THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 10

RESEARCH ARTICLE

Insights from comprehensive evaluation of children and adolescents with Duchenne Muscular Dystrophy using cardiac magnetic resonance imaging and pulmonary function testing

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OPEN ACCESS

PUBLISHED
31 October 2025

CITATION
Husain, M., Dual, SA., et al., 2025. Insights from comprehensive evaluation of children and adolescents with Duchenne Muscular Dystrophy using cardiac magnetic resonance imaging and pulmonary function testing. Medical Research Archives, [online] 13(10). https://doi.org/10.18103/mra.v13i10.7021

DOI
https://doi.org/10.18103/mra.v13i10.7021
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ISSN
2375-1924

ABSTRACT

Introduction: Duchenne muscular dystrophy (DMD) is fatal X-linked neuromuscular disorder characterized by progressive dilated cardiomyopathy, respiratory insufficiency, and autonomic dysfunction. Cardiac, pulmonary, and autonomic function are thought to decline with disease progression in a co-dependent manner. However, these relationships have not been systematically evaluated. Right ventricular health, which depends on normal pulmonary hemodynamics, also remains understudied in DMD. The objective of this study was to characterize the relationships of pulmonary function test (PFT) parameters and indices of autonomic function, with cardiac magnetic resonance imaging (CMR) biomarkers of biventricular function and remodeling in children and adolescents with DMD.

Methods: We performed a prospective analysis of 27 boys with DMD who underwent CMR, PFT, and 24-hour ambulatory electrocardiogram (aECG) monitoring at two children's hospitals to evaluate cardiac, pulmonary, and autonomic function, respectively. The CMR protocol included conventional biventricular volumetric and functional assessment, late gadolinium enhancement (LGE) imaging to detect focal myocardial fibrosis, and T1 mapping to assess diffuse fibrosis. PFTs were performed per institutional protocols and included spirometry and respiratory muscle strength testing. Average heart rate and the standard deviation of the time between normal heartbeats (SDNN) were obtained from aECG. The cohort was stratified based on presence of LGE and predicted forced vital capacity (FVC) <80%, both suggestive of more advanced disease.

Results: Median age of the cohort was 13 years (IQR 11-15.5 years). 8 patients were LGE (+) and 19 were LGE (-). LGE (+) boys had significantly lower percent predicted maximum expiratory pressure (MEP%) (25.8 vs. 48.0, p=0.035). Other respiratory, autonomic, and right ventricular function indices did not correlate with LGE status. There were no significant differences in CMR or autonomic parameters between boys with normal (FVC ≥80%) and abnormal (FVC <80%) pulmonary function.

Conclusion: Our findings suggest that cardiac, pulmonary, and autonomic function may decline independently with disease progression; dysfunction in one system did not necessarily correlate with dysfunction in the other. Decline in respiratory muscle strength, as measured by MEP%, was seen more often in patients with myocardial scarring (indicative of more advanced disease). Further longitudinal investigation involving prospective modulation of respiratory support during CMR may elucidate more subtle cardiopulmonary-autonomic interactions in DMD.

Keywords: Autonomic dysfunction; Cardiac magnetic resonance; Cardiopulmonary interactions; Cardiopulmonary-autonomic interactions; Duchenne muscular dystrophy; Dilated cardiomyopathy; Late gadolinium enhancement; Pulmonary function test; Respiratory muscle strength

Abbreviations

Anthropomorphic data – BSA: Body surface area; BMI: Body mass index

Autonomic function – HR: Heart rate; SDNN: Standard deviation of the N-N interval

Respiratory mechanics – FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 second; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure

All values are listed as percent predicted save for FEV_1/FVC ratio.

CMR parameters – LGE: Late gadolinium enhancement; EDVi: End diastolic volume indexed; ESVi: End systolic volume indexed; LVMi: LV mass indexed; LVEF: LV ejection fraction; ECV: Extracellular volume; RVMi: RV mass indexed; RVEF: RV ejection fraction

Introduction

Duchenne muscular dystrophy (DMD) is a progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene resulting in lack of functional dystrophin protein in boys.[1,2] Dystrophin deficiency leads to structural instability and contraction-induced injury of skeletal, respiratory, and cardiac muscle cells. The result is loss of ambulation, respiratory insufficiency, and dilated cardiomyopathy (DCM).[3-7] Autonomic dysfunction due to loss of vagal tone is also frequently present.[8-10] In advanced stages of DMD, worsening cardiomyopathy and respiratory insufficiency lead to cardiopulmonary failure and early death despite optimal medical care.[11]

