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A Study of Cardiac Muscle Involvement in Muscular Dystrophies Using Echocardiography and its Correlation With Skeletal Muscle Involvement

KEYWORDS: Muscle Dystrophy, Echocardiography, Ejection Fraction, Fractional Shortening

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ABSTRACT *Muscular dystrophies are hereditary, progressive, degenerative diseases of skeletal muscle that have been found to involve the myocardium. Cardiac involvement has been described mainly in Duchenne Muscular Dystrophy (DMD), Limb Girdle Dystrophy(LGD) and Facio-scapulo-humeral Dystrophy (FSH). This study was conducted to establish the extent of cardiac muscle involvement in muscular dystrophies using Echocardiography and to determine the correlation, if any, between skeletal muscle involvement and cardiac muscle involvement.*
Forty patients with a diagnosis of Muscular Dystrophy were selected for the study. The types of Muscular Dystrophy studied were DMD, LGD, FSH, Becker's Muscular Dystrophy (BMD) and Myotonic Dystrophy (MD). The subjects were examined clinically and investigated in detail. Manual muscle testing, electrocardiogram, chest skiagram, serum muscle enzymes, electromyography and 2D Echocardiography were done.
The ejection fraction (EF) and the fractional shortening (FS) of the left ventricle were found to be lower in the study group compared to the controls. 2D Echocardiography, being non-invasive, should be used to serially follow up these patients since the common cause of death is respiratory infections and cardiac failure. There was no linear correlation between cardiac muscle and skeletal muscle involvement.

INTRODUCTION

Muscular dystrophies are progressive, hereditary degenerative diseases of skeletal muscle which have been found to involve the myocardium. Involvement of the myocardium in progressive muscular dystrophy is so frequent that the term "Cardiomyopathy of muscular dystrophy" has been coined (Perloff et al 1966).[1,] Cardiac involvement has been described in the three main varieties of muscular dystrophy: Duchenne Muscular Dystrophy (DMD), Limb Girdle Muscular Dystrophy (LGMD)and Facio-scapulo-humeral Dystrophy (FSH). Cardiac involvement occurs in a widely varying percentage of cases (50-85%). Histology of the myocardium reported in all three types of muscle dystrophies are similar, first described by Ross in 1883. A picture of ventricular hypertrophy with patchy fibrosis and increased fat deposition in the myocardium was described by Globus (1923).[2]

The cardiac involvement begins at the junction between the pericardial layer and the outer myocardium and first involves the postero-basal myocardium of the left ventricle free wall[3]. Initially fibrosis occurs in discrete small areas with a band-life distribution, but eventually it becomes more diffuse and transmural, and involves most of the outer half of the ventricular wall. This classical pathological picture was found to be most florid in DMD and is unique and allows differentiation histologically from the diffuse fibrosis seen in the ischemic heart disease. Matsuda studied 57 patients with Duchenne muscular dystrophy using systolic time intervals and suggested that the progressive deterioration of cardiac function in DMD parallels the progressive disability caused by skeletal muscle changes in both degree and timing. The myocardial changes are already present even in the moderately disabled patients, but not clinically obvious because of the patients' restricted activity. Even at this stage their indices of left ventricular function demonstrated very notable abnormalities, in the absence of clinical cardiac decompensation.[4,5]

The echocardiogram has been used to look at septal and posterior left ventricular wall thickness and movement in these patients. Kovick et al studied the maximal systolic endocardial velocity measurement (SEVM) and diastolic endocardial velocity measurement (DEVM) in the posterior left ventricular wall. The SEVM and DEVM both were significantly less in muscular dystrophy patients. They suggest that the posterior left ventricular wall DEVM is a more accurate detector of cardiac involvement in muscular dystrophy than the SEVM and both myocardial contractility and relaxation may be significantly abnormal in cardiomyopathic conditions.[6,7,8]

AIMS & OBJECTIVES

To study the extent of cardiac muscle involvement in muscular dystrophies using echocardiography as an indicator of cardiac function and to determine the correlation, if any, between skeletal muscle involvement and cardiac muscle involvement.

