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Natural history of cardiac function in Duchenne and Becker muscular dystrophies on home mechanical ventilation

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Abstract

Heart impairment is classical in dystrophinopathies and its management relies on medical drugs. Mechanical ventilation is used to treat respiratory failure, but can affect cardiac function. We aimed to investigate the natural history of cardiac function in patients with Duchenne (DMD) and Becker (BMD) muscular dystrophies on home mechanical ventilation (HMV).

We reviewed the chart of DMD and BMD patients, followed in our institution, to obtain ventilation setting at HMV initiation and echocardiographic data at baseline and end follow up, as well as onset cardiac events and thoracic mechanical complication. We analyzed cumulative incidence of cardiac events as well as echocardiographic parameters evolution and its association with ventilation settings.

We included 111 patients (101 DMD and 10 BMD). Median age was 21 years [18–26], median pulmonary vital capacity (VC) 15% of predicted [10–24]. All patients were on HMV and 46% ventilated using tracheostomy. After a median follow up of 6.3 years, we found a slight decrease of the left ventricular ejection fraction (LVEF) (45% at end follow up vs 50% at baseline $P = .019$) and a stabilization of the LV end diastolic diameter indexed (LVEDD $indexed$ 29.4 mm/m^2 vs 30.7 mm/m^2 at end follow up, $P = .17$). Tidal volume (VT) level was inversely associated with the annual rate of the LVEF decline ($r = -0.29$, $P = .025$). Left atrium (LA) diameter decreased with mechanical ventilation (24 mm vs 20 mm, $P = .039$) and we found a reduction of systolic pulmonary pressure (35 mm Hg vs 25 mm Hg, $P = .011$). The cumulative incidence of cardiac events was 12.6%. Pneumothorax occurred in 4% of patients. Hypoxic arrest secondary to the presence of tracheal plugin occurred in 4% of patients with invasive ventilation.

HMV is not harmful, decreases pulmonary pressure and may protect heart in dystrophinopathies, in addition with cardioprotective drugs. In patients with DMD and BMD on HMV, cumulative incidence of cardiac events remains moderate and incidence of pneumothorax is rare.

Abbreviations: ACE = angiotensin converting enzyme, BMD = Becker muscular dystrophy, DMD = Duchenne muscular dystrophy, HMV = home mechanical ventilation, LA = left atrium, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, PaCO$_2$ = arterial carbon dioxide partial pressure, PEEP = positive end-expiratory pressure, SPAP = systolic pulmonary arterial pressure, VC = pulmonary vital capacity, VT = tidal volume.

Keywords: Becker muscular dystrophy, Duchenne muscular dystrophy, echocardiography, heart failure, mechanical ventilation, pneumothorax, respiratory failure

1. Introduction

Duchenne muscular dystrophy (DMD) is an inherited myogenic disorder due to mutations in the dystrophin gene on chromosome Xp21.1. The prognosis is often determined by respiratory failure and heart involvement. Cardiomyopathy is present in 90% of adult patients.[1] Becker muscular dystrophy (BMD) is an X-linked muscular dystrophy due to mutations in the dystrophin gene, which is characterized by a reduction of dystrophin protein and a milder course compared with DMD[2] with a frequent heart involvement.[3]

Heart management in dystrophinopathies relies mainly on cardiac protective drugs including angiotensin converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists.[4] DMD patients exhibit simultaneously a restrictive respiratory failure, requiring long-term home mechanical ventilation (HMV), which may influence cardiac function. Indeed, positive pressure ventilation generates interactions between the respiratory system and the cardiovascular system, with a positive effect on LV function, resulting from a decrease in afterload.[5,6] In acute decompensated heart failure, applying of noninvasive ventilation relieves symptoms and improves heart performance.[7–9] Little is

known about the evolution of cardiac function in patients requiring mechanical ventilation because of chronic respiratory failure in neuromuscular disorders. We aimed to analyze the natural history of cardiac function in patients with DMD and BMD (dystrophinopathies) on HMV.

2. Methods

2.1. Study design and setting

We designed a retrospective cohort study in the Home Mechanical Ventilation Unit of the Raymond Poincare University Hospital, a tertiary neuromuscular center (Garches, France).

We included the charts of DMD and BMD patients (>18 years) addressed and followed in the unit for assessment and management of respiratory function because of chronic respiratory impairment, since 2006 to 2016. The date of inclusion was the date of the mechanical ventilation introduction, whatever the procedure was invasive or noninvasive. We considered the date of end follow up for each patient as the date with the last echocardiographic data available.

