

## RESPIRATORY DYSFUNCTIONS IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY

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### ABSTRACT

**Aim:** The prognosis for Duchenne Muscular Dystrophy (DMD) life depends to a large extent on the respiratory function. Inspiratory and expiratory muscles are affected and respiratory problems occur with or without spinal deformities. It is important to characterize the respiratory function in DMD to facilitate decision of timing of the intervention.

**Methodology:** 124 DMD male children whose parents gave written consent were recruited. The Pulmonary function tests were performed using Spirometry kit (Spiro instrument's software) (Microquark Cosmed, Italy). The values of Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Peak Inspiratory Flow (PIF), Tidal Volume (TV) and Maximum Voluntary Ventilation (MVV) were analyzed. These results were compared with the healthy children and correlated with semiology of the disease.

**Results:** One twenty four subjects with mean age at presentation were  $7.9 \pm 1.5$  years. Mean age of onset was  $2.8 \pm 0.6$  years (1.5 - 4.0 years). Mean duration of illness was  $5.1 \pm 1.5$  years (1 - 8 years). The respiratory functions were poor in DMD compared to healthy controls. Age and duration of illness were positively correlated with pulmonary function.

**Conclusion:** Our study enlightened large number Indian DMD children's pulmonary function parameters. Characterization of the pulmonary dysfunctions helped us in improving the quality of life in DMD children, by timely modifying the rehabilitation regime. This study also explained about the respiratory dysfunction in DMD in Indian population that can be used for choosing the suitable rehabilitation programs, targeted towards the symptomatic treatment of DMD children.

**KEY WORDS:** Pulmonary function, Duchenne Muscular Dystrophy.

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### INTRODUCTION

Respiratory disease in Duchenne Muscular dystrophy (DMD) is the major cause of morbidity and mortality. It is associated with a gradual

loss of muscle function over time. The muscle weakness in DMD is relatively symmetrical and begins proximally in the pelvic and shoulder girdle and trunk. Limitation in the Range of

movements (ROM) and Activity of Daily Living (ADL) begins at around 5 years of age and inability to climb stairs is seen between 7 and 13 years of age. The ability to ambulate is usually lost between 9 and 16 years of age [1]. DMD causes loss of ambulation and once the children are restricted to a wheelchair, many children develop secondary complications such as contractures, scoliosis and respiratory problems. Loss of respiratory muscle strength, with ensuing ineffective cough and decreased ventilation, leads to pneumonia; atelectasis and respiratory insufficiency in sleep and wakefulness has been observed [2-4].

Respiratory dysfunction starts with symptoms of nocturnal hypoventilation: insomnia, nightmares, frequent calls at night, nocturnal and morning headaches, daytime fatigue and sleepiness, decrease in intellectual performance, loss of appetite, weight loss, frequent respiratory infections and cardiac rhythm abnormalities. As the muscles of respiration become involved, pulmonary function is compromised, with death from respiratory dysfunction usually occurring before the age of 20 years [5-7]. Only one quarter of patients live beyond the age of 21 and survival beyond 25 years is rare [8]. Respiratory infection is a common cause of death in these children. The life expectancy of DMD depends to a large extent on the respiratory function. In India, DMD has been found to account for 30% of all reported forms of muscular dystrophies [9]. In a tertiary neuromuscular centre, DMD was found to be the commonest form of muscle diseases [10].

Pulmonary function test (PFT) is an integral part of evaluation of respiratory functions. It has evolved from tools of physiologic study to clinical tools with a wide variety of applications, including quantifying impairment, progression or regression of diseases, effect of rehabilitation intervention, occupational health screening and sports medicine testing. The availability of user-friendly testing devices has resulted in the widespread use of PFTs in different fields. They can be used to evaluate an array of physiological data, helping in the identification of obstructive or restrictive respiratory defects [11].

**Aim:** 1. To characterize the respiratory function in DMD to understand the sequence of respira-

tory muscle involvement as the disease progress.

2. To understand the course of the disease to develop a comprehensive rehabilitation program based on the respiratory function. That will facilitate decision making with regards to time and nature of intervention to improve the pulmonary functions and quality of life in DMD children.

## METHODOLOGY

One hundred and twenty four DMD and 50 healthy male children, whose parents gave written consent, were recruited for the study. Pulmonary function tests were performed to test the respiratory function. The Spirometry kit (Figure 1) manufactured by Microquark Cosmed, Italy was used for the present study. The procedure was explained to the child and best of three measurements were recorded at an interval of two minutes was used for analysis. Spirometry was recorded by having a seated subject breathe calmly several times at tidal volume, then draw a maximum inhalation followed by a forced exhalation that was continued for at least 6 seconds or more with sustained vigorous effort Forced Vital Capacity (FVC) and completed by a vigorous full inspiration (Inspiratory Vital Capacity). Flow-volume loops were scrutinized for special patterns that can indicate various clinical or anatomic conditions [11]. These manoeuvres were represented as a volume-time loop or as a flow-volume loop; Volume-time curve, showing volume (litres) along the Y-axis and time (seconds) along the X-axis; Flow-volume loop, which graphically depicts the rate of airflow on the Y-axis and the total volume inspired or expired on the X-axis.

