Ambulatory Monitoring and Arrhythmic Outcomes in Pediatric and Adolescent Patients With Duchenne Muscular Dystrophy

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Background—Patients with Duchenne Muscular Dystrophy (DMD) develop cardiac fibrosis and dilated cardiomyopathy. We described the frequency of significant Holter findings in DMD, the relationship between cardiac function and arrhythmia burden, and the impact of these findings on clinical management.

Methods and Results—A retrospective review was done of patients with DMD who received a Holter from 2010 to 2014. Clinical and arrhythmic outcomes were analyzed. Patients were classified based on left ventricular ejection fraction (LVEF): ≥55%, 35% to 54% and <35%. Significant Holter findings included atrial tachycardia, ventricular tachycardia and atrial fibrillation/flutter. Logistic regression was used to assess predictors of significant Holter findings and change in care. The study included 442 Holters in 235 patients. Mean age was 14±4 years. Patients with cardiac dysfunction were older, and had increased late gadolinium enhancement and left ventricular dilation (*P*<0.01). There were 3 deaths (1%), all with normal function and none cardiac. Patients with LVEF <35% had more arrhythmias including nonsustained atrial tachycardia (*P*=0.01), frequent premature ventricular contractions, ventricular couplets/triplets, and nonsustained ventricular tachycardia (*P*<0.001) compared to the other groups. LVEF <35% (*P*<0.001) was the only predictor of clinically significant Holter finding. Four patients (40%) had change in medication in the LVEF <35% group compared to 9 (3%) in the ≥55% and 4 (4%) in the 35% to 54% groups (*P*<0.001).

Conclusions—Sudden cardiac events are rare in DMD patients with an LVEF >35%. Significant Holter findings are rare in patients with DMD who have an LVEF >35%, and cardiac dysfunction appears to predict significant Holter findings. Holter monitoring is highest yield among DMD patients with cardiac dysfunction. (*J Am Heart Assoc*. 2016;5:e002620 doi: 10.1161/JAHA.115.002620)

Key Words: arrhythmia • dilated cardiomyopathy • Duchenne muscular dystrophy • Holter

D uchenne muscular dystrophy (DMD) is an X-linked disorder caused by mutations in dystrophin and characterized by muscular degeneration. Though the potential for development of dilated cardiomyopathy in DMD has been known for decades,[1,2] advances in respiratory care have improved life expectancy[3,4] and thus unmasked almost uniform progression to dilated cardiomyopathy in long-term survivors.

Advances in cardiac imaging, especially cardiac magnetic resonance imaging (CMR), have expanded our understanding of the cardiac changes in DMD, which are present prior to the development of global left ventricular (LV) systolic dysfunction. The development of late gadolinium enhancement (LGE), in particular, predates the development of LV dysfunction.[5–7] LGE is thought to represent the earliest evidence of myocardial damage, given that the distribution matches the fibrosis found on autopsy specimens[8,9] and thus has been used to guide the study of potentially cardioprotective medications.[10] The presence of LGE is also thought to be a potential risk factor for arrhythmia. The perceived risk of arrhythmia and for sudden cardiac death within the DMD is also reflected in the American Academy of Pediatrics Guidelines,[11] which suggests clinicians consider Holter monitors in patients with cardiac dysfunction. More recent data support this recommendation, because the development of LGE may not only predate cardiac dysfunction, but may also serve as a substrate for clinically important arrhythmias.[12] The clinical utility of LGE in predicting adverse events and disease-specific outcome is not without precedent. LGE has been reported to be a marker for malignant arrhythmia and sudden death in other cardiomyopathies.[13–16]

Given this concern, the recent National Heart, Lung, and Blood Institute/Parent Project Muscular Dystrophy (NHLBI/PPMD) Working Group[17] recommended further assessing the clinical utility of a variety of cardiac surveillance methods, notably CMR. The group also singled out the area of screening and therapies of cardiac arrhythmia in DMD as a particularly understudied area.

