Home mechanical ventilation in myotonic dystrophy type 1

Exploring patient-specific treatment response

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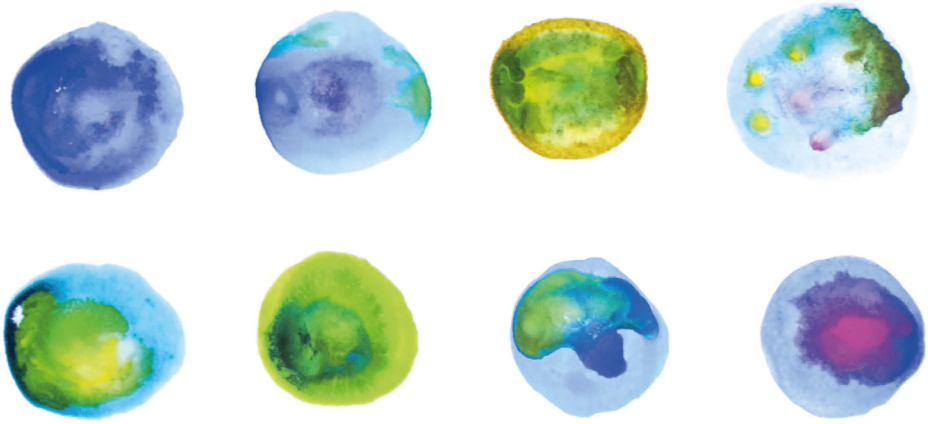
Contents

Chapter 1

General introduction



General introduction

Myotonic dystrophy type 1

Myotonic dystrophy type 1 (DM1), also known as Steinert's disease, is the most common form of adult-onset muscular dystrophy, with a population-based estimated prevalence of 1 in 2.100 individuals worldwide.[1,2] DM1 derives its name from two important fundamental characteristics of the disease: myotonia, the delayed muscle relaxation after voluntary contraction, and progressive muscle weakness (dystrophy), predominantly affecting the distal muscles, but also the proximal muscles in more advanced disease. However, its clinical manifestations extend far beyond the musculoskeletal system with involvement throughout the entire body including the cardiorespiratory system, the gastrointestinal system, the eyes, and the brain.[3] The life expectancy of individuals with DM1 is reduced. Mortality is most frequently associated with respiratory dysfunction, and cardiac arrhythmias.[4,5] The prognosis depends on the clinical phenotype, varying from frequent neonatal death in the congenital form to a life expectancy close to normal in the late-onset (mild) form of DM1.[6]

Genetic background and disease subtypes

DM1 is an autosomal dominant disorder that is caused by a cytosine-thymine-guanine (CTG) trinucleotide repeat expansion in the 3' untranslated region of the DMPK (dystrophia myotonica protein kinase) gene on chromosome 19q13.3.[7] Whereas the number of CTG repeats in healthy individuals ranges from 5 to 35, repeat expansions larger than 50 are associated with DM1.[8] The length of this repeat varies greatly between patients and correlates with disease severity, leading to a wide spectrum of clinical presentations.[1,9] The number of CTG repeats expands further when passed from one generation to the next, especially when inherited from the mother. Due to this phenomenon which is called genetic anticipation, successive generations exhibit earlier onset and more severe manifestations of the disease.[10] DM1 is typically classified into four major categories based on age of onset, clinical severity, and CTG repeat length which is depicted in Table 1.1.

Multisystem involvement

Although muscle weakness and myotonia are regarded as the cardinal symptoms of DM1, involvement of almost every organ system is possible and significantly contributes to disease morbidity and mortality. Figure 1.1 shows the most important abnormalities encountered in DM1.

Table 1.1 Myotonic dystrophy type 1 clinical phenotypes.

Subtype	Age of onset	Clinical features	CTG repeat length
Congenital	<1 year	infantile hypotonia bulbar weakness respiratory failure intellectual disability	>1000
Childhood-onset (juvenile DM1)	1 year – 20 years	intellectual disability behavioral problems gastrointestinal problems	100-1000
Adult-onset (classic DM1)	20 – 40 years	muscular weakness myotonia respiratory failure arrhythmias excessive daytime sleepiness	100-1000
Late-onset (mild DM1)	>40 years	cataract mild muscular weakness myotonia	50-150

Adapted from Turner and Hilton-Jones.[11]

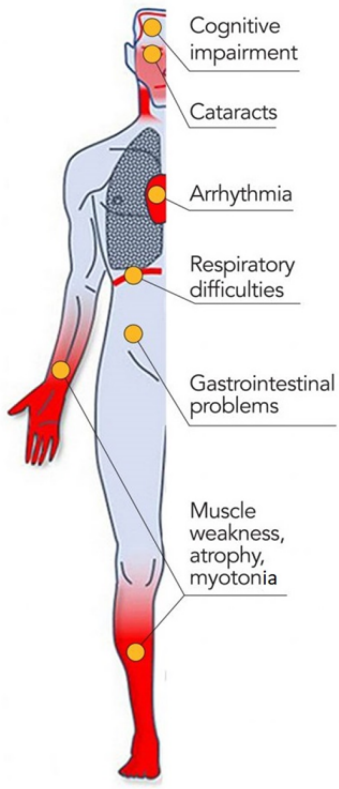


Figure 1.1 Multisystem involvement in DM1.
Adapted from Wenninger, Montagnese, and Schoser.[12]

Brain involvement in DM1 is phenotypically heterogeneous, and includes variable combinations of developmental disorders, cognitive impairment, behavioral disturbances, and affective symptoms.[13-15] Individuals with DM1 often show a reduced awareness of disease burden and its progression, also known as anosognosia, which may result in low adherence to treatment.[16] Apathy, a disorder of diminished motivation, is highly prevalent in DM1 and constitutes an additional barrier of patient participation in diagnostics and treatment of the disease.[17] DM1 patients report a high prevalence for gastrointestinal symptoms and clinical studies have identified chronic and progressive dysfunction of the esophagus, stomach, liver and gallbladder, small and large intestine, rectum and anal sphincters.[18] Cardiac disease in DM1 affects mainly the conduction system with conduction defects, and arrhythmias which can lead to sudden death. The cardiac contractility is relatively preserved, but heart failure may occur at later ages.[19] Cardiac disease is a major cause of mortality in DM1. Over 30% of deaths in DM1 patients are related to cardiac complications. However, the leading factor contributing to morbidity and mortality in DM1 is respiratory dysfunction, including alveolar hypoventilation and pulmonary infections.[4,20]

Respiratory dysfunction

The underlying etiology of respiratory dysfunction in DM1 is complex, combining both peripheral respiratory muscle weakness, and central respiratory drive dysfunction, as well as upper airway muscle dysfunction leading to a variety of problems including central sleep apnea (CSA) and obstructive sleep apnea (OSA), respiratory failure, and aspiration.[20] Symptoms related to respiratory dysfunction have a negative impact on the quality of life.[21,22]

Peripheral respiratory muscle weakness

Peripheral respiratory muscle weakness is the hallmark of respiratory dysfunction in DM1, arising from the progressive involvement of skeletal muscles, including the diaphragm and the accessory respiratory muscles. Weakness of the diaphragm, the most important breathing muscle, leads to diminished inspiratory capacity, while intercostal muscle involvement reduces chest wall compliance leading to restrictive pulmonary function problems. Consequently, this leads to nocturnal hypoventilation at first, as the supine position further compromises diaphragmatic function. In addition, during sleep, there is a decreased respiratory drive, a reduced muscle tone of the accessory respiratory muscles, and an increased upper airway resistance due to relaxation of the upper airway muscles. In later stages, hypoventilation can also manifest during daytime. The reduced function of the respiratory muscles will also give

rise to an impaired cough efficacy with an increased risk of respiratory complications including mucus retention and respiratory infections as a consequence.[6,20,23]

Central respiratory drive dysfunction

Central respiratory drive dysfunction, attributed to abnormalities in the central nervous system, is another contributor to respiratory issues in DM1. Independently of the pulmonary function impairment, DM1 patients show a reduced ventilatory response to hypercapnic stimulation, suggestive of a central cause of CO_2 insensitivity.[24] There is evidence for a direct involvement of the brainstem, with post-mortem studies demonstrating reduced serotoninergic and catecholaminergic neurons.[25,26] This abnormality can result in CSA and reduced arousal responses to hypoventilation, further predisposing patients to chronic hypercapnia and hypoxemia.[24,27]

Upper airway muscle dysfunction

Upper airway muscle dysfunction plays a critical role in the pathogenesis of OSA in DM1. Myotonia and weakness of the pharyngeal and laryngeal muscles contribute to airway collapse during sleep, leading to OSA. Additionally, impaired coordination of swallowing muscles increases the risk of aspiration, which can lead to recurrent respiratory infections and aspiration pneumonia.[23,28]

Home mechanical ventilation

Over the past years, noninvasive home mechanical ventilation (HMV) has emerged as a cornerstone in the management of patients with chronic respiratory failure due to different underlying causes such as neuromuscular diseases, restrictive lung diseases (e.g. post-polio, kyphoscoliosis), COPD, obesity hypoventilation and sleep-related breathing disorders.[29] In 2020, 22 out of 100.000 people in the Netherlands made use of HMV.[30]

Modern ventilators are increasingly compact, user-friendly, and equipped with advanced algorithms for pressure adjustment and leak compensation, enabling tailored therapy in the home environment.[31] However, HMV also poses significant challenges, including patient selection, interface fitting, and treatment adherence. Clinical trials in patients with neuromuscular diseases are challenging to conduct for several reasons, including disease rarity and progressive disability. In motor neuron disease (e.g. amyotrophic lateral sclerosis, ALS), HMV was found to confer a survival advantage and maintain health-related quality of life scores in ALS patients with more preserved bulbar function.[32] Patients with Duchenne muscular dystrophy were amongst the

earliest to receive HMV which has resulted in marked reductions in mortality and morbidity from respiratory failure and recurrent infections.[33,34] Because of the previously mentioned typical characteristics of DM1, results from trials involving other neuromuscular diseases cannot be directly applied to this population. Unfortunately, clinical research on HMV in DM1 is limited, but in every day practice, HMV is frequently used, mainly based on expert opinion.[23] However, the benefit of HMV for patients with DM1 varies to a great extent, ranging from a burdensome experience to a beneficial treatment.[35,36] Important challenges in the treatment of DM1 patients with HMV include patient selection and treatment adherence. The lack of knowledge on this topic and the desire to improve respiratory care for DM1 patients have been the motivation for writing this thesis.

Figure 1.2 Applying home mechanical ventilation in the home setting.

Outline of this thesis

The objective of this thesis is to enhance the understanding of HMV treatment in DM1 with the main goal to further optimize respiratory care for the individual DM1 patient.

Chapter 2 provides a detailed overview of the existing knowledge on HMV in DM1. This is followed by **Chapter 3** in which we performed a large observational study to investigate the role of the respiratory characteristics in the treatment adherence of DM1 patients with HMV. In **Chapter 4** we continued to examine treatment adherence with HMV, focusing on the potential impact of cognition, affective symptoms, and apathy in this context. In order to have the right tool to evaluate HMV, we assessed the validity and reliability of the Dutch version of the S^3-NIV questionnaire in **Chapter 5**. In **Chapter 6** we present our multicenter, prospective study on the treatment response to HMV in DM1. The final part of this thesis consists of a general discussion in **Chapter 7** and an elaboration on the scientific impact of the conducted research in **Chapter 8**. Finally, a summary in both English and Dutch language can be found in **Chapter 8**.

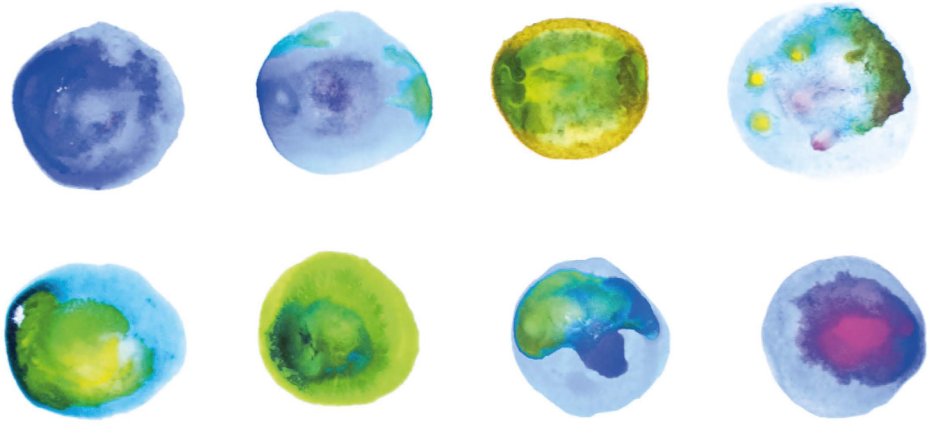
References

1. Thornton CA. Myotonic dystrophy. Neurol Clin. 2014;32(3):705-19, viii.
2. Johnson NE, et al. Population-Based Prevalence of Myotonic Dystrophy Type 1 Using Genetic Analysis of Statewide Blood Screening Program. Neurology. 2021;96(7):e1045-53.
3. Udd B, Krahe R. The myotonic dystrophies: molecular, clinical, and therapeutic challenges. Lancet Neurol. 2012;11(10):891-905.
4. Groh WJ, et al. Survival and CTG repeat expansion in adults with myotonic dystrophy type 1. Muscle Nerve. 2011;43(5):648-51.
5. de Die-Smulders CE, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998;121 (Pt 8):1557-63.
6. Mathieu J, et al. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999;52(8):1658-62.
7. Brook JD, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. Cell. 1992;69(2):385.
8. Kamsteeg EJ, et al. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. Eur J Hum Genet. 2012;20(12):1203-8.
9. Harper P. Myotonic dystrophy. Third edition ed. Major problems in neurology. 2001: W.B. Saunders.
10. Tsilfidis C, et al. Correlation between CTG trinucleotide repeat length and frequency of severe congenital myotonic dystrophy. Nat Genet 1992;1(3):192-5.
11. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry. 2010;81(4):358-67.
12. Wenninger S, Montagnese F, Schoser B. Core Clinical Phenotypes in Myotonic Dystrophies. Front Neurol. 2018;9:303.
13. Weijs R, et al. Human brain pathology in myotonic dystrophy type 1: A systematic review. Neuropathology. 2021; 41(1):3-20.
14. van der Velden BG, et al. Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. J Affect Disord. 2019;250:260-9.
15. Okkersen K, et al. The cognitive profile of myotonic dystrophy type 1: A systematic review and meta-analysis. Cortex. 2017;95:143-55.
16. Baldanzi S, et al. Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study. Orphanet J Rare Dis. 2016;11:34.
17. Gallais B, et al. Prevalence and correlates of apathy in myotonic dystrophy type 1. BMC Neurol. 2015; 15:148.
18. Peterson JAM, Cooper TA. Clinical and Molecular Insights into Gastrointestinal Dysfunction in Myotonic Dystrophy Types 1 & 2. Int J Mol Sci. 2022;23(23).
19. Groh WJ, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med. 2008;358(25):2688-97.
20. Hawkins AM, et al. Respiratory dysfunction in myotonic dystrophy type 1: A systematic review. Neuromuscul Disord. 2019;29(3):198-212.
21. Ahlstrom G, et al. Respiratory function, electrocardiography and quality of life in individuals with muscular dystrophy. Chest. 1994;106(1):173-9.
22. Araujo TL, et al. Respiratory muscle strength and quality of life in myotonic dystrophy patients. Rev Port Pneumol. 2010;16(6):892-8.
23. Boentert M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
24. Poussel M, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. 2015;25(5):403-8.
25. Ono S, et al. Loss of serotonin-containing neurons in the raphe of patients with myotonic dystrophy: a quantitative immunohistochemical study and relation to hypersomnia. Neurology. 1998;50(2):535-8.
26. Ono S, et al. Loss of catecholaminergic neurons in the medullary reticular formation in myotonic dystrophy. Neurology. 1998;51(4):1121-4.

27. Begin P, et al. Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. Am J Respir Crit Care Med. 1997;156(1):133-9.
28. Pilz W, Baijens LW, Kremer B. Oropharyngeal dysphagia in myotonic dystrophy type 1: a systematic review. Dysphagia. 2014;29(3):319-31.
29. Simonds AK. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc. 2016;13(11):2035-44.
30. van den Biggelaar RJM, et al. Home mechanical ventilation: the Dutch approach. Pulmonology. 2022; 28(2):99-104.
31. D'Cruz RF, Hart N. A history of home mechanical ventilation: The past, present and future. Chron Respir Dis. 2024;21:14799731241240776.
32. Bourke SC, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5(2):140-7.
33. Simonds AK, et al. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. Thorax. 1998;53(11):949-52.
34. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest. 1997;112(4):1024-8.
35. West SD, et al. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 2016;3(4):529-37.
36. Vivekananda U, Turner C. A model to predict ventilator requirement in myotonic dystrophy type 1. Muscle Nerve. 2019;59(6):683-7.

Chapter 2

Noninvasive home mechanical ventilation in adult myotonic dystrophy type 1: a systematic review



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* equally contributed to this paper

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Abstract

Introduction
Chronic hypercapnic respiratory failure induces considerable morbidity and mortality in patients with myotonic dystrophy type 1 (DM1). This study systematically reviews the effects of noninvasive home mechanical ventilation (HMV) on gas exchange, quality of life, survival and compliance in DM1 patients.

Methods
A systematic Medline and Embase search was performed (January 1995 to January 2020). Records were screened for eligibility criteria, data were extracted from included studies and risk of bias was assessed. We present findings mainly using a narrative synthesis.

Results
Twenty-eight relevant full-text articles were screened for eligibility criteria. Nine studies were included. Randomized controlled trials were not found. Studies had either an observational (n=8) or interventional (n=1) design. In the pooled data analysis, HMV showed to improve mean oxygen saturation with 4.8% and decreased mean carbon dioxide values with 3 mmHg. Compliance varied widely between studies, from no use to more than 12 hours per day. Quality of life was not studied extensively, but some studies reported positive effects of HMV on symptoms of chronic respiratory failure. HMV may improve survival in DM1 patients with chronic hypercapnic respiratory failure.

Conclusion
This review shows that HMV can improve gas exchange and relieve symptoms with a possible survival benefit in DM1 patients with chronic hypercapnic respiratory failure. Future studies should focus on developing strategies to optimize the timing of HMV initiation and to promote compliance.

Introduction

Myotonic dystrophy type 1 (DM1) is the most frequent inherited type of adult-onset muscular dystrophy, with a reported prevalence of 0.5 to 18.1 per 100.000 person years and an estimated prevalence as high as 1 per 2.500.[1,2] Patients have a reduced life expectancy of 54-60 years.[3,4] Respiratory failure is the primary cause of death in DM1, which is thought to result from a complex mechanism with important contribution of respiratory muscle weakness, but also a reduced central respiratory drive, decreased chest wall compliance and upper airway obstruction.[4-11] These factors result in reduced lung volumes, sputum stasis and atelectasis causing considerable morbidity due to increased risks of pneumonia and respiratory failure. Invasive or noninvasive home mechanical ventilation (HMV) can be used in case of chronic hypercapnic respiratory failure. Benefits of mainly noninvasive HMV on gas exchange, symptoms and survival have been described.[12-14] However, in daily clinical practice, treatment of DM1 patients with HMV is often complex due to lack of improvement of symptoms, and treatment intolerance which consequently leads to a reduced compliance to therapy in comparison with other neuromuscular disorders.[12,15,16] Therefore, HMV in DM1 patients can be perceived as a burdensome treatment for patients, their family, and healthcare professionals. The aim of this systematic review was to evaluate the effect of HMV on gas exchange, quality of life (QoL), survival and compliance to therapy in adult DM1 patients with chronic hypercapnic respiratory failure in order to improve daily clinical practice and provide future directions for further research.

Methods

Protocol

This review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews, www.crd.york.ac.uk/prospero; registration number CRD42020168349) and was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting standards.[17]

Search strategy

With the help of a clinical librarian, two authors (CS, BV) performed a comprehensive literature search in MEDLINE and Embase databases (from January 1995 to January 2020). The main search terms were “myotonic dystrophy”, “respiratory insufficiency”

and “artificial respiration”. Different synonyms, medical subheadings and Boolean pooling operators were used. The reproducible search strategy is included in Appendix 2.1. Searches were performed in title and abstract, and limited to studies in adult humans being presented in the English language. Supplementary searching techniques included hand-searching of included studies’ reference lists.

Study selection

Citations retrieved from electronic database searches were uploaded to Covidence (www.covidence.org). Titles and abstracts were independently screened by two reviewers (CS, BV) using eligibility criteria; a third reviewer resolved any uncertainties (PW). The absolute level of agreement between the two reviewers regarding study inclusion was >95%. Then, full texts were obtained and selection was performed based on predefined eligibility criteria shown in Table 2.1.

Table 2.1 Study eligibility criteria

Criterion	Eligibility criteria
Population	Studies in myotonic dystrophy type 1 patients with chronic hypercapnic respiratory failure.
Intervention	Studies involving long-term home mechanical ventilation, using noninvasive positive pressure ventilation.
Comparator	Studies with comparator and non-comparator designs.
Outcome	Studies reporting on gas exchange, quality of life, survival, and compliance with HMV.
Study design	Empirical quantitative and qualitative studies published in English in the past 25 years*, excluding case reports, conference reports, studies without original research, and studies in children <18 years.

*: The review was restricted to studies published in the past 25 years to ensure that findings are relevant to current practice. HMV, home mechanical ventilation.

Study outcomes

The primary outcome of this study was the effect of HMV on gas exchange (especially oxygen and carbon dioxide), QoL and survival in DM1 patients. Secondary outcome parameter was the compliance to HMV and factors that influence compliance.

Data collection process

The following data were extracted independently by two reviewers (CS, BV), using a standardized extraction form consisting of title, authors, publication year, study design, sample size, sample characteristics (mean age and gender), available forced vital capacity (FVC) and muscular impairment rating scale (MIRS), which was specifically

developed for DM1,[18] HMV indication and information about outcome measurements (gas exchange, QoL, survival and compliance).

Quality assessment

The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) designed for nonrandomized studies.[19] Two reviewers (CS, BV) independently scored the studies by their quality of patient selection, comparability, and outcome on a nine-star scoring system. Discrepancies were discussed and resolved. Due to significant between-study heterogeneity, risk of bias was not assessed across the cumulative evidence.

Data synthesis and statistical analysis

In case multiple studies reported on the same outcome parameter(s) and reported both baseline and follow-up values, we performed a meta-analysis. As the methods of the included studies were heterogeneous, we used the random-effects model to account for between-study heterogeneity. The I-squared statistic was used to estimate the percentage of variation in results due to between-study heterogeneity. In case a meta-analysis was not possible, we used a narrative synthesis method. We brought together studies examining similar processes or reporting similar outcomes, identified where data agreed and where it conflicted, and provided an indication of the volume and quality of the evidence.

Results

Study selection

After removing duplicates, the literature search resulted in 169 records (shown in Figure 2.1). Following title and abstract screening, 28 were considered for full-text evaluation. Of these we included 9 articles based on full-text. Reasons for exclusion were design (16), outcome (1) and patient population (2).

Study characteristics

An overview of included studies and main outcomes is presented in Table 2.2. No randomized controlled trials were found. All studies had a quantitative design. One interventional study was found and all other studies were of observational design (retrospective or prospective). The nine included studies were performed in 6 different countries. Two studies were performed by Boussaïd et al. who used, upon enquiry,

mainly the same cohort for both studies. In total, 841 DM1 patients were included, of which 385 started HMV, with variable age, disease severity (based on MIRS, FVC, triplet repeat length, available details in Table 2.2), and different indications for HMV (daytime hypercapnia, nocturnal hypoventilation, sleep-disordered breathing or restrictive pulmonary function with a vital capacity (VC) <50% of predicted).

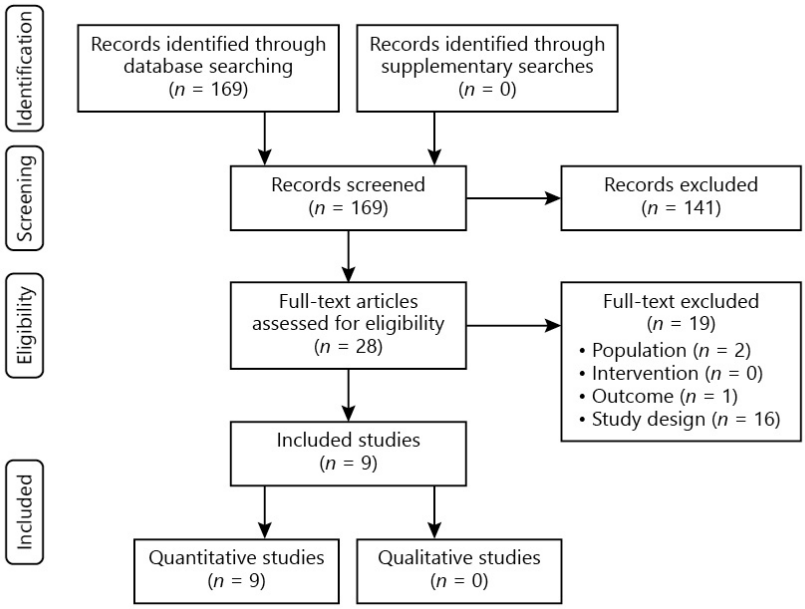


Figure 2.1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart illustrating the study selection process.

Quality assessment

The quality of the individual studies is shown in Table 2.2. The mean quality score (i.e. the mean number of stars awarded according to the NOS) of the studies was 4.8 (range 3 to 7). The comparability item, which scores a maximum of two stars, could only be assessed in one study. The level of agreement between the two reviewers was >93% and, after discussion, disagreements were resolved.

Table 2.2 Summary of findings.

