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CARDIORESPIRATORY FUNCTION IN DUCHENNE AND BECKER MUSCULAR DYSTROPHY*

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SUMMARY: Taşdemir HA, Çil E, Topaloğlu H, Yalaz K, Aysun S, Renda Y, Özme Ş. (Neurology and Cardiology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Cardiorespiratory function in Duchenne and Becker muscular dystrophy. Turk J Pediatr 1996; 38: 307-314.

The purpose of this study was to investigate the cardiorespiratory function in Duchenne (DMD) and Becker muscular dystrophy (BMO) patients and to determine whether there is a correlation between these functions and muscular strength. The study involved 32 patients with progressive muscular dystrophy (28 DMD and four BMD). The mean age of the patients was 9.6±3.5 years. Cardiac investigations were performed in all of the patients, and pulmonary function tests were obtained in 16 cases. In five cases (31%), vital capacity (VC) was less than 80 percent of the predicted value. There was a good correlation between VC and muscular strength. There were various cardiologic findings in 50 percent of the cases with DMD. Electrocardiographic changes were present in 43 percent of the patients. Left ventricular systolic function in the patients who could not walk was significantly lower than that of the patients who could walk. There may be some unknown mechanisms that preserve left ventricular function relatively in the normal range in spite of cardiac involvement. *Key words: Duchenne muscular dystrophy, Becker muscular dystrophy, cardiomyopathy, echocardiography.*

Patients with Duchenne (DMD) or Becker muscular dystrophy (BMD) have a spectrum of clinical phenotypes that include skeletal myopathy, cardiomyopathy and mental retardation. They have been characterized by absent or diminished expression of the protein dystrophin in skeletal muscle, the heart and brain[1,2]. The abnormal gene is on the X-chromosome at the Xp21 locus which produces the protein dystrophin. The absence of dystrophin or the presence of structurally

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abnormal dystrophin results in degeneration and necrosis of muscle fibers and eventually in muscular weakness[1-3].

One of the most important problems in BMD and DMD patients is cardiorespiratory complications. Severe weakness of respiratory muscles produces a restrictive ventilatory defect due to inability to inflate the lungs sufficiently[4]. The combination of inadequate defense against infection and reduced pulmonary reserves may predispose patients to frequent and prolonged respiratory infections[5]. Similarly, cardiac involvement in DMD and BMD patients has been reported[6-11]. Left ventricular function has also been well investigated, however its relation to total point of muscle strength (TPMS), which demonstrates the clinical severity of cases, was not investigated. Therefore, the purpose of this study was to investigate the cardiorespiratory function in DMD and BMD patients and to determine whether there is a correlation between these functions and muscular strength.

Material and Methods

The study involved 32 patients with progressive muscular dystrophy (28 DMD and 4 BMD) ranging in age from three to 18 years. The diagnosis was assessed by the patient and family histories, physical examination, serum creatine kinase, electromyography, muscle biopsies and DNA analysis for Xp21 deletion by polymerase chain reaction (PCR).

The total muscular strength of the major muscle groups was evaluated on a point scale between 0 and 5 according to the "modified MRC muscle strength evaluation method" in half of the body with patients sitting, lying on one side, in the supine or prone position. The maximum "total point of muscular strength" (TPMS) was is 85 in a healthy person.

The following pulmonary function tests were obtained in 16 patients: vital capacity (VC), maximum voluntary ventilation (MVV), forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), peak expiratory flow (PEF), and maximal expiratory flow (MEF_{50}). When the VCs were less than 80 percent of the predicted value (% pred.), the subjects were considered to have respiratory impairment.

All children were examined by a pediatric cardiologist. Electrocardiographic and telecardiographic data were also available to the pediatric cardiologist. Echocardiography was performed with a Toshiba SSH 60-A Echocardiograph and 2.5-5 mHz transducers. The complete cardiac anatomy was examined for defects, valvar stenosis or insufficiency, and mitral valvar prolapsus. For all measurements, three consecutive cardiac cycles were evaluated and the mean was taken for further calculations.

M-mode echocardiographic studies: The images of the heart were obtained in parasternal long-axis views. Left ventricle chamber ($LVID_4$, $LVID_4$) and wall

dimensions (thicknesses of interventricular septum and posterior wall) were measured according to standard methods of the American Society of Echocardiography[12] over three cardiac cycles. Left ventricular ejection (LVEF) and shortening fraction (LVSF) were calculated. LVEF less than 55 percent and LVSF less than 28 percent were considered to be abnormal[8,9].