Our center has recommended screening Holter monitoring in DMD patients with evidence of LGE or systolic dysfunction as routine care, given the perceived risk of arrhythmia and sudden death. Herein, we report the results of this screening protocol and relate these findings to cardiac imaging findings and clinical outcomes in a large cohort of DMD patients.

Methods

Patient Demographics

This was a single-center retrospective analysis of patients with a diagnosis of DMD who received a Holter monitor from 2010 to 2014. The study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (IRB#2014-4394). Given that the study was retrospective and there was minimal risk to the participants, informed consent was waived by the Institutional Review Board. Patients for this study were identified from the Holter database. Patients were included in the analysis if there was either an echocardiogram or CMR with measured left ventricular ejection fraction (LVEF) performed within 2 years of the Holter study. Patient demographics, cardiac imaging (including echocardiogram and CMR) and electrophysiologic data were obtained from the patient's medical record. Patient age at time of Holter, sex, race, use of cardiovascular medications, history of cardiac arrhythmia, and placement of pacemaker or implantable cardioverter defibrillator (ICD) were reviewed. Outcome data including initiation or change in antiarrhythmic medication, death, aborted sudden death, and cardiac transplantation were reviewed.

Holter Monitoring

The decision to perform a Holter monitor was determined by each patient's cardiomyopathy physician. Holter monitors were 2-lead monitors (modified V1 and V5) and placed routinely for 24 hours. Patient age and Holter indication including asymptomatic screening, symptomatic screening, or follow-up of a clinical finding were analyzed.

Holter data evaluated included the following: heart rate, atrial ectopy, ventricular ectopy, supraventricular tachycardia, atrioventricular block, symptoms, and whether specific symptoms correlated with a rhythm disturbance. Atrial and ventricular ectopy were subclassified to rare/occasional (<720 ectopic beats over 24 hours), frequent (>720 ectopic beats over 24 hours), couplets/triplets (2–3 beats in a row), nonsustained tachycardia (4–30 beats in a row), and sustained tachycardia (>30 beats in a row).[18,19] Significant Holter findings included the following: nonsustained atrial tachycardia, sustained atrial tachycardia, nonsustained ventricular tachycardia, sustained ventricular tachycardia, nonsustained atrial flutter/fibrillation, sustained atrial flutter/fibrillation, and a new finding of conduction system disease.

Holter-based arrhythmia burden was analyzed (1) by each individual Holter as a separate event and (2) by individual patient with cumulative data from one or more Holter studies.

Cardiac Imaging

Patients' individual Holters were classified based on LVEF by echocardiogram or CMR. The functional classes were divided into: EF ≥55% (normal function), EF 35% to 54% (mild to moderate dysfunction), and EF <35% (severe dysfunction). The patient had to have either an echocardiogram or CMR with EF calculated within 2 years of the individual Holter and if they had multiple cardiac imaging studies performed, the study performed closest in time to the Holter was included. Echocardiogram data included LVEF, absolute LV end diastolic dimension, and LV end diastolic dimension indexed z-score. CMR data included LVEF, RVEF, presence of LGE, and LV end diastolic volume (mL/m^2). LV dilation was defined as LV end diastolic dimension >5.9 cm or LV end diastolic dimension z-score >2 in patients under 18 years of age[20] and LV end diastolic volume >90 mL/m^2 (magnetic resonance imaging data).

Patients with multiple Holters during the study period were included if there was cardiac imaging within 2 years of the Holter performed. Patients' overall LVEF classification for the study was based on the lowest LVEF measured during the study. Each individual Holter was classified based on the LVEF at the time the Holter was performed.

Change in Management

A change in response related to the Holter data was evaluated by chart review. Significant changes were assessed to be a result of the Holter if a change occurred within 60 days of the Holter monitor. Significant changes included pacemaker placement, ICD placement, electrophysiology study, implantable loop recorder placement, and initiation or dose change of anti-arrhythmic medication. Dose change in response to Holter findings was assessed based on clinical decision making as stated in clinical notes and attributed to Holter findings.

