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Clinical implication of maximal voluntary ventilation in myotonic muscular dystrophy

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Abstract

Patients with myotonic muscular dystrophy type 1 (DM1) tend to exhibit earlier respiratory insufficiency than patients with other neuromuscular diseases at similar or higher forced vital capacity (FVC). This study aimed to analyze several pulmonary function parameters to determine which factor contributes the most to early hypercapnia in patients with DM1.

We analyzed ventilation status monitoring, pulmonary function tests (including FVC, maximal voluntary ventilation [MVV], and maximal inspiratory and expiratory pressure), and polysomnography in subjects with DM1 who were admitted to a single university hospital. The correlation of each parameter with hypercapnia was determined. Subgroup analysis was also performed by dividing the subjects into 2 subgroups according to usage of mechanical ventilation.

Final analysis included 50 patients with a mean age of 42.9 years (standard deviation = 11.1), 46.0% of whom were male. The hypercapnia was negatively correlated with MVV, FVC, forced expiratory volume in 1 second (FEV_1), and their ratios to predicted values in subjects with myotonic muscular dystrophy type 1. At the same partial pressure of carbon dioxide, the ratio to the predicted value was lowest for MVV, then FEV_1, followed by FVC. Moreover, the *P* values for differences in MVV and its ratio to the predicted value between ventilator users and nonusers were the lowest.

When screening ventilation failure in patients with DM1, MVV should be considered alongside other routinely measured parameters.

Abbreviations: CTG = cytosine–thymine–guanine, DM1 = myotonic muscular dystrophy type 1, DMPK = dystrophia myotonica protein kinase, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, MMD = myotonic muscular dystrophy, MVV = maximal voluntary ventilation, pCO_2 = partial pressure of carbon dioxide.

Keywords: forced vital capacity, hypercapnia, maximal voluntary ventilation, myotonic muscular dystrophy, neuromuscular disease, ventilation failure

1. Introduction

Myotonic muscular dystrophy type 1 (DM1), caused by an abnormal cytosine–thymine–guanine (CTG) repeat expansion in the region of the dystrophia myotonica protein kinase (*DMPK*) gene,[1–4] is one of the most common neuromuscular diseases. The expanded repeat is transcribed in RNA and forms discrete inclusions in the nucleus, leading to muscle fiber hyperexcitability and impaired transmembrane conductance of either chloride or sodium ions.[5,6] Patients are characterized by "myotonia," a term referring to delayed relaxation of muscle fibers. Thus, unlike patients with other types of neuromuscular diseases who exhibit only progressive loss of muscle fibers, patients with DM1 exhibit difficulty in contraction–relaxation coordination before exhibiting actual muscle weakness.[7] Symptomatic patients demonstrate difficulty in relaxing their grip during repeated grasping and releasing movements. Cardiac muscles predominantly exhibit

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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rhythmic problems such as conduction abnormalities, and cardiomyopathies are usually secondary to arrhythmia and ventilatory failure.[4,7–9] Most likely, the diaphragm and intercostal muscles, which enable rhythmic breathing by contraction and passive relaxation, can also be affected by myotonia.[9,10]

Most neuromuscular disorders, including DM1, with progressive respiratory muscle weakness result in an increase in partial pressure of carbon dioxide (pCO_2),[11,12] and hypercapnia demonstrates a correlation with pulmonary function.[13] For example, decline in total lung capacity is strongly correlated with hypoxemia and hypercapnia in patients with myotonic muscular dystrophy (MMD).[14] However, in our experience, patients with DM1 tend to exhibit earlier respiratory insufficiency than patients with other neuromuscular diseases at similar or higher pulmonary function, including forced vital capacity (FVC).[15] Aside from respiratory muscle weakness, there are also other mechanisms that explain ventilation failure in DM1, including alterations in respiratory mechanics and abnormal central respiratory control.[14,16]

