disorders is variable but it is not insignificant. The development of cardiomyopathy and/or conduction disease (AV block or atrial/ventricular arrhythmias) are the most common cardiovascular abnormalities that occur in patients with neuromuscular disorders[3-5]. The true incidence and prevalence of cardiovascular complications amongst this patient population is often

difficult to accurately determine and the assessment is hampered by a number of factors including the following:

1. Low prevalence of inherited myogenic disorders amongst the general population.
2. Lack of obvious clinical signs and symptoms of cardiovascular disease due to the limited mobility amongst patients with neuromuscular disorders.
3. Lack of awareness amongst a board range of physicians (including internists and adult cardiologists) of the extent of associated cardiovascular disease in neuromuscular patients.

Of the known 519 genetic causative mutations resulting in neuromuscular disorders, the dystrophinopathies have the highest mortality rate due to complications related to the development of cardiomyopathy[6]. Although there is a paucity of evidence-based medicine regarding the management of neuromuscular-associated cardiomyopathy, there is emerging clinical data providing guidance in the management of dystrophinopathy-induced cardiomyopathy. Therefore, in the following sections we will focus on the dystrophinopathies, in particular Duchenne muscular dystrophy (DMD), and outline the clinical evidence supporting the current practice of managing DMD-associated cardiomyopathy. We will conclude by extrapolating this approach to the clinical management of neuromuscular-associated cardiomyopathy.

Dystrophinopathies and Duchenne Muscular Dystrophy

The dystrophinopathies are muscular dystrophies involving mutations within the dystrophin gene that results in partial or complete absence of dystrophin expression within the myocyte. The dystrophinopathies include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and X-linked dilated cardiomyopathy.

Duchenne muscular dystrophy is one of the most well characterized muscular dystrophies. DMD is an X-linked recessive neuromuscular disorder resulting from a mutation in the dystrophin gene and it affects 1 in approximately 3,500 to 5,000 live male births. There are over 3, 000 known mutations within the dystrophin gene that can cause DMD. Regardless of the specific site of the mutation, the subsequent loss of dystrophin expression within skeletal muscle leads to a cycle of muscle degeneration and regeneration[2, 7]. Over time there is a decreased capacity to regenerate muscle in response to degeneration due to a decrease in the number of myogenic progenitor cells and the life-span of skeletal myoblasts[8-11]. The continual cycle of muscle degeneration and regeneration results in the development of progressive muscle wasting and atrophy[2, 7, 12-15]. The clinical manifestation of the disease results in loss of ambulation by the early teenage years and development of restrictive lung disease due to diaphragmatic weakness and scoliosis. In addition, DMD patients develop progressive cardiomyopathy, as loss of dystrophin within cardiomyocytes results in cell death leading to cardiac fibrosis and a decrease in cardiac function. Finally, there is emerging data that suggests the genotype of the DMD patients may predict the development of a cardiomyopathy[16].

The molecular basis of DMD and the natural history of a DMD patient have been well investigated over the past two decades. Advances in pulmonary care, orthopedic and rehabilitative interventions, and the beneficial effects of certain medications (i.e.

corticosteroids and angiotensin-converting enzyme inhibitors) have collectively improved the morbidity of DMD patients with life expectancy reaching into the third and fourth decades of life[17-20]. Today, the mortality of the majority of DMD patients is secondary to cardiopulmonary complications[21, 22]. However, the recent wide spread use of the home ventilator [non-invasive positive pressure ventilators (NIPPV)] has dramatically decreased respiratory failure as a cause of death in these patients (Figure 1).

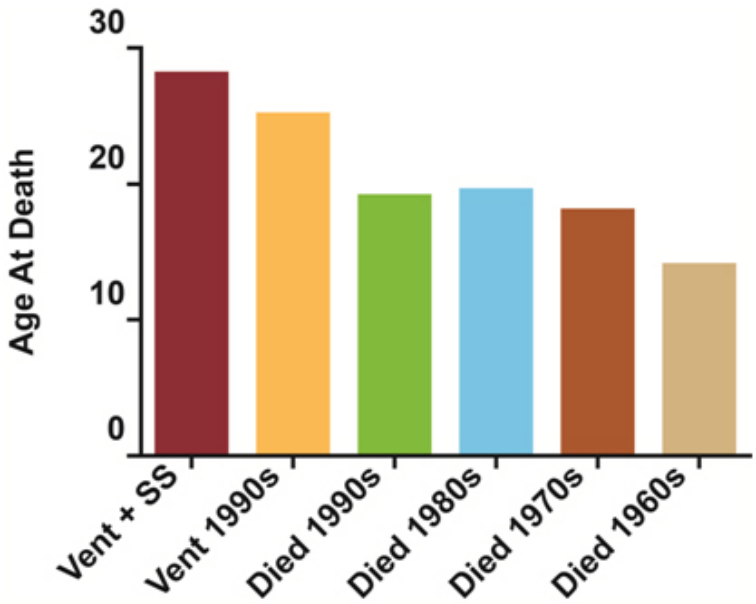

Figure 1: Non-cardiac Interventions prolonging survival in DMD. Innovative ventilatory strategies and spinal stabilization surgeries have markedly improved the survival rate amongst DMD patients since the 1960s[23].