Statistical Analysis

Data were recorded and entered into a REDCap database and analyzed by data management personnel for completeness

and accuracy. All critical variables had a 100% check for accuracy of entry. The patient demographics were compared between the LVEF groups: EF ≥55%, EF 35% to 54%, and EF <35%. Comparisons between the different LV EF groups based on the Holter study findings were performed using combined Holter results for each patient. Tests of differences in proportions were made by Fischer's exact test or other χ^2 test. Continuous variables were tested for normality. Comparisons of means or medians were made using 1-way ANOVA or Kruskal–Wallis, respectively. Analyses for the composite outcome of (1) significant Holter finding and (2) change in care were performed using the variables: age, LVEF, RVEF, LV dilation, presence of LGE, steroid medications, carvedilol, angiotensin converting enzyme inhibitor-l, angiotensin receptor blocker, Aldactone (spironolactone), frequent premature atrial contractions, frequent ventricular contractions, nonsustained atrial tachycardia, and nonsustained ventricular tachycardia. Logistic regression with backward elimination was used, and variables with *P*-value <0.05 were included in the final model.

Results

Patient Demographics

During the 5-year study period, 235 patients met inclusion criteria. The majority of patients had normal function, with 184 in the LVEF ≥55% group, 46 in the LVEF 54% to 35%, and 5 in the LVEF <35% group (Table 1). Most patients were white, treated with steroids at the time of their study inclusion, and all were male. Patients with LV dysfunction were less-often treated with deflazacort therapy and more frequently treated with carvedilol, angiotensin converting enzyme inhibitors, and Aldactone (spironolactone). A single patient was treated with digoxin. Patients with LV dysfunction were also significantly older and were more likely to have LV dilation, RV dysfunction, and evidence of LGE.

Individual Holter

A total of 442 Holters were performed during the study period (Table 2). The majority of the Holters (88%) were performed as a routine screen without symptoms. Atrial ectopy was common, observed in 68% of the Holters. In patients with cardiac dysfunction, frequent premature atrial contractions and nonsustained atrial tachycardia were seen more commonly. No patients had sustained atrial tachycardia.

Ventricular ectopy was also frequent, observed in 45% of the Holters. All ventricular arrhythmia subgroups were more commonly observed in patients with cardiac dysfunction. Notably, 30% of patients in the LVEF <35% group had nonsustained ventricular tachycardia compared to 0% and 2% in the EF ≥55% and EF 35% to 54% groups, respectively. No patients had sustained ventricular tachycardia.

Significant Holter findings were rare (3%) in the full cohort, but were seen more frequently in patients with an LVEF <35% (40%). Nonsustained atrial tachycardia and nonsustained ventricular tachycardia occurred most frequently in patients with an LVEF <35%. Of note, there was 1 patient with nonsustained atrial fibrillation and 1 patient with supraventricular tachycardia, both in the normal LVEF group.

Though Holter monitoring rarely led to change in care (4%), change in care occurred at a higher rate in patients with severe cardiac dysfunction (40%), and the only change in care seen in the entire cohort was either initiating or changing the dose of antiarrhythmic medications.

Individual Patient

When assessing Holter data by each individual patient, similar results were found. Nonsustained atrial tachycardia and all ventricular arrhythmias (premature ventricular contractions, ventricular couplets, and triplets and nonsustained ventricular tachycardia) were more common among patients with LV dysfunction (Table 3). Significant Holter findings rarely occurred (5%) within the full cohort but increased in frequency as cardiac dysfunction progressed. Most notably, nonsustained atrial and nonsustained ventricular tachycardias were more common in patients with LV dysfunction. Initiation or change in antiarrhythmic medications was seen more frequently in patients with cardiac dysfunction.