Authors, year, country	Study characteristics	Baseline characteristics	Gas exchange	Quality of life	Survival	Compliance	Quality §
Nugent et al., 2002 (UK)[11]	Single center, observational DM1 cohort study: N=13. Follow-up: mean 2.5 years (range 1.5-3.0y). HMV started in N=13. Mean age 48 years.	N=13; 6 male. Mean age: 48 years. Mean FVC: 1.66L. Genetics: N/A.	Daytime PaO_2 increased from 53.0 to 59.0 mmHg. $PaCO_2$ decreased from 64.3 to 52.4 mmHg. Overnight SaO_2 increased from 80.5 to 90.4%. $TcCO_2$ decreased from 59.3 to 43.7 mmHg.	Data not shown: 8 patients experienced overall benefit from treatment.	3 patients died during follow-up.	Mean compliance 6.3 h.	Selection: *** Comparability: - Outcome: ***
Monteiro et al., 2013 (Portugal)[12]	Single center, observational DM1 cohort study: N=42. Follow-up during HMV: mean 4.6 years (range 0.2-12y). HMV started in N=25. Mean age 38 years.	N=42; 19 male. Mean age: 38 years. Mean FVC: 74% pred. Genetics: mean triplet repeats 643±439 (available in N=31).	Data not shown: ventilation did not change daytime gas analysis.	Data not shown: symptoms of hypoventilation improved in all compliant patients.	5 patients died during follow-up.	7 (28%) patients stopped HMV. Long-term HMV was provided to 16 patients, mean daily use 8h, range 4.1-14.3h/day.	Selection: *** Comparability: - Outcome: **
West et al., 2016 (UK)[15]	Single center, observational DM1 cohort study: N=120. Follow-up: N/A. HMV started in N=27. Mean age 52 years.	N=120; In HMV group: Mean age: 52 years. Mean FVC 53% pred. Median MIRS ≥ 4 for total group. Genetics: DM1 diagnosis confirmed by genetic testing	N/A	Data not shown: 37% of patients continued HMV with beneficial effects.	1 patient died.	N/A N=14 could not tolerate or had no benefit.	Selection: ** Comparability: - Outcome: -

Table 2.2 (continued)

Authors, year, country	Study characteristics	Baseline characteristics	Gas exchange	Quality of life	Survival	Compliance	Quality §
Boussaid et al., 2016 (France)[14]	Single center, observational DM1 cohort study, N=128. Follow-up: mean 4.5 ± 2.8 years. HMV started in N=128. Mean age 45 years.	N=128; 78 male. Mean age: 45 years. Mean FVC: 59% pred. Genetics: N/A.	N/A	N/A	N/A	Patients prescribed 8h/day: 58% use ≥4h/day. Patients prescribed ≥12h/day: 5% use less than 6h/day.	Selection: ** Comparabaility: - Outcome : **
Boussaïd et al., 2018 (France)[13]	Single center, observational DM1 cohort study, N=218. Follow-up: mean 4.4 ± 3.8 years. HMV started in N=127. Mean age 44 years.	N=218, 128 male. Mean age: 44 years. VC <50% pred. in 19% of early HMV and 36% patients with late /no HMV. Genetics: N/A.	N/A	N/A	10 year survival was 71% in HMV users. Patients who refused or delayed (>1yr) HMV were at higher risk for invasive ventilation or death. Risk of death was associated with orthopnea ($p<0.02$) and compliance ($p<0.03$).	Patients described HMV ≤ 10h/day: 76% of patients used it ≥4h/day. Patients described HMV>12h/day: 96% of patients used it ≥6h/day.	Selection: **** Comparability: * Outcome: **
O'Donoghue et al., 2017 (Australia)[20]	Multicenter, interventional study (discontinuation of HMV for 1 month) in DM1, N=12. Follow-up: at least 2 months. HMV withdrawal in N=12. Mean age 50 years.	N=12; 5 male. Mean age: 50 years. Mean: VC 81% pred. Genetics: N/A.	After 1 month withdrawal: Mean SaO_2 decreased from 95 to 92%, mean $PaCO_2$ increased from 43.1 to 46.3 mmHg. One month after recommencing HMV, values returned to baseline.	No significant change in any SF36 domain; neither subjective or objective change in daytime fatigue and somnolence.	N/A	N/A	Selection: ** Comparability: - Outcome: **

Table 2.2 (continued)

Authors, year, country	Study characteristics	Baseline characteristics	Gas exchange	Quality of life	Survival	Compliance	Quality §
Spiesshoefer et al., 2019 (Germany)[21]	Single center, observational DM1 cohort study, N=36. Follow-up: max. of 1.6 ± 0.8 years. HMV started in N=32. Mean age 41 years.	N = 36; 16 male. Mean age: 41 years. Mean MIRS: 3.0. Mean FVC: 67% pred. Genetics: DM1 genetically-proven in all patients.	Mean SaO_2 improved from 92 to 95%. Mean $tcCO_2$ decreased from 46.4 to 37.9 mmHg.	N/A Self-reported sleep outcomes did not significantly change from baseline to later time points.	N/A	Median use of HMV (hours/day): After 5-6 months (N=23): 3.4 After 1-1.5 years (N=20): 2.6 After 1.6-2.5 years (N=12): 5.3	Selection: ** Comparability: - Outcome: ***
Vivekanandа et al., 2019 (UK)[23]	Single center, observational DM1 cohort study, N=126. Follow-up: N/A. HMV started in N=54. Mean age 45 years.	N = 126 Mean age: 45 years. Genetics: mean repeat years 118±4.2. Median MIRS: 3	N/A	N/A	N/A	N/A 22/54 patients stopped HMV, due to intolerance or absence of positive effects.	Selection: *** Comparability: - Outcome: *
Rossi et al., 2019 (Italy)[22]	Multicenter, observational DM1 cohort study, N=268. Follow-up for HMV: N/A. HMV started in N=83. Mean age 46 years.	N = 268; 151 male. Mean age: 46 years. Mean FVC: 78% pred. Genetics: molecular diagnosis of DM1 in all patients.	N/A	N/A	N/A	Compliance (>4h/day) in N=48 (57%). Patients with FVC<80% were more compliant than patients with FVC>80%.	Selection: ** Comparability: - Outcome: *

DM1: Myotonic Dystrophy type 1; HMV: home mechanical ventilation; FVC: forced vital capacity; VC: vital capacity; MIRS: Muscular Impairment Rating Scale; PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; SaO_2: oxygen saturation; $tcCO_2$: transcutaneous carbon dioxide; SF36: 36-item Short Form Health Survey.
§ Assessment using the Newcastle-Ottawa quality assessment scale.[19]

Gas exchange

Four studies reported the effects of HMV on gas exchange.[12,13,20,21] After one night on HMV, oxygenation and transcutaneous carbon dioxide ($tcCO_2$) significantly improved in 32 patients, showing that the mean $tcCO_2$ normalized from 46.4±5.3 to 39.5±5.2 mmHg and the mean oxygen saturation (SaO_2) improved from 92 to 95%.[21] These results were found to be long lasting for more than 2 years. In addition, gas exchange improved more in patients with higher treatment compliance.[21] A smaller study of 13 patients also showed improvement in gas exchange using HMV, without reaching normocapnia.[12] Another small study describes that daytime gas analysis did not change in 25 patients, but baseline and outcome data were not presented.[13] A prospective pilot study of O' Donoghue et al. found that elective withdrawal of long term HMV during one month in 12 patients with chronic hypercapnic respiratory failure (mean diurnal $PaCO_2$ [partial pressure of carbon dioxide in arterial blood] <45 mmHg on HMV) resulted in a decrease of SaO_2 and an increase of $PaCO_2$, while both values returned to baseline after starting HMV again.[20] The pooled results of two retrospective observational studies and one prospective study showed an overall positive effect on PCO_2, PO_2 (partial pressure of oxygen in blood) and SaO_2 as shown in Figure 2.2.[12,20,21] After approximately 1 month of HMV, PCO_2 decreased while PO_2 and SaO_2 increased. PCO_2 and PO_2 were measured in arterial blood gases in two studies[12,20] and in capillary blood gases in the third study.[21]

Quality of life

The effects of HMV on QoL were only investigated in the withdrawal study of O' Donoghue et al.[20] No significant changes were found in any SF36 (36-item Short Form Health Survey) domain between '1 month withdrawal of HMV' and after '1 month reintroduction', although non-significant changes (p-values 0.11-0.18), favoring HMV, were found for the physical functioning, role limitation due to physical problems, social functioning and vitality domains.[20] In three studies the effects of HMV on symptoms were described.[12,13,16] Results were variable, with the smallest effects described by West et al., who found that 37% patients with respiratory failure using HMV continued it with beneficial effects.[16] Nugent et al. described that 8 of 10 patients subjectively experienced an overall benefit from treatment with less daytime sleepiness and improved nocturnal sleep.[12] The study of Monteiro et al. confirmed the findings that symptoms of chronic respiratory failure improved in compliant patients.[13] The effects of HMV on sleep were investigated in two studies.[20,21] Positive effects were only found regarding the apnoea-hypopnoea index (AHI) and oxygen desaturation index.[21] Both

studies did not find clinically relevant differences for neither subjective nor objective sleep parameters.[20,21]

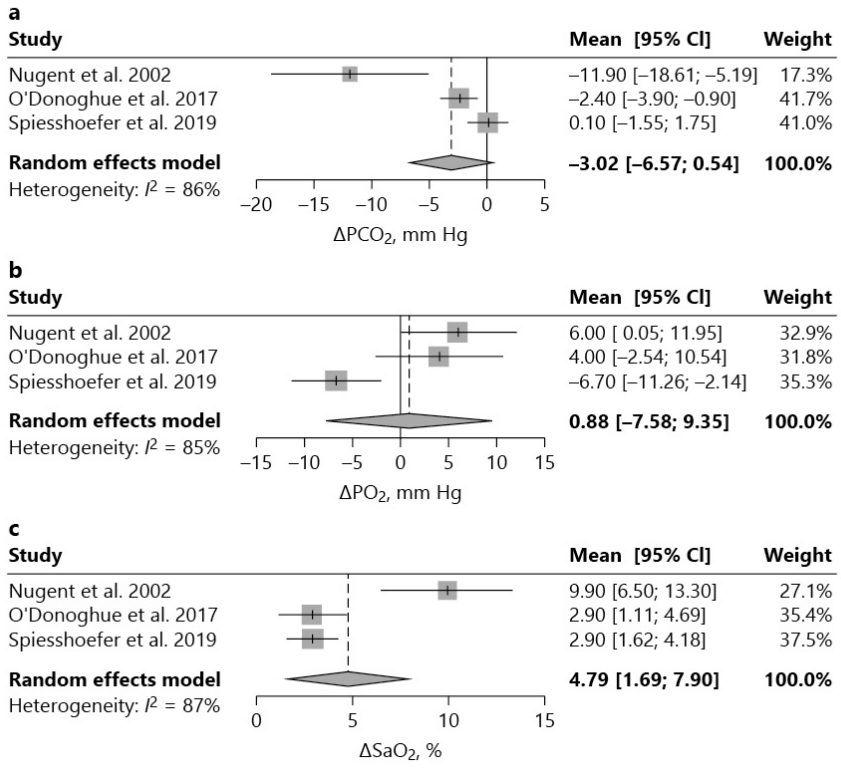


Figure 2.2 Forest plots: pooled data on gas exchange. A. Change in PCO_2 after 1 month on HMV; B. Change in PO_2 after 1 month on HMV; C. Change in SaO_2 after 1 month on HMV. PCO_2: partial pressure of carbon dioxide in blood; PO_2: partial pressure of oxygen in blood; SaO_2: oxygen saturation; HMV: home mechanical ventilation.

Compliance

Six studies described the compliance to HMV.[12-15,21,22] These were difficult to summarize due to differences in definitions and a lack of information about cessation reasons. Mean hours of HMV use ranged from 3.4 to 8 hours per day. In 57-76% of patients HMV was used for more than 4 hours per day. The percentage of patients who did not use or stopped HMV varied between 20% to 54%. One prospective study of 128 DM1 patients investigated the compliance with HMV and cessation predictors.[15] They demonstrated that compliance during the first year was 25% higher when symptoms of respiratory failure were initially present, whereas initiation during acute respiratory failure reduced the relative compliance by 29%. Long term compliance data showed that 42% of

patients who were prescribed 8 hours HMV/day used it for less than 4 hours per day and 28% did not use it at all. From the patients who were prescribed ≥12 hours/day, 5% used it less than 6 hours/day. Long-term compliance was positively associated with symptoms of respiratory failure (+52%, p<0.01) and nocturnal arterial oxygen desaturation (+23%, p<0.01). Risk of HMV cessation was associated with excessive leaks (HR=7.81, IC [1.47–41.88], p<0.01), dysfunctions that required emergency technical interventions (HR=12.58, IC [1.22–129.69], p<0.03), and an increase of body mass index (BMI), especially BMI≥30.0 (HR=33.8 IC [2.63–433.7]. Risk of HMV cessation was lower in patients with a professional occupation or who were undergoing professional training (HR=0.11 IC [0.02–0.77]).[15] Other frequently described reasons for stopping treatment were intolerance to HMV, absence of positive effects, uncomfortable mask and excessive noises of the device.[16,23] Eighteen percent of long-term HMV users experienced problems (which are not significantly related to HMV cessation), such as excessive leaks, skin or mucosa irritation and gastric inflation.[15]

Survival

One of the first studies published regarding HMV in DM1 suggested a survival benefit in their cohort of patients receiving assisted ventilation (n=13). Three patients died (one of them was not compliant) while the rest received long-term assisted ventilation for a mean period of 27 months (range 2-76).[12] Other studies describe mortality in their cohort using different periods of follow-up.[13,16] Most evidence for an association between HMV and mortality is derived from a large prospective cohort study conducted in France which compared survival in patients who accepted HMV promptly with those who refused or delayed HMV. Of the 127 patients who used HMV, the 10-year mortality was 29%. In the whole group, during a follow-up period of 959 patient-years, 53 patients died with an annual rate of 53/959 (1 per 6 person-years). Mean age at death was 58.2±8.7 years. Patients died due to respiratory causes (45%), cardiac causes (6%), cancer (4%) and unknown causes (45%). The risk of a severe event (defined as invasive mechanical ventilation or death) was significantly higher in the group of patients who started HMV later or not at all as compared to the group who started HMV within 1 year after meeting the criteria to start HMV. In the HMV group orthopnoea and poor compliance to the HMV were independently and significantly associated with death (respectively HR 2.37, 95% CI 1.17-4.8, p<0.02 and HR 3.26, 95% CI 1.32-8.04, p<0.03).[14]

Discussion

This review shows that the current evidence for HMV in DM1 patients is mainly based on clinical expertise and a small number of observational studies. Nevertheless, these studies provide important information and enable us to determine future directions with regard to research questions aiming to optimize HMV care in DM1.

Gas exchange was positively influenced by HMV in DM1 patients, at daytime as well as overnight,[12,20,21] which is similar to other neuromuscular and chest wall disorders.[24] In general, the efficacy of HMV is based on two rationales. Firstly, it may rest the fatigued respiratory muscles, thereby increasing strength and endurance, which may improve pulmonary mechanics by increasing chest wall compliance and lung volumes. Secondly, it leads to an increased ventilatory response to carbon dioxide (CO_2), which is probably the main mechanism for long term improvement of daytime gas exchange in patients treated with HMV.[25-27] However, hypercapnia in DM1 patients is sometimes disproportionate to the respiratory muscle weakness, which suggests a central cause of CO_2 insensitivity and may explain why DM1 patients tend to experience less HMV treatment benefits.[7,11]

With regard to indication for HMV initiation in DM1 patients, consensus meetings are mainly based on expert opinion in combination with low evidence studies, and have suggested to start HMV when there are symptoms suggestive of chronic respiratory insufficiency in combination with daytime or nocturnal hypercapnia, or FVC <50% of predicted.[28,29] However, certain symptoms, like excessive daytime sleepiness and fatigue may be classified as signs of hypoventilation, but in DM1 patients they are likely of multifactorial origin and therefore the result of HMV on such symptoms may be disappointing and discouraging for patients and caregivers.[30,31] Also, patients with preserved respiratory muscle strength and hypercapnia may respond differently and may therefore need another approach with regard to (timing of the initiation of) HMV.

Data about the effects of HMV on QoL and symptoms in DM1 are limited. QoL was investigated in only one pilot study and remained unchanged after elective withdrawal of HMV and restart 1 month later.[20] Beneficial effects on symptoms are described, although this was only descriptively studied in a small subset of patients.[12,13,16] Regarding sleep aspects, the AHI improved, but HMV did not change sleep efficiency and sleep architecture.[20,21] In other diseases, HMV improved QoL,[32] mainly assessed by the Severe Respiratory Insufficiency (SRI) questionnaire and the Maugeri Respiratory

Failure (MRF-26) questionnaire.[33,34] The S^3-NIV questionnaire, a new and easy to use short questionnaire is validated to measure the experience of HMV users.[35]

Compliance to HMV ranged from no use at all to 2-12 hours per night.[12,13,15,16] Better compliance resulted in more improvement of symptoms, whereas poor compliance is associated with higher mortality.[14,23] One of the predictors of non-compliance was HMV initiation during acute respiratory failure. It is questionable whether those patients have indeed chronic respiratory failure. Do they actually have the right indication for chronic HMV? Patients might recover from an acute event and become non-compliant because of absence of indication for HMV. Another reason could be that these patients are not well informed in advance about the burden and the intended aim of treatment. Increase of BMI is another worrisome predictor for non-compliance, as overweight is present in 50% of DM1 patients which further decreases lung volumes and therefore probably accelerates the development of respiratory failure.[36,37] Compliance was found to be better in patients with symptoms of respiratory failure at time of initiation, and patients having a professional occupation or training had a lower risk of NIV cessation.[15] To our knowledge, the impact of intelligence, cognition and affective symptoms such as apathy has never been studied in relation to compliance to HMV, while we know that intellectual impairment and apathy are very common in DM1 patients.[38,39] In our clinical experience these factors might obstruct therapy due to difficulties in clarifying its importance and negatively influencing the motivation to continue.

Survival is markedly reduced in DM1 patients with respiratory failure as primary cause of death (50%) next to cardiac causes (30%).[3] Only one large study on HMV and survival has been published, and found a significantly higher risk of dying in patients who refused to start HMV or started later than in patients with an early HMV initiation.[14] However, this result could also be due to baseline differences with a lower VC, which is a known independent risk factor for mortality, and a higher $PaCO_2$ in the patients who refused or started HMV later.[40] Therefore survival benefits of HMV in DM1 patients are still questionable.

Future directions

In general, studies with DM1 patients are complex, mainly because DM1 is a very heterogeneous disorder with variable involvement of multiple organs, resulting in severe impairment in some patients, and only mild symptoms in others. Since HMV in DM1 patients has been offered for more than 20 years it is considered unethical to

perform a randomized controlled trial to answer questions about optimal compliance and treatment effectiveness. Based on the presented benefits, we recommend that every DM1 patient is subjected to a basic respiratory evaluation (spirometry and preferably blood gas analysis) in order to screen for the need of HMV. For future HMV studies in this population, more knowledge should be gained about which patients benefit the most of HMV, what is the optimal timing of initiating HMV, and what is the required minimal compliance to HMV. In order to achieve this optimal personalized HMV therapy, the effects of education, supportive follow up, as well as the role of social support (including a bed partner) will be meaningful topics for future research.

Extensive specific patient- and therapy-related items should be collected. Specific patient-related factors need to include respiratory and neurological functioning, as well as assessment of QoL and symptoms. Socio-economic status and care dependency are additional factors. It is preferred to use disease specific questionnaires, such as the DM1 Activity and Participation Scale (DM1-Activ) to assess daily functioning and the Rasch-built Fatigue and Daytime Sleepiness Scale (FDSS) to assess fatigue and sleepiness.[41,42] Therapy-related factors such as ventilator settings and interfaces used should be taken into account. Survival studies should correct for independent predictors for mortality in DM1, such as diabetes, need for walking support, cardiac measurements and VC.[40] Recently, the multicenter study REMeDY (differential Response to non-invasive vEntilation in Myotonic DystrophY) was started in the Netherlands (www.trialregister.nl; registration number NL7972) with the aim to profile a multidimensional response to noninvasive HMV and identify patients with DM1 that do (or do not) respond well to NIV.

Conclusion

Noninvasive HMV can improve gas exchange and relieve symptoms with a possible survival benefit in DM1 patients with chronic hypercapnic respiratory failure. It is recommendable that every DM1 patient is subjected to a respiratory assessment. Compliance to HMV is variable and influences the effect of treatment. In order to achieve an optimal personalized HMV treatment, future studies should focus on developing strategies which enable optimization of the timing of HMV initiation and promotion of compliance.

References

1 Theadom A, Rodrigues M, Roxburgh R, Balalla S, Higgins C, Bhattacharjee R, Jones K, Krishnamurthi R, Feigin V: Prevalence of muscular dystrophies: a systematic literature review. Neuroepidemiology 2014;43:259-268.

2 Johnson NE: Myotonic Muscular Dystrophies. Continuum (Minneap Minn) 2019;25:1682-1695.

3 Groh WJ, Groh MR, Shen C, Monckton DG, Bodkin CL, Pascuzzi RM: Survival and CTG repeat expansion in adults with myotonic dystrophy type 1. Muscle Nerve 2011;43:648-651.

4 de Die-Smulders CE, Howeler CJ, Thijs C, Mirandolle JF, Anten HB, Smeets HJ, Chandler KE, Geraedts JP: Age and causes of death in adult-onset myotonic dystrophy. Brain 1998;121 (Pt 8):1557-1563.

5 Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, Pourmand R, Otten RF, Bhakta D, Nair GV, Marashdeh MM, Zipes DP, Pascuzzi RM: Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med 2008;358:2688-2697.

6 Mathieu J, Allard P, Potvin L, Prevost C, Begin P: A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology 1999;52:1658-1662.

7 Begin P, Mathieu J, Almirall J, Grassino A: Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. Am J Respir Crit Care Med 1997;156:133-139.

8 Kilburn KH, Eagan JT, Sieker HO, Heyman A: Cardiopulmonary insufficiency i myotonic and progressive muscular dystrophy. N Engl J Med 1959;261:1089-1096.

9 Begin R, Bureau MA, Lupien L, Bernier JP, Lemieux B: Pathogenesis of respiratory insufficiency in myotonic dystrophy: the mechanical factors. Am Rev Respir Dis 1982;125:312-318.

10 Carroll JE, Zwillich CW, Weil JV: Ventilatory response in myotonic dystrophy. Neurology 1977;27: 1125-1128.

11 Poussel M, Thil C, Kaminsky P, Mercy M, Gomez E, Chaouat A, Chabot F, Chenuel B: Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord 2015;25:403-408.

12 Nugent AM, Smith IE, Shneerson JM: Domiciliary-assisted ventilation in patients with myotonic dystrophy. Chest 2002;121:459-464.

13 Monteiro R, Bento J, Goncalves MR, Pinto T, Winck JC: Genetics correlates with lung function and nocturnal ventilation in myotonic dystrophy. Sleep Breath 2013;17:1087-1092.

14 Boussaid G, Prigent H, Laforet P, Raphael JC, Annane D, Orlikowski D, Lofaso F: Effect and impact of mechanical ventilation in myotonic dystrophy type 1: a prospective cohort study. Thorax 2018

15 Boussaid G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, Orlikowski D, Bahrami S: Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord 2016;26:666-674.

16 West SD, Lochmuller H, Hughes J, Atalaia A, Marini-Bettolo C, Baudouin SV, Anderson KN: Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis 2016;3:529-537.

17 Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.

18 Mathieu J, Boivin H, Meunier D, Gaudreault M, Begin P: Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology 2001;56:336-340.

19 Wells GS, B. O'Connell, D. Peterson, J. Welch, V. Losos, M. Tugwell, P.: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Assessed in June, 2020

20 O'Donoghue FJ, Borel JC, Dauvilliers Y, Levy P, Tamisier R, Pepin JL: Effects of 1-month withdrawal of ventilatory support in hypercapnic myotonic dystrophy type 1. Respirology 2017

21 Spiesshoefer J, Runte M, Heidbreder A, Dreher M, Young P, Brix T, Boentert M: Sleep-disordered breathing and effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with myotonic dystrophy type I. Neuromuscul Disord 2019;29:302-309.

22 Rossi S, Della Marca G, Ricci M, Perna A, Nicoletti TF, Brunetti V, Meleo E, Calvello M, Petrucci A, Antonini G, Bucci E, Licchelli L, Sancricca C, Massa R, Rastelli E, Botta A, Di Muzio A, Romano S, Garibaldi M, Silvestri G: Prevalence and predictor factors of respiratory impairment in a large cohort of patients with Myotonic Dystrophy type 1 (DM1): A retrospective, cross sectional study. J Neurol Sci 2019;399:118-124.
23 Vivekananda U, Turner C: A model to predict ventilator requirement in myotonic dystrophy type 1. Muscle Nerve 2019;59:683-687.
24 Annane D, Chevrolet JC, Chevret S, Raphael JC: Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev 2000:CD001941.
25 Annane D, Quera-Salva MA, Lofaso F, Vercken JB, Lesieur O, Fromageot C, Clair B, Gajdos P, Raphael JC: Mechanisms underlying effects of nocturnal ventilation on daytime blood gases in neuromuscular diseases. Eur Respir J 1999;13:157-162.
26 Nickol AH, Hart N, Hopkinson NS, Moxham J, Simonds A, Polkey MI: Mechanisms of improvement of respiratory failure in patients with restrictive thoracic disease treated with non-invasive ventilation. Thorax 2005;60:754-760.
27 Hill NS: Noninvasive ventilation. Does it work, for whom, and how? Am Rev Respir Dis 1993;147: 1050-1055.
28 Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, Holland V, Katz SL, Orlikowski D, Sannicolo G, Wijkstra P, Hellerstein L, Sansone VA: Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration 2020;99:360-368.
29 Sansone VA, Gagnon C, participants of the 207th EW: 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: management and implications for research, 27-29 June 2014, Naarden, The Netherlands. Neuromuscul Disord 2015;25:432-442.
30 Laberge L, Gagnon C, Dauvilliers Y: Daytime sleepiness and myotonic dystrophy. Curr Neurol Neurosci Rep 2013;13:340.
31 Laberge L, Dauvilliers Y, Begin P, Richer L, Jean S, Mathieu J: Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: to lump or split? Neuromuscul Disord 2009;19:397-402.
32 MacIntyre EJ, Asadi L, McKim DA, Bagshaw SM: Clinical Outcomes Associated with Home Mechanical Ventilation: A Systematic Review. Can Respir J 2016;2016:6547180.
33 Windisch W, Freidel K, Schucher B, Baumann H, Wiebel M, Matthys H, Petermann F: The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol 2003;56:752-759.
34 Carone M, Bertolotti G, Anchisi F, Zotti AM, Donner CF, Jones PW: Analysis of factors that characterize health impairment in patients with chronic respiratory failure. Quality of Life in Chronic Respiratory Failure Group. Eur Respir J 1999;13:1293-1300.
35 Dupuis-Lozeron E, Gex G, Pasquina P, Bridevaux PO, Borel JC, Soccal PM, Windisch W, Pepin JL, Janssens JP, Adler D: Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S(3)-NIV questionnaire. Eur Respir J 2018;52
36 Seijger CG, Drost G, Posma JM, van Engelen BG, Heijdra YF: Overweight Is an Independent Risk Factor for Reduced Lung Volumes in Myotonic Dystrophy Type 1. PLoS One 2016;11:e0152344.
37 Gagnon C, Chouinard MC, Laberge L, Brisson D, Gaudet D, Lavoie M, Leclerc N, Mathieu J: Prevalence of lifestyle risk factors in myotonic dystrophy type 1. Can J Neurol Sci 2013;40:42-47.
38 van der Velden BG, Okkersen K, Kessels RP, Groenewoud J, van Engelen B, Knoop H, Raaphorst J: Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. J Affect Disord 2019;250:260-269.
39 Jean S, Richer L, Laberge L, Mathieu J: Comparisons of intellectual capacities between mild and classic adult-onset phenotypes of myotonic dystrophy type 1 (DM1). Orphanet J Rare Dis 2014;9:186.
40 Wahbi K, Porcher R, Laforet P, Fayssoil A, Becane HM, Lazarus A, Sochala M, Stojkovic T, Behin A, Leonard-Louis S, Arnaud P, Furling D, Probst V, Babuty D, Pellieux S, Clementy N, Bassez G, Pereon Y, Eymard B, Duboc D: Development and Validation of a New Scoring System to Predict Survival in Patients With Myotonic Dystrophy Type 1. JAMA Neurol 2018;75:573-581.
41 Symonds T, Randall JA, Campbell P: Review of patient-reported outcome measures for use in myotonic dystrophy type 1 patients. Muscle Nerve 2017;56:86-92.

42 Hermans MC, Merkies IS, Laberge L, Blom EW, Tennant A, Faber CG: Fatigue and daytime sleepiness scale in myotonic dystrophy type 1. Muscle Nerve 2013;47:89-95.

Appendix 2.1

Embase search strategy:

'myotonic dystrophy'/exp OR 'myoton* dystroph*':ab,ti,kw OR 'myoton* atrophica':ab,ti,kw OR 'steinert* disease':ab,ti,kw
AND
'sleep disordered breathing'/exp OR 'sleep disordered breathing':ti,ab,kw OR 'respiratory failure'/exp OR 'apn* sleep':ti,ab,kw OR 'nocturnal apn*':ti,ab,kw OR 'obstructive apn*':ti,ab,kw OR 'respiratory insufficiency':ti,ab,kw OR 'sleep apn*':ti,ab,kw OR 'sleep hypopn*':ti,ab,kw OR 'central apn*':ti,ab,kw OR osa*:ti,ab,kw OR hypercapn*:ti,ab,kw OR hypoventilation:ti,ab,kw
AND
'artificial ventilation'/exp OR niv:ti,ab,kw OR hmv:ti,ab,kw OR 'bilevel positive airway pressure':ti,ab,kw OR 'ventilator* support':ti,ab,kw OR 'positive pressure respiration':ti,ab,kw OR 'ventilator requirement':ti,ab,kw OR ventilation:ti,ab,kw OR bpap:ti,ab,kw

Pubmed search strategy:

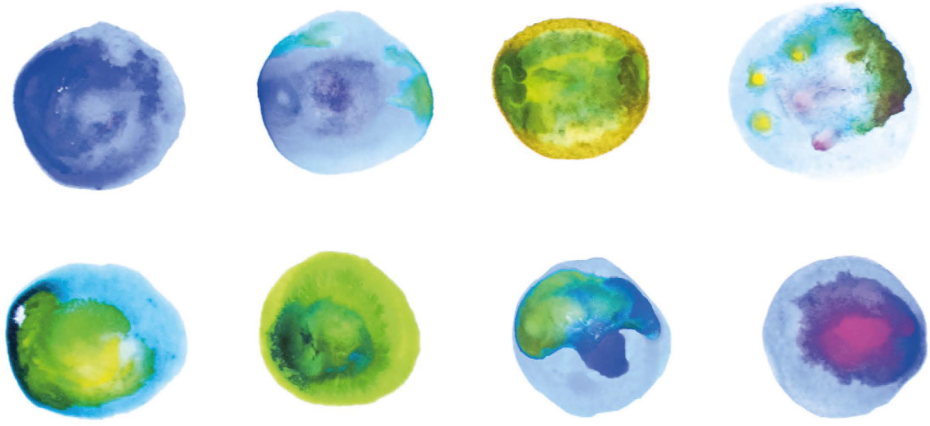
("Myotonic Dystrophy"[Mesh] OR myotonic dystroph*[tiab] OR myotonia atrophica[tiab] OR steinerts disease[tiab] OR steinert's disease[tiab] OR steinert disease[tiab])

AND
("Respiratory Insufficiency"[Mesh] OR respiratory failure*[tiab] OR respiratory insufficienc*[tiab] OR "sleep apnea syndromes"[Mesh] OR sleep apn*[tiab] OR sleep hypopn*[tiab] OR sleep-disordered breathing[tiab] OR central apn*[tiab] OR alveolar hypoventilation*[tiab] OR obstructive apn*[tiab] OR OSA*[tiab] OR hypercapn*[tiab] OR apn*[tiab] OR hypoventilation[tiab])

AND
("Respiration, Artificial"[Mesh] OR artificial respiration*[tiab] OR noninvasive ventilation[tiab] OR non-invasive ventilation[tiab] OR NIV[tiab] OR HMV[tiab] OR bilevel positive airway pressure[tiab] OR ventilator* support[tiab] OR positive pressure respiration[tiab] OR ventilator requirement[tiab] OR ventilation[tiab])

Chapter 3

Role of respiratory characteristics in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy type 1, a retrospective study



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Neuromuscul Disord. 2023;33(9):57-62

Abstract

Chronic respiratory insufficiency is common in patients with myotonic dystrophy type 1 (DM1) and can be treated with noninvasive home mechanical ventilation (HMV). HMV is not always tolerated well resulting in low treatment adherence. We aimed to analyze if baseline respiratory characteristics such as pulmonary function, level of pCO_2 and presence of sleep apnea are associated with HMV treatment adherence in DM1 patients.

Pulmonary function testing, polysomnography and blood gas measurement data of DM1 patients were retrospectively collected. Initiation of HMV and treatment adherence after one year was documented. Patients with low treatment adherence (average daily use of HMV <5h) were grouped with patients that discontinued HMV and compared with patients with high treatment adherence (average daily use of HMV >5h).

HMV was initiated in 101 patients. After one year, 58 patients had low treatment adherence. There were no differences between the low and high treatment adherence group regarding the respiratory characteristics. None of the included predictors (gender, age, body mass index, cytosine-thymine-guanine repeat length, forced vital capacity, daytime pCO_2, bicarbonate, nighttime pCO_2, nighttime base excess, apnea-hypopnea index and mean saturation during sleep) was able to significantly predict high treatment adherence.

In conclusion, the respiratory characteristics are not associated with treatment adherence with HMV in DM1 patients and cannot be used to identify patients at risk for low HMV treatment adherence.