Cardiac magnetic resonance imaging (CMR) provides comprehensive gold standard quantitative assessment of both left (LV) and right (RV) ventricular volumes and function, as well as several sensitive and validated biomarkers of myocardial fibrosis and remodeling.[12,13] Specifically, the presence of discrete myocardial fibrosis, seen as late gadolinium enhancement (LGE) on dedicated CMR images, indicates maladaptive focal tissue fibrosis on a macroscopic level. LGE is a well-recognized, but often late, finding in DMD and is associated with clinical worsening and DCM.[14] T1-mapping with extracellular volume (ECV) calculation can detect and quantify the presence of diffuse tissue fibrosis on a microstructural level, preceding the appearance of LGE and ventricular dysfunction.[13-15] LV and RV T1-mapping in DMD patients has been demonstrated by our group and others to identify early myocardial disease in boys with DMD, even in the absence of LGE.[15-17] Comprehensive evaluation of these CMR biomarkers can provide valuable insight into overall cardiac health and plays a crucial role in cardiomyopathy surveillance.[12]

Pulmonary function testing (PFT) via spirometry is used to monitor respiratory capacity in DMD patients.[18] Maximum static airway pressures, namely, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), have emerged as sensitive markers in detecting early respiratory muscle dysfunction in neuromuscular disease compared with standard spirometry indices.[19,20] Collectively, studies have defined the decline in these parameters with increasing age, loss of ambulation, and overall disease progression.[21,22]

In terms of autonomic function, evaluation of boys with DMD with ambulatory electrocardiogram (aECG) monitoring often reveals elevated resting heart rates and loss of heart rate variability (HRV), presumably due to a loss of parasympathetic activity.[8,9] Standard deviation of the time between normal heartbeats (normal-to-normal intervals (NN), also known as RR) over a specific period, can be used to assess HRV. It is reported to be the most sensitive parameter for detecting autonomic dysfunction.[23-25] This autonomic dysfunction is in turn thought to be a major contributing factor of cardiac dysfunction in this patient population.[8-10]

The current understanding of DMD is predominantly based on independent evaluations of myocardial performance, respiratory mechanics, and autonomic function. While they are all thought to be clinically interrelated,[9,26] their interaction has not been systematically evaluated, and assessments involving the RV remain significantly understudied. Therefore, the objective of this study was to characterize the relationship of pulmonary and autonomic function with CMR biomarkers of biventricular remodeling and function in boys with DMD.

Methods

We conducted a prospective analysis of 27 boys with genetically confirmed DMD who were followed at two children's hospitals. The cohort was prospectively enrolled as part of a larger trial (ClinicalTrials.gov Identifier: NCT02834650)[16,17] which spanned February 2017 to March 2022. Each subject underwent CMR, PFT, and 24-hour aECG monitoring as part of the study protocol. To optimize data completeness, PFT or aECG performed as part of routine clinical surveillance within six months of the CMR were included for analysis. Exclusion criteria included incomplete imaging data or a CMR–PFT/aECG interval exceeding six months. The study was approved by the Institutional Review Boards at the participating institutions. Informed consent, and patient assent where appropriate, were obtained for each subject.

CARDIAC MAGNETIC RESONANCE IMAGING PROTOCOL

All study participants underwent CMR at 3.0T (Skyra, Siemens Healthineers, Erlangen, Germany) using the same imaging protocol at both sites. The CMR exam included standard volumetric and functional imaging using a free-breathing high spatial and temporal resolution retrospectively gated balanced steady state free precession (bSSFP) cine sequence,[27] spanning the entire LV from base to apex. LV and RV myocardial native and post-contrast T1 measurements were acquired using a breath-held and ECG-gated motion-corrected modified Look-Locker inversion recovery (MOLLI) sequence in a single mid-ventricular short-axis plane. Either gadobenate dimeglumine (Gd-BOPTA,

MultiHance, Bracco Diagnostics, Milan, Italy) or gadobutrol (Gadavist, GBCA, Bayer HealthCare Pharmaceuticals, New Jersey, USA) was administered to boys for LGE imaging utilizing a free-breathing motion-corrected phase-sensitive inversion recovery (PSIR) sequence. This was acquired in the short axis view spanning from base to apex. Blood hematocrit levels were measured in all subjects on the day of the CMR exam in order to calculate extracellular volume fraction (ECV). Post-processing and analysis were performed by two expert CMR-trained clinicians (PR or AP). Specific information regarding CMR image acquisition, sequence parameters, imaging protocol, and quality assessment has been previously published.[16,17]

Several CMR parameters were evaluated including: End-diastolic and end-systolic ventricular volumes indexed to body surface area (EDVi, ESVi), biomarkers of tissue remodeling (native T1, post-contrast T1, ECV), LGE status (negative or positive), and ventricular function in terms of ejection fraction (EF).

PULMONARY FUNCTION TESTING (PFT)

Pulmonary Function Testing was performed and interpreted in accordance with standards set by the American Thoracic Society (ATS) and European Respiratory Society (ERS).[28] Reference data used to report percent predicted values was based on clinical standards for spirometry and lung volumes. PFT included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/ FVC. Maximal static respiratory pressures were tabulated as surrogate measurements of respiratory muscle strength, including maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). All values are reported as percent predicted save for FEV_1/FVC ratio. Testing was performed in the upright position. The studies were interpreted by pediatric pulmonologists at each institution. All results are expressed as percent predicted. Abnormal pulmonary function was defined as FVC <80% predicted.

