

# Implication of regular pulmonary function evaluation in Duchenne muscular dystrophy

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## Research

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# Abstract

## Background

Various factors are considered when determining the need to initiate noninvasive ventilation (NIV), for example hypoventilatory symptoms, forced vital capacity (FVC), maximal inspiratory pressure (MIP), and end-tidal carbon dioxide. We aim to reveal the clinical importance of regular pulmonary function evaluation before the initiation of NIV by comparing Duchenne muscular dystrophy (DMD) patients with and without regular medical surveillance.

## Methods

This retrospective study analyzes successful applications of NIV in our pulmonary rehabilitation center. We assigned 200 DMD patients, hospitalized between June 2006 and August 2019, to one of two groups, according to their follow-up status before NIV initiation. Group 1 (n = 102) had been followed-up regularly via the outpatient clinic at least twice a year. Group 2 (n = 98) was hypercapnic, either at the first visit, or re-visit after having missed the outpatient clinic appointment for more than one year.

## Results

Significantly more patients were admitted via emergency room in group 2 (2.0% in group 1 and 28.6% in group 2). The patients' age was higher in group 2 ( $18.3 \pm 3.7$  years in group 1 and  $21.2 \pm 4.8$  years in group 2). Ventilatory status evaluated by arterial blood gas analysis and transcutaneous continuous monitoring was better in group 1 than that of group 2. And all measures of pulmonary function, including FVC, peak cough flow, MIP, maximal expiratory pressure, and ventilatory status, were superior in group 1, too.

## Conclusions

Regular follow-up before the onset of ventilatory insufficiency is crucial for the timely application of NIV, and appropriate NIV can exert a preventive effect on respiratory function deterioration.

## 1. Introduction

Duchenne muscular dystrophy (DMD), an X-linked recessive and progressive muscular disorder, is the most common form of genetic muscular dystrophy. Just a few decades ago, respiratory and cardiac deterioration were a major cause of death for DMD patients in their twenties. However, appropriate management of ventilatory insufficiency and medical treatment of dilated cardiomyopathy enables prolonged life in DMD patients [1, 2]. The protocol for cardiac management is relatively simple and well established in DMD patients. Regular checkups of cardiac function and timely medication based on left ventricular ejection fraction are the basis of cardiac management [3, 4]. However, respiratory care is more

complicated than cardiac management. Pulmonary rehabilitation includes air-stacking exercise, respiratory muscle training, airway secretion management, and ventilatory support, amongst others. To determine whether noninvasive ventilation (NIV) should be initiated, various factors such as hypoventilatory symptoms, forced vital capacity (FVC), maximal inspiratory pressure (MIP), and end-tidal carbon dioxide (EtCO<sub>2</sub>), should be considered [5, 6, 1]. However, the clinical significance of timely application of NIV is not yet clear. We aim to reveal the clinical importance of regular pulmonary function evaluation before the initiation of NIV by comparing DMD patients with and without close medical surveillance.

## **2. Patients And Methods**

### **2.1. Grouping of the patients**

The medical records of 200 patients who had been hospitalized and received NIV as of August 2019 were retrospectively collected and analyzed. DMD diagnosis in all patients was confirmed through genetic studies or muscle biopsy.

The patients were categorized into two groups according to their follow-up status before NIV initiation. Patients in group 1 had been followed-up regularly and evaluated for pulmonary function via the outpatient department (OPD) more than twice a year. FVC, peak cough flow (PCF), MIP, maximal expiratory pressure (MEP) and EtCO<sub>2</sub> were measured, and hypoventilatory symptoms including nightmares, morning headaches, daytime sleepiness, fatigue, dyspnea, and orthopnea[7] were determined via detailed interviews at each visit. Patients were trained in the performance of air-stacking exercise using a manual resuscitator bag when FVC was lower than 70% of the normal predicted value. The patient was admitted if FVC was less than 30% of the normal predicted value, if EtCO<sub>2</sub> when awake was more than 40 mmHg, or if hypoventilatory symptoms were reported. In such cases, nocturnal NIV was initiated when hypercapnia was confirmed by noninvasive and continuous monitoring of ventilatory status whilst patients were sleeping.

