ORIGINAL ARTICLES

Pulmonary and Nonpulmonary Alterations in Duchenne Muscular Dystrophy

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OBJECTIVE: To describe our experience in managing patients with Duchenne muscular dystrophy.

PATIENTS AND METHODS: We analyzed the following variables in a group of 27 patients with Duchenne muscular dystrophy: arterial blood gases, lung function before and after mechanical ventilation, oxygen saturation (measured by pulse oximetry), nocturnal $PaCO_2$ (measured transcutaneously by capnography), heart function, and dysphagia.

RESULTS: The mean (SD) age was 26 (6) years, and the mean age at which mechanical ventilation had been initiated in the 27 patients was 21 (5) years. Sixty-two percent had undergone tracheostomy and invasive mechanical ventilation. Arterial blood gas levels returned to normal once mechanical ventilation was administered and remained so for the entire treatment period (mean duration of follow-up, 56 [49] months). Thirteen patients had cardiac symptoms and they all presented abnormal electrocardiograms and echocardiograms indicating dilated cardiomyopathy, left ventricular dysfunction, and posterior hypokinesis. Only 9 patients were receiving enteral nutrition (7 through a gastrostomy tube and 2 through a nasogastric tube). The videofluoroscopic swallowing study confirmed that dysphagia was related to neuromuscular disease rather than the presence or not of a tracheostomy. Five patients (18%), 4 of whom were receiving invasive mechanical ventilation, died during the follow-up period. Three patients had serious heart disease.

CONCLUSIONS: Mechanical ventilation confers clinical benefits and prolongs life expectancy in patients with Duchenne muscular dystrophy. Heart disease and feeding difficulties are determining factors in the prognosis of these patients.

Key words: *Duchenne muscular dystrophy. Noninvasive mechanical ventilation. Cardiomyopathy. Dysphagia.*

Alteraciones pulmonares y no pulmonares en la distrofia muscular de Duchenne

OBJETIVO: Describir nuestra experiencia en el manejo de pacientes con distrofia muscular de Duchenne (DMD).

PACIENTES Y MÉTODOS: En 27 pacientes con DMD analizamos los gases arteriales y la función pulmonar antes y después de la ventilación mecánica (VM); la pulsioximetría (saturación de oxihemoglobina) y la capnografía (presión arterial de anhídrido carbónico por determinación transcutánea) nocturna; la función cardíaca y la evaluación de la disfagia.

RESULTADOS: Se incluyó en el estudio a 27 pacientes con una edad media ± desviación estándar de 26 ± 6 años, 24 de los cuales recibían VM, que se había iniciado cuando contaban 21 ± 5 años. El 62% eran portadores de traqueostomía y VM invasiva. Una vez iniciada la VM, se observó la normalización de los gases arteriales, que se mantuvo durante todo el tiempo de tratamiento (seguimiento medio: 56 ± 49 meses). Trece pacientes presentaban síntomas cardíacos y en todos ellos se observaban anormalidades en el electrocardiograma y ecocardiograma: miocardiopatía dilatada, disfunción ventricular izquierda o hipocinesia de la pared posterior. Sólo 7 pacientes llevaban una sonda de gastrostomía para alimentación y 2 una sonda nasogástrica. El estudio con videofluoroscopia permitió afirmar que los problemas de disfagia estaban relacionados con la enfermedad neuromuscular y no con la presencia o no de traqueostomía. Durante el período de seguimiento, 5 pacientes fallecieron (18%), 4 de ellos con VM invasiva; 3 pacientes presentaban una enfermedad cardíaca grave.

CONCLUSIONES: La VM proporciona beneficios clínicos y prolonga la vida de los pacientes con DMD. Las alteraciones cardíacas y nutricionales son factores determinantes en el pronóstico de estos pacientes.