Introduction

Myotonic dystrophy type 1 (DM1) is the most common form of adult-onset muscular dystrophy and is considered a multisystem disorder characterized by skeletal muscle weakness, myotonia, and multiple organ impairment involving especially the heart, respiratory system and gastrointestinal tract.[1] DM1 is caused by an expansion of an unstable cytosine-thymine-guanine (CTG) repeat in the myotonic dystrophy protein kinase (DMPK) gene.[2] Respiratory disturbances are a significant consequence of DM1 and represent, together with cardiac involvement, the most frequent primary cause of death in DM1 affected individuals.[3-5] Respiratory involvement is caused by peripheral abnormalities such as weakness of the respiratory musculature, upper airway obstruction, and reduced chest wall compliance leading to decreased lung volumes, atelectasis and pneumonia, often aggravated by the presence of overweight and a decreased central respiratory drive.[6,7] Subsequent chronic respiratory insufficiency is described in approximately 30% of the general DM1 population and may be potentially life-threatening.[8,9] Moreover, obstructive and central sleep apnea are reported in 28-86% of DM1 patients, and is associated with an increased incidence of cardiac abnormalities.[10-14] Chronic respiratory insufficiency, with or without sleep apnea, can be successfully treated with noninvasive home mechanical ventilation (HMV). HMV has proven to improve gas exchange and to relieve symptoms with a possible survival benefit in DM1 patients.[15] However, HMV is not always tolerated well by this specific patient population, which potentially leads to low treatment adherence or even discontinuation of HMV in up to 54% of patients.[15,16] Based on current care recommendations, HMV is indicated in case of symptoms suggestive of chronic respiratory insufficiency in combination with abnormalities in baseline respiratory characteristics such as daytime hypercapnia, abnormal pulmonary function testing, or evidence of nocturnal hypoventilation.[17,18] In other words, HMV indication is based on subjective information (i.e. patients' symptoms and performance) and objective information (respiratory characteristics). However, symptoms of chronic respiratory insufficiency may be difficult to distinguish from general symptoms of DM1 such as fatigue and day time sleepiness, and therefore difficult to use as decisive criterion for HMV initiation.[19,20] Therefore, in this large observational study, we focused on the objective information, i.e. the baseline respiratory characteristics. Based on previous research, we hypothesized that the respiratory characteristics are not associated with treatment adherence with HMV in DM1 patients.[15]

Materials and methods

Patients

A retrospective data study was carried oud, including all ambulatory adult DM1 patients, referred to the Department of Pulmonary Diseases and Home Mechanical Ventilation of the Maastricht University Medical Centre+ (MUMC+) from March 2009 until March 2020. The MUMC+ is a national expertise centre for DM1 patients in the Netherlands. Patients underwent standard respiratory characterization by means of pulmonary function testing, polysomnography and blood gas measurements. All clinical measurements were carried out as part of routine clinical care. CTG-repeat length and DM1-subtype was retrieved from the patient's file. The start date of HMV was documented as well as the status after one year of HMV (i.e. HMV discontinuation or ongoing). The reasons for HMV discontinuation were documented as well as the treatment adherence rates after one year in the ongoing HMV group.

Pulmonary function testing

All pulmonary function tests met appropriate standards of the European Respiratory Society/American Thoracic Society.[21] Spirometry was performed in the upright sitting position and in the supine position. Data were compared with the predicted normal values and expressed as a percentage of the normal value.[22,23] Investigation of respiratory muscle strength was performed with the measurement of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) in the upright sitting position. MIP was measured from the residual volume and MEP was measured from the total lung capacity according to Black and Hyatt.[24] Weight and height was measured prior to lung function testing. All tests were performed by skilled pulmonary function technicians.

Polysomnography

All patients had one overnight in-hospital polysomnography (PSG) comprising three electroencephalography (EEG) leads, two electro-oculogram (EOG) leads, electrocardiography (ECG), submental and tibial electromyography (EMG) leads, measurement of thoracic and abdominal movements by respiratory inductance plethysmography, nasal flow and pulse oximetry. PSGs were scored by experienced staff for sleep stages, arousals, periodic leg movements, saturation dips and apneas and hypopneas according to American Academy of Sleep Medicine guidelines.[25] Presence of sleep apnea was defined as an apnea-hypopnea index (AHI) >5 per hour, with an AHI of

5-15/h classified as mild, AHI 15-30/h as moderate and AHI >30/h was classified as severe sleep apnea.

Blood gas measurements

Arterial blood gases were assessed at daytime (between 8 am and 8 pm) from the radial artery while the patient was seated, with a sterile, self-filling and disposable pre-heparinized syringe. When an arterial blood gas was not available, a daytime capillary blood gas was analyzed instead. Capillary blood gases were taken from the fingertip using a disposable pre-heparinized capillary tube. Nighttime capillary blood gases were taken between 8 pm and 10 pm, prior to the initiation of HMV. Analysis of the samples was performed in our hospital laboratory according to the local standard operating procedure. In our study, we used pCO_2 values from arterial blood gases and capillary blood gases together for analytic purposes as it is known that capillary blood sampling accurately reflects arterial pCO_2.[26]

Home mechanical ventilation

Criteria based on the 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies were used to determine whether patients needed HMV.[27] Patients were eligible for HMV when they experienced symptoms suggestive for chronic respiratory insufficiency such as orthopnea, dyspnea, poor sleep, apnea, morning headaches, fatigue and excessive daytime sleepiness, chest infections, in combination with:

1) daytime hypercapnia (PCO_2 ≥6.0 kPa), and/or,
2) evidence of nocturnal hypoventilation and/or,
3) sleep apnea and/or,
4) FVC below 50% of predicted.

HMV (bi-level positive pressure ventilation in a spontaneous/timed mode) was initiated clinically in all patients under strict supervision of specialized nurses and doctors from the Centre of Home Mechanical Ventilation Maastricht. After initiation, patients were followed closely by the same team with regularly planned home visits and outpatient clinic visits. Patients with low treatment adherence were scheduled for extra visits for ventilator and mask check-ups, education and motivational support. Treatment adherence rates were retrieved from the ventilator's software. Treatment adherence was expressed as percentage of days that the ventilator was used and the average daily use of the ventilator. Treatment adherence was considered high and adequate when patients used the ventilator for more than five hours per night because this is

associated with better survival in DM1 patients.[28] Patients with low treatment adherence (<5 hours per night) were grouped with patients that discontinued HMV and are later referred to as the low treatment adherence group. This group was compared to patients with high treatment adherence (>5 hours per night). Reasons for HMV discontinuation were documented by the treating physician after questioning the patient during standard follow-up outpatient clinic visit and were retrieved from the patient's file for this study.

Statistical analysis

All statistical analyses were performed using IBM SPSS software version 28. Normally distributed data were described as mean with standard deviation (SD) for continuous variables and comparisons were made using independent t-tests. Non-normally distributed continuous variables were described as median and interquartile range (IQR), and compared using Mann-Whitney U test. Categorical variables were described as frequency and compared using Pearson chi-squared test or Fisher's exact test when appropriate. A p-value less than 0.05 was considered to be statistically significant. Univariable binary logistic regression was performed to identify predictors for high HMV treatment adherence, presented as odds ratios (OR) with confidence intervals (CI).

Results

Patient characteristics

The respiratory characteristics of 200 consecutive DM1 patients were collected. Upon pulmonary function testing, 128 out of 200 patients (64%) showed a restrictive pattern with an FVC <80% of predicted and a FEV1/FVC >0.70. Twenty-four patients out of 200 patients (12%) had an FVC <50% of predicted. Sleep apnea was present in 170 out of 200 patients (85%), varying from mild in 59 out of 170 patients (35%) to moderate in 66 patients (39%) and severe in 45 patients (26%). The events were scored as mainly central in 105 out of 170 patients (62%), mainly obstructive in 27 patients (16%), mixed in 27 patients (16%), and unclassified in 11 patients (6%).

Within the follow-up period of at least two years, a total of 101 out of 200 (51%) started with HMV treatment (Figure 3.1). The remaining 99 patients did not have an indication for HMV or refused HMV. Baseline characteristics of patients that initiated HMV are shown in Table 3.1. The diagnosis of DM1 was genetically proven in 78 patients. For the remaining 23 patients, the diagnosis was confirmed by a

neuromuscular neurologist based on the clinical phenotype and a positive family history with genetically proven DM1 in a first or second degree family member.

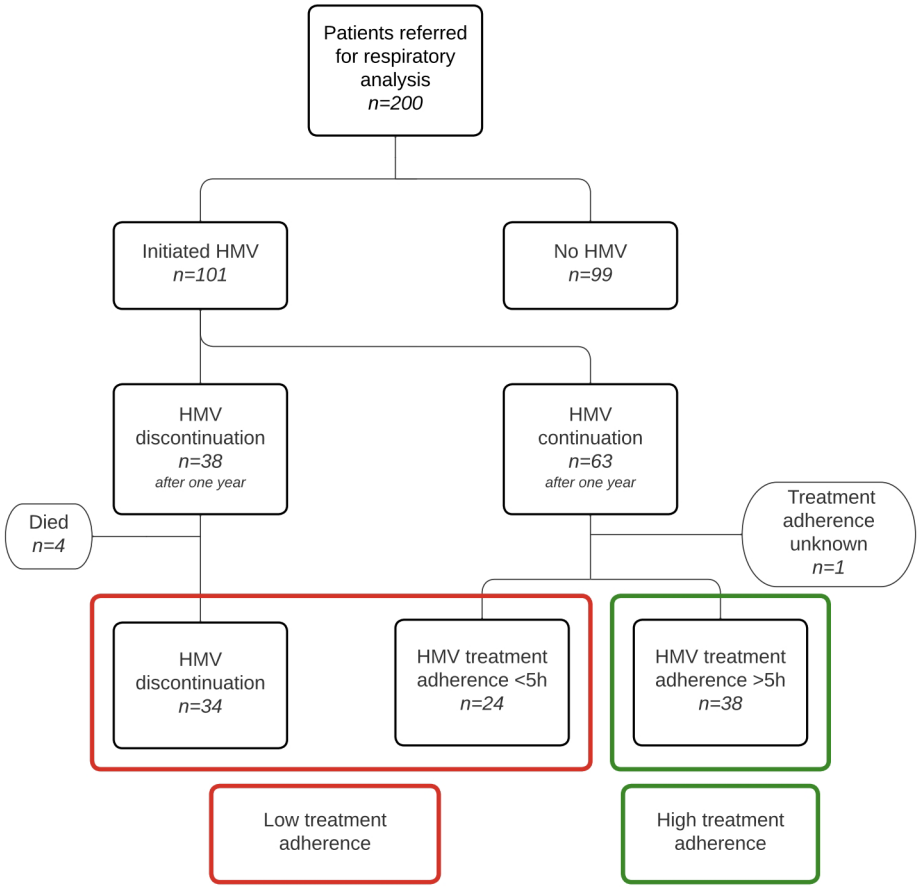


Figure 3.1 Flowchart of included myotonic dystrophy type 1 patients. HMV=home mechanical ventilation

Home mechanical ventilation

HMV was initiated in 101 patients based on different (and often multiple) indications: sleep apnea was present in 93%, nocturnal hypoventilation in 62%, daytime hypercapnia in 32%, FVC <50% of predicted in 19% of the patients. Within the first year of treatment, 38 patients (38%) discontinued their HMV; in four patients the reason for discontinuation was death (Figure 3.1). Two out of the four deceased patients had low treatment adherence and died of pulmonary complications (pneumonia and aspiration,

respectively). The other two patients had high treatment adherence; one died of heart failure, the other due to an accident. Eight patients discontinued HMV immediately after initiation, another eight patients discontinued within the first three months, another eight patients discontinued after 3-6 months and the last 14 patients discontinued after 6-12 months of treatment. Patients reported different reasons for discontinuation of HMV (Table 3.2). Some patients mentioned more than one reason. No improvement of symptoms was the most common reason for discontinuation, mentioned by 22 out of 34 patients (65%), followed by mask problems (15 out of 34 patients, 44%) impossibility to sleep with HMV (12 out of 34 patients, 35%). Sixty-three patients continued HMV after one year (Figure 3.1). The treatment adherence of 62 patients continuing HMV is shown in Table 3.3 (treatment adherence data were lacking in one patient) and average daily use is depicted in Figure 3.2. Twenty-four out of the 101 patients (24%) that started HMV had an average daily use of less than five hours per night (Figure 3.1). Treatment adherence did not differ between patients with sleep apnea as main indication for HMV compared to patients with multiple indications (Table 3.3).

Table 3.1 Baseline characteristics (n=101).

Male*	49 (48.5%)
Age (yrs.)	46.6 ± 12.9
BMI (kg/m^2)	27.1 ± 5.4
DM1 subtype*	
congenital	2 (2%)
juvenile onset	15 (14.9%)
adult onset	81 (80.2%)
late onset	3 (3%)
CTG repeat length**	209 [150-380]
FVC (% of predicted)	68.4 ± 19.7
FVC <50% of predicted*	19 (19%)
FVC supine (% of predicted)	62.3 ± 19.4
MIP (kPa)	4.2 ± 1.7
MEP (kPa)	4.7 ± 1.8
Daytime pCO_2 (kPa)	5.9 ± 0.7
Daytime pCO_2 >6.0 kPa*	32 (32%)
Nighttime pCO_2 (kPa)	6.1 ± 0.8
Nighttime base excess	2.3 ± 3.2
Bicarbonate (mmol/L)	26.5 ± 2.4
AHI (nr/h)**	25.5 [14.6-37.6]
Mean saturation sleep (%)	91.8 ± 2.9

BMI=body mass index, DM1=myotonic dystrophy type 1, CTG=cytosine-thymine-guanine, FVC=forced vital capacity, MIP=maximal inspiratory pressure, MEP=maximal expiratory pressure, pCO_2=partial pressure of CO_2, AHI=apnea hypopnea index; *data expressed as mean ± SD,* frequency (%) ** median [IQR].*

Table 3.2 Reasons for discontinuation of HMV

Absence of improvement of symptoms	22
Mask problems	15
Impossibility to sleep with HMV	12
Psychological problems	5
Other medical problems	3
Technical issues	1

HMV=home mechanical ventilation

Table 3.3 Home mechanical ventilation treatment adherence data.

	Total group	**Indication sleep apnea**	**Multiple indications**	**P value**
HMV ongoing after 1 year	62	18	44	
Adherence after 1 year				
- percentage of days used	88 [61-97]	90 [68-97]	87 [60-97]	0.352
- average daily use (minutes)	389 [224-480]	408 [231-480]	380 [222-478]	0.768

HMV=home mechanical ventilation. *Data expressed as median [interquartile range].*

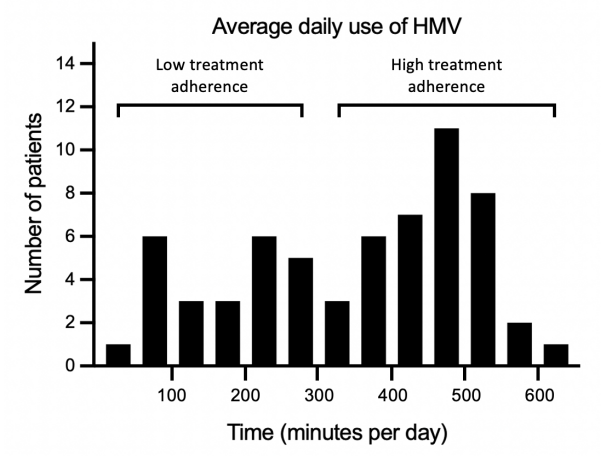


Figure 3.2 Distribution of average daily use of noninvasive home mechanical ventilation (HMV) in 62 patients that continued HMV treatment after the first year.

Low versus high treatment adherence

The low HMV treatment adherence group (consisting of patients with low HMV treatment adherence or HMV discontinuation) was compared to patients with high HMV treatment adherence (>5 hours per night, Figure 3.1). We excluded four patients from data analysis who died during the observational period. We found no statistical differences between both groups (Table 3.4). In addition, there was no significant difference between the groups regarding the indication for HMV (sleep apnea as only indication versus multiple indications, p-value 0.140). Logistic regression analysis was

performed to assess the impact of various predictors on having high HMV treatment adherence. None of the included predictors (gender, age, BMI, CTG repeat length, FVC, daytime pCO_2, nighttime pCO_2, nighttime base excess, bicarbonate, AHI and mean saturation during sleep) was able to significantly predict high HMV treatment adherence (Table 3.5).

Table 3.4 Home mechanical ventilation: low treatment adherence versus high treatment adherence.

	Low HMV adherence (n=58)	**High HMV adherence (n=38)**	**P value**
Male*	29 (50%)	17 (45%)	0.614
Age, yrs.	47.2 ± 12.5	45 ± 13.4	0.410
BMI (kg/m^2)	26.4 ± 5.2	28.1 ± 5.8	0.132
CTG repeat length**	209 [150-384]	200 [143-334]	0.542
FVC (% of predicted)	67 ± 17.5	72 ± 22.5	0.249
Daytime pCO_2 (kPa)	5.8 ± 0.67	5.8 ± 0.78	0.908
Nighttime pCO2 (kPa)	6.1 ± 0.67	6.0 ± 0.86	0.383
Nighttime base excess	2.2 ± 3.85	2.4 ± 1.96	0.442
Bicarbonate (mmol/L)	26.4 ± 2.4	26.5 ± 2.4	0.895
AHI** (nr/h)	24 [13-34]	25 [16-37]	0.577
Mean saturation sleep (%)	91.7 ± 3.2	92 ± 2.5	0.581

HMV=home mechanical ventilation BMI=body mass index, CTG=cytosine-thymine-guanine, FVC=forced vital capacity, pCO_2=partial pressure of CO_2, AHI=apnea hypopnea index; *data expressed as mean ± SD * count (%) ** median [IQR].*

Table 3.5 Binary logistic regression analysis for the prediction of high treatment adherence.

		Univariable	
	OR	**CI**	**P value**
Male	1.235	0.544-2.807	0.614
Age	1.014	0.982-1.047	0.406
BMI	0.943	0.874-1.018	0.134
CTG repeat length	1.000	0.998-1.001	0.616
FVC (% of predicted)	0.987	0.966-1.008	0.223
Daytime pCO_2 (kPa)	0.963	0.516-1.800	0.907
Nighttime pCO_2 (kPa)	1.293	0.728-2.298	0.380
Nighttime base excess	0.990	0.871-1.127	0.883
Bicarbonate (mmol/L)	0.987	0.819-1.189	0.893
AHI (nr/h)	0.988	0.967-1.010	0.283
Mean saturation sleep (%)	0.959	0.829-1.111	0.578

BMI=body mass index, CTG=cytosine-thymine-guanine, FVC=forced vital capacity, pCO_2=partial pressure of CO_2, AHI=apnea hypopnea index.

Discussion

In this observational study, the treatment adherence with HMV was monitored in a large group of DM1 patients. Upon follow-up after one year, 38% of patients that had initiated HMV discontinued treatment and another 24% had a low HMV treatment adherence. Not only HMV discontinuation, but also low treatment adherence was considered as treatment failure because adequate adherence is required for effective treatment. In accordance with our hypothesis this study confirms that the respiratory characteristics are not associated with treatment adherence with HMV. This highlights the complexity of HMV treatment in DM1 patients and emphasizes the need to search for other, potentially amendable factors. The most frequent reasons for discontinuation of treatment were 1) no improvement of symptoms, 2) impossibility to sleep with HMV and 3) mask problems. With regard to the first reason for discontinuation, it should be taken into account that patients with DM1 are not always aware of symptoms of respiratory failure and seem to adjust to unusually high levels of hypercapnia and respiratory muscle weakness.[6,29] Moreover, almost every DM1 patient experiences excessive daytime sleepiness, which makes it difficult to differentiate between sleepiness as a symptom of respiratory failure or sleep apnea, or as a general symptom of disease.[19] This might be an explanation for the large group of patients that discontinue HMV because they do not perceive improvement of complaints. DM1 patients who report symptomatic benefit from treatment, have higher treatment adherence with HMV than patients without reported symptomatic benefit.[16] With regard to the second most common reason for discontinuation of HMV (impossibility to sleep with HMV), it would be interesting for future research to focus more on the technical side of the HMV in order to find a ventilation mode that is most comfortable and tolerable for each individual patient, also taken into account the mask problems which are reported as third reason for HMV discontinuation.[30]

Although not investigated in this study, the risk of HMV discontinuation has been demonstrated before to be lower in patients with a professional occupation or training.[16] Other risk factors for low treatment adherence and HMV discontinuation are initiation during acute respiratory failure, side effects (such as excessive leaks, technical problems) or HMV intolerance.[9,16,31] Based on this study and previous studies on the subject, it is likely that other factors than respiratory characteristics and symptoms play a pivotal role in achieving a successful treatment with HMV. As a result of brain involvement, cognitive impairment and psychological dysfunction are common in DM1.[32,33] Therefore, DM1 patients may require more guidance and education than other patient populations in using their home ventilator. Apathy is also frequently

reported in DM1 affected individuals and may contribute to low treatment adherence because of low initiative to use the ventilator every night.[34]

Our study showed a good treatment adherence (>5 hours per night) in almost half of the ongoing patients one year after start of HMV. Although this is still less than desirable, it is higher than previously reported treatment adherence rates in other countries, in comparable patients.[35,36] In another Dutch cohort of DM1 patients, high treatment adherence rates were also reported by Seijger et al.[28] In the Netherlands, a unique organization exists, where only four centers in the entire country are responsible for all patients requiring HMV. This has enabled us to develop our own national guideline and national learning management system for all caregivers and professionals involved in the treatment of HMV patients.[37] This system provides the opportunity for special guidance and for patient-centered care which is essential for DM1 affected individuals. Nonetheless, there is still a high rate of treatment failure which calls for further optimization. In order to achieve improvement of HMV care in DM1 patients, more studies are needed that incorporate all aspects involved, including cognitive functioning, living status and care dependency. Also, response to therapy should be monitored carefully by overnight measurements of respiration and blood gas measurements, as well as health-related quality of life and side effects. Currently, the multicenter REMeDY study (differential Response to non-invasive vEntilation in Myotonic DystrophY study) includes all DM1 patients in the Netherlands that start with HMV (https://trialsearch.who.int; registration number NL7972). The study aims to profile a multidimensional response to HMV and identify patients with DM1 that do (or do not) respond well to treatment.

Limitations

The current study has a number of limitations due to its retrospective observational nature. Some baseline respiratory measurements were missing such as early morning blood gases and overnight transcutaneous capnometry to detect sleep-related hypoventilation. Data on treatment response such as overnight measurements of respiration or blood gas measurements were lacking. Unfortunately it was not possible to add data on symptoms prior to HMV initiation and perceived improvement of those symptoms with HMV treatment. One might argue that almost all patients suffered from sleep apnea and that part of this group could possibly have been treated with continuous positive airway pressure (CPAP) therapy instead of HMV. However, because of the nature of the disease, it is expected that these patients would need bi-level positive pressure ventilation in the (near) future, so we easily opt to initiate HMV. With

regard to respiratory characteristics, we did not find differences between patients in the sleep apnea group and patients in the group with multiple indications for HMV.

Conclusion

In conclusion, the respiratory characteristics are not associated with treatment adherence with HMV in DM1 patients and cannot be used to identify patients at risk for low HMV treatment adherence. Treatment failure was common as more than half of DM1 patients that initiated HMV had low treatment adherence or discontinued therapy after one year. It is likely that other factors, such as awareness of symptoms and perceived benefit, cognitive functioning and care dependency play an important role in HMV treatment adherence. These factors should therefore be incorporated in future research to further optimize care for DM1 patients.

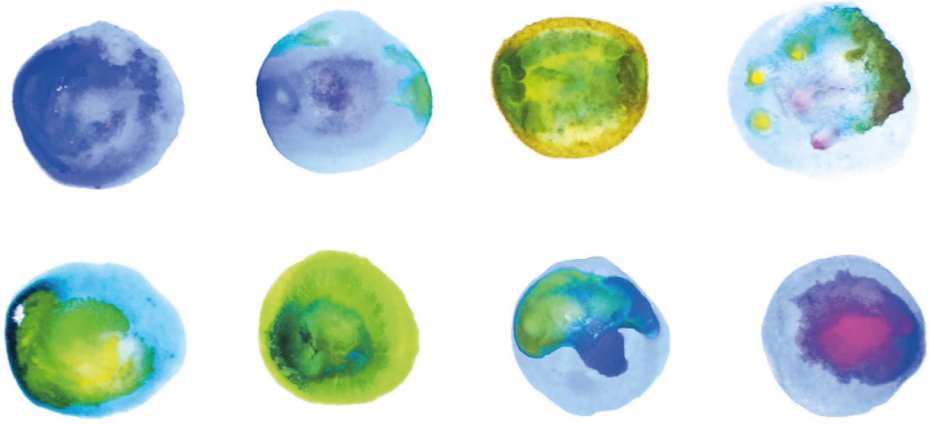
References

1. Kaminsky P, Poussel M, Pruna L, Deibener J, Chenuel B, Brembilla-Perrot B. Organ dysfunction and muscular disability in myotonic dystrophy type 1. Medicine (Baltimore). 2011;90(4):262-8.
2. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. Cell. 1992;69(2):385.
3. de Die-Smulders CE, Howeler CJ, Thijs C, Mirandolle JF, Anten HB, Smeets HJ, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998;121 (Pt 8):1557-63.
4. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med. 2008;358(25):2688-97.
5. Mathieu J, Allard P, Potvin L, Prevost C, Begin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999;52(8):1658-62.
6. Hawkins AM, Hawkins CL, Abdul Razak K, Khoo TK, Tran K, Jackson RV. Respiratory dysfunction in myotonic dystrophy type 1: A systematic review. Neuromuscul Disord. 2019;29(3):198-212.
7. Seijger CG, Drost G, Posma JM, van Engelen BG, Heijdra YF. Overweight Is an Independent Risk Factor for Reduced Lung Volumes in Myotonic Dystrophy Type 1. PLoS One. 2016;11(3):e0152344.
8. De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B, et al. Unravelling the myotonic dystrophy type 1 clinical spectrum: A systematic registry-based study with implications for disease classification. Revue Neurologique. 2016;172(10):572-80.
9. West SD, Lochmuller H, Hughes J, Atalaia A, Marini-Bettolo C, Baudouin SV, et al. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 2016;3(4):529-37.
10. Yu H, Laberge L, Jaussent I, Bayard S, Scholtz S, Raoul M, et al. Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. Sleep. 2011;34(2):165-70.
11. Romigi A, Izzi F, Pisani V, Placidi F, Pisani LR, Marciani MG, et al. Sleep disorders in adult-onset myotonic dystrophy type 1: a controlled polysomnographic study. Eur J Neurol. 2011;18(9):1139-45.
12. Laberge L, Begin P, Dauvilliers Y, Beaudry M, Laforte M, Jean S, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry. 2009;80(6):642-6.
13. Kumar SP, Sword D, Petty RK, Banham SW, Patel KR. Assessment of sleep studies in myotonic dystrophy. Chron Respir Dis. 2007;4(1):15-8.
14. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, Initiative I. Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. Circulation. 2017;136(19):1840-50.
15. Vosse BAH, Seijger C, Cobben N, van Engelen B, van Kuijk SMJ, Faber C, et al. Noninvasive Home Mechanical Ventilation in Adult Myotonic Dystrophy Type 1: A Systematic Review. Respiration. 2021;100(8):816-25.
16. Boussaid G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord. 2016;26(10):666-74.
17. Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
18. Sansone VA, Gagnon C. 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: management and implications for research, 27-29 June 2014, Naarden, The Netherlands. Neuromuscul Disord. 2015;25(5):432-42.
19. Laberge L, Gagnon C, Dauvilliers Y. Daytime sleepiness and myotonic dystrophy. Curr Neurol Neurosci Rep. 2013;13(4):340.
20. Peric S, Bjelica B, Bozovic I, Pesovic J, Paunic T, Banovic M, et al. Fatigue in myotonic dystrophy type 1: a seven-year prospective study. Acta Myol. 2019;38(4):239-44.
21. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

22. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993;16:5-40.
23. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.
24. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696-702.
25. Iber C A-IS, Chesson A, and Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.: Westchester, I11: American Academy of Sleep Medicine; 2007.
26. Zavorsky GS, Cao JG, Mayo NE, Gabbay R, Murias JM. Arterial versus capillary blood gases: A meta-analysis. Resp Physiol Neurobi. 2007;155(3):268-79.
27. Sansone VA, Gagnon C, participants of the 207th EW. 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: management and implications for research, 27-29 June 2014, Naarden, The Netherlands. Neuromuscul Disord. 2015;25(5):432-42.
28. Seijger C, Raaphorst J, Vonk J, van Engelen B, Heijerman H, Stigter N, et al. New Insights in Adherence and Survival in Myotonic Dystrophy Patients Using Home Mechanical Ventilation. Respiration. 2021;100(2):154-63.
29. Poussel M, Thil C, Kaminsky P, Mercy M, Gomez E, Chaouat A, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. 2015;25(5):403-8.
30. Pierucci P, Portacci A, Carpagnano GE, Banfi P, Crimi C, Misseri G, et al. The right interface for the right patient in noninvasive ventilation: a systematic review. Expert Rev Respir Med. 2022;16(8):931-44.
31. Vivekananda U, Turner C. A model to predict ventilator requirement in myotonic dystrophy type 1. Muscle Nerve. 2019;59(6):683-7.
32. Antonini G, Soscia F, Giubilei F, De Carolis A, Gragnani F, Morino S, et al. Health-related quality of life in myotonic dystrophy type 1 and its relationship with cognitive and emotional functioning. J Rehabil Med. 2006;38(3):181-5.
33. Okkersen K, Buskes M, Groenewoud J, Kessels RPC, Knoop H, van Engelen B, et al. The cognitive profile of myotonic dystrophy type 1: A systematic review and meta-analysis. Cortex. 2017;95:143-55.
34. van der Velden BG, Okkersen K, Kessels RP, Groenewoud J, van Engelen B, Knoop H, et al. Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. J Affect Disord. 2019;250:260-9.
35. Ferrari Aggradi CR, Falcier E, Lizio A, Pirola A, Casiraghi J, Zanolini A, et al. Assessment of Respiratory Function and Need for Noninvasive Ventilation in a Cohort of Patients with Myotonic Dystrophy Type 1 Followed at One Single Expert Center. Can Respir J. 2022;2022:2321909.
36. Rautemaa V, Roberts ME, Bentley A, Felton TW. The role of noninvasive ventilation in the management of type II respiratory failure in patients with myotonic dystrophy. ERJ Open Res. 2021;7(3).
37. van den Biggelaar RJM, Hazenberg A, Cobben NAM, Gommers D, Gaytant MA, Wijkstra PJ. Home mechanical ventilation: the Dutch approach. Pulmonology. 2022;28(2):99-104.