In 2016, the primary mode of death in the vast majority of DMD patients is secondary to complications from advanced cardiomyopathy. Although there is increasing evidence-based medicine outlining the clinical approach to the management of DMD-associated cardiomyopathy, the number of well-designed randomized clinical trials demonstrating the proven beneficial effects of standard of care heart failure medications in other forms cardiomyopathy is lacking in this field.

The approach to managing DMD-associated cardiomyopathy adopted by many of the heart failure cardiologists across the country is based on our in approach in managing non-ischemic cardiomyopathy patients. Therefore, in order to better appreciate the management of DMD-associated cardiomyopathy we will briefly outline in the following section the evidence-based management of patients with dilated cardiomyopathy.

Standard of Care in the Management of Cardiomyopathy

In 2016, there are a multitude of large randomized double-blind clinical studies supporting beneficial effects of various heart failure medications, devices (AICD and biventricular pacemaker(BiV)/AICD, and advanced heart failure therapies [left ventricular assist devices (LVAD) and heart transplantation] that have been demonstrated to improve the mortality and morbidity of patients with ischemic and non-ischemic cardiomyopathy. Based on the results of these clinical studies, guidelines for the management of chronic heart failure have been established jointly by the American College of Cardiology and the American Heart Association[24].

Table 1: Management of Cardiomyopathy in 2016

Medications	Devices	Advanced Heart Failure Therapies
Beta-Blockers (Carvedilol, Toprol XL, Bisoprolol)	AICD (LVEF<35% despite optimal medical therapy)	Left Ventricular Assist Devices (LVAD)
ACEI or ARB	BiV/AICD (QRS>120msec and/or cardiac dyssynchrony noted by ECHO)	Heart Transplantation
Aldosterone Inhibitors (Spironolactone or Eplerenone)		
ARNI (ARB + inhibitor of neprilysin; Entresto)		
BiDil (or Isordil/Hydralazine)		
Ivabradine (Corlanor)		
Diuretics (only if volume overloaded)		
Digoxin		

Initiation of optimal medical therapy can induce significant reverse cardiac remodeling and markedly improved survival and morbidity in patients with both ischemic and non-ischemic cardiomyopathy. In non-ischemic cardiomyopathy, there exists the 33% rule. With optimal medical therapy 33% of patients achieve complete reverse cardiac remodeling, 33% of patients achieve only partial reverse cardiac remodeling, and finally the remaining 33% of patients develop only minimal reverse cardiac remodeling and often will progress to end-stage cardiomyopathy requiring either implantation of a LVAD or a heart transplant (Figure 2)[25, 26].

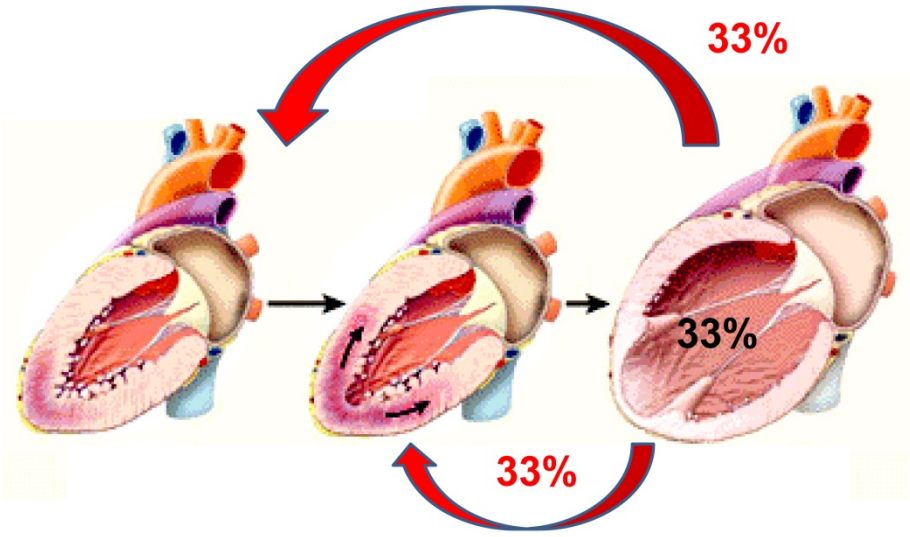

Figure 2: Optimization of heart failure medications results induces reverse cardiac remodeling.