**Fig. 1:** Spirometry kit.



A. Spirometer

B. Spirograph

The values of Forced Vital Capacity (FVC), Forced Expiratory Volume 1 (FEV<sub>1</sub>), FVC/FEV<sub>1</sub> (%), Peak Expiratory Flow rate (PEFr), Peak Inspiratory Flow (PIF), Tidal Volume (TV) and tidal volume during maximum voluntary ventilation (MVT) were considered for analysis. KIT Spiro instrument's software was used to analysis and it is based according to Europe reference mode using Knudson's correction factor for Flow-Volume Curve. These results were compared with the healthy children and also correlated with age, age of onset, height, weight, BMI and duration of disease.

### Acceptability and Reproducibility of PFTs:

Acceptability is best determined by studying the flow-volume loops. Acceptability criteria for PFTs those followed for our study were:

(i) Graphs should be free from artefacts (coughing, glottis closure, early termination, leak, variable (effort).

(ii) Good starts (i.e., the initial portion of the curve that is most dependent on patient effort is free from artefact).

(iii) Satisfactory expiratory time (at least 6 seconds of expiration on the volume-time curve, or at least a 1-sec plateau in the volume-time curve).

Once the minimum of three acceptable flow-volume loops have been obtained, the reproducibility of the PFTs is assessed.

Reproducibility criteria for PFTs those followed for our study were:

(i) The difference between two largest forced vital capacity (FVC) measurements should be within 0.2 L or 5%.

(ii) The two largest FEV<sub>1</sub> measurements should be within 0.2 L or 5% of each other.

### Pulmonary Function Tests- Interpretation:

The measured values for FEV<sub>1</sub> and FVC were compared to the predicted values for FEV<sub>1</sub> and FVC as a percentage. Values >80% were considered as normal. For the lung volume, values between 80% and 120% were considered as normal. The predicted values were based on age, height, weight and ethnicity (north / south India). A correction was incorporated in computing the predicted values and implemented by the software of the

computerized spirometer used in the study (Spirometry Kit, MicroquarkCosmed, Italy).

**Statistics:** SPSS 15.0, statistical software was used for the analysis of the data. Results on continuous measurements are presented as Mean  $\pm$  SD. Significance was assessed at 5 % level of significance. Relationship between the variables was analyzed using Pearson's correlations depending upon the normality of distribution of the variables. Since the values were not following normal distribution, the non-parametric test was carried out (Mann Whitney 'U' test) for the comparison of PFT parameter between DMD and healthy children.

## RESULTS

**Table 1:** Comparison of Pulmonary Functions between Healthy Subjects and DMD Children.

PFT	Healthy subjects (n-50)	DMD children (n-124)	Mann Whitney 'U'	P value
FVC (litres)	1.3 $\pm$ 0.5 (n-50)	0.8 $\pm$ 0.3 (n-117)	1278	<0.001***
PEFr (lit/min)	164.8 $\pm$ 66.9 (n-50)	101.2 $\pm$ 43.0 (n-116)	1255.5	<0.001***
VT(litres)	0.5 $\pm$ 0.2 (n-50)	0.4 $\pm$ 0.2 (n-116)	2006	0.002**
MVV (lit/min)	54.3 $\pm$ 23.5 (n-50)	27.2 $\pm$ 9.8 (n-114)	840.5	<0.001***
MVT (litres)	0.7 $\pm$ 0.3 (n-50)	0.4 $\pm$ 0.1 (n-113)	732	<0.001***

Values Are Expressed As Mean  $\pm$  Sd; Mann Whitney 'U' Test Was Performed And The Level Of Significance Kept At (\*P<0.05, \*\*P<0.005, \*\*\*P<0.001).

Lit- Litre; Min - Minute, N- Number Of Children; PFT-Pulmonary Function Test; FVC- Forced Vital Capacity; PEFr - Peak Expiratory Flow Rate; VT- Tidal Volume; MVV- Maximum Voluntary Ventilation; MVT- Tidal Volume During MVV.

Among the 124 boys recruited, the age ranged from 5-10 years. The mean age at presentation was (7.9  $\pm$  1.5 years). Mean height was 118.2  $\pm$  8.4cms (95 - 147cms). Mean weight was 20.6  $\pm$  4.3 Kg (11-32kg). Mean age of onset was 2.8  $\pm$  0.6 years (1.5 - 4.0 years). Mean duration of illness was 5.1  $\pm$  1.5 years (1 - 8 years). The respiratory functions were poor in DMD compared to healthy controls (FVC, PEFr, VT, MVV and MVT values were significantly lower in DMD



children than healthy subjects) (Table 1). Age positively correlated with FVC, PEFr, VT, MVV, MVT. Duration of illness was also positively correlated with FVC, PEFr, VT, MVV and MVT (Table 2). Forced Expiratory Volume 1 (FEV1), FVC/FEV1 (%) and Peak Inspiratory Flow (PIF) were not coming under acceptability criteria, so not analysed.