AMBULATORY ELECTROCARDIOGRAM

A 24-hour recording was performed using various aECG monitors based on patient's primary institution and insurance provider (monitor manufacturers included BardyDx, Philips, Carnation, BioTel). The recording was reviewed and interpreted by pediatric cardiologists at each institution. Average heart rate and SDNN were obtained for the purposes of the study.

STATISTICAL METHODS

Numerical data are reported as medians and interquartile ranges (IQR). Categorical variables are summarized by counts and percentages. The cohort was stratified based on presence or absence of LGE and pulmonary function based on percent predicted FVC (normal defined as ≥80%). Differences between LGE (-) and LGE (+) boys, and those with normal and abnormal FVC%, was assessed via the Wilcoxon rank-sum test. Statistical significance was set at the 0.05 level. All analyses were age-adjusted and performed using R Statistical Software (v4.3.1; R Core Team 2023).

Results

Median age of the cohort was 13 years (IQR 11-15.5 years). None of the boys were ventilator-dependent and 3 (11%) were ambulatory at the time of enrollment. In terms of medications, 20 (74%) were on an angiotensin-converting enzyme inhibitor, 4 (14.8%) on an angiotensin receptor blocker, 7 (25.9%) on a beta-blocker, 17 (62.9%) on a mineralocorticoid receptor antagonist, and 18 (66.7%) on corticosteroid therapy. None received antisense oligonucleotide or gene therapy during the study period. Patient characteristics, as well as CMR, PFT, and aECG parameters are listed in Table 1.

Table 1: Patient characteristics, autonomic function, respiratory mechanics, and CMR parameters for the entire cohort

Characteristics	**N =27**
Age (years)	13 (11 - 15.5)
Height (m)	1.34 (1.25 - 1.47)
Weight (kg)	49.76 (33.36 - 59.45)
BSA (m^2)	1.36 (1.1 - 1.52)
BMI (kg/m^2)	25.36 (21.06 - 31.23)
Autonomic Function	
Average HR (bpm)	99 (89.5 - 105)
SDNN (ms)	101.1 (93 - 123.6)
Respiratory Mechanics	
FVC%	88 (77.45 - 103.75)
FEV_1%	79.7 (70.85 - 97.2)
FEV_1/FVC	1.002 (0.887 – 1.035)
MIP%	55.0 (46.67 - 71.08)
MEP%	40.45 (27.35 - 57.35)
CMR Parameters	
Left Ventricle (LV)	
LGE (+)	8 (30%)
EDVi (ml/m^2)	84.23 (66.25 - 93.83)
ESVi (ml/m^2)	39.34 (30.79 - 45.21)
LVMi (g/m^2)	35.9 (30.32 - 39.76)
LVEF (%)	50.1 (44.55 - 55.8)
Native T1 (ms)	1352 (1329 - 1382)
Post-contrast T1 (ms)	591 (571- 662)
ECV (ratio)	0.31 (0.28 - 0.33)
Right Ventricle (RV)	
EDVi (ml/m^2)	70.45 (54.02 - 83.71)
ESVi (ml/m^2)	33.11 (25.25 - 40.28)
RVMi (g/m^2)	23.74 (19.85 - 25.36)
RVEF (%)	51.6 (46.5 - 56.39)
Native T1 (ms)	1549 (1467 - 1645)
Post-contrast T1 (ms)	449 (421 - 560)
ECV (ratio)	0.44 (0.41 - 0.49)

STRATIFICATION BY LGE STATUS

Eight boys (29.6%) were LGE (+) and 19 (70.4%) were LGE (-). LGE (+) boys had significantly lower MEP% (25.8 [19.1-36.0] vs. 48.0 [35.1-59.9], p = 0.035). FEV_1% trended lower in LGE (+) boys but did not reach statistical significance (64.4 [53.7-79.7] vs. 80.4 [77.9-97.2], p = 0.067). FVC%, FEV_1/FVC, and MIP% were preserved across LGE status. There was no significant difference in measures of autonomic function between the groups.