Having gained an understanding of the management of patients with ischemic and non-ischemic cardiomyopathy, we will shift the discussion back to the assessment and management of DMD-associated cardiomyopathy.

DMD-Associated Cardiomyopathy

The reduction of respiratory related deaths due to nocturnal ventilation and spinal stenosis has resulted in DMD patients living longer but ultimately succumbing to complications related to DMD-associated cardiomyopathy[21, 27, 28]. Cardiac involvement is nearly ubiquitous in older DMD patients as more than 90% of young men over the age of 18 demonstrate evidence of cardiac dysfunction [29]. Dilated cardiomyopathy typically has an onset in the mid-teen years and there is progressive maladaptive cardiac remodeling that eventually contributes to the demise of DMD patients [29, 30]. Distinct dystrophin mutations have been correlated to an increased incidence of cardiomyopathy and possible response to treatment [16]. Recognition of cardiomyopathy in DMD patients can be challenging due to physical inactivity and other respiratory complaints that can obscure the diagnosis [31]. Currently, clinical guidelines recommend the initial cardiac screening at the time of diagnosis of DMD, and every 2 years until age 10 and then yearly[19].

DMD-Associated Cardiomyopathy: Cardiac Imaging

Cardiac imaging can be challenging in patients with end-stage DMD due to scoliosis, ventilation, and contractures. Current imaging modalities that are commonly used include echocardiography and cardiac magnetic resonance imaging (cMRI). Echocardiography in DMD cardiomyopathy has demonstrated regional wall motion abnormalities in the posterior basal wall, left ventricular dilation, and overall reduced systolic function [32]. Current guidelines recommend obtaining an echocardiogram at the time of diagnosis or by age 6 with repeat echocardiograms every 1-2 years until the age of 10. After the age of 10, it is recommended that patients have an annual echocardiogram to assess left ventricular function [18]. While echocardiography is easily accessible, relatively quick, and a cost-effective imaging modality, it can be technically challenging in patients with DMD due to chest wall deformities, scoliosis, and respiratory dysfunction, thus limiting the diagnostic yield [33]. Therefore, cMRI is rapidly becoming the gold standard imaging modality to assess the cardiac structure and function in DMD patients. cMRI has been demonstrated to be more sensitive in assessing overall left ventricular size and function [34-37]. Silva et al. performed gadolinium contrast enhanced cMRI on 10 patients with dystrophinopathies (8 DMD and 2 BMD patients) and were the first to demonstrate late gadolinium enhancement (LGE) by cMRI in dystrophic heart. They further reported that LGE was present even with normal left ventricular function by echocardiography[35]. Pulchalski et al. subsequently performed a study of 74 patients with DMD where the majority of patients had LGE in the posterobasal region of the left ventricle in a subepicardial distribution [38]. This pattern of LGE in the basal inferior and inferolateral walls is consistent with the pathological findings of fibrosis in the inferior basal wall[39, 40]. A large single center retrospective study by Hor et al. evaluated LGE in 314 DMD patients, and demonstrated that LGE increased with age and with decreasing LVEF [41]. Thus cMRI, provides an earlier and more sensitive detection of cardiovascular involvement in DMD and allows for accurate and reproducible quantification of left ventricular function and size, which will promote initiation of earlier cardioprotective therapies. Although cMRI has

many imaging benefits for patients with DMD, it can also be challenging, especially in the pediatric population due to the need for sedation, cost, and lack of accessibility.

DMD-Associated Cardiomyopathy: Medical Therapy

Previous studies have demonstrated the benefits of corticosteroid therapy and support the notion that steroid treatment delays left ventricular dysfunction in DMD patients using echocardiography and cMRI[30]. Duboc et al. evaluated the impact of ACE inhibitors, which have been demonstrated to be effective in asymptomatic adults with left ventricular dysfunction, in patients with DMD with preserved left ventricular function [17]. The investigators randomized 57 children with DMD (mean age of 10.7 years) to the ACE inhibitor perindopril (2-4mg/day) or placebo. At three years of follow up there was no significant difference in LV function between the children treated with perindopril or placebo. However, at the three year mark all patients were switched to perindopril treatment and followed for an additional two years. After crossing over to perindopril at two years, there was no difference in mean LV function between those patients treated with perindopril initially versus those initially treated with placebo. However, in the initial placebo group there were 8 of 29 patients with LVEF < 45% and only 1 of 27 patients in the perindopril group (p = 0.02), which was suggestive that early treatment with perindopril was effective in preventing progression to left ventricular dysfunction in DMD (Figure 3). Subsequently these patients were followed for 10 years, and in the initial placebo group only 65% of patients were alive versus 92.9% in the initial perindopril group (p = 0.013) , which emphasized that early initiation of an ACE inhibitor reduced mortality in patients with DMD [42].