MATERIAL & METHODS

Forty patients with a diagnosis of Muscular Dystrophy were selected for the study from the pediatric and medicine outpatient departments of our medical college. The types of Muscular Dystrophy studied were Duchenne Muscular Dystrophy (DMD), Becker's Muscular Dystrophy (BMD), Limb Girdle Muscle Dystrophy (LGMD), Fascio-scapulo-humeral Dystrophy (FSH) and Myotonic Dystrophy (MD). The subtypes in the group studied consisted of DMD 13, BMD 7, LGMD 5, FSH 12 and MD 3. The subjects were examined thoroughly, a detailed neurological. cardiovascular and general examination was done. After a clinical diagnosis, these patients were investigated in detail. Manual muscle testing, electrocardiogram, chest X-ray, serum muscle enzymes, electromyography and 2D-echocardiography were done. Parents and siblings of patients were exercised and CPK levels estimated.

Twelve controls were carefully chosen from the Neurology

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and Medicine Departments. The controls were matched with age, sex, and body surface area. A detailed history was taken and a family history of muscle disease in the siblings and in up to two generations was carefully asked for. None of those chosen as controls gave a family history. They were examined and muscle function testing, ECG and 2D ECHO were done. Muscle biopsies were done in all the patients. The controls were not subjected to invasive tests like EMG and Muscle biopsy.

PHYSICAL EXAMINATION:
Detailed clinical examination including that of CNS and the cardiovascular system was done specifically looking for resting tachycardia, congestive cardiac failure and S3 gallop. The clinical staging of muscular dystrophy was done as follows:

Stage 1 -Pre-symptomatic, creatinine kinase levels are usually elevated.

Stage 2- Early ambulatory. Waddling gait, inexorable progressive weakness, Gower's sign positive, toe walking, can climb stairs.

Stage 3 – Late ambulatory. Difficulty climbing stairs, respiratory muscle strength starts declining, forced vital capacity wanes, nocturnal hypoxemia leading to lethargy and early morning headaches.

Stage 4- Early non- ambulatory. Cannot walk, but can self-propel, maintains posture.

Stage 5- Late non-ambulatory. Scoliosis, wheelchair bound, profoundly weak, terminal respiratory or cardiac failure[9].

INVESTIGATIONS
Standard 12 lead electrocardiograms were done on each subject. (a) Heart rate in resting patients as estimated. (b) The ratio of the R to the S wave in Lead 1 (R/S V1) was calculated, and (c) q waves, if present in lead I, II and V_5, were measured and expressed as a ratio to the R wave in that lead (Q/R). [10] The Q/R ratio in the 3 leads was then summed up and expressed as a single value EQ/ER. Additional abnormalities were also observed. Chest X-rays were done to look for associated chest wall deformities or bony cage abnormalities which might in any way alter the cardiac findings. Chest X-rays showed no cardiomegaly or pulmonary congestion in any patient

Serum creatinine phosphokinase (CPK) concentration of each patient was determined by Biochemical Kit Method (Boehringer-Mannheim). Electromyography and nerve conduction studies were done in all patients. Concentric needles were used for electrodes. The muscles were chosen for examination depending on the involvement pattern.

Echocardiogram: Each patient was subjected to 2D echocardiography. In each record, average values were calculated for the following variables, measuring in millimeters (mm). Left ventricular diastolic internal diameter (LVIDd), Left ventricular systolic internal diameter (LVIDs), Diastolic left atrial diameter (LADd), Systolic left atrial diameter (LADs), Diastolic-aortic diameter (AOD), systolic aortic diameter (AOS), Diastolic right ventricular internal diameter (RVIDd), Diastolic posterior ventricular wall thickness (WALLd), Systolic posterior left ventricular wall thickness (WALLs) and Interventricular septal thickness (IVST).[11,12] The following were calculated from the dimensions measured in each subject as follows:

End systolic volume (ESV) = 47 mm End diastolic volume (EDV) = 59 mm

LVIDs = 120 mm (N 24-42)
LVIDd = 153 mm (n 35-57)