2.2. Cardiac function

We collected echocardiographic, respiratory function, and HMV setting data from medical records. Doppler Echocardiography was performed according to the guidelines issued by the American Society of Echocardiography.[10,11] For the assessment of the natural history of cardiac function, we recorded the following echocardiographic parameters at inclusion and at end of follow up: left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), mitral E/A ratio, left atrial (LA) diameter, peak tissular diastolic Ea lateral velocity and systolic pulmonary pressure.

We calculated the annual LVEF decline rate as the ratio: (LVEF at baseline – LVEF at end follow up)/year's number of ventilation.

2.3. Respiratory function

Spirometry variables and lung volumes were routinely measured using a Vmax 229 SensorMedics System (Yorba Linda, CA) according to standard guidelines The pulmonary function tests with spirometry were performed according to standard guidelines while the patient was comfortably seated.[12] Measurements of vital capacity (VC) during slow volumes measurements maneuver was recorded for each patient.

2.4. Ventilation

To characterize mechanical ventilation, we collected data on the ventilator's settings: positive end-expiratory pressure (PEEP), set tidal volume (VT) (expressed both as rough value and indexed to ideal body weight), respiratory rate, and daily duration of mechanical ventilation. The results of daytime blood gases and nocturnal oximetry (performed with a Covidien Nellcor oximeter) were also collected at end follow up.

2.5. Cardiac events and complications related to HMV

To describe the cardiac natural history of patients with dystrophinopathies on HMV, we also collected, during the follow up, cardiac events (acute heart failure, cardiac arrhythmia, and ischemic stroke) and the following thoracic complications

with mechanical ventilation: documented pneumothorax and hypoxic arrest secondary to the presence of tracheal plugin in patients with invasive ventilation.

The study was performed in compliance with the ethical principles formulated in the declaration of Helsinki and was approved by the *Comité de Protection des Personnes* and the *Commission Nationale de l'Informatique et des Libertés*. This study was registered in ClinicalTrials.gov (identifier: NCT02501083).

2.6. Statistical analysis

Continuous variables were described by median ± interquartile range (IQR) and compared by Wilcoxon test; dichotomous or categorical variables were described by number of subjects and percentage and compared by Fisher exact test. The associations between cardiac continuous parameters and ventilation data were explored by the nonparametric Spearman correlation coefficient. Statistical analysis was performed using R (http://www.R-project.org/).

3. Results

3.1. Study population

We included 111 patients with dystrophinopathies (101 DMD and 10 BMD). Median age was 21 years [18–26] in patients and all DMD patients were wheelchair-bound. Respiratory insufficiency was severe with a median VC at 15% of predicted. Patients were steroid naïve. Forty-six percent of patients were invasively ventilated with a tracheostomy. All patients were in sinus rhythm and disclosed a median LVEF at 50% [40–55]. Table 1 summarizes respiratory data, HMV setting, and cardiac drugs at inclusion.

3.2. Cardiac function evolution on HMV

After a median follow up of 6.3 years, we found a slight decrease of the LVEF (45% at end follow up vs 50% at baseline, $P = .019$),

Table 1

Respiratory function, mechanical ventilation setting, and cardiac drugs at inclusion.

Clinical and respiratory characteristics	Median [interquartile range]
Age of patients in the study, y	21 [18; 26]
Disease (N=111 patients)	DMD (91%), BMD (9%)
Weigh, kg	44 [36; 60]
Height, cm	165 [160; 170]
CV, %	15 [10; 24]
Age at HMV initiation, y	21 [18–26]
Invasive ventilation	46%
Biphasic ventilation mode	28%
ACV mode	71%
Ventilator respiratory rate	16 [15–18]
Duration of HMV/24 h, h	14 [8–24]
IPAP level, cmH$_2$O	16.5 [15–20]
PEEP level, cmH$_2$O	1 [0–4]
Tidal volume, mL	500 [450–600]
ACE inhibitors	87%
Beta-blockers	52%
Diuretics	11%

Values are expressed as median [interquartile range].