LGE (+) boys had significantly increased LV size (LV EDVi (ml/m²): 93.8 [84-115.1] vs 81.3 [65.4-88.7], p = 0.019 and LV ESVi (ml/m²): 47.4 [44.8-71.8] vs 37.5 [29.3-40.7], p = <0.001), reduced LV systolic function (%) (43.8 [37.9-48.6] vs 55.2 [47.5-57.7], p = 0.005), and increased LV myocardial mass (g/m²) (39.5 [37.6-44.9] vs 32.4 [29.3-38], p = 0.034). In terms of biomarkers of maladaptive myocardial remodeling, LGE (+) was associated with a greater LV native T1 (ms) (1379 [1362-1418] vs 1337 [1319-1366], p = 0.047), lower post-contrast T1 values (ms) (553 [492-588] vs 617 [586-721], p = 0.007) and increased ECV values (0.34 [0.32-0.37] vs 0.29 [0.28-0.32], p = 0.004). Although there was a trend toward decreased RV ejection fraction in the LGE (+) group, there were no statistically significantly differences in CMR biomarkers of the RV when comparing boys with LGE (+) versus LGE (-). A complete list of parameters for these subgroups can be found in Table 2.

Table 2: Comparison of LGE (+) vs LGE (-) subgroups: Patient characteristics, autonomic function, respiratory mechanics, and CMR parameters. Note: p-values are calculated using Wilcoxon rank sum test.

Characteristics	**LGE (-)** **N = 19 (70.4%)**	**LGE (+)** **N = 8 (29.6%)**	**P-value**
Age (years)	13 (11-14.5)	14.5 (10.8-17.2)	0.31
Height (m)	1.3 (1.2-1.5)	1.4 (1.2-1.4)	0.73
Weight (kg)	47.6 (31.2-60.1)	49.9 (46-52.6)	0.894
BSA (m²)	1.4 (1.1-1.5)	1.4 (1.2-1.5)	0.811
BMI (kg/m²)	24.1 (20-32.7)	25.5 (24.3-26.5)	>0.9
Autonomic Function			
Average HR (bpm)	99 (91.5-105)	96.5 (88-100.2)	0.395
SDNN (ms)	101.9 (89.5-123.6)	97.5 (94.7-107.3)	>0.9
Respiratory Mechanics			
FVC%	92.1 (79.2-104.3)	85.7 (60.9-93.8)	0.198
FEV_1%	80.4 (77.9-97.2)	64.4 (53.7-79.7)	0.067
FEV_1/FVC	1.008 (0.940-1.048)	0.930 (0.842-0.973)	0.182
MIP%	54 (45.8-72.8)	56 (49.3-57.8)	0.622
MEP%	48 (35.1-59.9)	25.8 (19.1-36.0)	0.035
CMR Parameters			
Left Ventricle (LV)			
EDVi (ml/m²)	81.3 (65.4-88.7)	93.8 (84-115.1)	0.019
ESVi (ml/m²)	37.5 (29.3-40.7)	47.4 (44.8-71.8)	<0.001
LVMi (g/m²)	32.4 (29.3-38)	39.5 (37.6-44.9)	0.034
LVEF (%)	55.2 (47.5-57.7)	43.8 (37.9-48.6)	0.005
Native T1 (ms)	1337 (1319-1366)	1379 (1362-1418)	0.047
Post-contrast T1 (ms)	617 (586-721)	553 (492-588)	0.007
ECV (ratio)	0.29 (0.28-0.32)	0.34 (0.32-0.37)	0.004
Right Ventricle (RV)			
EDVi (ml/m²)	69.1 (52.6-85.1)	71 (65.1-76.8)	0.897
ESVi (ml/m²)	31.6 (23.3-41.2)	35.9 (31.4-38.6)	0.481
RVMi (g/m²)	24.4 (19.9-25.9)	22.7 (20.4-24.5)	0.696
RVEF (%)	54.6 (47.2-59)	48.1 (46.7-51.7)	0.147
Native T1 (ms)	1549 (1476-1634)	1523 (1452-1648)	0.834
Post-contrast T1 (ms)	457 (442-560)	430 (385-496)	0.297
ECV (ratio)	0.43 (0.41-0.49)	0.45 (0.42-0.50)	0.91

STRATIFICATION BY FVC%

No subject was ventilator-dependent or on positive-pressure ventilation at the time of this study. Nine (33.3%) of the 27 boys had abnormal FVC% (defined as <80% predicted). Compared to boys with normal FVC%, those with FVC <80% were significantly older (years) (16 [13-17] vs 11.5 [10.2-13], p = 0.012) and had higher BSA (m^2) (1.5 [1.4-1.5] vs 1.3 [1.1-1.4], p = 0.042). They also had worse FEV_1% (70.6 [55-79] vs. 90.4 [77.3-100.3], p = 0.006) and increased FEV_1/FVC (1.055 [1.005-1.099] vs. 0.943 [0.810-1.012], p = 0.012). There were no significant differences between MIP% and MEP%, CMR measurements of ventricular size, function and myocardial tissue characteristics, and measures of autonomic function. A complete list of parameters for these subgroups can be found in Table 3.

Table 3: Comparison of autonomic function, respiratory mechanics, and CMR parameters in patients with FVC ≥ 80% and FVC < 80%. Note: p-values are calculated using Wilcoxon rank sum test.

