Respiratory morbidity in neuromuscular diseases, with focus on Spinal Muscular Atrophy

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Blowing dandelions is a challenge for many patients with neuromuscular diseases. This thesis hopefully supports patients with planting some seeds, answering some questions and raising many more.
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Respiratory morbidity in neuromuscular diseases, with focus on Spinal Muscular Atrophy

Respiratoire problemen bij patiënten met spierziekten en spinale spieratrofie in het bijzonder

(met een samenvatting in het Nederlands)

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Contents

CHAPTER 1

Introduction

Neuromuscular diseases

Neuromuscular diseases (NMDs) are a heterogeneous group of disorders that affect the motor neuron, neuromuscular junction, and muscle fibers, with variable age of onset, presentation, natural history and prognosis [1]. Current estimates of the number of different types of NMDs are 500-600. Although each of these disorders is rare, it is estimated that between 6 to 8 million people worldwide are suffering from some form of NMDs [2]. The diversity of symptoms is associated with large genetic and clinical heterogeneity, complicating treatment [2]. Historically, pediatric NMDs were deemed to have a poor prognosis, as no treatments were available. This perception is gradually changing thanks to the development of symptomatic and genetic treatment strategies, starting with the use of corticosteroids in boys with Duchenne Muscular Dystrophy (DMD) [3].

Respiratory problems in neuromuscular diseases

In addition to the significant levels of disability, many of the more severe NMDs are further complicated by progressive respiratory muscle weakness [1]. Progressive respiratory muscle weakness is an important cause of morbidity and mortality in patients with NMDs. Respiratory failure is caused by parenchymal lung disease or respiratory pump dysfunction, resulting in, respectively, hypoxemic or hypercapnic respiratory failure. The respiratory pump comprises the chest wall, respiratory muscles and respiratory control center in the central nervous system. The primary cause of respiratory failure in NMDs is hypercapnic, respiratory pump failure. This can be aggravated by hypoxic respiratory failure, caused by lower respiratory tract infections (RTIs) or aspiration [4].

Sufficient ventilation requires a balance between respiratory muscle performance and the respiratory load, determined by the lung, thoracic and airway mechanics. Both respiratory muscles and respiratory load are controlled by the central respiratory drive.

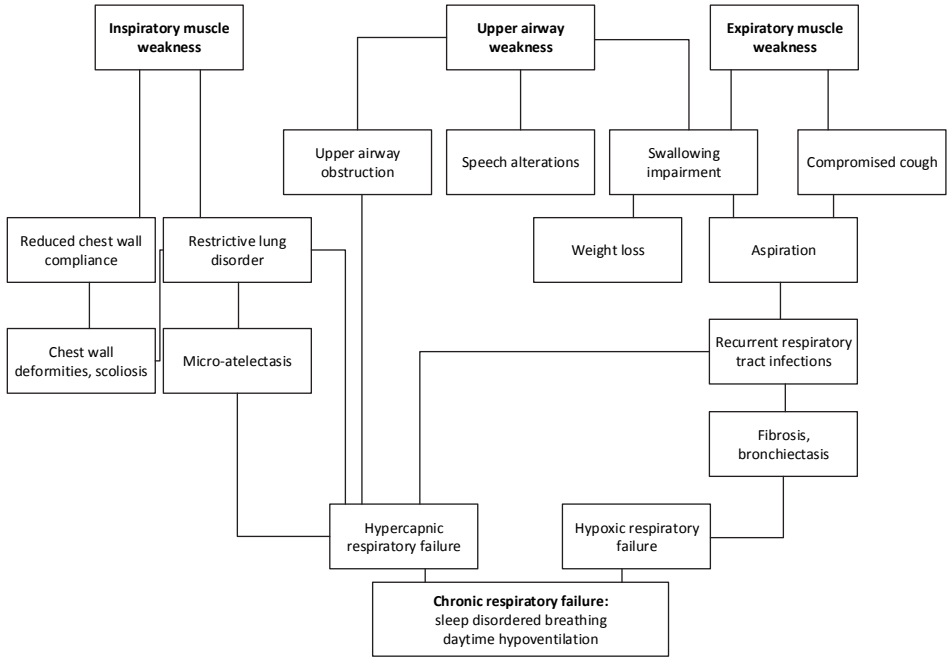
In healthy people, ventilation is maintained within the normal range during rest, exercise and sleep, as the respiratory muscle power exceeds the respiratory load and the central respiratory drive is normal.

In patients with NMDs the respiratory load may become proportionally high for the weakened muscles. The respiratory load is increased, due to progressive diminished chest wall compliance, micro-atelectasis of the lung due to reduced thoracic movements and thoracic scoliosis [5]. By distorting thoracic anatomy and rib alignment, severe (kypho) scoliosis decreases the compliance of the chest wall, thereby restricting vital capacity (VC) [6]. Scoliosis also aggravates this imbalance by adding a mechanical disadvantage to

the diaphragm and intercostal muscles [5]. To compensate for this imbalance the central respiratory drive increases. With further progression of the respiratory muscle weakness, alveolar hypoventilation may occur despite increased central respiratory drive. This will initially occur during RTIs and sleep, but it may eventually progress to daytime chronic respiratory failure as respiratory muscle weakness progresses.

Sleep is associated with physiological changes in respiratory mechanics, with increased ventilation/perfusion mismatch, increased airflow resistance and decreased functional residual capacity [7,8]. Especially patients with NMDs that predominantly affect the diaphragm (e.g. DMD, Pompe's disease, distal spinal muscular atrophy (DSMA) type 1 and some congenital myopathies) are at risk of severe and early nocturnal hypoventilation, as during sleep the activity of intercostal and the upper airway muscles decreases significantly, whereas activity of the diaphragm is preserved. Finally, central respiratory drive and chemoreceptor sensitivity are less efficient during sleep than during wakefulness. Alveolar hypoventilation predominates during rapid eye movement (REM) sleep [1].

Figure 1: Summary of pathophysiology of respiratory failure in neuromuscular diseases



NMDs differ in patterns of weakness of muscle groups in the extremities. The same is true for the involvement of respiratory muscles. A useful distinction is, as shortly outlined above, NMDs with and without weakness of the diaphragm. This is illustrated by two of the most common NMDs, i.e. DMD and spinal muscular atrophy (SMA). DMD is characterized by a predominant weakness of the diaphragm and the expiratory muscles, whereas the diaphragm in patients with SMA is relatively spared in contrast to the intercostal muscles that are the most affected respiratory muscles [5]. Even more striking patterns can be seen in NMDs that are less prevalent, such as congenital myopathies/muscular dystrophies associated with mutations in the collagen 6 (COL6) gene [9] and patients with DSMA (also known as spinal muscular atrophy with respiratory distress (SMARD)) [10] that are characterized by an isolated dysfunction of the diaphragm. Finally, not only the pattern of respiratory muscle involvement varies within a specific NMD, but also the severity of the respiratory muscle weakness [5]. This variation indicates that 'neuromuscular respiratory failure' is not a uniform concept.

Onset of clinically relevant respiratory problems varies from infancy to adulthood in different NMDs. This explains the wide variation in timing of respiratory failure and occurrence of RTIs. Onset in infancy poses an additional problem, since it is associated with a risk of impaired lung and chest wall growth and thoracic deformity [11].

Lung function and respiratory muscle strength tests in neuromuscular diseases

Clinical examination with observation of breathing pattern is important, although not sensitive to rank NMD progression [5]. An example of abnormal breathing pattern is the thoraco-abdominal asynchrony in young children with SMA.
Monitoring of breathing pattern can be done by the recording of respiratory rate (RR) and tidal volume (VT), which allows calculation of the rapid shallow breathing index (RSBI = RR/VT). Initially, any increase of RSBI observed in patients with NMDs is interpreted as a strategy to minimize respiratory effort and dyspnea perception. However, a high RSBI leads to progressive alveolar hypoventilation by increasing dead space ventilation [12]. This is reflected by an increased ratio of dead space and tidal volume (VD/VT) [13].
Despite the limited predictive power, the RSBI is an index commonly used to predict the possibility for sustaining spontaneous ventilation in NMDs [12]: this index has been shown to be significantly higher in children requiring nocturnal non-invasive mechanical ventilation as compared with those not requiring mechanical ventilation [5].

The increase in central respiratory drive, secondary to the imbalance between respiratory load and weakened respiratory muscles in NMDs, can be objectified by the increase in

the airway occlusion pressure (P0.1), which is the pressure generated in the first 100 ms of inspiration against an occluded airway. The timing of P0.1 is not influenced by the conscious response to occlusion, and as an index of central respiratory drive, it has the advantage over ventilation to be independent of the mechanical properties of the lungs.
Respiratory inductance plethysmography (RIP) is a noninvasive technique used to monitor breathing patterns. It can be used in young patients, as it involves minimal patient cooperation and can be completed within 5-10 min. RIP uses two elastic bands and measures the movement and synchrony of the patient's rib cage and diaphragm, i.e. the thoracoabdominal asynchrony (TAA) [14,15]. With increased work of breathing (WOB), the rib cage lags behind abdominal wall movement. TAA is increased in the setting of increased respiratory resistance, decreased lung compliance and increased chest wall compliance [16].

Although not possible in young children because of required cooperation, spirometry is sensitive to rank NMD progression [5].Vital capacity (VC) is determined by inspiratory muscle strength and lung and chest wall compliance. Vital capacity can be reliably measured with spirometry by a slow maneuver where the patient is asked to breathe in as deeply as possible, followed by as long as possible expiration [17].
Reduced VC is not specific and may have other causes than respiratory muscle weakness [5]. A fall in VC in the supine position (compared with upright) is used as an indirect indicator of diaphragm weakness [13].
Forced vital capacity (FVC) is measured with spirometry as the volume of gas which is exhaled during a forced expiration after maximal inspiration.

Multiple breath washout (MBW) tests assess ventilation distribution inhomogeneity during tidal breathing by examining inert gas clearance over a series of relaxed breaths. Once washout is complete, different indices of ventilation inhomogeneity can be produced, with lung clearance index (LCI) being regarded as the most robust and sensitive [18]. LCI represents a measure of the number of times the resting or end-tidal lung volume has to be "turned over" to clear the tracer gas from the lungs and is independent of tidal volume[18]. It has been shown to be a reproducible and repeatable measure of ventilation inhomogeneity in (young) children, independently of respiratory muscle strength or chest wall geometry[19]. Few studies are available on these techniques in patients with NMDs [19,20].

The most widely applied tests of inspiratory and expiratory muscle strength are the maximal expiratory (PE_{max}) and inspiratory (PI_{max}) pressures measured at the mouth. These non-invasive tests measure the strength of expiratory and inspiratory muscles. The patient is breathing through a mouthpiece and wearing a noseclip. When the airway is occluded and the glottis is open, mouth pressure equals alveolar pressure [5]. For measuring PI_{max} the patient is asked to breathe out to residual volume, followed by maximal inspiration against an occluded airway. PE_{max} is measured by taking a maximal expiratory effort against an occluded airway, from total lung capacity [17].

Sniff Nasal Pressure (SNIP) is a measure of inspiratory muscle strength. SNIP is the nasal pressure in an occluded nostril measured during a maximal sniff performed through the other nostril . Normal SNIP values exclude inspiratory muscle weakness [17,21]. Although SNIP is easy to perform, it may underestimate inspiratory muscle strength in case of nasal obstruction or severe respiratory muscle weakness [21].
Peak expiratory flow (PEF) and peak cough flow (PCF) consists in generating respectively a maximal expiratory flow or cough [5].
Assessment of lung function and respiratory muscle strength is challenging in severely affected patients with NMDs or invasively ventilated patients. Very young children are not able to perform lung function and respiratory muscle testing at all. Other tools or parameters may thus be needed to assess the respiratory muscle weakness and its consequences in young children [5].

Relevance of lung function in neuromuscular diseases

Weakness of respiratory muscles is often subtle and more difficult to evaluate than peripheral loss of strength [1]. Available guidelines generally suggest to measure vital capacity in patients with NMDs who are capable of performing spirometry as part of the respiratory assessment [22–24]. This advice is mainly based on studies in patients with DMD: VC is a valuable predictor of susceptibility to infection, need for respiratory support and survival in children and adolescents with DMD [17]. For many other NMDs the predictive value of lung function tests are less well or even not known.

Respiratory muscle testing is an essential tool to understand the involvement of different respiratory muscles in a particular patient or at the group level. Testing is therefore useful to improve our knowledge on pathophysiology and natural history of the disease. Some studies suggest that quantification of respiratory muscle weakness is also necessary to guide therapeutic management [5,25]. For example, initiation of airway clearance techniques or cough augmenting treatment is guided by peak cough flow. Patients older than 12 years are vulnerable to respiratory failure during otherwise trivial RTIs if peak cough flow is below 270 L/min. This is often considered the threshold of starting cough augmenting treatments. Secretion clearance becomes ineffective if peak cough flow drops below 160 L/min [17].

With emerging genetic therapies for NMDs, respiratory muscle testing will become an important tool to monitor treatment efficacy. To assess the effectiveness of these treatments, it is vital to have a set of reliable, clinically meaningful pulmonary outcome measures [26].

Current respiratory treatment of neuromuscular diseases

Current management of NMDs relies upon proactive measures in an multidisciplinary clinic. This includes treatment of respiratory infections, proactive cough augmenting treatment and ventilatory support, adequate nutrition and interventions for skeletal deformities like scoliosis [3]. These advices are summarized in several consensus statements [22,24,27,28]. Despite limited evidence from RCTs, cough augmenting treatment is routinely used in patients with NMDs [29]. Their use possibly results in a reduced number of RTIs and associated hospital admissions as well as shorter duration of hospital stays [17,30–35]. International guidelines recommend initiation of cough augmenting treatment when PCF falls below 270 L/min and/or FVC is below 50% of predicted capacity [36], but do not specify preferred techniques [36]. Different techniques exist, which support expiration (manually assisted cough), inspiration (glossopharyngeal breathing, air stacking), or both (mechanical insufflation-exsufflation). Expiratory muscle function can be augmented manually with appropriately timed chest-wall or upper abdominal thrusts, i.e. manually assisted cough [37]. Glossopharyngeal breathing or frog-breathing is a more difficult technique to increase inspiratory volumes, and for that reason not commonly used in children [37]. Air stacking increases the inspiratory lung volume to its maximum by manually assisting the inspiration using a self-inflating resuscitation bag, thereby aiming to increase PCF [38]. Advantages of air stacking include its low costs and availability. Air stacking can be combined with manually assisted cough, to increase the effect by supporting both inspiration and expiration. Mechanical Insufflation-Exsufflation is often initiated when air stacking is impossible (e.g. in young children) or no longer effective [17,39]. Unlike air stacking, Mechanical Insufflation-Exsufflation also assists the expiration, by using a positive inspiratory pressure which is rapidly followed by a negative expiratory pressure. This rapid change in pressure mimics the flow changes that occur during a cough, thereby removing bronchial secretions [39–41]

In comparison to air stacking, Mechanical Insufflation-Exsufflation is much more expensive and not reimbursed in all countries [32]. Less commonly used techniques in the Netherlands include intrapulmonary percussive ventilation and high-frequency chest-wall compressions via an inflatable vest. These treatments are believed to enhance the movement of secretions from the peripheral to the more central airways [37].

In some, but not all patients with NMDs, (non)invasive mechanical ventilation is needed. The goals of chronic mechanical ventilation in patients with NMDS are to prolong survival, relieve dyspnea, normalize gas exchange, correct sleep disordered breathing, prevent cor pulmonale, improve daytime function, promote growth and development, and improve quality of life [37]. For patients with progressive NMDs, mechanical ventilation has changed the natural history and improved survival [42,43].

Supportive respiratory treatment- a historic perspective

Ventilation

The first description of positive pressure ventilation dates back to 1543. Andreas Vesalius wrote: " an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air" [44]. In the late 19th century, ventilators were developed using subatmospheric pressure delivered around the body of the patient to replace or augment the work being done by the respiratory muscles. In 1864, Alfred Jones invented one of the first such body enclosing devices [44]. The first widely used 'iron lung' was developed by Philip Drinker in 1928, and used in the 1930s through 1950s in patients with poliomyelitis [45]. A cylindrical tank enclosed the patient's body and chest, leaving the head outside the chamber under atmospheric pressure. Air pumps raised and lowered pressure within the tank to assume the entire work of breathing [46]. Tracheostomy tubes were placed at that time for suctioning, not for ventilation [47]. However, in 1952 Ibsen suggested to initiate ventilatory support via tracheostomy during poliomyelitis epidemic in Copenhagen. This dramatically improved survival [45].

In the early 1950s the first post-poliomyelitis patients using body ventilators were discharged home in the United States. By 1956, 92% of the estimated 1800 post-poliomyelitis patients with respiratory failure were discharged home using ventilatory support with iron lungs, intermittent abdominal pressure ventilator belts, and mouthpiece intermittent positive pressure ventilation [47].

In 1955 the first patients, including young children, were invasively ventilated in the Netherlands. In 1960 the first patient with post-poliomyelitis chronic respiratory failure was discharged from the hospital with invasive ventilation in the Netherlands [45].

Increasing numbers of patients with NMDs are supported by home mechanical ventilation over the last decades. In contrast to the recent past, there is no controversy or ethical discussion about initiation of respiratory support in the majority of patients with NMDs [48].

Airway clearance techniques

The combination of inspiratory and expiratory aids was first used in drowning victims. The Barrel method was described in 1766. A drowning victim was rolled forward and back on top of a barrel to alternately compress the chest and abdomen, thereby aiming to move air in and out of the lungs [47].

Manually Assisted Cough and glossopharyngeal breathing were first described in 1951 [47]. Air stacking was first described in 1966 in a patient with spinal cord injury [47]. First

descriptions of mechanical insufflator-exsufflation devices date back before descriptions of manually assisted cough, glossopharyngeal breathing and air stacking. In the late 1940s Henry Seeler developed a mechanical insufflator-exsufflator, which was used to ventilate and exsufflate the lungs of chemical victims [47]. In the same period Gustav Beck and Alvin Barach developed a mechanical cough chamber that created a major pressure change of 150 cmH_2O with a frequency of 25 times per minute [47].

In 1951 the exsufflator valve for the iron lung and a "vacuum cleaner" connected to the iron lung were developed, as well as a portable exsufflation-with-negative pressure device with facial interface. This portable device was marketed one year later as the Cof-flator, delivering alternately positive and negative pressures of 54 cm H_2O during 1-3 seconds. The production of this device was discontinued in 1967 due to eradication of poliomyelitis and introduction of invasive ventilation [47]. In 1993 the Jack Emerson's In-Exsufflator became commercially available in the United Stated [47]. At present there is still discussion on evidence of these techniques and clinical practice varies world-wide [29].

Focus on SMA

Hereditary proximal Spinal Muscular Atrophy is a severe autosomal recessive neuromuscular disease with an estimated incidence of 1:6000 to 1:12.000 living birth. It is not only one of the more common genetic disorders [49], but also one of the most important genetic causes of infant mortality and childhood morbidity [50]. As of 2016/2017 SMA is the first NMD for which genetic treatment has become available. Treatment for patients with SMA is centralized in The Netherlands in the Netherlands SMA center of the UMC Utrecht. This center gathers clinical information for the national SMA registry, which contains detailed clinical data of around 500 children and adults with SMA. This all offered me the opportunity to focus my research specifically on SMA.

SMA was first described in the 1890s by Guido Werdnig and Johan Hoffman [51,52]. In the course of the 20th century, it became clear that there is a wide range of severity, with infantile, early childhood and later childhood to adult onset. In the 1990s, consensus was reached to classify SMA into three types (Table 1). Type 1 SMA, the most severe phenotype, was originally named Werdnig-Hoffman disease even though their original description was of the intermediate variant or SMA type 2. The mild ambulant form of SMA with onset in adolescence, SMA type 3, was comprehensively documented by Kugelberg and Welander and carries the eponymous title of Kugelberg–Welander disease [53–55]. The clinical characteristics of the different types of SMA are summarized in table 1 [50,56–67].

Table 1: Clinical characteristics of different types of SMA

	Type 1 Werdnig-Hoffman	Type 2 Intermediate	Type 3 Kugelberg-Welander	Type 4 Mild
Proportion of SMA (%)	50	30	20	<1
Age at onset	1a: Prenatal	6-18 months	3a: 18-36 months	≥ 18 years
	1b: < 3 months		3b: > 3 years	
	1c: 3-6 months			
Highest achieved motor function	No unsupported sitting	Unsupported sitting	Walk unsupported	Walk unsupported
	1a: None	2a: No standing		
	1b: None	2b: Standing with		
	1c: Usually some	assistance		
	additional motor			
	motor skills (head			
	control, rolling from			
	supine to prone)			
Survival without treatment or mechanical ventilation	< 2 years (median	>2 years, usually	Normal	Normal
	6-8 months)	early adulthood		
Scoliosis	1a-b: Not present due	Nearly all patients	Majority of	Not present
	to short survival		patients with	
	1c: Important		type 3a	
	feature			
Typical SMN2 copy number	2-3	3	3-4	4

The genetic defect in SMA was unraveled in 1995. SMA is caused by mutation or deletion of the *survival motor neuron 1* (*SMN1*) gene at the 5q11.2-q13.3 locus. Humans have a nearly identical *SMN2* gene, in contrast to other species. This *SMN2* gene produces residual levels of SMN protein. *SMN2* copy number acts as the main modifier of the SMA phenotype: higher *SMN2* copy numbers are associated with higher levels of SMN protein and milder disease phenotype [3,66].

New genetic based therapies, such as or *SMN2* mRNA splicing modification and *SMN1* gene replacement therapy were developed in recent years.

Nusinersen (Spinraza, Biogen), the first-ever approved treatment for SMA patients, is an antisense oligonucleotide, which targets the *SMN2*-mRNA, alters splicing and thereby increases SMN protein production. It is administered via intrathecal injection. Clinical trials demonstrated improvements of survival in infants and motor function in infants and young children [68,69]. Current evidence suggests that early initiation of treatment, preferably pre-symptomatically, would maximize therapeutic benefits [70]. It remains uncertain whether treatment provides long-term effects. More recently alternative treatments have become available, that do not have the drawbacks of intrathecal ASO treatment (i.e. frequent intrathecal injections and the challenge of drug administration to individuals with severe scoliosis). Risdiplam is a second *SMN2* spicing modifier that is orally administered [3,70]. Finally, *SMN1* gene replacement therapy using an adeno-associated (AAV9) viral vector (Onasemnogene abeparvovec-xioi, Avexis) and administered via single intravenous injection, has been approved for use in young presymptomatic children and those with SMA type 1 [71]. These new treatments result in a substantial increase in resource requirements due to the excessive costs and will result in new management strategies as these therapies change the natural course of SMA. Supportive, symptomatic treatment will be necessary to complement SMN augmenting therapies.
Effect of these new treatments on respiratory muscle weakness is largely unknown, partly due to lack of natural history data.

Aim and outline of this thesis

For the last decades advances have been made in the respiratory supportive treatment of patients with NMDs. Despite these advances, there are still many unanswered questions and many of these treatments are not evidence-based but experience-based. This is partly due to heterogeneous group of patients with rare NMDs.
Although consensus statements are available, there are still important differences (inter) nationally in the respiratory management of patients with NMDs.
This thesis aims to answer some of these questions, and raised many more questions.

Not only advances have been made in the respiratory management of patients with NMDs. It is as very special era for patients with NMDs and the professionals treating them: treatments are being developed for specific NMDs, like SMA.
These treatments will probably change the natural history of these NMDs.
However, there are still gaps in our knowledge on the natural history of respiratory problems in these patients. This knowledge is required to evaluate the effect of these new treatments in the future.

General aims of his thesis

The following three general aims were formulated for this thesis:

1. To study the natural history of respiratory problems in Spinal Muscular Atrophy.
2. To gather evidence for commonly used supportive treatments in patients with neuromuscular diseases, such as airway clearance techniques and surgical correction of scoliosis.
3. To explore feasibility and reliability of surrogate measures of lung function in patients with neuromuscular diseases.

Thesis outline

Part 1 Natural history of respiratory problems in Spinal muscular atrophy

Chapter 2 *Natural history of lung function in spinal muscular atrophy.*
Aim: To assess the longitudinal course of lung function in treatment-naïve patients with different types of SMA.
Orphanet Journal of Rare Diseases 2020; 15:88

Chapter 3 *Natural history of respiratory muscle strength in spinal muscular atrophy.*
Aim: To study the longitudinal course of respiratory muscle strength for the different SMA types.
Orphanet Journal of Rare Diseases 2022; 17;70

Chapter 4 *Lung function decline preceding chronic respiratory failure in spinal muscular atrophy: a national prospective cohort study.*
Aim: To study the course of commonly used lung function outcomes the years preceding chronic respiratory failure, thereby hopefully being able to predict impending respiratory failure.

Chapter 5 *Relative hyperventilation in non-ventilated patients with spinal muscular atrophy*
Aim: To describe the clinical observation of lower range of carbon dioxide levels in patients with SMA, with an accelerated increase of carbon dioxide levels to normal prior to respiratory failure.
European Respiratory Journal 2020: 56: 2000162

Part 2 Supportive treatment in neuromuscular diseases

Chapter 6 *Evidence for beneficial effect of daily use of mechanical insufflation-exsufflation in patients with neuromuscular disorders: a systematic review and meta-analysis.*
Aim: Systematic review on the effect of daily use of MI-E on respiratory tract infections and admissions, lung function test results, respiratory characteristics, laryngeal response and qualitative outcome measures.

Chapter 7 *Short term effect of airway clearance on lung function in patients with neuromuscular diseases.*

Aim: To prospectively study the effect of air stacking and mechanical insufflation-exsufflation on lung function tests up to 2 hours after treatment in patients with neuromuscular diseases familiar with daily treatment.

Chronic Respiratory Disease 2022; 19: 14799731221094619

Chapter 8 *Effect of mechanical insufflation-exsufflation in children with neuromuscular weakness*

Aim: To study the number of respiratory tract infections requiring hospital admission the years before and after initiation of daily MI-E in a single center cohort of 37 children.

Pediatric Pulmonology; 2020: 55:510-513

Chapter 9 *Short term effect and effect on rate of lung function decline after surgery for neuromuscular or syndromic scoliosis.*

Aim: To prospectively compare the trends in lung function test results prior to and after scoliosis surgery in children with neuromuscular diseases, or dysmorphic syndromes.

Pediatric Pulmonology 2022; 57: 1303-09

Part 3 Lung function

Chapter 10 *Oscillometry: a substitute of spirometry in children with neuromuscular diseases?*

Aim: To prospectively assess the relation between results of oscillometry and spirometry in children with neuromuscular diseases

Pediatric Pulmonology 2022; 57: 1618-24

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CHAPTER 2

2

Natural history of lung function in spinal muscular atrophy.

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Abstract

Background

Respiratory muscle weakness is an important feature of spinal muscular atrophy (SMA). Progressive lung function decline is the most important cause of mortality and morbidity in patients. The natural history of lung function in SMA has, however, not been studied in much detail.

Results

We analysed 2098 measurements of lung function from 170 treatment-naïve patients with SMA types 1c–4, aged 4–74 years. All patients are participating in an ongoing population-based prevalence cohort study. We measured Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), and Vital Capacity (VC). Longitudinal patterns of lung function were analysed using linear mixed-effects and non-linear models. Additionally, we also assessed postural effects on results of FEV_1 and FVC tests. In early-onset SMA types (1c–3a), we observed a progressive decline of lung function at younger ages with relative stabilisation during adulthood. Estimated baseline values were significantly lower in more severely affected patients: $\%FEV_1$ ranged from 42% in SMA type 1c to 100% in type 3b, %FVC 50% to 109%, and %VC 44% to 96%. Average annual decline rates also differed significantly between SMA types, ranging from –0.1% to –1.4% for FEV_1, –0.2% to –1.4% for FVC, and +0.2% to –1.7% for VC. In contrast to SMA types 1c–3a, we found normal values for all outcomes in later-onset SMA types 3b and 4 throughout life, although with some exceptions and based on limited available data. Finally, we found no important differences in FVC or FEV_1 values measured in either sitting or supine position.

Conclusions

Our data illustrate the longitudinal course of lung function in patients with SMA, which is characterised by a progressive decline in childhood and stabilisation in early adulthood. The data do not support an additional benefit of measuring FEV_1 or FVC in both sitting and supine position. These data may serve as a reference to assess longer-term outcomes in clinical trials.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder (NMD), characterised by a progressive loss of spinal cord motor neurons. This is caused by survival motor neuron (SMN) protein deficiency due to homozygous loss of *SMN1* gene function in all patients.[1–3] SMA demonstrates a remarkably broad range in clinical disease severity, largely explained by variation in the *SMN2* gene copy number.[4] The current classification system distinguishes four SMA types based on age at symptom onset and whether patients acquire the ability to sit or walk independently.[3] The infantile-onset SMA type 1 is the most severe form and characterised by severe muscular weakness, hypotonia, severe morbidity and early mortality due to respiratory failure. Childhood-onset SMA types 2 and 3 are characterised by delayed gross motor development and progressive loss of motor function and muscle strength. SMA type 4 is the mildest type and has an onset in adulthood.[1–3,5]

Increased understanding of the disease course through natural history studies of the past decade has helped clinicians with providing timely supportive care[3,6] and facilitated clinical trial design to test efficacy of recently developed SMN protein augmenting drugs.[7,8] Nonetheless, there is still a lack of reference data on several aspects of SMA's natural history, including lung function, but obtaining additional 'treatment-naïve' patient data has become increasingly difficult now that *SMN2*-antisense oligonucleotide treatment is reimbursed in many countries.[9]

Reduced lung function is caused by weakness of respiratory muscles and underlies the increased susceptibility to respiratory tract infections. It is the most important cause of morbidity and mortality in patients with SMA.[2,6] Previous longitudinal studies of lung function included relatively small numbers of SMA patients, did not encompass the entire spectrum of severity or ages, focused on Forced Vital Capacity only, or had limited follow-up.[10–15] Additional natural history data of SMA patients treated according to the standards of care,[6] but prior to receiving recently introduced therapies, are important to further improve timing of supportive care and to explore its potential as an outcome measure to evaluate longer-term effects of new treatment strategies.[2,9,16,17] To study the natural history of lung function in SMA, we studied outcomes of several commonly used lung function tests (LFTs) longitudinally, using data from treatment-naïve patients participating in a large, population-based prevalence cohort study. We used Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), and Vital Capacity (VC) and here report their longitudinal course across the spectrum of SMA severity.

Methods

Design and participants

Patients enrolled in this study are participating in our ongoing prospective population-based prevalence cohort study on SMA in The Netherlands.[18,19] The study was approved by the local Medical Ethics Committee (No. 09-307/NL29692.041.09) and registered in the Dutch clinical studies and trials registry (https://www.toetsingonline.nl/). Written informed consent was obtained from all participants and/or their parents in case of minors. The reporting of this study conforms to the STROBE statement.[20]

For all patients we used multiplex ligation-dependent probe amplification (MLPA; SALSA MLPA kit P021-B1-01, MRC-Holland) to confirm homozygous loss of *SMN1* function and to determine *SMN2* copy numbers. We distinguished SMA types based on age at symptom onset and acquired motor milestones. In case of discrepancies, acquired motor milestones determined final classification. We used previously published additions to also distinguish subtypes (e.g., 2a-b, 3a-b; **Table 1**).[2,3,18,19,21] This is of importance, as a relationship between best acquired motor function and lung function has been reported in several NMDs, including SMA.[22] Patient data were used only if obtained prior to participation in a clinical trial or treatment with SMN protein augmenting drugs (i.e., 'treatment-naïve').

Table 1: Clinical classification of spinal muscular atrophy

SMA type	Age at symptom onset	Highest achieved motor milestone
1	0-6 months	Never acquires ability to sit unsupported
0/1a	Prenatal/neonatal	No head control
1b (classic SMA)	1-6 months	No head controle, unable to roll over
1c	3-6 months	Some additional motor skills, like head control or rolling over
2	6-18 months	Able to sit unsupported, unable to walk
2a		Unsupported sitting, able to stand or walk with help
2b		Unsupported sitting, able to stand or walk a few steps with help
3	> 18 months	Able to walk unsupported
3a	18-36 months	
3b	> 36 months	
4	≥ 18 years	Able to walk unsupported

Lung function tests (LFTs)

We retrieved lung function data from prospectively enrolled patients from two sources. First, we used spirometry data (FEV_1 and FVC) obtained from patients in our ongoing study,[18] using a handheld calibrated spirometer (MicroLab 3500®, PT Medical). These data were obtained prospectively between March 2013 and June 2018, at every study visit. Secondly, we included patients' (retrospective) spirometry data (Geratherm Spirostik®), collected between July 1991 and July 2018 at the department of pulmonology and Centre of Home Mechanical Ventilation at our hospital.[18] This allowed us to retrieve additional longitudinal FEV_1 and FVC data, and longitudinal data on VC. All LFTs were measured in sitting position, without corsets or braces.

Additionally, we evaluated the effect of posture by also measuring FEV_1 and FVC in supine position at every study visit. Normally, measurements in supine position would yield a lower FEV_1 and FVC,[23] but for SMA this was previously assessed only in a small number of patients. We obtained measurements in sitting position first, followed by measurements in supine position after a resting period to prevent a significant influence of fatigability. Lung function tests were performed by a small team of professionals experienced in conducting LFTs in children and adults with NMDs.

All LFTs were measured and reported according to the European Respiratory Society guidelines.[24] We report standardised LFT values, according to the Global Lung Function Initiative[25] and have therefore not transformed data to improve model fitting. Measuring height in SMA patients can be challenging. Arm span was used in most instances as a surrogate measure. In some cases, however, height was used. If so, it was measured preferably in standing position if patients were able to stand, or otherwise in sitting or supine position, using a flexible ruler. The use of a flexible ruler helped avoiding large underestimations due to contractures as much as possible.

Statistical analysis

We used descriptive statistics to describe baseline characteristics. All available patient data were used for analyses. We assessed longitudinal changes of lung function using linear mixed-effects models (LMMs). We hypothesised a progressive decline of lung function depending on SMA type over time, thus LMMs for the different outcomes contained age (at measurement), SMA type, and an interaction term of these two predictors as fixed factors. Dependency in the data due to repeated measures was accounted for by a random intercept per individual. A random slope for age was added to assess whether there were differences in rates of decline between patients (as measure of disease heterogeneity or between-patient slope variability). We used a likelihood ratio test to evaluate whether the rate of decline over age was significantly different between SMA types. We used estimated baseline values (i.e., the projected intercepts on the y-axes) as a surrogate for

lung function outcomes in the earliest stages of life, when these outcomes could not be measured. Model summary statistics and parameters estimates are reported (**Table 3**).