Meanwhile, maximal voluntary ventilation (MVV) is one of the pulmonary function parameters used to determine respiratory muscle endurance. The standard method of measuring MVV is to let the patient breathe as fast and hard as possible for 12 seconds, then multiply the total flow volume by 5 to yield the total volume of ventilation per minute (expressed as L/min).[17] Unlike most of other parameters that measure the pulmonary function for brief seconds, MVV enables measurement of longer flows. Reductions in MVV were known to be associated with expiratory phase slowing in the previous report.[17] Theoretically, it reflects both inspiratory and expiratory phase dysfunction and airway resistance, for MVV measures maximal volume of air inspired and expired for >12 seconds.[18] Myotonia of the diaphragm—typical in patients with DM1—might not be easily detected in shorter phase examinations such as FVC or forced expiratory volume in 1 second (FEV_1). However, it can be revealed in examinations conducted for longer phases, such as MVV.

We hypothesized that MVV decreases before other parameters, such as FVC, in patients with DM1, and that MVV would decline more abruptly in correlation with the progression of respiratory dysfunction in these patients. Accordingly, this study aimed to analyze several pulmonary function parameters to determine which factor contributes the most to early hypercapnia in patients with DM1.

2. Materials and methods

2.1. Participants

This is an observation study enrolling subjects with DM1 who were admitted to a single university hospital for routine annual check-up between March 2015 and March 2018. Individuals who were not able to undergo the pulmonary function tests (e.g., those with intellectual disabilities), and those with acute pulmonary disease conditions (e.g., pneumonia, pneumothorax, and so on) which may have affected the test results, were excluded. This study was approved by the institutional review board of the authors' hospital (3-2016-0182).

2.2. Study design

We retrospectively collected the data of pulmonary function testing, including FVC, FEV_1, and MVV. Data of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were also collected.

FVC which is the complete expiratory volume from a position of full inspiration[19] and FEV_1 which reflects elastic recoil and airway resistance[20] (both measured simultaneously) were tested using spirometry (Pony FX, COSMED, Rome, Italy) at least 3 times, and the best results were recorded. Normal predicted values for FVC were determined,[19,21] and the ratio of actual measurements and the predicted value (FVC_{Pred}%) in each subject were calculated. The ratio of FEV_1 to FVC (FEV_1/FVC) was also calculated. The MVV, which is understood as maximum ventilatory capacity[22] reflecting both inspiratory and expiratory phase dysfunction and airway resistance,[18] was tested also using Pony FX for a 12-second period, and the result was calculated to obtain a L/min value. At least 2 MVV data points were obtained with at least 1-minute time interval, and the highest value was recorded. Predicted value for MVV (MVV_{Pred}%) was also determined based on previous studies[17,23]; and the ratio of actual measurements and the predicted value of each subject were calculated. Both MIP and MEP which measure the strength of each inspiratory and expiratory muscles[24] were performed using respiratory pressure manometer (MicroRPM, CareFushion, Hoechberg, Germany) until 2 maximal values were reproducible, and the greatest pressure value obtained with variation <10% among the 3 highest values was chosen. The measured value and the percentage of the expected normal value (MIP_{Pred}% and MEP_{Pred}%) were considered.[21] Each test maneuver was performed together by a doctor and a trained physical therapist, and brief demonstration of each maneuver was conducted before initiating the test.

The pCO_2 was measured overnight in a noninvasive and continuous manner using a transcutaneous oximetry/capnometry device (SenTec AG; Therwil, Milwaukee, WI),[25] without a mechanical ventilator, and the maximal value of measured transcutaneous CO_2 was considered. We considered the pCO_2 value because the ventilatory dysfunction in this group is generally due to alveolar hypoventilation,[11,12] which can be predicted by isolated nocturnal hypercapnia.[26] Apnea–hypopnea index was also calculated from polysomnography performed on the same night (SleepTrek3; Grass Technologies, West Warwick, RI).