ACE inhibitors = angiotensin converting enzyme, ACV = assist-control volume, BMD = Becker muscular dystrophy, CV = forced vital capacity, DMD = Duchenne muscular dystrophy, HMV = home mechanical ventilation, IPAP = inspiratory positive airway pressure, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, PCO$_2$ = diurnal arterial carbon dioxide partial pressure, PEEP = positive end-expiratory pressure, Y = years.
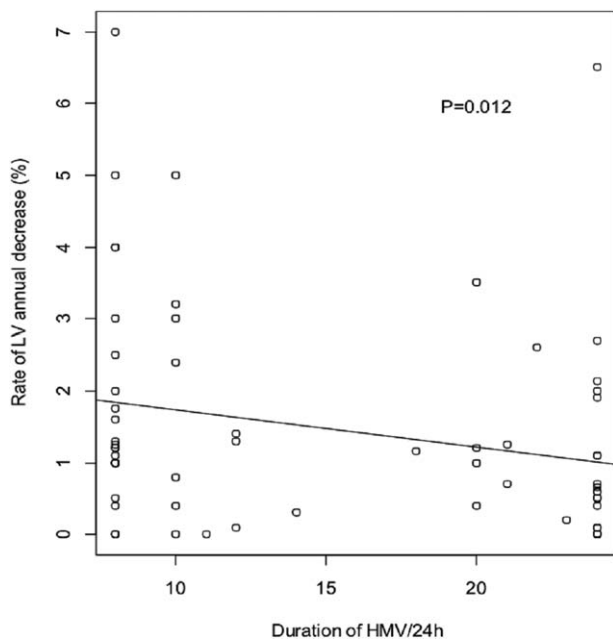
Figure 1. Relationship between rate of LVEF decline and duration of mechanical ventilation per 24 hour. HMV = home mechanical ventilation, LV = left ventricular ejection fraction.

Cardiac function at admission (TTE1) and end follow up (TTE2) in patients with dystrophinopathies.

Parameters	TTE1	TTE2	P
LVEF%	50 [40; 55]	45 [37; 54]	.019
LVEDD, mm	42 [37; 45.5]	44 [37.5; 50]	.09
LVEDDi, mm/m^2	29.4 [25.9; 35.1]	30.7 [26.8; 37.1]	.17
LA diameter, mm	24 [20; 28]	20 [17; 25]	.039
Mitral E/A ratio	1.56 [1.31; 1.77]	1.5 [1.1; 1.7]	.16
Mitral deceleration time, ms	176 [136; 204]	176 [148; 188]	.64
Peak Ea lateral, cm/s	11 [9; 14]	12.5 [10; 14]	.10
sPAP, mm Hg	35 [27; 38]	25 [24; 28]	.011

Values are expressed as median [interquartile range].
Median follow up = 6.3 years IQR: [4.1; 11.2].
LA = left atrium, LVEDD = left ventricular end diastolic diameter, LVEDDi = indexed left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, peak Ea lateral = peak early diastolic velocity at the mitral lateral annulus, sPAP = systolic arterial pulmonary pressure, TTE = transthoracic echocardiography, TTE1 = TTE at baseline, TTE2 = TTE at end follow up, Y = years.
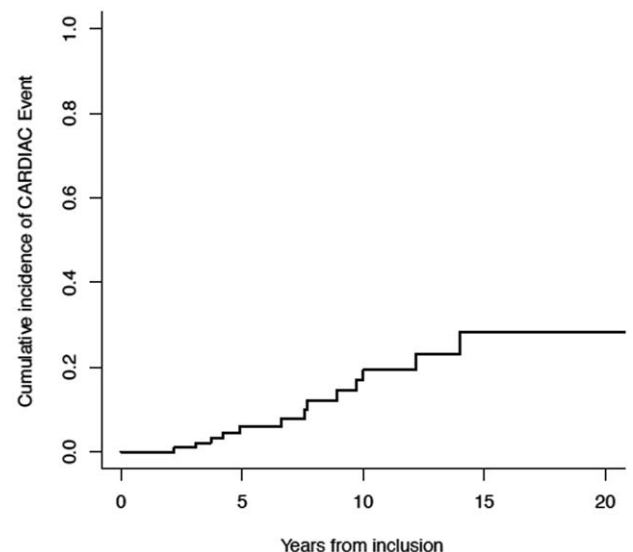
Table 2 summarizes the evolution of cardiac function with HMV in patients.

3.3. Pulmonary pressure evolution on HMV

Systolic pulmonary arterial pressure (SPAP) decreased with mechanical ventilation (35 mm Hg at baseline vs 25 mm Hg at end follow up, $P = .011$). In the meantime, at end follow up, median diurnal arterial carbon dioxide partial pressure ($PaCO_2$) was 5.09 kPa [4.4–5.9] and median percentage of sleep time with oxygen saturation (SaO_2) < 90% was 0% [0–1].