Palabras clave: *Distrofia muscular de Duchenne. Ventilación mecánica no invasiva. Miocardiopatía. Disfagia.*

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Introduction

Duchenne muscular dystrophy is an X-linked recessive disorder caused by mutations in the cytoskeletal dystrophin protein.[1] It affects 1 in every 3000 to 3500 males.[2]

The disease is characterized by progressive symmetrical muscle weakness that begins in childhood. It first affects the lower limbs and gradually spreads to the upper limbs and trunk. Patients are generally completely dependent

by around the age of 12 years. Diagnosis is made between the ages of 3 and 5 years and a wheelchair is required between the ages of 6 and 12 years. Respiratory failure develops by the time patients are 20 years old.[1-3] Most develop heart disease, with dilated cardiomyopathy, arrhythmia, and congestive heart failure, although the condition is not always symptomatic.[2,4-6] Duchenne muscular dystrophy can be further complicated by the presence of scoliosis,[2,7] swallowing disorders, weight loss,[2,8] gastric dilation, and constipation.[2,9,10] Prognosis is generally poor, with death occurring between the ages of 10 and 20 years. The most common cause of death is respiratory failure (>80% of cases), followed by heart failure (10%-20%).

Mechanical ventilation has been shown to confer several benefits in patients with Duchenne muscle dystrophy: it improves arterial blood gas values, stabilizes clinical manifestations of respiratory disorders, reduces the need for hospitalization, improves patient well-being, and increases life expectancy.[1,11-15] Elective noninvasive ventilation is often administered when symptoms appear and/or when alterations in daytime or nocturnal gas exchange are detected. Nonetheless, many patients remain asymptomatic and arterial blood gases are often not measured. In these cases, disease onset is defined by acute hypercapnic respiratory failure, a condition that requires intensive care with endotracheal intubation and invasive mechanical ventilation. Patients in this situation generally cannot be disconnected from the ventilator and need a tracheostomy.[16,17]

The aim of this study was to describe our experience in managing patients with Duchenne muscular dystrophy and report on the different features and course of pulmonary and nonpulmonary alterations.

Patients and Methods

We reviewed the medical records of 27 patients with Duchenne muscular dystrophy who had been referred to the department of respiratory medicine at West Park Hospital, Toronto, Canada in the preceding 15 years. West Park Hospital specializes in the rehabilitation and treatment of patients with long-term ventilation needs. The department of respiratory medicine has a rehabilitation unit that evaluates and treats both patients on home mechanical ventilation and patients receiving long-term mechanical ventilation in hospital.

Duchenne muscular dystrophy had been diagnosed in the 27 patients using standard diagnostic criteria,[18] and most had been referred to our center from the Hospital for Sick Children in Toronto, where they had been receiving continuous mechanical ventilation on an inpatient basis since early childhood. Only 3 patients had not received mechanical ventilation previously and they had all been referred to our center to evaluate whether or not ventilatory support was necessary.

We analyzed the following variables using information extracted from the patients' medical records: arterial blood gases, lung function (including maximal inspiratory and expiratory pressures) before (where available) and after mechanical ventilation; nocturnal oxygen saturation (measured by pulse oximetry); $PaCO_2$ (measured transcutaneously by capnography); heart function; dysphagia; and social status.

Statistical Analysis

Lung function and gas exchange data were expressed as means (SD) for quantitative variables. The *t* test was used to compare the values of paired data before and after mechanical ventilation. All analyses were performed using the Statistical Package for Social Sciences software package, version 11.5. Statistical significance was set at a value of at *P*<.05 in all cases.

Results

Twenty-seven patients with Duchenne muscular dystrophy were enrolled in the study. The mean (SD) age was 26 (6) years (range, 20-43 years). Diagnosis had been made at a mean age of 4 (2) years and wheelchair use started at a mean age of 10 (1) years. All the patients had undergone spine surgery for scoliosis by the time they were 12 years old.

At the time of the review, the patients had been receiving mechanical ventilation for 56 (49) months (range, 1-174 months). Ventilatory support had been initiated when the 27 patients had a mean age of 21 (5) years. Seventeen patients were receiving invasive mechanical ventilation via tracheostomy and 10 were receiving noninvasive ventilation. A switch to invasive ventilation was required in 3 patients after 18 (11) months due to an episode of acute respiratory failure or a lung infection. Table 1 shows the factors that prompted the need for mechanical ventilation.