Outcomes

LVEF <35% was the only independent predictor of significant Holter findings via logistic regression analysis (odds ratio of 122 [versus EF ≥55%] and odds ratio of 7 [versus EF 35–54%] [*P*=0.002]). Patients with symptoms as the indication for Holter were more likely to have significant Holter findings compared to those without symptoms. Holters were placed for clinical symptoms in 15 patients, most commonly for palpitations 11 (73%), of which 10 patients (67%) had clinical symptoms during the Holter. Significant Holter findings occurred more frequently when placed for symptoms 3 (20%) compared to 9 (2%) of asymptomatic Holters (*P*<0.001). The Holter findings included nonsustained ventricular tachycardia, nonsustained atrial fibrillation, and supraventricular tachycardia when placed for symptoms. There was no difference in change in care, which occurred in 2 (13%) of Holters with symptoms compared to 15 (4%) asymptomatic Holters (*P*=0.052). Holter monitoring resulted in change of

Table 1. DMD Patient Demographics

	Total	EF ≥55%	EF 54% to 35%	EF <35%	P Value
Number of patients, n	235	184	46	5	
Number of Holters, n (mean per patient)	442 (1.9)	317 (1.7)	112 (2.4)	13 (2.6)	<0.001
Race, n (%)					1
White	223 (95)	174 (95)	44 (96)	5 (100)	
Black or African American	1 (<1)	0	1 (2)	0	
Asian	3 (1)	2 (1)	1 (2)	0	
Other	8 (3)	8 (4)	0	0	
Age at last follow-up, median (IQR)	14 (11, 17)	13 (11, 16)	17 (15, 20)	19 (18, 20)	<0.001
Steroid therapy, n (%)					
Deflazacort	173 (74)	142 (77)	30 (65)	1 (20)	<0.001
Prednisone	44 (19)	31 (17)	12 (26)	1 (20)	0.02
Cardiovascular medications, n (%)					
Carvedilol	70 (30)	32 (17)	34 (74)	4 (80)	<0.001
Digoxin	1 (<1)	0	0	1 (20)	0.02
ACE-I	124 (53)	80 (43)	39 (85)	5 (100)	<0.001
ARB	31 (13)	26 (14)	5 (11)	0	0.08
Aldactone	48 (20)	23 (13)	22 (48)	3 (60)	<0.001
Right ventricular ejection fraction, n (%)					<0.001
RVEF ≥50%	192 (81)	154 (83)	36 (78)	2 (40)	
RVEF 30% to 49%	4 (2)	0	3 (7)	1 (20)	
RVEF <30%	0	0	0	0	
Late gadolinium enhancement (at any time), n (%)	96 (41)	61 (33)	32 (70)	3 (60)	<0.001
Left ventricular dilation, n (%)	44 (19)	28 (15)	12 (26)	4 (80)	<0.001
ICD, n (%)	0	0	0	0	
Pacemaker, n (%)	0	0	0	0	
Syncope, n (%)	1 (<1)	1 (<1)	0	0	0.78
Death, n (%)	3 (1)	3 (2)	0	0	0.48
Sudden cardiac death	0	0	0	0	
Other	3 (1)	3 (2)	0	0	
Aborted sudden death, n (%)	0	0	0	0	
Transplant, n (%)	0	0	0	0	
Arrhythmia history, n (%)					
Atrial flutter/fibrillation	2 (1)	2 (1)	0	0	0.61
SVT	3 (1)	1 (1)	2 (4)	0	0.09
Ventricular arrhythmias	2 (1)	0	1 (2)	1 (20)	0.008
History of conduction system disease, n (%)	1 (<1)	1 (1)	0	0	0.78

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DMD, Duchenne muscular dystrophy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; RVEF, right ventricular ejection fraction; SVT, supraventricular tachycardia.

care in 4% of all studies, all being initiation or change in medications, and was most commonly seen in patients with LVEF <35%. Frequent premature ventricular contractions was an independent factor for change in care in logistic regression analysis (odds ratio 8.6, *P*<0.001).

There were only 3 deaths (1%) within the study cohort. Of these 3 patients, all had normal cardiac function and none of the deaths were cardiac related (sepsis, respiratory failure, likely fat embolus after a fracture). No patients received an ICD during the study period.