Group 2 consisted of patients who presented with hypoventilatory symptoms or hypercapnia at the first visit, or re-visit after having missed the OPD appointment for more than one year. Patients whose ventilatory failure had not been corrected appropriately despite the use of mechanical ventilators prescribed at other hospitals, and those who unnecessarily used tracheostomy ventilators, were also included in group 2.

Patients having at least FVC results available were included in this study. Those patients whose pulmonary function data were missing, or who could not be evaluated accurately because of intellectual disability, were excluded from this study. Furthermore, patients who had to maintain the tracheostomy tube and did not need a mechanical ventilator were also excluded.

### **2.2. Adjustment for hypercapnia**

Partial pressure of carbon dioxide (PCO<sub>2</sub>) and O<sub>2</sub> saturation were measured continuously and noninvasively via a transcutaneous method (SenTec System<sup>®</sup>, SenTec AG, Therwill, Switzerland) or EtCO<sub>2</sub> (DASH series<sup>®</sup>, GE Healthcare, Milwaukee, WI, USA) during the first night of hospitalization. Ventilatory status of a patient was monitored during their usual ventilatory conditions. In other words, a patient who did not use a ventilator was evaluated without a ventilator, and a patient who was already supported by a ventilator prescribed from another hospital was monitored during their usual ventilator use. If hypercapnia or desaturation was confirmed, either NIV was initiated or the existing ventilator setting was adjusted until hypercapnia was corrected. In intubated patients, NIV was initiated after extubation. In tracheostomized patients, NIV was initiated after replacing the tracheostomy tube with a fenestrated type, and the tracheostomy tube was removed after adaptation to NIV.

### 2.3. Evaluation of the patients

Between the groups, we analyzed various parameters that reflect pulmonary function, including FVC, PCF, MIP, and MEP. Pulmonary function was evaluated with patients in a medically stable condition and after extubation or decannulation. In accordance with our previous research, expert clinicians measured the pulmonary function parameters [8,9]. The maximum value of each parameter was selected from among more than three trials of each parameter. Percentages of the normal predicted values were calculated for FVC, MIP, and MEP [8]. Measurements of arterial blood gas analysis (ABGA) taken when awake, upon hospitalization, were compared. Noninvasive and continuous monitoring of ventilatory status evaluated by a transcutaneous method were also compared. For comparing between the groups, independent t-test was used and statistical analysis was performed in SPSS (version 23, IBM Corp., Armonk, NY, USA).

This study was approved of the Institutional Review Board of Gangnam Severance Hospital (No. 3-2019-0371-001).

## 3. Results

From June 2006 to August 2019, 231 DMD patients were hospitalized at Gangnam Severance Hospital. Thirty-one patients were excluded from our analysis because of intellectual disability, permanent tracheostomy, or a missing pulmonary function evaluation. The mean age of the 200 patients included in the study was 19.7 ( $\pm$  4.5) years. There were 102 patients in group 1 and 98 patients in group 2. Of the group 2 patients, 80 had not been followed-up for more than one year, and the remaining 18 patients had never been visited, when ventilatory insufficiency occurred. Of the group 1 patients, two (2.0%) were hospitalized via the emergency room (ER) because of symptoms of respiratory failure. Of these, hospitalization had previously been recommended to one, but he delayed admission until visiting the ER. The other patient visited the ER before appointed OPD that was planned to decide whether to be hospitalized or not. In contrast, among the 98 patients in group 2, 28 (28.6%) were hospitalized via the ER, a significantly higher proportion than in group 1 ( $P < 0.0001$ ). Of these 28 group 2 patients, seven were transferred with endotracheal intubation from other hospitals, seven were supported by tracheostomy ventilation, and one had a tracheostomy tube without a mechanical ventilator. Emergent endotracheal

intubation was performed in four patients after visiting the ER. Eight patients were receiving inappropriate NIV: five with uncorrected hypoventilation, one without adaptation to NIV, and the other two with insufficient hours of ventilatory support. No patients received emergent endotracheal intubation in group 1 (Table 1).