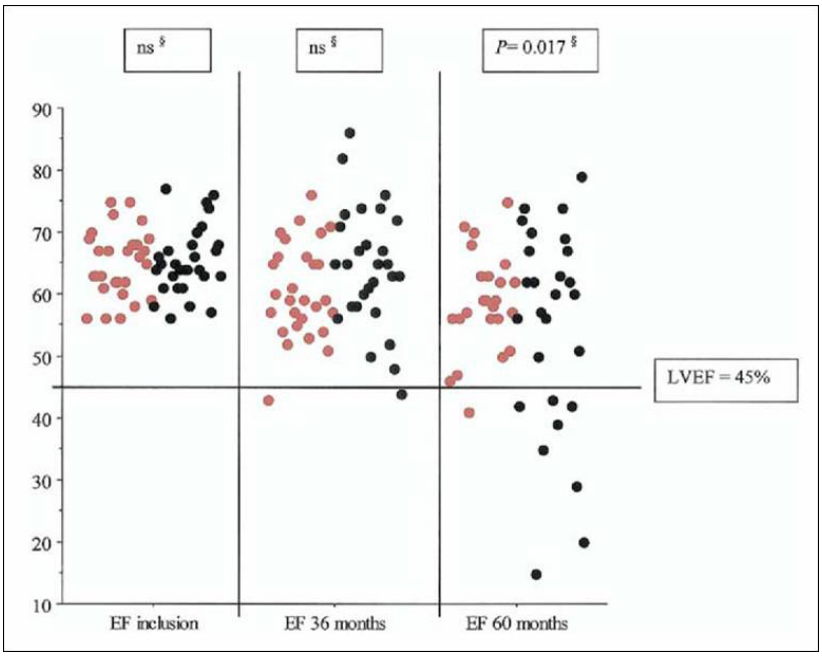

Figure 3: Perindopril prevents or delays the onset of cardiomyopathy in DMD patients[17].

The current guidelines for DMD recommend initiation of ACE inhibitors in patients with DMD only once LV dysfunction has developed [18]; however, based on the studies by Duboc et al. a recent set of cardiac specific guidelines for DMD patients recommends

initiation of an ACE inhibitor before the development of left ventricular dysfunction in DMD patients, as they are at high risk for developing left ventricular dysfunction (ACC Heart Failure Stage A) [17, 42, 43]. Additionally, for those patients who are intolerant to ACE inhibitors, angiotensin receptor blockers (ARBs) can also be used as ARBs have been demonstrated to be as effective as ACE inhibitors in DMD [44].

While the benefit of ACE inhibitors in DMD cardiomyopathy has been definitive, the efficacy of beta blockers in DMD cardiomyopathy has been less clear. The use of carvedilol has been assessed in pediatric DMD patients with elevated atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) and a low ejection fraction (EF < 40%) by echocardiography with no significant difference in carvedilol treated patients with reference to symptoms or left ventricular dysfunction [45]. However, in a study by Rhodes et al., carvedilol was shown to be efficacious in patients with DMD cardiomyopathy [46]. When superimposed on background therapy of ACE inhibitors, the use of carvedilol in this patient population remains unclear. An analysis of 13 patients with DMD who were treated with ACE-I vs. ACE-I and carvedilol revealed a beneficial effect of beta blocker therapy in increasing left ventricular shortening and decreasing left ventricular end diastolic dimensions using echocardiography [47]. In contrast, a recent study by Viollet et al. tested ACE inhibitor alone vs. ACE inhibitor and metoprolol, however in this study low dose beta blocker was added only for heart rates above 100 bpm or if arrhythmias occurred [48]. The results of this study showed an improvement from pretreatment LVEF in both groups, but no difference between the treatment groups. Further research with larger groups of patients and more robust trial designs are needed to definitively address the use of beta-blockers in DMD, however based on current ACC/AHA/HFSA guidelines we would recommend that beta-blockers be initiated in DMD patients with left ventricular dysfunction [49].