Arterial blood gas levels, which had only been measured in half of the patients before mechanical ventilation was initiated, revealed mild hypoxemia and marked hypercapnia. The gases returned to normal levels once ventilation was administered and remained so for the entire follow-up period. Nocturnal gas exchange measurements before mechanical ventilation were only available for 6 patients, but they showed that both oxygen saturation and $PaCO_2$ improved considerably after mechanical ventilation had been initiated (Table 2).

Noninvasive ventilation was administered using a bilevel positive airway pressure ventilator (BiPAP S/T; Respironics Inc., Murrysville, Pennsylvania, USA) and commercial masks. Patients who had undergone a tracheostomy received ventilation through a volume-cycled ventilator (LP-6+, LP-10, or PLV-100; Lifecare, Lafayette, Colorado, USA). A cuffless tracheostomy tube was used wherever possible.

Fourteen patients required nocturnal mechanical ventilation only. Of these, 7 received noninvasive ventilation and 7 invasive ventilation via tracheostomy. The 7 patients with a tracheostomy tube used a speaking valve during the day. The remaining 13 patients received continuous ventilatory support via tracheostomy (>20 hours a day).

Lung function data were only available for 13 patients, and we observed no significant changes between measurements before and after mechanical ventilation (Table 3).

Thirteen patients had cardiac symptoms, mainly palpitations and chest discomfort. They all had abnormal electrocardiogram findings, as did 2 patients without symptoms (Table 4). The symptomatic patients all had abnormal echocardiograms too. The most common disorders detected were dilated cardiomyopathy, left ventricular dysfunction, and posterior hypokinesia.

On arrival at our center, 18 patients were still capable of oral intake. Of the remaining 9 patients, 7 were receiving

nutrition through a gastrostomy tube and 2 through a nasogastric tube. All the patients reported considerable weight loss in the year prior to initiation of mechanical ventilation. A videofluoroscopic swallowing study was performed on 14 patients who reported dysphagia; all of them were receiving invasive mechanical ventilation via tracheostomy. The most common findings were *a)* difficulties forming and controlling the bolus (reduced protrusion and retraction movements, weak lingual propulsion which at times gave rise to split swallowing,

TABLE 1
Factors That Prompted the Need for Mechanical Ventilation

	No. of Patients
Acute respiratory failure	21
Pneumonia	9
Pneumothorax	1
Heart failure	2
Myocardial infarction	1
Abdominal distension	1
Unknown	7
Arterial blood gas abnormalities	6

TABLE 2
Gas Exchange Data for Patients Studied*

	Before MV	After MV	Most Recent
Daytime PaO_2, mm Hg†	61 (19)	87 (14)	89 (15)§
Daytime $PaCO_2$, mm Hg†	60 (10)	42 (8)	42 (8) ‖
Nocturnal SaO_2, %‡	95 (1)	96 (1)	96 (2)
Nocturnal $TcPaCO_2$, mm Hg‡	63 (17)	45 (8)	40 (5)‡

*Data are expressed as means (SD).
MV indicates mechanical ventilation; SaO_2, arterial oxygen saturation; $TcPaCO_2$, transcutaneous $PaCO_2$.
†Studied in 13 patients.
‡Studied in 6 patients.<0}
§$P<.01$
‖$P<.001$

TABLE 3
Lung Function

	Before MV	Most Recent
Patients, n	13	8
Vital capacity, % reference	19 (7)	13 (3)
FVC, %	15 (6)	11 (3)
FEV_1, % ref	18 (8)	12 (3)
PImax, cm H_2O	–24 (10)	–40 (24)
PE_{max}, cm H_2O	22 (14)	28 (12)

FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; MV, mechanical ventilation.

TABLE 4
Electrocardiogram Alterations in 15 Patients Studied

	No. of Patients
Myocardial infarction	1
Sinus tachycardia	6
Left ventricular enlargement	2
Right ventricular enlargement	2
Nonspecific changes in ST segment	1
Early repolarization	1
Changes in ST segment (asymptomatic)	1
Right bundle branch block (asymptomatic)	1

a reduced range of maxillary movements, and presence of oral residue); and *b)* increased oral transit time (which can lead to malnutrition as a result of reduced caloric intake). All the patients whose nutritional needs were met entirely through a gastrostomy tube had abnormal findings in both the oral and pharyngeal swallowing phases. In the pharyngeal phase, they all had very restricted hyoid and laryngeal elevation, no epiglottic deflection, and mild aspiration of liquids (which resulted in the presence of considerable pharyngeal residue).