Because we cannot assume that the natural course of the outcomes of the different lung function tests is completely linear, we also fitted non-linear models. We used smoothed B-spline models with 3 knots, in which polynomial continuous regression lines are computed in between knots.[26] We have provided the visual output of these models to further aid interpretation of the natural history data, as coefficients for such models are not interpretable.

We assessed possible postural influences on FEV_1 and FVC by comparing repeated LFT measurements of individuals obtained on the same day. As data followed a non-normal distribution (Shapiro-Wilk test $P<0.05$, non-normally distributed residuals on visual inspection), the Wilcoxon signed-rank test was used. We used *R* (v3.6.0 with RStudio v1.2.1335) for all analyses.[27] The LMMs were fitted using the lmer function of *lme4* (v1.1–21) and *ggplot2* (v3.1.1) was used for data visualisation.[28,29]

Results

Demographics

We included 170 patients with SMA types 1c–4, between 4.1 and 73.9 years. Average follow-up was 4.4 years. We were unable to determine *SMN2* copy numbers in two participants (1.2%) due to insufficient quantities of DNA. Baseline characteristics of patients and performed LFTs are shown in Table 2.

Forced expiratory volume in 1 second

We analysed a total of 784 FEV_1 measurements from 163 patients with SMA types 1c–4 (**Table 2**). We found a progressive decline of FEV_1 in SMA types 1c–3a, but not in type 3b. The findings for type 3b likely also extend to type 4, but the limited number of observations precluded reliable estimations. After stratification for SMA type, linear analyses demonstrated significant differences in baseline $\%FEV_1$ values, i.e., 42% in SMA type 1c, 62% in type 2a, 81% in type 2b, 98% in type 3a, and 100% in type 3b (**Fig. 1**, **Table 3**). Average annual rates of $\%FEV_1$ decline differed significantly between SMA types over time ($\chi^2_{(5)} = 16.381$, $p = 0.0058$). There was a decline of 1.29% per year in type 2a, 1.37% in type 2b, and 0.73% in type 3a. Due to the limited number of observations, the slope parameters for patients with SMA types 1c (–0.40%) and 3b (–0.11%) were not significant (**Table 3**). Based upon our findings in patients with SMA types 2a and 2b, however, it is likely that FEV_1 in patients with type 1c will decline, while FEV_1 values in tube 3b appear to be stable over time and within normal ranges.

Table 2: Baseline characteristics and measurements of lung function

Patients

SMA type	Type 1c *(n = 6)*	Type 2a *(n = 48)*	Type 2b *(n = 34)*	Type 3a *(n = 43)*	Type 3b *(n = 35)*	Type 4 *(n = 4)*
M : F	3 : 3	19 : 29	12 : 22	18 : 25	18 : 17	4 : 0
***SMN2* copies**						
2	1	1	1	1	1	-
3	5	44	27	21	5	-
4	-	3	5	21	25	4
5	-	-	-	-	3	-
n/a	-	-	1	-	1	-
Mechanical ventilation: *n* (% of total)	5 (83.3%)	23 (47.9%)	3 (8.8%)	5 (11.6%)[b]	1 (2.9%)[b]	0
Median age at start of mechanical ventilation (IQR)	14.6[a] (13.1; 25.9)	12.3[b] (8.2; 16.9)	16.8 (12.7; 20.8)	39.9[c] (35.9; 48.3)	40.0[c]	n/a

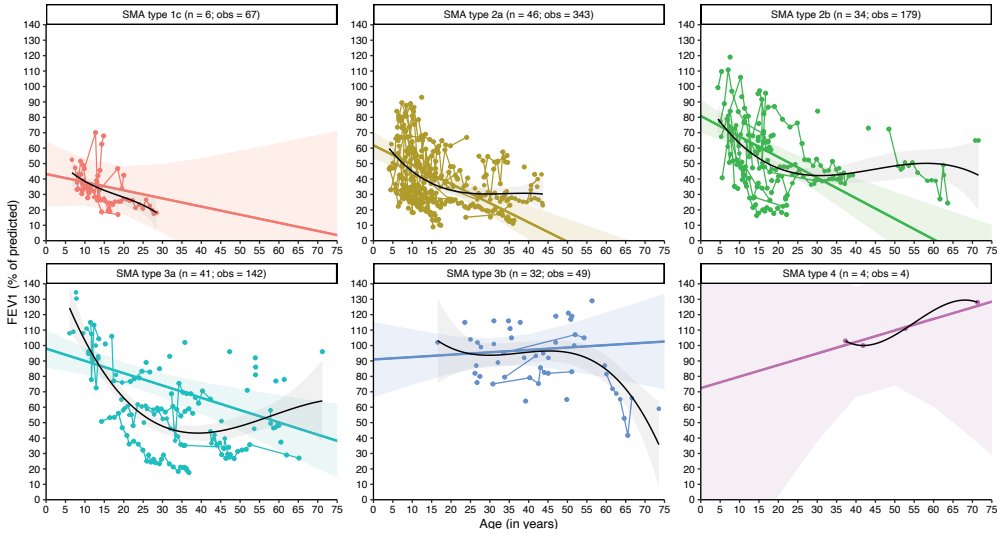
Assessments

Lung function test	Patients, *n (%)*	No. of patient assessments	Median no. of assessments per patient (range)
FEV_1	163 (95.9)	784	5 (1 – 40)
FVC	167 (98.2)	668	4 (1 – 32)
VC	80 (47.1)	646	6 (1 – 38)

SMA: spinal muscular atrophy; n number of patients or assessments; M: males, F: females; SMN2: survival motor neuron 2 gene; IQR: interquartile range; n/a: not available; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; VC: vital capacity; [a]: the high median age at which mechanical ventilation was initiated in patients with SMA type 1c is explained by the fact that in The Netherlands it was uncommon to initiate mechanical ventilation for infants with SMA type 1 until recent years, as it was considered not ethical to prolong life without any realistic outlook for further improvements of motor function at a later time. This has changed in the past years, following the introduction of SMN protein augmenting drugs and current clinical drug trials. [b]: the exact age at which mechanical ventilation was started is unknown for one patient; [c]: excluded are two patients with SMA type 3a and one patient with type 3b using either bi-level or continuous positive airway pressure for obstructive sleep apnoea syndrome. Ages are shown in years.

Non-linear analyses further confirmed the association of baseline FEV_1 values and SMA severity, and its progression over time (**Fig. 1**). The fastest FEV_1 decline was present at younger ages – exceeding the estimated annual rates of decline from our linear models (**Table 3**) – followed by a slower further decline during adulthood in SMA types 1c–3a. The available data suggest relatively stable FEV_1 values over time in types 3b and 4. The limited number of observations of patients with type 3b over 60 years ($n = 4$) likely explains the marked FEV_1 decline in elderly patients. When stratifying by *SMN2* copy number and SMA type, we found no differences in the longitudinal trajectories for any of the SMA types, with the possible exception of SMA type 3a. Here, patients with type 3a and 4 *SMN2* copies had a slower longitudinal decline in comparison to those with 3 *SMN2* copies.

Figure 1: Longitudinal changes of FEV_1 in SMA



Linear mixed-model (coloured lines) and non-linear (black) analyses of longitudinal changes in FEV_1 stratified by SMA type. Solid regression lines indicate the mean values of FEV_1 and its mean rate of decline over time. Shades represent 95% confidence intervals for the mean rates of decline.
n = number of patients; obs = number of observations.

Table 3: Model parameters

		Fixed Effects				Random effects	
	n	Intercept (SE)	95% CI Intercept	Slope	95% CI Slope	Std. dev. Intercept	Std. dev. Slope
FEV_1							
SMA type 1c	6	42.13 (4.58)	33.89; 50.59	−0.40	−1.42; 0.60 (*n.s.*)	6.11	1.12
SMA type 2a	46	61.71 (4.51)	52.44; 70.60	−1.29	−1.78; −0.81	24.35	1.21
SMA type 2b	34	81.37 (6.15)	68.36; 93.53	−1.37	−2.04; −0.73	25.06	1.18
SMA type 3a	41	97.61 (6.30)	84.80; 110.02	−0.73	−1.11; −0.35	23.20	0.64
SMA type 3b	32	100.35 (9.17)	81.91; 118.90	−0.11*	−0.55; 0.32* (*n.s.*)	16.62	n/a*
FVC							
SMA type 1c	5	49.71 (7.34)	34.65; 68.07	−1.15	−3.29; 0.70 (*n.s.*)	12.60	1.70
SMA type 2a	47	64.20 (5.29)	53.65; 74.64	−1.32	−1.90; −0.76	28.46	1.39
SMA type 2b	34	84.53 (6.07)	71.85; 96.50	−1.40	−2.10; −0.71	23.68	1.28
SMA type 3a	43	96.65 (6.17)	84.08; 108.73	−0.67	−1.06; −0.31	23.14	0.63
SMA type 3b	34	109.00 (7.42)	94.46; 123.50	−0.23*	−0.58; 0.11* (*n.s.*)	15.35	n/a*
VC							
SMA type 1c	6	44.09 (7.06)	28.41; 60.01	−0.78	−2.35; 0.63 (*n.s.*)	12.84	1.21
SMA type 2a	32	61.01 (4.62)	51.78; 70.16	−1.57	−2.23; −0.94	23.17	1.40
SMA type 2b	22	85.54 (6.98)	69.33; 98.18	−1.65	−2.59; −0.60	25.04	1.46
SMA type 3a	16	96.34 (9.05)	78.17; 114.60	−1.06	−1.71; −0.45	30.07	0.98
SMA type 3b	4	80.99 (19.67)	35.90; 124.82	0.21	−0.77; 1.23 (*n.s.*)	35.12	0.75

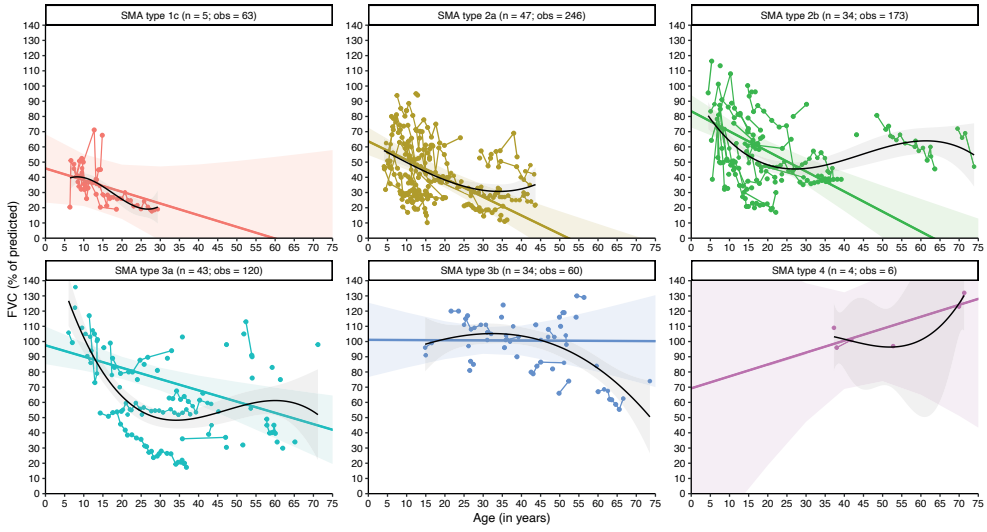
Model parameter estimates, standard errors, and confidence intervals for the linear mixed-effects models are shown. n: number of patients in each group; SE: standard error; CI: confidence interval; Std. dev: standard deviation; n.s.: slope parameter is not significant; n/a: not available; * due to a too limited number of repeated-measurements 'age at measurement' was omitted as a random factor from the mixed-effects model. The slope parameter (i.e. the annual rate of decline in % of predicted) will therefore likely be an overestimation of the true value.

Forced vital capacity

In total, we analysed 668 FVC measurements from 167 patients with SMA types 1c–4 (**Table 2**). Similar to FEV_1, we observed an FVC decline in the majority of patients over time. After stratification for SMA type, we found a progressive FVC decline in all SMA types, except for type 4 (**Fig. 2**). At baseline, linear analyses of %FVC demonstrated large differences, i.e., 50% in type 1c, 64% in type 2a, 85% in type 2b, 97% in type 3a, and 109% in type 3b. Significant differences in the average annual rate of decline between SMA types were present ($\chi^2(_5)$ = 14.202, p = 0.014). FVC declined 1.32% per year in type 2a, 1.4% in type 2b, and 0.67% in type 3a. The slope parameters for SMA types 1c (–1.15%) and 3b (–0.23%) were not statistically significant (**Table 3**). The differences in annual average decline between SMA types 2a and 2b, or 3a and 3b were not significant (p >0.05). Due to the limited repeated-measurements for type 3b, the estimated annual decline (–0.23%) will likely be an overestimation. In fact, the available data indicate relatively stable values over time for type 3b.

Comparable to FEV_1, non-linear analyses show that FVC decline is most pronounced at younger ages, exceeding the estimated annual rates of decline from our linear analyses. This is followed by a slower rate of decline or even stable course during adulthood in SMA types 1c–3a, whereas FVC remained relatively stable in type 3b throughout life. The steep decline in SMA type 3b from 55 years onwards is likely explained by limited measurements from older patients. The number of observations for patients with type 4 was too small for reliable estimations (**Fig. 2**).

Figure 2: Longitudinal changes of FVC in SMA

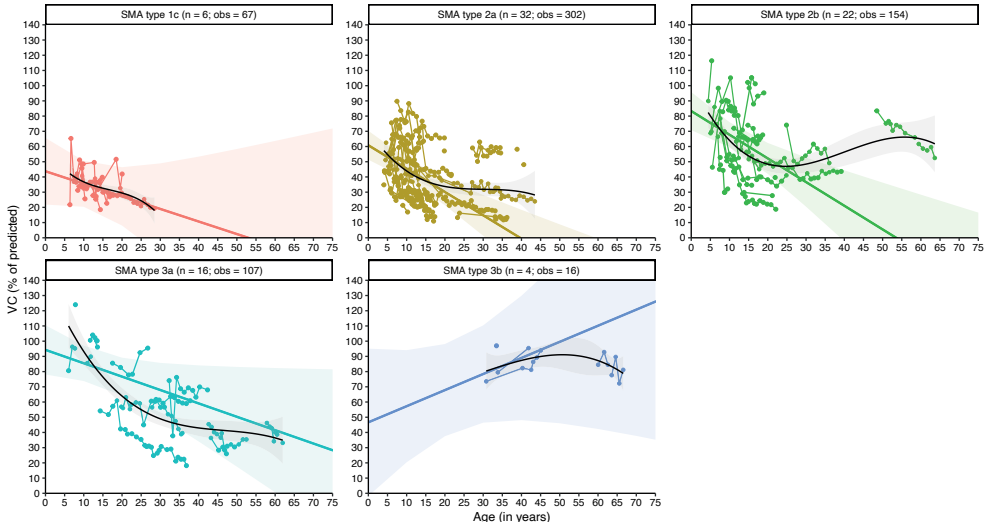


Linear mixed-model (coloured lines) and non-linear (black) analyses of longitudinal changes in FVC stratified by SMA type. Solid regression lines indicate the mean values of FVC and its mean rate of decline over time. Shades represent 95% confidence intervals for the mean rates of decline.
n = number of patients; obs = number of observations.

Vital capacity

Our FVC findings were further supported by a total of 646 VC measurements from 80 patients with SMA types 1c–3b (**Table 2**). Similar to FVC and FEV_1, in the majority of patients we observed a VC decline with increasing age. Linear analyses demonstrated large differences in baseline %VC values, i.e., 44% in SMA type 1c, 61% in type 2a, 86% in type 2b, and 96% in type 3a. The predicted average baseline value of 81% for SMA type 3b is likely an underestimation due to the limited number of observations (**Fig. 3, Table 3**). Average rates of yearly VC decline were significantly different between SMA types ($\chi^2(_4)$ = 10.223, p = 0.037) and averaged 1.57% in type 2a, 1.65% in type 2b, and 1.06% in type 3a, whereas the slope parameters were not significant for SMA types 1c (–0.78%) and 3a (+0.21%) due to the limited number of observations for these groups (**Table 3**). The small difference in slope parameters between patients with types 2a and 2b was not significant (p >0.05). Available data suggest that VC in type 3b was relatively stable over time and within normal ranges. Non-linear analyses further indicate that the longitudinal pattern of VC decline is similar to what we found for FEV_1 and FVC, i.e., the steepest decline is expected at younger ages in the majority of SMA types, followed by a relatively stable course or slower further decline during adulthood (**Fig. 3**).

Figure 3: Longitudinal changes of VC in SMA

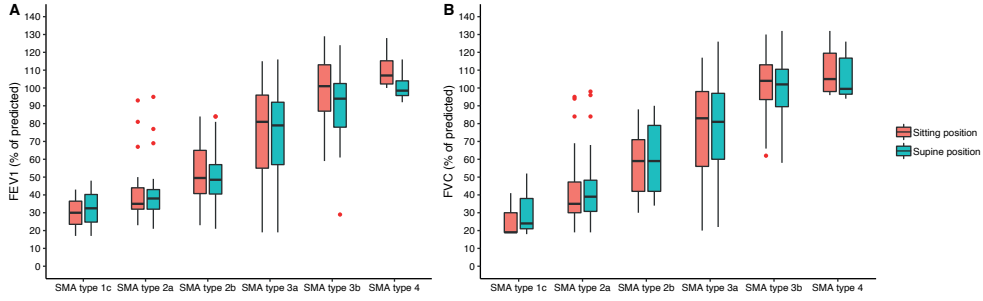


Linear mixed-model (coloured lines) and non-linear (black) analyses of longitudinal changes in VC stratified by SMA type. Solid regression lines indicate the mean values of VC and its mean rate of decline over time. Shades represent 95% confidence intervals for the mean rates
of decline. n = number of patients; obs = number of observations.

Postural influence on lung function tests

We assessed postural effects on FEV_1 and FVC using data from 117 and 162 patients, respectively (**Fig. 4**). FEV_1 values differed significantly at group level, although with very small absolute differences: median FEV_1 was 73% vs. 72%, and mean FEV_1 was 70.4% vs. 67.9%, respectively ($W = 4107$, $p = 0.0101$, $r = 0.166$, sitting vs. supine position). FVC values, however, did not differ significantly: median FVC was 75.0% vs. 77.5% and mean FVC was 72.7% vs. 73.1%, respectively ($W = 5485.5$, $p = 0.847$, $r = 0.01$). Differences between FEV_1 or FVC obtained in sitting vs. supine position were not influenced by disease duration.

Figure 4: Postural influence on FEV_1 and FVC measurements



Comparison of FEV_1 (**4A**) and FVC (**4B**) measurements obtained in sitting (red) and supine (blue) position, stratified for SMA type. Small red circles indicate outliers.

Discussion

Here, we describe the natural history of lung function in treatment-naïve patients with SMA based on a large number of assessments of FEV_1, FVC, and VC, in a cohort that encompasses the entire spectrum of SMA severity. At baseline, FEV_1, FVC, and VC are significantly lower in more severe SMA types (1c, 2a), affected to a lesser extent in type 2b and virtually normal in type 3a. Longitudinal decline of lung function in SMA patients is most pronounced during childhood and stabilises in early adulthood. Patients with late-onset SMA (types 3b and 4) are likely to have a stable lung function throughout life, with some exceptions to the rule.

Several relatively small studies previously evaluated the natural history of lung function in patients with SMA.[10–14,30–38] FVC was studied most frequently and progressive FVC decline has been reported, caused by progressive respiratory muscle failure, limited lung and chest wall growth, and scoliosis progression.[39,40] Previously reported rates of FVC decline are, however, different from our data. For example, Khirani suggested that patients with

SMA type 2 (n = 7) had an earlier but comparable rate of decline compared to patients with type 3 (n = 9).[13] Werlauff found no significant difference between patients with SMA type 2 younger and older than 20 years (n = 42, cross-sectional data).[33] By contrast, our findings indicate that rates of decline differ between SMA types 2 and 3, are not constant over time, and may even stabilise in adulthood. Our data also suggest that there are important differences of lung function already at a very young age (i.e., from 'baseline' onwards), possibly caused by a more rapid decline in the first years of life, specifically in more severely affected patients. These differences with previous studies are likely explained by the much larger number of observations in our work, facilitating more accurate comparisons between SMA types.

Non-linear FVC analyses showed that the fastest progression is expected during childhood, followed by relative stabilisation during early adulthood in SMA types 1c–3a. This pattern has previously also been noticed by Ioos in a study in which virtually all FVC measurements were obtained before the age of 25 years,[37] and more recently by Trucco in a cohort of paediatric patients with SMA types 2 and 3.[15] For SMA types 3b and 4 there are, to the best of our knowledge, no longitudinal studies available for comparison. Our data suggest that in most of these patients FVC remains relatively stable.

In addition to FVC, we longitudinally analysed FEV_1 and VC. There are very few previous studies on these outcomes for patients with SMA, impeding meaningful comparisons. Given the large number of observations in our work, we conclude that both FEV_1 and VC seem to follow a pattern similar to FVC: significant differences are already present at baseline between SMA types, possibly caused by a rapid decline in the first years of life, specifically in more severely affected patients. This is followed by a yearly decline of 0.2–2% during childhood and adolescence, and a relative stable phase during adulthood. At group level, VC and FEV_1 values remain normal throughout life in SMA type 3b. The available data for patients with SMA type 4 in our work was very limited. However, given the characteristics of SMA type 4 it is likely that these patients will have normal longitudinal values as well. Nonetheless, some individuals with type 3b or 4 may show progressive worsening of lung function that warrants continued awareness. The limited available data on older patients with types 3b and 4 precluded further analyses to identify the characteristics that predict for such a decline.

In our work we stratified patients using the SMA classification system with some modifications that reflect acquired motor milestones other than sitting (type 2) or walking unsupported (type 3). This approach has been helpful in previous studies to uncover differences of the natural history between SMA types. For example, in comparison to type 2a, patients with SMA type 2b are less likely to use mechanical ventilation later in life and require scoliosis surgery at older ages.[18,41]. Here, we have shown that these differences

are also present for lung function at baseline. Together, it underscores the prognostic usefulness of additional motor milestones, such as rolling and standing with assistance (**Table 1**), in addition to sitting and walking unsupported that are used in the current classification system.[3,42,43]

The general progressive pattern of lung function decline in patients with SMA identified in our work is rather similar to the observed progressive pattern of muscle strength decline in patients with SMA,[19] but in adults and particularly those with milder SMA types (i.e., types 3b and 4) lung function may be more stable than skeletal muscle strength. As previously suggested, lung function is therefore a suitable longitudinal outcome measure for patients with SMA, at least until early adulthood.[17]

An effect of posture on LFT outcomes has previously been reported for patients with NMDs. Higher outcomes are usually reported for measurements obtained in supine position, possibly due to a mechanical advantage of the diaphragm and muscle fibre stretching.[31,33,37,44] However, we found no significant differences when comparing FVC measured in sitting and supine position. Furthermore, the differences between FEV_1 measurements were so small that we consider them clinically irrelevant. Given the size of our cohort, measurement standardisation, and consistency across SMA types and patients' ages, our findings question the usefulness of measurements in both positions, especially as they are time-consuming and relatively difficult to perform in wheelchair-bound patients.

Our work has several strengths. First, we provided baseline and longitudinal reference data not only for FVC, but also for FEV_1 and VC. Secondly, the large size of our cohort, including a large number of repeated-measurements and relatively long follow-up, allowed for more detailed longitudinal analyses. Finally, LFT therapists and physicians experienced in performing LFTs in paediatric and adult patients with NMDs conducted all tests, assuring measurement reliability.

We also acknowledge several limitations of our work. Broad confidence intervals around both intercept and slope in very young children and elderly patients indicate considerable inter-individual variation. This is partly explained by the inability to reliably perform LFTs in young children and inclusion of a limited number of elderly patients. Secondly, the observed patterns of pulmonary function decline, characterized by relative stabilization during adulthood, may partially also be explained by the fact that the most severely affected patients could have been lost to follow-up at higher ages, for example due to shorter survival or need for invasive mechanical ventilation. This could particularly be the case for patients with SMA types 1c and 2a. However, we have also observed this pattern in patients with SMA types 2b and 3a, in whom invasive mechanical ventilation

is not initiated frequently and survival is not shortened or to such a limited extent that it becomes irrelevant in this context.[18,21,45,46] A similar caution for the interpretation of data of more mildly affected patients applies (i.e., types 3b and 4), as patients with long term stable symptoms could have been lost to follow-up as well.

Our analyses are based upon an uneven distribution of repeated-measures data across SMA types. Most patients with repeated lung function assessments had SMA types 2a, 2b, or 3a. This is caused by the fact that these patients regularly have follow-up visits at the pulmonology department or Centre of Home Mechanical Ventilation at our hospital, because of a higher likelihood of requiring supportive therapy (e.g., cough assistance or mechanical ventilation) in comparison to those with types 3b and 4. The relatively limited number of (repeated) observations for SMA type 1 is explained by the fact that survival in type 1 is short and most of these patients will require (invasive) mechanical ventilation and usually will be lost to follow-up for regular LFTs. Furthermore, we were not able to report LFT results related to known confounders, like severity of (corrected) scoliosis, use of airway clearance techniques, or mechanical ventilation. However, we consider this less important as we focussed on the natural history with treatment according to the standards of care, which include scoliosis correction, airway clearance techniques, and/or mechanical ventilation.[3,6] LFTs are known to be influenced by respiratory tract infections,[17] which were not taken into account. Finally, lung function it not solely defined by the 3 main outcomes used in our work. Data on several other outcomes, including peak cough flow, peak expiratory flow, and maximal inspiratory and expiratory pressures would further improve our understanding of lung function in patients with SMA and should be addressed in future work.

Conclusions

The natural history of lung function in SMA is characterised by a progressive decline, particularly in SMA types 1c, 2, and 3a. This decline is most pronounced in (early) childhood and stabilises in early adulthood. Our data do not support additional benefits of measuring FEV_1 or FVC in both sitting and supine position. Our data may serve as a reference to assess longer-term outcomes in clinical trials.

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CHAPTER 3

Natural history of respiratory muscle strength in spinal muscular atrophy.

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Background

Respiratory complications are the most important cause of morbidity and mortality in Spinal Muscular Atrophy (SMA). Respiratory muscle weakness results in impaired cough, recurrent respiratory tract infections and eventually can cause respiratory failure. We assessed longitudinal patterns of respiratory muscle strength in a national cohort of treatment-naïve children and adults with SMA, hypothesizing a continued decline throughout life.

Methods

We measured Maximal Expiratory and Inspiratory Pressure (PE_{max} and PI_{max}), Sniff Nasal Inspiratory Pressure (SNIP), Peak Expiratory Flow (PEF), and Peak Cough Flow (PCF) in treatment-naïve patients with SMA. We used mixed-models to analyze natural history patterns.

Results

We included 2172 measurements of respiratory muscle function from 80 treatment-naïve patients with SMA types 1c-3b. All outcomes were lower in the more severe phenotypes. Significant differences in PEF were present between SMA types from early ages onwards. PEF decline was linear (1-2%/year). PEF reached values below 80% during early childhood in types 1c-2, and during adolescence in type 3a. PE_{max} and PI_{max} were severely lowered in most patients throughout life, with PE_{max} values abnormally low (i.e. < 80 cmH_2O) in virtually all patients. The PE_{max}/PI_{max} ratio was < 1 throughout life in all SMA types, indicating that expiratory muscles were most affected. All but SMA type 3b patients had a lowered PCF. Patients with types 2b and 3a had PCF levels between 160 and 270L/min, those with type 2a around 160L/min and patients with type 1c well below 160L/min. Finally, SNIP was low in nearly all patients, most pronounced in more severely affected patients.

Conclusions

There are clear differences in respiratory muscle strength and its progressive decline between SMA types. We observed lower outcomes in more severe SMA types. Particularly PEF may be a suitable outcome measure for the follow-up of respiratory strength in patients with SMA. PEF declines in a rather linear pattern in all SMA types, with clear differences at baseline. These natural history data may serve as a reference for longer-term treatment efficacy assessments.

Background

Spinal muscular atrophy (SMA) is a severe neuromuscular disease (NMD) caused by deficiency of survival motor neuron (SMN) protein, due to homozygous loss of *SMN1* gene function. SMA demonstrates a broad range in clinical disease severity, which is reflected by the distinction of 4 types in the clinical classifications system (1,2). Improved understanding of the natural history of SMA has facilitated improvements of standards for supportive care and clinical trial design (1,3–6). Respiratory complications, such as hypoventilation and impaired secretion clearance, are the most important cause of morbidity and mortality in SMA (1,2) but respiratory outcome measures have not yet been used as primary outcomes in clinical trials. This is, at least partially, caused by a lack of reference data (7,8).

Respiratory muscle weakness in SMA is characterized by a rather unique pattern with predominant weakness of (mainly expiratory) intercostal muscles and relative sparing of (inspiratory) diaphragm function (9,10). Respiratory muscle weakness is associated with decreased pulmonary compliance, lung underdevelopment, decreased ability to cough, and it may ultimately lead to respiratory failure (11).

Improved insights into the natural history of respiratory muscle strength could guide therapeutic management (12), improve timing of supportive care (1), and facilitate its use as an outcome measure for longer-term follow-up of patients or treatment efficacy assessments (2,7,13,14). Tests of respiratory muscle strength may detect respiratory insufficiency earlier than more frequently used measurements of expiratory lung function (e.g. Forced Vital Capacity (FVC)). Longitudinal studies on the decline of respiratory muscle strength have been performed in other NMDs but not in SMA (15). Therefore, we studied the natural history of respiratory muscle strength and assessed differences between SMA types in a large, population-based, treatment-naïve cohort of SMA patients.

Methods

Patient characteristics and general procedures

Patients participated in a prospective clinical cohort study on SMA. We captured patient characteristics using standardized questionnaires and physical examinations, including motor function assessments and lung function tests, as described previously (8,16,17). We used patient data obtained prior to participation in a clinical trial or treatment with SMN protein augmenting drugs (i.e., 'treatment-naïve'). The local Medical Ethical Committee approved this study (09-307/NL29692.041.09) and informed consent was obtained from all participants and/or their parents in case of minors. The reporting of this study conforms

to the STROBE statement (18). Homozygous loss of *SMN1* function and *SMN2* copy number were determined using multiplex ligation-dependent probe amplification (MLPA; SALSA kit P021-B1-01, MRC-Holland) (16). Using the SMA classification system, we distinguished different SMA types as described previously (Additional File 1) (2,6,17,19).

Respiratory muscle strength tests

We used respiratory muscle strength data of included patients collected during regular visits to the outpatient departments of pulmonology and the Center for Home Mechanical Ventilation at our hospital. Not all tests were performed at each visit. Data were not collected during hospital admissions, to prevent inclusion of measurements that are influenced by, for example, the presence of respiratory tract infections. For this study we used tests on expiratory (Maximal Expiratory Pressure (PE_{max}), Peak Expiratory Flow (PEF), Peak Cough Flow (PCF)) and inspiratory strength (Maximal Inspiratory Pressure (PI_{max}), Sniff Nasal Inspiratory Pressure (SNIP)). All measurements were unassisted, i.e. not following manual compression or lung volume recruitment with frog-breathing, air stacking or mechanical insufflation-exsufflation.

PE_{max} and PI_{max} are non-invasive tests for the direct measurement of strength of expiratory and inspiratory muscles (15). We measured PE_{max} and PI_{max} from Total Lung Capacity and Residual Volume respectively, using the Geratherm Spirostik®. A nose-clip and flanged mouthpiece were used. Air leakage was prevented by a technician holding the lips. In some cases an oronasal mask was used. At least 5 repeated attempts were made. We recorded largest pressures and compared to the reference values provided by Wilson (20). We calculated the PE_{max}/PI_{max} ratio to assess the relative impairment of expiratory versus inspiratory muscles (21,22). SNIP is nasal pressure measured during a maximal sniff. It is a simple test of inspiratory muscle strength. We measured SNIP in both nostrils using the Micro Medical MicroRPM®. Maximal nasal pressure during at least 5 sniffs, performed from Functional Residual Capacity, was compared to reference values (23,24). Finally we measured maximal flow during expiration and cough: PEF and PCF. We obtained PEF values from flow-volume curve data as the maximal expiratory flow achieved from forced expiration following maximal lung inspiration, using the Geratherm Spirostik® spirometer. We recorded the largest outcome from at least 3 qualitatively acceptable attempts. We reported absolute PEF values and standardized values (25,26). We measured PCF by maximal cough using both spirometry (Geratherm Spirostik®) and a peak flow meter (Assess®, PT-medical). We recorded the best outcome of 3 qualitatively acceptable attempts. Outcomes were reported as absolute values and compared to reference values (27,28).

We measured all outcomes according to international guidelines (29), with patients in sitting position, without wearing corsets or braces. We used strong verbal encouragement

and visual feedback to achieve maximal and reproducible test results. A resting period between tests prevented a significant influence of fatigability. All tests were performed by a small team of experienced professionals. We reported some outcomes as standardized values, i.e. as a percentage of the predicted value for age, height, weight, and sex. It is important to recognize that measuring height in SMA patients can be challenging. Tape-measured arm span was used preferably as a surrogate measure in patients unable to stand (8,30).

Statistical analysis

We performed longitudinal analyses of PE_{max}, PI_{max}, PE_{max}/PI_{max} ratio, PEF and PCF. We used a cross-sectional analyses to assess the differences in SNIP outcomes between SMA types. A longitudinal analysis was hampered due to a too limited number of observations.

For the longitudinal analyses we used all available measurements and hypothesized progressive worsening of respiratory muscle strength over time, depending on SMA type. As it was unlikely that the longitudinal patterns were completely linear, we used non-linear analyses. We fitted smoothed B-spline models with 3 knots, in which polynomial continuous regression lines were computed in-between knots (31). For PEF we additionally assessed the longitudinal pattern with a linear mixed-effects model (LMM). The model contained age, SMA type and an interaction term of these two predictors as fixed factors. Dependency in data due to repeated measures was accounted for by a random intercept per individual. A random slope for age was added to assess differences in rates of decline between patients (as a measure of disease heterogeneity or between-patient slope variability). We evaluated whether the rate of decline over age was significantly different between SMA types using a likelihood ratio test. For cross-sectional analysis of SNIP the first measurement of all patients was used. For the cross-sectional comparisons between SMA types we hypothesized that patients with milder SMA types would be less affected. As the assumptions of normality were met, a one-way ANOVA was used for comparisons between SMA types. A possible trend of increasing respiratory muscle strength with milder SMA types was assessed using the Jonckheere-Terpstra trend test.