Chapter 4

The role of cognition, affective symptoms, and apathy in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy



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Abstract

Background

Chronic respiratory failure often occurs in myotonic dystrophy type 1 (DM1) and can be treated with noninvasive home mechanical ventilation (HMV). Treatment adherence with HMV is often suboptimal in patients with DM1, but the reasons for that are not well understood.

Objective

The aim of this exploratory study was to gain insight in the prevalence of mild cognitive impairment, affective symptoms, and apathy and to investigate their role in HMV treatment adherence in DM1.

Methods

The Montreal Cognitive Assessment (MoCA), the Hospital Anxiety and Depression Scale (HADS), and the Apathy Evaluation Scale (AES) were used to assess cognition, affective symptoms, and apathy in DM1 patients that use HMV. Patients with low treatment adherence (average daily use HMV <5h or <80% of the days) were compared with patients with high treatment adherence (average daily use of HMV ≥5h and ≥80% of the days).

Results

Sixty patients were included. Abnormal scores were found in 40% of the total group for the MoCA, in 72-77% for the AES, and in 18% for HADS depression. There was no difference between the high treatment adherence group (n=39) and the low treatment adherence group (n=21) for the MoCA, AES, and HADS depression. The HADS anxiety was abnormal in 30% of the total group, and was significantly higher in the low treatment adherence group (p=0.012). Logistic regression analysis revealed that a higher age and a higher BMI were associated with a greater chance of high treatment adherence.

Conclusions

This exploratory study showed that cognitive impairment and apathy are frequently present in DM1 patients that use HMV, but they are not associated with treatment adherence. Feelings of anxiety were associated with low treatment adherence. Higher age and higher BMI were associated with high treatment adherence with HMV.

Introduction

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy among adults. It is a hereditary autosomal dominant disorder affecting not only the peripheral muscles, but also multiple organ systems including the respiratory system, the heart, and the central nervous system.[1,2] Chronic respiratory failure (CRF) often occurs and can be treated with noninvasive home mechanical ventilation (HMV).[3] In DM1, HMV improves gas exchange and relieves symptoms with a possible survival benefit.[4,5] HMV can, however, only be applied successfully to cooperative and motivated patients, and its effect depends on the amount of hours the ventilator is used every night, which is referred to as treatment adherence.[5] Unfortunately, treatment adherence with HMV is often suboptimal in DM1 patients. Low treatment adherence (defined as use of the ventilator less than 5 hours per night) and discontinuation of HMV is reported in 24-72% of DM1 patients.[6-12] The reasons for low treatment adherence with HMV in DM1 are not well understood, but they are not solely determined by physiological factors or the severity of the respiratory dysfunction.[9] Patients who report symptomatic benefit have higher treatment adherence than those who do not feel benefit.[12] Identifying additional influencing factors can potentially result in new modifiable targets to enhance treatment adherence. There is currently very limited data available on the role of cognition, affective symptoms, and apathy in the context of HMV treatment adherence.[13] Cognitive impairment, depressive and anxiety symptoms, and apathy are known to be major predictors of poor treatment adherence, and they are often present in DM1 patients.[14-19] Also, lack of treatment adherence cannot be fully understood without taking into account the social context in which it occurs, including the living situation and care dependency of the treated patient.[20,21] The aim of this exploratory study was to gain insight in the prevalence of mild cognitive impairment, affective symptoms, and apathy and to investigate their role in HMV treatment adherence in DM1. We hypothesized that the presence of cognitive impairment, affective symptoms, and apathy is common in DM1 patients, and that it is negatively associated with treatment adherence with HMV.

Materials and methods

Study design and participants

A cross-sectional study was conducted at the Home Mechanical Ventilation (HMV) center of the Maastricht University Medical Center+ (MUMC+). Data was collected between October 2021 and October 2022 during a regular follow-up visit in the hospital

or during a regular home consultation. The local Medical Ethics Committee of the MUMC+ concluded that the study protocol falls outside the scope of the Medical Research Involving Human Subjects Act (registration number METC 2021-2665). The study was conducted according to the applicable research principles. Written informed consent was obtained from all included participants. All DM1 patients who were treated with HMV at the HMV Center of MUMC+ were approached to take part in the study. HMV initiation and treatment were in accordance with the current consensus-based care recommendations for DM1 patients.[22] To avoid selection bias, patients who had recently (within the past year) discontinued HMV were also asked to participate. Patients were required to meet the following criteria to be eligible for participation: (1) having confirmed DM1, (2) undergoing HMV treatment for at least three months, or having undergone HMV treatment, but discontinued in the past year, (3) ≥18 years old, (4) no recent history of pulmonary infection or hospitalization, (5) able to read and write the Dutch language, and (6) able to give informed consent.

Materials

Patient characteristics such as age, sex, body mass index (BMI), CTG (cytosine-thymine-guanine) repeat length, pulmonary function (forced vital capacity sitting and supine), pCO_2, and apnea-hypopnea-index (AHI) were obtained from the patients' medical file. The muscular impairment rating scale (MIRS), a DM1-specific scale for muscle weakness, was used to rate muscular impairment. Ventilator settings and treatment adherence data were retrieved from the patients' ventilator and expressed as amount of days that the ventilator was used (as percentage of total amount of days that the ventilator could possibly be used), and average time (in minutes) that the ventilator was used per night. Data on the living situation, care dependency, and level of education were collected. Low level of education was defined as primary school, lower vocational education, or secondary vocational education as highest level of education.

Test battery

An overview of the test battery can be found in Table 4.1. The Montreal Cognitive Assessment (MoCA) was used as a screening tool for global cognitive functioning. The MoCA is a one-page-30-point test which evaluates eight different domains of cognition: short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation to time and place. A score below 26 is considered abnormal.[23,24] The MoCA was carried out by trained researchers. The Hospital Anxiety and Depression Scale (HADS) was used to assess emotional functioning. The HADS is a fourteen-item scale and consists of an anxiety

subscale and a depression subscale, each with seven items. The items are rated on a four-point scale ranging from zero to three. A higher score on the scale indicates more (severe) symptoms, and a domain score of seven or more indicates the possible presence of anxiety or depression.[25,26] To evaluate the presence of apathy, the short version of the Apathy Evaluation Scale (AES) was used. The AES-S is the self-rated version and the AES-I is the informant version based on observations of a family member, friend, or caregiver. The AES contains 14 items that address the affective, behavioral, and cognitive domains of apathy. The items are rated on a four-point scale that ranges from zero ('not at all present') to three ('a lot'). A score of 14 or higher indicates the presence of apathy, and a higher score indicates more symptoms of apathy.[27-29] The Care Dependency Scale (CDS) was used to determine the extent to which a patient is dependent on others for everyday tasks and self-care with a total score ranging from 15 (totally dependent) to 75 (totally independent).[30] The S^3-NIV questionnaire was used to determine HMV-related side effects, symptoms and sleep quality. The S^3-NIV questionnaire is a self-reported questionnaire containing 11 items. Patients score each item on a five-point Likert-scale (zero: always true; one: mostly true; two: sometimes true; three: mostly untrue; four: completely untrue) based on their agreement with each statement in the four preceding weeks. The total score can be computed as the average of all answered items multiplied by 2.5. The lowest possible score (0) corresponds to the highest impact of disease and treatment, while the highest possible score (10) corresponds to the lowest impact of disease and treatment.[31,32]

Table 4.1 Test battery

Test/questionnaire	Measurement
Montreal Cognitive Assessment (MoCA)	Cognitive functioning
Hospital Anxiety and Depression Scale (HADS)	Affective symptoms
Apathy Evaluation Scale (AES)	Degree of apathy
Care Dependency Scale (CDS)	Degree of care dependency
S^3-NIV questionnaire	HMV related symptoms, side effects, and sleep quality

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics software version 28. Continuous variables were expressed as mean with standard deviation (SD) or as median with 1st and 3rd quartile in case of skewed distribution. Categorical variables were expressed as count and percentage. Patients were stratified into two group based on their treatment adherence. The 'high treatment adherence' group consisted of patients that used the ventilator for more than five hours per night on average and at least 80% of the days in the last three months. Patients that used the ventilator less

than five hours per night or less than 80% of the days were grouped with the patients who discontinued HMV in the 'low treatment adherence' group. A minimum treatment adherence of five hours per night was chosen because this is associated with better survival in DM1.[5] Differences between the high treatment adherence group and the low treatment adherence group were analyzed using Pearson's chi-squared (χ^2) test or Fisher's exact test for categorical data. The independent-samples t-test or the Mann-Whitney U test was used for continuous variables. Logistic regression was performed to identify potential independent predictors of HMV treatment adherence. Covariates with a *p*-value <0.25 in the univariable analyses were selected: age, BMI, inspiratory positive airway pressure (IPAP), MoCA, CDS and HADS anxiety. Although the *p*-value was <0.25 for expiratory positive airway pressure (EPAP), this variable was not selected, because IPAP was preferred as a representative ventilator setting. Results were quantified as odds ratio (OR) with 95% confidence interval (CI). A *p*-value of <0.05 was considered statistically significant.

Results

Patients characteristics

Ninety-eight DM1 patients were eligible for participation, including eight patients who discontinued HMV in the past year. Main reasons for discontinuation of HMV were 'unable to sleep with HMV' and 'lack of improvement of symptoms'. Of the 19 excluded patients, six patients were unable to give informed consent, five patients were unreachable, two patients died before participation took place, two patients were medically unstable, two patients were under 18 years of age, one patient participated in another study, and one patient was physically not able to fill in the MoCA. Another 19 patients refused participation. A total of 60 patients was included in the study and subsequently divided into the two predefined groups based on treatment adherence with HMV (Figure 4.1). Baseline characteristics and ventilator settings of the cohort are shown in Table 4.2. Patients with high treatment adherence were on average older (*p*=0.007) and had a higher BMI (p=0.012) compared to the low treatment adherence group. Out of the 60 included patients, 55 (92%) lived at home, one patient (1%) lived in a nursing home, and four patients (7%) lived in an assisted-living project. With regard to the living situation, there was no difference between the high and low treatment adherence group (*p*=1.000). Of the patients who lived at home, 11 patients (20%) received professional home care, 16 patients (29%) received care from an informal caregiver and 28 patients (51%) did not have any form of care. With regard to the care situation, there was no difference between the high and low treatment adherence

group (p=0.515). Of the total group, half of the patients had a low education level; this did not significantly differ between the low treatment adherence group and the high treatment adherence group (p=0.417). In the high treatment adherence group, the median percentage of days that participants used the HMV was 100 [100-100] and the median number of hours per day was 8.5 [7.3-10]. In the low treatment group, the median percentage of days that participants used the HMV was 51 [0-82], and the median number of hours per day was 3.5 [3.5-5.0].

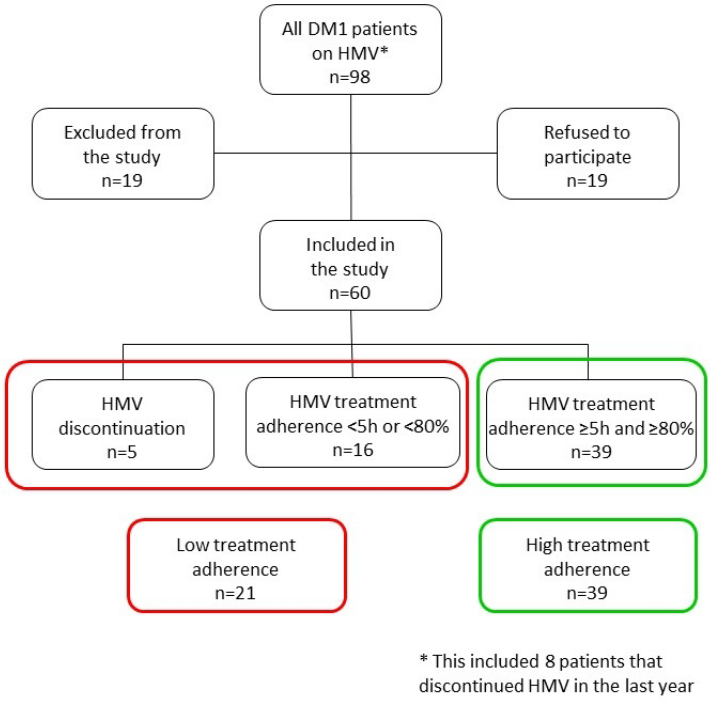


Figure 4.1 Flow chart of the selection procedure.

Cognitive impairment, affective symptoms, and apathy

Abnormal scores were found in 40% of the patients for the MoCA and in 72%-77% for the AES, whereas a minority of patients showed abnormal scores for HADS anxiety and HADS depression (Figure 4.2). There was no difference between the high treatment adherence group and the low treatment adherence group with regard to the median MoCA score (Table 4.3). Apathy and depression scores were similar in the high and low treatment adherence group, but the anxiety score was higher in the low treatment adherence group (p=0.012, Table 4.3). HMV-related side effects, symptoms and sleep

quality were equally present in both groups (S^3-NIV, Table 4.3). Logistic regression analysis revealed that a higher age and a higher BMI were associated with a greater chance of high treatment adherence (Table 4.4).

Table 4.2 Baseline characteristics and ventilator settings.

	Total group (n=60)	**High treatment adherence (n=39)**	**Low treatment adherence (n=21)**	**p-value**
Age (yrs)*	52 ± 12.8	55 ± 11.8	46 ± 12.8	**0.007**
Male	28 (47%)	17 (44%)	11 (52%)	0.515
BMI*	29 ± 6.6	31 ± 6.4	26 ± 5.9	**0.012**
CTG repeat length	150 [100-200]	163 [100-200]	150 [100-200]	0.742
50-150	n=15	n=9	n=6	
150-250	n=19	n=12	n=7	
≥250	n=7	n=5	n=2	
DM1 type				
juvenile	n=7	n=4	n=3	
adult-onset	n=50	n=33	n=17	
late-onset	n=3	n=2	n=1	
High MIRS score (4-5)	20 (33%)	14 (36%)	6 (29%)	0.566
pCO_2 before HMV (kPa)	6.2 ± 0.7	6.1 ± 0.7	6.3 ± 0.6	0.343
FVC sitting (% of predicted)	62 ± 21	61 ± 21	64 ± 20	0.542
FVC supine (% of predicted)	54 ± 21	53 ± 20	56 ± 22	0.596
AHI (nr/h)	19 [10-29]	20 [12-29]	17 [5-31]	0.357
current pCO_2 (kPa)	5.7 ± 0.8	5.6 ± 0.7	5.7 ± 1.0	0.749
IPAP (cm H_2O)	17 [14-19]	18 [15-20]	17 [14-18]	0.131
EPAP (cm H_2O)*	7 [6-9]	8 [6-9]	6 [5-8]	**0.026**
Backup frequency	13 [12-14]	13 [12-14]	13 [12-14]	0.953

BMI=body mass index, CTG=cytosine-thymine-guanine, MIRS=muscular impairment rating scale, FVC=forced vital capacity, pCO_2=partial pressure of CO_2, AHI=apnea hypopnea index, IPAP=inspiratory positive airway pressure, EPAP=expiratory positive airway pressure; *data expressed as mean ± SD, frequency (%), or median [IQR]; *p<0.05.*

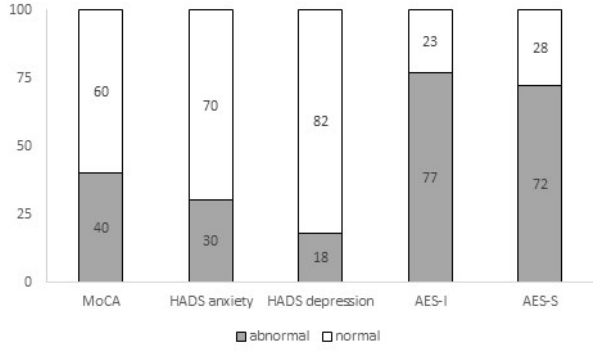


Figure 4.2 Display of abnormal and normal scores of the main test results.
MoCA=Montreal Cognitive Assessment, HADS=Hospital Anxiety and Depression Scale, AES-I=Apathy Evaluation Scale-Informant, AES-S=Apathy Evaluation Scale-Self.

Table 4.3 Cognition, affective symptoms, apathy, HMV related symptoms and side effects.

	Total group (n=60)	High treatment adherence (n=39)	Low treatment adherence (n=21)	*p*-value
MoCA	26 [23-28]	26 [23-27]	27 [25-28]	0.148
AES-I	19 ± 6.2	18.4 ± 6.3	18.7 ± 6.2	0.864
AES-S	17 ± 5.0	17.3 ± 5.1	16.3 ± 4.9	0.476
HADS anxiety*	4 [2-7]	3 [2-7]	6 [3-8]	**0.012**
HADS depression	4 [2-5]	4 [2.8-6]	4 [2-5]	0.743
CDS	70 [61-73]	69 [60-73]	72 [63-75]	0.107
S^3-NIV	6.4 ± 1.4	6.5 ± 1.6	6.3 ± 1.1	0.662

MoCA=Montreal Cognitive Assessment, AES-I=Apathy Evaluation Scale-Informant, AES-S=Apathy Evaluation Scale-Self, HADS=Hospital Anxiety and Depression Scale, CDS=Care Dependency Scale, S^3-NIV=S^3 noninvasive ventilation questionnaire; *data expressed as mean ± SD, or median [IQR]; *p<0.05.*

Table 4.4 Logistic regression analysis for the prediction of high treatment adherence.

	OR	95% CI	P value
Age*	1.084	1.013-1.160	**0.019**
BMI (kg/m²)*	1.151	1.001-1.324	**0.049**
IPAP	1.047	0.839-1.306	0.684
MoCA	1.022	0.812-1.287	0.853
HADS anxiety	0.830	0.663-1.038	0.102
CDS	1.006	0.947-1.068	0.847

IPAP=inspiratory positive airway pressure, MoCA=Montreal Cognitive Assessment, HADS=Hospital Anxiety and Depression Scale, CDS=Care Dependency Scale; **p<0.05.*

Discussion

This exploratory study showed that cognitive impairment and apathy are frequently present (40% and 77% respectively) in DM1 patients that use HMV, but they are not associated with treatment adherence. Feelings of anxiety were reported in 30% of the study sample and this was found to be associated with low treatment adherence. In addition, higher age and higher BMI were associated with high treatment adherence with HMV. The presence of cognitive impairment has been suggested as a possible factor influencing low treatment adherence in HMV, but this has not been confirmed, nor did we find this in the present study.[33] In daily clinical practice, presence of cognitive impairment in DM1 patients in need of HMV should therefore not be a reason to withhold HMV, but it should be taken into account to ensure adequate support and guidance. Moreover, in patients with CRF, cognitive impairment is common (up to 62%) and may even be partly due to physiological disturbances as a result of the CRF.[16] In these patients, treatment with HMV often leads to improvement of cognitive functioning, further emphasizing the necessity of treating CRF with HMV.[16] In this study, anxiety was associated with low treatment adherence with HMV. Previous

studies have been unable to reveal a clear relationship between anxiety and treatment adherence, although this might also have to do with methodological issues.[34] The cause of the elevated anxiety scores in the present study was unknown, leaving the question unanswered whether this is directly related to the CRF and/or the HMV. But it seems plausible that a patient with anxiety complaints may struggle to comply with the prescribed therapy. Confronting patients with their low treatment adherence and actively asking about anxiety in this context may result in opportunities to improve treatment adherence by offering patients extra support.

Higher age and higher BMI were found to be associated with higher treatment adherence in the current study. It has been reported before that treatment adherence is higher when symptoms of respiratory failure are present with initiation of HMV, whereas 'absence of improvement of symptoms' often is reported as reason for low treatment adherence or discontinuation of HMV.[7,9] Because of the progressive nature of DM1, patients with a higher age are more likely to have (more) symptoms of respiratory failure and therefore experience more improvement of symptoms. On the other hand, it should be taken into account that older patients with DM1 might present with the mild (or late-onset) form of DM1 which is associated with less severe symptoms.[35] However, in this study, the vast majority of the patients suffered from the adult-onset form of DM1 (Table 4.2). In DM1 patients, overweight is an independent risk factor for reduced lung volumes, which can further aggravate respiratory failure.[36] Previous research found that patients with obesity, hypoventilation and symptoms such as sleepiness and dyspnea improve with HMV, as do measures of health-related quality of life.[37] In DM1 patients with a higher BMI, respiratory failure may be more pronounced and symptoms may originate from obesity hypoventilation and therefore lead to more symptom reduction and better treatment adherence. Unfortunately, data on symptoms were not available in the current study.

To our knowledge, this is the first time that cognition, affective symptoms, and apathy were studied in the context of treatment adherence with HMV. It is also the first time that the MoCA was used in DM1 patients. Because of the small sample size and the exploratory nature of the study, it is difficult to draw definitive conclusions from this study, but it can create awareness and reject prejudices. Selection bias may have influenced the results, because severely cognitive impaired patients were excluded for this study as they could not provide informed consent. In general, research in the DM1 group is challenging because of the heterogeneity of the disease.

Conclusion

The current study explored the role of cognition, affective symptoms, and apathy in treatment adherence with HMV in DM1 patients. Presence of anxiety was negatively associated with treatment adherence, but no association was found for cognition or apathy emphasizing that HMV should not be withheld in patients with cognitive impairment or signs of apathy. Future research is needed to confirm these results in a larger study sample and should focus on influencing the factors that are negatively associated with treatment adherence with HMV.

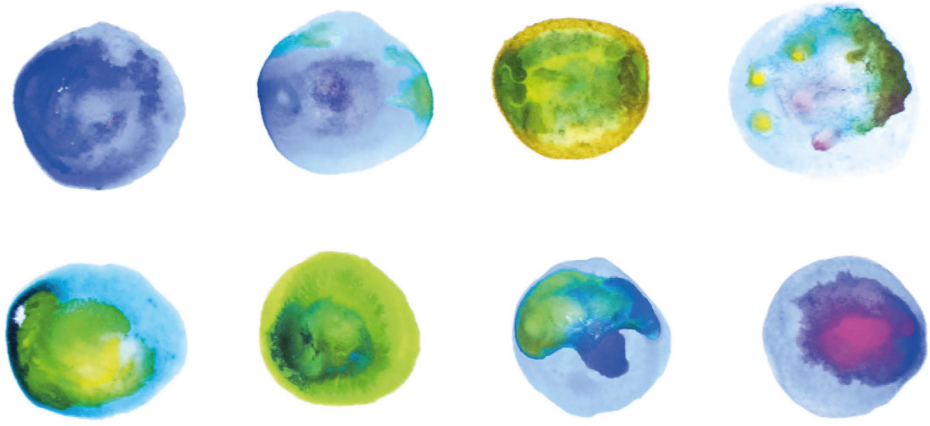
References

1. Kaminsky P, Poussel M, Pruna L, Deibener J, Chenuel B, Brembilla-Perrot B. Organ dysfunction and muscular disability in myotonic dystrophy type 1. Medicine (Baltimore). 2011;90(4):262-8.
2. Weijs R, Okkersen K, van Engelen B, Kusters B, Lammens M, Aronica E, et al. Human brain pathology in myotonic dystrophy type 1: A systematic review. Neuropathology. 2021;41(1):3-20.
3. Hawkins AM, Hawkins CL, Abdul Razak K, Khoo TK, Tran K, Jackson RV. Respiratory dysfunction in myotonic dystrophy type 1: A systematic review. Neuromuscul Disord. 2019;29(3):198-212.
4. Vosse BAH, Seijger C, Cobben N, van Engelen B, van Kuijk SMJ, Faber C, Wijkstra P. Noninvasive Home Mechanical Ventilation in Adult Myotonic Dystrophy Type 1: A Systematic Review. Respiration. 2021;100(8):816-25.
5. Seijger C, Raaphorst J, Vonk J, van Engelen B, Heijerman H, Stigter N, Wijkstra P. New Insights in Adherence and Survival in Myotonic Dystrophy Patients Using Home Mechanical Ventilation. Respiration. 2021;100(2):154-63.
6. Monteiro R, Bento J, Goncalves MR, Pinto T, Winck JC. Genetics correlates with lung function and nocturnal ventilation in myotonic dystrophy. Sleep Breath. 2013;17(3):1087-92.
7. Boussaid G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord. 2016;26(10):666-74.
8. Rossi S, Della Marca G, Ricci M, Perna A, Nicoletti TF, Brunetti V, et al. Prevalence and predictor factors of respiratory impairment in a large cohort of patients with Myotonic Dystrophy type 1 (DM1): A retrospective, cross sectional study. J Neurol Sci. 2019;399:118-24.
9. Vosse BAH, Horlings CGC, Joosten IBT, Cobben NAM, van Kuijk SMJ, Wijkstra PJ, Faber CG. Role of respiratory characteristics in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy type 1, a retrospective study. Neuromuscul Disord. 2023.
10. West SD, Lochmuller H, Hughes J, Atalaia A, Marini-Bettolo C, Baudouin SV, Anderson KN. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 2016;3(4):529-37.
11. Vivekananda U, Turner C. A model to predict ventilator requirement in myotonic dystrophy type 1. Muscle Nerve. 2019;59(6):683-7.
12. Rautemaa V, Roberts ME, Bentley A, Felton TW. The role of noninvasive ventilation in the management of type II respiratory failure in patients with myotonic dystrophy. ERJ Open Res. 2021;7(3).
13. Annunziata A, Calabrese C, Simioli F, Coppola A, Pierucci P, Mariniello DF, Fiorentino G. Psychological Factors Influencing Adherence to NIV in Neuromuscular Patients Dependent on Non Invasive Mechanical Ventilation: Preliminary Results. J Clin Med. 2023;12(18).
14. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. J Acquir Immune Defic Syndr. 2002;31 Suppl 3:S123-7.
15. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav Med. 2004;27(2):117-24.
16. Patout M, Razakamanantsoa L, D'Cruz R, Arbane G, Similowski T, Hart N, Murphy PB. Cognitive Function in Patients with Chronic Respiratory Failure: Effect of Treatment with Home Noninvasive Ventilation. Am J Respir Crit Care Med. 2023;208(8):900-3.
17. van der Velden BG, Okkersen K, Kessels RP, Groenewoud J, van Engelen B, Knoop H, Raaphorst J. Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. J Affect Disord. 2019;250:260-9.
18. Okkersen K, Buskes M, Groenewoud J, Kessels RPC, Knoop H, van Engelen B, Raaphorst J. The cognitive profile of myotonic dystrophy type 1: A systematic review and meta-analysis. Cortex. 2017;95:143-55.
19. Fujino H, Shingaki H, Suwazono S, Ueda Y, Wada C, Nakayama T, et al. Cognitive impairment and quality of life in patients with myotonic dystrophy type 1. Muscle Nerve. 2018;57(5):742-8.
20. Kierkegaard M, Harms-Ringdahl K, Holmqvist LW, Tollback A. Functioning and disability in adults with myotonic dystrophy type 1. Disabil Rehabil. 2011;33(19-20):1826-36.

21. Oates GR, Juarez LD, Hansen B, Kiefe CI, Shikany JM. Social Risk Factors for Medication Nonadherence: Findings from the CARDIA Study. Am J Health Behav. 2020;44(2):232-43.
22. Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
23. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.
24. Thissen AJ, van Bergen F, de Jonghe JF, Kessels RP, Dautzenberg PL. [Applicability and validity of the Dutch version of the Montreal Cognitive Assessment (moCA-d) in diagnosing MCI]. Tijdschr Gerontol Geriatr. 2010;41(6):231-40.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
26. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
27. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38(2):143-62.
28. Gallais B, Gagnon C, Cote I, Forgues G, Laberge L. Reliability of the Apathy Evaluation Scale in Myotonic Dystrophy Type 1. J Neuromuscul Dis. 2018;5(1):39-46.
29. Lampe IK, Kahn RS, Heeren TJ. Apathy, anhedonia, and psychomotor retardation in elderly psychiatric patients and healthy elderly individuals. J Geriatr Psychiatry Neurol. 2001;14(1):11-6.
30. Dijkstra A, Tiesinga LJ, Plantinga L, Veltman G, Dassen TW. Diagnostic accuracy of the care dependency scale. J Adv Nurs. 2005;50(4):410-6.
31. Dupuis-Lozeron E, Gex G, Pasquina P, Bridevaux PO, Borel JC, Soccal PM, et al. Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S(3)-NIV questionnaire. Eur Respir J. 2018;52(5).
32. Seijger CG, Vosse BA, la Fontaine L, Raveling T, Cobben NA, Wijkstra PJ. Validity and reliability of the Dutch version of the S3-NIV questionnaire to evaluate long-term noninvasive ventilation. Chron Respir Dis. 2024;21:14799731241236741.
33. Gigante AR, Tinoco EM, Nogueira C, Conde S, Ribeiro C. Factors influencing non-acceptance of home non-invasive ventilation. Respir Med Res. 2022;82:100938.
34. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101-7.
35. De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B, et al. Unravelling the myotonic dystrophy type 1 clinical spectrum: A systematic registry-based study with implications for disease classification. Rev Neurol (Paris). 2016;172(10):572-80.
36. Seijger CG, Drost G, Posma JM, van Engelen BG, Heijdra YF. Overweight Is an Independent Risk Factor for Reduced Lung Volumes in Myotonic Dystrophy Type 1. PLoS One. 2016;11(3):e0152344.
37. Masa JF, Pepin JL, Borel JC, Mokhlesi B, Murphy PB, Sanchez-Quiroga MA. Obesity hypoventilation syndrome. Eur Respir Rev. 2019;28(151).

Chapter 5

Validity and reliability of the Dutch version of the S^3-NIV questionnaire to evaluate long-term noninvasive ventilation



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Abstract

Objectives

Noninvasive ventilation (NIV) is an effective treatment for chronic respiratory failure (CRF). Patient-centered outcomes need to be evaluated regularly and the S^3-NIV questionnaire seems an applicable tool. We translated this short, self-administered questionnaire into a Dutch version and tested its construct validity and reliability.

