Altered Atrial Remodeling in the Muscular Dystrophies

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Introduction:
Muscular dystrophies (MD) are genetic disorders that cause progressive peripheral skeletal myopathies. The specific mutations lead to a cycle of muscle degeneration and regeneration in MD patients, ultimately producing progressive skeletal muscle wasting. Many of the MD patients also develop associated cardiomyopathies and is currently the leading cause of death. Our group has demonstrated that MD patients have very small left ventricular (LV) masses as well as depressed LV Ejection Fraction (LVEF). This data suggest that the mode of maladaptive cardiac remodeling may be different in MD vs. non-ischemic cardiomyopathy (NICM) patients. However, it remains unknown the degree of atrial remodeling that occurs in MD patients. Therefore, the central hypothesis of this study is that atrial remodeling in MD patients is altered in comparison to NICM patients.

Methods:
Using the UT Southwestern Cardiomyopathy Clinic, MD and NICM patients were identified. Data was extracted from cardiac MRIs to measure left and right atrial (LA, RA) volumes and function. The variables used were the LA and RA end systolic volume (LA-ESV, RA-ESV), LA and RA end diastolic volume (LA-EDV, RA-EDV), and LA and RA ejection fraction (LAEF, RAEF). These measures were normalized to the body surface area (BSA). We collected data on 80 MD patients (34 MD females, 46 MD males) and 82 NICM patients (29 NICM females, 53 NICM males). Using an unpaired two-sided Student's *t*-test, LA and RA data were analyzed between the matched MD and NICM patients.

Results:
The MD and NICM patient cohorts showed significant differences in both the LA and RA structure and function. MD patients were characterized with higher ejection fraction, as well as, diminished end systolic and end diastolic volume seen in both atria when compared to NICM patients.

Conclusion:
Collectively, the data suggests an alternative mode of maladaptive cardiac remodeling in MD vs. NICM patients. Thus, further investigation into the mechanism that leads to MD-associated cardiomyopathy may ultimately identify novel therapeutic targets for the amelioration of this disease entity.

Hypothesis

The central hypothesis of this study is that atrial remodeling in muscular dystrophy patients is altered in comparison to non-ischemic cardiomyopathy patients.

Background

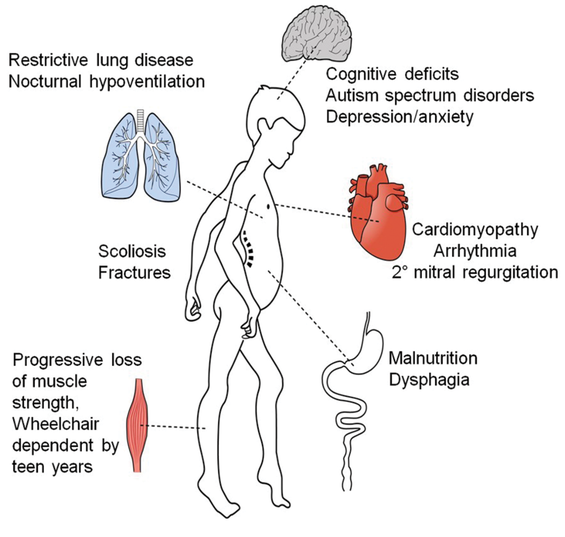

Figure 1. Clinical Manifestation in Muscular Dystrophy Patients. Muscular dystrophy encompasses an array of congenital disorders such as Duchenne, Becker, Limb-Girdle, Myotonic, and Emery-Dreifuss muscular dystrophy. Although these disorders may vary in pathophysiology, they clinically present with much similarity, especially in regards to cardiac involvement.