CHARACTERISTICS	FVC % ≥ 80 N = 18 (66.7%)	FVC % < 80 N = 9 (33.3%)	P-VALUE
Age (years)	11.5 (10.2-13)	16 (13-17)	0.012
Height (m)	1.3 (1.2-1.4)	1.4 (1.3-1.5)	0.269
Weight (kg)	45.5 (31.2-50.4)	58.6 (50-61.7)	0.054
BSA (m^2)	1.3 (1.1-1.4)	1.5 (1.4-1.5)	0.042
BMI (kg/m^2)	24.4 (19.5-30.7)	25.4 (24.1-33.9)	0.316
Autonomic Function			
Average HR (bpm)	98 (93.8-104.8)	99 (86-105)	0.738
SDNN (ms)	95.3 (89.5-121.5)	125 (115.2-130.9)	0.06
Respiratory Mechanics			
FVC%	99.6 (88.9-104.6)	64 (54-76.1)	<0.001
FEV_1%	90.4 (77.3-100.3)	70.6 (55-79)	0.006
FEV_1/FVC	0.943 (0.810-1.012)	1.055 (1.005-1.099)	0.012
MIP%	57 (44.7-78)	55 (51-57.3)	0.639
MEP%	45.5 (24.9-58.3)	35.5 (32.8-42.8)	0.616
CMR Parameters			
Left Ventricle (LV)			
EDVi (ml/m^2)	82.8 (67-94.8)	86.7 (65.9-89.4)	0.781
ESVi (ml/m^2)	38.7 (30.6-44.8)	43.9 (36.4-49.2)	0.631
LVMi (g/m^2)	35.9 (30.6-38.7)	35.9 (30.5-47.1)	0.561
LVEF (%)	52.6 (48.3-56)	46 (43.2-54.4)	0.341
Native T1 (ms)	1346 (1290-1378)	1364 (1335-1424)	0.238
Post-contrast T1 (ms)	600 (571-698)	586 (567-601)	0.528
ECV (ratio)	0.31 (0.28-0.33)	0.31 (0.29-0.32)	0.724
Right Ventricle (RV)			
EDVi (ml/m^2)	71 (55.7-85.2)	69.1 (53-79.4)	0.433
ESVi (ml/m^2)	32.5 (27.5-40.2)	35.7 (23-39.7)	0.90
RVMi (g/m^2)	24.4 (20.8-25.9)	20.1 (14.8-25)	0.176
RVEF (%)	52.4 (48.8-56.8)	48 (44.5-55)	0.348
Native T1 (ms)	1528 (1461-1600)	1627 (1502-1698)	0.12
Post-contrast T1 (ms)	454 (422-560)	444 (433-511)	0.868
ECV (ratio)	0.44 (0.43-0.50)	0.42 (0.39-0.49)	0.384

Discussion

While cardiac, pulmonary, and autonomic function decline with disease progression in boys with DMD, it is intuitive to expect interrelation between these processes. In this study, we systematically investigated the relationship of pulmonary and autonomic function with sensitive and validated CMR biomarkers of biventricular size, function, and remodeling, with particular emphasis on a comprehensive evaluation of the RV. Our findings show that degree of disease progression in one system does not necessarily correlate with another, suggesting that cardiac, pulmonary, and autonomic function may

decline independently of each other. These domains may not be as tightly linked at earlier stages of the disease process. Another important consideration is the genotypic heterogeneity within DMD – this broad range of mutations consequently yields diverse phenotypes, and it is possible that interdependence between cardiac, pulmonary, and autonomic function may be more apparent in specific genotypes with distinct progression patterns.

In keeping with prior literature, we observed that the presence of LGE is associated with worsening cardiomyopathy and LVEF.[29] LGE (+) boys also had significantly increased LV volumes (EDVi and ESVi) and mass, and worse indices of maladaptive microstructural changes (ECV, and native and post-contrast T1). Interestingly, despite CMR evidence of significant LV disease – reflected by the presence of focal fibrosis, an established hallmark of advanced cardiomyopathy[29], there were no statistically significant differences in biomarkers of RV size, myocardial tissue characteristics, or function between boys that were LGE (+) compared to those that were LGE (-). Save for MEP%, there was no significant difference in pulmonary or autonomic function across these groups. These findings suggest that RV health, respiratory mechanics, and autonomic function may be independent of LV dysfunction.

The abovementioned findings also raise several important physiologic and methodological considerations. The LV may deteriorate earlier in DMD cardiomyopathy because of its chronic exposure to systemic afterload, rendering it more susceptible to myocardial stress, injury, and progressive fibrosis, whereas the thinner-walled RV operates at lower pressures despite being perceived as more "vulnerable." Methodologically, LV parameters are more easily standardized and reproducible, while RV assessment – despite significant advancements, remains limited by its thin wall, complex geometry, and greater measurement variability. Thus, the predominance of LV abnormalities in LGE (+) patients may represent true earlier LV involvement as well as superior sensitivity of CMR for LV evaluation, highlighting the need for improved RV imaging techniques to clarify the timing and extent of biventricular disease progression.