Methods

An observational study was conducted, including 127 stable long-term NIV users with CRF or complex sleep related breathing disorders due to different underlying diseases: chronic obstructive pulmonary disease (25%), slowly progressive neuromuscular disorders (35%), rapidly progressive neuromuscular disorders (12%) and 'other disorders' (28%) including complex sleep apnea and obesity hypoventilation syndrome. Construct validity and reliability were tested.

Results

The Dutch version of the questionnaire was obtained after a translation and back-translation process. Internal consistency of the total score was good (Cronbach's α coefficient of 0.78) as well as for the 'respiratory symptoms' subdomain and the 'sleep and side effects' subdomain (Cronbach's α coefficient of 0.78 and 0.69, respectively). The reproducibility was excellent with an intraclass correlation of 0.89 (95% CI 0.87-0.93). Construct validity was good for the 'respiratory symptoms' subdomain.

Conclusion

The Dutch S^3-NIV questionnaire is a reliable and valid tool to evaluate symptoms, sleep, and NIV related side effects in long-term NIV users.

Introduction

Long-term noninvasive ventilation (NIV) is used for patients with chronic hypercapnic respiratory failure (CRF) due to neuromuscular disorders, thoracic cage disorders and pulmonary diseases such as chronic obstructive pulmonary disease (COPD).[1,2] In addition, NIV can be beneficial for patients with complex sleep-related breathing disorders (SRBD) such as complex sleep apnea and obesity hypoventilation syndrome (OHS).[3,4] NIV has shown to improve symptoms, quality of life, and survival.[5-7] In the Netherlands, the number of patients has quadrupled from 5,6/100.000 in 2001 to 22/100.000 almost 20 years later.[8] Currently, NIV is evaluated mainly by measuring physiological factors, such as blood gasses or transcutaneous gas-exchange measurements, but these factors show weak correlations with patient-centered outcomes such as health-related quality of life (HRQL).[9,10] Nowadays, several Dutch questionnaires are available to evaluate symptoms and HRQL in patients with CRF. In clinical practice, these are of limited use due to their length and complex scoring algorithms and they do not consider NIV related side effects. The French S^3-NIV questionnaire provides a patient-completed tool to evaluate patients on long-term NIV, which overcomes the described shortcomings.[11] It was developed based on a reflective model and contains eleven short questions, which cover three patient-oriented dimensions related to NIV: 'respiratory symptoms', 'sleep quality', and 'NIV related side effects'.[11] Internal consistency, construct validity and reproducibility were shown to be promising.[11] The S^3-NIV questionnaire was translated to Portuguese and showed a good internal consistency, but construct validity and test-retest reliability were not assessed.[12] In both studies, patients with neuromuscular disorders were in minority.[11,12] However, in the Netherlands, these patients represent the majority of long-term NIV users.[8] Therefore, this study aims to test the construct validity and reliability of the Dutch version of the S^3-NIV questionnaire in a large cohort of long-term NIV users including neuromuscular disorders, COPD and other disorders such as OHS, thoracic cage disorders and SRBD. We hypothesize that the construct validity and reliability of the Dutch S^3-NIV questionnaire are good in all categories of long-term NIV-users.

Materials and methods

Study design

This prospective observational study was conducted by the home mechanical ventilation centers of the University Medical Center Groningen and the Maastricht University Medical Center in the Netherlands from August 2021 until November 2022.

The local Medical Ethics Committee of Groningen concluded that the study protocol falls outside the scope of the Medical Research Involving Human Subjects Act (WMO). The study was conducted according to the applicable research principles and the COSMIN reporting guideline for studies on measurement properties of patient reported outcome measures (PROMs).[13] Written informed consent was obtained from all included patients. NIV users who visited one of the out-patient clinics for regular evaluation were asked to participate in this study.[14-16] Adult patients (age ≥18 years) with CRF or complex SRBD, using long-term NIV for at least three months were eligible for this study. Based on other respiratory PROMs studies, the aimed number of patients was set on 120.[14-16] Exclusion criteria were a pulmonary infection, exacerbation COPD or hospitalization in the past three months or the inability to understand Dutch. We categorized patients in four groups representing the main indications for long-term NIV in the Netherlands: (1) COPD, (2) slowly progressive neuromuscular disorders (S-NMD), (3) rapidly progressive neuromuscular disorders (R-NMD) and (4) 'other disorders' including thoracic cage disorders, OHS and complex SRBD. Baseline patient characteristics, ventilator settings, NIV treatment adherence data, and results of transcutaneous measured carbon dioxide (CO_2) and oxygen saturation (SenTec DM, SenTec AG, Therwil, Switzerland) were collected from the medical file.[17] NIV treatment adherence data were collected from the ventilator's software in all patients. Treatment adherence data were expressed as the number of hours the ventilator was used per day.

Questionnaires

The original S^3-NIV questionnaire was developed based on a reflective model, by first selecting all items pertaining to 'respiratory complaints' and 'attendant symptoms and sleep' from the Severe Respiratory Insufficiency (SRI) questionnaire.[18] A new dimension regarding comfort and NIV related side effects was obtained via in depth qualitative interviews in 15 patients. The S^3-NIV questionnaire is a self-administered questionnaire containing 11 items that patients score on a five-point Likert-scale (0: always true; 1: mostly true; 2: sometimes true; 3: mostly untrue; 4: completely untrue) according to how true each statement was perceived in the four preceding weeks. The total score is computed as the average of all answered items multiplied by 2.5. The total scores ranges from 0 to 10, with a higher score indicating the lowest impact of disease and treatment. The 'respiratory symptoms' subscore is calculated as the average of answered items 1, 4, 5, 6 and 7 multiplied by 2.5 and the 'sleep and side effects' subscore is calculated as the average of answered items 2, 3, 8, 9, 10 and 11 multiplied by 2.5.[11] Validated Dutch versions of the Clinical COPD Questionnaire (CCQ), the Chronic Respiratory Questionnaire (CRQ), the Maugeri Foundation Respiratory Failure

(MRF-28) questionnaire, and the Hospital Anxiety and Depression Scale (HADS) were used to test for construct validity of the S3-NIV questionnaire.[14,15,18-21] Patients filled in the questionnaires at home, on paper or digitally (Castor eClinical Data Management Platform). One week after completing all questionnaires, the S3-NIV questionnaire was completed a second time to assess test-retest reliability. The test conditions were similar. A one-week interval was chosen to minimalize effects on the questionnaires by infections, exacerbations COPD or other medical issues which could interfere with the results. Patients who failed to fill in all items on the questionnaires were excluded from the analyses.

Dutch translation

The Dutch S3-NIV questionnaire was composed using the existing Dutch translation of the seven questions about 'respiratory symptoms' and 'sleep quality' from the SRI questionnaire.[18,22] The remaining four questions about NIV related side effects and mask fitting were translated from the presented English variant of the S3-NIV questionnaire, respecting international WHO guidelines.[23,24] First a forward translation was performed and discussed by all investigators followed by a backward translation by an independent English and Dutch native speaking scientific translator. After pre-testing in five patients the final Dutch version was prepared.

Statistical analysis

All statistical analyses were performed using IBM SPSS software version 28. Normality was determined using the Kolmogorov-Smirnov test. Normally distributed data were described as mean with standard deviation (SD) and comparisons between different patient categories were analyzed using one-way analysis of variance including a post hoc comparison with Bonferroni correction. Non-normally distributed data were described as median and interquartile range [IQR] and comparisons between different patient categories were analyzed using the Kruskal Wallis test including a post hoc comparison with Bonferroni correction. Categorical variables were described as frequencies and compared using Pearson's chi-squared test. Cronbach's reliability coefficient α was used to assess the internal consistency of each subscale and Cronbach's α >0.7 was considered good.[25] The test-retest reliability was assessed by the intraclass correlation coefficient (ICC). Spearman correlation coefficient was used to test construct validity between comparable domains of the S3-NIV questionnaire to the other questionnaires as well as patient characteristics and ventilator settings. A *p*-value <0.05 was considered as statistically significant.

Results

Baseline characteristics

Regarding the translation process, no major issues were found and the questionnaire was adapted to the Dutch language (available in the supplementary data). A total number of 127 patients completed all questionnaires. The baseline characteristics are presented in Table 5.1.

Table 5.1 Baseline demographics and ventilation characteristics.

	COPD	**S-NMD**	**R-NMD**	**other disorders**	**total**
	n=32	**n=45**	**n=15**	**n=35**	**n=127**
Age, years	68.3 ± 7.2	56.8 ± 14.4	67.5 ± 8.2	65.2 ± 13.6	63.3 ± 12.9*
BMI, kg/m^2	27.4 ± 4.7	30.2 ± 6.8	24.5 ± 3.4	37.7 ± 11.7	30.8 ± 8.9*
Male sex, n	9 (28.1)	23 (51)	11 (73)	18 (51)	61 (48)*
NIV duration, months	42 [26, 57]	67 [34, 116]	28 [19, 48]	57 [22, 107]	45 [25, 92]*
Treatment adherence,	07:56	08:25	09:38	08:12	08:25*
hours/night	[06:38, 09:07]	[06:38, 09:07]	[08:01, 14:00]	[06:45, 08:53]	[06:45, 09:12]
IPAP, cmH_2O	24 [22, 26]	19 [16, 22]	18 [16, 20]	22 [19, 26]	20 [18, 24]*
EPAP, cmH_2O	6 [5, 7]	7 [6, 9]	7 [6, 8]	9 [7, 11]	7 [6,9]*
P_{tcCO2}, kPa	5.6 [5.2, 6.1]	5.4 [4.6, 5.6]	5.5 [5.2, 6.0]	5.4 [4.8, 5.8]	5.5 [5.0, 5.8]*
SO_2, %	94 [90, 96]	95 [94, 96]	94 [94, 97]	95 [93, 96]	95 [93, 96]*

NIV=noninvasive ventilation; COPD=chronic obstructive pulmonary disease; S-NMD=slowly progressive neuromuscular disorders; R-NMD=rapidly progressive neuromuscular disorders; BMI=body mass index; IPAP=inspiratory positive airway pressure; EPAP=expiratory positive airway pressure; P_{tcCO2}=nocturnal transcutaneous measured carbon dioxide level; SO_2=nocturnal oxygen saturation. *Note: data expressed as mean ± SD, frequency (%), median [IQR]. *Statistically significant differences between disease groups (p<0.05).*

The median time since NIV initiation was 45 months (IQR 25, 92) and patients were adherent to long-term NIV, with nocturnal transcutaneous CO_2 monitoring showing normocapnia in all groups indicating effective treatment with NIV. The S-NMD group included patients with myotonic dystrophy type 1 (15), hemi- (5) or complete diaphragmatic paralysis (4), neuralgic amyotrophy (3), spinal muscular atrophy (2), facioscapulohumeral dystrophy (2), myasthenia gravis (2), Duchenne muscular dystrophy (2), limb-girdle muscular dystrophy (2), Pompe disease (2), and other neuromuscular disorders (6). The R-NMD group included patients with ALS (12), progressive spinal muscular atrophy (2) and primary lateral sclerosis (1). The 'other disorders' group consisted of patients with OHS (20), thoracic cage disorders (8) and SRBD (7).

Distribution of the S3-NIV questionnaire

In Figures 5.1 and 5.2, the distributions of the S3-NIV scores are expressed. The entire scaling range was used without floor or ceiling effect in any subgroup. Of the total 127 patients, 80% used 38.7% of the total range, 10% had a score of <3.86 and 10% had a score >7.73. The median total S3-NIV score was 5.5 (IQR 4.3, 6.6). In Table 5.2, the S3-NIV scores per subgroup are shown.

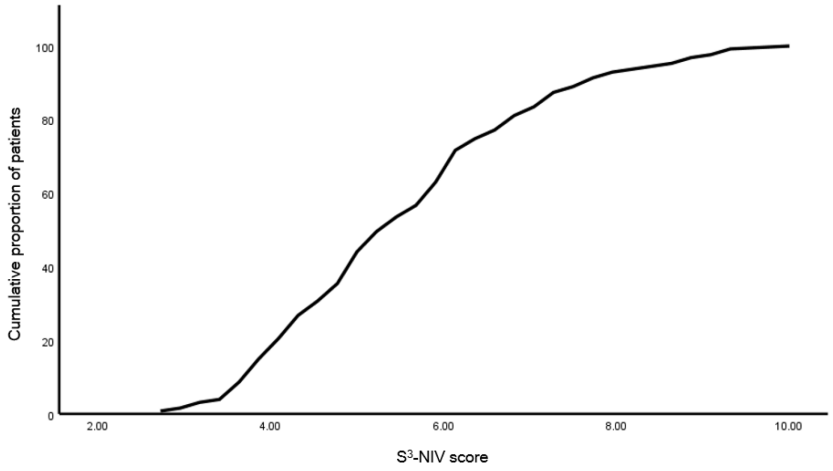


Figure 5.1 Cumulative distribution of the S3-NIV questionnaire total score for all participants.

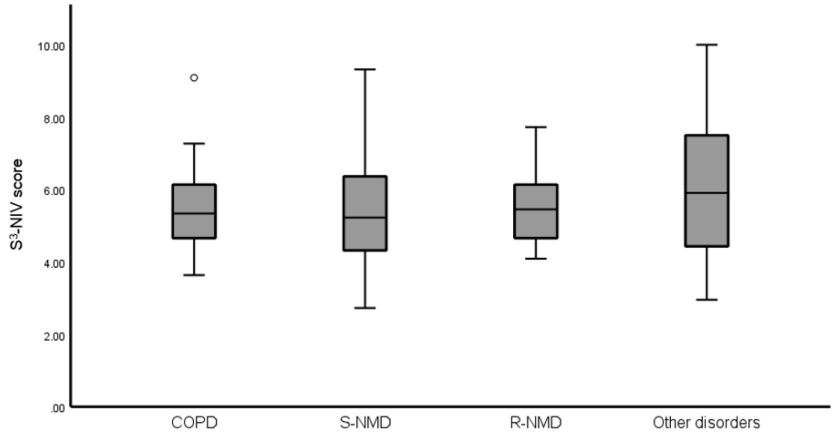


Figure 5.2 Distribution of the S3-NIV questionnaire total score stratified per diagnosis. Note the outlier score in the COPD group depicted with an open circle. COPD=chronic obstructive pulmonary disease; S-NMD=slowly progressive neuromuscular disorders; R-NMD=rapidly progressive neuromuscular disorders.

Table 5.2 S^3-NIV questionnaire (sub)scores per category.

	Total score	Respiratory symptoms subscore	Sleep and side effects subscore
COPD	5.3 [4.6, 6.1]	4.8 [3.5, 5.9]	6.3 [5.4, 7.1]
S-NMD	5.2 [4.2, 6.5]	4.5 [3.5, 6.0]	5.8 [4.8, 7.1]
R-NMD	5.5 [4.5, 6.1]	4.5 [4.0, 6.0]	6.3 [5.4, 7.5]
Other disorders	5.9 [4.3, 7.7]	5.5 [3.5, 8.0]	6.3 [5.0, 7.1]
Total	5.5 [4.3, 6.6]	4.5 [3.5, 6.0]	6.3 [5.0, 7.1]

COPD=chronic obstructive pulmonary disease; S-NMD=slowly progressive neuromuscular disorders; R-NMD=rapidly progressive neuromuscular disorders. *Note: data expressed as median [IQR].*

The S-NMD group and the 'other disorders' group had larger standard deviations than the COPD and R-NMD group, but there were no statistically significant differences between the groups.

Reliability

The internal consistency of the total score and subdomains was good, Cronbach α of 0.78 for the total score and the 'respiratory symptoms' subdomain, and 0.69 for the 'sleep and side effects' subdomain. The S^3-NIV questionnaire was completed again one week after the initial assessment by 123 patients out of 127. Despite reminders, four patients did not complete the S^3-NIV questionnaire for a second time. The ICC was 0.89 (95% CI 0.87-0.93), which indicates excellent test-retest reliability.

Construct validity of the S^3-NIV questionnaire

Table 5.3 shows the outcomes of the Spearman's rank correlation test between the S^3-NIV questionnaire and the other questionnaires (CRQ, MRF-28, HADS, and CCQ).

High correlations were found between the 'respiratory symptoms' subdomain with several subdomains of the tested questionnaires, such as the CCQ 'symptoms' and the CRQ 'dyspnea' subdomain (rho=-0.75, p<0.001, rho=0,50, p<0.001 respectively). On the contrary, only weak to moderate correlations were found between the 'sleep and side effects' subdomain with the other questionnaires. Baseline characteristics such as age, body mass index, ventilator settings, treatment adherence to NIV and CO_2 values were not correlated to the S^3-NIV scores (data not shown).

Table 5.3 Correlations between subdomains S3-NIV questionnaire and CRQ, MRF-28, HADS and CCQ.

	S3-NIV questionnaire subdomains		
	Respiratory symptoms	**Sleep and side effects**	**Total**
CRQ subdomains			
Dyspnea	0.50***	-0.05	0.33**
Fatigue	0.60***	0.29***	0.53***
Emotional	0.59***	0.28**	0.52***
Mastery	0.48***	0.19*	0.40***
MRF-28 subdomains			
Daily activity	-0.30***	0.10	-0.12
Cognitive function	-0.55***	-0.27**	-0.49***
Invalidity	-0.34***	-0.22**	-0.33***
HADS subdomains			
Anxiety	-0.51***	-0.31***	-0.49***
Depression	-0.53***	-0.23**	-0.44***
CCQ subdomains			
Symptoms	-0.75***	-0.33***	-0.67***
Functional state	-0.55***	-0.27**	-0.48***
Mental state	-0.54***	-0.24**	-0.47***

CRQ=chronic respiratory questionnaire; MRF-28=Maugeri respiratory failure questionnaire; HADS=hospital anxiety and depression scale; CCQ=clinical COPD questionnaire. *Note: * p-value <0.05; ** p-value <0.01; *** p-value <0.001.*

Discussion

This study shows that the Dutch version of the S3-NIV questionnaire has a good construct validity and reliability in a large cohort of patients using long-term NIV due to different etiologies. The S3-NIV questionnaire can be used in the entire long-term NIV population in the Netherlands and other Dutch speaking countries.

The reliability was investigated by assessing the internal consistency and test-retest reliability. The Cronbach's α coefficient of 0.78 in the present study is comparable to the original study and the first available translated (Portuguese) version (respectively 0.84 and 0.76).[11,12] In addition, this is the first study that confirms an excellent reproducibility with an ICC of 0.89 (95% CI 0.87-0.93), which is higher than in the original study (0.72, 95% CI 0.54-0.84).[11] Validity was tested by comparison of the S3-NIV questionnaire with the CRQ, MRF-28, HADS and CCQ questionnaires. The construct validity for the 'respiratory symptoms' subdomain was found to be good. However, it was difficult to test the construct validity for the 'sleep and side effects' subdomain due to the absence of a comparable (Dutch) questionnaire. For the development of the S3-NIV questionnaire the Quebec Sleep Questionnaire (QSQ) was used to validate the 'sleep and side effects' subdomain. Unfortunately, the QSQ is not

available in Dutch and there is currently no other (Dutch) questionnaire covering this domain. Moreover, there is no questionnaire containing questions on NIV related side effects. Evaluation of side effects of long-term NIV is essential because side effects negatively influence treatment adherence and are the main reason that patients discontinue NIV.[26] Taken together, the S^3-NIV questionnaire meets the need of evaluating patients-centered outcomes in long-term NIV users in a short and easy way. Additionally, long-term NIV is more frequently initiated at the patients' home using tele-monitoring and the S^3-NIV questionnaire may be a promising tool that can facilitate tele-monitoring.[27-30]

The present study included more patients with neuromuscular diseases compared to the previous studies with the S^3-NIV questionnaire, therefore better reflecting the Dutch long-term NIV population.[5,8] Remarkably, we found lower S^3-NIV scores in all patient groups compared to previous studies, indicating a higher impact of disease and treatment.[11,12] Unfortunately, additional information, such as pulmonary function tests and functional status were not available to explain these differences. A possible reason could be that this Dutch population reflects more severely affected patients, because within Europe, there are wide variations in selection criteria for initiating NIV.[5] In the Netherlands, a national guideline describes strict criteria about referral of patients and initiation of NIV, which might explain that the selected group is more severely affected.[31]

There might be some limitations to this study. Firstly, our study population represent the Dutch long-term NIV population well, but it might differ from populations elsewhere in the world, although it seems unlikely that this cohort is fundamentally different from other cohorts.[4,5] Secondly, we have chosen to translate the presented English version of the S^3-NIV questionnaire instead of the original French version as seven out of eleven questions were already available in the Dutch SRI questionnaire. To incorporate the S^3-NIV questionnaire in daily care a future longitudinal study is needed to assess cut off values and to determine the minimal clinically important difference of the questionnaire. This is needed to monitor both worsening of the underlying disorder as well as evaluating the effects of modifications in NIV settings or interfaces. In order to meet the growing demand of NIV users, who are more frequent subjected to home initiation in the Netherlands, this short and easy Dutch S^3-NIV questionnaire is an important additional tool in (tele-)monitoring.[27-30]

Conclusion

In this study, the Dutch version of the S3-NIV questionnaire has been shown to be a simple, valid and reliable tool to evaluate symptoms, sleep and NIV related side effects in long-term NIV users.

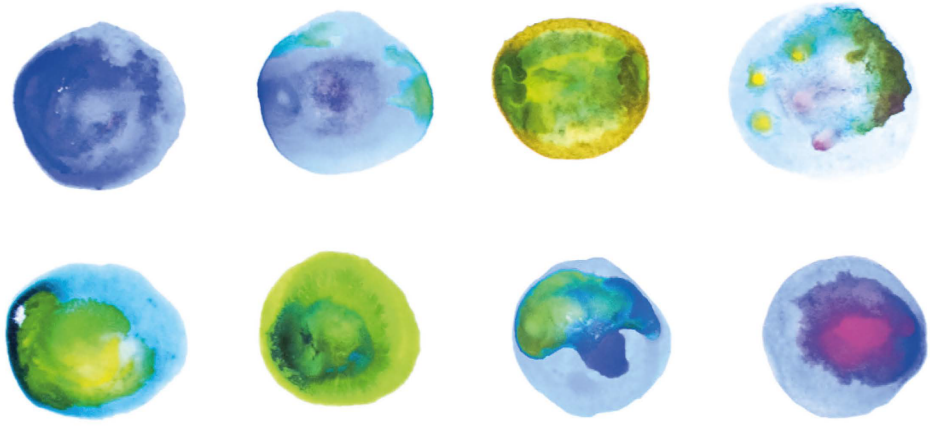
References

1. Raveling T, Vonk J, Struik FM, et al. Chronic non-invasive ventilation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2021; 8: CD002878. 2021/08/10. DOI: 10.1002/14651858.CD002878.pub3.
2. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006; 5: 140-147. 2006/01/24. DOI: 10.1016/S1474-4422(05)70326-4.
3. Janssens JP, Derivaz S, Breitenstein E, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. *Chest* 2003; 123: 67-79. 2003/01/16. DOI: 10.1378/chest.123.1.67.
4. Patout M, Lhuillier E, Kaltsakas G, et al. Long-term survival following initiation of home non-invasive ventilation: a European study. *Thorax* 2020; 75: 965-973. 20200907. DOI: 10.1136/thoraxjnl-2019-214204.
5. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005; 25: 1025-1031. 2005/06/03. DOI: 10.1183/09031936.05.00066704.
6. Simonds AK. Home Mechanical Ventilation: An Overview. *Ann Am Thorac Soc* 2016; 13: 2035-2044. 2016/08/26. DOI: 10.1513/AnnalsATS.201606-454FR.
7. D'Cruz RF, Kaltsakas G, Suh ES and Hart N. Quality of life in patients with chronic respiratory failure on home mechanical ventilation. *Eur Respir Rev* 2023; 32 2023/05/04. DOI: 10.1183/16000617.0237-2022.
8. van den Biggelaar RJM, Hazenberg A, Cobben NAM, et al. Home mechanical ventilation: the Dutch approach. *Pulmonology* 2022; 28: 99-104. 2021/12/15. DOI: 10.1016/j.pulmoe.2021.11.001.
9. Jones PW. Issues concerning health-related quality of life in COPD. *Chest* 1995; 107: 187S-193S. 1995/05/01. DOI: 10.1378/chest.107.5_supplement.187s.
10. Curtis JR, Deyo RA and Hudson LD. Pulmonary rehabilitation in chronic respiratory insufficiency. 7. Health-related quality of life among patients with chronic obstructive pulmonary disease. *Thorax* 1994; 49: 162-170. 1994/02/01. DOI: 10.1136/thx.49.2.162.
11. Dupuis-Lozeron E, Gex G, Pasquina P, et al. Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S(3)-NIV questionnaire. *Eur Respir J* 2018; 52 2018/09/29. DOI: 10.1183/13993003.011822018.
12. Ribeiro C, Conde S, Oliveira P, et al. Portuguese adaptation of the S3-non-invasive ventilation (S3-NIV) questionnaire for home mechanically ventilated patients. *Pulmonology* 2022; 28: 262-267. 2021/01/04. DOI: 10.1016/j.pulmoe.2020.11.006.
13. Gagnier JJ, Lai J, Mokkink LB and Terwee CB. COSMIN reporting guideline for studies on measurement properties of patient-reported outcome measures. *Qual Life Res* 2021; 30: 2197-2218. 20210405. DOI: 10.1007/s11136-021-02822-4.
14. Wijkstra PJ, TenVergert EM, Van Altena R, et al. Reliability and validity of the chronic respiratory questionnaire (CRQ). *Thorax* 1994; 49: 465-467. 1994/05/01. DOI: 10.1136/thx.49.5.465.
15. van der Molen T, Willemse BW, Schokker S, et al. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003; 1: 13. 2003/05/30. DOI: 10.1186/1477-7525-1-13.
16. Janssens JP, Heritier-Praz A, Carone M, et al. Validity and reliability of a French version of the MRF-28 health-related quality of life questionnaire. *Respiration* 2004; 71: 567-574. DOI: 10.1159/000081756.
17. De Braekeleer K and Toussaint M. Transcutaneous Carbon Dioxide Measurement in Adult Patients with Neuromuscular Disorders: A quality Level Assessment. *J Neuromuscul Dis* 2021; 8: 305-313. 2020/09/15. DOI: 10.3233/JND-200516.
18. Windisch W, Freidel K, Schucher B, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Clin Epidemiol* 2003; 56: 752-759. 2003/09/05. DOI: 10.1016/s0895-4356(03)00088-x.
19. Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42: 773-778. 1987/10/01. DOI: 10.1136/thx.42.10.773.

20. Carone M, Bertolotti G, Anchisi F, et al. Analysis of factors that characterize health impairment in patients with chronic respiratory failure. Quality of Life in Chronic Respiratory Failure Group. *Eur Respir J* 1999; 13: 1293-1300. 1999/08/13. DOI: 10.1183/09031936.99.13613019.
21. Spinhoven P, Ormel J, Sloekers PP, et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997; 27: 363-370. DOI: 10.1017/s0033291796004382.
22. Struik FM, Kerstjens HA, Bladder G, et al. The Severe Respiratory Insufficiency Questionnaire scored best in the assessment of health-related quality of life in chronic obstructive pulmonary disease. *J Clin Epidemiol* 2013; 66: 1166-1174. 20130705. DOI: 10.1016/j.jclinepi.2013.04.013.
23. World Health Organization. Translation methodology, https://cdn.who.int/media/docs/default-source/publishing-policies/whoqol-100-guidelines/translation-methodology.pdf?sfvrsn=74cdb8f5_2 (2020, May 3).
24. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005; 8: 94-104. 2005/04/05. DOI: 10.1111/j.1524-4733.2005.04054.x.
25. Cortina JM. What is coefficient alpha? An examination of theory and applications. *Journal of applied psychology* 1993; 78: 98.
26. Arnal JM, Texereau J and Garnero A. Practical Insight to Monitor Home NIV in COPD Patients. *COPD* 2017; 14: 401-410. 2017/03/25. DOI: 10.1080/15412555.2017.1298583.
27. van den Biggelaar R, Hazenberg A and Duiverman ML. The role of telemonitoring in patients on home mechanical ventilation. *Eur Respir Rev* 2023; 32 2023/04/06. DOI: 10.1183/16000617.0207-2022.
28. Hazenberg A, Kerstjens HA, Prins SC, et al. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. *Respir Med* 2014; 108: 1387-1395. 2014/08/02. DOI: 10.1016/j.rmed.2014.07.008.
29. Duiverman ML, Vonk JM, Bladder G, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. *Thorax* 2020; 75: 244-252. 2019/09/06. DOI: 10.1136/thoraxjnl-2019-213303.
30. van den Biggelaar RJM, Hazenberg A, Cobben NAM, et al. A Randomized Trial of Initiation of Chronic Noninvasive Mechanical Ventilation at Home vs In-Hospital in Patients With Neuromuscular Disease and Thoracic Cage Disorder: The Dutch Homerun Trial. *Chest* 2020; 158: 2493-2501. 2020/07/20. DOI: 10.1016/j.chest.2020.07.007.
31. Richtlijn Chronische beademing, https://richtlijnendatabase.nl/richtlijn/chronische_beademing/startpagina_-_chronische_beademing.html (2021).

Chapter 6

Response to noninvasive home mechanical vEntilation in Myotonic Dystrophy type 1: the multicenter REMeDY study



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Abstract

Myotonic dystrophy type 1 (DM1) frequently leads to chronic respiratory failure, yet the effectiveness of noninvasive home mechanical ventilation (HMV) remains understudied. Our objective was to assess the effects of HMV on gas exchange, health-related quality of life (HRQL), and daily functioning, and to explore baseline predictors of treatment response.

A prospective multicenter study was conducted in which clinical data, pulmonary function tests, blood gas analysis, polysomnography or nocturnal oximetry, and validated questionnaires were collected at baseline and after six months of treatment. Paired t-tests and correlation analyses assessed treatment outcomes and predictive factors.