Results

Demographics

We included 80 patients with genetically confirmed SMA types 1c–3b in this study. Ages at measurements ranged from 4.1 to 66.6 years. Baseline characteristics are shown in Table 1.

Table 1: Baseline characteristics

	Participants					
	Total number (n)	**SMA type 1c *(n)***	**SMA type 2a *(n)***	**SMA type 2b *(n)***	**SMA type 3a *(n)***	**SMA type 3b *(n)***
Patients	80	6	32	22	16	4
Female gender	52	3	20	14	12	3
SMN2 copies:						
2	4	1	1	1	1	-
3	66	5	29	18	12	2
4	10	-	2	3	3	2
Tests of respiratory muscle strength						
Peak expiratory flow (PEF)						
Patients	79	6	31	22	16	4
Tests	651	67	297	156	114	17
Follow-up (years) [IQR]	6.7 [1.2-12]	6.8 [3.5-8.2]	7.3 [1.3-12.2]	6.2 [1.2-11.8]	2.1 [0.4-9.8]	11.1 [7.7-15.3]
Peak cough flow (PCF)						
Patients	61	4	27	19	9	2
Tests	288	27	144	76	35	6
Follow-up (years) [IQR]	3.6 [0.3-8.1]	6.6 [4.7-8.8]	5.6 [0.8-7.9]	3.4 [0.3-8.3]	0.9 [0.0-2.2]	2.0 [1.0-3.0]
Maximum expiratory pressure (PEmax)						
Patients	75	6	28	22	15	4
Tests	586	59	261	148	102	16
Follow-up (years) [IQR]	5.8 [1.1-10.2]	4.4 [1.8-7.1]	6.1 [1.5-11.2]	6.2 [1.0-11.5]	3.0 [0.4-9.2]	7.3 [4.9-9.6]
Maximum inspiratory pressure (PImax)						
Patients	76	6	28	22	16	4
Tests	590	60	263	148	103	16
Follow-up (years) [IQR]	6.3 [1.1-10.6]	6.7 [3.5-7.6]	6.6 [1.5-13.0]	6.2 [1.0-11.5]	2.5 [0-9.2]	7.3 [4.9-9.6]
PEmax / PImax ratio						
Patients	75	6	28	22	15	4
Tests	582	57	259	147	103	16
Follow-up (years) [(IQR]	5.8 [1.1-10.2]	4.4 [1.8-7.1]	6.1 [1.5-11.2]	6.2 [1.0-11.5]	3.0 [0.4-9.2]	7.3 [4.9-9.6]
Sniff inspiratory pressure (SNIP)						
Patients	57	3	22	19	11	2

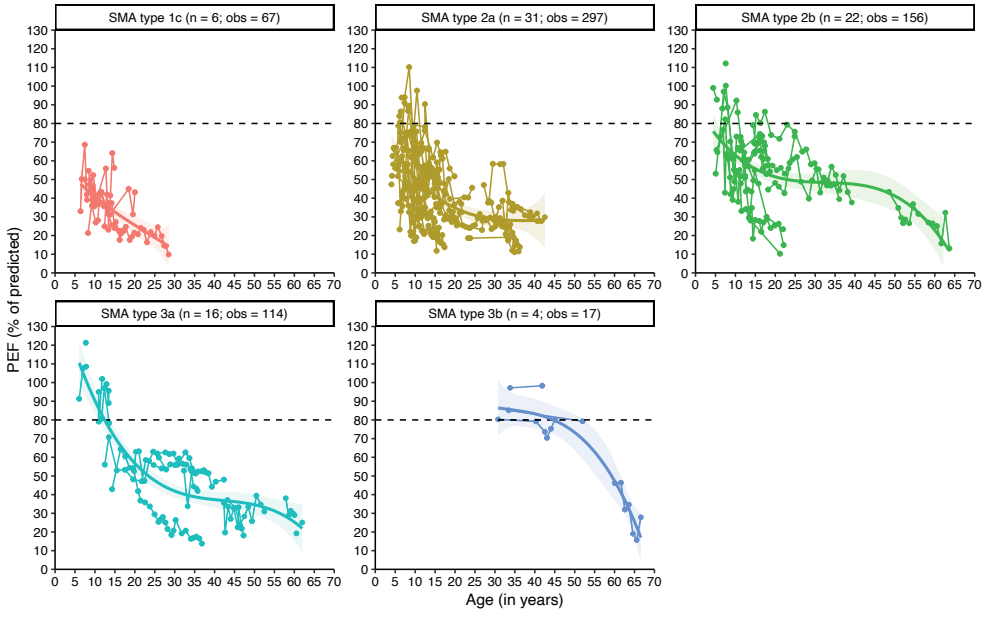
Legend: IQR = interquartile range; n = number; PCF = Peak Cough Flow; PEF = Peak Expiratory Flow; PEmax = Maximal Expiratory Pressure; PImax = Maximal Inspiratory Pressure; SNIP = Sniff Nasal Inspiratory Pressure

Peak Expiratory Flow (PEF)

We analyzed 651 longitudinal measurements of PEF from 79 patients (Table 1). At baseline, PEF values differed significantly between SMA types (Fig. 1), i.e. 49%, 73%, 87% and 96% in SMA types 1c, 2a, 2b and 3a, respectively. The estimate for patients with SMA type 3b is unreliable, due to a limited number of observations (Table 1). PEF decline to values <80% was observed in early childhood in SMA types 1c–2b, but not until adolescence or early adulthood in type 3a. In our linear analyses the average annual rates of decline did not differ significantly between SMA types ($\chi^2_{(4)} = 6.2533$, P = 0.181). PEF declined with 0.9%, 2.0%, 1.8%, 1.3% and 1.4% per year in SMA type 1c, 2a, 2b, 3a, and 3b respectively (model parameter estimates are shown in Additional File 2).

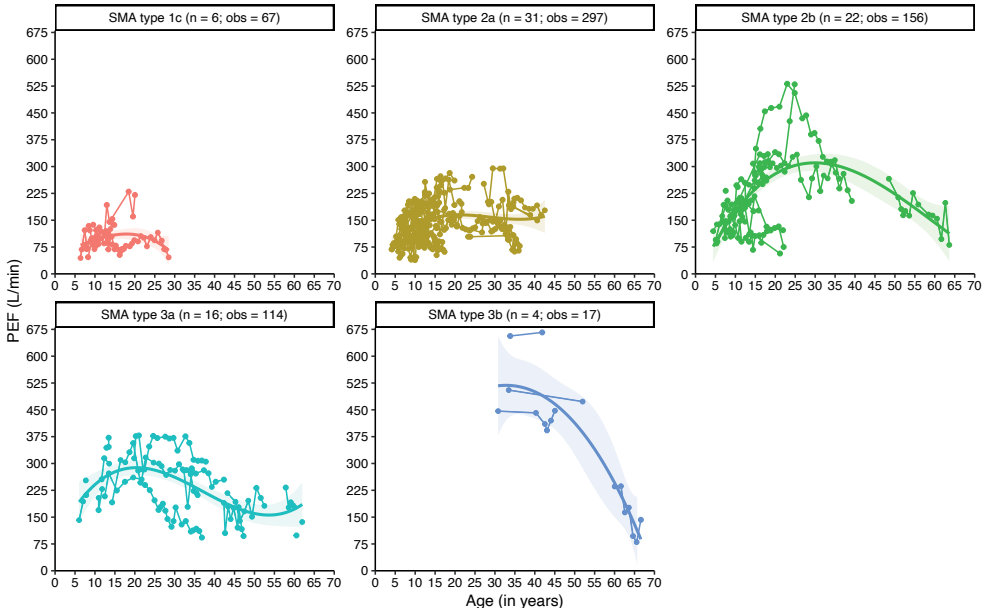
Non-linear analyses corroborate that PEF decline during early life is largely linear in most SMA types. In SMA type 2a this decline appears to be much faster during early childhood in comparison to children with type 2b. In adults with SMA types 2a, 2b and 3a we observed relative stabilization, although the data suggest that PEF decline can still occur during adulthood. Absolute values of PEF for the different SMA types are shown in Figure 2.

Figure 1: Longitudinal patterns of Peak Expiratory Flow (PEF) (in % of predicted) in different SMA types



Legend: n = number of patients; obs = number of observations
The horizontal line at 80% of predicted PEF represents the lower limit of the normal range.

Figure 2: Longitudinal patterns of Peak Expiratory Flow (PEF) in L/min in different SMA types



Legend: n = number of patients; obs = number of observations

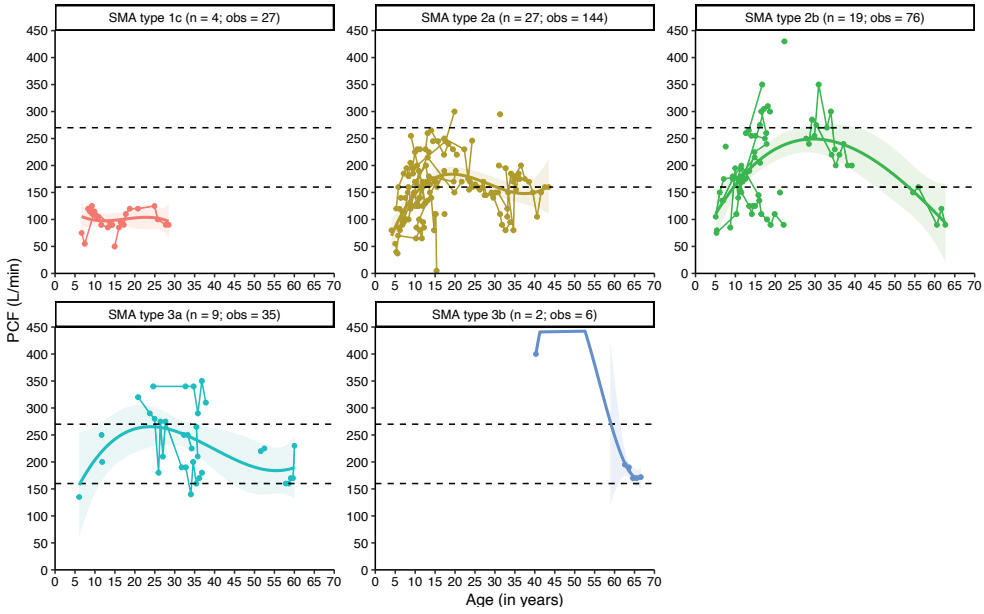
Peak Cough Flow (PCF)

We obtained 288 measurements from 61 patients. Longitudinal analyses are shown in Figure 3, in which the important therapeutic thresholds of 270 L/min (indicating vulnerability to respiratory failure during otherwise trivial respiratory tract infections (RTIs)) and 160 L/min (indicating the boundary below which secretion clearance becomes ineffective) are marked (32).

PCF was lowest in SMA type 1c, with values <160 L/min throughout life. After early childhood, patients with SMA type 2 reached values between 160 and 270 L/min, with clear differences between types 2a and 2b. Median PCF remained around 160 L/min in type 2a

during adolescence and early adulthood, whereas in type 2b median PCF steadily increased until (early) adulthood. Patients with SMA type 3a had higher PCF values from earlier ages onwards in comparison to type 2b, but median values were still well below normal. The limited available data obtained from patients with type 3b indicate that even for these more mildly affected patients, PCF values may decrease in aging individuals.

Figure 3: Longitudinal patterns of Peak Cough Flow (PCF) in L/min in different SMA types

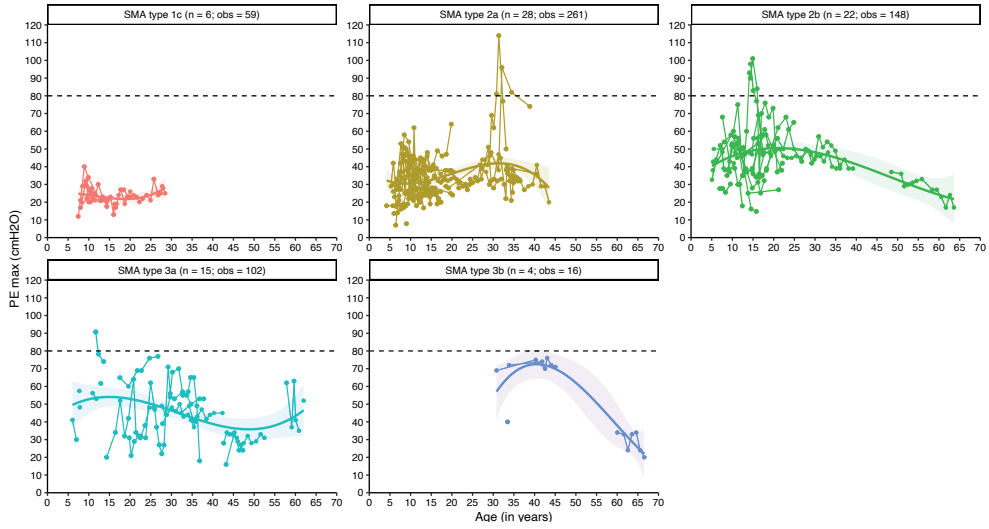


Legend: n = number of patients; obs = number of observations
The horizontal lines represent two important thresholds. In adults and children over 12 years of age a PCF of 160 L/min is necessary for effective secretion clearance and a PCF of 270 L/min or more is associated with resilience to respiratory infection.

Maximal Expiratory Pressure (PE_{max})

We analyzed 586 measurements from 75 patients (Fig. 4), showing lower PE_{max} values from early childhood onwards in patients with SMA types 1c–3a compared to the reference population, where PE_{max} values are usually ≥80 cmH_2O during adulthood (20). Patients with type 1c had severely lowered PE_{max}, without improvements with increasing age. PE_{max} in types 2a and 2b increased in adolescence to 40–50 cmH_2O. It is noteworthy that, despite limited data, all PE_{max} values from patients with SMA type 3b were < 80 cmH_2O and suggestive of a decline later in life.

Figure 4: Longitudinal patterns of Maximal Expiratory Pressure (PEmax) in cmH2O in different SMA types



Legend: n = number of patients; obs = number of observations
The horizontal line represents the lower limit of normal PEmax.

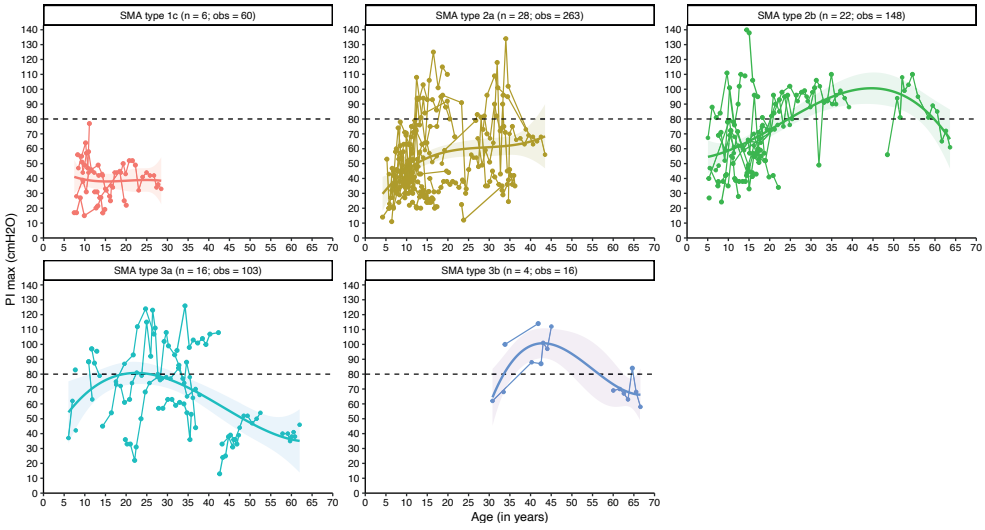
Maximal Inspiratory Pressure (PI_{max})

We assessed PI_{max} longitudinally using 590 measurements from 76 patients (Fig. 5). Large intra- and inter-individual differences were present, in accordance with findings in the reference population (33). Overall, PI_{max} was most affected in type 1c without improvements with increasing age. In patients with type 2a, PI_{max} increased to approximately 50–60 cmH_2O in adolescence. By contrast, patients with SMA type 2b reached PI_{max} values >80cmH_2O during adulthood. Patients with type 3a had a similar pattern, although in our cohort they did decline well below 80 cmH_2O from approximately 30 years onwards. The limited number of observations precludes definite conclusions for SMA type 3b.

PE_{max}/PI_{max} ratio

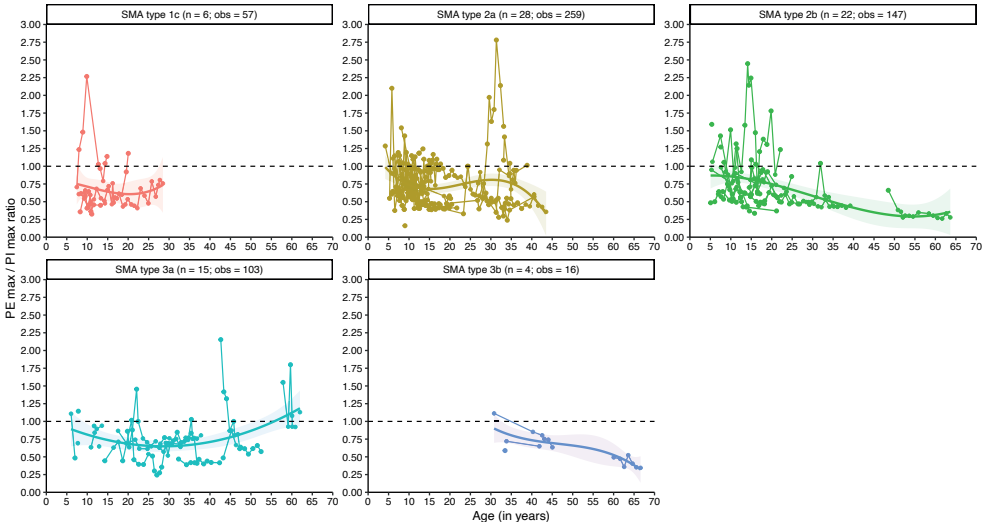
We obtained 582 measurements from 75 patients. Figure 6 summarizes the longitudinal course, with a median ratio < 1 for all SMA types, except for a small number of older patients with SMA type 3a (but not type 3b).

Figure 5: Longitudinal patterns of Maximal Inspiratory Pressure (PImax) in cmH2O in different SMA types



Legend: n = number of patients; obs = number of observations
The horizontal line represents the lower limit of normal PImax.

Figure 6: Longitudinal patterns of PEmax/ PImax- ratio

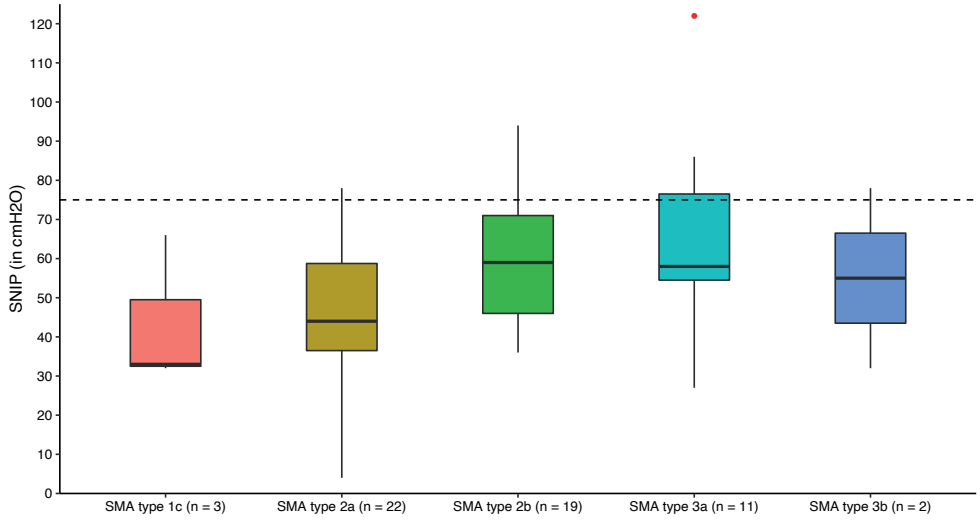


Legend: n = number of patients; obs = number of observations

Sniff Nasal Inspiratory Pressure (SNIP)

We used the available SNIP data from 57 patients (median age: 12.9 years (IQR 9.9-29.0)). SNIP was not statistically different between SMA types ($F(4,52) = 2.219$, $P = 0.080$). Median SNIP was 33, 44, 59, 58 and 55 cmH_2O in SMA types 1c, 2a, 2b, 3a, and 3b, respectively. We found a significant trend of increasing SNIP values with milder types ($JT = 743$, $P=0.0053$). Importantly, virtually all SNIP outcomes were below 75 cmH_2O, which is considered the lower limit of normal (Fig. 7).

Figure 7: Sniff Nasal Inspiratory Pressure (SNIP) for the different SMA types.



Legend: Boxplot of median SNIP values for each SMA type; red dots indicate outliers.

Discussion

Here, we present natural history data on the longitudinal course of respiratory muscle strength in treatment-naïve patients with SMA. We show that there are clear differences in respiratory muscle strength between SMA types with a progressive decline. In general, measurements of respiratory muscle strength are most affected in the more severe SMA types. Based upon our data, particularly PEF may be a suitable outcome measure for follow-up of patients with SMA.

Progressive respiratory muscle weakness is the most important cause of morbidity and mortality in patients with SMA (1,2) and contributes to the increasing dependency on mechanical ventilation of patients with SMA types 1 and 2 (34). The absence of respiratory function measures as a primary outcome in the pivotal clinical trials of recently introduced

genetic therapies for SMA is at least partially explained by the scarcity of reference data (4,5). Recent studies on the effect of nusinersen treatment in adult patients have focussed on motor scores and indicate that identification of the 'ideal' outcome parameter, reflecting both worsening or improvement in motor function at all grades of disease severity, might not be feasible. This has contributed to the advice that future studies should focus on the long-term effect of nusinersen on other motor-related functions such as ventilation (35). We recently published a large body of natural history data on lung function in SMA (8), but these spirometry endpoints may be affected by factors that are independent of respiratory muscle dysfunction (36). Respiratory muscle strength may be an even more appropriate outcome measure (36).

PE_{max} and PI_{max} were severely affected in SMA types 1c–3a. PE_{max} may be the most suitable outcome of these two, as expiratory muscle function is predominantly affected in patients with SMA (9,10). Interestingly, PE_{max} was low in patients with SMA type 3a from early ages on, whilst we have previously shown that lung volumes in these patients remain normal at least until (early) adulthood (8). Based on these data, we believe PE_{max} is a sensitive screening parameter to detect respiratory muscle weakness in SMA patients.

Our findings corroborate the results of some previous cross-sectional studies indicating decreased PE_{max} and PI_{max} with normal lung volumes in patients with SMA types 2 and 3 (15,21), although different results in two other small studies have also been reported (9,37).

SNIP has been proposed as an alternative or complementary test to PI_{max}. It measures inspiratory strength and normal values exclude inspiratory muscle weakness (32,38). In our cohort, SNIP was abnormally lowered in virtually all patients without significant differences between SMA types, although a trend of decreasing SNIP values with more severe phenotypes was present. Our observations are in accordance with the recent work of Kapur (37). Although SNIP is easy to perform, it may underestimate inspiratory muscle strength in case of nasal obstruction or severe respiratory muscle weakness (38), which may be present from young ages onwards in patients with SMA types 1 and 2. Even though strong correlations between SNIP, PI_{max} and vital capacity have been shown (28), we believe it may be less suited to discriminate between SMA types or as an outcome measure for longitudinal follow-up.

In the absence of bronchial obstruction, PEF reflects maximal expiratory flow (12,39). We observed differences at baseline between SMA types and a rather linear decline of PEF in most types over time, resembling the course of FVC in patients with SMA (8). As the average annual PEF decline did not differ significantly between SMA types, SMA types are primarily separated by differences already present at baseline or occurring very early

in life. The observed pattern of relative stabilization in adults with SMA types 2 and 3a could be caused by relative disease stabilization, but we believe it is more likely the consequence of either a floor effect due to difficulties with quantification of very low PEF values or loss to follow-up of most severely affected patients due to death or initiation of invasive mechanical ventilation. Based upon our findings, PEF may be used as an outcome measure for SMA in future studies, as has also been suggested for Duchenne Muscular Dystrophy (40).

Coughing is essential for airway clearance and requires coordinated use of both inspiratory and expiratory muscles, which can be assessed by PCF (28). PCF in SMA patients had previously only been studied in small cohorts (37). In our study, nearly all patients had a PCF <270 L/min. In SMA type 1c and a large number of patients with type 2 PCF was even <160 L/min. Since low PCF is associated with an increased occurrence of RTIs, PCF could represent a clinically meaningful endpoint for trials.

Our work has important strengths and expands the scarce natural history data on respiratory strength in patients with SMA. First, we investigated a range of measurements reflecting respiratory muscle strength in a large population-based cohort, covering a broad spectrum of SMA severity and a wide age range. Secondly, the large cohort allowed for analyses to assess differences between SMA types. We studied several tests of respiratory muscle weakness as it is known that combining these tests increases diagnostic precision (41). Finally, to overcome the risk of including inaccurate data from weaker patients, especially young children, professionals experienced in performing these tests in pediatric and adult patients with NMDs conducted all tests.

The generally broad confidence intervals around both intercepts and slopes are a limitation of our work. It reflects the uncertainty of the predicted longitudinal patterns. This can partly be explained by the inability of young children to reliably perform these tests, but also the limited number of observations at older ages for some of the SMA types. The limited number of elderly patients in our cohort is possibly partly explained by SMA-related death or loss to follow-up. However, we do not believe that this changes our conclusion that the general pattern of respiratory muscle strength is one of decline over time. Finally, our study lacks an assessment of possible confounders, such as severity of (corrected) scoliosis, use of airway clearance techniques, or mechanical ventilation. However, we consider this less important as our study focuses on the natural history of SMA with treatment according to the standards of care (1,6).

Conclusion

There are clear differences in respiratory muscle strength and its progressive decline between SMA types. In general, measurements of respiratory muscle strength are most affected in the more severe SMA types. PEF declines in a rather linear pattern in all SMA types and is among the most suitable measures to be used for the longer-term follow up of patients and treatment efficacy assessments.

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Additional Files

Additional file 1: Classification of SMA types

SMA type	Age at symptom onset	Highest achieved motor milestone
1	0-6 months	Never acquires ability to sit unsupported
0/1a	Prenatal/neonatal	No head control
1b (classic SMA)	1-6 months	No head controle, unable to roll over
1c	3-6 months	Some additional motor skills, like head control or rolling over
2	6-18 months	Able to sit unsupported, unable to walk
2a		Unsupported sitting, able to stand or walk with help
2b		Unsupported sitting, able to stand or walk a few steps with help
3	> 18 months	Able to walk unsupported
3a	18-36 months	
3b	> 36 months	
4	≥ 18 years	Able to walk unsupported

Additional File 2: Standardized PEF (in %) stratified by SMA type: model parameters estimates

		Fixed effects				Random effects	
SMA type	n	Intercept (SE)	95% CI intercept	Slope	95%CI slope	SD intercept	SD slope
1c	6	49.30 (4.52)	41.41; 57.92	-0.89	-1.71; 0.14	3.58	0.64
2a	31	72.52 (5.10)	62.18 ; 82.56	-2.04	-2.73; -1.37	24.76	1.46
2b	22	86.90 (5.67)	74.99; 98.21	-1.82	-2.63; -1.05	18.32	1.12
3a	16	95.86 (7.55)	79.91; 110.68	-1.31	-1.80; -0.87	24.06	0.65

Legend: CI = confidence interval; *n* = number of patients in each group; SD= standard deviation; SE = standard error.

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CHAPTER 4

Lung function decline preceding chronic respiratory failure in spinal muscular atrophy: a national prospective cohort study.

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Submitted

Background

Progressive lung function decline, resulting in respiratory failure, is an important complication of spinal muscular atrophy (SMA). The ability to predict the need for mechanical ventilation is important. No natural history data are available on lung function decline prior to chronic respiratory failure.

Research Question

Is there an accelerated decline of lung function prior to initiation of mechanical ventilation in patients with SMA, similar to the previously described accelerated increase of carbon dioxide levels?

Study Design and Methods

We included treatment-naïve SMA patients participating in a prospective national cohort study if they required mechanical ventilation because of chronic respiratory failure and if lung function test results were available from the years prior to initiation of ventilation. We analyzed Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), Peak Expiratory Flow (PEF) and Maximum Expiratory Pressure (PE_{max}). We studied the longitudinal course using linear mixed-effects models.

Results

We analyzed 1171 lung function tests from 38 patients with SMA types 1c–3a . At initiation of ventilation median age was 18.8 years (IQR: 13.2–30.1) and median standardized FVC, FEV_1 and PEF were 28.8% (95%CI: 23.5; 34.2), 28.8% (95%CI: 24.0; 33.7) and 30.0% (95%CI: 23.4; 36.7), with an average annual decline of 1.75% (95%CI: 0.86; 2.66), 1.72% (95%CI: 1.04; 2.40) and 1.65% (95%CI: 0.71; 2.59), respectively. We did not observe an accelerated decline in the year before initiation of mechanical ventilation. Median PE_{max} was 35.3 cmH_2O (95%CI: 29.4; 41.2) at initiation of mechanical ventilation and relatively stable in the years preceding ventilation.

Interpretation

Patterns of lung function decline cannot predict impending respiratory failure: SMA is characterized by a gradual decline of lung function, without an accelerated deterioration in the year preceding respiratory failure. In addition, PE_{max} remains stable in the years preceding the initiation of mechanical ventilation.

Abstract

Background

Hereditary proximal spinal muscular atrophy (SMA) is primarily characterized by progressive weakness of axial, proximal limb and respiratory muscles. Respiratory complications are among the most prevalent and can be life threatening [1,2]. Natural history studies have shown that lung function and respiratory muscle strength deteriorate in treatment-naïve patients with early onset SMA, i.e. types 1, 2 and 3a [3–6]. It may remain relatively stable in late onset SMA types 3b and 4 [5]. The majority of treatment-naïve patients with SMA types 1 and 2 eventually needs mechanical ventilation [1,4,7]. Ventilation risk is associated with SMA type and therefore with achieved motor milestones [7]. There is consensus that patients with SMA types 2 and 3 with symptomatic nocturnal hypoventilation or daytime hypercarbia should start home mechanical ventilation to correct hypoventilation and associated symptoms [1,8].

The current standards of care propagate early assessments of lung function and use of supportive respiratory care in patients with SMA, specifically in types 1-3a. This includes mechanical ventilation, physiotherapy, air stacking, or mechanical insufflation-exsufflation techniques [1]. Although the natural history of lung function has been studied in the past years, its decline in the years prior to initiation of mechanical ventilation in patients with SMA has not been studied in detail. Such data would help to steer clinical decision making with regards to respiratory care, facilitate timing of counseling for impending chronic respiratory failure and may also be helpful for the evaluation of effects of newly introduced SMA therapies [9].

Therefore, we longitudinally assessed how lung function and expiratory muscle strength change in the years preceding the initiation of mechanical ventilation in treatment-naïve patients with SMA. We hypothesized that lung function would decline more steeply in the year preceding initiation of mechanical ventilation, in accordance with the increases of carbon dioxide levels we described previously [10].

Materials and methods

Patients enrolled in this study participate in an ongoing national prospective cohort study on SMA. Patients with genetically confirmed SMA were included if they required mechanical ventilation because of chronic respiratory failure and if lung function test (LFT) results were available from the years prior to initiation of mechanical ventilation. In accordance with national guidelines, mechanical ventilation was electively initiated in case of symptoms of nocturnal hypoventilation and a carbon dioxide (pCO_2) level $\geq$45 mmHg, or when pCO_2 reached $\geq$52.5 mmHg without symptoms. Also, in some cases mechanical

ventilation was continued after an episode of acute respiratory failure because of surgery or infection.

We determined the presence of homozygous loss of *SMN1* function and *SMN2* copy number with multiplex ligation-dependent probe amplification (MLPA; SALSA kit P021-B1-01, MRC-Holland) [11]. We used the SMA classification system as described previously with some additions, i.e. SMA type 1c for patients who had learned to roll or lift their head in prone position, SMA type 2a for patients who had learned to sit independently and SMA type 2b for patients who had reached the motor milestones of standing with support [2,12–14]. We captured patient characteristics as described previously [5,11,13]. We used patient data obtained prior to participation in a clinical trial or treatment with SMN protein augmenting drugs (i.e., 'treatment-naïve'). Parameters of lung function and expiratory muscle strength were measured longitudinally at the department of pulmonology and Center of Home Mechanical Ventilation. Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV_1), Peak Expiratory Flow (PEF) and Maximum Expiratory Pressure (PE_{max}) were measured using Geratherm Spirostik® [5].

We included tests of expiratory muscle strength (PE_{max}) because respiratory muscle weakness in SMA is characterized by a rather unique pattern with predominant weakness of (mainly expiratory) intercostal muscles and relative sparing of (inspiratory) diaphragm function [15,16].

LFTs were performed by a small team of professionals experienced in conducting LFTs in children and adults with neuromuscular diseases. All LFTs were measured and reported according to the European Respiratory Society guidelines [17,18]. All LFTs were measured in sitting position, without corsets or braces. All studied outcomes were reported as standardized LFT values, according to the Global Lung Function Initiative, with the exception of PE_{max} [19]. Arm span was used preferably as a surrogate measure for height in patients unable to stand or with a severe scoliosis [5,20].

The local Medical Ethical Committee approved this study (09-307/NL29692.041.09) and informed consent was obtained from all participants and/or their parents in case of minors. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [21].

Statistical analyses

We used all available patient data for analysis. For baseline characteristics, we used descriptive statistics. We used linear mixed-effects models (LMMs), hypothesizing a progressive decline of lung function over time, depending on SMA type. The fixed part of our models contained time (in years prior to the initiation of mechanical ventilation),

SMA type, and an interaction term of these two predictors as fixed factors. The random part contained an intercept and slope for time per patient. Using a likelihood ratio test, we evaluated whether the rate of decline was significantly different between SMA types. We used estimated baseline values (i.e., projected y-axis intercepts at t = 0) as surrogates for lung function and expiratory muscle strength at initiation of mechanical ventilation. Additionally, to assess whether there was a non-linear change in lung function and expiratory muscle strength over time, we also fitted non-linear models using cubic splines. We used penalized-likelihood criteria (AIC and BIC) to select the optimal model fits. As we found no significant improvements of the models fits, i.e. no evidence for a non-linear change over time for our outcomes, we here report the findings of our LMMs. We used *R* (v4.0.3 for Windows with RStudio v1.4.1103) for all statistical analyses [22]. The statistical models were fitted using the lmer function of *lme4* (v1.1–27.1) [23]. *Ggplot2* (v3.3.5) was used for all data visualization [24].