All the patients receiving ventilation via tracheostomy, regardless of whether they were using a cuffless tube, a fenestrated tube, or a speaking valve, had intelligible speech.

Five patients (18%), 4 of whom were receiving invasive mechanical ventilation, died during the monitoring period. At the time of death, they had been on mechanical ventilation for 63 (47) months (range, 10-108 months). The exact cause of death was not recorded. Three of the patients had serious heart disease with considerable left ventricular dysfunction; they had experienced rapid weight loss prior to death and had also reported increased fatigue.

Discussion

Our experience, like that of other authors, shows that mechanical ventilation offers clinical benefits and prolongs life expectancy in patients with Duchenne muscular dystrophy. The course of disease in our patients was also similar to that described in earlier reviews,[1-3] particularly in terms of age at diagnosis, age at which the patients required a wheelchair, and age at onset of respiratory failure.

The administration of mechanical ventilation in these patients improves prognosis dramatically,[11-17,19] and noninvasive methods are preferred wherever possible. For obvious reasons, no controlled prospective trials have been performed to support the hypothesis of prolonged survival with noninvasive ventilation, but it seems evident that this is the effect. Simonds et al[11] reported a 1-year and 5-year survival rate of 85% and 73%, respectively, for their series of patients with Duchenne muscular dystrophy. It has also been shown that patients on noninvasive mechanical ventilation need less hospitalization due to respiratory complications than do patients receiving ventilation via tracheostomy.[20] Noninvasive methods, however, are not sufficient to correct ineffective cough and/or hypercapnic respiratory failure; in these cases, only ventilation via tracheostomy seems to prolong survival.[21] The need to change from noninvasive to invasive ventilation varies from one series to the next,[11,15] and as Simonds and colleagues indicated, the switch may not always be necessary.

In our series, 62% of the patients had a tracheostomy tube for invasive mechanical ventilation. This figure is considerably higher than those reported for other series, and the difference does not seem to be related to different degrees of severity of respiratory failure (arterial blood gases) or differences in lung mechanics (lung function).[11,14,15] In our opinion, there are 2 possible reasons for our higher figure. The first is the lack of experience with noninvasive mechanical ventilation in the field of pediatrics in the 1990s and the second, more important,

reason is the fact that the majority of our patients required intubation and mechanical ventilation following an acute hypercapnic respiratory failure episode. This indicates a lack of regular monitoring of these patients. The stage of disease at which mechanical ventilation is initiated is a key factor in the choice of ventilation route. According to our findings and those of other series, mechanical ventilation generally needs to be initiated in patients with Duchenne muscular dystrophy when they are between 18 and 20 years old. Respiratory function should therefore be monitored regularly between the ages of 10 and 15 years. The recording of changes in symptoms and arterial blood gas levels, lung function, and nocturnal gas exchange measurements could prevent an acute hypercapnic respiratory failure episode. A consensus conference report published in 1999[22] established the criteria for determining when to implement noninvasive mechanical ventilation and prevent both acute hypercapnic respiratory failure and the need for tracheostomy in order to improve the patient's clinical and social situation and prolong life expectancy. Noninvasive mechanical ventilation has proven to be an effective means of treating hypercapnic respiratory failure (evidence level III) when instituted in a programmed manner.[22] Initiation is recommended when patients report symptoms related to hypercapnic respiratory failure or when altered daytime or nocturnal gas exchange is detected. The monitoring of vital capacity and respiratory muscle function is also recommended in these patients. Ragette et al[23] observed that a vital capacity of <60% and/or a maximal inspiratory pressure of <4.5 kPa are predictors of abnormal nocturnal gas exchange, and that a vital capacity of <25% and/or a maximal inspiratory pressure of <3.5 kPa were predictors of daytime hypercapnic respiratory failure. Raphael et al[24] showed that the prophylactic use of noninvasive mechanical ventilation was not effective in patients with Duchenne muscular dystrophy when $PaCO_2$ levels were normal or when there were no symptoms.

