

# Duchenne muscular dystrophy: Survival by cardio-respiratory interventions

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## Abstract

We describe survival in Duchenne dystrophy by invasive and noninvasive ventilation vs. untreated.

Patients were untreated prior to 1984 (Group 1), underwent tracheotomy from 1984 until 1991 (Group 2), and were managed by non-invasive mechanical ventilation and cardioprotective medications subsequently (Group 3). Symptoms, vital capacity, and blood gases were monitored for all and spirometry, cough peak flows, carbon dioxide tension, and oximetry for Group 3. Sleep nasal ventilation was initiated for symptomatic hypoventilation. An oximeter and mechanical cough assistance were prescribed for maximum assisted cough peak flow <300 L/m. Patients used continuous noninvasive ventilation and mechanically assisted coughing as needed to maintain pulse oxyhemoglobin saturation  $\geq 95\%$ . Survival was compared by Kaplan–Meier analysis.

The 56 of Group 1 died at  $18.6 \pm 2.9$ , the 21 Group 2 at  $28.1 \pm 8.3$  years of age with three still alive, and the 88 using noninvasive ventilation had 50% survival to 39.6 years,  $p < 0.001$ , respectively.

We conclude that noninvasive mechanical ventilation and assisted coughing provided by specifically trained physicians and therapists, and cardioprotective medication can result in more favorable outcomes and better survival by comparison with invasive treatment.

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**Keywords:** Cough; Mechanical ventilation; Respiratory paralysis; Respiratory therapy; Muscular dystrophy; Mechanical insufflation-exsufflation; Noninvasive ventilation

## 1. Introduction

The vital capacity (VC) peaks between ages 9 and 16 for patients with Duchenne muscular dystrophy (DMD) and

then decreases by 5–10% per year until ventilatory support is required for survival [1]. It has been estimated that up to 90% [2–4] of patients with DMD who do not use ventilatory support die from pulmonary complications associated with respiratory muscle weakness between 16.2 and 19 years of age and uncommonly after age 25 [3,5]. It has also been reported that 90% of episodes of pneumonia and ARF requiring intubation occurred during otherwise benign upper respiratory infections (RTIs) mainly because of inability to cough effectively [6]. When unable to ventilator wean, these intubated patients conventionally undergo tracheotomy for ventilatory support. Most deaths not due to respiratory complications are due to cardiomyopathy [7].

**Abbreviations:** CPF, cough peak flows; DMD, Duchenne muscular dystrophy; LVEF, left ventricular ejection fraction; MAC, mechanically assisted coughing; MIC, maximum insufflation capacity; NIV, noninvasive mechanical ventilation;  $P_{\text{etCO}_2}$ , end-tidal carbon dioxide tension;  $P_{\text{tcCO}_2}$ , transcutaneous carbon dioxide ( $\text{CO}_2$ ) tension; RTI, respiratory tract infection;  $\text{SpO}_2$ , pulse oxyhemoglobin saturation; VC, vital capacity; VFBA, ventilator-free breathing ability

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Life has been described as being statistically prolonged by the use of part-time NIV [8], and by the use of cardioprotective medications [9], but life is indisputably prolonged by continuous full-time NIV for patients with little or no VC of ventilator-free breathing ability (VFBA) [10,11] whether delivered by invasive or noninvasive interface [12]. No previous publication has compared the natural course of the disease with invasive and noninvasive respiratory management. This work also compares the causes of death with these various approaches.

## 2. Methods

Essentially all DMD patients in Hokkaido, Japan are referred to one inpatient and ambulatory care medical institution in Yakumo, Japan. This included a total of 227 patients from 1964 to 2010. They were diagnosed by DNA analysis and/or muscle biopsy since 1988. Before 1987 diagnosis was made by electromyography, muscle biopsy, creatinine kinase levels, and clinical evolution including loss of ambulation before 12 years of age and continuous ventilator dependence by 25 years of age. Many patients' muscle tissues were stained for dystrophin once this became available.

The DMD patients too young to require ventilatory assistance were excluded from this study except for those who died before beginning NIV. This chart review was approved by our Institutional Ethics Committee.

The DMD patients were separated into three groups and evaluated at least annually. The first group from 1964 to 1984 did not receive cardio-respiratory interventions other than supplemental oxygen. Group 2 patients from August 1984 through November 1991 received supplemental oxygen and underwent tracheotomy for carbon dioxide narcosis or following intubation for ARF but did not routinely receive cardiac medications until 1992.