3.4. Incidence of cardiac events

After a median follow up of 6.3 years, among the 111 patients, cardiac events occurred in 14 patients (12.6%): acute heart failure in 10 patients, supraventricular arrhythmia in 2 patients and acute ischemic stroke in 2 patients. Figure 3 shows the

despite a stabilization of the LV end diastolic diameter (LVEDD) ($P = .17$). HMV duration/24 hour was significantly inversely associated with the annual rate of LVEF decline ($r = -0.31$, $P = .012$) (Fig. 1). Tidal volume (VT) level was inversely associated with the annual rate of LVEF decline ($r = -0.29$, $P = .025$) (Fig. 2).

HMV did not affect neither the mitral E/A ratio ($P = .16$) nor the E/Ea lateral ratio ($P = .10$). However, the left atrium (LA) diameter decreased significantly with HMV ($P = .039$).

Figure 2. Relationship between annual rate of LVEF decline and VT level. LV = left ventricular ejection fraction (%), VT = tidal volume (mL).

Figure 3. Cumulative incidence of cardiac events in patients on HMV. HMV = home mechanical ventilation.
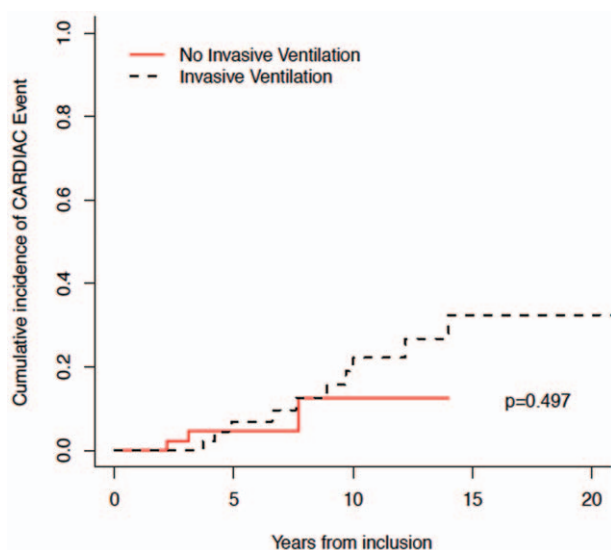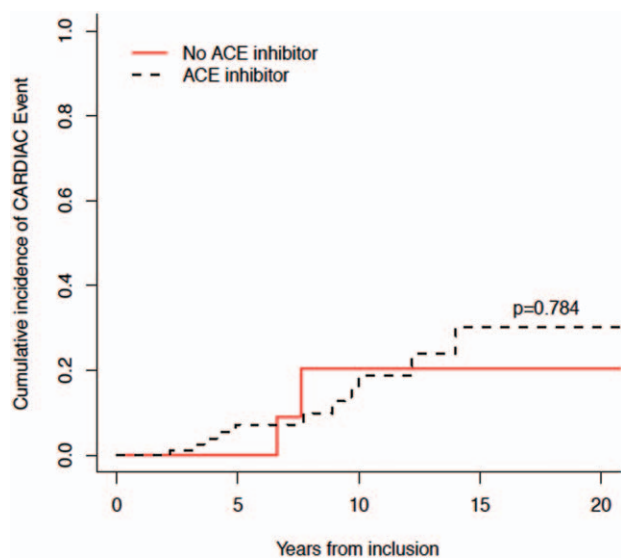
Figure 4. Cumulative incidence of cardiac events in patients with invasive ventilation versus noninvasive ventilation.

cumulative incidence of cardiac events. Figure 4 shows the incidence of cardiac events in patients with invasive ventilation versus patients with noninvasive ventilation. 87.6% of patients were treated with ACE inhibitors. The cumulative incidence of cardiac events in patients on HMV and treated with ACE inhibitors did not differ from the incidence of cardiac events in patients on HMV without ACE inhibitors (Fig. 5).

3.5. Thoracic complications

During the follow up, 4/111 patients (4%) disclosed documented pneumothorax: 2 patients with invasive ventilation and 2 patients with noninvasive ventilation. Hypoxic arrest secondary to the presence of tracheal plugin occurred in 2/51 patients (4%) with invasive ventilation.

Figure 5. Cumulative incidence of cardiac events in patients on HMV with ACE inhibitors versus HMV without ACE inhibitors. ACE = angiotensin converting enzyme.

4. Discussion

Heart involvement is frequent in patients with dystrophinopathies and affects morbidity and mortality.[3,13–15] Its management relies mainly on cardiac protective drugs, currently. We found that with mechanical ventilation, systolic pulmonary pressure decreases as well as left atrial size. Also, tidal volume seems to reduce rate of left ventricular function decline in dystrophinopathies, in addition with cardioprotective drugs.