Results

We included 38 patients, most of whom had SMA type 2 (71%). Median follow up (prior to initiation of mechanical ventilation) was 7.1 years (IQR: 4.8; 12.7). Median age at initiation of mechanical ventilation was 18.8 years (IQR: 13.2; 30.1). Baseline characteristics are shown in Table 1.

Table 1 Baseline characteristics

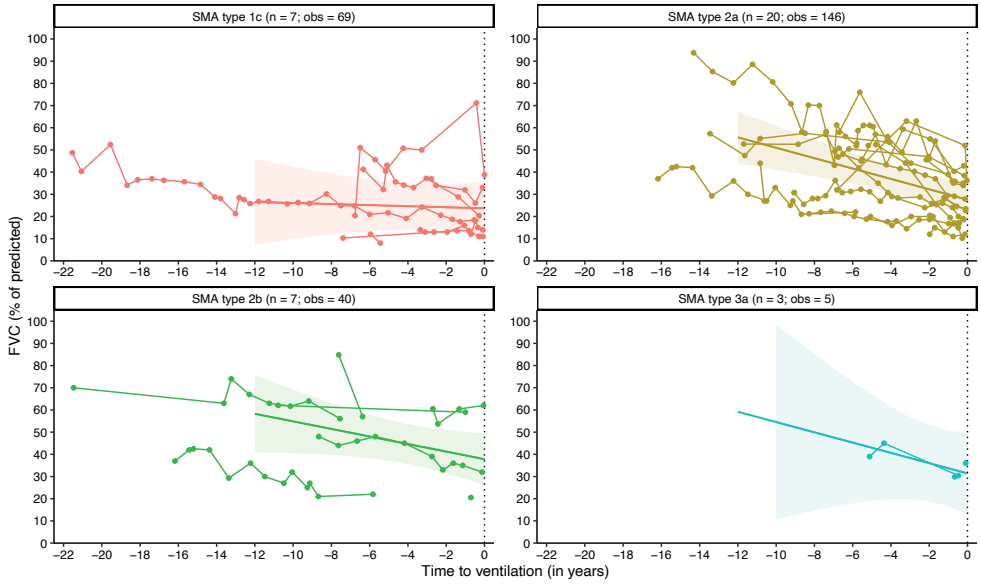
SMA type	1c	2a	2b	3a
Number of patients	8	20	7	3
Age (years) at start ventilation	20.45	15.98	24.80	47.75
(median, IQR)	(14.25; 23.60)	(12.86; 27.61)	(16.16; 28.08)	(41.80; 55.20)

Legend: *IQR = interquartile range;*

Forced Vital Capacity (FVC)

In total, 260 FVC measurements of 37 patients were available for longitudinal analyses. Median FVC at initiation of ventilation was 28.84% (95% CI: 23.48; 34.17). The rate of %FVC change over time prior to the initiation of mechanical ventilation averaged –1.75%/year (95%CI: –2.66; –0.86). Both FVC at initiation of mechanical ventilation and rate of FVC decline preceding ventilation did not differ significantly between SMA types (Table 2, Figure 1).

Figure 1: Longitudinal course of Forced vital Capacity (FVC) in the years preceding mechanical ventilation



Legend: time = 0: initiation of mechanical ventilation; n = number of patients; obs= number of observations

Forced Expiratory Volume in 1 second (FEV_1)

We obtained a total of 385 FEV_1 measurements from 38 patients for longitudinal analyses. The estimated FEV_1 at initiation of mechanical ventilation for all included patients was 28.82% (95% CI: 23.99; 33.69). The rate of %FEV_1 change prior to mechanical ventilation averaged –1.72%/year (95% CI: –2.40; –1.04). As with FVC, we did not observe differences in annual rates of FEV1 decline preceding mechanical ventilation between SMA types (Table 2, Figure 2).

Peak Expiratory Flow (PEF)

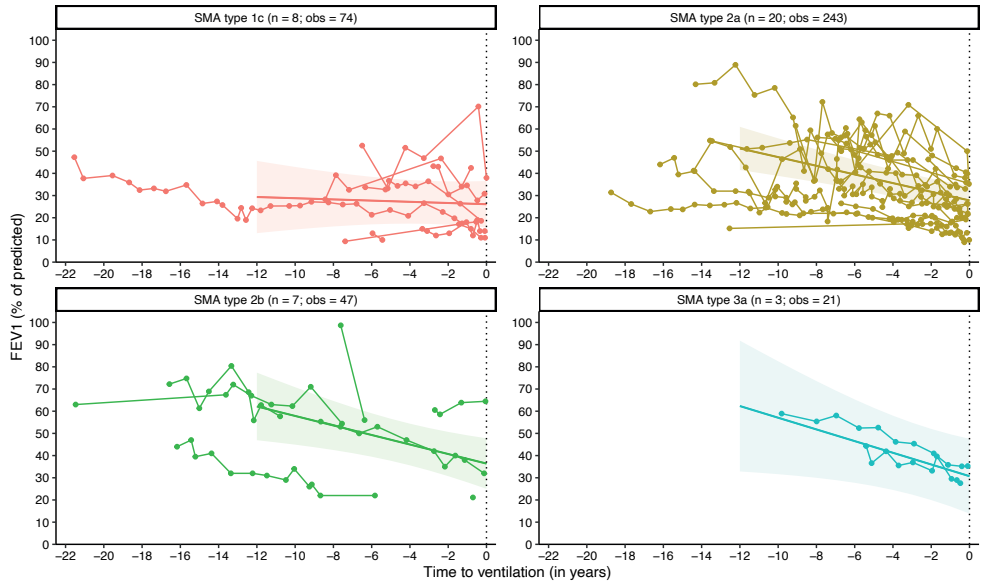
A total of 247 assessments of PEF from 20 patients with SMA types 1c and 2a, obtained prior to the start of mechanical ventilation, were available for analyses. At initiation of mechanical ventilation median PEF was 29.96% (95% CI: 23.35; 36.67). We found an average annual decline of 1.65%/year (95%CI: 0.71; 2.59). The average change in SMA type 1c (–0.64%/year) was smaller than in type 2a (–1.99%/year), but this difference was not significant (Table 2, Figure 3).

Table 2: Lung function test results at start of mechanical ventilation (=intercept) and average annual change in the years prior to start mechanical ventilation (=slope)

Lung function test (LFT)	SMA type	n (obs)	Annual change LFT (SE)	95% CI	LFT at start MV (SE)	95% CI
Standardized FVC (%)	**total group**	**37 (260)**	**-1.75 (0.45)**	**-2.66; -0.86**	**28.84 (2.69)**	**23.48; 34.17**
	1c	7 (69)	-0.24 (0.94)	-1.99; 1.53	23.69 (6.03)	12.19; 34.99
	2a	20 (146)	-2.34 (0.58)	-3.42; -1.26	27.57 (3.54)	20.89; 34.27
	2b	7 (40)	-1.70 (0.94)	-3.49; 0.06	37.82 (5.93)	26.80; 49.27
	3a	3 (5)	-2.31 (2.40)	-6.81; 2.19	31.40 (9.29)	13.78; 49.03
Standardized FEV_1 (%)	**total group**	**38 (385)**	**-1.72 (0.34)**	**-2.40; -1.04**	**28.82 (2.44)**	**23.99; 33.69**
	1c	8 (74)	-0.27 (0.72)	-1.62; 1.09	26.10 (5.31)	15.96; 36.15
	2a	20 (243)	-1.95 (0.43)	-2.76; -1.15	27.79 (3.24)	21.67; 33.99
	2b	7 (47)	-2.15 (0.78)	-3.62; -0.67	36.40 (5.79)	25.65; 47.73
	3a	3 (21)	-2.63 (1.26)	-5.01; -0.25	30.72 (8.56)	14.41; 47.01
Standardized PEF (%)	**total group**	**20 (247)**	**-1.65 (0.46)**	**-2.59; -0.71**	**29.96 (3.31)**	**23.35; 36.67**
	1c	5 (60)	-0.64 (0.89)	-2.40; 1.11	33.88 (6.75)	20.78; 47.16
	2a	15 (187)	-1.99 (0.51)	-3.00; -0.97	28.71 (3.91)	21.12; 36.38
PE_{max} (cmH_2O)	**total group**	**32 (279)**	**-0.03 (0.34)**	**-0.78; 0.66**	**35.30 (2.97)**	**29.41; 41.36**
	1c	6 (55)	0.02 (0.86)	-1.58; 1.62	25.21 (6.44)	13.22; 37.36
	2a	17 (175)	0.17 (0.44)	-0.74; 0.99	36.40 (3.89)	29.08; 43.72
	2b	6 (37)	-0.35 (0.83)	-1.93; 1.19	41.63 (7.61)	27.43; 55.99
	3a	3 (12)	-0.13 (1.95)	-3.85; 3.52	40.03 (11.68)	17.92; 61.99

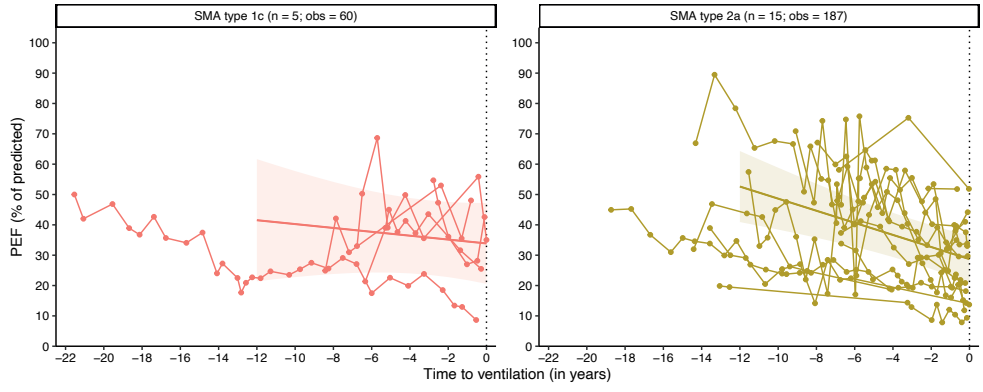
Legend: CI = confidence interval; FEV_1 = Forced Expiratory Volume after 1 second; FVC = Forced Vital Capacity; MV= mechanical ventilation; n = number of patients; obs = number of observations; PEF = Peak Expiratory Flow; PE_{max} = Maximum Peak Expiratory Pressure; SE = standard error;

Figure 2: Longitudinal course of Forced Expiratory Volume after 1 second (FEV_1) in the years preceding mechanical ventilation



Legend: time = 0: initiation of mechanical ventilation; n = number of patients; obs= number of observations

Figure 3: Longitudinal course of Peak Expiratory Flow (PEF) in the years preceding mechanical ventilation

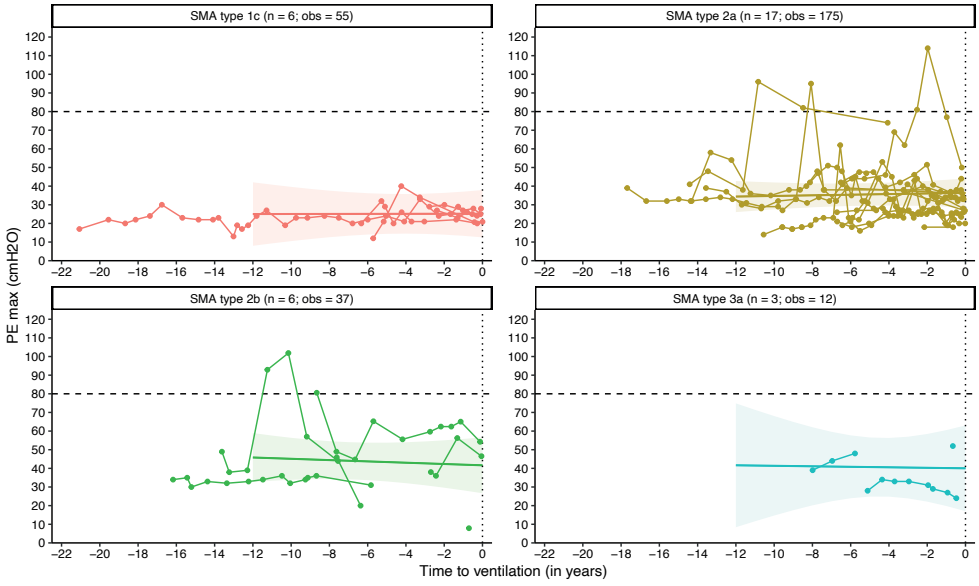


Legend: time = 0: initiation of mechanical ventilation; n = number of patients; obs= number of observations

Maximum Expiratory Pressure (PE_{max})

We obtained a total of 279 observations of PE_{max} from 32 patients for longitudinal analyses. Estimated PE_{max} at initation of mechanical ventilation was 35.30 cmH_2O (95%CI: 29.41; 41.36), which is far below the lower limit of normal (80 cmH_2O). In contrast to the other studied outcomes, PE_{max} remained stable in the years preceding mechanical ventilation. There was an average change of –0.03 cmH_2O/year (95%CI: –0.78; 0.66). We did not find significant differences between SMA types (Table 2, Figure 4).

Figure 4: Longitudinal course of Maximum Peak Expiratory Pressure (PE_{max}) in the years preceding mechanical ventilation



Legend: time = 0: initiation of mechanical ventilation; n = number of patients; obs= number of observations. Dotted horizontal line represents the lower limit of normal.

Discussion

The natural history of lung function in SMA types 1c-3a is characterized by a decline from an early age. In this study we analyzed the natural course of lung function in the years preceding initiation of mechanical ventilation in treatment-naïve SMA patients, in order to identify LFT patterns that predict impending respiratory failure. However, lung function decline rates remained stable in the year preceding respiratory failure. This is in contrast to the previously described accelerated increase in carbon dioxide levels [10].

Both inspiratory and expiratory functions become severely compromised in patients with SMA. At initiation of mechanical ventilation, median FVC, FEV_1 and PEF scores were around 30% of predicted, while median PE_{max} was 35 cmH_2O. The average annual decline of FVC, FEV_1 and PEF in the years preceding initiation of mechanical ventilation was 1.7%, which is in line with previous studies. Although baseline values of LFTs differed between SMA types, the annual decline rates were not significantly different between different SMA types. This is probably due to the relatively small patient sample, since rates of decline observed in natural history studies over longer periods of time differed between SMA types [5]. In contrast to the other parameters, PE_{max} remained relatively stable in the years prior to mechanical ventilation, indicating that the main loss of expiratory muscle strength occurs earlier in the disease course.

There are only a few studies that have analyzed lung function in patients with SMA and, to the best of our knowledge, none focused specifically on the period preceding chronic respiratory failure, which necessitates initiation of mechanical ventilation [3–6,25–28]. Bach et al. described a correlation between vital capacity and definitive dependence on continuous mechanical ventilation in patients with SMA type 1 and 2. However, the relation between lung function decline and initiation of mechanical ventilation was not studied as non-invasive ventilation during sleep was already prescribed from the time of diagnosis in all patients SMA type 1 and 2a with paradoxal breathing [25]. Most previous studies have used FVC to study lung function. Median FVC before the start of mechanical ventilation in our study was in line with some previous findings, e.g. of a mean FVC of 30% at initiation of nocturnal non-invasive mechanical ventilation in 11 patients with SMA type 1c and 34 with type 2 [4]. However, other studies have reported slightly different results. A recent study reported a higher median FVC (44%, IQR 28.5-57) in 55 treatment-naïve patients with SMA type 2 at the start of mechanical ventilation. This difference is probably explained by the younger median age (5 years, range: 1.8-16.6) in comparison to our study population [6]. Another retrospective study reported a much lower FVC of < 20% at initiation of mechanical ventilation in 4 patients with SMA type 2 [29]. The small sample size or possible selection bias may have caused the differences in comparison to our findings, as well as the more pro-active use of mechanical ventilation and airway

clearance techniques in more recent years. This may be further illustrated by a study that reported comparable median FVC outcomes to our findings (i.e. 31.5%, range 11.3-82.8) in 11 patients with SMA type 2 with a median age of 25.8 years who did not use mechanical ventilation. Three patients even had an FVC <30% [30]. We cannot exclude the possibility that these patients eventually started mechanical ventilation after publication of these studies. Despite the scarcity of data and the obvious differences between studies, recent standards of care indicate that FVC values <40% are associated with an increased risk of (N)REM-related sleep disordered breathing, requiring mechanical ventilation [1,8]. Our data suggest that the predictive value of LFTs may also have its limitations.

Data on other lung function parameters than FVC are even more scarce. Lyager et al. reported a median FEV_1 of 31.6 % (range 22.4-87) and a median PEF of 41.6% (range 23.7-96.6) in respectively 11 and 10 non-ventilated patients with SMA type 2, but did not report if these patients eventually started mechanical ventilation [30]. More recently, a few studies documented on the longitudinal course of lung function in treatment-naïve SMA patients, but they did not address the relationship between lung function decline and the initiation of mechanical ventilation [3,5,6,25–28]. Gilgoff et al. were, to the best of our knowledge, the only to report longitudinal data from the years preceding initiation of mechanical ventilation, but with only 8 observations obtained from 4 patients [29].

Our and other data showed a decline of lung function in treatment-naïve patients with SMA type 1c-3a, which is most pronounced in childhood. Lung function may reach a plateau in early adulthood, while patients with late onset SMA (types 3b and 4) are likely to have a stable lung function throughout life [5]. Of note is that the varying inclusion of both ventilated and non-ventilated patients in previous studies may partially explain the differences in observed rates of decline. The observed LFT values described here, in treatment naïve patients during the years preceding initiation of mechanical ventilation, may therefore reflect the range in which respiratory reserve capacity is likely to be exhausted. Our longitudinal analysis suggests that the previously described natural course of decline does not accelerate prior to the start of mechanical ventilation. This is in contrast to our previously reported accelerated increase in pCO_2 values in the years prior to start of mechanical ventilation [10].

The ability to predict the need for mechanical ventilation is important to ensure that patients will not be confronted with emergency decision regarding the start of ventilation. The current data will therefore not help to improve counseling of patients about the best timing for interventions that could prevent or treat respiratory failure, in contrast to previously described pCO_2 levels [10].

Our work has important strengths. First, we provided longitudinal data in non-ventilated SMA patients not only for FVC, but also for FEV_1, PEF and PE_{max}. It is important to include expiratory lung function tests, as expiratory muscle strength is mainly affected in SMA with relative sparing of the diaphragm. This is the first study describing the course of lung function with a full range of LFTs prior to start of mechanical ventilation in a relatively large cohort. Secondly, the cohort of genetically and clinically well-defined patients with SMA with a relatively large number of repeated measurements and long follow-up allowed for more detailed longitudinal analyses.

We also acknowledge limitations of our work. The sample size limits the power of this study. Nevertheless, our cohort was sufficiently large to model the natural history in the years preceding respiratory failure in different types of SMA.

The age at which mechanical ventilation was initiated was relatively old, especially in patients with SMA type 1c. This is explained by the study design, since we only included patients who performed lung function testing prior to initiation of mechanical ventilation [7]. We only included a limited number of patients with SMA type 3, as respiratory failure is rare in this group [7]. However, these data are important, as very limited data are available on lung function and respiratory failure in the milder SMA phenotypes.

Interpretation

This study is the first study to describe the longitudinal course of lung function in the years preceding chronic respiratory failure necessitating mechanical ventilation in a cohort of treatment-naïve SMA patients. The deterioration of lung function does not accelerate prior to the start of mechanical ventilation and therefore does not help to improve counseling of patients about the best timing for interventions that could prevent or treat respiratory failure.

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CHAPTER 5

5

Relative hyperventilation in non-ventilated patients with spinal muscular atrophy.

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To the Editor:

Spinal muscular atrophy (SMA) is a relatively common autosomal recessive neuromuscular disorder, characterised by progressive degeneration of spinal cord and bulbar motor neurons. It is caused by survival motor neuron (SMN) protein deficiency, due to homozygous loss of function of the *SMN1* gene. Due to the effects of genetic modifiers, SMA displays a broad range in severity. The current clinical classification system distinguishes 4 types, based on age at onset and acquired motor milestones, i.e. infantile onset without achieving the ability to sit (type 1), childhood onset with the ability to sit but not to walk (type 2), childhood onset with the ability to walk for at least a short period of time (type 3), or adult onset with mild symptoms (type 4) [1,2]. Disease course is progressive, irrespective of type [3] and patients with SMA type 1, 2 and 3 are at high or moderate risk of developing respiratory insufficiency, which may necessitate initiating mechanical ventilation [4,5].

Reduced lung function in SMA is probably the most important cause of morbidity and mortality in patients with SMA [1,6,7] and is caused by a rather unique pattern of weakness that predominates in the intercostal muscles and relatively spares the diaphragm [8]. Both inefficient secretion clearance, leading to recurrent respiratory tract infections and lung damage, as well as hypoventilation can occur from early ages on [6,9].

There is consensus that patients with SMA type 2 and 3 with symptomatic nocturnal hypoventilation or daytime hypercarbia should start home mechanical ventilation [6] to correct hypoventilation and associated symptoms [10]. In accordance with national guidelines, mechanical ventilation is initiated in our centre in case of symptoms of nocturnal hypoventilation and a carbon dioxide (pCO_2) level $\geq$45 mmHg, or when pCO_2 increases $\geq$52.5 mmHg without symptoms. Measurements of capillary pCO_2 during routine follow-up visits are therefore used to screen for hypoventilation. In case of symptoms of nocturnal hypoventilation or increased daytime pCO_2, overnight measurements are obtained to confirm or exclude nocturnal hypoventilation.

In daily practice we noticed that pCO_2 levels are regularly lowered or within the lower range of normal, rather than increased in patients with SMA without ventilatory support. Therefore, we retrospectively analysed capillary pCO_2 levels. We only used samples from patients who were not mechanically ventilated at the time of sample collection. Blood samples were obtained during visits to our outpatient clinic. Measurements obtained during hospital admissions or emergency department visits were excluded.

We assessed longitudinal changes of pCO_2 levels in non-ventilated patients with a linear mixed effects model, which included a random intercept and random slope for time per individual. We accounted for the non-linear increase in pCO_2 by modelling the fixed effect of time as a cubic function. Confidence intervals were estimated using bootstrapping (n=1000) and significance tests were based on the likelihood ratio test. This study was

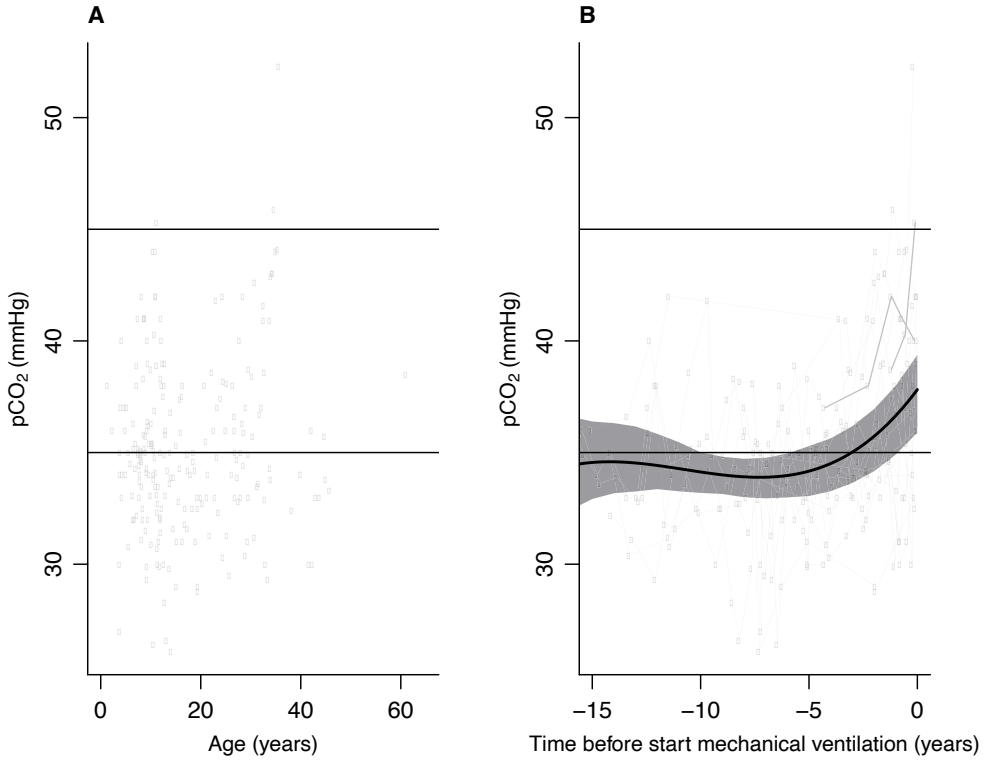
approved by the local Medical Ethics Committee. Informed consent was obtained from all participants and/or their parents in case of minors.

We analysed 708 capillary blood samples from 69 patients with genetically confirmed SMA. The median number of samples per patients was 9 (IQR 4-14) with 9 years median follow up (IQR 3-13). Median age at sample collection was 16.2 years (IQR 10.6-28.4). The majority of patients had SMA type 2 (*n* = 52, 75%), the remainder type 3 (*n* = 14, 20%) or type 1 (*n* =3, 4%). Mean pCO_2 was 35.5 mmHg (95% CI 34.7 -36.2; reference range of 35 - 45 mmHg), (Fig 1a). Lowered pCO_2 levels were not the result of concomitant metabolic acidosis, as mean pH was 7.44 (95% CI 7.43 - 7.44) and mean bicarbonate level was 23.6 mmol/L (95% CI 23.3 - 24.1; reference range of 22.0 - 29.0 mmol/L).

At the time of writing, 48 patients (70%) did not require (non-)invasive ventilation, whereas in the other 21 patients (non-)invasive ventilation was initiated. Eight patients (38%) could not be weaned off mechanical ventilation after an episode of acute respiratory failure due to infection (*n* = 7) or surgery (*n* = 1); the other 13 (62%) developed nocturnal hypoventilation. Median age at initiation of ventilation for these 21 patients was 18.5 years (IQR 11.4 - 37.0).
As all samples were taken prior to initiating (non-)invasive ventilation, we compared blood pCO_2 levels over time between the two groups. Levels of pCO_2 were lowered or within the lower range of normal in blood samples of the 48 patients in whom mechanical ventilation has not been initiated (mean pCO_2 35.4 mmHg, 95% CI 34.5- 36.3, 192 samples). Similar results were found for the 21 patients that ultimately required ventilation, in their samples obtained more than one year prior to start of (non-)invasive mechanical ventilation. However, a significant increase in pCO_2 levels was observed in the year prior to initiation of mechanical ventilation (Figure 1b): five years prior to initiation of ventilation mean daytime capillary pCO_2 was 34.2 mmHg (95% CI 32.9 - 35.3, *n* = 21), increasing to 36.7 mmHg (95% CI 35.2 - 38.1) one year prior to start of mechanical ventilation ($p<0.001$) and further to 37.8 mmHg (95% CI 36.2 - 39.5) at the start of mechanical ventilation.

Together, these data show that most non-ventilated patients with SMA have daytime pCO_2 levels in the lower range of normal. These levels increase to or beyond the upper limit of normal in the year prior to initiation of (non-)invasive ventilation. Additionally, overnight pCO_2 levels in non-ventilated patients show similar results. Mean overnight arterial pCO_2 (187 measurements, 34 patients) was 36.1 mmHg (95% CI 35.0 - 37.2). In patients who ultimately required (non-)invasive ventilation (n = 16), there was a significant increase of 0.38 mmHg per year (95% CI 0.08- 0.86; P=0.013), whereas it remained stable in patients not requiring ventilation (n = 18).

Figure 1: Capillary carbon dioxide levels in all patients at different ages (A) and in patients who ultimately required ventilation, at time before initiation of ventilation (B).



Legend: horizontal lines represent normal range of carbon dioxide levels (35 - 45 mmHg). Regression line in Figure 1B: $pCO_2 = 38.0 + (1.272 \times Time) + (0.126 \times Time^2) + (0.004 \times Time^3)$

Levels of pCO_2 in SMA have previously been studied by Khirani. They reported pCO_2 levels within normal range in 16 SMA patients and slight increase with age in patients with SMA type 2. Although mean values were not specified, their published longitudinal data suggest pCO_2 levels $\leq$35 mmHg in at least 15 out of 35 measurements, similar to our observations [11]. To the best of our knowledge this phenomenon is not described in other neuromuscular diseases.

A possible explanation of this phenomenon is the changed mechanics of respiration due to respiratory muscle weakness in patients with SMA. Tidal volumes are known to decrease over time, leading to a compensatory increase in respiratory rate. The consequential rapid shallow breathing pattern is assumed to minimize breathing effort and to reduce diaphragmatic fatigue and would explain an increased pCO_2 washout [11]. However, in general rapid shallow breathing is associated with increased dead space ventilation,

which primarily results in increased pCO_2 levels. We observed lowered pCO_2 levels long before mechanical ventilation was initiated. Therefore, hyperventilation could also be a specific disease characteristic of SMA.

There is evidence that tissues other than alpha-motor neurons are involved in the SMA disease process, including vasculature 6,12,13. Relative hyperventilation may therefore be caused by altered CO_2 sensing in brain(stem) or carotid bodies, adding a dimension to the complexity of respiratory care for patients with SMA. Limitations of this study are related to the retrospective nature. Only blood samples taken during routine follow up were included for analysis, aiming to include clinically stable patients. However, we can not exclude that higher pCO_2 levels may be explained by intercurrent problems, like respiratory tract infections. We included mainly patients with SMA type 2a (n=30) and 2b (n=22). Data are representative of the recently published longitudinal study on survival and respiratory failure. This study showed that 50% of patients with SMA type 2a (n=75) were depended on at least nocturnal mechanical ventilation after 17.4 years compared to 14.3% of patients with type 2b (n=51) after 25 years [5].

This observational study highlights the low or low-normal range pCO_2 levels in non-ventilated SMA patients. Increases of pCO_2 levels to normal may be a sign of pending respiratory insufficiency in some patients with SMA.

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CHAPTER 6

Evidence for beneficial effect of daily use of mechanical insufflation-exsufflation in patients with neuromuscular disorders: a systematic review and meta-analysis.

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Submitted

Abstract

Background

Daily application of mechanical insufflation-exsufflation (MI-E) is used increasingly in patients with neuromuscular disorders (NMDs) to prevent pulmonary congestion and thereby respiratory tract infections (RTIs), although its beneficial effect remains uncertain. We therefore conducted a systematic review, registered in PROSPERO (CRD42020158278), to compile available evidence for daily MI-E use in patients with NMDs and stable respiratory condition.

Methods

We performed a systematic comprehensive search of MEDLINE,EMBASE, Cinahl and Web of Science up to 23 December 2021. We excluded studies studying the effect of MI-E in case of acute respiratory failure or RTI and studies comparing different MI-E devices and settings. Studied outcomes were prevalence and severity of RTIs, lung function test results, respiratory characteristics, and patient satisfaction. We performed a meta-analysis using DerSimonian-Laird random effects model and assessed methodological quality by using the Alberta Heritage Foundation for Medical Research tool.

Results

Totally, 498 records were screened, of which 25 were included studying 608 patients. One randomized controlled trial found a trend towards reduced duration of RTIs compared to air stacking. Long-term effects on lung function test results were reported in one RCT and one retrospective study, with respectively no significant and a significant improvement of vital capacity. Majority of studies compared lung function test results before and immediately after MI-E use. Meta-analysis showed an overall beneficial effect of MI-E on peak cough flow (PCF) compared to unassisted PCF (mean difference 91.6 L/min (95% CI 28.3; 155.0), $p < 0.001$). Patient satisfaction was high, possibly influenced by major bias.

Conclusion

There is limited evidence to support beneficial effects of daily use of MI-E in clinically stable patients with NMDs, with the possible exception of increased PCF immediately after MI-E application. Lack of follow-up studies preclude conclusions regarding long-term effects. The very limited data comparing MI-E to air stacking preclude comparisons.

Introduction

The primary cause of morbidity and mortality in patients with neuromuscular disorders (NMDs) is respiratory failure due to progressive respiratory muscle weakness [1] . Respiratory muscle weakness causes insufficient cough thereby increasing the risk of recurrent respiratory tract infections (RTIs), resulting in hospital admissions and further lung function decline [1–4].

To prevent pulmonary congestion, several consensus statements of respiratory care for children and adults with NMD recommend initiation of airway clearance techniques (ACTs) when cough is weak, i.e. when Peak Cough Flow (PCF) is less than 270 L/min [5–7]. ACTs employ expiratory support (manually assisted cough (MAC)) or inspiratory support (air stacking (AS) or glossopharyngeal breathing) or both (mechanical insufflation-exsufflation (MI-E). MI-E uses positive pressure to promote maximal lung inflation followed by an abrupt switch to negative pressure to the upper airway. The rapid change from positive to negative pressure is aimed at simulating the flow changes that occur during a cough, thereby assisting sputum clearance [8]. MI-E does not require active cooperation and can, therefore, also be performed in patient groups that are more difficult to instruct, in particular young children or patients with intellectual impairment, but is also more expensive [2,7,9].

Although expert opinion has facilitated the introduction of MI-E in individual patients or for specific indications [2,7,10,11], reimbursement of MI-E may be complicated by the perceived scarcity of evidence for its efficacy. For this reason, we conducted a systematic literature review using a comprehensive search strategy to document evidence for regular, daily MI-E use in patients with NMDs with a stable respiratory condition, i.e. absence of RTIs. We were aware that studies on the most important outcome, i.e. prevalence and severity of RTIs, were limited. For this reason the studied outcome was the overall efficacy, including prevalence and severity of RTIs, lung function test (LFT) results, respiratory characteristics, and patient comfort and satisfaction.

Methods

For this systematic literature review, we followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (the PRISMA checklist)[12]. The protocol was registered on PROSPERO (ID: CRD42020158278).