End-tidal ( $P_{\text{etCO}_2}$ ) or transcutaneous  $\text{CO}_2$  ( $P_{\text{tcCO}_2}$ ), oximetry (daytime and nighttime), VC, maximum insufflation capacity (MIC), and unassisted and assisted CPF were monitored since November 1991 (Group 3). Patients were trained to "air stack" manual resuscitator or ventilator delivered volumes of air to the deepest lung insufflations that the glottis could hold in a daily regimen once the VC was below 1000 ml and to air stack by glossopharyngeal breathing [13,24]. If the glottis was too weak or the patient unable to cooperate for air stacking, the exhalation valve of the manual resuscitator was manually blocked and the lungs deeply insufflated passively in this manner or by using the insufflation phase of in-exsufflators at pressures of 40 cm  $\text{H}_2\text{O}$  or greater. The lung recruitment was used to prevent atelectasis, maintain pulmonary compliance, augment cough flows, and raise voice volume [13,25]. Assisted CPF were obtained by air stacking to maximum lung inflation and coughing into a peak flow meter while a firm abdominal thrust is applied [26].

Since 1991 Group 3 patients have been managed by NIV, mechanically assisted coughing (MAC) as needed,

and cardioprotective medications once left ventricular ejection fraction (LVEF) was  $\leq 45\%$ . They received no routine supplemental oxygen therapy. They were prescribed nocturnal NIV for symptomatic hypercapnia with the predominant symptoms being fatigue, morning headaches, daytime somnolence, decreased appetite, depression, and weight loss. They used portable ventilators on control mode with delivered volumes of 550–1000 ml with the goals of alleviating symptoms, normalizing alveolar ventilation, facilitating inspiratory muscle rest, and permitting air stacking [13]. When aerophagia occurred, two patients switched to pressure control mode at 12–30 cm  $\text{H}_2\text{O}$ . Respiratory rates were 15–24 and inspiratory/expiratory ratio was 1/1–1/2.

With advancing weakness, dyspnea resulted when discontinuing NIV in the morning so its use was extended into daytime hours and 15 mm angled mouth pieces used for diurnal NIV. If the lips were too weak to grab the mouth piece the patients used nasal prongs. When daytime hypoventilation resulted in  $\text{SpO}_2$  decreasing below 95%, oximetry feedback was used to guide the extent of need for daytime NIV to maintain  $\text{SpO}_2 \geq 95\%$  [14]. When this occurred, patients quickly went from 12 to 14 h a day to continuous NIV and eventually lost VFBA. That is, upon cessation of ventilator use, they developed dyspnea, hypercapnia, and oxyhemoglobin desaturation within seconds to minutes, necessitating continuous ventilator use. Since the patients were informed that episodes of ARF could be managed by extubation to NIV and MAC they were advised to refuse tracheotomy if intubated with no VFBA and be referred to our center for extubation [15,16].

Since 1995 MAC was instructed and a mechanical insufflator–exsufflator provided once assisted CPF were less than 270 L/m [10,14]. The MAC was used to maintain or return  $\text{SpO}_2 \geq 95\%$  during RTIs and following extubation or decanulation at pressures  $\geq 40$  cm  $\text{H}_2\text{O}$ . During RTIs patients were instructed to seek medical attention if  $\text{SpO}_2$  baseline could not be maintained  $\geq 95\%$  [10,14].

Cardioprotective medications, beta-blockers, angiotensin converting enzyme inhibitors, and at times, diuretics, were provided since 1992 [17–19]. These medications were prescribed according to standard protocols [9,20]. Neuroendocrines were monitored every 3–6 months since 1989 and echocardiograms monitored yearly along with isocitrate dehydrogenase (ICDH) [21] and cystatin C levels [22,23].

Death was presumed to be of respiratory etiology when: there were complaints consistent with a RTI, an increase in airway secretions, decrease in oxyhemoglobin saturation ( $\text{SpO}_2$ ) baseline, or loss of ventilating interface or ventilator malfunction prior to death. Death was considered to be of cardiac etiology when there were no respiratory symptoms, when  $\text{CO}_2$  and  $\text{SpO}_2$  had been normal at the last evaluation, and when there had been hospital admissions for congestive heart failure or the previous LVEF was estimated to be  $\leq 20\%$ . Deaths in patients who did not fit these criteria were considered of unknown etiology unless the etiology was determined by autopsy.

### 2.1. Data analysis

Data are expressed as means  $\pm$  standard deviation (SD). Survival probability was demonstrated by the Kaplan–Meier method and calculated by the log-rank test. A probability value of  $<0.05$  was considered statistically significant.