Table 2. DMD Holter Characteristics (Per Individual Holter)

	Total	EF ≥55%	EF 54% to 35%	EF <35%
Number of Holters, n	442	337	95	10
Age at time of Holter median (IQR)	13 (11, 16)	12 (10, 15)	17 (14, 20)	18 (16, 20)
Average heart rate median (IQR)	100 (93 106)	101 (95 108)	97 (89, 104)	88 (73, 98)
Holter indication asymptomatic screening, n (%)	388 (88)	309 (92)	75 (79)	4 (40)
Atrial arrhythmias, n (%)	301 (68)	232 (69)	61 (64)	8 (80)
Rare/Occ PACs	292 (66)	224 (66)	61 (64)	7 (70)
Frequent PACs	3 (<1)	1 (<1)	1 (1)	1 (10)
Atrial couplets/atrial triplets	30 (7)	24 (7)	5 (5)	1 (10)
Nonsustained atrial tachycardia	6 (1)	3 (1)	1 (1)	2 (20)
Sustained atrial tachycardia	0	0	0	0
Nonsustained atrial fib/atrial flutter	1 (<1)	1 (<1)	0	0
Sustained atrial fib/atrial flutter	0	0	0	0
Ventricular arrhythmias, n (%)	197 (45)	120 (36)	67 (70)	10 (100)
Rare/Occ PVCs	175 (40)	111 (33)	59 (62)	5 (50)
Frequent PVCs	21 (5)	8 (2)	8 (8)	5 (50)
Ventricular couplets/triplets	34 (8)	16 (5)	12 (13)	6 (60)
Nonsustained ventricular tachycardia	5 (1)	0	2 (2)	3 (30)
Accelerated ventricular rhythm	3 (<1)	2 (<1)	1 (1)	0
Sustained ventricular tachycardia	0	0	0	0
SVT, n (%)	1 (<1)	0	1 (1)	0
Heart block, n (%)	2 (<1)	2 <1)	0	0
First-degree AV block, n (%)	0	0	0	0
Mobitz Type I (non-significant), n (%)	2 (<1)	2 (<1)	0	0
AV block other than above, n (%)	0	0	0	0
Patient symptoms, n (%)	15 (3)	11 (3)	3 (3)	1 (10)
Significant Holter finding, n (%)	12 (3)	4 (1)	4 (4)	4 (40)
Nonsustained ventricular tachycardia	5 (1)	0	2 (2)	3 (30)
Sustained ventricular tachycardia	0	0	0	0
Nonsustained atrial tachycardia	6 (1)	3 (1)	1 (1)	2 (20)
Nonsustained atrial fib/atrial flutter	1 (<1)	1 (<1)	0	0
Sustained AT/atrial fib/flutter	0	0	0	0
SVT	1 (<1)	0	1 (1)	0
Conduction system disease	0	0	0	0
Other	0	0	0	0
Change in care, n (%)	17 (4)	9 (3)	4 (4)	4 (40)
Pacemaker implant	0	0	0	0
Defibrillator implant	0	0	0	0
EP study	0	0	0	0
Loop recorder	0	0	0	0
Change in medication	17 (4)	9 (3)	4 (4)	4 (40)
Other	0	0	0	0

AV indicates atrioventricular; AT, atrial tachycardia; DMD, Duchenne muscular dystrophy; EF, ejection fraction; EP, electrophysiology; fib, fibrillation; IQR, interquartile range; Occ, occasional; PAC, premature atrial contraction; PVC, premature ventricular contraction; SVT, supraventricular tachycardia.

Table 3. DMD Holter Characteristics (Per Patient Includes All Holters Per Patient)