**Table 2:** Correlation of Anthropometric Measures with PFT Parameters.

PFT	Age	Age of onset	Duration of illness	Height	Weight	BMI
FVC (litres) (n-117)	0.519**	0.184*	0.466**	0.653**	0.663**	0.308**
PEFr(lit/min) (n-116)	0.297**	0.146	0.268**	0.458**	0.297**	-0.019
VT (litres) (n116)	0.395**	0.089	0.342**	0.426**	0.330**	0.055
MVV (lit/min) (n-114)	0.441**	0.18	0.352**	0.533**	0.515**	0.241**
MVT (litres) (n-113)	0.298**	0.082	0.281**	0.397**	0.450**	0.284**

The Values are expressed as Pearson's Correlation 'R' Values. Significance Level is Kept at (\*P<0.05, \*\*P<0.005) N- Number of Children.

Lit- Litre; Min – Minute, N- Number of Children; PFT- Pulmonary Function Test; FVC= Forced Vital Capacity; PEFr- Peak Expiratory Flow Rate; VT- Tidal Volume; MVV- Maximum Voluntary Ventilation; MVT- Tidal Volume During MVV.

## DISCUSSION

**Characteristic of Pulmonary Function Test (PFT) in DMD:** Progressive respiratory failure is one of the major causes of death in children with DMD which usually occurs in the second or third decade of life [12,13]. Due to diaphragm weakness and fibrosis, there is a decrease in ventilation, leading to chronic respiratory insufficiency [14-16]. Expiratory lung strength begins to decline at the age 7 and continues to worsen with age [14] is that also proved in our study with Indian DMD children. Thirty percent of the children with DMD had a history of respiratory complications, and the frequency increased with age [17].

Forced vital capacity (FVC) is one of the best indicators of clinical condition of the lungs that was significantly affected in our children [18]. Previous studies in non-ambulatory patients have found that FVC declines rapidly when standing

ceases. Percent FVC was found to be the parameter of pulmonary function that was most strongly correlated with age and scoliosis measurements [19]. There was a direct relationship between percent predicted FVC and MMT scores. Decreased airway pressures, especially maximal expiratory pressure, appeared earlier than reductions in FVC but followed the same pattern [17].

Need of the study was to understand the DMD consequence on respiratory system. Although respiratory functions may not be normal and boys usually do not have trouble breathing or coughing while they are still walking. But later they develop problems with breathing while sleeping and further, may require assistance with breathing during the day as well. As this is a staged progression of problems, a planned and proactive approach to respiratory care is advocated and appropriate surveillance, prophylaxis and interventions is needed.

**Pulmonary functions in DMD compared to healthy children:** Annual spirometry is recommended for Duchenne children older than 6 years as they can have FVC values lower than 80% of predicted as early as 7 years of age [20]. Mc Donald et al., reported that percent predicted forced vital capacity declined at different yearly rates: ages 7-10, -0.3%; 10-20, -8.5%; after age 20, -6.2% [17]. In the present study, FVC, PEFr, VT, MVV and MVT values were significantly lower in children with DMD than healthy subjects. It is notable that none of our patients had any respiratory symptoms. The abnormalities in PFT provide evidence for presence of subclinical pulmonary dysfunction early in the course of disease that evolves later into clinical dysfunction. Abnormal respiratory function is detectable almost as soon as it can be measured reliably. Thus, it is imperative to start respiratory muscle exercises early to slow down the progression of pulmonary dysfunction. But in our study, DMD children showed a satisfactory performance in PFT, indicating that none of them had any major respiratory symptoms. It might be due to all DMD children were in their early part of the disease.

Correlation showed that, as the age and duration of illness advance, the PFT parameters also decline. Once the children are restricted to

wheel chair, many children will develop respiratory problems. The understanding of the disease and its course by performing this type of diagnostic and prognostic beneficiary test taken into consideration, when a planned and proactive approach to respiratory care is advocated

PFT is useful in differentiating obstructive and restrictive lung disorders, determining respiratory functional status, monitoring treatment responsiveness and in estimating prognosis. PFT is also useful in reproducing clinical symptoms, such as breathlessness or dyspnoea and to correlate these symptoms with the degree of physical limitation. By performing PFT on these children, we were able to design the physiotherapy and pharmacological approaches to improve the quality of life.

Our study centre being the major tertiary hospital for south Indians populations, by this study it was possible to rehabilitate them based on the respiratory function parameter on this large cohort of DMD children. These data lead to develop and design a comprehensive rehabilitation program that significantly improved their health and standard of living. These data could be used as standard for all other newly diagnosed DMD children and treatment can be started immediately.

## CONCLUSION

Our study enlightened large number of Indian DMD children's pulmonary function parameters. Characterization and course of the pulmonary dysfunctions helped us in improving the quality of life in DMD children, by timely modifying the rehabilitation regime. Our study explained about the respiratory dysfunction in DMD in Indian population that can be used for choosing the suitable rehabilitation programs, targeted towards the symptomatic treatment of DMD children.

**Conflicts of interest: None**

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