We first analyzed the pulmonary function parameters (i.e., FVC, FVC_{Pred}%, FEV_1, FEV_{1Pred}%, FEV_1/FVC, MVV, MVV_{Pred}%, MIP, MIP_{Pred}%, MEP, and MEP_{Pred}%) and demographic data (i.e., age, height, weight, body mass index, duration from initiation of mechanical ventilation, and number of CTG repeats), and their correlation with pCO_2. Then we performed subgroup analysis by dividing the subjects into 2 subgroups according to usage of mechanical ventilation. We compared the mean values of each pulmonary function parameters among the subgroups.

2.3. Statistical analysis

The aim of this study was to determine the correlation between pCO_2 and the pulmonary function parameters. As this was the first study to determine this correlation, we set to get significant result ($P < .05$) with sufficient power (80%) to detect at least correlation of 0.4. Therefore, the minimum required sample size for this study was 46.

Bivariate analysis was performed for each pulmonary function parameter, including MVV, FVC, FEV_1, MIP, MEP, and ratios of

their measure values to predicted values. Trend lines were drawn for the measured value/predicted values of FVC, FEV_1, and MVV on a scatter plot. The independent *t* test was used to compare the mean values of each parameter in the subgroup analysis. Missing data were not included in the analysis. The software SPSS version 24 (IBM Corp., Armonk, NY) was used. Values of $P < .05$ were considered statistically significant.

3. Results

3.1. Basic demographic information

Among the 87 eligible subjects, pulmonary function evaluation was performed in 50 subjects (mean age: 42.9 ± 11.1 years) with DM1. Test was not available in 13 subjects due to intelectual disabilities, and in 24 subjects due to acute medical conditions. Diagnostic confirmation was made by electrodiagnostic study and genetic study, showing abnormal GTC repeat expansion on *DMPK* gene. Sex was evenly distributed in the subject group with DM1, 46.0% of whom were male. Percussion myotonia was detected in all except 2 subjects, whereas grip myotonia was noticed in 26 subjects. The anthropometric data of the subjects are summarized in Table 1. Thirty-six out of the 50 subjects with DM1 were under mechanical ventilation. Only 14 subjects had polysomnography data.

3.2. Comparing ventilator users versus nonusers with DM1

We divided the subjects into 2 groups according to usage of mechanical ventilation. Thirty-six subjects were under mechanical ventilation with 35.9 months of mean duration since initiation and 14 subjects were nonusers. The initiation of mechanical ventilation in this group was decided under previously described criteria[27–29] and procedures.[29] Although they showed difference in age, the difference was not statistically significant. Mean pCO_2 of ventilator users and nonusers was 45.0 and 37.0 mm Hg, respectively ($P < .001$). The parameters FVC, FVC_{Pred}%, FEV_1, FEV_{1Pred}%, MVV, and MVV_{Pred}% all showed significant differences between the 2 subgroups, but the *P* values for the differences in MVV and MVV_{Pred}% were lower than those for other parameters (Table 1).

Table 1

Difference in each parameter among ventilator users and nonusers in subjects with DM1.