Proposed Mechanism of Action

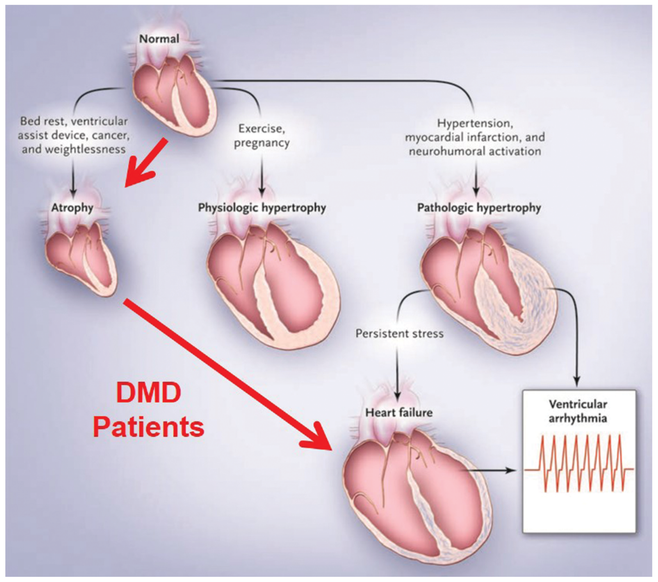

Figure 2. Cardiac Remodeling in Muscular Dystrophy Patients. According to the current understanding of cardiac remodeling, normal hearts undergo either physiological or pathological hypertrophy followed by persistent stress, which over time leads to heart failure presenting with enlarged chambers. However, we propose that MD hearts deviate from the established mechanism of action of heart failure. Because MD patients are born with congenitally smaller hearts, the atypical structure is inherently inadequate to support typical cardiovascular loading conditions, thus also resulting in heart failure.

Methods

MD and NICM patients were identified and their clinical data were extracted from the UT Southwestern Cardiomyopathy Clinic. Measurements that were acquired consisted of demographics, lab values, and cardiac MRI.

Left and right atrial chambers were outlined using QMASS and four values were determined:

1. Area of atria in ESV
2. Length of atria in ESV
3. Area of atria in EDV
4. Length of atria in EDV

Left and right atrial ESV and EDV were calculated by using the respective area and length measurements to find volume (LAV, RAV) and volume index (LAVI, RAVI). Indexing the calculated volumes to body surface area (BSA) was imperative in calibrating for body size and gender.

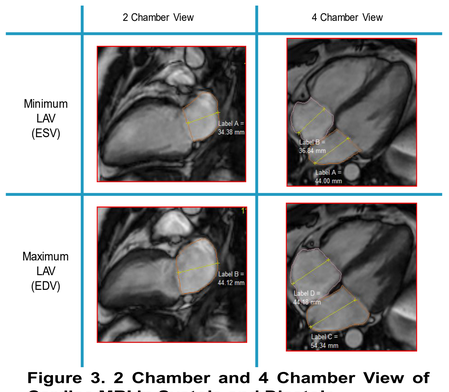

Figure 3. 2 Chamber and 4 Chamber View of Cardiac MRI in Systole and Diastole.

$$Atrial\ Volume = \frac{8}{3\pi} * \frac{A_1 * A_2}{L} = (0.85) * \frac{A_1 * A_2}{L} \qquad Atrial\ Volume\ Index = \frac{Atrial\ Volume}{BSA}$$

Variable	Definition
A_1	Max. LA area in apical 4-chamber (A4C) view
A_2	Max. LA area in apical 2-chamber (A2C) view
L	Min. length measured from back wall to line across mitral valve hinge points - MIN (4C length, 2C length)
BSA	Body Surface Area

Atrial ejection fractions were then calculated by:

$$Ejection\ Fraction = \frac{EDV - ESV}{EDV} * 100$$

Results

Left Atrium Analysis

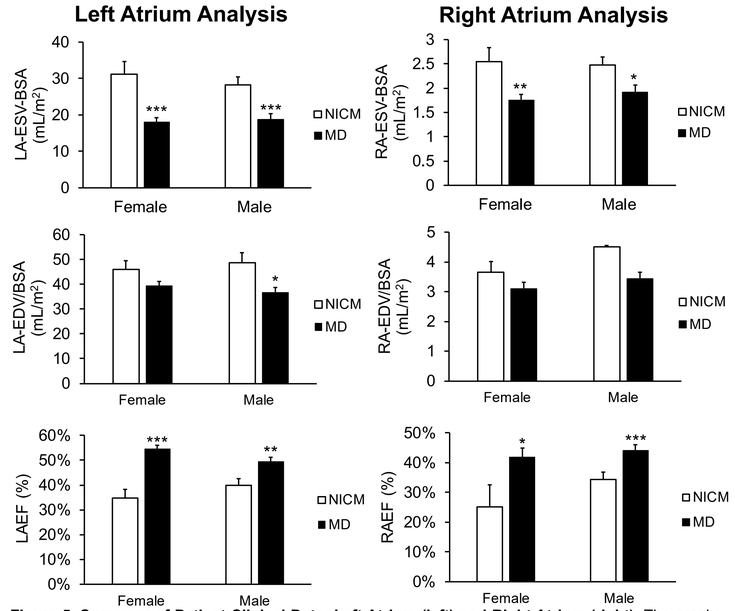

Figure 5. Summary of Patient Clinical Data: Left Atrium (left) and Right Atrium (right). The graphs above show a comparison of averages between NICM and MD LA-ESV/BSA, LA-EDV/BSA, LAEF, RA-ESV/BSA, RA-EDV/BSA, and RAEF by females and males.

MD Patients	LA-ESV/BSA			LA-EDV/BSA			LAEF		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Average	18.03	18.85	18.50	39.39	36.75	37.87	54.54%	49.41%	51.59%
SEM	1.16	1.54	0.00	1.67	2.00	0.00	1.52%	1.91%	0.00%
NICM Patients									
	LA-ESV/BSA			LA-EDV/BSA			LAEF		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Average	31.15	28.25	29.28	46.00	48.58	47.67	34.76%	39.79%	38.01%
SEM	3.50	2.20	0.00	3.53	4.16	0.00	3.54%	2.66%	0.00%
t-test	3.48E-04	9.75E-04	1.37E-06	8.08E-02	1.62E-02	3.19E-03	1.12E-06	5.22E-03	2.26E-07

Table 1. Left Atrium Measurements: MD (top) and NICM (bottom) Patient Clinical Data. Calculated Average, SEMs and statistics with paired Student's *t*-tests: ***p<0.005, **p<0.01, *p<0.05; females: n=29 NICM, 34 MD; males: n=53 NICM, 46 MD.

MD Patients	RA-ESV/BSA			RA-EDV/BSA			RAEF		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Average	1.75	1.92	1.85	3.11	3.45	3.30	42.00%	44.10%	43.21%
SEM	0.12	0.15	0.10	0.20	0.22	0.15	2.90%	1.94%	1.65%
NICM Patients									
	RA-ESV/BSA			RA-EDV/BSA			RAEF		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Average	2.54	2.48	2.50	3.66	4.52	4.21	25.23%	34.46%	31.20%
SEM	0.29	0.16	0.15	0.36	0.02	0.57	7.29%	2.45%	3.04%
t-test	9.84E-03	1.56E-02	3.64E-04	1.68E-01	2.60E-01	1.29E-01	2.73E-02	3.21E-03	7.16E-04

Table 2. Right Atrium Measurements: MD (top) and NICM (bottom) Patient Clinical Data. Calculated Average, SEMs and statistics with paired Student's *t*-tests: ***p<0.005, **p<0.01, *p<0.05; females: n=29 NICM, 34 MD; males: n=53 NICM, 46 MD.

Conclusions

- The NICM cohort was characterized by decreased cardiac function due to dilated atria and accompanying systolic function.
- The atria of the MD cohort were not structurally dilated but still had depressed systolic function. Events in the MD atria reflect what has been molecularly and clinically observed in the MD ventricles.
- Collectively, these data suggest an alternative mode of maladaptive cardiac remodeling distinct from the current model of cardiomyopathy, under which there are only two broad modalities—ICM and NICM.
- All NICM remodeling may not be the same, and genetic factors may influence a divergent mechanism of remodeling in which the congenitally smaller heart faces an inherently larger load.
- The chronic imbalance between the structurally limited nature of MD hearts and normal circulatory load predisposes MD patients to cardiomyopathy unique in both nature and mechanism.
- Thus, further investigation into the mechanism that leads to MD-associated cardiomyopathy may ultimately identify novel therapeutic targets for the amelioration of this disease entity.

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