Stroke volume (SV) = EDV – ESV

Ejection fraction (EF) = SV/EDV = 0.55 - 0.78

Stroke Index (SI) (cc/M^s) = SV/BSA
=30-65 ml/beat

Cardiac Index (CI) (l/min/m^2) = Heart rate x SI/1000 = 2.8 - 4.2 l/min/m^2

Percentage Fractional Shortening (FS%) = (% LV) LVIDd–LVIDs/LVIDd= 34 - 44%

The data obtained were analysed using the student 't' test for significance and correlation coefficient.

RESULTS:
The results of physical examination, electrocardiogram, muscle biopsy, CPK and echocardiography are given below.

Physical Examination The subjects ranged from 3 years to 40 years of age. There were 33 males and 7 females.

Electrocardiogram: The resting heart rate in patients with muscular dystrophy was much higher than the control group. This was dependent on the age. The patients are divided into two groups with their age matched controls (Table I). **R/S Ratio in V1** was 0.781 in patients with muscular dystrophy as compared to 0.405 in the control group. This was statistically significant (P<0.050) (Table II)**. EQ/ER Ratio-** The sum total of Q/R ratio in Lead II, IIIV5 and V6 was deep (greater than 3 mm) in mainly the DMD (33%), LGMD (20%), FSH (11%) and not present in BMD and MD (Table III). The deep Q waves in the lateral and left ward precordial leads were seen in 8 (28.6%) of patients as compared to 2 (12.5%) in the control group where. Other changes seen were incomplete right bundle branch block (iRBBB) in 3 patients and nonspecific ST-T changes in 2 patients.

TABLE-I

	Disease Group 3-12 Yrs.	Controls 3-12 Yrs.	Disease Group 13-20 Yrs.	Control 13-40 Yrs.
Mean Heart Rate	106.9/min	90.4/min	88.4/min	82.2/mn
Standard Deviation	9.13	3.97	16.80	14.6
Test Significance	****	****	****	****
"t" TEST	P(<0.001) significant	P(<0.001) significant	"t"= 1.1127	Not significant

Average heart rate in patients with Muscular Dystrophy and normal controls

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Table II.

STATISTICS	GROUP I (MD)	GROUP II CONTROL
MEAN	0.781	0.405
STANDARD DEVIATION	0.52	0.327
"t" TEST OF SIGNIFICANCE		P(<0.050) Significant

The R/S ratio was increased in 100% of DMD, 80% in the LGMD group, 31.7% in the F.S.H group, 14.3% in the BMD group and not elevated in the MD Group.

TABLE III

STATISTICS	GROUP I(MD)	GROUP II (CONTROL)
MEAN	0.19	0.07
STANDARD DEVIATION	0.33	0.11
SIGNIFICANCE	**	**
"T" TEST	t=1.4068	Not Significant

Echocardiographic Data Left ventricular size, posterior wall thickness and septal wall thickness was normal in all patients. The right ventricle was slightly enlarged in four patients. Left atrial and aortic root dimensions were increased in one patient. Dextrocardia was seen in one patient. The EF calculated on the 2D- echo was found to be much lower in the patients with muscular dystrophy especially of the DMD and FSH and LGMD (Table IV)[13]. EF and % FS was lower in the patients with muscular dystrophy (Table IV and V). It was also noticed that patients tended to have a lower EF than that mentioned in western literature (0.55- 0.78).[14] This was noticed irrespective of age, but varied with the type of muscular dystrophy worse in those with DMD (92.3%), LGMD (100%) and FS(91.7%) and less in the other types.[15]

TABLE IV
EJECTION FRACTION

	DISEASE	CONTROL
SAMPLE	40	12
MEAN	0.30	0.43
STANDARD DEVIATION	0.06	0.15
TEST OF SIGNIFICANCE	(P<0.001)	

TABLE V
PERCENTAGE OF LEFT VENTRICULAR FRACTIONAL SHORTENING

	DISEASE	CONTROL
SAMPLE	40	12
MEAN	11.0	29
STANDARD DEVIATION	6.32	15.8
TEST OF SIGNIFICANCE	(P<0.001)	

Comparison of Skeletal Muscle Involvement with Cardiac Muscle Involvement: The co-relation between the skeletal muscle involvement and ejection fraction of cardiac muscle was statistically analysed using the co-relation coefficient formula. Cardiac muscle involvement using FS was compared with skeletal muscle involvement using MMT and there was no correlation between the two (r= 0.24, not significant).