Forty participants were enrolled. After six months of treatment, significant improvements in gas exchange were observed, including reductions in daytime (<0.4 kPa, $p=0.001$) and nocturnal pCO_2 (<0.9 kPa $p<0.001$). HRQL, assessed with the Severe Respiratory Insufficiency (SRI) questionnaire, improved significantly (>9.9 points, $p<0.001$). No significant changes were seen in daily functioning. Improvements in nocturnal pCO_2 correlated with HRQL gains ($r=0.427$, $p<0.05$), while baseline characteristics were not predictive of response.

This is the first prospective multicenter study to demonstrate that HMV improves gas exchange and HRQL in DM1, with most patients perceiving benefit despite variable treatment adherence.

Introduction

Myotonic dystrophy type 1 (DM1) is the most common form of adult-onset muscular dystrophy with a population-based estimated prevalence of 1 in 2.100, and with a reduced life expectancy of 54-60 years for adult-onset DM1.[1,2] Respiratory failure is the most frequent cause of death and is due to a complex mechanism of decreased respiratory muscle strength, reduced central respiratory drive, diminished chest wall compliance, and upper airway obstruction.[2-4] It is presumed that chronic respiratory failure in DM1 can be effectively treated with noninvasive home mechanical ventilation (HMV), but studies on this topic are scarce and mainly observational designed without predefined outcome measurements.[5] Randomized controlled trials or prospective studies are lacking. In addition, it is known that HMV is not successful in every DM1 patient, and varies greatly from a very burdensome experience in some, to a highly beneficial treatment in others. Patient selection and treatment adherence remain challenging despite consensus-based recommendations which are completely based on expert opinion rather than backed up by empirical evidence.[6] There is no general agreement on the precise definition of treatment success with regard to HMV. Prolonged survival, reduction of carbon dioxide levels (pCO_2) and improvement of oxygenation are regarded as important aims to achieve when treating patients with HMV.[7] On the other hand, from a patient's perspective it might be more important to focus on symptom relief, and enhancing or maintaining quality of life and daily functioning. Extrapolating findings from studies in other patient groups to the DM1 population is undesirable because DM1 is a very unique and heterogeneous multisystem disorder with a wide variability in symptoms, disease burden, and morbidity, therefore not easily comparable to other (neuromuscular) diseases with respiratory failure.[8] Accordingly, in this prospective multicenter study, we aimed to evaluate the effect of HMV on gas exchange, quality of life, and daily functioning in DM1 patients following six months of treatment with HMV. A secondary objective was to explore associations between baseline clinical characteristics and treatment response to HMV.

Methods

A prospective multicenter study was conducted at the four centers of HMV in the Netherlands: Maastricht, Rotterdam, Groningen and Utrecht. These four centers are responsible for all Dutch patients who need HMV. The local Medical Ethics Committee of the Maastricht University Medical Center+ (MUMC+) concluded that the study

protocol falls outside the scope of the Medical Research Involving Human Subjects Act (registration number METC2018-0853). The study was conducted according to the applicable research principles. Written informed consent was obtained from all included participants. All adult DM1 patients with an indication to start with noninvasive HMV were asked to participate. HMV indication was in accordance with the current consensus-based care recommendations for DM1 patients: at least one or more daytime or nighttime symptoms suggestive of chronic respiratory failure in combination with daytime hypercapnia ($PaCO_2$ ≥6.0 kPa) or evidence of nocturnal hypoventilation (transcutaneous PCO_2 >6.7 kPa for >50% of total sleep time).[6] Exclusion criteria included: previous treatment with Continuous Positive Airway Pressure (CPAP) or HMV in the past five years; other condition leading to hypercapnia; heart failure New York Heart Association (NYHA) classification 4; unstable angina pectoris.

Prior to initiation of HMV, extensive data was collected to characterize the study population. Demographics included CTG (cytosine-thymine-guanine) repeat length, and neurological characterization: the ordinal Medical Research Council (MRC) sum score was used to test muscular strength with a higher score indicating higher muscular strength.[9] The Muscular Impairment Rating Scale (MIRS), a DM1-specific scale for muscle weakness, was used to rate muscular impairment.[10] To assess the pulmonary function, spirometry was performed in every patient (upright sitting and supine). Arterial blood gas analysis was used to assess daytime hypercapnia. When an arterial blood gas was not available, a capillary blood gas was used as an alternative.[11] In order to detect sleep apnea and/or nocturnal hypoventilation, a polysomnography (BrainLab RT and Morpheus, Natus Group (OSG) Kontich, Belgium) was performed in a subset of participants, and an overnight pulse oximetry with transcutaneous CO_2 monitoring (Sentec, Therwil, Switzerland) was performed in the whole group.

A selection of questionnaires was filled out prior to HMV initiation. The DM1-Activ^C reflects the patients' daily activity and social participation with 100 points representing the best possible score and 0 points representing the worst possible score indicating a total limitation in activity and participation.[12] The Severe Respiratory Insufficiency (SRI) questionnaire was used to measure health-related quality of life (HRQL) with a score between 0 and 100 with higher values indicating a better HRQL.[13,14] The Fatigue and Daytime Sleepiness Scale (FDSS) measures symptoms of fatigue and daytime sleepiness with a score of 0 indicating no fatigue and daytime sleepiness, and 100 indicating severe fatigue and daytime sleepiness.[15] A visual analogue scale was used to measure perceived health on a scale of 0-100 with a higher number representing a better perceived health (EQ-VAS health). The Hospital Anxiety and Depression Scale (HADS)

was used to assess emotional functioning with a maximum score of 21 and scores of 8 or more are indicative of the possible presence of anxiety or depression.[16,17] The Care Dependency Scale (CDS) was used to determine the extent to which a patient is dependent on others for everyday tasks and self-care with a total score ranging from 15 (totally dependent) to 75 (totally independent).[18] The Caregiver Strain Index (CSI) identifies strain among caregivers with a higher score indicating higher strain (maximum score of 13).[19]

Patients were initiated on HMV at home or during a planned hospital stay, under close supervision of specialized physicians and nurses of the HMV center. Both situations are interchangeable as it was shown that initiation at home is not inferior compared to initiation at a hospital.[20] Patients were carefully followed for 6 months and after 6 months an end visit was planned. Next to spirometry, blood gas analysis, and polysomnography or overnight pulse oximetry with transcutaneous CO_2 monitoring, data were collected on treatment adherence with the ventilator, ventilator settings, and the previously mentioned questionnaires (DM1-Activ^C, FDSS, EQ-VAS health, HADS, SRI, CSI, CDS) with the addition of the S^3-NIV questionnaire. The S^3-NIV questionnaire was used to determine HMV-related side effects, symptoms and sleep quality. The lowest possible score (0) corresponds to the highest impact of disease and treatment, while the highest possible score (10) corresponds to the lowest impact of disease and treatment.[21,22]

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics software version 28. Continuous variables were expressed as mean with standard deviation or as median with 1st and 3rd quartile in case of skewed distribution. Categorical variables were expressed as count and percentage. Paired samples t-test was performed to compare BMI, pulmonary function parameters, gas exchange parameters and parameters on quality of life and daily functioning before and after six months of treatment. Bivariate correlations (Pearson's r) were conducted to assess the relationship between baseline characteristics (age, BMI, MRC sum score on muscle strength, daytime pCO_2, nocturnal pCO_2, and SRI sum score), response to HMV (delta SRI, delta daytime pCO_2, delta nocturnal pCO_2), and treatment adherence after six months of treatment. A p-value of <0.05 was considered statistically significant.

Results

Between August 2019 and September 2023, 93 patients were screened for eligibility, and 40 patients were included in the study. A flow chart of the screening procedure can be found in Figure 6.1.

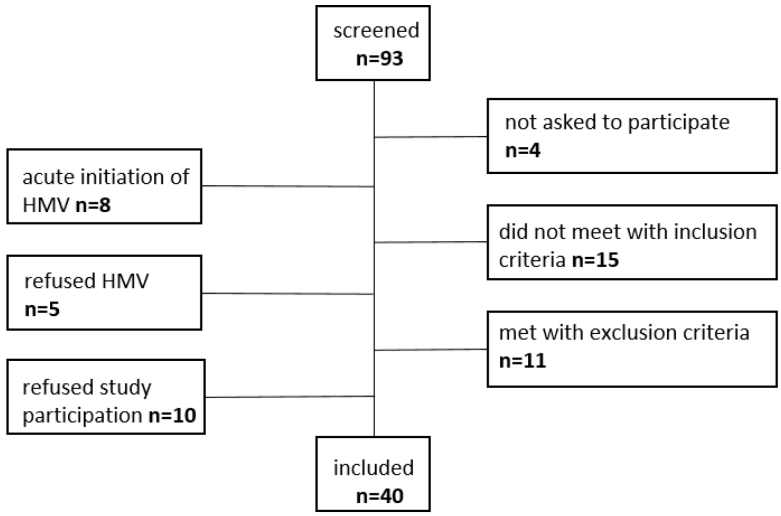


Figure 6.1 Flowchart of the screening process.

Home initiation of HMV was done in 19 patients, while 21 patients started HMV during a scheduled hospital stay. Indication for HMV was daytime hypercapnia (and nocturnal hypoventilation) in 28 patients and nocturnal hypoventilation in 12 patients. Due to difficulty in including enough patients, we decided to abandon the exclusion criterion of previously treated with CPAP or HMV halfway through the inclusion period. Prior to this adjustment, 6 patients were excluded because they used CPAP. After modification of the protocol, five patients were included that had been previously treated with CPAP or were still using CPAP at the time of inclusion. The baseline characteristics of the study sample can be found in Table 6.1. The CTG repeat length was known in 23 patients, the other 17 patients had been tested positive in the past, but the exact CTG repeat length could not be retrieved. The majority of patients had the adult subtype of DM1 (n=33), the other patients had the juvenile subtype (n=5) or congenital subtype (n=2). Twenty-three patients underwent a PSG with a diagnosis of sleep apnea in 20 patients (87%). One patient died during the follow-up period (cause of death: pancreatitis) and was excluded from the response analysis at 6 months. Another patient had to be excluded from the response analysis because of missing data at 6 months.

Table 6.1 Characteristics at baseline and response at 6 months of treatment.

Parameters	Baseline	At 6 months	p
Age	46.6 ± 14.4		
Male	25 (63%)		
BMI	25.9 ± 6.5	25.0 ± 6.4	0.665
MRC sum score on muscle strength	93.0 ± 12.6		
MIRS	4 [3-4]		
FVC sitting (% of predicted)	57.1 ± 21.2	59.2 ± 22.2	0.504
FVC supine (% of predicted)	50.6 ± 24.7	52.7 ± 26.2	0.088
Peak cough flow (L/min)	221.0 ± 69.2	214.1 ± 88.9	0.357
Daytime blood gas pCO_2 (kPa)	6.5 ± 0.75	6.1 ± 0.69	0.001*
Apnea hypopnea index (events/h)	25.6 ± 19.3	5.2 ± 5.3	<0.001*
Nocturnal mean SpO_2 (%)	91.8 ± 4.2	93.3 ± 3.6	0.001*
Nocturnal mean pCO_2 (kPa)	6.6 ± 0.73	5.7 ± 0.88	<0.001*
Maximum nocturnal pCO_2 (kPa)	7.9 ± 1.1	6.7 ± 1.0	<0.001*

BMI=body mass index, MRC= Medical Research Council, MIRS=muscular impairment rating scale, FVC=forced vital capacity, pCO_2=partial pressure of CO_2, SpO_2=peripheral oxygen saturation; *data expressed as mean ± standard deviation, frequency (%), or median [IQR]; *p<0.05*.

After six months of treatment with nocturnal HMV there was a significant improvement in gas exchange at daytime as well as at night (Table 6.1). Also, HQRL measured with the SRI questionnaire showed a significant increase after six months of HMV (Table 6.2).

Table 6.2 Questionnaires at baseline and response at 6 months of treatment.

	Baseline	At 6 months	p
DM1-Activ	53.8 ± 17.3	55.0 ± 18.7	0.981
SRI sum score	57.2 ± 7.4	67.1 ± 10.5	<0.001
FDSS	46.5 ± 9.6	44.4 ± 9.4	0.112
EQ-VAS health	61.5 ± 17.6	62.6 ± 19.5	0.401
HADS anxiety	3.4 ± 2.2	3.5 ± 2.6	0.793
HADS depression	4.5 ± 2.7	3.9 ± 3.0	0.393
CDS	62.8 ± 11.6	62.3 ± 11.3	0.328
CSI	7.4 ± 3.1	7.6 ± 3.3	0.625
S^3-NIV		6.7 ± 1.5	

FDSS=Fatigue and Daytime Sleepiness Scale, SRI=Severe Respiratory Insufficiency questionnaire, EQ-VAS=EuroQol-visual analogue scales; HADS=Hospital Anxiety and Depression Scale, CDS=Care Dependency Scale, S^3-NIV=S^3 noninvasive ventilation questionnaire; *data expressed as mean ± standard deviation; *p<0.05.*

The ventilator settings and data on treatment adherence after six months can be found in Table 6.3. Data on treatment adherence were lacking in 3 patients. The following ventilators were used: Löwenstein Prisma VENT50-C, Bad Ems, Germany (n=18), ResMed Stellar™ 150, Didcot, United Kingdom (n=10), Philips Respironics A40, Eindhoven, the Netherlands (n=9) and Philips Respironics Trilogy 100, Eindhoven, the Netherlands (n=3). Almost all patients used a full face mask with the exception of three patients who used a nose mask. Treatment adherence was variable with a majority of the patients using the HMV >80% of the days and >4h per night.

Table 6.3 Ventilator settings and treatment adherence after 6 months of treatment.

IPAP (cmH_2O)	14.7 ± 3.0
EPAP (cmH_2O)	6.1 ± 1.4
Back up rate per minute	12.7 ± 2.4
Days used (%)	66.3 ± 39.1
0-30%	8
31-79%	7
>80%	18
Average use per night	
0-2h	8
2-4h	5
>4h	22

IPAP=inspiratory positive airway pressure, EPAP=expiratory positive airway pressure; *data expressed as mean ± standard deviation.*

After six months, 34 patients were interviewed and answered questions on effect, tolerability and side effects of HMV (Table 6.4). Of the total group, 28 out of 40 patients (70%) were motivated to continue the use of HMV. The reasons for continuation were: 'because I feel better' (n=19), 'because it is good for my health' (n=27), 'because the doctor tells me to do' (n=11). Other reasons were: 'because I feel less short of breath', 'because my headaches disappeared' (n=2), 'because I participate in this research' (n=2). The patients that discontinued HMV gave as reasons: 'no benefit from the treatment' (n=5), 'unable to sleep with HMV' (n=9), 'mask problems' (n=3).

Table 6.4 Tolerability and side effects after 6 months of treatment

	Yes	**Moderate**	**No**
Fall asleep with HMV	21 (62%)	7 (21%)	6 (17%)
Sleep all night through with HMV	14 (41%)	11 (32%)	9 (27%)
Tolerate HMV all night	21 (62%)		13 (38%)
Problems with using HMV	3 (9%)		31 (91%)
Alarms	6 (18%)		28 (82%)
Technical problems	2 (6%)		32 (94%)
Mask leakage	6 (18%)	10 (29%)	18 (53%)
Mask decubitus	2 (6%)	14 (41%)	18 (53%)
Dry mouth	15 (50%)		15 (50%)
Nose obstruction	4 (14%)		25 (86%)
Aerophagia	3 (10%)	3 (10%)	23 (80%)

HMV=home mechanical ventilation; *data expressed as counts (percentage).*.

Using bivariate correlations, the change in nocturnal pCO_2 (Δ nocturnal pCO_2) was positively correlated with the change in SRI scores (Δ SRI; $r=0.427$, $p<0.05$). This suggests that patients who exhibited greater reductions in nocturnal pCO_2 following treatment also experienced more substantial improvements in their HRQL (Table 6.5). Baseline demographic and clinical characteristics were not significantly associated with treatment response to HMV (Table 6.5).

Table 6.5 Correlation between baseline characteristics and treatment response variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Age	-											
2. BMI	.126	-										
3. MRC score on muscle strength	-.528**	.079	-									
4. FVC	-.291	-.168	.644**	-								
5. Daytime pCO_2	-.060	.013	-.033	-.181	-							
6. Nocturnal pCO_2	-.065	.188	-.281	-.395*	.342*	-						
7. SRI	-.289	-.384*	-.141	.192	.094	.018	-					
8. Treatment adherence: days used	.088	.004	.183	-.120	-.057	-.140	.011	-				
9. Treatment adherence: use per night	-.028	-.026	.0002	-.057	-.040	.088	.088	.476**	-			
10. Δ SRI	.037	.270	.432*	.268	-.274	-.161	-.199	.183	.055	-		
11. Δ daytime pCO_2	.084	.096	.250	.235	.593**	-.014	-.127	-.080	-.057	-.022	-	
12. Δ nocturnal pCO_2	.124	.198	-.101	.003	-119	.323	.003	.143	.036	.427*	.182	-

BMI=body mass index, MRC= Medical Research Council, MIRS=muscular impairment rating scale, FVC=forced vital capacity, pCO_2=partial pressure of CO_2, SRI=Severe Respiratory Insufficiency questionnaire; *values represent Pearson correlation coefficients (r) with *p<0.05, **p<0.01.*

Discussion

This is the first prospective multicenter study that conclusively proves the beneficial effects of noninvasive HMV in DM1 patients with chronic respiratory failure. Six months of nocturnal HMV significantly improved both daytime and nocturnal gas exchange, as reflected by reductions in pCO_2 and increase in nocturnal oxygenation. While a positive effect of HMV on gas exchange in DM1 has been previously reported, the evidence primarily came from observational studies in small cohorts.[23-25] Moreover, in our study, there was a significant increase in HRQL measured with the SRI questionnaire, and improvements in nocturnal gas exchange were associated with better HRQL.

The use of HRQL as outcome measure has not been reported before in this context, although there has been mentioning of beneficial effects of HMV in DM1.[23,26,27] Unfortunately, we did not observe an effect on symptoms of fatigue and daytime sleepiness, as measured by the FDSS questionnaire. This may be due to the fact that these symptoms are not solely attributable to sleep-disordered breathing and respiratory failure, but likely stem from a more complex and still unclear origin, with existing evidence suggesting a central component.[28,29] Nevertheless, the majority of the patients (70%) in the current study chose to continue HMV after six months, indicating a favorable overall experience.

Treatment adherence is thought to be essential to effectively reduce pCO_2 levels, but remains an area of concern in a subset of DM1 patients. In our study, treatment adherence with HMV varied greatly between patients and was considered insufficient in 37-45%. Also in previous studies, treatment adherence is highly variable.[5,30-32] Interestingly, we did not find a correlation between treatment adherence and the improvement in gas exchange or HRQL, leaving the optimal duration of ventilator use an open question, although previous research has shown a positive effect on survival in DM1 patients with a treatment adherence of ≥5 hours per night.[33]

With regard to initiation of HMV, it was previously common practice in the Netherlands to initiate HMV during a hospital admission. However, it has since been demonstrated that home initiation is noninferior to hospital initiation regarding improvement of gas exchange and HRQL.[20] In our study, both home and hospital initiation were included, yielding comparable outcomes confirming that home initiation is a good alternative for hospital initiation, also in patients with DM1 [34,35]

In DM1, respiratory failure is typically multifactorial, arising from a combination of impaired ventilatory drive, reduced muscle strength, and upper airway

obstruction.[4,36,37] However, the relative contribution of each of these components may vary widely between individuals. Sleep apnea is very prevalent in DM1 which was confirmed in our findings with proven sleep apnea in almost 90% of the patients that underwent a PSG.[38-40] Because of the additional hypercapnia, these patients were all treated with HMV instead of CPAP, with a positive effect on the AHI. It is plausible that patients with predominant central dysregulation may respond differently to HMV than those in whom respiratory muscle weakness is the primary driver of hypoventilation.[36] Similarly, the degree of baseline pCO_2 could influence both physiological and subjective responses to HMV. Unfortunately, due to our relatively small sample size it was not possible to stratify patients based on the severity of respiratory failure, or distinguish between different underlying mechanisms of respiratory failure. Moreover, the small sample size limits the power to detect more subtle effects of predictors of response. The rarity of DM1 limited our ability to include a larger number of patients within the study period, despite a substantially higher number of individuals being screened for eligibility. Therefore, a selection bias cannot be ruled out, particularly since 10 patients (11%) declined to participate. Another limitation of our study is the relatively short follow-up period of six months. Long term results including survival data are not available at this moment. Despite these limitations, this study offers valuable clinical insights into the response to HMV in patients with DM1.

Overall, our findings indicate that the majority of patients responded favorably to HMV. However, the inherent heterogeneity of DM1 remains a significant factor influencing treatment outcomes, including the degree of treatment adherence and the extent of benefit perceived by individual patients. Integrating objective clinical parameters with patient-reported outcomes is essential to determine treatment effectiveness, along with individualized treatment strategies instead of a one-size-fits-all approach. Future research should incorporate larger patient cohorts with a longer follow-up period, and focus on detailed phenotyping at baseline in order to better predict which patients are most likely to benefit from HMV and to refine patient selection criteria.

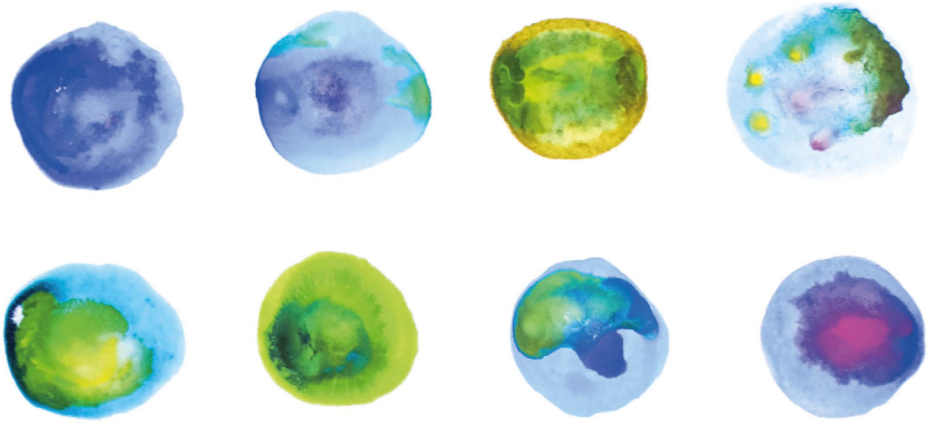
References

1. Johnson NE, et al. Population-Based Prevalence of Myotonic Dystrophy Type 1 Using Genetic Analysis of Statewide Blood Screening Program. Neurology. 2021;96(7):e1045-53.
2. de Die-Smulders CE, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998;121(Pt 8):1557-63.
3. Groh WJ, et al. Survival and CTG repeat expansion in adults with myotonic dystrophy type 1. Muscle Nerve. 2011;43(5):648-51.
4. Hawkins AM, et al. Respiratory dysfunction in myotonic dystrophy type 1: A systematic review. Neuromuscul Disord. 2019;29(3):198-212.
5. Vosse BAH, et al. Noninvasive Home Mechanical Ventilation in Adult Myotonic Dystrophy Type 1: A Systematic Review. Respiration. 2021; 100(8):816-25.
6. Boentert M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
7. Ergan B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J. 2019;54(3).
8. Wenninger S, Montagnese F, Schoser B. Core Clinical Phenotypes in Myotonic Dystrophies. Front Neurol. 2018;9:303.
9. Compston A. Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942;48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain. 2010;133(10):2838-44.
10. Mathieu J, et al. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology. 2001;56(3):336-40.
11. Zavorsky GS, et al. Arterial versus capillary blood gases: A meta-analysis. Respiratory Physiology & Neurobiology. 2007;155(3):268-79.
12. Hermans MC, et al. Reconstructing the Rasch-Built Myotonic Dystrophy Type 1 Activity and Participation Scale. PLoS One. 2015;10(10):e0139944.
13. Windisch W, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol. 2003; 56(8):752-9.
14. Struik FM, et al. The Severe Respiratory Insufficiency Questionnaire scored best in the assessment of health-related quality of life in chronic obstructive pulmonary disease. J Clin Epidemiol. 2013;66(10):1166-74.
15. Hermans MC, et al. Fatigue and daytime sleepiness scale in myotonic dystrophy type 1. Muscle Nerve. 2013;47(1):89-95.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
17. Spinhoven P, et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
18. Dijkstra A, et al. Diagnostic accuracy of the care dependency scale. J Adv Nurs. 2005;50(4):410-6.
19. Robinson BC. Validation of a Caregiver Strain Index. J Gerontol. 1983; 38(3):344-8.
20. van den Biggelaar RJM, et al. A Randomized Trial of Initiation of Chronic Noninvasive Mechanical Ventilation at Home vs In-Hospital in Patients With Neuromuscular Disease and Thoracic Cage Disorder: The Dutch Homerun Trial. Chest. 2020;158(6):2493-501.
21. Dupuis-Lozeron E, et al. Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S(3)-NIV questionnaire. Eur Respir J. 2018;52(5).
22. Seijger CG, et al. Validity and reliability of the Dutch version of the S3-NIV questionnaire to evaluate long-term noninvasive ventilation. Chron Respir Dis. 2024;21:14799731241236741.
23. Nugent AM, Smith IE, and J.M. Shneerson JM. Domiciliary-assisted ventilation in patients with myotonic dystrophy. Chest. 2002;121(2): 459-64.
24. O'Donoghue FJ, et al. Effects of 1-month withdrawal of ventilatory support in hypercapnic myotonic dystrophy type 1. Respirology. 2017.

25. Spiesshoefer J, et al. Sleep-disordered breathing and effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with myotonic dystrophy type I. Neuromuscul Disord. 2019; 29(4):302-9.
26. Monteiro R, et al. Genetics correlates with lung function and nocturnal ventilation in myotonic dystrophy. Sleep Breath. 2013;17(3):1087-92.
27. West SD, et al. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 2016;3(4):529-37.
28. Hoxhaj D, et al. Excessive daytime sleepiness in myotonic dystrophy: a narrative review. Front Neurol. 2024;15:1389949.
29. Dauvilliers YA, Laberge L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. Sleep Med Rev. 2012;16(6): 539-45.
30. Boussaid G, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord. 2016;26(10):666-74.
31. Boussaid G, et al. Effect and impact of mechanical ventilation in myotonic dystrophy type 1: a prospective cohort study. Thorax. 2018.
32. Rossi S, et al. Prevalence and predictor factors of respiratory impairment in a large cohort of patients with Myotonic Dystrophy type 1 (DM1): A retrospective, cross sectional study. J Neurol Sci. 2019;399: 118-124.
33. Seijger C, et al. New Insights in Adherence and Survival in Myotonic Dystrophy Patients Using Home Mechanical Ventilation. Respiration. 2021;100(2):154-63.
34. Sheers NL, et al. NIV@Home: a pilot randomized controlled trial of in-home noninvasive ventilation initiation compared to a single-day admission model. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26(3-4):239-48.
35. Duiverman ML, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. Thorax. 2020;75(3):244-52.
36. Poussel M, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. 2015;25(5):403-8.
37. Begin P, et al. Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. Am J Respir Crit Care Med. 1997;156(1):133-9.
38. Laberge L, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry. 2009;80(6): 642-6.
39. Bianchi ML, et al. Prevalence and clinical correlates of sleep disordered breathing in myotonic dystrophy types 1 and 2. Sleep Breath. 2014;18(3):579-89.
40. Vosse BAH, et al. Role of respiratory characteristics in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy type 1, a retrospective study. Neuromuscul Disord. 2023.

Chapter 7

General discussion



Introduction

Evidence-based guidelines do not currently exist to guide the treatment of patients with myotonic dystrophy type 1 (DM1). Consensus-based care recommendations are available and can help to standardize and improve the quality of care received by DM1 patients, and can assist clinicians who may not be familiar with the significant variability, range of symptoms, and severity of the disease.[1,2] Further research is essential to support or adjust the consensus-based care recommendations, but remains challenging because of the heterogeneity of this disease that is also described as 'one of the more variable diseases found in medicine'.[1]

Short outline of this thesis

The current thesis focused on different aspects of home mechanical ventilation (HMV) in patients with DM1, with the objective to enhance the understanding of HMV treatment in DM1 and with the main goal to further optimize respiratory care for the individual DM1 patient. After providing a detailed review on the existing knowledge about HMV in DM1, we investigated the influence of different factors on treatment adherence with HMV. Respiratory characteristics as well as cognition, affective symptoms, and apathy were studied in patients with DM1. In addition, we assessed the validity and reliability of the Dutch version of the S^3-questionnaire, suitable to evaluate symptoms, sleep, and side effects in all patients with noninvasive HMV. We concluded this thesis with our prospective, multicenter REMeDY study (**R**esponse to noninvasive home mechanical v**E**ntilation in **M**yotonic **DY**strophy type 1) in which we assessed the treatment response to HMV in DM1 patients.

Medical care for DM1 patients

Despite being the most common form of adult-onset muscular dystrophy, with a population-based estimated prevalence of 1 in 2.100, DM1 is still considered a rare disease, and not all individuals affected by DM1 are accurately diagnosed or receive appropriate follow-up care.[3] Patients with a rare disease should ideally be treated by specialized multidisciplinary teams of experts within a center of expertise. Not only will this be beneficial for the individual patient, it also offers opportunities for conducting scientific research on clinically relevant topics. In the Netherlands, care for patients with DM1 is centralized within two specialized centers of expertise that work in close

collaboration: Maastricht University Medical Center+ (MUMC+) in Maastricht, and Radboud University Medical Center in Nijmegen. In these centers, clinical care is successfully combined with research purposes. In the MUMC+, all DM1 patients are referred to the pulmonologist of the expertise center for respiratory evaluation. In addition, DM1 patients from the region that are in need for ventilatory support are referred to the Center of Home Mechanical Ventilation of the MUMC+.