A recent study addressed the effect of pulmonary function on right heart function. The authors found that RV indexed stroke volume obtained by CMR was significantly reduced in subjects who had <80% predicted FVC compared to patients who had more than 80% predicted FVC.[30] A similar study consisting of 57 boys with a mean age of 15.5 years reported that subjects with abnormal FVC% had lower RVEF and RVEDVi.[31] Our study found contrary results in that FVC% did not correlate with CMR biomarkers of RV volume, mass, myocardial tissue characteristics, and function between boys with normal versus abnormal predicted. Similar to the aforementioned study, we also found no significant difference in the LVEF between these groups. Furthermore, we found no differences in CMR biomarkers of LV volume, mass, tissue characteristics or autonomic function between boys with ≥80% predicted FVC% compared to those with <80%.

Interestingly, we found that MEP% was significantly worse in boys that were LGE (+). Notably, this group had normal FVC%. That is, worsening expiratory muscle strength correlated with the relatively late finding of LV dysfunction in the setting of preserved forced vital capacity. In a recent study, MEP and MIP demonstrated earlier impairment than conventional PFT measures in patients with DMD.[32] Not surprisingly, these indices have emerged as sensitive markers in detecting early respiratory dysfunction in neuromuscular disease compared with traditional spirometry.[19,20] In summary, decline in MEP% in DMD patients may be an early warning sign of pulmonary disease progression, before the decline in FVC%, and coincident with the appearance of discrete LV myocardial fibrosis. This may inform the earlier employment of respiratory support therapy in this patient population.

Overall, our findings suggest that perhaps cardiac, respiratory, and autonomic dysfunction are less influenced by each other, and more by overall patient functional capacity and ambulatory ability for example. Specifically, if the abdominothoracic or respiratory pump is compromised due to deconditioning, venous return and cardiac output is inhibited and no longer augmented. This decreased cardiac output may lead to the maladaptive macro and microstructural changes resulting in increased ventricular volumes, size, mass, and decreased function. Therefore, future studies may focus on optimizing pulmonary function with more aggressive ventilation strategies and employing active parasympathetic stimulation to reinstate vagal activity with controlled longitudinal assessment of their effects on cardiac function and remodeling.

Limitations

The primary limitation of the study was the small cohort size and lack of longitudinal data. Data from patients whose CMR and PFT were completed beyond the accepted 6-month interval of each other was excluded, further limiting the sample size. Importantly, 9 (33%) of boys did not have available MIP% and MEP% data. The correlations and trends we have described between the CMR biomarkers and PFT measures do not prove causality. Finally, we recognize the inherent selection bias in our study towards patients with less advanced disease, given the inclusion of relatively young patients and the overall ability of the subjects to adequately complete CMR and spirometry. However, this also underscores the importance of investigating early markers of dysfunction, as identifying and understanding these subtle changes may offer opportunities to intervene and potentially alter the trajectory of disease progression.

Conclusion

To our knowledge, this is one of the first prospective multicenter studies of DMD patients investigating the relationship between pulmonary and autonomic function and sensitive and validated CMR biomarkers of biventricular remodeling and function, with an emphasis on a comprehensive evaluation of the RV. Our findings suggest that cardiac, pulmonary, and autonomic function may decline independently of each other. While there is

certainly some interplay among these various parameters, clinical trials involving prospective implantation of ventilation strategies with real-time assessment of changes in cardiac function may help elucidate the mechanisms behind complex cardiopulmonary interactions in this patient population.

Supplemental Materials: Additional analyses are provided in the Supplemental Materials. Table 4 presents the results of age-adjusted logistic regression assessing the association between study variables and the presence of LGE. Tables 5 and 6 further explore disease stratification, comparing autonomic function, respiratory mechanics, and CMR parameters by LV ejection fraction (Table 5) and RV ejection fraction (Table 6).

Acknowledgements: The authors of this study would like to express their sincere gratitude to the patients and the families for their participation and contributions to the growing understanding of DMD. We would also like to thank our ancillary service collaborators. This study was additionally made possible by funding through NIH R01 HL131975 grant and the Molly and Samuel Kaplan Fellowship in Pediatric Cardiology at UCLA. The research described was additionally supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881.

Disclosure: The authors report no financial or other conflicts of interest related to the research described in this paper.