### 3. Results

Of 227 total DMD patients, 187 were included in this study. The mean age when they became wheelchair dependent was  $9.9 \pm 1.5$  (range 8–12) years of age. There were 56 patients in Group 1, 35 in Group 2, and 96 in Group 3.

In Fig. 1 a Kaplan–Meier analysis compares survival of the three groups. The 56 Group 1 patients died at  $18.6 \pm 2.9$  (range 14.3–25.1) years of age, 54 from respiratory failure and two from cardiac failure. The 50% survival age was 18.1 years.

Of the 35 Group 2 patients, 11 died from cardiac causes before beginning NIV without receiving cardioprotective medications at  $17.5 \pm 3.0$  (range 13.9–23.9) years of age. The other 24 lived to  $29.1 \pm 8.5$  (range 15.9–42.0) years of age with three still alive at  $36.7 \pm 2.4$  (range 36.7–38.9) years of age. Their 50% survival age was 28.9 years. Twenty-one died at  $28.1 \pm 8.3$  (range 15.9–42.0) years of age, 12 from cardiac failure/dysrhythmias despite nine of the 12 receiving cardioprotective medications, eight from respiratory causes including six from tracheal hemorrhages, one from ARF associated with bronchial mucus plugging, and one from ventilator battery failure, and one died for unknown reasons.

Of the 96 Group 3 patients, despite receiving cardioprotective medications 8 died from cardiac causes before beginning NIV at  $22.8 \pm 3.6$  (range 18–25.9) years of age. The 88 NIV users lived to  $27.4 \pm 6.6$  (range 14.9–42.9) years of age with 71 still alive. Fifty-eight of the 88 received cardioprotective medications as described [17–19], including 20 of 32 part-time NIV and 38 of 56 full-time NIV users. In addition, seven of the Group 3 patients received prednisone at 0.75 mg/kg 10 days per month for

6–18 months while still able to walk. Of the 88 NIV users, eight developed ARF and were intubated but were extubated according to recently described methods [15,16]; and two tracheostomy patients with no VFBA were decannulated. All 10 were transferred from other institutions to avoid/eliminate tracheostomy. Seventeen of 88 died (seven part-time and 10 full-time NIV users), 16 from cardiac failure/arrhythmias and one from pneumonia/pneumothorax at  $27.1 \pm 5.8$  (range 18.0–39.6) years of age. Seven of 32 part-time NIV users died at  $22.8 \pm 3.6$  (18.0–25.9) years of age and 25 are still alive at  $21.5 \pm 4.5$  (range 14.9–31.6) years of age. Ten of 56 full-time NIV users died at  $30.2 \pm 5.1$  (range 21.8–39.6) years of age and 46 were still alive at  $30.7 \pm 5.4$  (range 20.9–42.9) years of age.

The 88 NIV users began nocturnal use with a VC of  $673 \pm 320$  ml at  $18.9 \pm 3.3$  years of age and used it for  $5.4 \pm 3.3$  years before 56 required full-time NIV once their VCs were  $328 \pm 194$  ml at  $24.7 \pm 4.6$  years of age. They thus far require continuous NIV for  $5.8 \pm 3.4$  years. Twenty-seven (33%) of these patients could also glossopharyngeal breathe for air stacking and security in the event of ventilator failure day or night [13,24].

### 4. Discussion

This study demonstrated significantly longer survival using NIV/MAC along with cardioprotective medications and ancillary noninvasive techniques like intermittent lung expansion, glossopharyngeal breathine, and assisted coughing, than tracheostomy ventilation ( $p = 0.0002$  with log-rank test), and significantly longer by tracheostomy ventilation than with no treatment ( $p = 0.0001$  with log-rank test), 50% survival age of 39.6, vs. 28.9, vs. 18.1 years, respectively (Table 1). Group 3 received more cardioprotection (66 of 96, vs. 9 of 35, respectively), used glossopharyngeal breathing for security and VFBA (33% vs. 0, respectively) [13,24], received more glucocorticoid therapy (7 vs. 2, respectively), received lung recruitment and MAC (100% vs. 0, respectively), received no routine supplemental oxygen, may have benefited from better nutrition, scoliosis treatment, and antibiotic therapy, and did