Search strategy

We performed a systematic comprehensive electronic search of MEDLINE, EMBASE, Cinahl and Web of Science from inception to 23 December 2021, using a detailed search. We used the following search items: "(mechanical insufflation exsufflation) OR (mechanical insufflation-exsufflation) OR (mechanical in-exsufflation) OR (mechanical in-exsufflator) OR (mechanical cough assistance) OR (cough assist) OR (cough assist therapy)". We purposely did not include outcome or NMD in the search, as this narrowed the search with risk of missing studies on this topic. No filters were applied to the search. We conducted hand-searching of the reference lists of included articles.

Inclusion and exclusion criteria

We used the following criteria for inclusion: the study data pertained to clinically stable patients (children or adults) with documented NMD. Clinically stable was defined as the absence of RTI or acute respiratory failure at enrollment to the study. We excluded studies that used artificial lung or animal models. We only included original studies. We excluded conference abstracts, reviews, editorials, letters, case reports, duplicate reports and studies of which we could not access full text (even after contacting the authors). We focused only on English-language articles. We excluded studies studying the effect of MI-E in case of acute respiratory failure or a RTI. We excluded studies comparing different MI-E devices and different MI-E settings if no comparison to unassisted or other ACTs was described.

Selection of studies and data extraction

Two authors (EV and RW) independently screened titles and abstracts of all studies identified by the literature search. Studies for which at least one reviewer concluded that it possibly met the inclusion criteria, were selected for full-text screening. Finally, all references of included studies were checked for missing studies. Next, both authors independently extracted data from included studies to a standard form. Discrepancies in data interpretation were discussed until consensus. If necessary, we asked a third assessor (LVO) to resolve the discrepancy. We extracted the following data from each study for final analysis: study design, study objectives, years of study conduct, setting, patients' age, underlying NMD, MI-E settings and outcome.

Assessment of quality

We assessed methodological quality of each study by using the tools developed by the Alberta Heritage Foundation for Medical Research: Standard quality assessment criteria for evaluating primary research papers from a variety of fields [13]. For the quantitative studies, 14 items were scored depending on the degree to which the specific criteria were met ("yes" = 2, "partial" = 1, "no" = 0). Items not applicable to a particular study design were excluded from the calculation of the summary score. For the qualitative studies, 10 items

were scored 0-2 points. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total possible score.

Data analysis

In case of multiple studies using the same comparison and outcome parameters, we performed a meta-analysis using DerSimonian-Laird random effects model to obtain overall pooled effect with 95% confidence intervals (CIs). The mean and standard deviations (SD) in individual studies were estimated from those that were reported as median and (interquartile) range (IQR) by using the method described by Wan et al. [14]. Because in amyotrophic lateral sclerosis (ALS) upper airway collapse may be present in the absence of or before the onset of bulbar symptoms [15,16], we performed a subgroup analysis on studies without ALS patients. Heterogeneity of pooled data was assessed by using I^2 statistic. The I^2 statistic describes the percentage of total variation across studies due to true heterogeneity rather than chance. All analyses were performed using OpenMeta[analyst] (http://www.cebm.brown.edu/open-meta). Data are not publicly available, but available upon reasonable request.

Results

Study selection

Totally, 498 records were screened (Fig. 1). After title and abstract screening, 50 articles were considered for full-text analysis. Twenty-five were excluded because they did not meet inclusion criteria. The remaining 25 studies were included in our review [15–39].

Description of included studies

The characteristics of included studies are summarized in Table 1. The majority of studies were single center cohort studies. Totally, 608 patients were studied. Sample sizes ranged from 5 to 62 subjects. In- and exclusion criteria and study population varied significantly between studies. Fifteen studies included patients with different NMD diagnoses [17,20,24,27–32,34–39]. Ten studies included a more homogeneous group of diagnoses, such as ALS (n=7) [15,16,21–23,25,26], Duchenne Muscular Dystrophy (DMD) (n=2)[17,33], and both DMD and Spinal Muscular Atrophy (SMA) (n=1)[19]. Outcomes of studies were respiratory-related events including RTIs or hospital admissions (Table 2), LFT results (Table 3), respiratory characteristics (Table 4), laryngeal response (Supplementary Table 1) and quality of life (Supplementary Table 2).

Table 1: Study characteristics

Author, year	Study design	Year of study	Follow up	Number of patients	Age(years)	Inclusion criteria	Underlying disease	Outcome	Adverse events
Andersen, 2017	Prosp pat control	2011-2013	Immediate effect	20 (and 20 healthy controls)	68.7 (control 66.9)	No tracheostomy, no RTI < 1 month	ALS	Laryngeal response	NS
Andersen, 2018	Prosp observational	2011-2016	Median 17 (6-59) months	13	50-83	No tracheostomy, no RTI < 1 month	ALS	Laryngeal response	NS
Bach, 1993	Prosp; retrosp survey	NS	Survey:16.4 years; PFT: immediate effect	n=16 prosp, n=46 survey	16-74	Ventilator-dependent, PFT in patients within 2 hours traveling	Mixed	LFT, resp charact, chest wall	0
Cesareo, 2018	Prosp observational	NS	Immediate effect	20	mean 20.8 ± 4.4	≥ 1 year MI-E use	DMD	LFT, resp charact, chest wall	NS
Chatwin, 2003	Prosp pat control	NS	Immediate effect	22 (and 19 healthy controls)	median 21 (10-56)	No AB <1 month, SpO_2 ≥ 90%, $PetCO_2$ ≤ 7 kPa, no bulbar dysfunction	Mixed	LFT, PS	0
Fauroux, 2008	Prosp observational	NS	Immediate effect	17	5-18	≥ 1 month stable	Mixed	LFT, PS	0
Kim, 2016	RCT	NS	Immediate effect	40 (and 16 healthy controls)	20.9 ± 7.2	Non-invasive ventilator-dependent, familiar with MI-E, no RTI, no severe bulbar dysfunction	Mixed	LFT	0
Lacombe, 2014	RCT	2012-2013	Immediate effect	14	21-68	No RTI < 1 month, PCF <3 L/s or MEP< 45cmH2O, no MI-E use	Mixed	LFT, PS	NS
Lalmolda, 2019	Prosp	NS	Immediate effect	21	63.9 ± 15.75	PCF < 160 L/min, ≥ 18 years, no tracheostomy, no contra-indication for MI-E, good tolerance	Mixed	LFT	0
Mahede, 2015	Retrosp	2007-2011	health records 25 years (1988-2012)	37	Mean 19.8 (1-59)	Home MI-E use	Mixed	ED presentations, hosp adm, PS	NS
Meric, 2017	Prosp	2014-2015	Immediate effect	9	18-30	No RTI < 1 month, NIV, VC <30%	DMD	LFT, resp charact, chest wall motion, PS	NS

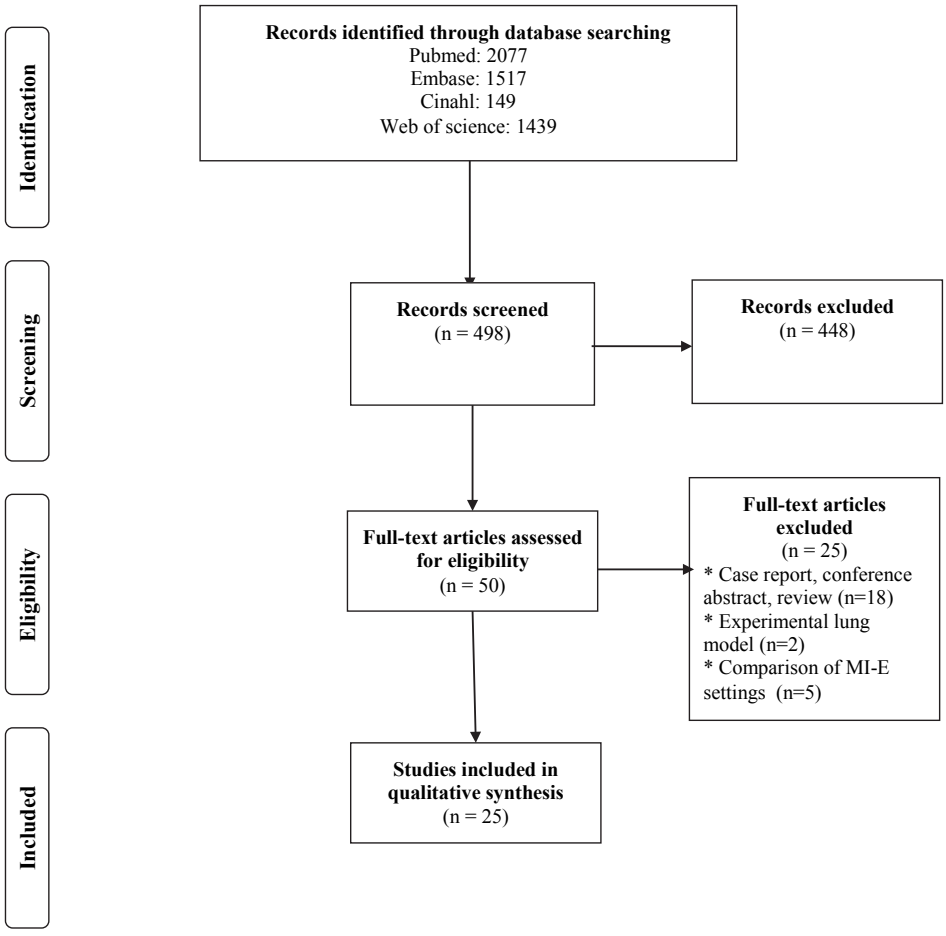
Miske, 2004	Retrosp	1998-2001	Median 13.4 months (0.5-45.5 months)	62	0.2-28.6	MI-E use at home (PE_{max} < 60 cmH_2O, history of RTI/ atelectasis, home ventilation)	Mixed	PS, QoL	1
Moran, 2013	Retrosp	NS	Mean 2.3 years (1.2 -4.9 years)	n=10 child, n=10 parent	1.4-18.1	MI-E use at home	Mixed	Resp related hosp adm, PS, QoL	0
Moran, 2015	Qual	NS	Single interview	11 (n=8 parents, n=3 child > 10 years)	4-18	0.5-10 years MI-E use	SMA and DMD	PS, QoL	NS
Mustfa, 2003	Prosp pat control	NS	Immediate effect	47 (10 healthy controls)	NS	ALS (diagnosis according to El Escorial criteria)	ALS	LFT	NS
Rafiq, 2015	RCT	2009-2013	≥ 12 months or till death	40 (21 AS and 19 MI-E)	Mean 64.1	Non-invasive ventilator-dependent, no frontotemporal cerebral dysfunction	ALS	LFT, RTI, admissions, QoL, PS	0
Sancho, 2004	Prosp	NS	Immediate effect	26	Mean 61	Consecutively referred, ALS, no antecedent lung disease, no significant kyphoscoliosis	ALS	LFT	NS
Santos, 2017	Prosp observational	2013-2014	Immediate effect	47	Mean 41 ± 14	VC < 80%, no tracheostomy	Mixed	LFT	NS
Senent, 2011	Prosp	NS	Immediate effect	16	63 (57-68)	No tracheostomy, > 2 months home ventilation, no RTI < 1 month, PCF < 270 L/min	ALS	LFT, PS	NS
Siewers, 2013	Qual	2009-2010	No follow up	n=5 pats, n=3 fam, n=3 health prof	43-81	ALS patients using MI-E with mask	ALS	PS, QoL	NS
Sivasothy, 2001	Prosp pat control	NS	Immediate effect	12 (and 8 COPD, 9 healthy controls)	27-73 (control 17-71)	Respiratory muscle weakness diagnosed by neurologist, no other respiratory disease	Mixed	LFT, resp charact	NS
Stehling, 2015	Retrosp	2009-2012	1-2 years before and after	21	5-27	VC< 30%, PCF<160, NIV	Mixed	LFT	NS

Table 1: Continued

Travlos, 2016	Qual	NS	Single interview	9 (=n=3 child, n=3 parent, n=3 PT)	6-8	5-15 years, > 6 months MI-E use	Mixed	PS, QoL	NS
Veldhoen, 2019	Retrosp	2005-2019	up to 3 years before and after	37	median 5.2 (IQR 2.7-12.4)	Children, daily use of MI-E at home	Mixed	RTI related hosp adm, PS	1
Winck, 2004	Prosp	2002-2003	Immediate effect	20 (and 9 COPD)	26-68	≥ 1 episode resp failure, ↓ SpO2, no AB < 1 month, resp stable > 3 months	Mixed (65% ALS)	LFT, resp charact, PS	0

Legend: AB = antibiotics, ALS = amyotrophic lateral sclerosis, AS = air stacking, COPD = chronic obstructive pulmonary disease, DMD = Duchenne Muscular Dystrophy, ED = emergency department, fam = family, hosp adm = hospital admission, ED = emergency department, IPPB = Intermittent Positive Pressure Breathing, IQR= interquartile range, LFT = lung function test, MAC = manually assisted cough, MI-E = mechanical insufflation-exsufflation, NIV = non-invasive ventilation, NS = not specified, pat = patient, PCF = peak cough flow, PE_{max} = maximal expiratory pressure , $petCO_2$ = endtidal pCO_2, prof = professionals, prosp = prospective, PS = patient satisfaction, PT = physiotherapist; QoL = quality of life, Qual = qualitative; RCT = randomized controlled trial, resp = respiratory, resp charact = respiratory characteristics, retrosp = retrospective, RTI = respiratory tract infection, SCI = spinal cord injury, SMA = spinal muscular atrophy, SpO_2 = oxygen saturation, VC = vital capacity, 0 = data on adverse events collected and not present, 1 = data on adverse events collected and present

Figure 1: PRISMA Flow diagram



Legend: n = number

Respiratory-related outcomes

Respiratory-related outcomes were studied in four studies [20,22,31,39]. One randomized controlled trial (RCT) studied number and duration of RTIs and RTI related hospital admissions in ALS patients, comparing AS and MI-E. This study reported a trend towards reduced duration of RTI in the MI-E group [22]. The other three studies were observational studies comparing RTI rate and respiratory-related hospital presentations years before and after introduction of MI-E [20,31,39] (Table 2). One of these observational studies, studying 37 children using MI-E, showed a significant effect on RTI-related admissions [31]. Two of these observational studies, including totally 47 children, showed reduced hospital length of stay[20,31]. Meta-analysis was not possible due to limited number of studies and different outcome measures.

Table 2: Outcome: Respiratory tract infections and hospital admissions

Outcome studied	Study	Study design	Follow up	Conclusion
Respiratory tract infection (RTI)	Rafiq, 2015	MI-E versus airstacking	≥ 12 months or till death	Number of patients with ≥ 1 RTI: 32% vs 33% (p > 0.5) Number of RTIs: 19 vs 13 (p > 0.5) Mean duration RTI symptoms: 3.9 vs 6.9 days (p = 0.16)
RTI-related admissions	Rafiq, 2015	MI-E versus airstacking	≥ 12 months or till death	Number of admissions 6 vs 6 (p > 0.5) 32% vs 46% admissions of all RTIs (p=0.47)
	Veldhoen, 2019	Before and after MI-E introduction	3 years before and 3 years after	Number of admissions/ 1000 eligible days: 3.7 vs 0.9 (p <0.05) Number of admission days/ 1000 eligible days: 33.6 vs 2.7 (p <0.05)
Respiratory- related hospital presentations				
Hospital presentation	Mahede, 2015	Before and after MI-E introduction	Total: 8 years. After: mean 2.3 years (0.1-4.0)	ED presentation: RR 1.76 vs 1.0 (p < 0.05)
	Moran, 2013	Before and after MI-E introduction	Before: 12 months After : mean 1.4 years (0.3-3.8)	0 - 6 months: 1.9 vs 1.4 (p > 0.5) 0 - 12 months: 2.9 vs 2.7 (p > 0.5)
Hospital admissions	Mahede, 2015	Before and after MI-E introduction	Total: 8 years. After: mean 2.3 years (0.1-4.0)	RR 1.82 vs 1.0 (p > 0.05)
	Moran, 2013	Before and after MI-E introduction	Before: 12 months After : mean 1.4 yrs (0.3-3.8)	0 - 6 months: 1.6 vs 1.1 (p = 0.45) 0 -12 months: 2.0 vs 1.7 (p > 0.5)
Length of hospital stay	Mahede, 2015	Before and after MI-E introduction	Total: 8 years. After: mean 2.3 years (0.1-4.0)	RR 2.83 vs 1.0 (p > 0.05)
	Moran, 2013	Before and after MI-E introduction	Before: 12 months After : mean 1.4 yrs (0.3-3.8)	Hospital: 0-6 months: 39 vs 9.3 days (p < 0.05); 0-12 months: 43.7 vs 13.3 days (p < 0.05) ICU: 0-6 months: 17.7 vs 2.1 days (p = 0.06) 0-12 months: 19.9 vs 4.6 days (p = 0.06)

Legend: ED= emergency department, ICU= intensive care unit, MI-E= mechanical insufflation-exsufflation, RR= relative risk, RTI= respiratory tract infection, vs= versus.

Lung function test (LFT) results

Although LFT results were reported as outcome in 16 studies (Table 3), only two studies reported the longer term effects [22,29]. One of these was a RCT comparing AS and MI-E in patients with ALS [22]. This study showed no difference between both groups with a smaller vital capacity (VC) decline per month (p=0.47) and a small increase of PCF compared to decline of PCF in the AS group (p=0.43) [22]. The second retrospective observational study showed a significant beneficial effect of MI-E comparing VC 1 year before and 1 year after MI-E introduction in a group with mixed NMDs [29].

Fourteen studies studied the immediate rather than the longer term effect of MI-E comparing LFT results before and immediately after application of MI-E[17,21, 23–25,28,32–38]. Two of these studies were RCTs comparing MI-E to unassisted maneuver [36,37]. These RCTs showed increased PCF after MI-E application[36,37]. These 2 RCTs compared MI-E with and without addition of MAC [36,37] and one RCT compared MI-E with and without MAC to AS with MAC [36]. This last study in 40 patients showed that MI-E alone improved PCF significantly more than AS with MAC. MI-E used in conjunction with MAC improved PCF even further [36]. All other studies were observational studies comparing LFT results before and immediately after application of MI-E [17,21, 23–25,27,28,32–35,38]. Studied LFT outcomes varied between studies. Five of these observational studies were unique in studying a specific outcome [17,24,27,28,35]. Three studies studied inspiratory capacity comparing unassisted maneuver to MI-E with and without MAC [24,33,37]. Peak cough flow (PCF) was studied in eight studies: PCF after MI-E was compared to unassisted PCF [23,25,32–34,36–38], PCF after MAC [25,34], PCF after AS with MAC[25,36], and PCF after MI-E with MAC [36,37] . We contacted the corresponding author of the study by Lacombe et al to obtain the exact values of means and range of PCF, allowing us to include this study in the meta-analysis [37]. Meta-analysis showed an overall beneficial effect of MI-E on PCF compared to unassisted PCF (mean difference 91.61 L/min (95% CI 28.3; 155.0), p < 0.001) (Supplementary Figure 1). There was considerable heterogeneity regarding the effects on PCF across 8 studies (I^2 = 95%, p < 0.001). Subgroup analysis on 6 studies after the exclusion of studies on ALS, showed similar effects on PCF (mean difference 83.1 L/min (95% CI 59.4;- 106.7), p < 0.001) (Supplementary Figure 2). Moderate heterogeneity was observed across these 6 studies (I^2 = 48%, p = 0.09).

Respiratory characteristics

Effects on respiratory characteristics varied considerably between studies (Table 4). There was no significant effect on oxygen saturation in all [17,35] but one study [32]. Transcutaneous CO_2 levels did not change in one study [17], in contrast to end-tidal CO_2 which improved in one study [35]. Data on respiratory rate after MI-E application were conflicting [17,33,35]. Only one study observed a statistically significant reduction in respiratory rate [33]. None of the studies showed a significant effect on tidal volume comparing unassisted maneuver to MI-E [17,32,33,35]. The rapid shallow breathing index (RSBI), which is the ratio of respiratory rate and tidal volume, increased significantly immediately after MI-E application in one study [33], and 1 hour after MI-E use in another study [35].

Table 3: Outcome: lung function test results.

Outcome studied	Study	Study design	Setting MI-E	Conclusion
Longer term effect				
PCF/PEF	Rafiq, 2015	AS vs MI-E, follow up ≥ 12 months or till death	≥ 2x/day, 3-5 insp/exp, ≥ +40/-40 cmH_2O	PCF ↓5.77L/min/month vs↑ 0.9 L/min/month (p=0.43)
VC	Rafiq, 2015	AS vs MI-E, follow up ≥ 12 months or till death	≥ 2x/day, 3-5 insp/exp, ≥ +40/-40 cmH_2O	VC ↓0.94%/month vs 0.45%/month (p=0.47)
	Stehling, 2015	1-2 years before and after MI-E introduction: -2 vs-1 vs 0 vs 1 vs 2	10 minutes 3x insp/exp +18/-20 vs +40/-40 cmH_2O (mean +25/-25 cmH_2O)	0.88 vs 0.71 vs 0.5 vs 0.64 vs 0.65 L (year after introduction compared to before: p< 0.002)
Immediate effect				
Cough expiratory volume	Sivasothy, 2001	Unassisted vs MAC vs MI-E vs MI-E+MAC	3 x insp/exp +20/-20 cmH_2O	Without scoliosis: 0.5 vs 0.7 vs 0.6 vs 0.6 L (p>0.01)
				With scoliosis: 0.9 vs 0.5 vs 0.7 vs 0.6 L (p>0.01)
Expiratory reserve volume	Santos, 2017	Unassisted vs passive MI-E vs active MI-E	3 x insp/exp passive (+20, +30, +40/-40 cmH_2O) and active +40/-40 cmH_2O	Passive: 5-24% ↑ (p>0.05) Active: 7-32% ↑(p<0.05)
FEF25%-75%	Bach, 1993	Unassisted vs MI-E	5x insp/exp with maximum comfortable pressures (not quantified)	0.80 L/s ± 0.59 vs 0.91 ± 0.69
FVC	Bach, 1993	Unassisted vs MI-E	5x insp/exp with maximum comfortable pressures (not quantified)	0.49 L ± 0.37 vs 0.54 L ± 0.39
FEV_1/FVC	Bach, 1993	Unassisted vs MI-E	5x insp/exp with maximum comfortable pressures (not quantified)	89.3% ± 12.5 vs 91.0% ± 8.2
Inspiratory capacity	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp , pressures as at home (not quantified)	0.73 vs 0.67 L (p>0.5)
	Lacombe, 2014	Unassisted vs MI-E vs MI-E+MAC	Number of cycles not specified, up to +40/-40 cmH_2O	Unassisted < MI-E (p<0.001), unassisted < MI-E +MAC (p<0.001), MI-E ≈ MI-E+ MAC (p>0.001)
	Santos, 2017	Unassisted vs passive MI-E vs active MI-E	3x insp/exp passive (+20, +30, +40/-40 cmH_2O) and active +40/-40 cmH_2O	Passive: 18-23% ↑ (p<0.05); Active: 23-31% ↑ (p<0.05)
PCEF	Bach, 1993	Unassisted vs MI-E	5x insp/exp with maximum comfortable pressures (not quantified)	1.81 L/s ± 1.03 vs 7.47 L/s ± 1.02
	Mustfa, 2003	Unassisted vs MAC vs MI-E	Not specified, except from maximal tolerated expiratory pressure	MAC 11-13% ↑(p< 0.001); MI-E 26-28% ↑(p<0.001)

	Sivasothy, 2001	Unassisted vs MAC vs MI-E vs MI-E+MAC	3 x insp/exp +20/-20 cmH_2O	Without scoliosis: 104 vs 185 vs 156 vs 248 L/min (p<0.01)
				With scoliosis: 288 vs 193 vs 231 vs 362 L/min
PCF	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp , pressures as at home (not quantified)	163 vs 165 L/min (p=0.86)
	Chatwin, 2003	Unassisted vs MAC vs NIV vs M-E vs MI-E	Pressures at patients comfort (mean mask pressure +15/-15 cmH_2O), cycles and applications not specified	169 vs 188 vs 182 vs 235 (p<0.01) vs 297 L/min (p< 0.001)
	Kim, 2016	Unassisted vs AS +MAC vs MI-E vs MI-E+MAC	5x insp/exp +40/-40 cmH_2O	96 vs 156 vs 177 vs 202 L/min (p<0.01)
	Lacombe, 2014	Unassisted vs MI-E vs MI-E+MAC	Number of cycles and applications not specified, up to +40/-40 cmH_2O	Unassisted < MI-E (p=0.003); MI-E < MI-E + MAC (p<0.03)
	Lalmolda, 2019	Unassisted vs MI-E with +40/-40 cmH2O vs MI-E with settings resulting in maximum PCF	maximum pressures tolerated up to +40/-40 cmH2O (increase with 10cmH2O in each step)	57 vs 198 vs 214 L/min (p <0.005)
				ALS bulbar: 57 vs 164 vs 189 ; non-bulbar 44 vs 243 vs 251
				Non-ALS: 75 (dystrophies) and 95 (other NMDs) vs 186 (all non-ALS) vs 202 (all non-ALS)
	Sancho, 2004	Unassisted vs MI-E	Number of cycles and applications not specified, +40/-40 cmH_2O	4.47 vs 3.75 L/s; baseline PCF < 2.7 vs >2.7L/s: after MI-E 2.79 vs 4.12 L/s
	Senent, 2011	Unassisted vs max inspiration vs max inspiration +MAC vs MAC +AS vs MAC +NIV vs MAC + NIV (30 cmH_2O) vs MI-E	4-6 cycles, +40/-40 cm H_2O	84 (35-118) vs 79 (36-142) vs 104 (80-140) vs 284 (146-353) vs 212 (99-595) vs 233 (100-389) vs 488 (243-605) L/min
	Winck, 2004	Unassisted vs MI-E	3x 6 insp/exp, +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 170 vs 200 L/min (P < 0.005)
				Other NMD 180 vs 220 L/min (p < 0.005)
Peak value time	Sivasothy, 2001	Unassisted vs MAC vs MI-E vs MI-E+MAC	3 x insp/exp +20/-20 cmH_2O	Without scoliosis: 80 vs 118 vs 85 vs 75 ms (p>0.01)
PE_{max}	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	24 vs 22 vs 23 (p>0.05)

Table 3: Continued

PI_{max}	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	24 vs 22 vs 21 (p>0.05)
SNIP	Fauroux, 2008	Unassisted vs MI-E with +15/-15vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp, +15/-15, +30/-30, +40/-40 cmH_2O	29 vs 30 vs 28 vs 31 cmH_2O
VC	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp , pressures as at home (not quantified)	0.75 vs 0.59 L (p=0.78)
	Fauroux, 2008	Unassisted vs MI-E with +15/-15vs +30/-30 vs +40/-40 cmH_2O	3x 6 insp/ exp, +15/-15, +30/-30, +40/-40 cmH_2O	1.04 vs 1.01 vs 1.00 vs 1.04 l
	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	↑ 108% of unassisted (p=0.018), after 1 hour ↓ as unassisted
	Santos, 2017	Unassisted vs passive MI-E vs active MI-E	3x insp/exp passive (+20, +30, +40/-40 cmH_2O) and active +40/-40 cmH_2O	Passive: 16-22% ↑ (p<0.05); Active: 23-28% ↑ (p<0.05)

Legend: ALS = amyotrophic lateral sclerosis, AS = air stacking, exp = expiratory, FEF25-75% = forced mid-expiratory flow, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, insp = inspiratory, MAC = manually assisted cough, MI-E = mechanical insufflation- exsufflation, NIV= non-invasive ventilation, NMD = neuromuscular disease, PCEF = peak cough expiratory flow, PCF = peak cough flow, PEF = peak expiratory flow, PE_{max} = maximal expiratory pressure, PI_{max} = maximal peak inspiratory pressure, SNIP = sniff nasal pressure, VC = vital capacity, vs = versus

Table 4: Outcome: respiratory characteristics

Outcome studied	Study	Study design	Setting MI-E	Conclusion
Minute ventilation	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	6.3 vs 5.9 vs 6.2 vs 6.3 L/min (p>0.05)
	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 8.5 vs 8.9 vs 9.8 vs 10.6 L/min (p>0.05)
				Other NMD: 12.7 vs 11.4 vs 10.4 vs 11.4 L/min (p>0.05)
$PetCO_2$	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	39.9 vs 38.0 vs 37.7 vs 37.8 mmHg (p<0.0003)
$PtcCO_2$	Meric, 2017	Unassisted vs MI-E	15 x insp/exp, +30/-30 cmH_2O	48 vs 47 vs 49 (after 1hr) (p>0.05)
PEFMF	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 1.54 vs 1.51 vs 1.54 vs 1.54 (p>0.05)
				Other NMD: 1.55 vs 1.54 vs 1.55 vs 1.52 (p>0.05)
PIFMF	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 1.38 vs 1.45 vs 1.44 vs 1.43 (p>0.05)
				Other NMD: 1.45 vs 1.47 vs 1.43 vs 1.40 (p>0.05)
Respiratory comfort	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	73 vs 75 vs 76 vs 83/100 (p<0.05)
Respiratory rate (RR)	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp +15/-15 to +45/-45 cmH_2O	24 vs 19/min (p=0.001)
	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	26 vs 27 vs 26 vs 26/min(p>0.05)
	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	21 vs 19 vs 23/min (after 1 hour) (p>0.05)
RSBI (=RR/TV)	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp +15/-15 to +45/-45 cmH_2O	Unassisted > MI-E (p=0.007)
	Fauroux, 2008	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	66 vs 61 vs 84 (after 1hr) (p<0.05)

Table 4: Continued

Saturation	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	97.1 vs 96.6 vs 96.5 vs 96.4 (p>0.05)
	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	97 vs 97 vs 97 (after 1 hour) (p>0.05)
	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 94 vs 95 vs 95 vs 98% (p<0.005)
				Other NMD: 94 vs 96 vs 95 vs 98% (p<0.05)
Subjective scores				
-Borg score	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	1.16 vs 1.33 vs 1.61 (after 1 hour) (p>0.05)
	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 2.0 vs 1.0 (p>0.05)
				Other NMD: 2.0 vs 0.75 (p<0.05)
-Cough comfort	Senent, 2011	Unassisted vs max inspir vs max inspir +MAC vs MAC +AS vs MAC +NIV vs MAC + NIV (30 cmH_2O) vs MI-E	4-6 cycles, +40/-40 cm H_2O	5 (4-7) vs 5 (5-7) vs 7 (5-7) vs 6 (5-8) vs 8 (7-8) vs 6 (5-7) vs 7 (3-8) (p>0.05)
-Cough efficacy	Senent, 2011	Unassisted vs max inspir vs max inspir +MAC vs MAC +AS vs MAC +NIV vs MAC + NIV (30 cmH_2O) vs MI-E	4-6 cycles, +40/-40 cm H_2O	4 (2-7) vs 6 (4-7) vs 7 (4-8) vs 7 (5-8) vs 7 (6-8) vs 6 (5-7) vs 8 (6-8) (p>0.05)
Tidal volume (TV)	Cesareo, 2018	Unassisted vs MI-E	5 x 5 insp/exp +15/-15 to +45/-45 cmH_2O	Unassisted ≈ MI-E (p>0.05)
	Fauroux, 2008	Unassisted vs MI-E with +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3 x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	0.27 vs 0.27 vs 0.27 vs 0.28 L (p>0.05)
	Meric, 2017	Unassisted vs MI-E	15 x insp/exp +30/-30 cmH_2O	316 vs 310 vs 275 (after 1 hr)mL (p>0.05)
	Winck, 2004	Unassisted vs MI-E +15/-15 vs +30/-30 vs +40/-40 cmH_2O	3x 6 insp/exp +15/-15, +30/-30, +40/-40 cmH_2O	ALS: 408 vs 390 vs 408 vs 494 mL (p>0.05)
				Other NMD: 468 vs 460 vs 440 vs 588 mL (p>0.05)

Legend: ALS = amyotrophic lateral sclerosis, exp = expiratory, insp = inspiratory, inspir = inspiration; MAC = manually assisted cough, MI-E = mechanical insufflation-exsufflation, NMD = neuromuscular disease, NIV= non-invasive ventilation, $PaCO_2$ = arterial pCO_2, PaO_2 = arterial pO_2, PEFMF = peak expiratory flow to mean expiratory flow ratio, $PetCO_2$ = endtidal pCO_2, PIFMF = peak inspiratory flow to mean inspiratory flow ratio, $PtcCO_2$ = transcutaneous pCO_2, RR = respiratory rate, RSBI = rapid shallow breathing index, TV = tidal volume, vs = versus

Laryngeal response

Two studies from the same author(s) warned for upper airway collapse during MI-E treatment in ALS patients, which can be prevented by individually customized MI-E settings [15,16] (Supplementary Table 1).

Patient satisfaction

Satisfaction of subjects and carers was reported in 7 studies [18–20,22,26,30,31](Supplementary Table 2). Patient satisfaction was generally high. In nearly all cases treatment with MI-E was perceived as a valuable improvement of subjects' health by managing the disease at home, preventing hospital admissions and maintain social participation.

Methodological quality and risk of bias

Summary of quality assessment of the included studies is provided in the Supplementary Table 3. Median summary score was 0.85 (IQR 0.79-0.87). Blinding of investigator was only done in 1 study [25]. Control of confounding was limited in most studies. Sample size was limited in many studies and method of subject selection sometimes not clearly described [20,21,27,28] . Supplementary table 4 shows PRISMA 2020 checklists of this systematic review.

Discussion

This systematic review shows that there is limited evidence for efficacy of daily use of MI-E in clinically stable patients with NMDs, with the possible exception of increased PCF immediately after MI-E application. Very limited evidence exists on superiority of effects of MI-E compared to other ACTs. Only one RCT showed a superior effect of MI-E on PCF compared to AS and MAC. Unfortunately there is no evidence on long term efficacy, implying that additional studies are needed.

Since RTIs are the primary cause of acute respiratory deterioration and hospital admission in patients with NMDs, the clinically most relevant outcome of MI-E for the longer term is reduction of number, duration and severity of RTIs [4].This would have an important impact on quality of life of patients and their relatives and would probably reduce care costs [41–43]. However, there is only one RCT that compared AS and MI-E using RTI frequency as an outcome measure. This study included patients with ALS and reported a possible trend towards reduced duration of RTI [22]. The study had a small sample size and may not be representative for other NMDs. The reported effect may be more pronounced if this RCT included patients with other NMDs instead of patients with ALS, due to the reported counterproductive effects of MI-E in patients with ALS if no individualized settings were

used [15,16]. The difference in effect between a study population with and without inclusion of ALS patients was not supported by the forest plots in our results (Supplementary Figure 1 and 2). This may be explained by the number of included patients, which was 43% more if all studies were included in the meta-analysis (n=183) compared to analysis of studies without ALS patients (n=128). Observational studies were of limited quality and confounding factors preclude a conclusion regarding the effect of MI-E on RTIs.