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Supplemental Tables

Table 4: Age-adjusted Logistic Regression of the presence of LGE on study variables

CHARACTERISTICS	OR (95% CI)	P-VALUE
Height (m)	0.02 (0, 35.03)	0.302
Weight (kg)	0.98 (0.9, 1.05)	0.494
BSA (m^2)	0.17 (0, 11.91)	0.421
BMI (kg/m^2)	0.99 (0.86, 1.13)	0.901
Autonomic Function		
Average HR (bpm)	0.98 (0.9, 1.06)	0.656
SDNN (ms)	1.03 (0.96, 1.13)	0.411
Respiratory Mechanics		
FVC%	0.98 (0.92, 1.03)	0.361
FEV_1%	0.96 (0.9, 1.01)	0.176
FEV_1/FVC	0.96 (0.89, 1.02)	0.181
MIP%	0.97 (0.9, 1.02)	0.241
MEP%	0.94 (0.85, 1)	0.107
CMR Parameters		
Left Ventricle (LV)		
EDVi (ml/m^2)	1.06 (1.01, 1.12)	0.041
ESVi (ml/m^2)	1.08 (1.02, 1.18)	0.037
LVMi (g/m^2)	1.09 (0.99, 1.25)	0.122
LVEF (%)	0.85 (0.72, 0.96)	0.024
Native T1 (ms)	1.01 (1, 1.03)	0.162
Post-contrast T1 (ms)	0.99 (0.97, 1)	0.048
ECV (ratio)	*Not estimatable**	-
Right Ventricle (RV)		
EDVi (ml/m^2)	1.01 (0.96, 1.06)	0.726
ESVi (ml/m^2)	1.04 (0.95, 1.15)	0.399
RVMi (g/m^2)	1.01 (0.89, 1.13)	0.898
RVEF (%)	0.95 (0.83, 1.07)	0.418
Native-T1 (ms)	1 (0.99, 1.01)	0.549
Post-contrast T1 (ms)	1 (0.99, 1)	0.476
ECV (ratio)	0.98 (0.86, 1.11)	0.776

* OR for LV ECV (ratio) is not estimatable due to quasi-complete separation. Nearly all with higher LV ECV had LGE present, and those with lower values did not.

Table 5: Stratification by LV ejection fraction (LVEF) and comparison of autonomic function, respiratory mechanics, and CMR parameters.

CHARACTERISTICS	LVEF ≥ 55% N = 10 (37%)	LVEF 45-54% N = 9 (33.3%)	LVEF < 45% N = 8 (29.6%)	P-VALUE
Age (years)	12 (11-13)	13 (10-15)	15 (11-17)	0.485
Height (m)	1.3 (1.2-1.4)	1.3 (1.3-1.4)	1.4 (1.2-1.5)	0.72
Weight (kg)	37.4 (28.6-45.8)	50.5 (49.8-60.3)	52.2 (44.9-56.9)	0.09
BSA (m^2)	1.2 (1-1.4)	1.5 (1.3-1.5)	1.4 (1.3-1.6)	0.153
BMI (kg/m^2)	21.7 (19.5-29.3)	27.7 (26.1-33.9)	25.1 (22.7-27.8)	0.245
Autonomic Function				
Average HR (bpm)	98 (90.8-107.8)	100 (96-105)	96.5 (88-100.5)	0.594
SDNN (ms)	107.3 (86.6-123.1)	100.4 (94.7-119.1)	101.9 (95.3-119.9)	0.878
Respiratory Mechanics				
FVC%	101.1 (82.7-104.5)	92.1 (79.7-104.3)	80 (68.4-87.5)	0.083
FEV_1%	82.8 (72.7-100)	85.4 (75.2-98.3)	73.9 (55.7-79.3)	0.143
FEV_1/FVC	1.006 (0.941-1.031)	0.938 (0.873-1.013)	1.012 (0.923-1.082)	0.657
MIP%	49.9 (42.4-68.1)	56 (54-60)	57.8 (49.6-69.7)	0.854
MEP%	44.9 (24.5-71.4)	42.9 (38-48)	35.1 (22.5-50.6)	0.562
CMR Parameters				
Left Ventricle (LV)				
LGE (+)	0	4	4	-
EDVi (ml/m^2)	84.8 (69.8-90.5)	81.3 (66.6-91.8)	81.5 (67.6-115.1)	0.809
ESVi (ml/m^2)	37 (29.1-39.9)	43.9 (30.4-45)	47.3 (37.9-71.8)	0.058
LVMi (g/m^2)	32.7 (30.1-37.6)	31.9 (30.1-38.8)	39.3 (37.5-45.8)	0.157
Native T1 (ms)	1337 (1282-1370)	1350 (1329-1377)	1373 (1327-1424)	0.584
Post-contrast T1 (ms)	634 (591-698)	578 (536-688)	584 (557-596)	0.24
ECV (ratio)	0.30 (0.28-0.32)	0.32 (0.30-0.35)	0.31 (0.28-0.33)	0.471
Right Ventricle (RV)				
EDVi (ml/m^2)	83.7 (52-88)	69.1 (67.8-76.2)	56.5 (52.9-73.3)	0.381
ESVi (ml/m^2)	33.8 (22.2-42)	33.1 (24.3-37)	34.9 (26.4-39.7)	0.795
RVMi (g/m^2)	25.9 (21.6-29.2)	21.7 (20.1-24.4)	21.8 (15.7-24.6)	0.211
RVEF (%)	54.9 (50.6-59.6)	54.6 (51.6-57.3)	45.5 (42.5-47.3)	0.005
Native T1 (ms)	1577 (1508-1666)	1470 (1420-1500)	1615 (1571-1681)	0.035
Post-contrast T1 (ms)	466 (457-547)	415 (353-572)	444 (433-482)	0.138
ECV (ratio)	0.49 (0.44-0.53)	0.44 (0.41-0.45)	0.42 (0.40-0.49)	0.311