	Total (n=235)	EF ≥55 (n=184)	EF 54 to 35 (n=46)	EF <35 (n=5)	P Value
Age at time of study median (IQR)	13 (11, 16)	12 (10, 15)	17 (15, 20)	18 (18, 19)	<0.001
Atrial arrhythmias, n (%)	190 (81)	147 (80)	38 (83)	5 (100)	0.7
Rare/Occ PACs	188 (80)	145 (79)	38 (83)	5 (100)	0.6
Frequent PACs	3 (1)	1 (<1)	1 (2)	1 (20)	0.03
Atrial couplets/triplets	26 (11)	20 (11)	5 (11)	1 (20)	0.7
Nonsustained AT	6 (3)	3 (2)	1 (2)	2 (40)	0.007
Sustained AT	0	0	0	0	
Atrial fib/atrial flutter	1 (<1)	1 (<1)	0	0	1
Ventricular arrhythmias, n (%)	119 (51)	79 (43)	35 (76)	5 (100)	<0.001
Rare/Occ PVCs	114 (49)	76 (41)	34 (74)	4 (80)	<0.001
Frequent PVCs	13 (6)	4 (2)	6 (13)	3 (60)	<0.001
Ventricular couplets/triplets	25 (11)	11 (6)	10 (22)	4 (80)	<0.001
NSVT	5 (2)	0	3 (7)	2 (40)	<0.001
Sustained VT	0	0	0	0	
Accelerated vent rhythm	3 (1)	2 (11)	1 (2)	0	0.5
SVT, n (%)	1 (<1)	0	1 (2)	0	0.2
Heart block, n (%)	2 (1)	2 (1)	0	0	1
First-degree AV block, n (%)	0	0	0	0	
Mobitz Type I (nonsignificant), n (%)	2 (1)	2 (1)	0	0	1
AV block other than above, n (%)	0	0	0	0	
Patient symptoms, n (%)	15 (6)	11 (6)	3 (7)	1 (20)	0.34
Significant Holter finding, n (%)	12 (5)	4 (2)	5 (11)	3 (60)	<0.001
Nonsustained VT	5 (2)	0	3 (7)	2 (40)	<0.001
Sustained VT	0	0	0	0	
Nonsustained AT	6 (3)	3 (2)	1 (2)	2 (40)	0.01
Nonsustained atrial fibrillation/atrial flutter	1 (<1)	1 (<1)	0	0	1
Sustained atrial tachycardia/atrial fibrillation/atrial flutter	0	0	0	0	
Supraventricular tachycardia	1 (<1)	0	1 (2)	0	0.2
Conduction system disease	0	0	0	0	
Other	0	0	0	0	
Change in care, n (%)	12 (5)	7 (4)	3 (7)	2 (40)	0.01
Pacemaker implant	0	0	0	0	
Defibrillator implant	0	0	0	0	
EP study	0	0	0	0	
Loop recorder	0	0	0	0	
Change in medication	12 (5)	7 (4)	3 (7)	2 (40)	0.01
Other	0	0	0	0	

AT indicates atrial tachycardia; AV, atrioventricular; DMD, Duchenne muscular dystrophy; EF, ejection fraction; EP, electrophysiology; fib, fibrillation; IQR, interquartile range; NSVT, nonsustained ventricular tachycardia; Occ, occasional; PAC, premature atrial contraction; PVC, premature ventricular contraction; vent, ventricular; VT, ventricular tachycardia.

Discussion

In an analysis of Holter results in a large cohort of patients with DMD, we found that clinically significant findings are rare among patients with normal (1%) or even moderate dysfunction (4%). LV dysfunction was the sole predictor of significant Holter findings, while Holter results dictated a change in clinical care in only 3% of patients with an LVEF >35%.

Patients in whom the Holter was placed for symptoms were more likely to have significant findings compared to asymptomatic screening Holters. There were no cardiac deaths, life-threatening arrhythmias, or ICDs placed during the course of the study. These data suggest that screening Holter monitoring should focus on patients with significant dysfunction or concerning symptoms and may also be a model to help guide further studies aimed at assessing risk of sudden death in patients with DMD.