LFT results are an important surrogate outcome measure, as studies in patients with DMD suggest that VC is a valuable predictor of susceptibility to RTI, need for respiratory support and survival[7]. Longer term effects on LFT results were reported in one RCT [22] and one retrospective observational study [29], with respectively no significant and a significant improvement of vital capacity after MI-E introduction. The studies that reported LFT results immediately after application of MI-E suggest direct improvement of lung volumes [17,24,27,37], but not on respiratory muscle strength [17,35]. It is unclear how long these immediate, mainly beneficial effects of MI-E application last.

The majority of studies show no significant immediate effect on respiratory characteristics.

Qualitative research reported high patient satisfaction of MI-E. This is important, especially when evidence for beneficial effect is limited. However, selection and study bias probably influenced these results considerably.

The included studies had clear limitations. We identified and included only three RCTs in our analysis [22,36,37]. Results from other included studies should be interpreted with caution due to the retrospective nature of these studies on respiratory related hospital admissions and RTIs, which render them susceptible to potential flaws and bias. Most prospective observational studies only described the immediate effect on LFT results but did not assess longer term outcome. Forced maneuvers during lung function testing prior to MI-E application may have resulted in lung volume recruitment, thereby underestimating the effect of MI-E [45]. On the other hand, respiratory muscle fatigue may underestimate the effect of MI-E [46]. In our meta-analysis on the effect of MI-E on PCF we combined absolute PCF measurements obtained with different devices. Different measurement devices perform variably, leading to potentially substantial inaccuracy in PCF measurements [47].

NMDs are a large and heterogeneous group of disorders. This heterogeneity, the variation in clinical characteristics (type and severity of disease, affected respiratory muscle groups, age, scoliosis deformity), the small sample sizes and varying MI-E settings preclude definite conclusions. Inclusion of predominantly ALS patients limits generalizability and may even have resulted in underestimation of beneficial effects. In addition to the two studies on laryngeal response [15,16], five other studies exclusively included ALS patients [21–23,25,26] and

in three studies the majority of included patients with NMDs consisted of patients with ALS [28,32,38]. The RCT [22] that did not show a statistically significant effect on the number and duration of RTIs only included patients with ALS.

Rarity of NMDs complicates the inclusion of larger numbers of patients, in particular in single center studies. Future studies on MI-E should ensure increased statistical power. Due to the heterogeneity of patients, interventions and outcome measures, we could only perform a meta-analysis on effect on PCF.

Compliance to treatment was not described in any study, whereas it is possible to check MI-E use for the preceding months in most, if not all, MI-E devices. Blinding of the researcher, although possible, was very uncommon. Blinding of the patient was not possible but may have caused a placebo-effect in some studies. Patients naïve to MI-E treatment may have a different response to treatment than patients who regularly use MI-E. Being an experienced or naïve user of MI-E was not specified in many studies. In addition, the technical and methodological information was often very limited. In studies comparing different ACTs or different settings of MI-E, the order of treatments was not always specified, nor the use or length of pauses between treatments. Some qualitative studies did not describe the selection process of patients for inclusion, which complicates the interpretation of patient satisfaction and the possibility of bias.

Only few studies reported adverse events (Table 1). Evaluation of the benefits alone, without evaluation of harm, is likely to bias conclusions about the net efficacy or effectiveness of the intervention [48]. The current review was restricted to English-language articles. Publication bias cannot be excluded as beneficial effects of MI-E are more likely to be published. No studies looked at the total costs of different ACTs, including the purchase and maintenance of the device, hospital visits and admissions.

Reproducibility and transparency of reported results is ensured by our methodology. The broad search strategy has reduced the chance of incomplete overview of studies. We included 25 studies, considerably more than recent reviews. Cochrane review on cough augmenting therapy included 11 trials, with minority including data on MI-E [10]. A systematic review on MI-E use in patients with NMDs published a few years ago included 12 studies published before 2015 [49].

Although there is an increase in the number of studies on MI-E the last 5 years, we cannot draw conclusions on the longer term effects of MI-E. The results of this systematic review help to identify knowledge gaps with regard to the use of MI-E. High-quality controlled studies, preferably RCTs, are required not only to study the longer term effects of daily MI-E use on the most clinically relevant outcomes measures including RTIs or hospital

admissions but also to compare different ACTs. RCTs are the preferred study design as it will be a challenge of studying the effect of MI-E on longer term respiratory outcomes in the presence of potential confounders, such as concomitant use of ventilatory support, disease progression and introduction of (gene-modifying) treatments. We would advise a follow up of at least two years, to reduce seasonal influence on results and to be able to study the longer term effects on LFT results. RTIs are difficult to define and the decision to start antibiotic treatment and to admit a patient are prone to subjectivity. LFT results may be an alternative outcome, because it possibly predicts susceptibility to RTIs, need for respiratory support and survival. Because some countries do not reimburse MI-E, we would suggest to also study total cost of care as outcome measure. Future studies should focus on NMDs such as DMD, other muscular dystrophies, congenital myopathies and SMA. These studies should be performed separate from studies in patients with ALS, given the fact that in this disorder upper airway collapse may be present in the absence of or before the onset of bulbar symptoms [15,16]. Additional studies or subgroup analyses are needed to identify patient subgroups in whom MI-E has superior effect compared to other ACTs, allowing future patient selection for MI-E treatment. Optimal MI-E settings need to be investigated, and most likely should be individualized in order to obtain maximal beneficial effect or avoid side effects.

Conclusion

At this moment there is very limited data available to analyze the effect of MI-E on RTI or respiratory-related admissions. Although MI-E has an immediate beneficial effect on peak cough flow, evidence on longer term lung function improvement is lacking. There is evidence for counterproductive effect in patients with ALS, even prior to the onset of bulbar symptoms, if MI-E treatment is not individualized.

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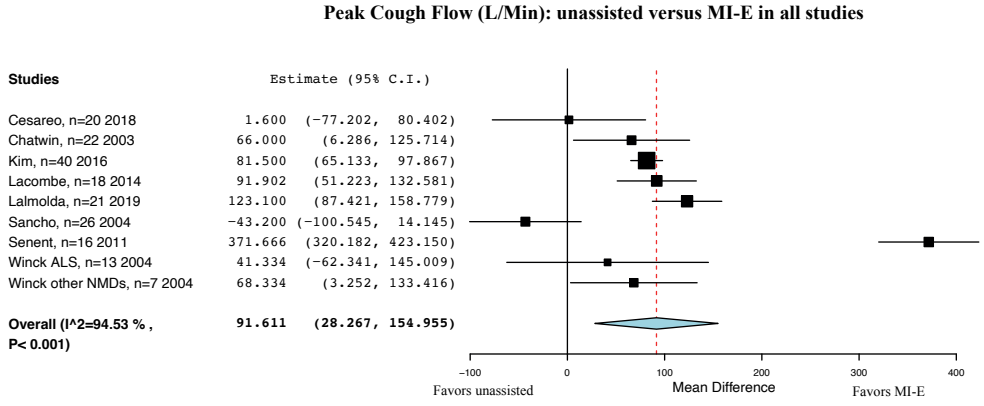
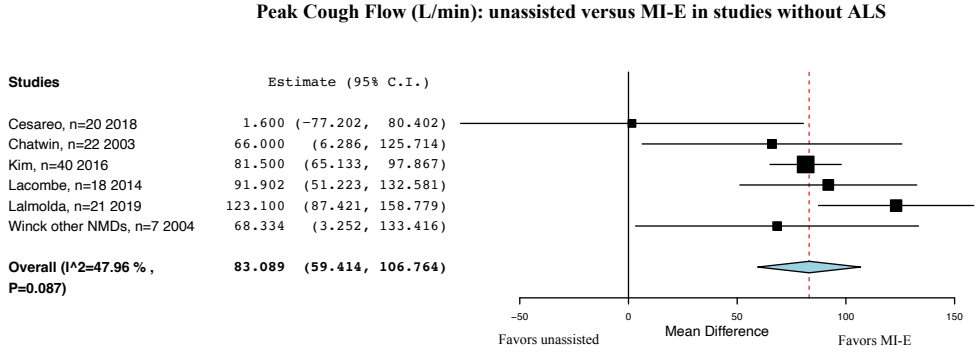
Supplemental material

Supplementary figure 1: Meta-analysis: Peak Cough Flow (PCF) after MI-E versus unassisted PCF



Legend: CI = confidence interval

Supplementary figure 2: Meta-analysis: Peak Cough Flow (PCF) after MI-E versus unassisted PCF in studies without patients with ALS



Legend: CI = confidence interval

Supplementary Table 1: Outcome: Laryngeal response

Study	Study design	Setting MI-E	Conclusion
Andersen, 2017	Cross-sectional pat-control	Cycles and applications not specified, +20/-20 to +50/-50 cmH_2O	Bulbar ALS: supraglottic adduction during insp
Andersen, 2018	Prosp longitudinal	2-4x insp/exp +15/-30 to +40/-40 cmH_2O	Insp: adduction vocal cords and aryepiglottic folds at lower pressures with disease progression

Legend: ALS = amyotrophic lateral sclerosis, exp = expiration, insp = inspiration, MI-E = mechanical insufflation-exsufflation, pat = patient, prosp = prospective

Supplementary Table 2: Outcome: Patient satisfaction and Quality of Life

Study	Study design	Subjects studied	Outcome	Conclusion
Miske, 2004	Retrosp	Patients (child)	Patient satisfaction	90% well-tolerated
			Secretion clearance	6% ↓chronic atelectasis; 8% ↓RTI
			Safety	No pneumothorax; no emergency tracheostomy
Moran, 2013	Retrosp: purpose-designed survey	Patients (child), parents	Parents's views of positive and negative factors on patient and family	Pos: ↑QoL (n=9/10); ability to stay at home during RTIs. Neg: ↑housebond (n=1/10)
			Complications	None reported
			Effect on number of hospital presentations	All: prevention of hospital presentations
Moran, 2015	Qual: semi-structured interviews	Patients (child), parents	Lifestyle implications	Negative: disruption when parent is sole operator of MI-E; positive: ↓ hospitalization, facilitated outings
			Parents becoming experts	Initially parents concerned, daunted; over time comfortable
			Parents developing sense of control over their child's condition	Mostly ↑ sense of control (improve child's health, avoid admissions)
			Element of extra care	Respiratory care quicker and easier
			Impacts on parents-child relationship	Generally no changed relationship
Rafiq, 2015	RCT (MI-E vs AS): questionnaires	Patients and carers	QoL (SF-36 and sleep apnea quality-of-life index)	>75% in 205 days vs 329 days (p=0.41),
			Caregiver strain index (CSI)	Mean whole cohort: 2.83-5.5 (no significant difference between MI-E and AS)
Siewers, 2013	Qual: semi-structured in-depth interviews	Patients, carers	User confidence	Important: confidence with MI-E, trustful relationship patient and carer
			Influence on relationships	Tool to help patient, which could strengthen the relationship
			Patients illness perception	Some patients: MI-E made illness progression more apparent
Travlos, 2016	Qual: interviews (phenomenological inquiry)	Patients (child), parents, physiotherapist	Self-reported QoL	Benefit respiratory health; maintain social participation; ↓anxiety

Veldhoen, 2019	Questionnaires with likert scale	Parents	Secretion removal	Score 9/10 (IQR 8-10)
			RTI prevention	Score 9/10 (IQR 8-10)
			Comfort during MI-E treatment	Score 8.5/10 (IQR 6.8-10)
			Recommend MI-E to other patients	100% (even patients who discontinued MI-E treatment)

Legend: AS = air stacking, MI-E = mechanical insufflation-exsufflation, neg = negative, pos = positive, QoL= quality of life, qual = qualitative, RCT = randomized controlled trial, retrosp = retrospective, RTI = respiratory tract infection

Supplementary Table 3 : Quality assessment of included studies using the AHFMR tool

	Quant/Qual	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Score
Andersen, 2017	Quant	2	2	2	2	n/a	0	n/a	1	2	2	n/a	n/a	2	2	0.85
Andersen, 2018	Quant	2	2	2	2	n/a	0	n/a	1	1	2	n/a	n/a	2	2	0.80
Bach, 1993	Quant	2	2	1	2	n/a	0	n/a	2	2	1	2	1	2	2	0.79
Cesareo, 2018	Quant	2	1	2	2	n/a	0	n/a	2	1	2	2	1	2	2	0.79
Chatwin, 2003	Quant	2	1	2	2	n/a	0	n/a	2	2	2	2	2	2	2	0.88
Fauroux, 2008	Quant	2	2	2	2	n/a	0	n/a	2	2	2	2	1	2	2	0.88
Kim, 2016	Quant	2	2	2	2	n/a	0	n/a	2	1	2	2	2	2	2	0.88
Lacombe, 2014	Quant	2	1	2	2	2	0	n/a	2	1	2	2	2	2	2	0.85
Lalmolda, 2019	Quant	2	2	2	2	n/a	n/a	n/a	2	2	2	2	1	1	2	0.90
Mahede, 2015	Quant	2	1	2	1	n/a	n/a	n/a	2	1	2	2	0	2	2	0.71
Meric, 2017	Quant	2	1	2	2	n/a	0	n/a	2	1	2	2	1	2	2	0.79
Miske, 2004	Quant	1	2	2	2	n/a	n/a	n/a	0	1	0	n/a	n/a	0	1	0.50
Moran, 2013	Quant	2	2	1	2	n/a	n/a	n/a	1	1	2	2	n/a	2	2	0.85
Moran, 2015	Qual	1	2	2	2	2	2	2	0	2	2	n/a	n/a	n/a	n/a	0.85
Mustfa, 2003	Quant	1	1	1	1	n/a	0	n/a	2	1	2	2	1	2	2	0.67
Rafiq, 2015	Quant	2	2	2	2	2	0	n/a	1	2	2	2	1	2	2	0.85
Sancho, 2004	Quant	2	1	2	2	n/a	0	n/a	2	2	2	2	1	2	1	0.79
Santos, 2017	Quant	2	1	2	2	n/a	0	n/a	2	2	2	2	1	2	2	0.83
Senent, 2011	Quant	2	1	2	2	n/a	2	n/a	2	1	2	2	n/a	2	1	0.86
Siewers, 2013	Quant	2	2	2	2	1	2	2	0	2	2	n/a	n/a	n/a	n/a	0.85
Sivasothy, 2001	Quant	2	1	1	2	n/a	0	n/a	2	1	2	2	1	2	1	0.71
Stehling, 2015	Quant	2	2	2	2	n/a	n/a	n/a	2	2	2	2	1	2	2	0.95
Travlos, 2016	Qual	2	2	2	2	1	2	1	2	1	2	n/a	n/a	n/a	n/a	0.85
Veldhoen, 2019	Quant	2	2	2	2	n/a	n/a	n/a	2	2	2	2	0	2	2	0.91
Winck, 2004	Quant	2	2	2	2	n/a	0	n/a	2	1	2	2	1	2	2	0.83

Legend: AHFMR = Alberta Heritage Foundation for Medical Research; n/a = not applicable; Qual = qualitative; Quant = quantitative; 0= criteria not met; 1 =criteria partially met; 2 = criteria met

Supplementary table 4 : PRISMA (abstract) checklist
PRISMA 2020 checklist

Section/Topic	Item	Checklist item	Reported
Title			
Title	1	Identify as systematic review	yes
Abstract			
Abstract	2	See prisma 2020 abstract checklist	yes
Introduction			
Rationale	3	Rationale in context of existing knowledge	yes
Objectives	4	Statement objective(s) or questions	yes
Methods			
Eligibility criteria	5	In- and exclusion criteria, grouping of studies	yes
Information sources	6	Specify all databases and other sources, incl dates	yes
Search strategy	7	Present full search strategies	yes
Selection process	8	Methods used, number of (independent) reviewers	yes
Data collection process	9	Methods used, number of (independent) reviewers	yes
Data items	10a	List and define all outcomes	yes
	10b	List and define all other variables	yes
Study risk of bias	11	Methods used, tools, number of (independent) reviewers	yes
Effect measures	12	Specify for each outcome the effect measure used	not specified
Synthesis methods	13a	Describe process to decide if studies were eligible	yes
	13b	Methods required to prepare data for synthesis	yes
	13c	Methods used to visually display results	yes
	13d	Methods used to synthesize results (incl meta-analysis)	yes
	13e	Methods used to explore causes of heterogeneity	yes
	13f	Sensitivity analyses	yes

Reporting bias assessment	14	Methods used to assess risk of bias due to missing results	not done
Certainty assessment	15	Methods used to assess certainty/confidence	not reported
Results			
Study selection	16a	Results of search and selection process (flow diagram)	7, Fig 1
	16b	Reason for exclusion	Fig 1
Study characteristics	17	Characteristics for each included study	Table 1
Risk of bias in studies	18	Assessment of risk of bias for each included study	Suppl table 3
Results individual studies	19	Summary statistics for alle outcomes	(Suppl) tables
Results of syntheses	20a	Briefly summarize characteristics and risks of bias	yes
	20b	Statistical syntheses results	yes
	20c	Results of investigations and causes of heterogeneity	yes
	20d	Results of sensitivity analyses	yes
Reporting biases	21	Assesment of risk of bias due to missing results	not done
Certainty of evidence	22	Assessment of certainty/confidence	yes
Discussion			
Discussion	23a	General interpretation in context of other evidence	yes
	23b	Limitations of the evidence	yes
	23c	Limitations of the review processes	yes
	23d	Implications for future	yes
Other information			
Registration and protocol	24a	Registration (name and number)	yes
	24b	Assessment of protocol can be assessed or not prepared	yes
	24c	Describe and explain any amendments in protocol	not applicable
Support	25	Describe sources of (non)financial support	yes
Competing interests	26	Declare competing interests	yes
Availability of data, codes	27	Declare which is publicly available	yes

PRISMA 2020 abstract checklist

Title			
Title	1	Identify as systematic review	yes
Background			
Objectives	2	Provide eplicit statement of objective(s)	yes
Methods			
Eligibility criteria	3	Specify in- and exclusion criteria	yes
Information sources	4	Specify information sources and dates	yes
Risk of bias	5	Specify methods used to assess risk of bias included studies	yes
Synthesis of results	6	Specify methods used to present and synthesize results	yes
Results			
Included studies	7	Total number included studies and participants. Characteristics.	yes
Synthesis of results	8	Main outcomes, meta-analysis with summary estimate and CI	yes
Discussion			
Limitations of evidence	9	Limitations of evidence included	yes
Interpretation	10	General interpretation and implications	yes
Other			
Funding	11	Specify primary source of funding	yes
Registration	12	Provide register name and registration number	yes

CHAPTER 7

Short term effect of airway clearance on lung function in patients with neuromuscular diseases.

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Chronic Respiratory Disease 2022; 19: 14799731221094619

Abstract

Air stacking (AS) and mechanical insufflation-exsufflation (MI-E) aim to increase cough efficacy by augmenting inspiratory lung volumes in patients with neuromuscular diseases (NMDs).We studied the short-term effect of AS and MI-E on lung function.

We prospectively included NMD patients familiar with daily AS or MI-E use. Studied outcomes were forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) prior to, immediately after, and up to two hours after treatment. Paired sample T-test and Wilcoxon Signed Rank test was used.

Sixty-seven patients participated. We observed increased FVC and FEV_1 immediately after AS with a mean difference of respectively 0.090 L (95% CI 0.045; 0.135, P<0.001) and 0.073 L (95% CI 0.017; 0.128, P=0.012). Increased FVC immediately after MI-E (mean difference 0.059 L (95% CI 0.010; 0.109, P=0.021)) persisted one hour (mean difference 0.079 L (95% CI 0.034; 0.125, P=0.003)). The effect of treatment was more pronounced in patients diagnosed with Spinal Muscular Atrophy, compared to patients with Duchenne Muscular Dystrophy.

AS and MI-E improved FVC immediately after treatment, which persisted one hour after MI-E. There is insufficient evidence that short-lasting increases in FVC would explain the possible beneficial effect of AS and MI-E.

Introduction

Respiratory muscle weakness causes cough impairment and respiratory failure and is a major cause of morbidity and mortality in patients with neuromuscular diseases (NMDs), including spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) [1–4]. Cough impairment primarily compromises airway clearance and increases the risk of recurrent respiratory tract infections (RTIs) and hospital admissions [1–6]. RTIs can further reduce lung function and this cycle may ultimately contribute to higher morbidity and mortality [3,7]. The use of airway clearance techniques (ACTs) including air stacking (AS) and mechanical insufflation-exsufflation (MI-E) are therefore routinely used in patients with NMDs. Their use possibly results in a reduced number of RTIs and associated hospital admissions and shorter duration of hospital stays [5,8–13].

International guidelines recommend initiation of ACTs when peak cough flow (PCF) falls below 270 L/min and/or forced vital capacity (FVC) is below 50% of predicted capacity [2], but do not specify preferred techniques. AS increases the inspiratory lung volume to its maximum by manually assisting the inspiration, resulting in an increased PCF [14]. By increasing the inspiratory volume, AS enhances expiratory flow by a combination of static recoil and expiratory muscle recruitment [2,15]. Advantages of AS include its low costs and availability. MI-E is often initiated when AS is impossible (e.g. in young children) or no longer effective [3,11]. Unlike AS, MI-E also assists the expiration, by using a positive inspiratory pressure which is rapidly followed by a negative expiratory pressure. This rapid change in pressure mimics the flow changes that occur during a cough, thereby removing bronchial secretions [3,16,17]. In comparison to AS, MI-E is much more expensive and not reimbursed in all countries [9,18]. Studies show that both AS and MI-E improve cough strength immediately after treatment [1,13,19–29], yet the duration of this effect remains unclear [24]. For this reason, we prospectively studied the effect of either AS and MI-E on lung function tests (LFTs) up to two hours after ACT in patients with NMDs not naïve to this treatment. This hopefully helps to better understand the pathophysiological mechanism of these ACTs and may then improve and optimize ACT treatment in order to obtain maximal beneficial effect. We hypothesized that both AS and MI-E result in improved LFT, lasting at least one hour after treatment.

Methods

Design and participants

In this prospective, single-center cohort study we included patients with NMDs without intercurrent RTI, who were already familiar with daily use of AS or MI-E at home at time of inclusion. All participants regularly attended the center for home mechanical ventilation

at the University Medical Center Utrecht in the Netherlands, that serves large parts of the north-western, central and eastern parts of the Netherlands. Participants either used home mechanical ventilation or were at risk of chronic respiratory failure at the time of enrolment, i.e. the second semester of 2020. Patients could not participate if they were unable to perform a spirometry, had a RTI at time of enrolment or when they did not understand Dutch or English, since this would interfere with informed consent. This study was approved by the institutional Medical Ethical Committee . Written informed consent was obtained from all participants and their parents in case of a minor.

Airway Clearance Technique

All patients brought their own AS equipment and/or MI-E device. Patients used a self-inflating resuscitation bag (AMBU, Spur II, 1475 mL) for AS. The used MI-E device was the cough assist E70 (Philips Respironics). Patients were initiated o

Lung function tests (LFTs)

The primary outcome measures of this study were Forced Expiratory Volume in one second (FEV_1), FVC and Peak Expiratory Flow (PEF), obtained with a handheld spirometer (CareFusion Microloop Spirometer) with an oronasal mask. Both absolute and standardized LFTs were measured and reported according to the European Respiratory Society Guidelines and the Global Lung Function Initiative [30]. Although a recent Cochrane review suggested that Peak Cough Flow (PCF) improves after a range of cough augmenting techniques compared to unassisted cough [31], we decided not to use this as an outcome parameter. Measurement of PCF requires an additional maneuver which may result in fatigue with negative impact on LFT results. We used PEF as an alternative, because of the relation between PEF and PCF [32]. Additionally, visual feedback on quality of LFT is possible with PEF measurement. We used tape-measured arm span as estimate for height in patients who were not able to stand without support [33]. All subjects performed LFT in seated position, without corsets or braces. We performed spirometry before, immediately after, and one and two hours after ACT. We documented the highest values out of three attempts.

Statistical analysis

To describe baseline characteristics, we used descriptive statistics. We used IBM SPSS 25.0 and R (v3.6.0 with R Studio v1.2.1335). We used independent samples T-Test for normally distributed variables and Mann-Whitney U test for parametric distributed variables to compare groups. All LFT parameters were tested for normality. We used paired sample T-test to determine improvement of LFT parameters after ACT for parameters with a normal distribution and Wilcoxon signed-rank test for parameters without normal distribution. Finally, we used linear regression to analyze the relationship between the

effect of ACT and patient characteristics, such as the presence or severity of scoliosis and mechanical ventilation.

Results

Sixty-nine patients were screened for eligibility. Two patients were excluded as we were not able to obtain reproducible LFT results, resulting in 67 included patients (54 children and 13 adults; median age 13.8 years (IQR 10.0; 17.2)). The patient characteristics are shown in table 1. Forty-eight patients (72%) used AS and 19 patients (28%) used MI-E. Patients in the MI-E group predominantly had SMA (89%), the remainder had Ullrich Congenital Muscular Dystrophy (UCMD) (11%). The AS group consisted of a more mixed group of NMDs, but the majority had SMA or DMD. We divided patients who used AS into three groups: SMA (type 1c and 2), DMD and other NMDs. Other NMDs included amyotrophic lateral sclerosis (N=4), congenital myopathy (N=4), limb girdle muscular dystrophy (N=2), myotonic dystrophy (N=2), hereditary motor sensory neuropathy (N=2) and Kennedy's disease (N=1). Patients using MI-E were younger than patients treated with AS (median age 8.6 years (IQR 12.0; 18.3) and 15.3 years (IQR 12; 18.3), respectively (P<0.001). Patients who used MI-E more frequently used mechanical ventilation (74%, compared to 46% for AS (P=0.04). Scoliosis with a Cobb angle of more than 40 degrees was more frequently present in the MI-E group (63%, compared to 37% for AS (P=0.053). There were no significant differences in baseline standardized lung function parameters between the two groups.

Effects of Air Stacking (AS)

We observed a significant improvement in FVC immediately after AS treatment with a mean difference of 0.090 L (95% CI 0.045; 0.135, P<0.001). This effect was short-lasting, since one and two hours after treatment FVC had returned to baseline levels. We observed a similar transient improvement of FEV_1 immediately after AS with a mean difference of 0.073 L (95% CI 0.017; 0.128, P=0.012) (table 2, figure 1), with return to baseline levels within hours. PEF was not different before and after AS treatment. The degree of scoliosis and use of mechanical ventilation did not influence outcome. Standardized LFT results before and after AS treatment are shown in Supplemental table 1.

Table 1: Baseline characteristics

	AS (N =48)			MI-E (N=19)	
	SMA (N=16)	**DMD (N=14)**	**Other (N=18)**	**SMA (N=17)**	**UCMD (N=2)**
Male gender, N (%)	8 (50)	14 (100)	7 (39)	13 (76)	2 (100)
Age in years, median (IQR)	12.4 (9.7; 14.9)	17.4 (15.1; 18.2)	29.6 (12.8; 55.8)	9.0 (5.5; 14.6)	8.2
Ventilation, N (%)					
No ventilation	8 (50)	5 (36)	13 (72)	3 (18)	2 (100)
Non-invasive	8 (50)	9 (64)	5 (28)	13 (76)	0 (0)
Invasive	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)
Scoliosis, N (%)					
No scoliosis	0 (0)	5 (36)	12 (67)	0 (0)	0 (0)
Cobbs <40	5 (31)	6 (43)	1 (6)	5 (29)	2 (100)
Cobbs 40-80	9 (56)	2 (14)	4 (22)	11 (65)	0 (0)
Cobbs >80	2 (13)	0 (0)	0 (0)	1 (6)	0 (0)
Cobbs unknown	0 (0)	1 (7)	1 (6)	0 (0)	0 (0)
FEV_1 in liter, mean (SD)	0.861 (0.389)	1.160 (0.484)	1.15 (0.59)	0.542 (0.208)	0.410 (0.156)
FEV_1 in %, median (IQR)	42 (27; 52)	32 (23; 45)	42 (32; 54)	35 (20; 49)	38
FVC in liter, mean (SD)	0.978 (0.491)	1.47 (0.623)	1.39 (0.736)	0.651 (0.208)	0.510 (0.071)
FVC in %, median (IQR)	43 (24; 51)	38 (23; 45)	40 (32; 56)	38 (24; 46)	40
PEF in liter/min, mean (SD)	102 (48)	114.7 (56.8)	122 (65.9)	102.3 (47.8)	64.5 (50.2)
PEF in %, median (IQR)	31 (23; 40)	20 (15; 33)	30 (22; 56)	25 (17; 38)	36

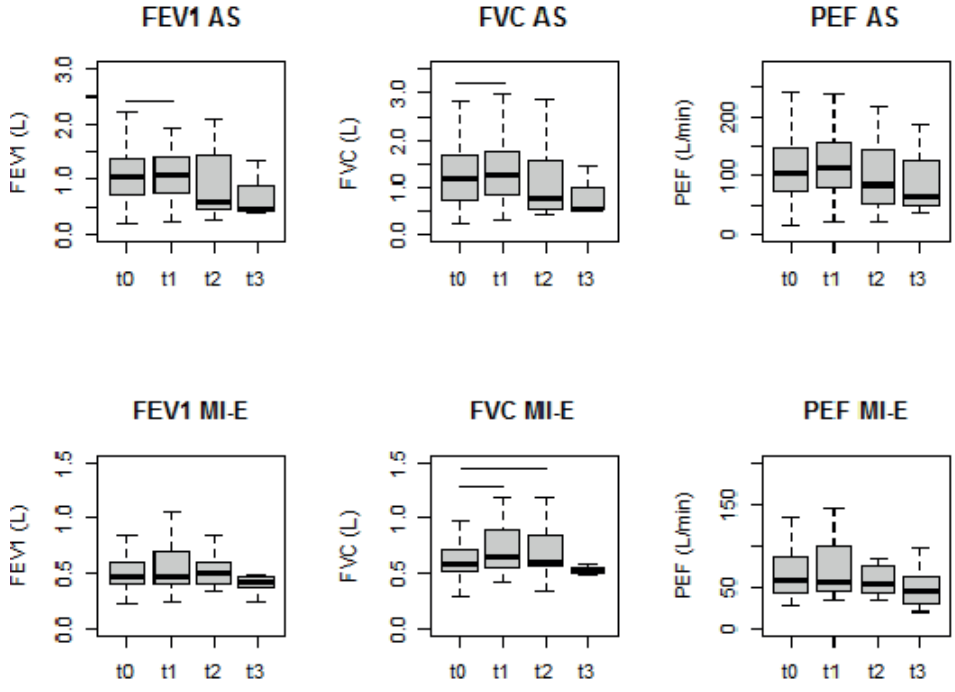
Legend: AS = Air stacking, DMD = Duchenne Muscular Dystrophy, FEV1 = Forced Expiratory Volume in 1 second, FVC = Forced Vital Capacity, IQR = Inter Quartile Range, MI-E = Mechanical Insufflation-Exsufflation, Min=Minute, N= Number, PEF = Peak Expiratory Flow, SD = Standard Deviation, SMA = Spinal Muscular Atrophy, UCMD = Ullrich Congenital Muscular Dystrophy

Table 2: Effects of air stacking and mechanical insufflation-exsufflation on lung function immediately after (T1), one hour after (T2) and two hours (T3) after treatment compared to prior to air stacking or mechanical insufflation-exsufflation treatment (T0)

	AS (N=48)				MI-E (N=19)			
	N	**Mean diff**	**95% CI**	**P**	**N**	**Mean diff**	**95% CI**	**P**
FEV_1 (L)								
T0-T1	46	0.073	0.017; 0.128	0.012*	19	0.028	-0.006; 0.063	0.105
T0-T2	12	-0.020	-0.133; 0.093	0.703	12	0.007	-0.058; 0.072	0.825
T0-T3	3	-0.010	-0.204; 0.184	0.845	8	0.026	-0.083; 0.135	0.587
FVC (L)								
T0-T1	48	0.090	0.045; 0.135	0.000*	18	0.059	0.010; 0.109	0.021*
T0-T2	13	0.049	-0.053; 0.151	0.313	12	0.079	0.034; 0.125	0.003*
T0-T3	3	-0.070	-0.242; 0.102	0.222	8	-0.008	-0.056; 0.041	0.724
PEF (L/min)								
T0-T1	46	6.865	-4.423; 18.153	0.227	18	-0.889	-9.639; 7.862	0.833
T0-T2	12	-12.033	-38.852; 14.785	0.345	12	-6.417	-25.411; 12.578	0.473
T0-T3	4	3.333	-37.510; 44.177	0.759	4	-2.625	-20.974; 15.724	0.745

Legend: AS= Air stacking, CI= Confidence Interval, Diff= Difference, FEV1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, MI-E= Mechanical Insufflation-Exsufflation, N= number, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver, *= statistically significant (P<0.05)

Figure 1: Effects of air stacking and mechanical insufflation-exsufflation on lung function immediately after (T1), one hour after (T2) and two hours (T3) after treatment compared to prior to air stacking or mechanical insufflation-exsufflation treatment (T0)



Legend: AS= Air stacking, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, MI-E= Mechanical Insufflation-Exsufflation, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver, *= statistically significant (P<0.05)

Effects of Mechanical Insufflation-Exsufflation (MI-E)

Median pressures of MI-E used were +30 cmH_2O (IQR 20; 39 cmH_2O) and -35 cmH_2O (IQR 30; 40). We observed a significant improvement of FVC immediately after treatment with a mean difference of 0.059 L (95% CI 0.010; 0.109, P=0.021) (table 2, figure 1) that, in contrast to the AS group, persisted one hour after treatment with a mean difference of 0.079 L (95% CI 0.034; 0.125, P=0.003). All other LFT results, including FEV_1, did not change after MI-E treatment. The degree of scoliosis and use of mechanical ventilation did not influence the effect of MI-E on lung function. Standardized LFT results before and after MI-E treatment are shown in Supplemental table 1.

Subgroup analyses: DMD and SMA

We performed a subgroup analysis for disease categories. The 33 SMA patients constituted the largest patient group. Sixteen patients used AS and 17 used MI-E. In the AS group, all patients had SMA type 2, in the MI-E group five patients (29%) had SMA type 1c. SMA patients treated with MI-E, although not significant, were younger than SMA patients treated with AS (median age of 9.0 years (IQR 5.5; 14.6) and 12.4 years (IQR 9.7; 14.9) respectively (P=0.201). The standardized baseline lung function parameters did not significantly differ between the AS and MI-E group (P>0.2). FVC improved significantly immediately after AS and MI-E and remained so after one hour in the MI-E group (table3).