Spironolactone, an aldosterone inhibitor, is standard heart failure therapy and has also been demonstrated in the mouse model to improve cardiomyopathy [50]. In a recently completed randomized double-blinded clinic trial, eplerenone, an aldosterone antagonist versus placebo was added to background therapy of ACE inhibitors or ARBs in DMD patients with normal LV function to assess the efficacy of eplerenone in preventing cardiomyopathy in DMD. Twenty patients were randomized to eplerenone and 20 to placebo and were followed for 6 and 12 months with cardiac MRI. The primary endpoint was change in left ventricular circumferential strain, which is a marker of contractility, at 12 months. At 12 months, the decline in LV circumferential strain was lower in the group treated with eplerenone than the placebo group though there was no overall change in left ventricular function in either group[51]. This study while small demonstrated attenuation of progressive left ventricular dysfunction that occurs in DMD; while this study is positive further studies to assess the impact of eplerenone in DMD survival are warranted.

DMD-Associated Cardiomyopathy: Advanced Medical Therapies

The gold-standard for end-stage or advanced heart failure remains cardiac transplantation. Heart failure with multisystem organ involvement and inability to rehabilitate after cardiac transplantation have been relative contraindications to heart transplant, and thus has limited the applicability in the muscular dystrophy population.

Rees et al. were the first to describe heart transplantation in patients with muscular dystrophies in a single German center [52]. Of 582 transplants performed, they had 3 patients with DMD and 1 patient with BMD who underwent cardiac transplantation with a mean duration of follow up of 40 months. They described that these patients tolerated immunosuppression, had no difference in postoperative intubation, and were able to be rehabilitated [52]. Ruiz-Cano et al. also described a Spanish single center experience with heart transplantation in 3 patients with BMD who underwent cardiac transplantation with a mean follow up duration of 57 months. These investigators also demonstrated that BMD patients had an intraoperative and postoperative course comparable to non-muscular dystrophy patients undergoing heart transplantation [53]. Patane et al. also described a single case of successful transplantation in a patient with cardiomyopathy secondary to BMD [54]. Recently, the UTSouthwestern Heart Transplant Program performed a multicenter registry analysis of cardiac transplantation from the Cardiac Transplant Research Database and identified 29 patients with muscular dystrophies of which 15 had BMD and 3 had DMD who underwent cardiac transplantation between 1995 and 2005 and compared them to 275 non-muscular dystrophy non-ischemic patients who were matched for age, body mass index, gender and race [55]. The study demonstrated that there was no significant difference in survival at 1 or 5 years, transplant rejection, infection, or allograft vasculopathy between the muscular dystrophy and non-muscular dystrophy patients. These studies have described comparable outcomes of cardiac transplantation in a small and select group of patients with DMD and BMD with end-stage cardiomyopathy; however, the functional status of these patients prior to transplantation was not known and these studies may have a selection bias. Further research regarding cardiac transplantation in patients with DMD and BMD with end-stage cardiomyopathy is warranted.

Given the scarcity of organs for heart transplantation, left ventricular assist devices (LVADs) have been demonstrated to be to be effective in treating patients with end-stage or advanced heart failure as well, and is applicable to a larger population including those with muscular dystrophies as it can be used as destination therapy without the need for transplantation [56, 57]. Two groups have recently reported cases of successful implantation of LVADs as destination therapy in DMD patients [58, 59]. Amedeo et al. were the first to describe LVAD implantation in two pediatric DMD patients [58]. These investigators implanted the Jarvik 2000 LVAD in a 15 year-old boy with DMD who had inotrope refractory heart failure and in a 14 year-old boy with DMD who was bridged from extracorporeal membrane oxygenation to a Jarvik 2000 LVAD. The first patient was discharged 3 months after LVAD implantation and the second patient 6 months after LVAD implantation. Ryan et al. subsequently described the HeartMate II LVAD implantation in a 29 year-old male patient with DMD and end-stage heart failure and a HeartWare LVAD implantation in a 23 year-old female symptomatic DMD carrier with end-stage heart failure [59].

LVAD as destination therapy is a potentially promising therapy to address the end-stage heart failure in patients with dystrophin-deficient heart failure, however post-operative complications including respiratory failure, rehabilitation, bleeding, stroke, and arrhythmias will need to be evaluated further in this population. Extensive preoperative and post-operative management in an experienced center would be necessary for LVAD

implantation in the DMD population and larger studies will be needed to evaluate the efficacy and outcomes in this population.

UTSouthwestern Neuromuscular Cardiomyopathy

With the rapidly growing and robust UTSouthwestern Pediatric & Adult MDA-Sponsored Neuromuscular Disorders Clinics, there has been a growing need to provide state-of-the-art cardiovascular care to patients with neuromuscular disorders. Therefore, in the Summer of 2010 the UTSouthwestern Neuromuscular Cardiomyopathy Clinic was established. The mission of the Clinic is based on four principles noted below:

1. **Clinical:** Providing outstanding, comprehensive cardiovascular care to adults patients with neuromuscular disorders.