	Total (n = 50)	Ventilator users (n = 36)	Nonusers (n = 14)	*P*
Age, y	42.9 ± 11.1	42.9 ± 11.1	22.2 ± 5.3	.06
Height, cm	162.8 ± 7.8	162.2 ± 8.2	164.4 ± 6.9	.35
Weight, kg	59.9 ± 15.2	59.4 ± 16.5	61.2 ± 11.7	.66
BMI	22.6 ± 5.6	22.5 ± 6.1	22.7 ± 4.2	.93
CTG repeat*	530.1 ± 338.5	540.2 ± 401.3	533.3 ± 134.3	.94
AHI†	32.6 ± 20.8	32.6 ± 20.8	N/A	—
pCO_2, mm Hg	42.7 ± 7.0	45.0 ± 6.8	37.0 ± 3.2	<.001‡
FVC, L	2.0 ± 0.9	1.8 ± 1.0	2.4 ± 0.7	.04‡
FVC_{Pred}, %	54.2 ± 19.4	50.4 ± 19.5	63.8 ± 16.2	.02‡
FEV_1, L	1.5 ± 0.6	1.4 ± 0.7	1.8 ± 0.4	.02‡
FEV_{1Pred}, %	54.2 ± 19.4	46.7 ± 18.5	57.6 ± 14.2	.03‡
FEV_1/FVC, %	77.6 ± 16.6	77.6 ± 17.4	77.7 ± 14.8	.99
MVV, L/min	46.5 ± 22.5	42.0 ± 24.0	58.1 ± 12.2	.003§
MVV_{Pred}, %	44.0 ± 17.8	39.9 ± 18.1	54.5 ± 12.2	.002§
MIP, cmH_2O	41.2 ± 16.1	40.6 ± 17.7	42.9 ± 11.3	.58
MIP_{Pred}, %	50.4 ± 18.6	49.4 ± 19.2	53.0 ± 17.4	.54
MEP, cmH_2O	44.5 ± 15.4	43.9 ± 17.5	45.9 ± 8.2	.68
MEP_{Pred}, %	40.2 ± 14.6	39.3 ± 15.2	42.6 ± 13.5	.45

Data presented as mean ± standard deviation.

AHI = apnea-hypopnea index, BMI = body mass index, CTG = cytosine–thymine–guanine, DM1 = myotonic muscular dystrophy type1, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, MVV = maximum voluntary ventilation, N/A = not applicable, pCO_2 = partial pressure of carbon dioxide, Pred = predicted.

* Mean CTG repeat was calculated among 32 out of 36 ventilator user and 9 out of 14 nonusers in subjects with DM1.

† Polysomnography was performed among 14 subjects only in the ventilator user group.

‡ $P < .05$ and § $P < .01$ comparing the values among ventilator users and nonusers.

3.3. Correlation between pulmonary function parameters and trends of decline

Most of the pulmonary function test parameters demonstrated significant correlation with one another in subjects with DM1 in the bivariate analysis. Table 2 shows bivariate correlation between hypdercapnia and the pulmonary function parameters. It shows significant correlation of FVC, FVC_{Pred}%, FEV1, FEV_{1Pred}%, MVV, and MVV_{Pred}% with hypercapnia. Furthermore, hypercapnia showed significant correlation with duration from initiation of mechanical ventilation for subjects under mechanical ventilation ($r = -0.390$, $P = .02$). However, it did not show significant correlation with age ($r = -0.031$, $P = .83$), height ($r = -0.009$, $P = .95$), weight ($r = 0.099$, $P = .49$), body mass index ($r = 0.115$, $P = .43$), CTG repeats ($r = -0.021$, $P = .90$), nor apnea–hypopnea index ($r = 0.475$, $P = .09$).

Figure 1 shows the trend lines drawn for measured/predicted value (%) of FVC, FEV_1, and MVV on a scatter plot. The trend lines for DM1 ran parallel. At the same given pCO_2, the measured/predicted value of MVV was the lowest while that of FVC was the highest.

4. Discussion

This prospective study aimed to analyze several pulmonary function parameters in subjects with DM1 to reveal clues explaining early ventilation failure in these individuals, focusing on differences in the declining patterns of pulmonary function parameters. We assumed that delayed relaxation of the

Table 2

Bivariate correlation between hypercapnia and each pulmonary function parameter.

	DM1 (n = 50)
FVC	−0.298* (.04)
FVC_{Pred}	−0.362** (.01)
FEV_1	−0.301* (.03)
FEV_{1Pred}V	−0.345* (.01)
FEV_1/FVC	0.003 (.98)
MVV	−0.291* (.04)
MVV_{Pred}	−0.353* (.01)
MIP	−0.140 (.33)
MIP_{Pred}	−0.185 (.20)
MEP	−0.156 (.28)
MEP_{Pred}	−0.236 (.10)

Data are shown as Pearson coefficient (*P* value).

* $P < .05$.