Proactive screening for respiratory dysfunction in DM1

The proactive referral strategy of DM1 patients to the pulmonologist of the DM1 expertise center or the Center of Home Mechanical Center of the MUMC+ has enabled the research conducted in **Chapter 3** where we could use the results of a pulmonary function test, a polysomnography, and a blood gas measurement of 200 individual DM1 patients. Over half of the patients exhibited a restrictive pattern on pulmonary function testing, and 85% were diagnosed with sleep apnea, although a considerable number did not report typical symptoms of respiratory dysfunction, emphasizing the need for proactive screening. Conversely, it is debatable whether asymptomatic abnormalities such as asymptomatic sleep apnea should be treated. Although observational studies have shown independent associations between sleep apnea and cardiovascular events, randomized controlled trials have not consistently demonstrated that positive airway pressure therapy provides clear cardiovascular benefits.[4,5] However, given the high rates of cardiac morbidity and mortality in DM1 patients, there is additional justification for considering treatment of asymptomatic sleep apnea in this population.[6] In the DM1 population described in **Chapter 3**, noninvasive HMV was liberally offered for patients with sleep apnea and/or respiratory failure. This resulted in low treatment adherence in 62% of the 101 DM1 patients that started with HMV. Given the high rate of low treatment adherence—effectively a form of treatment failure—it was essential to further investigate the underlying causes which will be addressed later in this general discussion.

Treatment of respiratory dysfunction in DM1

Timely diagnosis of respiratory dysfunction allows for early interventions. Although definitive evidence on the usefulness of early respiratory treatment in DM1 is limited, case reports and experience from other neuromuscular disorders suggest that early management is recommended.[7,8] Manual and/or mechanical cough assistance

techniques such as air stacking techniques, or the mechanical insufflator/exsufflator (MI-E) are indicated for DM1 patients having ineffective cough and recurrent respiratory infections.[2] However, reimbursement for the costly MI-E machines is not formally regulated in the Netherlands, and this, amongst other factors, limits their use in DM1 patients. The effectiveness of inspiratory muscle training (IMT) with regard to improvement or stabilization of respiratory muscle strength is still a matter of debate in DM1, although positive effects have been described and research on the topic is ongoing.[8,9]

Indications for noninvasive HMV in DM1

According to the 207th European Neuromuscular Centre Workshop (2015), noninvasive HMV should be initiated when there is at least one or more daytime or nighttime symptoms suggestive of chronic respiratory failure in combination with:
- daytime hypercapnia, pCO_2 ≥6.0 kPa *or*
- forced vital capacity <50% of predicted based on the best of three measures and maximum inspiratory pressure <60 cm H_2O *or*
- evidence of nocturnal hypoventilation.[10]

Although these criteria seem feasible and easy to apply, the matter of 'symptoms suggestive of chronic respiratory failure' is not so straightforward in patients with DM1. Symptoms of fatigue and daytime sleepiness are very common in patients with DM1, also in patients *without* respiratory failure. These symptoms are probably not solely attributable to respiratory failure and sleep-disordered breathing, but likely stem from a more complex and still unclear origin.[11] Secondly, the long duration of respiratory muscle disease is such that the body adapts to daytime hypercapnia and nocturnal hypoventilation and therefore, classical symptoms of respiratory failure will not always be perceived by patients with DM1. Lastly, the reduced insight and avoidant or passive personalities these patients may have, can contribute to the lack of complaints in the respiratory domain.[12,13]

Effects of HMV in DM1

Both daily clinical practice and scientific literature have raised questions regarding the effectiveness of HMV in DM1, as well as concerns about treatment adherence in these patients.[14,15] In **Chapter 2** of this thesis, we presented a comprehensive systematic

review on the effects of noninvasive HMV in DM1, providing insights into this insufficiently understood topic and outlining directions for future research in the field. Although we observed some evidence of favorable outcomes in terms of gas exchange and symptom relief, these findings were derived from small observational studies lacking predefined outcome measures. Since HMV has been offered to DM1 patients for more than 20 years, it may be considered unethical to perform a randomized controlled trial to answer questions about treatment response and treatment adherence. However, it became evident that further research was needed to establish the effects of HMV in DM1. In addition, there was a need for greater insight into which patients benefited most from HMV.

Treatment response and outcome measures

Objective outcome measures, standardized assessment scales and validated questionnaires can help clinicians and researchers to evaluate effects of treatment. For the evaluation of the effects of HMV it is necessary to use a combination of objective clinical outcomes next to a more subjective patient-reported outcome measure (PROM). Survival and gas exchange are objective clinical measurements, but health-related quality of life (HRQL) and daily functioning might be even more important from patients' point of view. The Severe Respiratory Insufficiency questionnaire is available to measure specific HRQL in patients receiving noninvasive HMV.[16] In addition, a specific PROM was recently developed to evaluate symptoms, sleep, and side effects in HMV users.[17] In order to be able to apply this S^3-NIV questionnaire in a Dutch setting, we translated the questions and conducted a study for validation and reliability as presented in **Chapter 5**. Long-term HMV users were included with different underlying diseases as cause for respiratory failure: slowly progressive neuromuscular disorders (including DM1), rapidly progressive neuromuscular disorders, chronic obstructive pulmonary disease, and other diseases such as obesity hypoventilation syndrome. Future research on noninvasive HMV should definitely incorporate this new questionnaire, as it holds promise not only for clinical studies but also for routine use in evaluating HMV in everyday practice. It would be specifically interesting to assess cut off values and to determine the minimal clinically important difference. Exploring its applicability in everyday care is especially relevant in light of emerging developments in telemonitoring. As HMV becomes more widely adopted and technologically advanced, health care systems are concurrently experiencing a declining workforce. The integration of telemonitoring presents a promising approach to addressing this challenge. Nevertheless, several hurdles remain. The large volumes of data produced

must be securely stored with full protection of patient privacy. Continuous monitoring and interpretation—ideally supported by artificial-intelligence algorithms—are required, and the resulting clinical actions must be implemented without placing undue strain on the already limited healthcare workforce.[18,19]

In our multicenter, prospective REMeDY study—described in **Chapter 6**—we aimed to capture a comprehensive view of the effects of HMV in patients with DM1. To achieve this, we included a range of outcome measures, such as gas exchange, HRQL, and daily functioning. Overall, treatment with HMV led to improvements in gas exchange and HRQL. However, the response was not uniform across all patients. Unfortunately, we were unable to clearly differentiate between 'responders' and 'non-responders', which may be attributed to the small sample size and the considerable clinical variability inherent to the disease. The underlying cause of respiratory failure may be a significant factor. In some cases, it is primarily driven by respiratory muscle weakness, while in others, central dysregulation and sleep apnea play a more dominant role.[20,21] While treatment of sleep apnea in the general population typically leads to a reduction in daytime sleepiness and improvements in HRQL, this effect is less evident in patients with DM1.[22] In many individuals with DM1, even when apneas are effectively reduced, symptoms do not improve to the same extent. This may be partly attributed to the underlying etiology of the sleep apnea, as obstructive sleep apnea is typically more amenable to treatment than central sleep apnea which is frequently found in DM1 as we saw in **Chapter 3**.[23] Moreover, the symptoms experienced by patients with DM1, such as fatigue and excessive daytime sleepiness, are likely attributable to factors beyond sleep-disordered breathing alone.[11]

Treatment adherence with HMV in DM1

Treatment adherence is essential to effectively reduce pCO_2 levels, but is an area of concern in a subset of DM1 patients. As outlined in our review in **Chapter 2**, treatment adherence in DM1 varies widely, with reported usage ranging from complete non-use to 2–12 hours per night.[15,24-26] In our REMeDY study (**Chapter 6**), treatment adherence after six months varied, with 37–45% of patients demonstrating low adherence. In **Chapter 3**, we reported a discontinuation rate of 38% and low adherence in 24% of patients after one year of treatment. In **Chapter 4**, 8% of DM1 patients discontinued treatment, while 27% showed low adherence.

Based on the assumption that patients with more severe respiratory dysfunction would rely more heavily on ventilatory support, we conducted the retrospective study presented in **Chapter 3**. However, respiratory parameters did not predict treatment adherence in patients with DM1. A key reason for discontinuation was the lack of perceived symptom improvement by patients. This supports previous findings that individuals with more pronounced symptoms of respiratory failure are more likely to adhere to treatment.[15] In clinical practice, some patients present with severe pulmonary function restriction and/or respiratory failure despite the absence of overt symptoms. Due to the slow progression of respiratory muscle involvement in DM1, the body may gradually adapt to chronic daytime hypercapnia and nocturnal hypoventilation, leading patients to under recognize or not perceive classical symptoms of respiratory failure.[27] Additionally, reduced disease insight (anosognosia) commonly seen in this population may further contribute to the lack of reported respiratory complaints.[28] Alongside anosognosia, DM1 patients often exhibit other features that may influence treatment adherence such as cognitive impairment and apathy.[29-31] Despite the high prevalence of cognitive impairment (40%) and apathy (77%) observed, no association with treatment adherence was found, as described in **Chapter 4**. These findings counter the assumption often encountered in clinical practice that cognitively impaired patients with DM1 are unlikely to adhere to treatment. The presence of cognitive impairment should not be a reason to withhold HMV treatment. Treatment adherence can also be affected by a patient's living situation. For example, does the patient live alone, or with an informal caregiver who encourages the use of HMV? Is the patient in a care facility where healthcare professionals ensure therapy is followed? These factors should be considered when starting HMV and explored again if treatment adherence proves to be low. In addition, peripheral muscle weakness—particularly involving the hands and arms—combined with myotonia may make it challenging for patients to position the ventilation mask on the face.

Towards better treatment adherence to HMV in DM1

Although the variety in treatment adherence to HMV in DM1 is not yet fully understood, this should not prevent us from actively seeking ways to optimize it in the meantime. In the Netherlands, HMV is uniquely organized, with only four specialized centers responsible for all patients requiring this form of care. Nationwide criteria for referral and initiation of HMV are outlined in a national guideline, and a distinctive national learning management system is developed to support caregivers and healthcare professionals.[32] This system provides an ideal foundation for improving

treatment adherence in DM1 patients, though achieving this will be complex given the multisystemic nature of the disease, encompassing cognitive, behavioral, and respiratory involvement next to muscle weakness. However, several strategies can be considered to move forward. A key starting point is patient-centered education and personalized communication. Clearly explaining the benefits of treatment and actively involving family members or caregivers in discussions is essential. Additionally, screening for cognitive impairment and apathy can support a more individualized approach to care. From recent literature and from our own findings in **Chapter 6**, we know that home initiation of HMV is a feasible alternative to hospital-based initiation and is likely more comfortable for DM1 patients, offering greater opportunity for personalized support and guidance.[33] Accessible follow-up care—including low-threshold monitoring, potentially supported by telemonitoring, and readily available assistance from the home ventilation center—is essential in the post-initiation phase. Early identification of low treatment adherence creates opportunities to intensify follow-up and provide additional support, possibly with the involvement of informal caregivers in the patient's immediate environment. Finally, if HMV treatment proves unsuccessful despite the best efforts of the patient and their formal and informal caregivers, it is important to address this openly with the patient. In some cases, it may be more appropriate to jointly decide to discontinue treatment rather than continue a burdensome trajectory that offers no clear benefit. Importantly, this decision should leave room for a future attempt if the patient becomes motivated again. Particularly in patients with unsuccessful HMV trajectories and severe, life-threatening respiratory failure—but ideally in all DM1 patients with respiratory involvement—advanced care planning and palliative care should be integrated as valuable components to enhance overall care.

Future perspectives

The first step in considering future perspectives on HMV in DM1 is to define the most important goals, with the patient's perspective playing a central role. Subjective outcomes, such as relief of symptoms and enhancement of HRQL, should be valued as highly as improvements in gas exchange, since patients are more likely to adhere to treatment when they notice a meaningful change in how they feel. In addition, greater attention should be given to identifying which patients are most likely to benefit from HMV. The current literature does not yet allow us to reliably predict, in advance, who will respond well to this treatment. Gaining clearer insight into this area is essential, as initiating an expensive and burdensome therapy that ultimately proves to be ineffective

is undesirable for both the patient and society. Due to the heterogeneity of the disease, research in this area is challenging and will require large patient cohorts to adequately address these questions. In the future, extensive databases such as MYODRAFT, END-DM1, and DMScope may contribute to more precise patient phenotyping and improved prediction of treatment response, potentially supported by artificial intelligence.[34,35]

In patients with hypercapnia, it is crucial to distinguish between elevated pCO_2 levels resulting from respiratory muscle weakness and those caused by impaired central regulation of breathing. As is well established, HMV is an effective treatment for hypercapnia resulting from respiratory muscle weakness.[36] However, in cases where hypercapnia arises from impaired central regulation of breathing, the clinical significance of the elevated carbon dioxide levels remains uncertain. It is not yet clear how harmful this form of hypercapnia is, nor what the most appropriate and effective treatment strategies might be for these patients. Diaphragm pacing represents an intriguing area for further exploration, given its potential benefits in conditions such as congenital central hypoventilation syndrome and certain spinal cord injuries.[37,38] However, clinical trials in ALS have shown potential harm, and to date, no studies have demonstrated its use in neuromuscular diseases including DM1.[39] Patients who exhibit hypercapnia despite normal respiratory muscle strength could represent a particularly interesting subgroup in which to evaluate this intervention. In patients with predominantly respiratory muscle weakness, treatment should be directed at this specific aspect of the disease, incorporating interventions such as cough assistance techniques and, where appropriate, inspiratory muscle training (IMT). Although IMT has been studied only in small cohorts of individuals with DM1, it may offer benefit—particularly as patients often seek strategies they can implement themselves to help preserve their respiratory muscle strength at the highest possible level.[8,9]

Finally, from this thesis it has become clear once more that the heterogeneity of DM1 clearly precludes a ‘one-size-fits-all’ approach to respiratory care of DM1 patients. Future research should aim to refine and individualize respiratory management in DM1, guided by standardized and patient-centered outcomes. In daily practice, incorporating telemonitoring and digital health tools will be essential to support treatment adherence with HMV and enable timely interventions. Finally, integrating advance care planning and palliative care into respiratory management—particularly for patients with a poor prognosis or limited response to treatment—will help ensure that care remains both effective and aligned with the patient’s values.

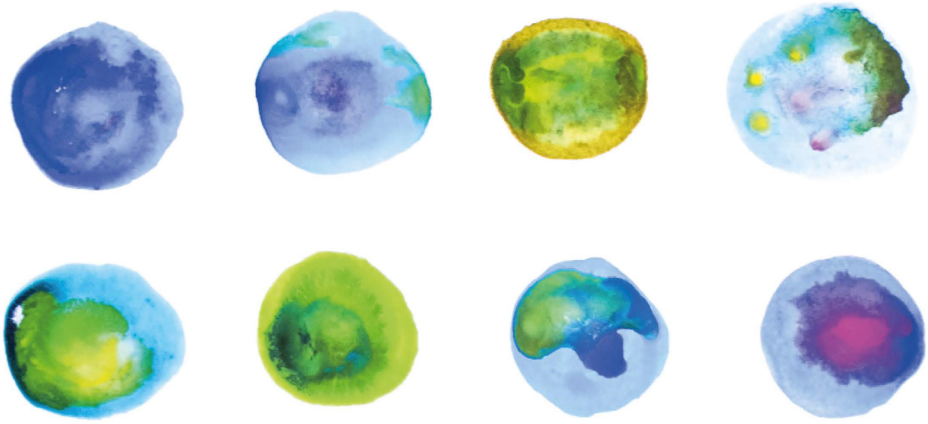
References

1. Ashizawa T, et al. Consensus-based care recommendations for adults with myotonic dystrophy type 1. Neurol Clin Pract. 2018;8(6):507-20.
2. Boentert M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
3. Johnson NE, et al. Population-Based Prevalence of Myotonic Dystrophy Type 1 Using Genetic Analysis of Statewide Blood Screening Program. Neurology. 2021;96(7):e1045-53.
4. Cohen O, et al. The Great Controversy of Obstructive Sleep Apnea Treatment for Cardiovascular Risk Benefit: Advancing the Science Through Expert Consensus. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2024;22(1):1-22.
5. Kundel V, et al. Insights, recommendations, and research priorities for central sleep apnea: report from an expert panel. J Clin Sleep Med, 2025;21(2):405-16.
6. Petri H, et al. Cardiac manifestations of myotonic dystrophy type 1. Int J Cardiol. 2012;160(2):82-8.
7. Terzano C, Romani S. Early use of non invasive ventilation in patients with amyotrophic lateral sclerosis: what benefits? Eur Rev Med Pharmacol Sci. 2015;19(22):4304-13.
8. Seijger CGW, et al. Benefits of Inspiratory Muscle Training in Myotonic Dystrophy: A Case Report. Arch Bronconeumol. 2024;60(5):296-7.
9. Seijger CGW, et al. Effective IMT Starts With a Feasible Training Protocol and Identification of Clinical Relevant Outcome Parameters. Arch Bronconeumol. 2024;60(5):326.
10. Sansone VA, Gagnon C, Participants of the 207th, 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: management and implications for research, 27-29 June 2014, Naarden, The Netherlands. Neuromuscul Disord. 2015;25(5):432-42.
11. Hoxhaj D, et al. Excessive daytime sleepiness in myotonic dystrophy: a narrative review. Front Neurol. 2024;15:1389949.
12. Meola G, et al. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2). Neuromuscul Disord. 2003;13(10):813-21.
13. Meola G, Sansone V. Cerebral involvement in myotonic dystrophies. Muscle Nerve. 2007;36(3):294-306.
14. Fiorentino G, Esquinas AM. Non invasive mechanical ventilation in myotonic dystrophy type 1? Hypoventilation versus quality of life perspective. Neuromuscul Disord. 2018;28(2):193.
15. Boussaid G, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: A prospective cohort. Neuromuscul Disord. 2016;26(10):666-74.
16. Windisch W, et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol. 2003; 56(8):752-9.
17. Dupuis-Lozeron E, et al. Development and validation of a simple tool for the assessment of home noninvasive ventilation: the S(3)-NIV questionnaire. Eur Respir J. 2018;52(5).
18. van den Biggelaar R, Hazenberg A, Duiverman ML. The role of telemonitoring in patients on home mechanical ventilation. Eur Respir Rev. 2023;32(168).
19. Bianquis C, et al. Relevance of telemonitoring algorithms for the management of home noninvasive ventilation. ERJ Open Res. 2025;11(2).
20. Begin P, et al. Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. Am J Respir Crit Care Med. 1997;156(1):133-9.
21. Poussel M, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. 2015;25(5):403-8.

22. Patil SP, et al. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2019;15(2):301-34.
23. Pinto A, et al. Non-invasive positive pressure ventilation for central sleep apnoea in adults. Cochrane Database Syst Rev. 2022;10(10):CD012889.
24. Nugent AM, Smith IE, Shneerson JM. Domiciliary-assisted ventilation in patients with myotonic dystrophy. Chest. 2002;121(2):459-64.
25. Monteiro R, et al. Genetics correlates with lung function and nocturnal ventilation in myotonic dystrophy. Sleep Breath. 2013;17(3):1087-92.
26. West SD, et al. Sleepiness and Sleep-related Breathing Disorders in Myotonic Dystrophy and Responses to Treatment: A Prospective Cohort Study. J Neuromuscul Dis. 2016;3(4):529-37.
27. Thil C, et al. Longitudinal course of lung function in myotonic dystrophy type 1. Muscle Nerve. 2017.
28. Baldanzi S, et al. Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study. Orphanet J Rare Dis. 2016;11:34.
29. van der Velden BG, et al. Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. J Affect Disord. 2019;250:260-9.
30. Okkersen K, et al. The cognitive profile of myotonic dystrophy type 1: A systematic review and meta-analysis. Cortex. 2017;95:143-55.
31. Patout M, et al. Cognitive Function in Patients with Chronic Respiratory Failure: Effect of Treatment with Home Noninvasive Ventilation. Am J Respir Crit Care Med. 2023;208(8):900-3.
32. van den Biggelaar RJM, et al. Home mechanical ventilation: the Dutch approach. Pulmonology. 2022; 28(2):99-104.
33. van den Biggelaar RJM, et al. A Randomized Trial of Initiation of Chronic Noninvasive Mechanical Ventilation at Home vs In-Hospital in Patients With Neuromuscular Disease and Thoracic Cage Disorder: The Dutch Homerun Trial. Chest. 2020;158(6):2493-501.
34. De Antonio M, et al. The DM-scope registry: a rare disease innovative framework bridging the gap between research and medical care. Orphanet J Rare Dis. 2019;14(1):122.
35. la Fontaine LA, et al. Comprehensive four-year disease progression assessment of myotonic dystrophy type 1. Neuromuscul Disord. 2024;43:44-52.
36. Annane D, et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2000(2):CD001941.
37. Diep B, et al. Diaphragm Pacing without Tracheostomy in Congenital Central Hypoventilation Syndrome Patients. Respiration. 2015;89(6):534-8.
38. Wijkstra PJ, et al. Diaphragm Pacing in Patients with Spinal Cord Injury: A European Experience. Respiration. 2022;101(1):18-24.
39. McDermott CJ, et al. DiPALS: Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis - a randomised controlled trial. Health Technol Assess. 2016;20(45):1-186.

Chapter 8

Summary
Nederlandse samenvatting
Impact paragraph
Dankwoord
Curriculum vitae
List of publications



Summary

Myotonic dystrophy type 1 (DM1) is a hereditary disorder characterized by progressive muscle weakness, myotonia (delayed muscle relaxation), and multisystemic organ involvement including respiratory dysfunction due to respiratory muscle weakness and central respiratory drive dysfunction. This can lead to respiratory failure which is the most common cause of death in DM1. Respiratory failure can be treated with noninvasive home mechanical ventilation (HMV), but clinical research on HMV in DM1 is scarce, and consensus-based recommendations are mainly based on expert opinion rather than empirical evidence. Therefore, the aim of this thesis was to enhance the understanding of HMV treatment in DM1 with the main goal to further optimize respiratory care for the individual DM1 patient.

Chapter 2 consists of a systematic review on the effects of noninvasive HMV on gas exchange, quality of life and survival in DM1 patients. Also, treatment adherence with HMV was evaluated. Nine studies were included, all with a quantitative design, representing 385 individual patients. No randomized controlled trials were found on the topic and the overall quality and usefulness of the individual studies was limited. Pooled data on the gas exchange of 3 studies showed an overall positive effect on pCO_2, pO_2, and SpO_2. Health-related quality of life (HRQL) was not systematically studied, but beneficial effects of HMV were mentioned in some studies. One study provided some evidence for a possible survival benefit for DM1 patients on HMV. In this study, survival was compared in patients who accepted HMV promptly with those who refused or delayed HMV, a study design with a high chance of bias. Six studies described treatment adherence with HMV, but these were difficult to summarize due to differences in definitions and measuring methods. Average use of HMV ranged from 3.4h/day to 8h/day. Discontinuation of HMV happened in 20-54% of the DM1 patients. *Our overall conclusion was that HMV in DM1 can improve gas exchange and relieve symptoms with a possible survival benefit although the evidence is limited.*

In **Chapter 3** we aimed to evaluate the role of the respiratory characteristics in DM1, with regard to treatment adherence with HMV. Therefore, a retrospective data study was carried out, including 200 DM1 patients that were referred for respiratory analysis. Pulmonary function tests as well as blood gas values and data on nocturnal respiration (polysomnography) were collected. HMV was started in 101 patients and their treatment adherence was reviewed after one year. High treatment adherence was defined as a daily use of the ventilator for at least 5 hours per night (n=38). Patients with low treatment adherence were grouped with the patients that discontinued HMV

(n=68). The low and high treatment groups were compared with regard to their baseline characteristics of the respiratory variables, but no difference was found between the groups. Also, we did not find a predictor for high or low treatment adherence within our predefined variables including gender, age, body mass index (BMI), CTG (cytosine-thymine-guanine) repeat length, forced vital capacity (FVC), daytime pCO_2, nocturnal pCO_2 and apnea hypopnea index (AHI). *From this study we concluded that the respiratory characteristics are not associated with treatment adherence with HMV in DM1 and cannot be used to identify patients at risk for low treatment adherence.*

In **Chapter 4** we continued our search to identify factors that influence treatment adherence with HMV in DM1. Cognitive impairment, affective symptoms, and apathy are known to be major predictors of poor treatment adherence in general. Although these features are described as highly prevalent in DM1, they had not been studied with regard to treatment adherence in general, nor specifically in treatment adherence with HMV. Therefore, a cross-sectional study was conducted including 60 patients with DM1 that were being treated with HMV, or that had recently stopped with HMV. By means of tests and questionnaires, we measured cognitive functioning (Montreal Cognitive Assessment, MoCA), affective symptoms (Hospital Anxiety and Depression Scale, HADS), and degree of apathy (Apathy Evaluation Scale, AES). Abnormal scores were found in 40% of the patients for the MoCA, and in up to 77% for the AES, whereas a minority of patients showed abnormal scores for the HADS anxiety (30%) and HADS depression (18%). The scores were equally distributed over the groups with low and high treatment adherence with HMV, except for the HADS anxiety score, which was significantly higher in the group with low treatment adherence. We did not find a significant influence of living situation, care dependency (measured with the Care Dependency Scale), or HMV related side effects (measured with the S^3-NIV questionnaire). *From this study we concluded that although cognitive impairment and apathy are frequently present in DM1 patients on HMV, its effect on treatment adherence is limited, and therefore HMV should not be withheld in patients with cognitive impairment or signs of apathy.*

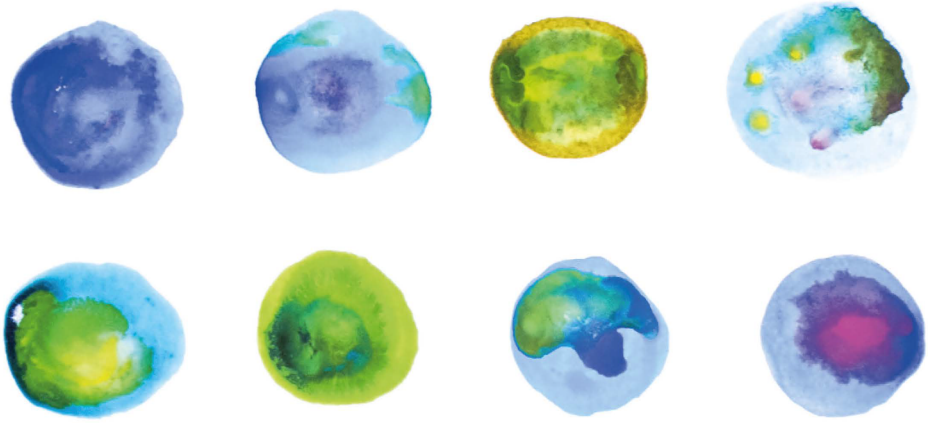
Chapter 5 provides a Dutch translation and evaluation of the S^3-NIV questionnaire which was originally developed in France. This questionnaire for patients on noninvasive ventilation (NIV) contains eleven short questions which cover three patient-oriented dimensions related to NIV: respiratory symptoms, sleep quality, and NIV related side effects. We included 127 stable long-term NIV users with different underlying diseases including DM1. Internal consistency of the questionnaire was good

(Cronbach's α coefficient of 0.78) and the reproducibility was excellent with an intraclass correlation of 0.89. *We concluded that the S_3-NIV questionnaire is a reliable and valid Dutch tool to evaluate symptoms, sleep, and NIV related side effects in long-term NIV users.*

Chapter 6 shows the results of our prospective, multicenter study on response to noninvasive HMV in DM1 (REMeDY study). The objective of the study was to assess the effects of HMV on gas exchange, HRQL, and daily functioning, and to explore baseline predictors of treatment response. Forty DM1 patients initiated HMV and were included in the study after extensive characterization with clinical data, pulmonary function tests, blood gas analysis, polysomnography or nocturnal oximetry with transcutaneous pCO_2 measuring, and a set of validated questionnaires. After six months of treatment, significant improvements in gas exchange were observed, including reductions in daytime and nocturnal pCO_2. HRQL, assessed with the Severe Respiratory Insufficiency (SRI) questionnaire, improved significantly, and improvements in nocturnal pCO_2 correlated with HRQL gains. No significant changes were seen in daily functioning (measured with the DM1-Activ^C) or with regard to fatigue and daytime sleepiness (measured with the Fatigue and Daytime Sleepiness Scale), but 70% of the participants were motivated to continue the use of HMV. We did not find correlations between baseline characteristics and treatment response. Treatment adherence with HMV varied greatly between patients and was considered insufficient in 37-45%. *In conclusion, this is the first prospective multicenter study that demonstrated that HMV improves gas exchange and HRQL in DM1, with most patients perceiving benefit despite variable treatment adherence. It is not possible to predict treatment response prior to the initiation of HMV.*

In **Chapter 7** the results of this thesis are discussed, put in a broader perspective, and directions for future research are provided.

Chapter 8



Nederlandse samenvatting

Myotone dystrofie type 1 (DM1) is een erfelijke aandoening die wordt gekenmerkt door progressieve spierzwakte, myotonie (vertraagde spierontspanning) en systemische betrokkenheid, waaronder problemen met de ademhaling als gevolg van zwakte van de ademhalingsspieren en het disfunctioneren van de centrale besturing van de ademhaling. Dit kan leiden tot respiratoir falen, wat de meest voorkomende doodsoorzaak is bij DM1. Respiratoir falen kan worden behandeld met non-invasieve thuisbeademing, maar klinisch onderzoek naar thuisbeademing bij DM1 is beperkt, en de aanbevelingen die in de wetenschappelijke literatuur worden beschreven, zijn voornamelijk gebaseerd op de meningen en ervaringen van klinische experts in plaats van op wetenschappelijk bewijs. Daarom was het doel van dit proefschrift om de kennis te vergroten over thuisbeademing bij DM1, met als voornaamste streven de zorg voor de individuele DM1-patiënt verder te optimaliseren.