2. **Community Service:** Actively educating the biomedical and lay communities about the potential cardiovascular complications that are often observed in patients with neuromuscular disorders.
    a. Providing clinical/scientific talks at various regional, national, and international conferences.
    b. Providing educational talks to the lay community in the Dallas-Forth Area as well as across the country.

3. **Research:**
    a. Undertake translational studies that may identify novel targets for the treatment of heart failure in patients with neuromuscular disorders.
    b. Undertake clinical trials to establish appropriate guidelines for the treatment of heart failure in this patient population.

4. **Education:** Train physicians (medical students, medical & neurology residents/fellows, cardiology fellows), nurses, and other health care workers in the assessment and management of cardiovascular conditions that arise from neuromuscular disorders.

Referrals to this clinic have exploded over the past five years with approximately 400 patients to date receiving advanced cardiovascular care within the Clinic, demonstrating the great clinical need for such a Clinic in North Texas (Figure 4).

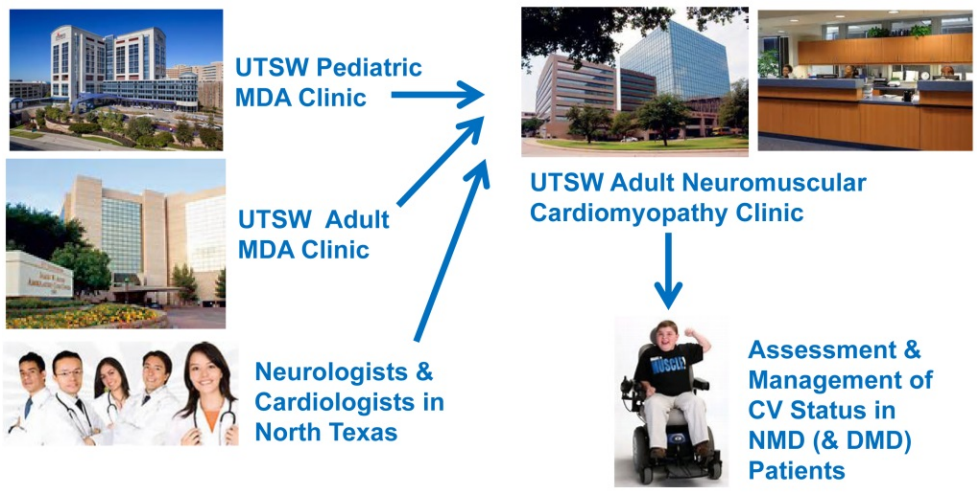

Figure 4: Referral patterns to the UTSouthwestern Neuromuscular Cardiomyopathy Clinic.

<u>Assessment and Management of Neuromuscular-Associated Cardiomyopathy</u>

Incorporating the results from the limited number of clinical studies involving DMD-associated cardiomyopathy noted above as well as extrapolating data from clinical trials involving non-neuromuscular cardiomyopathy patients, the UTSouthwestern Heart Failure Program has developed an algorithm to objectively evaluate the cardiovascular status of patients with neuromuscular disorders (Figure 5).