** $P < .01$.

DM1 = myotonic muscular dystrophy type1, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, MVV = maximum voluntary ventilation.

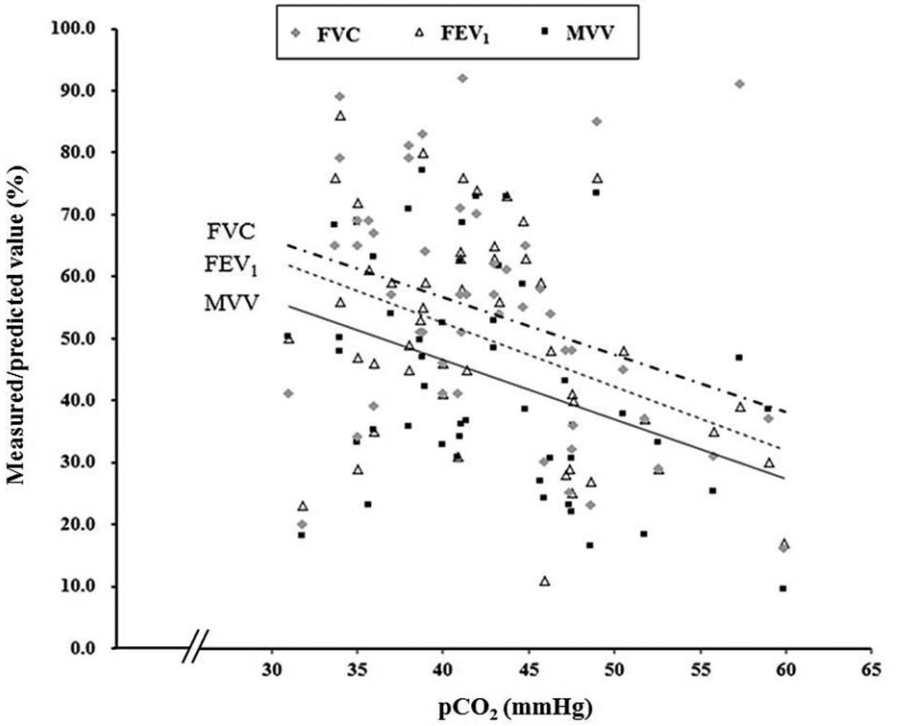

Figure 1. Ratio of measured and predicted values of pulmonary function parameters in relation to hypercapnia. Measured/predicted values of FVC (n = 50, gray diagonal), FEV_1 (white triangle), and MVV (black square) are depicted on the scatter plot in relation to hypercapnia. Trend lines were drawn for measured/predicted value of FVC (dash-single dotted line), FEV_1 (dashed line), and MVV (solid line) on the same scatter plot. FVC = functional vital capacity, FEV_1 = forced expiratory volume in 1 second.

diaphragm in DM1 would affect the physiologic breathing rhythm and lead to the progression of ventilation failure, even with adequate vital capacity. We hypothesized that MVV decreases before other parameters, such as FVC, in subjects with DM1, and that MVV would decline more abruptly in correlation with progression of respiratory dysfunction in subjects with DM1.

In this study, we performed correlation analysis of different pulmonary function parameters with hypercapnia in subjects with DM1 FVC, FEV_1, and MVV demonstrated a significant negative correlation with hypercapnia, whereas MIP and MEP did not. Although the declining pattern of MVV was not significantly different compared with FVC or FEV_1 as we hypothesized, MVV_{Pred}% decreased first among all the parameters. Moreover, the *P* value for the difference in MVV_{Pred}% between ventilator users and nonusers was the lowest. Although performed in part of the study population, apnea index did not show significant correlation with pCO_2.