Note: P-values are calculated using Kruskal Wallis test. Normal function: LVEF ≥ 55%; Mildly diminished function: LVEF 45-54%; Moderately to severely diminished function: LVEF <45%

Table 6: Stratification by RV ejection fraction (RVEF) and comparison of autonomic function, respiratory mechanics, and CMR parameters.

CHARACTERISTICS	RVEF ≥ 55% N = 9 (33.3%)	RVEF 45-54% N = 14 (51.9%)	RVEF < 45% N = 4 (14.8%)	P-VALUE
Age (years)	12 (10-13)	12.5 (11-15.8)	16.5 (15.5-18)	0.039
Height (m)	1.3 (1.3-1.3)	1.3 (1.2-1.5)	1.5 (1.5-1.6)	0.061
Weight (kg)	47.6 (31.3-58.6)	47.8 (32.2-53.6)	58.1 (53.3-65.7)	0.194
BSA (m^2)	1.3 (1.1-1.5)	1.3 (1-1.5)	1.6 (1.5-1.7)	0.057
BMI (kg/m^2)	27.3 (19.9-33.9)	25.5 (20.6-30.7)	24.4 (23.8-27.2)	0.927
Autonomic Function				
Average HR (bpm)	97 (85-105)	99.5 (90.8-104)	97.5 (94-101.8)	0.974
SDNN (ms)	93 (79.2-112.3)	110.6 (94.8-124.6)	110.9 (106.4-115.4)	0.446
Respiratory Mechanics				
FVC%	104.3 (79.7-112.5)	91.8 (84.8-100)	69.6 (56-79.1)	0.099
FEV_1%	79.7 (75.2-85.9)	87.3 (71.7-100.1)	73.7 (61.2-77.7)	0.324
FEV_1/FVC	0.968 (0.790-1.012)	1.006 (0.888-1.056)	1.046 (0.985-1.100)	0.260
MIP%	49.9 (41.1-65.1)	55 (47.3-63.1)	80.2 (73.5-86.9)	0.359
MEP%	63.6 (51.3-74.1)	37 (21.3-45.8)	47.5 (41.3-53.7)	0.177
CMR Parameters				
Left Ventricle (LV)				
LGE (+)	1	6	1	-
EDVi (ml/m^2)	81.3 (65-88.1)	88 (74.2-98)	65.9 (61.4-86.2)	0.345
ESVi (ml/m^2)	36.4 (29.2-40.6)	44.3 (38.4-49.1)	33.4 (28.4-64.6)	0.110
LVMi (g/m^2)	32.4 (30.5-36.3)	38.2 (32.8-44.2)	34.4 (28.1-42.7)	0.285
LVEF	55.3 (51-58.7)	48.6 (44.4-55)	41 (34.2-47.7)	0.072
Native T1 (ms)	1344 (1329-1358)	1360 (1294-1382)	1375 (1332-1424)	0.672
Post-contrast T1 (ms)	693 (647-754)	576 (542-591)	595 (510-613)	0.013
ECV (ratio)	0.32 (0.29-0.32)	0.32 (0.30-0.35)	0.29 (0.28-0.30)	0.360
Right Ventricle (RV)				
EDVi (ml/m^2)	78.4 (53-85.1)	73.9 (68-86.6)	42.1 (36.6-48.7)	0.027
ESVi (ml/m^2)	30.8 (22.3-34.8)	38.9 (32-42.1)	24.6 (21.8-29.4)	0.034
RVMi (g/m^2)	24.4 (20.1-25.6)	24.7 (21.9-26)	13.7 (11.9-15.1)	0.007
Native T1 (ms)	1477 (1443-1575)	1530 (1463-1593)	1704 (1667-1750)	0.027
Post-contrast T1 (ms)	538 (453-681)	443 (385-462)	455 (434-511)	0.140
ECV (ratio)	0.44 (0.38-0.53)	0.44 (0.43-0.49)	0.40 (0.34-0.43)	0.316

Note: P-values are calculated using Kruskal Wallis test. Normal: RVEF ≥ 55%; Mildly diminished: RVEF 45-54%; Moderately/severely diminished: RVEF <45