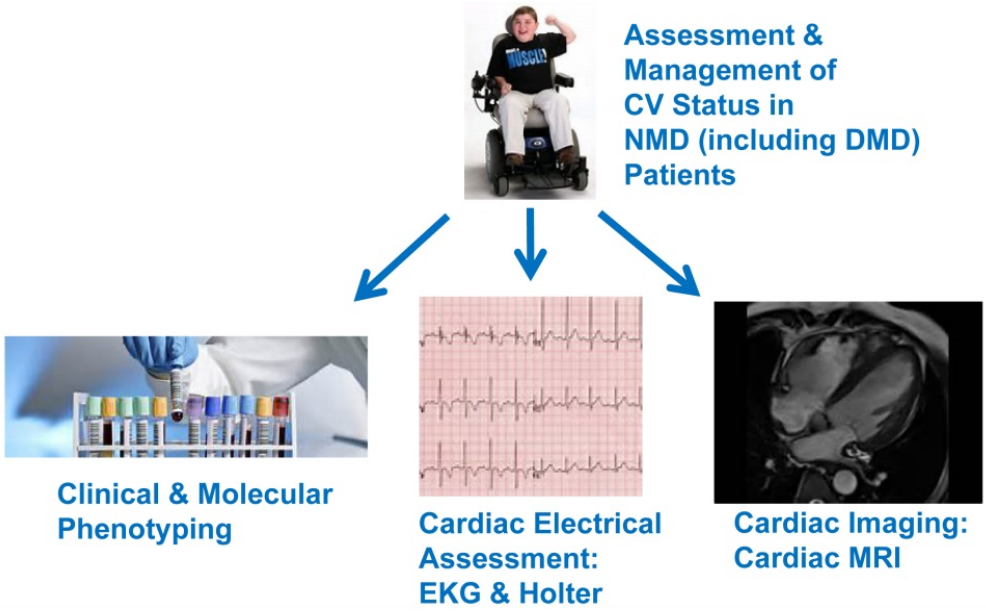

Figure 5: Cardiovascular assessment patients with neuromuscular disorders.

Table 2: Management of Cardiomyopathy in 2016

Biochemical Phenotyping	Genetic Phenotyping	Electrical Phenotyping	Structural Phenotyping with Cardiac Imaging
Comprehensive laboratory data to calculate the Seattle Heart Failure Score (CBC with diff, comprehensive metabolic panel, lipid profile, and uric acid level)	Genetic sequencing of the causative gene.	12-Lead EKG	Left Ventricular Assist Device (LVAD)
TSH/FT4		24-Hour Holter	Heart Transplantation
HgA1C		Loop recorder vs Medtronic Reveal LINQ	
Cardiac Biomarkers (total CK, CK-MB, TnT, Pro-BNP, and hs-CRP)			

Outlined below is an algorithm for the initiation of medical therapy in patients with neuromuscular disorders based on the results of the cMRI (Figure 6).

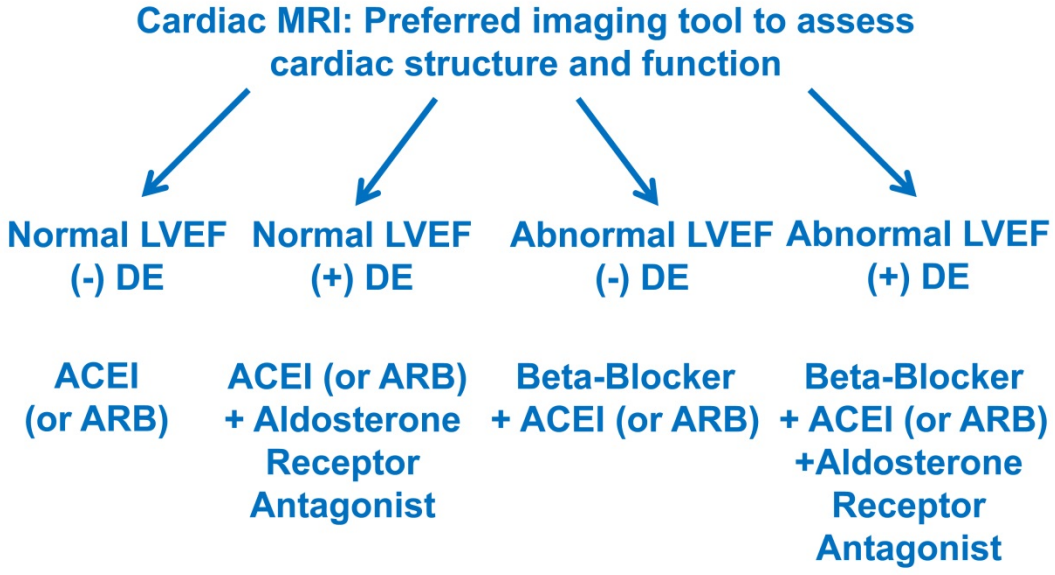

Figure 6: Algorithm for initiating medical therapy in patients with neuromuscular disorders.

UTSouthwestern Neuromuscular Cardiomyopathy: Platform for Translation

The Neuromuscular Clinic serves as a platform for translational studies focused on novel therapies directed specifically towards patients with neuromuscular disorders (Figure 7). These studies are aimed at improving both the overall care as well as the cardiovascular care we provide to this unique patient population.