Chronic hypoventilation in MMD has been explained in various prior studies. A central cause of hypoventilation is dominant among the theories posited by these studies. Carroll et al[30] suggested the possibility of a central factor underlying respiratory dysfunction in MMD by showing decreasing respiratory response with increasing CO_2 concentration. Although Begin et al opposed this idea by demonstrating that decreased respiratory response may not be due to a central factor,[31] and explained the phenomenon on the basis of inspiratory muscle weakness,[32] Serisier et al[33] insisted that dysfunction of medullary respiratory control is related to decreased respiratory response in MMD because this cannot be explained purely by respiratory muscle weakness. Poussel et al[14] insisted that alveolar hypoventilation in DM1 is independent of respiratory weakness, and provide evidences to support a central cause of CO_2 insensitivity. Furthermore, studies have reported neuronal loss in the medullary respiratory center in MMD.[34–36] Other evidences also support the association between respiratory muscle weakness and respiratory dysfunction. Misuri et al[16] reported that elastic load and respiratory muscle weakness are responsible for a rapid and shallow breathing pattern, leading to chronic CO_2 retention in patients with neuromuscular diseases, which is similar to the suggestion of Begin et al.[31,32]

Nevertheless, apnea index and pulmonary function parameters representing respiratory muscle power, such and MIP and MEP, did not show better correlation with hypercapnia than FVC, FEV_1, or MVV in subjects with DM1 in the present study. The earliest reduction was observed in MVV_{Pred}%, and the *P* values for the differences in MVV and MVV_{Pred}% were the least between the subjects with DM1 who were under mechanical ventilation and those who were not. We focused on dysfunction of elastic recoil or myotonic features of the respiratory muscles in this patient group to obtain an additional explanation of the cause of chronic hypoventilation.

Many studies have been conducted on myotonic movements in the respiratory muscles of patients with MMD. Fluoroscopic findings have revealed jerky movements of diaphragm and delayed relaxation patterns into normal position after contraction.[37] Electromyographic findings have revealed the myotonic movements in the respiratory muscles of these patients.[10,38] Recently, low maximum relaxation rate compared with healthy

subjects has also been shown to indicate delayed relaxation of the respiratory muscles in DM1.[39] However, previous studies have not investigated the relationship between the abnormal movement pattern of the respiratory muscle and respiratory dysfunction.

It is known that MVV is dependent on both inspiratory and expiratory breathing effort; inspiratory air flow is dependent only on inspiratory muscle power, whereas expiratory air flow relies mainly on lung recoil.[40] In normal subjects, lung recoil is known to be the major determinant of expiratory air flow in performing MVV. The same would apply to patients with DM1, given that they also perform MVV in the midrange of vital capacity. In this sense, MVV reflects the efficiency of lung recoil. The breathing pattern in MMD was described in a study by Bogaard et al,[41] who described a wide range of irregularity during the entire breathing period. Accordingly, pulmonary parameters that are based on instantaneous values, such as MIP, MEP, and even FVC, may not accurately reflect the variant pattern of respiration in patients with DM1. Thus, MVV may be more informative in reflecting the respiratory status of these patients.

The limitations of this study include lack of sensitivity/specificity evaluation of MVV in relation to actual electromyographic patterns of the respiratory muscles in subjects with DM1. The relatively small number of subjects who underwent polysomnography is another limitation. However, this study focuses on the declining trend of MVV in DM1 compared with other pulmonary function parameters, not its exact significance. Furthermore, this study does not aim to oppose the role of central dysfunction in chronic hypoventilation in this disease group, rather suggesting additional consideration. Further studies including sensitivity/specificity evaluation of MVV and its comparison with other measures, such as maximum relaxation rate[39] and larger sample sizes with more apnea index data, will be necessary to support our results.

This study demonstrates a correlation between MVV, along with FVC and FEV_1, and the progression of respiratory dysfunction in patients with DM1. Not being a well-studied pulmonary function parameter, MVV is excluded from routine pulmonary function tests in most laboratories. However, lower MVV may be one of the most relevant parameters and one of the early signs of CO_2 retention in patients with DM1. Thus, while screening ventilation failure in patients with DM1, MVV should be carefully considered alongside other routine measures.

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