The patients were classified into five groups as follows: DMD patients able to walk, TPMS>62 was classified as Group I a and TPMS<62 as Group Ib; among DMD patients unable to walk, TPMS>40 as Group IIa, and TPMS<40 as Group IIb; and BMD patients who were able to walk as group III.

Relationships were analyzed for statistical significance by the use of chi-square and Student's t tests. For testing correlations, Pearson's or Spearman's correlation analyses were performed. Statistical significance was accepted as $p<0.05$.

Results

The study group consisted of 32 male patients. Twenty-eight of them had DMD, and the other four had BMD. The mean age for DMD patients was 9.6 ± 3.5 years (range 3-18 years) and for BMD patients was 11.2±2.2 years (range 8.5-13.5 years).

Pulmonary function tests were performed in 16 patients, and in all of them the FEV/FVC rate was greater than 70. However, the predicted value of VC was less than 80 in five patients (31%). In the groups based on VC, other tests were investigated (Table I). In the groups based on TPMS, the pulmonary function test results are shown in Table II. In this table, the predicted values of VC and FVC of the patients who could walk were significantly higher than those of the other groups. The other pulmonary function test results were similar in all groups. A good correlation between VC and TPMS was demonstrated (p: 0.04, r: 0.5541). However, there was only a mild correlation between FVS and TPMS (p: 0.07, r: 0.4851). There was no correlation between TPMS and other tests.

There were various cardiac findings in 14 of the DMD patients (50%) (Table III). In the four patients with BMD, the cardiac investigations were all normal. Some electrocardiographic changes including conduction defects were present in 12 patients (43%) with DMD. Left ventricular systolic function was investigated in all groups (Table IV). The LVEF and LVSF data in the group whose clinical status was worst according to TPMS (Group IIb) were significantly lower than those of the other groups (Table IV). Left ventricular systolic function was abnormal in two patients in Group IIb. There was no correlation between left ventricular systolic function and age, TPMS or VC. In addition, there was no relation between the localization or length of the deletion in Xp21 locus and cardiac or respiratory functions.

Table I: Summary of Pulmonary Function Tests

	Groups (VC: % of Predicted value)			
	VC > 80	VC: 65-80	VC: 50-65	VC < 50
VC* (mean)	97**			
Range	83.134	66	53-55	14-28
MVV (L/m) (mean)	70			
Range	56-99	46	28	22-23
FVC* (mean)	93			
Range	67-129	64	55-56	14-27
FEV_1*	(Mean)	96		
Range	72-131	70	56-61	17-30
PEF* (mean)	72			
Range	42-96	50	38-58	19-24
MEF_5* (mean)				
Range	42-155	85	49-90	31-36
FEV1/FVC (%) (mean)	93			
Range	81-100	97	92-100	100-100
No. of cases (%)	11 (69)	1 (6)	2 (12.5)	2 (12.5)

* Percent of predicted values.

** The mean is not displayed for groups consisting of one or two patients.
FEV1: Forced Expiratory Volume at one second; FVC: Forced Vital Capacity; MEF_{50}: Maximal Expiratory Flow; MVV: Maximum Voluntary Ventilation; No: Number; PEF: Peak Expiratory Flow; VC: Vital Capacity.

Table II: Pulmonary Function Tests Related to the Clinical Groups

	Pts. able to walk	Pts. not able to walk	
	TPMS ≥ 54	TPMS ≥ 30	TPMS < 30
Number of cases	5	6	5
VC (% Pred)	109±15*	76±13	57±38
MVV (L/M)	66±21	62±25	43±26
FVC (% Pred)	104±18*	74±13	55±36
PEF (% Pred)	104±22	79±16	60±38
MEF50	94±37	82±41	76±46

* $p < 0.05$
% Pred: % of the predicted value; Pts: Patients; TPMS: Total Point of Muscle Strength; VC: Vital Capacity; MVV: Maximum Voluntary Ventilation; FVC: Forced Vital Capacity; PEF: Peak Expiratory Flow; MEF_{50}: Maximal Expiratory Flow.

Table III: Cardiologic Data of the Patients with Duchenne Muscular Dystrophy

	Pts who could walk		Pts who could not walk		Total	
	No.	%	No.	%	No.	%
Preclinical CM	3	11	2	7	5	18
Congestive CM	1	4	2	7	3	11
Hypertrophic CM	–	–	2	7	2	7
Conduction defect in EKG	8	29	4	14	12	43
Normal	8	29	6	21	14	50

CM: Cardiomyopathy, Pts: Patients
Total number of patients was greater than 28 because of the association of cardiomyopathy and electrocardiographic findings in some cases.