Concomitantly with cardiac involvement, most DMD patients exhibit a restrictive respiratory impairment requiring HMV. The resulting interactions between the positive pressure ventilation and the cardiovascular system,[16] which are described in the ICU population, may have an impact on cardiac function in chronically ventilated patients. The increase in intrathoracic pressure with mechanical ventilation has a positive effect on LV function,[5,6] related to a decrease in LV afterload[7,8] and studies have reported positive effects of mechanical ventilation on heart in acute decompensated situation.[7–9] We found a positive relationship between HMV and LV systolic function, which is consistent with previous reports in patients with acute heart failure treated with mechanical ventilation.[12,17]

In our study, we found that tidal volume level seems to protect against myocardial function decline ($r=-0.29$, $P=.025$), in addition with ACE inhibitors and beta-blockers. Also, HMV duration per 24 hour seems to protect against LV myocardial decline ($P=.012$). We did not find any increase of LV diameter, which corroborates physiological protective aspect of mechanical ventilation. Indeed, patients with LV dysfunction are particularly sensitive to afterload variations,[17] and mechanical ventilation reduces LV afterload by increasing intrathoracic pressure and thus decreasing transmural pressure of LV. We found a decrease of LA diameter and a nondeleterious action of HMV on mitral E/A and E/Ea ratios suggesting probable LV diastolic function improvement.

This finding is also not surprising. Indeed, application of continuous positive intrathoracic pressure unloads left ventricle and decreases LV filling in patients with heart failure.[18,19]

Finally, we found that long-term HMV provides a decrease of systolic pulmonary pressure in dystrophinopathies, probably due to blood gaze exchange improvement and reduction of pulmonary resistance. However, normal overnight oxymetry and daytime arterial blood gases are not sufficient to exclude nocturnal hypercapnia in patients needing long-term HMV.[20,21]

Our results underline the potential usefulness of chronic mechanical ventilation in patients with DMD and BMD by alleviating LV afterload. This instrumental therapy may be proposed, in addition with pharmacological approach including beta-blockers, ACE inhibitors, and aldosterone antagonists, particularly in patients with chronic respiratory failure. In our study, 87% of patients were treated with ACE inhibitors and 52% with beta-blockers. We admit that cardiac drugs' setting was not optimal, but in practice, arterial hypotension limits administration of cardiac drugs association and target of optimal drug dosing.

Finally, in parallel with the positive cardiac effect of mechanical ventilation, it is essential to search for possible thoracic complication due to the increase of intrathoracic pressure, particularly the onset of pneumothorax. In our study, the incidence of pneumothorax was relatively low (4%).

4.1. Strengths and limits

Our main strength relies on the number of patients included in our study. To the best of our knowledge, the cardiac function evolution of DMD and BMD patients on mechanical ventilation

have not been previously investigated in the chronic (home) setting in neuromuscular disorders. Our findings are of great significance in the neuromuscular field; since, our data corroborate the fact that HMV treat not only the respiratory function but may provide protective cardiac effects in DMD and BMD, in addition with cardioprotective drugs.[22,23] HMV decreases respiratory muscles loading, improves alveolar recruitment and blood gas exchange and has a positive impact on pulmonary vascular resistance.

The main limitation of our study is linked to its retrospective, observational design, which may weaken the investigated correlations because of the presence of unconsidered confounders. In addition, we do not have control group in this study; however, ethically, it is inconceivable to establish study with a control severe respiratory failure DMD group untreated with mechanical ventilation. The annual rate of LVEF decline reflects the natural cardiac function in patients with mechanical ventilation and treated with ACE inhibitors and beta-blockers. Also, we do not have data about potential cardiac drugs modification over time. Finally, the echocardiographic assessment represents a second limitation because of technical difficulties in nonambulant patients with thorax deformities.

A prospective study will be helpful to better define the place for HMV therapy in the cardiac management of this group of patients.

5. Conclusion

The coexistence of LV dysfunction and restrictive pulmonary failure is well described in patients with DMD. Pulmonary decline precedes cardiac decline in most of DMD patients. Pulmonary care is an important integral part of maintaining the well-being and medical stability of these patients, as underlined in the DMD care consensus statements.[24] Long-term HMV is not harmful and may protect heart in patients with dystrophinopathies, in addition with cardioprotective drugs. In patients with dystrophinopathies on HMV, incidence of cardiac events remains moderate and incidence of pneumothorax is rare.

Author contributions

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