In contrast to the total and SMA group, we did not observe significant improvement in any of the LFT results performed by patients with DMD immediately after AS treatment (table 4). We did not perform subgroup analysis in the mixed group, as the group was to heterogeneous.

Table 3: Subgroup analysis: Effect of air stacking and mechanical insufflation on lung function in patients with Spinal Muscular Atrophy

	AS (N=16)				MI-E (N=17)			
	N	**Mean diff**	**95% CI**	**P**	**N**	**Mean diff**	**95% CI**	**P**
FEV_1 (L)								
T0-T1	14	0.786	0.010; 0.167	0.077	17	0.031	-0.008; 0.070	0.116
T0-T2	7	0.050	-0.046; 0.146	0.250	11	0.020	-0.44; 0.084	0.504
T0-T3	2	0.015	-0.811; 0.841	0.856	8	0.263	-0.083; 0.135	0.587
FVC (L)								
T0-T1	16	0.141	0.057; 0.226	0.003*	16	0.056	0.001; 0.111	0.046*
T0-T2	8	0.110	-0.027; 0.247	0.099	11	0.087	0.041; 0.134	0.002*
T0-T3	2	-0.050	-0.812; 0.712	0.558	8	-0.008	-0.056; 0.041	0.724
PEF (L/min)								
T0-T1	14	-5.571	-23.169; 12.026	0.506	16	-2.250	-11.945; 7.445	0.628
T0-T2	7	-4.286	-23.207; 14.636	0.599	11	-1.000	-17.398; 15.398	0.895
T0-T3	2	-6.000	-44.119; 32.119	0.295	8	-2.625	-20.974; 15.723	0.745

Legend: AS= Air stacking, CI= Confidence Interval, Diff= Difference, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, MI-E= Mechanical Insufflation-Exsufflation, N= number, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver, *= statistically significant (P<0.05)

Table 4: Subgroup analysis: Effect of air stacking on lung function in patients with Duchenne Muscular Dystrophy

		AS (N=14)		
	N	**Mean diff**	**95% CI**	**P**
FEV_1 (L)				
T0-T1	14	0.032	-0.125; 0.190	0.666
T0-T2	2	0.060	-0.194; 0.314	0.205
T0-T3				
FVC (L)				
T0-T1	14	0.061	-0.031; 0.153	0.173
T0-T2	2	0.070	-0.692; 0.832	0.451
T0-T3				
PEF (L/min)				
T0-T1	14	4.500	-12.534; 21.535	0.578
T0-T2	2	27.600	-155.369; 210.569	0.306

Legend: AS= Air stacking, CI= Confidence Interval, Diff= Difference, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, N= number, PEF= Peak Expiratory Flow, T0= before AS maneuver, T1= immediately after AS maneuver, T2= 1 hour after AS maneuver, T3= 2 hours after AS maneuver,

Discussion

Summary of main findings

In this prospective cohort study, we observed that LFT improved immediately after AS (FVC and FEV_1) and MI-E (FVC) and that this effect persisted for one hour in the group that had used MI-E. Moreover, our results suggest that the effects of ACT may differ between NMDs, since the beneficial effects were most pronounced in SMA.

(Dis)agreements with existing literature

Long-term effects of ACT have been previously, although not extensively, studied. Daily use of ACT probably helps to preserve vital capacity (VC) and reduces the annual decline in VC associated with NMDs including DMD and SMA [9,34–36]. Importantly, ACT contributes to the prevention of RTIs and hospital admissions and may thus help to break the negative cycle of infections and declining LFT [8,9]. Studies on immediate effect of AS [37] and MI-E [38–41] on VC showed conflicting results. In addition, some studies reported increased PCF, most likely secondary to increased VC, after AS and/or MI-E [1,19–27,38–43]. To the best of our knowledge only one study evaluated the VC up to one hour after use of MI-E in nine patients with DMD. This study showed increased VC immediately after MI-E use, which returned to baseline within one hour [39]. We show that ACT improves LFT immediately,

but that the duration of these effects may differ between techniques and disorders. This information is crucial for the design of future studies that may aim to develop tailored treatment strategies.

Our results showed more improvement in FVC in patients with SMA than with DMD, while the representation of other disorders was too limited to draw additional conclusions. This finding deserves further scrutiny in larger patient cohorts. NMDs differ not only in the degree, but also the pattern by which inspiratory and expiratory muscle groups are affected [46,47] and what reserve capacity remains, which may be reflected by LFT. Other authors have suggested that cognitive and behavioral deficits may also influence efficacy of ACT and LFT outcomes, because active and conscient cooperation is necessary for optimal results [48,49]. Cognitive defects are part of the DMD but not SMA phenotype and may therefore explain part of our findings. On the other hand, both poor quality ACT maneuvers and non-reproducible LFT results were excluded.

Implications for future research and clinical practice

Our results demonstrate that FVC improved immediately after AS and MI-E, with even further improvement one hour after MI-E treatment. Limited endurance for repeated muscle activities is a specific characteristic of SMA [50] and may be a possible neuromuscular explanation for persistent improvement after one hour, since the majority (89%) of the MI-E group had SMA. We do not think that the differences in baseline characteristics can explain the observed differences in the duration of ACT effects. First, baseline LFT parameters were comparable between the AS and MI-E groups. Second, the MI-E group contained the majority of patients with the most severe phenotype (i.e. SMA type 1c). To overcome the problem of fatigability in future studies, we would advise a 10-15 minute break before performing LFTs after MI-E treatment. We can only speculate whether increased FVC of shorter duration could explain longer term effects of ACT. At this stage, there is insufficient evidence that short-lasting increases in FVC caused by the daily use of AS would explain the reduction RTIs. However, repeated AS and MI-E may help the preservation of lung and chest wall compliance that could be important in early phases of infections. Our study indicates similarities but also possible differences in efficacy of ACT that may be important for future clinical practice. The best instrument for future studies is probably a cross-over trial that would allow direct comparison of the effects of both ACTs in patients with SMA and possibly DMD. Multicenter collaborations would allow to study rarer neuromuscular disorders, including congenital muscular dystrophies and myopathies and limb-girdle muscular dystrophies in more detail.

Strengths and limitations

Strengths of this research include the prospective nature of the study. Patients were already familiar with the daily use AS or MI-E at home and with performing LFTing, thus

excluding the possibility that increases of FVC reflect a learning effect. AS technique and MI-E settings used in our study were similar to the settings used at home, and thus reflect real life situations. All patients were used to perform spirometry and all spirometry measurements were performed by the same professional, encouraging all patients in a similar way, thereby improving the quality of the data. This study is a relatively large study on a variety of rare NMDs and the study cohort was big enough to perform subgroup analysis. Finally, all study subjects were in good clinical condition at time of inclusion, therefore, the results were not influenced by RTI.

The present study has a few limitations. The Covid-19 pandemic negatively affected enrolment because fewer vulnerable patients attended the outpatient department. Despite the fact that none of the patients was naïve to spirometry, there might still be a learning effect in spirometry, which could alternatively explain part of our results. We think this is unlikely, because results showed an initial improvement immediately after treatment, followed by a return to baseline one and two hours after treatment. Through the occurrence of fatigue, especially in SMA patients, effects of ACT may have been underestimated. Allowing patients to rest for a certain amount of time after ACT before spirometry may improve the results. Unfortunately, we suspected that the time required to stay in the hospital to perform this study would pose too much of a burden for some patients. Therefore, we were not able to measure the effect of ACT up to hours after treatment in all patients. This reduced power to demonstrate a positive effect after 1 and 2 hours, especially in the AS group. Although the number of measurements after 2 hours was small, we considered them important to report as available literature of measurements at this time interval is limited. Also, the subgroup with measurements after 2 hours was more severely affected. Forced maneuvers during LFTing prior to ACT may have resulted in lung volume recruitment, thereby underestimating the effect of ACT on LFT results. Finally, the data is expressed as mean or median results for the patient cohort, obscuring individual variations. Our study population was heterogeneous, not only in type of NMD, but also in degree of lung restriction and possibly lung and chest wall compliance. Therefore, analyzing these variations in future studies might contribute to patient-tailored ACT and thereby optimize treatment for the individual patient. Despite these limitations, this study shows that a short-lasting improvement of FVC was observed after treatment with AS and MI-E in patients with NMDs.

Conclusion

This prospective study demonstrated that AS and MI-E improve FVC immediately after treatment. This effect persisted one hour after MI-E treatment. Additionally, the effect of ACT was more pronounced in patients diagnosed with SMA, compared to patients

diagnosed with DMD. At this stage, there is insufficient evidence that short-lasting increases in FVC caused by the daily use of AS or MI-E would explain the possible beneficial effect.

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Supplemental material

Supplementary table 1: Effects of air stacking and mechanical insufflation-exsufflation on standardized lung function results immediately after (T1), one hour after (T2) and two hours (T3) after treatment compared to prior to air stacking or mechanical insufflation-exsufflation treatment (T0)

	AS (N=48)			MI-E (N=19)		
	N	**Median (IQR)**	**P (Z)**	**N**	**Median (IQR)**	**P (Z)**
FEV_1 (%)						
T0	47	38 (27; 51)	NA	19	35 (22; 49)	NA
T1	47	40 (28; 55)	0.005* (-2.7821)	19	36 (24; 46)	0.257 (-1.134)
T2	13	30 (21; 49)	0.875 (-0.157)	12	36 (27; 45)	0.838 (-0.204)
T3	3	37	1.000 (0.000)	8	33 (21; 38)	0.944 (-0.070)
FVC (%)						
T0	48	40 (27; 51)	NA	19	38 (28; 45)	NA
T1	48	44 (30; 51)	0.000* (-3.851)	18	40 (31; 50)	0.014* (-2.456)
T2	13	31 (24; 40)	0.349 (-0.936)	12	43 (30; 52)	0.005* (-2.803)
T3	3	39	0.285 (-1.069)	8	36 (23; 40)	0.833 (-0.211)
PEF (%)						
T0	47	29 (18; 38)	NA	19	25 (16; 40)	NA
T1	47	30 (20; 39)	0.211 (-1.251)	18	26 (18; 37)	0.758 (-0.308)
T2	12	32 (14; 34)	0.326 (0.982)	12	26 (19; 30)	0.906 (-0.118)
T3	3	30	1.000 (0.000)	8	26 (19; 30)	0.395 (-0.851)

Legend: AS= Air stacking, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, IQR= Interquartile range, MI-E= Mechanical Insufflation-Exsufflation, N= number, NA= Not applicable, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver, *= statistically significant ($P<0.05$)

Supplementary table 2: Subgroup analysis: Effect of air stacking and mechanical insufflation on standardized lung function in patients with Spinal Muscular Atrophy

	AS (N=16)			MI-E (N=17)		
	N	**Median (IQR)**	**P (Z)**	**N**	**Median (IQR)**	**P (Z)**
FEV_1 (%)						
T0	15	42 (27; 52)	NA	17	35 (20; 49)	NA
T1	15	43 (28; 52)	0.135 (-1.493)	17	36 (23; 44)	0.295 (-1.047)
T2	8	40 (18; 49)	0.309 (-1.018)	11	36 (26; 45)	0.440 (-0.771)
T3	2	40	0.655 (-0.447)	8	33 (21; 38)	0.944 (-0.070)
FVC (%)						
T0	16	43 (24; 51)	NA	17	38 (24; 46)	NA
T1	16	46 (30; 50)	0.007* (-2.692)	16	40 (30; 50)	0.039* (-2.063)
T2	8	43 (23; 51)	0.128 (-1.521)	11	43 (29; 53)	0.005* (-2.805)
T3	2	41	0.655 (-0.447)	8	36 (23; 40)	0.833 (-0.211)
PEF (%)						
T0	15	33 (25; 43)	NA	17	25 (17; 36)	NA
T1	15	33 (15; 39)	0.638 (-0.471)	16	25 (17; 36)	0.864 (-0.171)
T2	8	31 (11; 34)	0.498 (-0.677)	11	26 (19; 31)	0.688 (-0.401)
T3	2	38	0.655 (-0.447)	8	19 (13; 28)	0.395 (-0.851)

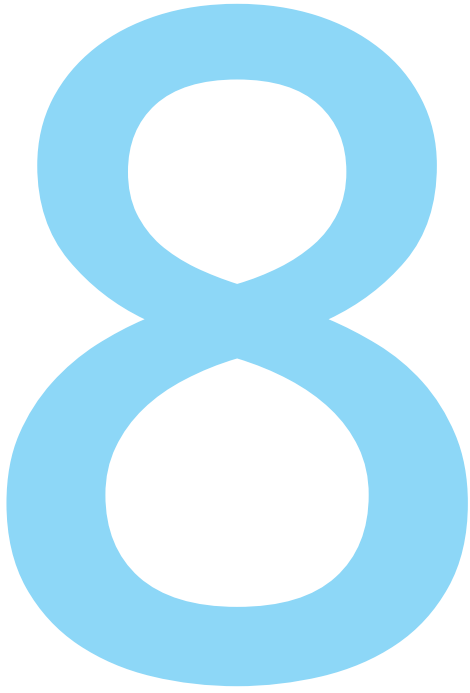
Legend: AS= Air stacking, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, IQR= Interquartile range, MI-E= Mechanical Insufflation-Exsufflation, N= number, NA= not applicable, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver, *= statistically significant (P<0.05)

Supplementary table 3: Subgroup analysis: Effect of air stacking on standardized lung function in patients with Duchenne Muscular Dystrophy

		DMD (N=14)	
	N	**Median (IQR)**	**p (Z)**
FEV_1 (%)			
T0	14	32 (23; 45)	NA
T1	14	34 (21; 48)	0.699 (-0.387)
T2	2	21	0.157 (-1.414)
T3	1		
FVC (%)			
T0	14	38 (23; 45)	NA
T1	14	39 (22; 48)	0.124 (-1.539)
T2	2	20	0.317 (-1.000)
T3	1		
PEF (%)			
T0	14	20 (15; 33)	NA
T1	14	25 (15; 30)	0.552 (-0.595)
T2	2	22	0.180 (-1.342)
T3	1		

Legend: AS= Air stacking, FEV_1= Forced Expiratory Volume in 1 second, FVC= Forced Vital Capacity, IQR= Interquartile range, MI-E= Mechanical Insufflation-Exsufflation, N= number, NA= Not applicable, PEF= Peak Expiratory Flow, T0= before AS or MI-E maneuver, T1= immediately after AS or MI-E maneuver, T2= 1 hour after AS or MI-E maneuver, T3= 2 hours after AS or MI-E maneuver

CHAPTER 8



Effect of mechanical insufflation-exsufflation in children with neuromuscular weakness.

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Abstract

Introduction

Children with neuromuscular diseases develop cough impairment. Airway clearance techniques (ACTs) may help to prevent recurrent respiratory tract infections (RTIs). A commonly used ACT is mechanical insufflation-exsufflation (MI-E), but evidence for efficacy is limited. We hypothesize that MI-E has beneficial effect on RTI related hospital admission rate.

Methods

In this single-center retrospective study we reviewed all children who used daily MI-E between 2005 till June 2019. Primary outcome studied was the number of RTIs requiring hospital admission. Patient satisfaction and burden experienced by MI-E use was explored by questionnaires using a Likert scale. The relative number of RTIs requiring admission and the number of admission days per eligible period before and after introduction of MI-E were compared using Friedman test and Wilcoxon Signed Rank test.

Results

Thirty-seven children were included.

The median number of RTI related hospital admissions per 1000 eligible days after introduction of MI-E was 0.9 (IQR 0.0 - 3.1) compared to the 3 preceding years (median 3.7, IQR 1.4 - 5.9; p= 0.006). The median number of RTI related admission days per 1000 eligible days after introduction of MI-E was significantly lower with a median of 2.7 (IQR 0.0 - 17.4) compared to the 3 preceding years (median 33.6, IQR 15.0 - 51.1; p= 0.001). Patient satisfaction was high with low burden, even in patients who discontinued treatment.

Conclusion

A significantly lower number of RTIs requiring hospital admission and shorter admission duration after introduction of MI-E was found, with high patient satisfaction and low burden.

Introduction

Neuromuscular disorders (NMDs) with onset in infancy and childhood such as spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) and congenital myopathies or muscular dystrophies may be complicated by weak cough and increased susceptibility to recurrent respiratory tract infections (RTIs). This is a major cause of morbidity and mortality[1-3] and various care guidelines therefore advise early start of airway clearance techniques (ACTs) to prevent RTIs[4-6].

Airstacking (AS) is probably the most accepted form of ACT in the Netherlands, but mechanical insufflation-exsufflation (MI-E) is used increasingly despite the fact that evidence for efficacy, especially in children, is scarce[5,7]. We identified only one randomized controlled trial that compared the effect of MI-E and AS on frequency of RTIs among patients with Amyotrophic Lateral Sclerosis, showing a trend towards better outcome for MI-E[8]. Experts prefer to use MI-E in very weak patients, those who cannot cooperate with AS and MAC, or in whom these techniques are not effective[4]. Recently, a consensus meeting of the European Neuromuscular Center concluded that the clinician can decide on what ACT to use, depending on FVC and PCF, but also on local availability, efficacy, tolerance and preference[5]. MI-E was introduced in The Netherlands in 2005, but the lack of evidence for its efficacy has hampered reimbursement arrangements with health insurance companies. The aim of this study was to retrospectively analyze the number of hospital admissions and admission days due to RTIs prior to and after initiation of MI-E in a large single-center cohort of children. Our second aim was to prospectively evaluate patient and caregiver experience and burden of MI-E use by using a questionnaire. We hypothesized that the number of RTIs requiring hospital admission would decrease after introduction of MI-E and that patient satisfaction would be high.

Materials and methods

Our center for home ventilation at the University Medical Center (UMC) Utrecht welcomes 131 children, approximately half of the pediatric patients in the Netherlands who need ventilation. We included all children (n=37) who had started daily MI-E at home. According to our protocol patients with reduced peak cough flow for age or recurrent RTIs start regular ACT at home by means of AS twice daily[4,5,9]. When technique (e.g. due to young age) or efficacy are insufficient, we switch to MI-E using Philips Respironics CoughAssist® or Philips Cough Assist E70®. Settings are individualized to optimize airway clearance using maximum tolerable pressures up to 40 cmH_2O. We teach caregivers to perform three cycles, each with 5 in- and exsufflations, at a frequency of at least twice a day and more frequently during RTIs. We evaluated all medical files systematically for admissions before

and after initiation of MI-E. We contacted PICUs in the other University Hospitals in The Netherlands to check for additional admissions. We collected patient data from birth until 1st of June 2019. In addition, we approached parents or legal guardians of all included study participants to explore their experiences and burden regarding MI-E use, using a questionnaire with answers on Likert scales.

Statistical analysis was performed using IBM SPSS Statistics (version 25). We compared both the number of RTIs requiring admission as well as the number of admission days in the 3 years before and the 3 years after the start of MI-E. As some patients started MI-E before finishing 3 years follow up or had not yet used MI-E for 3 years at the time of data analysis, we calculated the relative number of admissions per 1000 eligible days. Friedman test was used because of non-parametric distribution of data. The Wilcoxon signed-rank test was used to follow up the Friedman test in case of statistically significant outcomes. The Medical Ethical Committee of the University Medical Center Utrecht waived the need for informed consent.

Results

Totally, 37 children were included with a median age of 5.2 years. An overview of patient characteristics is shown in table 1.The majority of patients were patients with SMA. Of these 23 patients with SMA, 13 patients (56%) were treated with the SMN-protein augmenting drug Spinraza®. Six patients started treatment with Spinraza® after introduction of MI-E (median 7.5 months after introduction of MI-E, IQR 3.3-38.8 months), 6 patients started treatment with Spinraza® prior to introduction of MI-E (median 10 months before introduction of MI-E, IQR 7.0-17.3 months) and 1 patient simultaneously started treatment with MI-E and Spinraza®. We included 2 children with spinal cord injury, because they experience similar respiratory problems as children with NMDs. The youngest patients who started MI-E were children with infantile onset SMA (i.e. type 1). Four patients discontinued MI-E; two patients learned to perform AS manoeuvres later in childhood and two patients discontinued MI-E following an episode of pneumothorax, a known complication of MI-E. A 3 year old patient with SMA using MI-E with pressures of +20 and -30 cmH_2O developed pneumothorax during a RTI. The other patient with pneumothorax was a 15 year old girl with polyneuropathy and severe kyphoscoliosis and past medical history of pneumothorax after scoliosis surgery. She used MI-E with pressures of +30 and -35 cmH_2O.

An increase in frequency of MI-E use was observed over the years, mainly explained by a gradually more aggressive supportive treatment in younger SMA patients.

Table 1: patient characteristics

Age at start MI-E (years), median (IQR)	5.2 (2.7-12.4)
Male gender, n (%)	22 (59)
Diagnosis, n(%)	
Spinal Muscular Atrophy	23 (62)
Type 1	11 (48)
Type 2	12 (52)
Duchenne Muscular Dystrophy	2 (5)
Other neuromuscular disease	10 (27)
Cervical spinal cord injury	2 (5)
Tracheotomy, n(%)	
No tracheotomy	20 (54)
Tracheotomy before start MI-E	12 (32)
Tracheotomy after start MI-E	5 (14)
Chronic mechanical ventilation, n (%)	
No chronic mechanical ventilation	4 (11)
Chronic mechanical ventilation started before MI-E	23 (62)
Chronic mechanical ventilation started simultaneously	9 (24)
Chronic mechanical ventilation started after MI-E	1 (3)
Years of MI-E use, median (IQR)	2.4 (1.7-6.3)
Number of days of MI-E use during 3 years before introduction of MI-E, median (IQR)	1095 (531-1095)
Number of days of MI-E use during 3 years after introduction of MI-E, median (IQR)	1095 (523 -1095)
Year of MI-E introduction, n(%)	
2005 - 2009	4 (11)
2010 -2014	12 (32)
2015-2019	21 (57)

The median number of RTI related hospital admissions per 1000 eligible days after introduction of MI-E was 0.9 (IQR 0.0 - 3.1) and was lower than in the 3 preceding years (median 3.7, IQR 1.4 - 5.9; Z= -2.754 and p= 0.006). The median number of RTI related admission days per 1000 eligible days after introduction of MI-E was significantly lower with a median of 2.7 (IQR 0.0 - 17.4) than in the 3 preceding years (median 33.6, IQR 15.0 - 51.1; Z= -3.391 and p= 0.001). When excluding the 9 patients who initiated chronic mechanical ventilation simultaneously we found similar results: with significantly (p= 0.003) fewer RTI related hospital admissions 3 years after introduction of MI-E (median 0.0 per 1000 eligible days, IQR 0.0 - 2.2) compared to 3 years before introduction of MI-E (median 4.1 per 1000 eligible days, IQR 1.1 - 6.4). In this subgroup, the number of RTI related admission days per 1000 eligible days was also significantly (p= 0.007) lower 3

years after introduction of MI-E (median 0.0, IQR 0.0 - 8.9) compared to 3 years prior to introduction of MI-E (median 34.2 (IQR 10.3 - 57.5).

Thirty-one (84%) parents and caregivers returned the questionnaires. The median satisfaction score for secretion removal was 9.0 out of 10 (IQR 8.0 - 10.0) and 9.0 out of 10 (IQR 7.8 - 10.0) for RTI prevention. Comfort of the child during MI-E treatment had a median score of 8.5 out of 10 (IQR 6.8 - 10.0). Three patients reported occasional discomfort after MI-E treatment (sore throat, muscle pain, nausea). All parents, including parents of patients who discontinued MI-E treatment, would recommend MI-E to other patients.

Discussion

This retrospective study suggests that treatment of children with severe NMDs with MI-E may lead to a decrease in number of RTIs requiring admission and shorter hospital stays. Patients or their caregivers experienced important benefits with low burden. This is, to the best of our knowledge the first study exploring the possible effects of introduction of MI-E on the incidence of RTIs requiring admission in children with NMDs. A limited number of previous studies studied the effect of MI-E during RTI. These studies show reduced need for tracheotomy or intubation, shortening of airway-clearance sessions, shortened duration of symptoms of RTI and reduced odds of hospitalization[8,10,11]. One study in adult patients with spinal cord injury compared hospitalizations in general (and not only due to RTI), which showed a non-significant reduction of respiratory hospitalization rate of 34% after introduction of MI-E[12]. It is our impression that physicians often believe that burden of MI-E is high and that these believes, combined with lack of evidence for efficacy, may delay the introduction of MI-E. However, our data suggest that caregivers and patients experience important benefits and low burden.

The major limitation is obviously the retrospective nature of this study. We cannot exclude the possibility that other factors, such as differences in the adherence to standards of supportive care, the introduction of Spinraza® (SMA-specific treatment introduced in the course of May 2017 (for infants) to January 2018 (young children with SMA)), influence of aging on the incidence of RTIs or use of maintenance antibiotic therapy, may have confounded our results. Moreover, retrospective data collection could have led to an under- or overestimation of the number of RTIs. Since standardization of electronic patient files has led to the systematic questioning of RTIs occurrence during every visit, we expect less underreporting of RTIs in recent years compared to earlier years and potentially an underestimation of the beneficial effect of MI-E. We do not have information on satisfaction of ACT prior to MI-E. Therefore we can only conclude that patients using MI-E are satisfied, and we cannot draw conclusions on patient satisfaction with MI-E compared to other ACTs.

Despite these limitations, this study suggests a decline in hospital admission rate and admission-days after introduction of MI-E, without increased burden for patients. The results of this study call for a prospective evaluation comparing AS to MI-E in patients with decreased cough strength.

Conclusion

This retrospective cohort study is the first pediatric study which suggests decreased RTI related hospital admission rate and shorter admission duration after introduction of MI-E. Patient satisfaction was high, with low burden.

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CHAPTER 9

Short term effect and effect on rate of lung function decline after surgery for neuromuscular or syndromic scoliosis.

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Abstract

Introduction

Understanding the impact of scoliosis surgery on lung function is important for counseling patients about risks and benefits of surgery. We prospectively compared the trends in lung function test (LFT) results prior to and after scoliosis surgery in children with neuromuscular diseases, or dysmorphic syndromes. We hypothesized a stabilization.

Methods

We prospectively included children with neuromuscular or syndromic scoliosis able to perform LFTs. We studied (Forced) Vital Capacity ((F)VC), ratio of Forced Expiratory Volume in 1 second (FEV_1) and FVC, and Peak Expiratory Flow (PEF). Preoperative LFT results were compared with results 3-4 months after surgery. The mean monthly change in LFT results up to 2 years after surgery was compared with the preoperative natural history using linear mixed effects models.

Results

We included 43 patients. No significant change was observed in absolute values of (F) VC, FEV_1/FVC and PEF prior to and after surgery. In 23 neuromuscular patients median standardized VC, FVC and PEF decreased significantly after surgery from 43 to 33%, 42 to 31%, and 51 to 40% respectively. In 20 syndromic patients median FVC decreased from 68% to 65%. The monthly rate of change in FVC did not change significantly in both groups with a mean difference of 0.18% (95% CI -0.27; -0.61) and -0.44% (95% CI -1.05; 0.16).

Conclusion

No stabilization of lung function 3-4 months after scoliosis surgery was observed in children with neuromuscular and syndromic scoliosis with restrictive lung function disease. The effect on the rate of lung function decline remains inconclusive.

Introduction

Scoliosis is a common complication in patients with neuromuscular diseases (NMDs) and genetic syndromes and scoliosis surgery may be necessary for a number of reasons. It improves ease of nursing care, reduces back pain and allows the patient a much better sitting posture and balance, thereby improving the patient's overall quality of life and self-image [1,2]. One of the more significant factors causing morbidity and mortality in patients with neuromuscular scoliosis is the deterioration in pulmonary function to which scoliosis progression may contribute [1]. By distorting thoracic anatomy and rib alignment, severe scoliosis decreases the compliance of the chest wall, thereby restricting vital capacity (VC) [2], while lordotic deformation of the thoracic spine may cause bronchial kinking or compression and bronchial obstruction [3]. Straightening the spine has the potential to improve the ability to elevate the ribs and thus expand the chest on inspiration [2]. On the other hand, children with preexisting respiratory compromise have an increased risk of developing postoperative complications [4]. Understanding the impact of neuromuscular or syndromic scoliosis surgery on lung function is important for counseling patients about risks and longer term benefits of scoliosis surgery on respiratory function [2].

Research on the impact of scoliosis surgery on lung function has yielded conflicting results.

In this prospective cohort study, we compared lung function test (LFT) results of children with probable restrictive lung function due to neuromuscular disease (NMD) or syndromic syndromes prior to and after scoliosis surgery in a single center.

We aimed to study the short term improvement of lung function after surgery and determine the mean change in post-operative compared to pre-operative progression rate in lung function. We hypothesized that scoliosis surgery slows the rate of lung function decline.

Materials and methods

Eligibility was checked in pediatric patients planned for surgery for a neuromuscular or syndromic scoliosis at the preoperative clinic of the Pediatric Intensive Care Unit (PICU) of the Wilhelmina Children's Hospital Utrecht, the Netherlands in 2018 or 2019. Patients were included if they were able to perform lung function tests (LFTs). Only reproducible LFT results were included. We excluded patients with hereditary proximal spinal muscular atrophy (SMA) who had started treatment with genetic therapies during follow up, as this might provide an alternative explanation for improvement of LFT results. This study was

approved by the local Medical Ethics Committee. Written informed consent was obtained from all participants and/or their parents. The reporting of this study conforms to the STROBE statement [5].

Spirometry data (Geratherm Spirostick®) were collected at the department of pulmonology prior to and 3 months after surgery. We included results of (Forced) Vital Capacity ((F)VC), the ratio of Forced Expiratory Volume in 1 second (FEV_1) and FVC, and Peak Expiratory Flow (PEF). All LFTs were measured in sitting position, without corsets or braces by a small team of professionals experienced in conducting these tests in children with NMDs and other comorbidities. All LFTs were measured and reported according to the European Respiratory Society guideline [6]. If patients were unable to stand to measure height, tape-measured arm span was used as a surrogate measure [7,8]. We reported absolute and standardized LFT values, according to the Global Lung Initiative [9].

We compared values 0-3 months before and 3-4 months after scoliosis surgery. In patients with more than three months between the PICU clinic visit and surgery, LFTs were repeated on the day of admission. We chose this timing of 3-4 months after surgery, to combine it with regular orthopedic follow up and consequently minimize the burden for the patient .

To study the progression rate of LFT results before and after surgery, we used LFT results obtained during regular follow up in the 2 years before and after surgery whenever available.

Statistical analyses

For baseline characteristics, we used descriptive statistics. For comparisons of LFT results 0-3 months before and 3-4 months after scoliosis surgery, a Wilcoxon-signed rank test was used. To investigate the trend of function decline, linear mixed effects models were fitted, which included a random intercept and random slope for time per individual. We introduced a linear spline for time (both fixed as random) with one knot at the time of surgery. Subsequently, we determined the rate of progression before and after surgery. Confidence intervals were estimated using bootstrapping (n=1000) and significance tests were based on the likelihood ratio test.

Results

Patient characteristics

During 2018-2019, we assessed 111 patients prior to scoliosis surgery at the PICU clinic. In total, we included 43 patients. A large proportion of the patients referred to the pre-operative PICU clinic (61%) was excluded mainly due to the inability to obtain LFT results due to developmental delay.

Baseline characteristics of patients and intra- and postoperative details are shown in Table 1. Just over half of the patients suffered from a NMD, 48% of them were diagnosed with spinal muscular atrophy (SMA) type 2 (n=10) and type 3 (n=1). None of the patients initiated treatment with spinraza or were already using spinraza. None of the patients with Duchenne Muscular Dystrophy (DMD) initiated treatment with corticosteroids during follow up. The patients with DMD who used steroids, used this for at least 2 years prior to surgery. Eight patients with NMDs used home mechanical ventilation, all started years before surgery. Diagnoses of the syndromic group are specified in table 1. Miscellaneous were patients with a variety of syndromes (Fetal alcohol, Brain thyroid, Prader Willi, Goldenhar, Koolen de Vries, and chromosomal duplication syndrome). At baseline sixty percent of patients suffered from moderate to severe restriction of lung function , i.e., VC < 60%. Median standardized VC prior to surgery was 55% (IQR 41-76%). There was no obstructive lung disease with median FEV_1/FVC of 91% prior to surgery. Majority of patients had growth-friendly surgery, including traditional growing rod, magnetically controlled growing rods and spring distraction systems. Median Cobbs angle was 63 degrees pre-operatively and 29 degrees after surgery. In 4 patients severe adverse events occurred that fortunately resolved.

Short term effects of scoliosis surgery on lung function

Wilcoxon signed rank test was used to compare LFT results prior to and after surgery in 43 patients. No significant change was observed of absolute values of (F)VC, FEV_1/FVC and PEF prior to surgery compared to 3-4 months after surgery in both the neuromuscular and the syndromic group, except from a significant decrease of PEF in a subgroup of patients with SMA (table 2). Standardized values of (F)VC and PEF were significantly lower 3-4 months after surgery compared to results before surgery in the neuromuscular group. Standardized FVC was significantly lower after surgery in the syndromic group (table 2).