Historically, our understanding of cardiovascular changes present in DMD was limited to examination of autopsy specimens that revealed dilated cardiomyopathy, as well myocardial fibrosis.[8,9] The development of more advanced cardiac imaging tests has allowed the identification of cardiac abnormalities that predate the development of cardiac dysfunction.[5,7,12,21] CMR in particular has become the focus study, given its ability to assess early myocardial damage, along with providing reliable measures of ventricular function. The clinical utility of CMR is reflected in the content of the recent NHLBI/PPMD Working Group findings.[17] The Working Group made a number of recommendations and singled out the need to refine clinical care guidelines to reflect the phenotyping revolution that has occurred with the development of CMR. In addition, they also identified the areas of arrhythmia screening as an understudied area. This is reflected in the discrepant or missing arrhythmia monitoring recommendations in various DMD care guidelines.[11,22,23]

A recent study of 32 patients with DMD by Menon et al[12] attempted to address some of these deficiencies. They noted that increasing LGE burden was associated with worsening LV function and ventricular tachycardia. Our analysis showed that LV function alone predicted significant Holter findings. LGE, in particular, was not associated with significant Holter findings. While the results seem contradictory, we believe closer examination of the results of Menon et al suggests the data may be consistent. There were incremental increases in ventricular arrhythmias as LGE became more widespread and function decreased. Previous studies have shown LGE development not only predates systolic dysfunction, but the burden increases as systolic function decreases.[6] Thus, the limited number of patients in their study likely limited the ability to differentiate the effects of each, and it is plausible that the results noted are heavily weighted by the number of patients with LGE in the study that had more than mild dysfunction. Our results are also consistent with findings in patients with x-linked dilated cardiomyopathy and dystrophin defects where there is a high risk of progression to heart failure, but a low risk of life-threatening arrhythmias.[24] This is also consistent with recent data from other types of pediatric dilated cardiomyopathy where arrhythmia burden worsens as systolic function decreases.[25] Thus, while CMR may be of use for the many reasons described within the NHLBI/PPMD Working

Group findings,[17] our data suggest that obtaining a CMR solely to assess the presence of LGE in order to help gauge arrhythmia risk may have more limited utility.

While our data have shown that clinically significant Holter findings are rare in patients with an EF >35%, it is worth noting that this does not lead us to conclude that Holter monitoring in patients with an EF >35 is of no utility. In fact, it is quite possible that the clinical utility of Holter monitoring may only become appreciated over time and as harder outcomes are reached (mortality, sudden cardiac death, etc). This would need to be assessed with a more longitudinal study, over a longer period of time. While our study is the largest DMD Holter study to date, the mean number of Holters per patient is just less than 2 and the clinical utility of multiple studies may become evident with time.

Finally, we are unable to assess the utility of Holter monitoring as it relates to the risk of sudden cardiac death given the low event rate; however, the low event rate in this study suggests that studies attempting to quantify the risk of sudden cardiac death in the current era should focus on those with significant dysfunction. Given the small number of patients with severe dysfunction, we are unable to address the utility of screening Holter monitoring in these patients, but even with limited numbers the arrhythmia rate appears much higher as systolic function worsens, suggesting future study should focus on these subgroups. The potential of minimally invasive arrhythmia monitoring[26] may help to answer the question and address the issue of cause of death in patients where there is concern for possible sudden cardiac death. This also comes with the caveat that nonsustained ventricular tachycardia commonly increases in adults with dilated cardiomyopathy, though it has not been shown to be a predictor of adverse outcome independent of EF.[27,28]

Limitations

The data presented and interpretation of the data suffer from the limitations inherent to retrospective studies; however, some specific limitations should be noted. First, while there were a limited number of patients who died in our study, we only examined the outcomes of patients who received a Holter. Routine Holter monitoring has only become a more regimented part of our clinical evaluation within the last few years and some patients, especially early in the study period, did not receive a Holter.

Conclusions

Our findings begin to the fill the existing gap on the role of arrhythmia screening in patients with DMD. Future studies are needed to investigate whether Holter results alone, or in

composite with imaging data, are able to predict adverse clinical outcomes, notably sudden cardiac death, and the potential role of ICDs. Our data suggest that future studies should focus on patients with greater cardiac dysfunction or symptoms, as the arrhythmia burden appears small in DMD patients without severe dysfunction and without clinical symptoms, despite the theoretical nidus identified by LGE.

Disclosures

None.

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