DISCUSSION

Electrocardiogram ECGs done in patients with muscular dystrophy showed a resting tachycardia which was significant (P< 0.001) in the younger age group from 3-12 years. This group contained seventeen patients (DMD 13, BMD 1 and LGMD 3) who had a mean resting heart rate of 106.9. It was however not significant in the older age group from 13 to 40 years of age in patients with mainly FSH, MD and Adult onset LGMD. The most common abnormalities were a tall R wave with an R to S ratio greater than 1in lead VI (P < .05) and a Q wave greater than 3 mm in Lead II, III V5. The ECG changes are attributed to the histopathological changes that are observed in the form of focal areas of fibrosis and degenerative changes involving the posterior left ventricular wall and conduction system.[14] Other findings were dextrocardia in 1 patient with BMD (2.5%) which has not been documented, 2 had right ventricular enlargement (10%) which is not commonly seen since usually these patients have smaller right and left ventricular dimensions. This is probably due to poor physical development or inactivity or to decreased left ventricular compliance due to myocardial fibrosis. An enlarged left atrium was found in one patient (2.5%). No arrhythmias or interventricular conduction abnormalities were seen in the MD group.

Echocardiogram: Echo abnormalities have been described in 50-85% of patients with certain types of muscular dystrophy (especially DMD)[16]. The abnormalities are described for structural and functional changes, though the functional changes appear much earlier and only a small proportion of these patients have structural abnormalities. In our study, almost all patients had functional abnormalities (95%) as assessed by EF and FS. But only 2 of these 40 patients had structural abnormalities as evidenced by dilated right ventricle and left atrial enlargement (5%).

Though these patients had functional abnormality on echo, they did not manifest clinically with left ventricular dysfunction. The detection of cardiac dysfunction by echocardiography precedes the clinical appearance of cardiac failure. This is an important observation and may be applicable clinically. Earlier detection envisages early treatment and prevention of complication so serial echocardiographic examination is recommended for these patients. These children and adults can suddenly deteriorate if respiratory and cardiac functions are affected.[16] The EF and %FS were significantly lower than in the age matched normal control subjects (P < 0.001). The EF was lower than the known western values ranging from 32% to 74% in the controls and 22% to 49% in the patient group. Similarly, FS was lower in the study group with a mean of 11% and 29% in the control group. Reduced LV wall thickness and progressive decline in EF and FS result in lower values, though this has not been fully understood.

Correlation between severity of Skeletal Muscle and Cardiac Muscle Disease: Many controversial reports have been published regarding the correlation between skeletal disability and cardiomyopathy especially in patients of severe X-linked recessive form of DMD. In this study, there was no correlation however, between the impairment of left ventricular function and the severity of the skeletal muscle disease. Increased physical inactivity did not seem to be associated with more impairment in left ventricular function.

CONCLUSION:

The EF and the FS of the left ventricle were found to be lower in the study group of muscular dystrophies compared to the controls. Posterior left ventricular wall thinning and other structural changes were not observed, but functional abnormalities of cardiac muscle were detected in earlier studies. Functional change is the first abnormal-

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ity to be detected on ECG and these patients do benefit by earlier treatment.[17,18] There are a few Indian studies using systolic time intervals & ECG in the study of muscular dystrophy.[19,20] This is one of the few studies done with 2D Echocardiography. This non-invasive test could be used to serially follow up the patients of muscular dystrophy since cardiac failure is a common cause of death.[21,22] There was no linear co-relation between cardiac muscle and skeletal muscle involvement.

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