Table 1  
Initial status at the admission of the patients of each group.

<b>Initial status</b>	<b>Group 1</b>	<b>Group 2</b>
Total number	102	98
Admission via ER	2	28
Intubation	None	11
Tracheostomy before admission	None	8
Inappropriate NIV before admission	None	8
ER: emergency room, NIV: noninvasive ventilation		

Group 1 patients were significantly younger than group 2 patients (mean age:  $18.3 \pm 3.7$  years vs.  $21.2 \pm 4.8$  years; Table 2). ABGA performed when patients were awake, immediately after admission, revealed significantly higher  $O_2$  saturation and significantly lower  $PCO_2$  in group 1 than in group 2, but no significant difference in pH (Table 2). The daily duration of ventilatory support after final adjustment of NIV was significantly longer in group 2 than in group 1 (Table 2). All parameters of pulmonary function were significantly higher in group 1 than in group 2 (Table 2).

Table 2  
Comparison of pulmonary function between the groups.

Variable	Group 1	Group 2	P
Age (years)	18.3 ± 3.7 (N = 102)	21.2 ± 4.8 (N = 98)	< 0.0001 <sup>a</sup>
Arterial blood gas analysis			
O <sub>2</sub> saturation (%)	97.4 ± 3.4 (N = 102)	95.8 ± 4.7 (N = 98)	0.008 <sup>a</sup>
pH	7.333 ± 0.734 (N = 102)	7.401 ± 0.060 (N = 98)	0.331
PCO <sub>2</sub> (mmHg)	39.4 ± 7.0 (N = 102)	47.9 ± 15.2 (N = 98)	< 0.0001 <sup>a</sup>
Time of ventilatory support			
Hours/day <sup>*</sup>	8.5 ± 1.2 (N = 102)	9.9 ± 3.7 (N = 98)	0.0001 <sup>a</sup>
Pulmonary function			
FVC (%) <sup>†</sup>	28.0 ± 16.5 (N = 102)	16.2 ± 11.9 (N = 98)	< 0.0001 <sup>a</sup>
PCF (L/min)	166 ± 69 (N = 100)	103 ± 79 (N = 98)	< 0.0001 <sup>a</sup>
MIP (%) <sup>†</sup>	28.1 ± 17.6 (N = 94)	15.7 ± 10.7 (N = 89)	< 0.0001 <sup>a</sup>
MEP (%) <sup>†</sup>	17.7 ± 8.6 (N = 94)	11.7 ± 8.1 (N = 90)	< 0.0001 <sup>a</sup>
PCO <sub>2</sub> : partial pressure of carbon dioxide, FVC: forced vital capacity, PCF: peak cough flow, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure			
* After application or adjustment of noninvasive ventilator			
† These values calculated to percentage of normal predictive values.			
<sup>a</sup> P < 0.05			

Transcutaneous monitoring of ventilatory status without the support of a mechanical ventilator was performed during the first night of admission for 125 patients (75 in group 1 and 50 in group 2). Mean O<sub>2</sub> saturation was significantly higher in group 1, and maximal and mean PCO<sub>2</sub> were significantly higher in group 2, indicating the deterioration of ventilation in group 2 patients (Table 3).

Table 3  
Comparison of transcutaneous monitoring of ventilatory status during  
nighttime before application of noninvasive ventilator.

Parameter	Group 1 (N = 75)	Group 2 (N = 50)	P
Mean O <sub>2</sub> saturation (%)	97.0 ± 2.3	94.9 ± 4.6	0.003 <sup>a</sup>
Maximum PCO <sub>2</sub> (mmHg)	52.5 ± 6.2	58.0 ± 10.0	0.001 <sup>a</sup>
Mean PCO <sub>2</sub> (mmHg)	45.6 ± 4.4	50.3 ± 8.8	0.001 <sup>a</sup>
PCO <sub>2</sub> : partial pressure of carbon dioxide			
<sup>a</sup> P < 0.05			