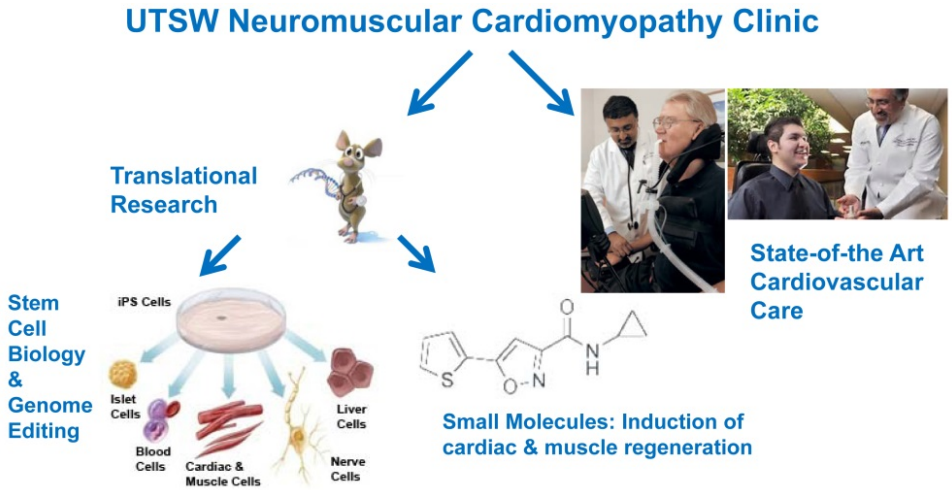

Figure 7: The UTSouthwestern Neuromuscular Cardiomyopathy Clinic services as a platform for translational studies.

In the Fall of 2015, the National Institute of Health awarded UT Southwestern one of six coveted Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRC). Dr. Eric Olson and I serve as Co-Directors of the UTSW Wellstone Center. The overall mission of the UTSW Wellstone Center is to rapidly translate the recent discoveries by Dr. Olson's research team on genome editing into an innovative therapy for the treatment of DMD patients (Figure 8)[60, 61].

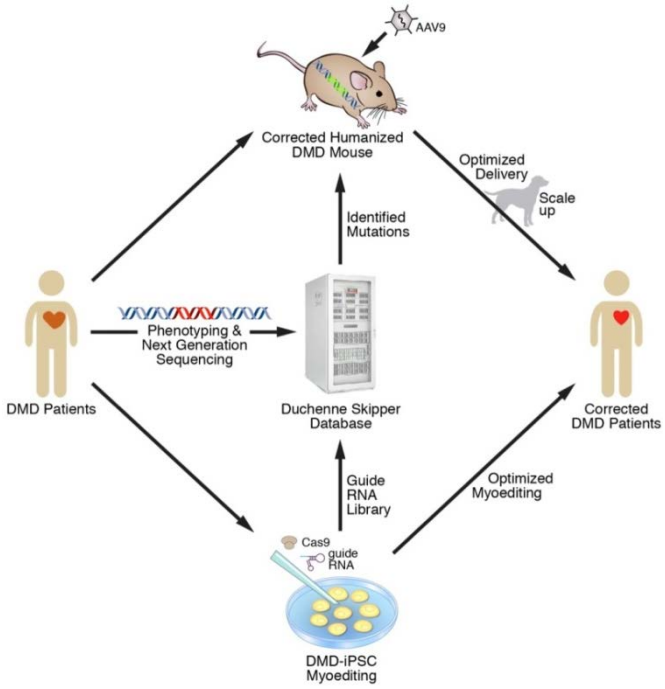

Figure 8: Schematic overview of the primary mission of the UTSW Wellstone Center emphasizing synergistic interactions and seamless integration of projects, patients, cores, and resources. Project 1 will initiate Cas9/guide-RNA myoediting studies of pre-existing DMD-iPSCs and genetic engineering of humanized DMD mice for testing AAV9-mediated myoediting therapeutics. Project 2 will feed into Project 1 by identifying, phenotyping, and sequencing new DMD patients. This information will be collected and collated in the "Duchenne Skipper Database," which will predict guide-RNA libraries to be used for myoediting. Selected mutations found in our patients will be used to generate additional humanized DMD mice to test myoediting *in vivo*.

Summary

In conclusion, patients with neuromuscular disorders are at risk of developing cardiovascular complications, especially the development of a cardiomyopathy. Therefore, all neuromuscular patients should undergo a cardiac assessment which should include a thorough history and physical, clinical phenotyping (including a cardiac MRI) and & genetic phenotyping. If a cardiomyopathy is identified then standard of care heart failure therapy should be initiated to decrease long term morbidity and mortality related to heart failure.

Of note, a portion of this protocol was extracted from a textbook chapter in with Dr. Mammen is a co-author. Kamdar, F., P.P.A. Mammen, and D.J. Garry. Neuromuscular cardiomyopathies. Textbook Chapter in Congestive Heart Failure and Cardiac Transplantation: Clinical, Pathology, Imaging, and Molecular Profiles. Editors: Daniel J. Garry, Robert F. Wilson, and Zeev Vlodaver. Publisher Springer. In Press.

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