Cardiac involvement was documented in 48% of the patients in our series, a figure similar to those reported in earlier reports of patient series.[4-6] Heart disease is not associated with disease severity or level of neurological impairment, although it has been described in the majority of patients over 18 years of age.[25] Chenard et al[26] demonstrated that premature ventricular heartbeats, left ventricular dysfunction, and dilated cardiomyopathy are all risk factors for sudden death. In our series, 3 of the 5 patients who died had serious heart disease. Given that their respiratory status was similar to that of the patients who survived, we can assume that heart disease was the underlying cause of death. The most common heart condition in patients with Duchenne muscular dystrophy is dilated cardiomyopathy.[4-6] Although the pathogenesis of this condition has not been identified, it is known that patients with muscular dystrophy have impaired coronary artery smooth muscle, according to Gnecchi-Ruscone et al,[27] and this could be a contributing factor; using positron emission tomography, those authors found that coronary vasodilator reserve was reduced in patients with Duchenne muscular dystrophy due to increased baseline myocardial blood flow. They suggested that the coronary vasodilator

reserve could be normalized by correcting the cardiac overload. Ishikawa et al[28] also indicated that the specific treatment of dilated cardiomyopathy could reverse the signs and symptoms of congestive heart failure. Accurate diagnosis and careful monitoring of heart function are therefore necessary in patients with this disease.

Our patients had experienced considerable weight loss in the year prior to initiation of mechanical ventilation. This time frame coincides with those described in previous studies,[29,30] which showed that weight loss occurs very quickly in advanced stages of the disease. Very few studies have analyzed nutrition in patients with Duchenne muscular dystrophy, but what information is available suggests that nutritional supplements can prevent weight loss and in some cases even contribute to weight gain.[8,29-32] These special diets, however, do not seem to alter the rate of deterioration of respiratory function or muscle strength.[31] Willig et al[8] found that weight loss and dysphagia symptoms improve once mechanical ventilation is initiated, reducing the number of patients that require a gastrostomy tube, even in more advanced stages of the disease. In our series, only 25% of the patients had a gastrostomy tube, and all of these were receiving mechanical ventilation via tracheostomy. No weight loss occurred in any of our patients, regardless of whether or not they were fed through a tube, during the follow-up period. One particularly interesting aspect of our review of cases is the information provided by our analysis of the videofluoroscopic studies on swallowing disorders in patients with Duchenne muscular dystrophy. All the difficulties detected in our patients (who were all mechanically ventilated via tracheostomy) seemed to be related to their muscular disorders rather than the tracheostomy. Different patterns of oral and pharyngeal muscle involvement are observed at different stages of this disease, and there is very little information in the literature regarding swallowing disorders in these patients. In 1991, Gilardeau[32] proposed a dysphagia classification system for Duchenne muscular dystrophy patients and established that aspiration risk was linked to impaired chewing function, food type, and the care patients took with food. The videofluoroscopic studies we performed on our patients are particularly interesting in that they provide detailed information on the different abnormalities that occur during the different swallowing phases (oral, pharyngeal, and esophageal) in patients receiving mechanical ventilation. Our findings clearly show that the disorders were related to the disease rather than the tracheostomy. We believe that it is important to design a prospective study to analyze swallowing disorders in patients with Duchenne muscular dystrophy before mechanical ventilation is initiated. Dysphagia is one of the predictors of success of noninvasive mechanical ventilation in patients who need a tracheostomy to protect the airway.

On the basis of our findings, we can conclude that mechanical ventilation confers important benefits in Duchenne muscular dystrophy and should be administered to all patients with this disease in order to prolong life expectancy. Careful monitoring of clinical and functional parameters from the time the patient is young is essential to prevent acute respiratory failure and the need for tracheostomy. Appropriate monitoring of cardiac and

swallowing function may also have a positive impact on prognosis. To conclude, close collaboration between pediatric and adult centers is necessary to ensure the optimal care of these patients.

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