## 4. Discussion

Because ventilatory insufficiency eventually occurs in DMD patients, ventilatory support is inevitable. In the early stage of ventilatory insufficiency, hypoventilatory symptoms are subtle, variable and non-specific [10]. Furthermore, symptoms such as dyspnea may rarely appear in DMD patients whose physical activity is greatly reduced. Usually, ventilation worsens during sleep at night [11], and it is difficult to determine the timing of ventilatory support via an OPD follow-up. Therefore, in this study, we believe that close surveillance of pulmonary function and hypoventilatory symptoms via regular OPD follow-ups significantly facilitated the timely application of mechanical ventilators and consequently prevented undesirable ER visits for acute respiratory deterioration and unwanted invasive ventilation via intubation or tracheostomy.

Hypercapnia is caused by the weakness of respiratory muscles, and uncorrected hypercapnia further exacerbates respiratory muscle weakness. Hypercapnia can increase the workload of, and cause fatigue in, inspiratory muscles. In animal experiments, hypercapnic conditions have changed the contractile properties of the diaphragm and the activity of ATPase [12]. In human studies, hypercapnia has been shown to increase the workload of respiratory muscles in healthy adults as well as in patients with chronic obstructive pulmonary disease (COPD) [13, 14]. Overload of respiratory muscles can cause fatigue in neuromuscular patients, accompanied by respiratory muscle weakness. Although refuted by a subsequent multicenter study [15], Delaubier et al [16] report the prevention of FVC decline by early NIV in DMD patients.

In DMD patients, pulmonary function rapidly deteriorates at the end of the second decade of life [17, 18]. However, few studies have reported changes in pulmonary function in patients beyond their 20 s. In a study evaluating various measures of pulmonary function according to age [17], Hahn et al report that FVC, MIP, and MEP were respectively 31%, 30%, and 18% of normal predicted values in patients of 17–18 years, showing similar values to group 1 patients in our study. FVC, MIP, and MEP deteriorated to 18%, 22%, and 12% respectively in patients of 21–22 years in the Hahn et al study. In contrast, the MIP of

group 2 patients in our study was much lower than in the Hahn et al study, despite patients being of similar age. Although patients in group 1 were younger than those in group 2, we assume that management through regular OPD follow-ups before the initiation of NIV had an effect on the preservation of respiratory muscle strength in DMD patients. Furthermore, sufficient respiratory surveillance facilitated appropriate treatment at an early stage of ventilatory insufficiency.

Even though group 2 included 15 patients who had already received mechanical ventilatory support, their pulmonary function was reduced compared to those in group 1 who had received regular rehabilitative surveillance without the use of a ventilator. This suggests that ventilatory support does not simply guarantee the prevention of deterioration in pulmonary function. We suggest that applying the ventilator is not important in itself, but that appropriate adjustment of hypercapnia is more important for the preservation of pulmonary function.

As well as pulmonary rehabilitation, various additional disease management techniques such as nutritional support and physical therapy may have been better fulfilled in group 1 patients, which may have affected the results of this study. Furthermore, in the case of patients who received treatments at other hospitals, there was limited information on how they received respiratory management and on whether they were followed-up regularly. Because this study focuses on the time of initiation of NIV, we suggest further research is needed on the long-term effects of the timing of NIV application.

## 5. Conclusions

Regular pulmonary function evaluation affects the preservation of respiratory function and is important for detecting ventilatory insufficiency at an early stage in order to provide appropriate and timely management in DMD patients.

## Declarations

**Ethics approval and consent to participate:** This study was approved by Institutional Review Board of Gangnam Severance Hospital (No. 3-2019-0371-001)

**Consent for publication:** Not applicable

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article. The datasets generated and analyzed during the current study are not publicly available because of the potential of identifying individual, but are available from the corresponding author on reasonable request

**Competing interests:** The authors declare that they have no competing interests.

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## Authors' contribution

JW Lee: design of the work, analysis and writing of the manuscript

SW Kang: interpretation of the data and review of the manuscript

EY Kim: design of the work and acquisition

WA Choi: review and revise of the manuscript

All authors have read and approved the manuscript and agree to be accountable for all aspects of the work.

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