Hoofdstuk 2 omvat een systematisch literatuuroverzicht van de effecten van thuisbeademing op de gasuitwisseling, kwaliteit van leven en overleving bij DM1 patiënten. Ook werd therapietrouw geëvalueerd. Negen studies werden geïncludeerd, allemaal kwantitatief van aard, met in totaal 385 individuele patiënten. Er werden geen gerandomiseerde gecontroleerde onderzoeken gevonden en de algehele kwaliteit en bruikbaarheid van de individuele studies was beperkt. Gecombineerde gegevens over de gasuitwisseling van drie studies toonden een positief effect op pCO_2, pO_2 en SpO_2. Kwaliteit van leven werd niet systematisch bestudeerd, maar positieve effecten van thuisbeademing werden in sommige studies genoemd. Eén studie toonde enig bewijs voor een mogelijk overlevingsvoordeel voor DM1 patiënten met thuisbeademing, door de overleving te vergelijken tussen patiënten die direct met thuisbeademing begonnen met degenen die thuisbeademing weigerden of uitstelden, een onderzoeksopzet met een hoge kans op bias. Zes studies beschreven therapietrouw, maar deze waren moeilijk te vergelijken vanwege verschillen in definities en meetmethoden. Het gemiddeld gebruik van thuisbeademing varieerde van 3,4 uur/dag tot 8 uur/dag. 20-54% van de DM1 patiënten stopten met thuisbeademing. *De algemene conclusie van dit artikel was dat thuisbeademing bij DM1 de gasuitwisseling kan verbeteren en symptomen kan verlichten, met een mogelijk overlevingsvoordeel, hoewel het bewijs beperkt is.*

Hoofdstuk 3 had als doel de rol van de respiratoire kenmerken bij DM1 te evalueren in relatie tot therapietrouw van de thuisbeademing. Hiervoor werd een retrospectieve studie uitgevoerd met 200 DM1 patiënten die waren doorverwezen voor respiratoire

analyse. Longfunctie onderzoek, bloedgaswaarden en gegevens over de nachtelijke ademhaling (polysomnografie) werden verzameld. Thuisbeademing werd gestart bij 101 patiënten en hun therapietrouw werd na een jaar geëvalueerd. Hoge therapietrouw werd gedefinieerd als dagelijks gebruik van de beademingsapparatuur van minimaal 5 uur per nacht (n=38). Patiënten met lage therapietrouw werden samengevoegd met degenen die stopten met thuisbeademing (n=68). Er werden geen verschillen gevonden in de respiratoire kenmerken tussen de groepen. Ook vonden we geen voorspeller voor hoge of lage therapietrouw binnen de vooraf gedefinieerde variabelen, zoals geslacht, leeftijd, BMI (body mass index), CTG (cytosine-thymine-guanine) repeat lengte, geforceerde vitale capaciteit (FVC), pCO_2 overdag, nachtelijke pCO_2 en apneu-hypopneu-index (AHI). *Hieruit concludeerden we dat respiratoire kenmerken die bepaald zijn voor de start van thuisbeademing, niet geassocieerd zijn met therapietrouw bij DM1 patiënten met thuisbeademing, en niet kunnen worden gebruikt om patiënten met een risico op lage therapietrouw te identificeren.*

Hoofdstuk 4 richtte zich verder op het identificeren van factoren die therapietrouw bij DM1 patiënten met thuisbeademing beïnvloeden. Cognitieve stoornissen, affectieve symptomen en apathie zijn belangrijke voorspellers van slechte therapietrouw in het algemeen. Hoewel deze kenmerken vaak voorkomen bij DM1, waren ze niet eerder onderzocht in relatie tot therapietrouw. Daarom werd een cross-sectionele studie uitgevoerd bij 60 DM1-patiënten die thuisbeademing gebruikten of hier recentelijk mee waren gestopt. Cognitieve functies, affectieve symptomen en mate van apathie werden gemeten met behulp van respectievelijk de Montreal Cognitive Assessment (MoCA), de Hospital Anxiety and Depression Scale (HADS) en de Apathy Evaluation Scale (AES). Afwijkende scores werden gevonden bij 40% van de patiënten voor de MoCA en tot 77% voor de AES, terwijl een minderheid afwijkende scores had voor HADS-angst (30%) en HADS-depressie (18%). Scores waren gelijkmatig verdeeld over de groepen met hoge en lage therapietrouw, behalve voor HADS-angst, die significant hoger was bij lage therapietrouw. Leefsituatie, zorgafhankelijkheid (gemeten met de Care Dependency Scale) of bijwerkingen van de thuisbeademing (gemeten met de S^3-NIV vragenlijst) hadden geen significante invloed. *We concludeerden dat, hoewel cognitieve stoornissen en apathie vaak voorkomen bij DM1 patiënten met thuisbeademing, hun effect op therapietrouw beperkt is en thuisbeademing daarom niet moet worden onthouden aan patiënten met cognitieve stoornissen of apathie.*

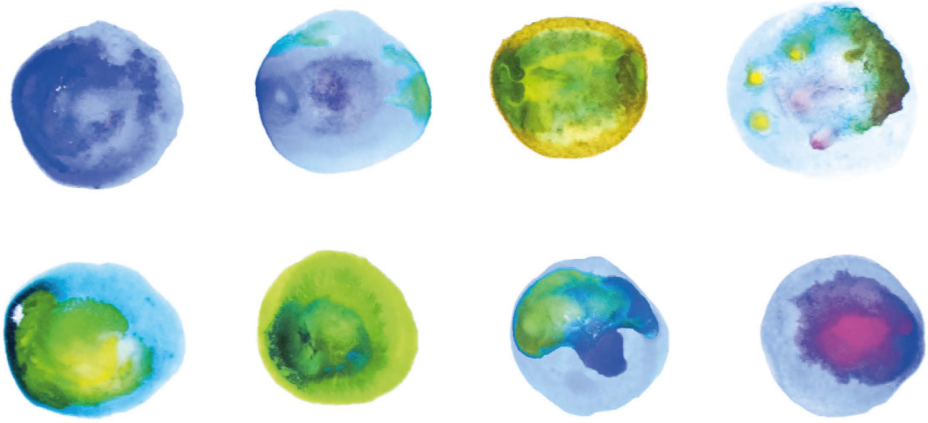
In **hoofdstuk 5** wordt de Nederlandse vertaling en evaluatie besproken van de S^3-NIV vragenlijst die oorspronkelijk ontwikkeld is in Frankrijk. Deze vragenlijst voor patiënten met non-invasieve ventilatie (NIV) bevat elf korte vragen over drie patiëntgerichte

dimensies: ademhalingssymptomen, slaapkwaliteit en NIV-gerelateerde bijwerkingen. In totaal werden 127 stabiele chronische NIV-gebruikers met verschillende onderliggende aandoeningen, waaronder DM1, geïncludeerd. De interne consistentie was goed (Cronbach's α van 0,78) en de reproduceerbaarheid was uitstekend (intraclass correlatie van 0,89). *We concludeerden dat de S^3-NIV vragenlijst een betrouwbaar en valide Nederlands instrument is om symptomen, slaap en NIV-gerelateerde bijwerkingen bij chronische NIV-gebruikers te evalueren.*

Hoofdstuk 6 toont de resultaten van onze prospectieve, multicenterstudie naar de respons op non-invasieve thuisbeademing bij DM1 (REMeDY studie). Het doel van de studie was om de effecten te meten van thuisbeademing op de gasuitwisseling, de kwaliteit van leven, en het dagelijks functioneren. Daarnaast wilden we onderzoeken of er factoren zijn die kunnen voorspellen hoe het effect van thuisbeademing is in de individuele patiënt. Veertig DM1 patiënten startten met thuisbeademing en konden geïncludeerd worden in de studie na uitgebreide karakterisering. Klinische gegevens, longfunctie onderzoek, bloedgasanalyse, polysomnografie of nachtelijke oximetrie met transcutane pCO_2 meting, en een set gevalideerde vragenlijsten werden gebruikt voor de analyses. Na zes maanden van behandeling werden er significante verbeteringen gezien in de gasuitwisseling, onder andere de pCO_2 verbeterde zowel overdag als 's nachts. De kwaliteit van leven, gemeten met de Severe Respiratory Insufficiency (SRI) vragenlijst, verbeterde significant, en deze verbetering correleerde met de daling van de nachtelijke pCO_2. Er werden geen significante veranderingen gezien in het dagelijks functioneren (gemeten met de DM1-Activ^C), of op het gebied van vermoeidheid en slaperigheid overdag (gemeten met de Fatigue and Daytime Sleepiness Scale), maar 70% van de deelnemers gaf aan gemotiveerd te zijn om thuisbeademing te blijven gebruiken. Er werden geen verbanden gevonden tussen basis karakteristieken en de respons op behandeling. De therapietrouw met thuisbeademing varieerde sterk tussen patiënten en werd als onvoldoende beschouwd bij 37-45%. *Concluderend is dit de eerste prospectieve multicenter studie die aantoont dat non-invasieve thuisbeademing de gasuitwisseling en kwaliteit van leven verbetert bij DM1, waarbij de meeste patiënten baat ervaren ondanks wisselende therapietrouw. Het is niet mogelijk om de respons op de behandeling te voorspellen vóór de start van thuisbeademing.*

In **hoofdstuk 7** worden de resultaten van het proefschrift besproken, in een breder perspectief geplaatst, en wordt richting gegeven voor toekomstig onderzoek.

Chapter 8



Impact paragraph

This thesis focused on the treatment of respiratory failure in patients with myotonic dystrophy type 1 (DM1) through the use of noninvasive home mechanical ventilation (HMV). The primary goal was to improve respiratory care for these patients, providing them with the opportunity to receive the most effective therapy enabling them to preserve and improve their quality of life and to support their social participation.

Background

From working as a pulmonologist at the Center of Home Mechanical Ventilation Maastricht, and from keeping in close contact with the other three centers of Home Mechanical Ventilation in the Netherlands, I know that the respiratory care for DM1 patients can be difficult and sometimes poses us for dilemmas. Although HMV is thought to be an efficient treatment for DM1 patients, robust scientific evidence was lacking. In addition, we saw in daily clinical practice that, despite the patient's and caregiver's best efforts, the treatment not rarely resulted in disappointment and frustration for the persons involved. DM1 patients starting with HMV generally hope to gain improvement of their symptoms which are often severe and restricting them in their daily functioning and social participation. Fatigue and daytime sleepiness are most frequently reported by patients and often described as the most debilitating symptoms of the disease.(1) While it is known that these symptoms may result from respiratory failure or sleep apnea, in daily clinical practice we often find that HMV treatment does not succeed in improving fatigue or daytime sleepiness. Sometimes, low treatment adherence with HMV averts adequate therapy and results. The motivation for patients to continue the treatment is then often decreasing and regularly leads to discontinuation of the treatment. Avoidance of such a burdensome, and expensive trajectory is desirable for all parties involved, but on the other hand, a subgroup of DM1 patients *do* experience relief of symptoms and an improved quality of life, so one would not want to withhold HMV from that group. Also, and maybe partly as a result of the failed HMV trajectories in some DM1 patients, health care professionals sometimes have prejudices about HMV in DM1 patients, and can be reluctant to start treatment. They estimate DM1 patients as less suitable candidates for HMV because of the possible cognitive impairment and the signs of apathy and anosognosia (lack of disease insight). Because the current HMV treatment in DM1 is mainly based on expert opinion and presumptions, it was clear that more research was needed in this field, desired by patients as well as health care professionals.

Scientific relevance

This thesis provides robust and extensive scientific evidence regarding HMV in DM1 patients. By reviewing the available literature in **Chapter 2**, the scientific gaps on this topic became clearer and gave direction to the content of this thesis. In the current health care system, medical specialists become more and more focused on a small area of health and disease in the individual patient. This can be beneficial, and needed, because of the rapidly evolving developments with regard to disease pathophysiology, diagnostics, and treatment. However, one should remain aware of the fact that the patient is a whole and should be regarded as such, instead of focusing on one organ system or one disease feature. To integrate the various disease aspects and patient characteristics into a prospective study, we first examined specific elements in **Chapters 3** and **4**, before uniting them in **Chapter 6**.

We studied the respiratory characteristics with regard to treatment response in DM1 (**Chapter 3**), but we could not find a relation between the respiratory characteristics and the treatment response. This is very relevant information, because the initiation of HMV heavily relies on the respiratory characteristics at the moment.(2) Our study highlighted the importance of looking beyond the respiratory characteristics. The next elements we researched in this context consisted of cognitive and behavioral features in relationship to treatment adherence with HMV in DM1 (**Chapter 4**). Mild cognitive impairment, and the presence of apathy were *not* negatively associated with treatment adherence. As described before, health care workers sometimes presume that DM1 patients with signs of cognitive impairment or apathy are less suitable candidates for HMV because of low treatment adherence. Our research has weakened this assumption which is particularly relevant in daily clinical practice. We *did find* a correlation between the presence of anxiety and low treatment adherence. This is especially relevant to take into account when seeing patients with low treatment adherence. Structured use of a questionnaire on anxiety can help identify anxiety problems in individual patients. This may guide the treatment of these complaints and potentially improve treatment adherence with HMV.

In our REMeDY study — a multicenter, prospective investigation — we explored multiple factors related to the response to HMV treatment in DM1 (**Chapter 6**). We provided definitive evidence that HMV is an effective therapy for improving gas exchange and health-related quality of life (HRQL), addressing a gap that previously existed in the scientific literature. Unfortunately, predicting treatment response prior to initiating therapy proved impossible in our research, and it is clear that there is no '*one size fits all*' approach to managing respiratory failure in DM1. Treating DM1

patients should be truly individualized and patient-centered, rather than just providing standard care on the basis of selected characteristics.

In **Chapter 5**, we broadened our focus beyond DM1 to include a wider patient population. There was a lack of a tool specifically designed to assess symptoms and side effects in patients with respiratory failure treated with chronic HMV. By translating and validating a Dutch version of the originally French S_3-NIV questionnaire, we introduced a valuable resource for all patients on chronic NIV in the Netherlands (around 4,000 people) and for the health care professionals involved in their care.[3] The use of this questionnaire is recommended in future research and daily clinical practice.

Target groups and societal relevance

The primary target group for this research consisted of patients with DM1 who are being considered for, or are already receiving HMV. In addition, patients with other causes of chronic respiratory failure who are treated with HMV may also benefit from the findings, particularly regarding symptom monitoring, and factors influencing treatment adherence. Health care professionals involved in the care of these patients—including pulmonologists, neurologists, rehabilitation physicians, and respiratory nurses—represent another key audience for this work. Caregivers and family members, who play a crucial role in supporting patients at home, are likewise important stakeholders who may benefit from the insights provided by this thesis.

By investigating factors that influence treatment adherence and response, this thesis takes an important step toward supporting a more targeted approach to therapy — aiming for treatment to be offered to those most likely to benefit, while avoiding unnecessary and burdensome interventions for those less likely to experience improvement. From a societal perspective, such a tailored approach promotes the responsible use of health care resources and helps to contain costs associated with prolonged or ineffective treatment. These costs are not limited to the expenses of disposables, ventilators, and the specialized care provided by the Centers of Home Mechanical Ventilation, but also include the additional care required to support these patients in the home setting or in specialized nursing homes. By moving toward more individualized therapy, this work contributes to the sustainability of the health care system.

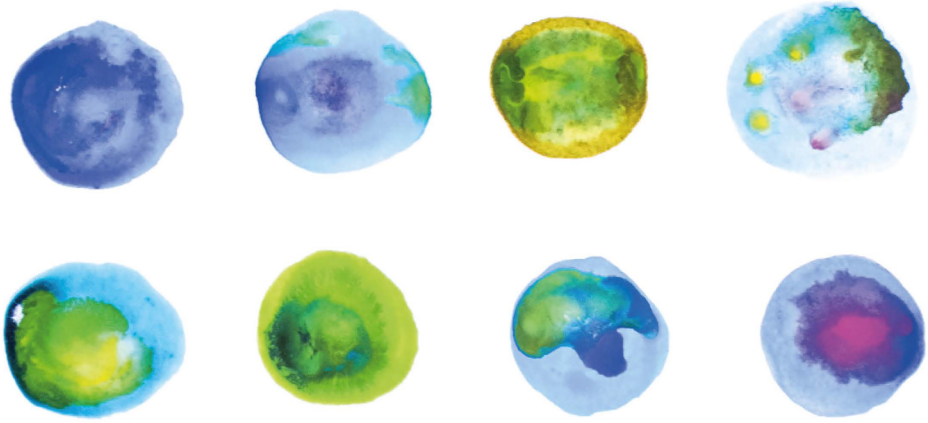
Dissemination of knowledge

Sharing research findings and knowledge is essential to improve clinical care for patients. The studies presented in this thesis have been published in international, peer-reviewed scientific journals. In addition to academic dissemination, the findings of this research—combined with clinical experience—have been shared within several relevant professional groups. Through regular meetings with health care professionals involved in the DM1 expertise centers at Maastricht University Medical Center+ and Radboud University Medical Center in Nijmegen, key insights were discussed and translated into daily clinical practice. The four Centers of Home Mechanical Ventilation in the Netherlands, located in Maastricht, Groningen, Rotterdam, and Utrecht, exchange knowledge regularly through national meetings and symposia. This research has been frequently highlighted at these events, contributing to the goal of ensuring that DM1 patients across the country receive comparable, state-of-the-art care. Participation in the 2024 edition of the International Myotonic Dystrophy Consortium Meeting (IDMC-14) in Nijmegen further supported international engagement with the field. Additionally, Dutch DM1 patients and their relatives are addressed each year at the Prinses Beatrix Spierfonds conference, helping to inform and improve care for patients and families.

References

1. Laberge L, Gagnon C, Dauvilliers Y. Daytime sleepiness and myotonic dystrophy. Curr Neurol Neurosci Rep. 2013;13(4):340.
2. Boentert M, Cao M, Mass D, De Mattia E, Falcier E, Goncalves M, et al. Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1. Respiration. 2020;99(4):360-8.
3. Richtlijn Chronische beademing: Kennisinstituut van de Federatie van Medisch Specialisten; 2021 [Available from: https://richtlijnendatabase.nl/richtlijn/chronische_beademing/startpagina_-_chronische_beademing.html.

Chapter 8



Dankwoord

Een proefschrift schrijven doe je niet alleen! Met plezier kijk ik terug op de afgelopen jaren waarbij ik mijn werk als longarts combineerde met het verrichten van wetenschappelijk onderzoek. Graag wil ik mijn dank uitspreken aan iedereen die heeft bijgedragen aan de realisatie van dit proefschrift.

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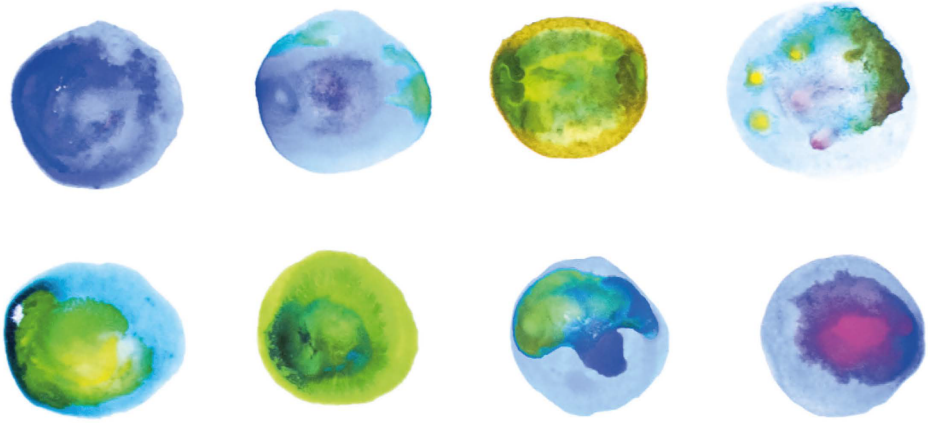
Tot slot de belangrijkste personen in mijn leven: mijn drie mannen **Alex**, **Max** en **Ruben**.

Lieve **Alex**, jij bent mijn grote liefde en mijn rots in de branding. Dank dat je er altijd voor mij bent en dat ik samen met jou mijn mooiste leven mag leiden. De wetenschap bracht ons in 2007 samen, maar inmiddels delen we zoveel meer dan dat. Jouw harde werken en passie voor onderzoek inspireerden mij tot het voltooien van mijn proefschrift, waarbij jij mij hielp en alle ruimte gaf die ik nodig had. Maar het mooiste van alles is het leven dat we samen hebben opgebouwd, met elkaar en met onze jongens. Ik hou van jou en kijk uit naar alle mooie jaren die voor ons liggen. Laat dat ‘tevredenheidsgen’ nog maar heel vaak tot expressie komen..

Lieve **Max** en **Ruben**, het is dan eindelijk zover! Het ‘boekje’ van mama is klaar en dat gaan we samen vieren met een spetterend feest waar jullie al lang naar uitkijken! Naast mijn onvoorwaardelijke liefde wil ik jullie graag meegeven in het leven dat hard werken beloond wordt met mooie prestaties waar je trots op mag zijn. Ik weet zeker dat er voor jullie nog veel moois in het verschiet ligt!

Chapter 8



Curriculum vitae

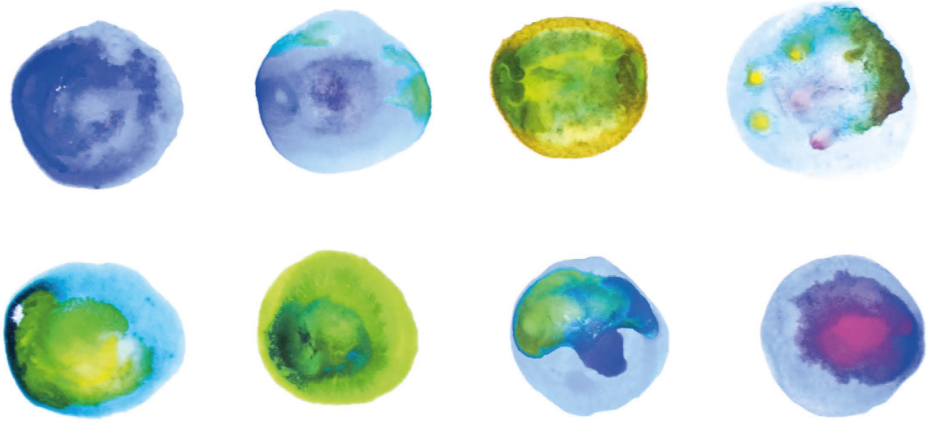
Bettine Vosse werd geboren op 17 januari 1983 in Sittard. In 2001 behaalde ze, cum laude, haar VWO diploma aan het Serviam College te Sittard. In datzelfde jaar startte ze met haar studie geneeskunde aan de Universiteit Maastricht welke zij in 2007, cum laude, afrondde. Na enige tijd werkzaam te zijn geweest bij de onderzoeksafdeling Pulmonologie op de Universiteit Maastricht, is zij in 2009 gestart met haar specialisatie tot longarts. Hiertoe werkte ze twee jaar in het Orbis Medisch Centrum in Sittard (nu Zuyderland Medisch Centrum) ten behoeve van de vooropleiding interne geneeskunde. Vervolgens zette zij haar opleiding tot longarts voort in het Maastricht Universitair Medisch Centrum+ (MUMC+) met een succesvolle afronding in 2016.

In 2016 ging zij werken als longarts in het MUMC+, met als aandachtsgebied thuisbeademing. Tevens werd zij in contact gebracht met haar huidige promotor, prof. dr. Karin Faber en startte zij met haar promotieonderzoek naar thuisbeademing bij myotone dystrofie patiënten. Bettine werd de vaste longarts van het myotone dystrofie expertisecentrum van het MUMC+. In die hoedanigheid begeleidt zij vele patiënten met myotone dystrofie en brengt zij verdere diepgang aan in haar wetenschappelijke onderzoek op dit terrein. Via haar klinische werkzaamheden bij het Centrum voor Thuisbeademing Maastricht kwam zij in contact met prof. dr. Peter Wijkstra van het Centrum voor Thuisbeademing Groningen, haar tweede promotor. Dit leverde een waardevolle wetenschappelijke samenwerking op hetgeen heeft bijgedragen tot de verdere totstandkoming van het huidige proefschrift.

Naast haar werkzaamheden bij het Centrum voor Thuisbeademing Maastricht, en het myotone dystrofie expertisecentrum, werkt Bettine ook als algemeen longarts en is ze betrokken bij het onderwijs voor de studie geneeskunde aan de Universiteit Maastricht. Binnen de Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT) is ze lid van de Commissie Visitatie Longziekten.

Bettine woont met veel plezier in Maastricht en is sinds 2007 samen met Alex met wie ze twee zonen heeft, Max (2014) en Ruben (2018).

Chapter 8



List of publications

B.A.H. Vosse, W. Seelentag, A. Bachmann, F.T. Bosman, Pu Yan. Background staining of visualization systems in immunohistochemistry. *Appl Immunohistochem Mol Morphol 2007 Mar;15(1):103-7*

A-M. Dingemans, V. van den Boogaart, **B.A. Vosse**, R-J. van Suylen, A.W. Griffioen, V.L. Thijssen. Integrin expression profiling identifies integrin alpha5 and beta1 as prognostic factors in early non-small cell lung cancer. *Mol Cancer. 2010 Jun 17:9:152*

B. van den Borst, I.G.M. Slot, V.A.C.V. Hellwig, **B.A.H. Vosse**, M.C.J.M. Kelders, E. Barreiro, A.M.W.J. Schols, H.R. Gosker. Loss of quadriceps muscle oxidative phenotype and decreased endurance in patients with mild-to-moderate COPD. *J Appl Physiol (1985). 2013 May;114(9):1319-28*

L.E.L. Hendriks, E.F. Smit, **B.A.H. Vosse**, W.W. Mellema, D.A.M. Heideman, G.P. Bootsma, M. Westenend, C. Pitz, G.J. de Vries, R. Houben, K. Grünberg, M. Bendek, E-J.M. Speel, A-M.C. Dingemans. EGFR mutated non-small cell lung cancer patients: More prone to development of bone and brain metastases? *Lung Cancer 2014 Apr;84(1):86-91*

B.A.H. Vosse, A.F. van Belle, G.J. de Vries, M. Das. Hemomediastinum due to spontaneous rupture of a mediastinal bronchial artery aneurysm – A rare cause of thoracic pain. *Respir Med Case Rep. 2014 Mar 14:12:27-9*

I.G.M. Slot, A.M.W.J. Schols, **B.A.H. Vosse**, M.C.J.M. Kelders, H.R. Gosker. Hypoxia differentially regulates muscle oxidative fiber type and metabolism in a HIF-1α-dependent manner. *Cell Signal. 2014 Sep;26(9):1837-1845*

A. Withers, T.C.Ching Man, R. D'Cruz, H. de Vries, C. Fisser, C. Ribeiro, N. Shah, M. Van Hollebecke, **B.A.H. Vosse**, L. Heunks, M. Patout. Highlights from the Respiratory Failure and Mechanical Ventilation 2020 Conference. *ERJ Open Res 2021 Feb 8;7(1):00752-2020*

B.A.H. Vosse, C. Seijger, N. Cobben, B. van Engelen, S.M.J. van Kuijk, C. Faber, P. Wijkstra. Noninvasive home mechanical ventilation in adult myotonic dystrophy type 1: a systematic review. *Respiration 2021;100(8):816-825*

S.T.H. Peeters, F. Vaassen, C. Hazelaar, A. Vaniqui, E. Rousch, D. Tissen, E. Van Enckevort, M. de Wolf, M.C. Öllers, W. van Elmpt, K. Verhoeven, J.G.M. van Loon, **B.A. Vosse**, D.K.M. De Ruysscher, G. Vilches-Freixas. Visually guided inspiration breath-hold facilitated with nasal high flow therapy in locally advanced lung cancer. *Acta Oncol.2021 May;60(5):567-574*

E.S.B. van Kleef, J.L.M. van Doorn, M.A. Gaytant, W. de Weerd, **B.A.H. Vosse**, C. Wallgren-Pettersson, B.G.M. van Engelen, C.A.C. Ottenheijm, N.C. Voermans, J. Doorduin. Respiratory muscle function in patients with nemaline myopathy. *Neuromuscul Disord. 2022 Aug;32(8):654-663*

I.B.T. Joosten, C.G.C. Horlings, **B.A.H. Vosse**, A. Wagner, D.S.H. Bovenkerk, R. Evertz, K. Vernooy, B.G.M. van Engelen, C.G. Faber. Myotonic dystrophy type 1: A comparison between the adult- and late-onset subtype. *Muscle Nerve. 2023 Feb;67(2):130-137*

B.A.H. Vosse, C.G.C. Horlings, I.B.T. Joosten, N.A.M. Cobben, S.M.J. van Kuijk, P.J. Wijkstra, C.G. Faber. Role of respiratory characteristics in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy type 1, a retrospective study. *Neuromuscul Disord. 2023 Sep;33(9):57-62*

E.E. Evers-Bikker, W. de Weerd, P.J. Wijkstra, L. Corel, L.P. Verweij, **B.A.H. Vosse**. Characteristics and outcomes in children with congenital central hypoventilation syndrome on long-term mechanical ventilation in the Netherlands. *Eur J Pediatr. 2024 Feb;183(2):791-797*

B.A.H. Vosse, J. de Jong, L.A. la Fontaine, C.G.C. Horlings, S.M.J. van Kuijk, N.A.M. Cobben, A-F. Domensino, C. van Heugten, C.G. Faber. The role of cognition, affective symptoms, and apathy in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy. *J Neuromus Dis. 2024;11(5):1123-1130*

C.G.W. Seijger, **B.A.H. Vosse**, L. la Fontaine, T. Raveling, N.A.M. Faber, P.J. Wijkstra. Validity and reliability of the Dutch version of the S3-NIV questionnaire to evaluate long-term noninvasive ventilation. *Chron Respir Dis. 2024 Jan-Dec:21*

E.S.B. van Kleef, S.A.J.H. van de Camp, J.T. Groothuis, C.E. Erasmus, M.A. Gaytant, **B.A.H. Vosse**, W. de Weerd, C.C. Verschuuren-Bemelmans, E.G. Medici-Van den Herik, C. Wallgren-Pettersson, B. Küsters, M. Schouten, B.G.M. van Engelen, C.A.C. Ottenheijm, J. Doorduin, N.C. Voermans. A cross-sectional study in 18 patients with typical and mild forms of nemaline myopathy in the Netherlands. *Neuromuscul Disord. 2024 Oct;43:29-38*