Table IV: Echocardiographic Left Ventricular Systolic Function of Clinical Groups

	No.	LVEF	LVSF
Pts who could walk TPMS ³ 62 (Ia)	7	66±9	37±7
Pts who could walk TPMS < 62 (Ib)	8	67±5	36±4
Pts who could not walk TPMS ≥ 40 (IIa)	6	65±4	38±6
Pts who could not walk TPMS < 40 (IIb)	7	58±7*	30±4*

LVEF: Left Ventricular Ejection Fraction; LVSF: Left Ventricular Shortening Fraction; No: Number; Pts: patients; TPMS: Total Point of Muscle Strength.
* $p<0.05$

Discussion

The most frequent cause of death in patients with myopathy is respiratory infection[13]. While the clinical presentation of the respiratory problem may be acute, it is almost always superimposed on chronic respiratory insufficiency, and irreversible pathophysiologic changes frequently underlie the acute presentation. Muscle weakness eventually results in the following changes: decreased ventilatory reserve, low lung volumes, inadequate handling of secretions, and late development of pulmonary fibrosis and pulmonary arterial hypertension[14]. One of the earliest changes is reduction in vital capacity due to weakness of the muscles of the chest wall and/or diaphragm[15]. The respiratory problem is exacerbated by the developing scoliosis[16,17].

Of the 16 patients (14 DMD, 2 BMD) who were suitable for the pulmonary function tests, 11 (69%) had normal VC levels (>80% pred.); however, in the remaining five patients (31%), VC was abnormal (<80% pred.). There was an obvious correlation between VC and TPMS, but there was no correlation between TPMS and other pulmonary function tests. Similarly, a large number of reports showed that VC was the most reliable test for monitoring pulmonary function tests in DMD or BMD patients[5,13,17,18]. In addition, this study also demonstrated that VC decreased with the inability to walk that is, VC is related to muscle weakness. There were two cases with scoliosis in the present study. One of them had normal pulmonary function tests, while the other was abnormal. Because of the low number of cases with scoliosis, the impact of scoliosis on the pulmonary function tests could not be investigated.

In the present study, 14 patients with DMD (505) had cardiac involvement. Nigro et al.[9] reported that the rate of cardiac involvement was 78% percent in DMD. The cause of this difference is the age range of the study subjects. In the study of Nigro et al.[9], one-third of the patients were greater than 14 years in age, while in the present study this rate was one-eighth. Nigro et al.[9] also showed that clinically detected cardiac involvement had an onset after the age of 10 years and gradually increased in incidence with age. This comment supports our thoughts. In progressive muscular dystrophy the heart is always affected and presents characteristic histological lesions: irregular, diffuse and intense rearrangements predominantly in the left ventricle, the septum, and conductive tissue, consisting of wide, poorly vascularized fibrous bands that are destructive but without an inflammatory aspect[19]. Roberds et al.[20] reported that dystrophin-associated proteins are decreased in abundance in the cardiomyopathic hamster heart; for this reason they proposed that the cardiomyopathy was more severe than the myopathy.

D'orsogna et al.[8] reported that all cases in their study had electrocardiographic abnormalities. We doubted this data because there is no other report supporting their findings. In the present study, 12 patients (43%) had some electrocardiographic abnormalities. The cause of the difference between these data may be the difference in the ages of the patients. The mean age in the present study was 9.6 years, whereas it was 15.7 years in the study of D'orsogna et al[8].

There was no correlation between TPMS and left ventricular systolic function such as LVEF or LVSF. The left ventricular systolic function data were similar in the three groups comprising patients who were able to walk; however in the patients who were unable to walk, LVEF and LVSF values were significantly lower than those of the other groups. Nevertheless, the left ventricular systolic function in the patients who were unable to walk was not less than the normal range.

Nowadays it is believed that the failure of cardiac function is due to the presence of abnormal dystrophin in the cardiac structures[1-3]. If so, there must be a positive correlation between the TPMS and left ventricular systolic function such as LVEF and LVSF; however, in the present study there was no correlation between these parameters. In conclusion, we propose that there may be some unknown mechanisms that preserve left ventricular function relatively in the normal range despite cardiac involvement.

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