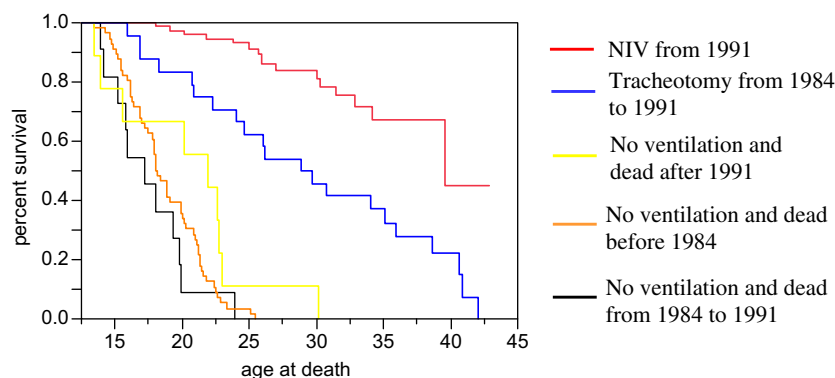


Fig. 1. Survival curve (Kaplan–Meier), showing comparison in percentage survival from no cardiopulmonary treatment to tracheostomy or noninvasive ventilation with cardioprotection.

Table 1  
Survival and cardio-respiratory interventions in each groups.

		N	Ventilation (IPPV)	Assisted cough	Cardio- protection	A mean survival age (years)		
Group 1	No ventilation and death from respiratory and/or cardiac failure or other causes (before 1984)	56	–	–	–	18.1	$p = 0.0001$	$p = 0.0001$
Group 2	Death from cardiomyopathy before tracheostomy IPPV	11	–	–	–	17.2		
	Tracheostomy IPPV	24	+Tracheostomy	–	–	28.9	$p = 0.0002$	
Group 3	Death from cardiomyopathy before noninvasive IPPV	8	–	+	+	21.9		
	Noninvasive IPPV	88	+Noninvasive	+	+	39.6		

not die from complications related to tracheostomy tubes. No patients have undergone tracheotomy since 1991 despite requiring continuous ventilatory support and, at times, intubation.

Three studies have reported DMD survival to 25.3–30.4 years associated with part-time NIV, generally nocturnal-only low span bi-level positive airway pressure [8,27,28]. In the Simonds study, nocturnal NIV was begun at 19.4 years of age which is similar to our population ( $18.9 \pm 3.3$  years of age) [28]. In none of the three studies was tracheotomy systematically avoided for continuous ventilator dependence, or was daytime support provided by simple mouth pieces or MAC used.

More recent consensus statements have emphasized that NIV can and should be used up to continuously long-term instead of resort to tracheostomy [29–33]. Despite these recommendations, there have been only three centers that have thus far reported the use of long-term continuous NIV for DMD ventilatory support [34,11,12]. In 1993 Bach et al. [34] reported a mean survival age of 32.5 years with continuous NIV; Toussaint et al. [11] reported 50% survival to age 31; and Kohler et al. [12] reported 50% survival to 35 years for 43 patients beginning nocturnal NIV at mean age 19.8. In the Bach and Toussaint reports daytime NIV was provided via 15 mm mouth pieces and MAC was used [11,34]. In none of these three papers was tracheotomy completely avoided for continuous NIV users. Our current work is the largest to date on NIV with no DMD patients requiring tracheotomy despite 16 years of continuous non-invasive ventilatory support. Mean survival for our patients was also 4.6 years longer (39.6 years) than in any previous study. This is likely because in the Kohler et al. [12] study some patients underwent tracheotomy, no mention was made of cardioprotection although the same group reported using cardioprotective medications in 2005 [35]; and there was no mention of assisted coughing, lung recruitment, or the use of mouth pieces for daytime support. Assisted coughing and daytime NIV via mouth piece can be especially important to reduce respiratory rate to facilitate eating.

We previously reported that the use of cardioprotective medications for asymptomatic left ventricular dysfunction

(LVEF < 45%) resulted in 5–7 years of additional survival compared with treating only episodes of heart failure due to cardiomyopathy for 52 DMD patients [9]. The consequences of DMD cardiomyopathy are exacerbated by sleep-disordered breathing with hypoxemia and hypercapnia and cor pulmonale [37]. Reduced pharyngeal muscle tone during periodic breathing and increased pharyngeal edema associated with congestion can contribute to obstructive apneas and hypopneas for patients with heart failure [7]. Thus, NIV can have direct cardioprotective effects.

Limitations of this study include the lack of autopsy confirmation of the causes of all of the deaths, and the lack of a controlled comparison in the same time period. However, since noninvasive management is effective, this may be unethical. Since (invasive) tracheostomy outcomes have not been shown to be superior, continuous NIV support should be the approach of choice as suggested in consensus [30,36,37]. A further limitation is the failure to perform a logistic regression analysis taking into account other possible factors for improved survival such as possibly better nutrition, scoliosis management, and antibiotic therapy.

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