Table 1: Patients, intraoperative and postoperative characteristics

Baseline, n=43 patients	
Age in years, median (IQR)	11.7 (9.4-15.1)
Male gender, n (%)	21 (49)
Underlying disease, n (%)	
Neuromuscular disease	23 (53)
Spinal Muscular Atrophy	11 (48)
Duchenne Muscular Dystrophy	5 (22)
Congenital Myopathy	5 (22)
Arthrogryposis multiplex congenita	1 (4)
Emery-Dreifuss Dystrophy	1 (4)
Other syndromes	20 (47)
Skeletal Dysplasia	3 (15)
VACTERL	2 (10)
Hurler syndrome	3 (15)
Neurofibromatosis	3 (15)
Spina Bifida	3 (15)
Miscellaneous	6 (30)
Home mechanical ventilation, n (%)	8 (19)
Cobbs angle, median (IQR)	63 (54-76)
Intraoperative	
Number of vertebrae, median (IQR)	11 (11.5-16)
Technique used, n (%)	
Growth friendly surgery	31 (72)
Posterior minimal invasive surgery	8 (19)
Posterior spinal fusion	4 (9)
Adverse events, n	1
Loss of neuromonitoring signal	1
Postoperative	
Adverse events, n	7
Woundinfection	1
Hematothorax	1
Pneumonia	2
Resuscitation (airway obstruction)	1
Hyperesthesia foot	1
PICU LOS, days median (range)	1 (1-14)
> 48 hours invasive ventilation, n	2
Hospital LOS, days median (IQR)	7 (6-9)
Cobbs angle, median (IQR)	29 (20-39)

Legend: IQR = interquartile range; LOS = length of stay; n= number; PICU = Pediatric Intensive Care Unit

Table 2: Lung function prior to and 3 months after surgery

Patients	Lung function parameter	Prior to surgery	3 months after surgery	p-value (Z-statistic)
NMDs (n=23)	VC (L), median (IQR)	0.99 (0.68 - 1.27)	0.86 (0.57 - 1.15)	0.097 (-1.661)
	VC stand (%), median (IQR)	43 (29-67)	33 (27-54)	0.021* (-2.310)
	FVC (L), median (IQR)	0.99 (0.62 - 1.30)	0.79 (0.60 - 1.15)	0.221 (-1.225)
	FVC stand (%), median (IQR)	42 (19-55)	31 (17-42)	0.027* (-2.205)
	FEV_1/FVC (%), median (IQR)	93.0 (88.0 -98.3)	94.0 (82.5 - 98)	> 0.5 (0.079)
	PEF (L/s), median (IQR)	2.45 (1.41 - 2.99)	2.03 (1.46 - 2.64)	0.087 (-1.712)
	PEF stand (%), median (IQR)	51 (35 -58)	40 (27-49)	0.009* (-2.624)
Subgroup: SMA (n=11)	VC (L), median (IQR)	1.11 (0.88; 1.46)	0.93 (0.75; 1.45)	0.108 (-1.609)
	VC stand (%), median (IQR)	49 (40; 70)	34 (32; 61)	0.024* (-2.254)
	FVC (L), median (IQR)	1.06 (0.8; 1.30)	0.85 (0.60; 1.15)	0.168 (-1.380)
	FVC stand (%), median (IQR)	50 (34; 64)	32 (27;51)	0.028* (-2.193)
	FEV_1/FVC (%), median (IQR)	93 (88; 98)	94 (86; 98)	>0.5 (-0.178)
	PEF (L/s), median (IQR)	2.45 (1.85; 2.99)	2.03 (1.37; 2.63)	0.028* (-2.192)
	PEF stand (%), median (IQR)	52 (44; 63)	42 (27; 53)	0.008* (-2.670)
Syndromes (n=20)	VC (L), median (IQR)	1.56 (0.99 - 2.20)	1.53 (1.04 - 2.22)	> 0.5 (-0.315)
	VC stand (%), median (IQR)	65 (54-87)	64 (54-80)	0.490 (-0.691)
	FVC (L), median (IQR)	1.49 (0.95 - 2.05)	1.47 (1.03 - 1.80)	>0.5 (-0.205)
	FVC stand (%), median (IQR)	68 (59-90)	65 (49-83)	0.001* (-3.181)
	FEV_1/FVC (%), median (IQR)	89.0 (81.8 - 94.5)	90.0 (80.5 - 97.5)	> 0.5 (-0.299)
	PEF (L/s), median (IQR)	2.81 (2.18 - 4.90)	3.10 (2.22 - 4.20)	0.305 (-1.027)
	PEF stand (%), median (IQR)	73 (58-95)	71 (53-86)	0.107 (-1.611)

Legend: FVC = Forced Vital Capacity; IQR= interquartile range; L= liter, NMDs = neuromuscular diseases; PEF = Peak Expiratory Flow; s= second; SMA = Spinal Muscular Atrophy; stand = standardized; VC = Vital Capacity, * = significant (p-value < 0.05)

Change in post versus pre-operative progression rate

To study the longitudinal course prior to and after surgery we analyzed 137 measurements of VC, 158 FVC measurements and 157 PEF results in 43 patients .

There was no significant change in the rate of decline of VC, FVC and PEF in both patients with NMDs and patients with syndromes (table 3).

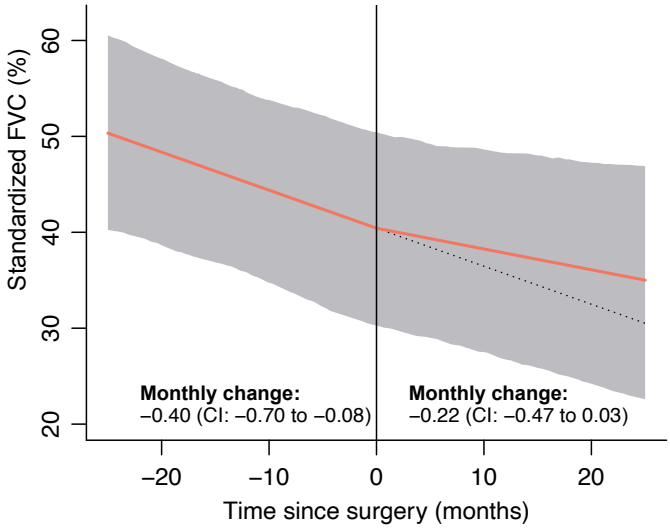
Analysis of 74 FVC measurements in patients with NMDs showed a monthly change of FVC prior to surgery of -0.40 % (95% CI -0.70 to -0.08) compared to -0.22% (95% CI -0.47 to 0.03), resulting in a mean difference in slope of 0.18% (95% CI -0.27 to -0.61) (Figure 1). In the syndromic group a monthly change of FVC prior to surgery of 0.14% (95%CI -0.33 to 0.59) compared to -0.30% (95% CI -0.64 to 0.03) was observed, resulting in a mean difference in slope of -0.44% (95% CI -1.05 to 0.16) (Figure 2).

Table 3: Change in monthly lung function test results 2 years before compared to 2 years after surgery

		Prior to surgery	After surgery	Change
Group	**Lung function parameter**	**Slope (95% CI)**	**Slope (95% CI)**	**Mean diff (95% CI)**
NMDs	FVC (%)	-0.40 (-0.70; -0.08)	-0.22 (-0.47; 0.03)	0.18 (-0.27; -0.61)
	FVC (mL)	0.95 (-8.47; 10.90)	-1.42 (-9.74; 6.51)	-2.37 (-15.57; 10.3)
	PEF (%)	-0.42 (-0.91; 0.05)	-0.34 (-0.72; 0.02)	0.08 (-0.54; 0.70)
Syndromes	FVC (%)	0.14 (-0.33; 0.59)	-0.30 (-0.64; 0.03)	-0.44 (-1.05; 0.16)
	FVC (mL)	12.07 (-4.07; 26.94)	4.28 (-7.66; 15.96)	-7.79 (-27.2; 11.67)
	PEF (%)	0.03 (-0.49; 0.52)	-0.14 (-0.56; 0.31)	-0.17 (-0.90; 0.55)

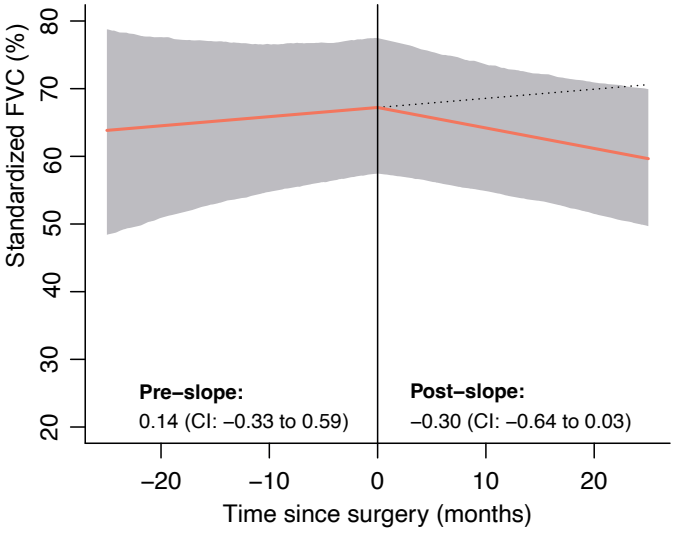
Legend: CI = confidence interval; diff = difference; FVC = Forced Vital Capacity; mL = milliliter; NMDs = neuromuscular diseases; PEF = Peak Expiratory Flow;

Figure 1: Standardized Forced Vital Capacity (FVC) months prior to and after surgery in patients with neuromuscular diseases



Legend: CI = confidence interval

Figure 2 Standardized Forced Vital Capacity (FVC) months prior to and after surgery in syndromic patients



Legend: CI = confidence interval

Discussion

This prospective cohort study on LFT results in children with neuromuscular and syndromic scoliosis with restrictive lung function disease shows no stabilization of lung function 3-4 months after surgery. The effect of surgery on the rate of lung function decline remains inconclusive in this study with 43 patients.

Research on the impact of scoliosis surgery on LFT results has yielded conflicting results. Previous studies have reported that scoliosis correction has beneficial effect on respiratory function [1,10,11], while other studies, including a recent Cochrane review in patients with Duchenne Muscular Dystrophy (DMD) [12], have demonstrated no obvious benefit in terms of respiratory function [13–15].

In a very recent retrospective study Farber reported decreased VC after scoliosis surgery in 14 out of 20 patients with SMA and muscular dystrophies. They were not able to conclude on changes in rate of VC decline[2]. All patients with SMA in this study had a decrease in VC after surgery. A large proportion of patients in our study were patients with SMA. We compared prospectively collected LFT results before and after surgery, both in a predefined limited time range. We observed a significant decrease of PEF 3-4 months after surgery in this subgroup of SMA patients.

Our results may be explained by the fact that 3-4 months after surgery, the majority of patients did not fully recover to their preoperative functional level [16]. For this reason, we also studied the course of LFT results over a longer period in a larger cohort than Farber [2]. Contrary to our study, two recent studies did show a positive effect in terms of a decreased rate of decline in FVC after scoliosis surgery.[1,11]. This may be explained by the retrospective nature[1] and inclusion of patients with less severe scoliosis [11].

We did not observe obstructive lung disease prior to surgery, in contrast to a study by McPhail. This study showed obstructive lung disease probably caused by mainstem airway compression from spine rotation in 33% of children with congenital scoliosis or syndromic scoliosis, compared to a population prevalence of 2 to 5% [17].

Our work has several strengths. First, we only included patients with (the risk of) restrictive lung disease and excluded idiopathic scoliosis. Even though we studied a heterogeneous group of patients, the majority of patients had a standardized VC <60% prior to scoliosis surgery, which a recent study found to be the most sensitive LFT for predicting prolonged postoperative mechanical ventilation [4]. Stabilization of lung function has major impact in these patients, as it probably results in a delayed onset of chronic respiratory failure and reduced incidence of RTIs.

Due to the prospective nature of the study, confounding was limited. None of the included patients with SMA or DMD initiated new therapies, like Spinraza or steroids during data collection. In addition, none of the patients initiated NIV during data collection. Previously published studies were observational [10,11,14] or retrospective [1,13,15], increasing the risk of bias.

We acknowledge also several limitations of our work. The rate of decline in LFT results had broad confidence intervals due to small sample, which possible explains the non-significant mean change in progression rate. However, compared to other studies we included more patients [1,2,10,13–15,18]. The follow up time of our study was limited. Introduction of new therapies, like genetic therapies for SMA, or other confounding factors may complicate interpretation of observational studies with longer follow up. Accurate predicted values of LFTs are difficult to obtain, due to error introduced by methods of height estimation [2]. For this reason we reported both absolute as well as standardized LFT results and used arm span as a well-established alternative [7,8].
We included a heterogeneous group of patients. The surgical technique varied, although in majority of patients growth friendly surgery was used.

Unfortunately, we did not prospectively study the effect on Maximal Inspiratory and Expiratory Pressures (PI_{max} and PE_{max}) . Saito retrospectively reviewed lung function and respiratory muscle strength preoperatively, 1 month and 6 months postoperatively in 16 patients with DMD. Although no significant difference was observed in FVC and VC, mean values of PI_{max} and PE_{max} significantly improved postoperatively [18].

The question remains if the positive effect on PI_{max} and PE_{max} in this retrospective study is the result of surgery. Also other factors such as training effect, chest wall configuration and stabilization may contribute to the results of Saito, as large variations of PI_{max} and PE_{max} are also observed in healthy children [19].

To increase the power, study the effect on individual NMDs and possibly compare different surgical techniques, a multicenter study is needed to include a large enough number of patients.

A Cochrane review concluded uncertainty of benefits and potential risks of scoliosis surgery in patients with DMD and stated that RCTs are needed to investigate effects of scoliosis surgery on respiratory function in patients with DMD [12]. Although our study cannot conclude that pulmonary function is expected to benefit from surgical treatment, this not a reason to withhold this treatment for progressive scoliosis in neuromuscular patients since untreated patients develop severe deformities that cause pain and inability to sit straight and severe difficulties in daily nursing care.

Systematic data collection however should be standard to allow high quality comparative cohort studies.

Conclusion

This prospective cohort study on LFT results in children with neuromuscular and syndromic scoliosis with restrictive lung function disease shows no short term beneficial effect of surgery on lung function . The effect of surgery on the rate of lung function decline remains inconclusive.

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CHAPTER 10

10

Oscillometry: a substitute of spirometry in children with neuromuscular diseases?

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Introduction

Spirometry plays an important role in the assessment of possible respiratory failure in children with neuromuscular diseases (NMDs). However, obtaining reliable spirometry results is a major challenge. We studied the relation between oscillometry and spirometry results. Oscillometry is an easy, non-invasive method to measure respiratory resistance R and reactance X. We hypothesized an increased R and reduced X in patients with more reduced lung function**.**

Methods

In this prospective single center study we included all children with NMDs able to perform spirometry. We consecutively measured R and X at 5, 11 and 19 Hz and (Forced) Vital Capacity, Peak Expiratory Flow. Spearman correlation coefficients and positive and negative predictive values were calculated. Regression curves were estimated.

Results

We included 148 patients, median age 13 years (IQR 8-16). A negative correlation was found between R and spirometry outcomes (spearman correlation coefficient (ρ) -0.5 to -0.6, $p < 0.001$). A positive correlation was found between X (i.e. less negative outcomes) and spirometry outcomes (ρ 0.4 to 0.6, $p < 0.001$). Highest correlation was found at lower frequencies. Regression analysis showed a non-linear relation. Measurement of inspiratory and expiratory R and X did not provide added value. Positive predictive values of 80-85% were found for z-scores of R measured at 5 Hz versus (F)VC≤ 60%.

Conclusion

We found a non-linear relation between oscillometry and spirometry results with increased R and reduced X in patients with more restrictive lung function decline. Given the difficulties with performing spirometry, oscillometry may be a promising substitute.

Abstract

Introduction

Children with neuromuscular diseases (NMDs) may develop progressive respiratory failure due to respiratory muscle weakness. This leads to a decline in lung function, which is often further aggravated by a scoliosis and recurrent respiratory tract infections. Timing of respiratory failure varies in different NMDs [1].

Guidelines suggest to measure vital capacity (VC) in all patients with NMDs who are capable of performing spirometry as part of the respiratory assessment [2].

In children with NMDs spirometry results may steer clinical decision making with regards to respiratory care, support counseling about timing of pending chronic respiratory failure, and may assist in the evaluation of effects of NMD-specific treatments (such as the recently introduced survival motor neuron protein augmenting therapies in spinal muscular atrophy (SMA)) [1–4]. In healthy children reproducible spirometry is generally achievable from 6 years of age. In children of all ages who are weak, obtaining reliable spirometry results may be challenging, especially forced maneuvers [2].

Respiratory function in children with NMDs is often impaired by the age at which spirometry is feasible [5]. For this reason, there is an urgent need for alternative noninvasive lung function tests in children unable to perform spirometry [1]. Oscillometry may serve as a surrogate test in children unable to perform spirometry. Oscillometry is a noninvasive, versatile method to measure respiratory mechanics. Small-amplitude pressure oscillations are superimposed on the normal breathing, thereby avoiding the need for any special breathing maneuver or any noticeable interference with respiration [6,7]. Oscillometry measures respiratory resistance R and respiratory reactance X. R describes the dissipative mechanical properties of the respiratory system [5], and mainly reflects the frictional opposition offered by the conducting airways to the flow of air [8]. With progression of NMDs it is expected that R values increase due to underinflation, secretions in the airways and micro-atelectasis [5]. X measures the relationship between pressure and volume (the elastic properties) at low oscillation frequencies and the relationship between pressure and volume acceleration (the inertive properties) which become progressively more important at increasing frequencies [5,9]. With progression of NMDs, X is expected to reduce due to less compliant chest wall and reduced lung volumes [5]. Different frequencies are used in oscillometry: lower frequency impulses travel deeper into the lung and reflect the mechanical behavior of smaller airways, while higher frequencies are more sensitive to upper airway pathology [7].

Previous studies have shown that oscillometry is feasible in children with SMA and Duchenne Muscular Dystrophy (DMD) as young as 3 years [5,8,10]. Here, we aimed to assess

the relation between results of oscillometry and spirometry in children with NMDs and hypothesized the presence of a correlation between these tests. We hypothesized an increased R and reduced X in patients with more restrictive lung function decline, due to reduced compliance of the chest wall and reduced lung volumes [5].

Methods

In this prospective cross-sectional study, all children with NMDs attending the outpatient department of the Center of Home Mechanical Ventilation of the University Medical Center Utrecht, and able to perform spirometry were included once between August 2019 and May 2021. Patients with tracheostomy were excluded.

Oscillometry (ResmonPro Restech®) and spirometry data (Geratherm Spirostik®) were measured consecutively at the department of pediatric pulmonology at the University Medical Center Utrecht. These lung function tests were performed by a small team of professionals experienced in conducting these tests in children.

To measure oscillometry, children were seated with the head in neutral position, connected to the oscillation device via a mouthpiece and a noseclip in place. Cheek and floor of mouth were supported by the lung function technician. Measurements were obtained according to the American Thoracic Society/European Respiratory Society guidelines [11]. Our oscillometry equipment measures at 5, 11 and 19 Hz in order to obtain more reliable measurements by not overlapping the impulses. . We studied (Forced) Vital Capacity ((F) VC) and Peak Expiratory Flow (PEF). Spirometry was measured and reported according to the European Respiratory Society guidelines [12]. All tests were performed in sitting position, without corsets or braces.

We studied the relation between R and X during inspiration (insp), expiration (exp) and total breath (tot) and (F)VC and PEF. We did a subgroup analysis in patients with SMA and DMD, the most common NMDs included in this study.

The study was approved by the medical ethical committee of the University Medical Center Utrecht (16-563/c). Informed consent was obtained from all participants and/or their parents in case of minors.

Statistical analysis

We used descriptive statistics to describe baseline characteristics. Only measurements obtained during the first visit after inclusion were used for analyses. Z-scores were calculated of oscillometry outcomes measured at 5 Hz [13]. We calculated the non-parametric two-tailed spearman correlation coefficients (ρ) to describe the relation between oscillometry and spirometry results. Regression curve was estimated using IBM SPSS 26.0. To study the ability to predict and exclude moderate (i.e. ≤ 60% of predicted) lung function restriction based on abnormal or normal z-scores of oscillometry results measured at 5 Hz, we calculated the positive and negative predictive values.

Results

We included 148 patients with a median age of 13 years. One third of the patients were patients with SMA, one quarter of the patients were patients with DMD. Fifteen percent of the patients were supported by home mechanical ventilation. Baseline characteristics are shown in Table 1.

Oscillometry measurement was feasible in all children. Spearman correlation coefficients of the relation between oscillometry and spirometry results are shown in Table 2.

Table 1: Patient characteristics

Age in years, median (IQR)	13 (8-16)
Male gender, n (%)	92 (62)
Home mechanical ventilation, n (%)	22 (15)
Body Mass Index, median (IQR)	19 (16-22)
Underlying disease	
Spinal Muscular Atrophy	46 (31)
Duchenne Muscular Dystrophy	36 (24)
Other Muscular Dystrophy	
Limb Girdle	8 (5)
Ullrich	5 (3)
Emery-Dreifuss	2 (1)
Becker	2 (1)
Other	5 (3)
Congenital Myopathy	
Central Core	3 (2)
Nemaline	2 (1)
Bethlem	2 (1)
Other	11 (7)
Myasthenic Syndrome	3 (2)
Heriditary Sensory and Motor Neuropathy	4 (3)
Mitochondrial myopathy	8 (5)
Myotonic Dystrophy	11 (7)

Legend : IQR= interquartile range; n= number

Table 2: Association between Oscillometry results (measured at 5, 11 and 19 Hz) and spirometry results using spearman correlation coefficients

	VC	FVC	PEF
R			
5 Hz			
insp	-0.564	-0.500	-0.619
exp	-0.559	-0.502	-0.637
tot	-0.568	-0.508	-0.637
11 Hz			
insp	-0.576	-0.512	-0.633
exp	-0.564	-0.518	-0.638
tot	-0.578	-0.521	-0.644
19 Hz			
insp	-0.537	-0.462	-0.584
exp	-0.558	-0.501	-0.605
tot	-0.551	-0.486	-0.597
X			
5 Hz			
insp	0.610	0.596	0.579
exp	0.512	0.524	0.539
tot	0.626	0.612	0.622
11 Hz			
insp	0.557	0.542	0.596
exp	0.511	0.508	0.574
tot	0.548	0.537	0.600
19 Hz			
insp	0.488	0.493	0.521
exp	0.435	0.434	0.522
tot	0.480	0.474	0.551

Legend: exp = expiratory; FVC = forced vital capacity; Hz = Hertz; insp = inspiratory; PEF = peak expiratory flow; R = respiratory resistance ; tot = total breath (inspiratory and expiratory); VC = vital capacity; X = respiratory reactance;

All correlation coefficients were statistically significant with $p < 0.001$. A negative correlation was found between R and spirometry outcomes (spearman correlation coefficient (ρ) between -0.5 and -0.6). A positive correlation was found between X (i.e. less negative outcomes) and spirometry outcomes (ρ between 0.4 and 0.6). Highest correlation was found at lower frequencies. This confirmed our hypothesis: an increased R and reduced X was observed in patients with lower (F)VC and PEF.

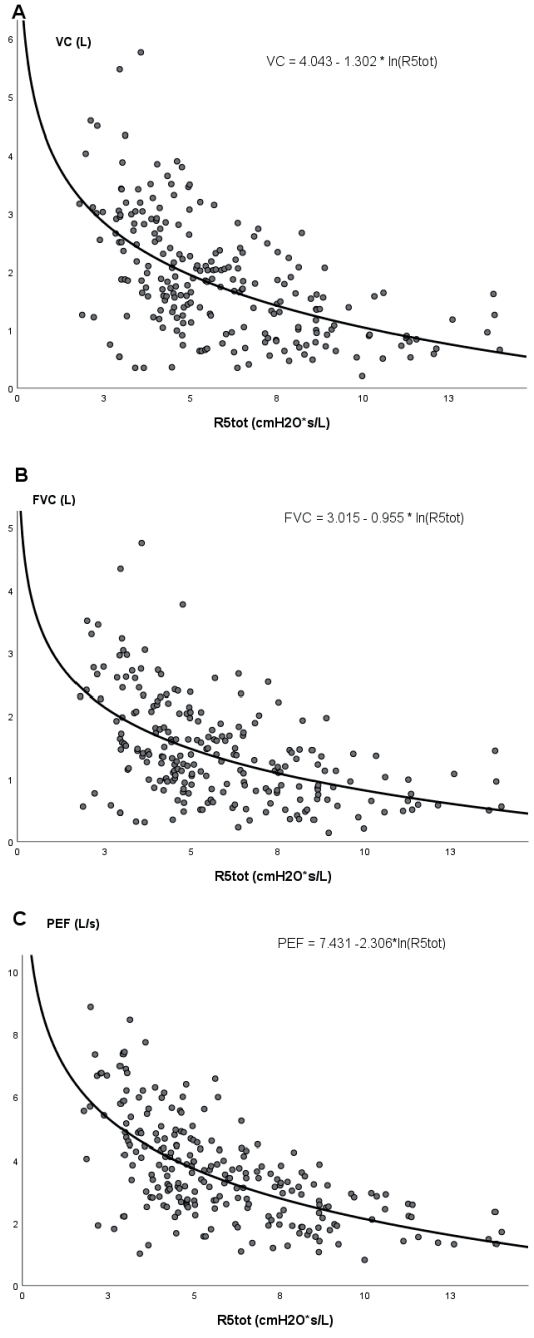
Measurement of inspiratory and expiratory R and X did not provide added value, as correlation coefficients were similar to total R and X. Regression curves showing the relation between both R and X measured at 5 Hz and spirometry results are shown in respectively Figure 1 and Figure 2.

Subgroup analysis in 46 patients with SMA and 36 patients with DMD showed that correlation between oscillometry and spirometry was poor in patients with DMD compared to patients with SMA. Highest correlation was found in patients with SMA between oscillometry results and PEF (ρ >0.5) (Table 3).

Median z-scores of R and X measured at 5 Hz were -0.16 (IQR -0.77; 0.93) and 0.27 (IQR -0.48; 0.76) respectively. We found no significant correlation between calculated z-scores of R and X measured at 5 Hz and standardized lung function test results.

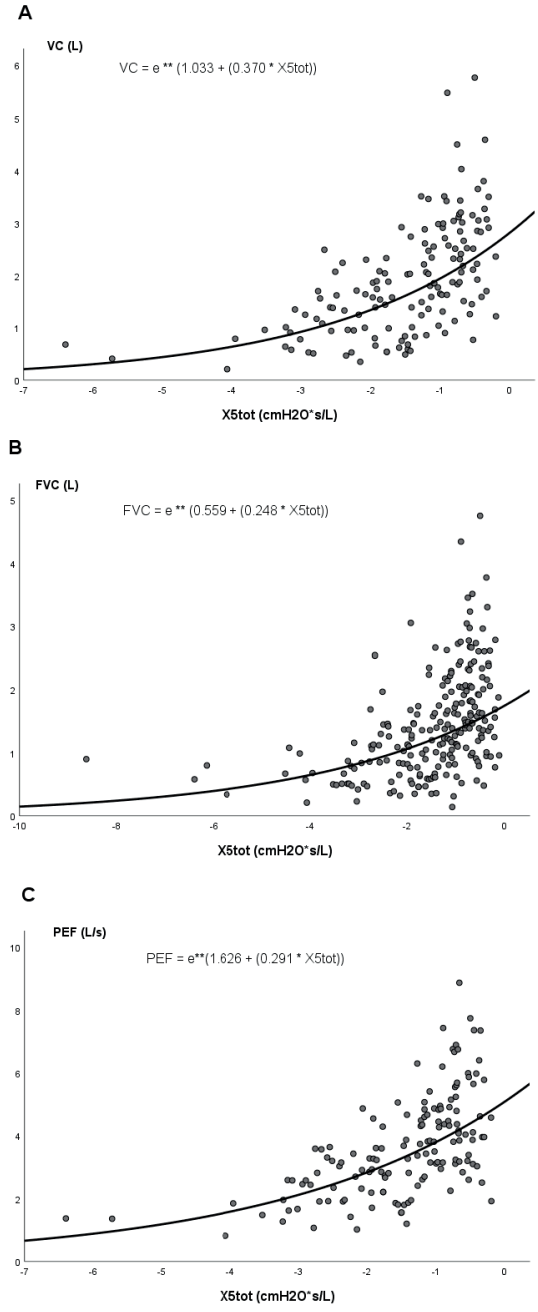
Finally we studied if (ab)normal z-scores of R and X measured at 5 Hz could exclude or predict presence of moderate lung function restriction by calculating negative and positive predictive values. Negative predictive values of 65% , 32% and 55% were found for R and X versus VC, FVC, and PEF. Positive predictive values of 80%, 85% and 62% were found for R versus VC, FVC and PEF.

Figure 1: Regression curves showing the relation between respiratory resistance measured at 5 Hz (R5tot) and spirometry results A) Vital Capacity; B) Forced Vital Capacity; C) Peak Expiratory Flow



Legend: FVC = forced vital capacity, L = liter, PEF = peak expiratory flow, R5tot = respiratory resistance measured at 5 Hz, s = second, VC = vital capacity

Figure 2: Regression curves showing the relation between respiratory reactance measured at 5 Hz (X5tot) and spirometry results A) Vital Capacity; B) Forced Vital Capacity; C) Peak Expiratory Flow



Legend: FVC = forced vital capacity, L = liter, PEF = peak expiratory flow, X5tot = respiratory reactance measured at 5 Hz, s = second, VC = vital capacity

Table 3: Association between Respiratory Oscillometry results (measured at 5, 11 and 19 Hz) and spirometry results using spearman correlation coefficients in patients with Duchenne Muscular Dystrophy and Spinal Muscular Atrophy

	NMDs	n	VC	FVC	PEF
R					
5 Hz	Total group	148	-0.568	-0.508	-0.637
	SMA	46	-0.500	-0.401	-0.550
	DMD	36	-0.262	-0.203	-0.355
11 Hz	Total group	148	-0.578	-0.521	-0.644
	SMA	46	-0.508	-0.447	-0.588
	DMD	36	-0.261	-0.195	-0.354
19 Hz	Total group	148	-0.551	-0.486	-0.597
	SMA	46	-0.477	-0.397	-0.553
	DMD	36	-0.261	-0.195	-0.354
X					
5 Hz	Total group	148	0.626	0.612	0.622
	SMA	46	0.450	0.413	0.587
	DMD	36	0.483	0.455	0.304
11 Hz	Total group	148	0.548	0.537	0.600
	SMA	46	0.462	0.362	0.547
	DMD	36	0.295	0.357	0.359
19 Hz	Total group	148	0.480	0.474	0.551
	SMA	46	0.457	0.356	0.559
	DMD	36	0.187	0.255	0.324

Legend: DMD = Duchenne Muscular Dystrophy, FVC = forced vital capacity; Hz = Hertz; n = number; PEF = peak expiratory flow; R = respiratory resistance SMA = Spinal Muscular Atrophy; VC = vital capacity; X = respiratory reactance;

Discussion

In this study we have shown that oscillometry may be used as a substitute for spirometry in children with NMDs, especially oscillometry measurements at lower frequencies. An increased R and reduced X was observed in patients with lower (F)VC and PEF. Positive predictive values of 80-85% were found for z-scores of R measured at 5 Hz versus (F)VC ≤ 60%, suggesting that oscillometry may be used to predict moderate lung function restriction, i.e. (F)VC ≤ 60% of predicted, in children with NMDs.

Although obtaining reliable spirometry results are challenging in young or severely affected patients with NMDs, spirometry results are important outcomes in patients with NMDs.

For example, in these patients significantly lowered FVC values, i.e. ≤ 60% of predicted, are associated with an increased risk of REM- and NREM-related sleep disordered breathing [2,14], and PEF has been shown to be a sensitive marker to monitor respiratory muscle strength in patients with DMD [15]. However, limited data are available on oscillometry in patients with NMDs [5,8,10,16] . Although oscillometry provides an objective measure, it does not measure the same aspects of respiratory function as other tests [5]. With progression of NMDs it is expected that R values increase due to underinflation, secretions in the airways and micro-atelectasis [5]. In this study we confirmed increased R values with decreased spirometry results. In patients with NMDs X is expected to be reduced due to reduced compliance of the chest wall and reduced lung volumes [5]. In this study we confirmed more reduced, i.e. more negative, X values in patients with more reduced spirometry outcomes. We found highest correlation at lower frequencies, probably explained by involvement of smaller airways due to micro-atelectasis and secretions.

Two previous studies by the same group have shown that the use of oscillometry as a surrogate outcome to measure lung function was feasible in children with SMA. Gauld, et al. showed a linear relationship between X measured at 8Hz and FVC in 4 children with SMA [5]. Kapur, et al. showed that children with SMA requiring non-invasive ventilation (NIV) (n=10) had an abnormal R measured at 8Hz compared to children not using NIV (n=15) [10]. Although not linear, we confirmed the significant relation between spirometry and R and X in this larger number of patients. A study in patients with DMD showed a poor correlation between oscillometry outcomes and spirometric variables, all expressed as z-scores, in healthy subjects as well as in patients with DMD [8]. These poor correlations were confirmed in our study.

Oscillometry has the potential of separate analysis of inspiratory and expiratory R and X, in order to determine disease-specific changes in the mechanical behavior over the breathing cycle. Inspiratory R has been proven to be a very sensitive index of airway caliber [7]. Airway caliber may be reduced in smaller airways of children with NMDs due to reduced compliance, micro-atelectasis and retention of airway secretions This study did not show added value of measuring inspiratory and expiratory R and X separately.

Our study has several limitations. Firstly, the lack of global reference equations for oscillometry is regrettable [17]. Generally, there is significant variability in the reported R and X values, depending on characteristics of the examined populations and the equipment and technique used [7]. We calculated z-scores based on a Polish study, which estimated regression equations based on oscillometry results in 626 healthy children aged 3-18 years [13] . Our study population had a heterogeneous ethnic background and we used different equipment. For this reason, calculated z-scores in this study may not be fully accurate.

Also, calculation of z-scores was limited to measurements at 5Hz, as we were unable to find reference equations for oscillometry measurements at 11 and 19 Hz in this age group. Secondly, as this study was not aimed at studying feasibility of oscillometry measurements in young or less cooperative children, we only included patients able to perform spirometry. It therefore remains unclear whether our results are generalizable to much younger children with NMDs, although we expect this to be the case as oscillometry has been shown to allow for evaluations of respiratory mechanics in neonates [18] and young children [5,8,10,17,19].

Although the number of included patients in this study was much higher than in previous studies in patients with NMDs, we did not study follow up data of these patients. Research is required to include repeated measures over time, to study the ability to predict lung function decline by using oscillometry.

Conclusion

We observed a non-linear relation between oscillometry measurements and spirometry results in children with NMDs. We confirmed our hypothesis and found an increased R and reduced X in patients with more restrictive lung function decline. Oscillometry may be promising as a surrogate measure of lung function in these children.

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CHAPTER 11

11

Discussion

Discussion

The studies compiled in this thesis aimed to fill some of the most important gaps in our understanding of the natural history of respiratory (dys)function associated with Spinal Muscular Atrophy (SMA). In addition, we tried to gather evidence on different supportive treatment strategies of neuromuscular disorders (NMDs) and to explore the value of a surrogate measure of lung function to use in patients with NMDs.

NMDs affect the function of anterior horn cells in the spinal cord, peripheral nerves, neuromuscular junction and skeletal muscle. Pediatric NMDs are mostly genetic and are without exceptions rare disorders, which affect not only skeletal muscle, but also heart and respiratory muscles. Children with NMDs are therefore historically well represented in clinics for chronic respiratory support. Recent advances in the development of drugs for genetic NMDs may change the natural history of NMDs and increase the need for pro-active supportive care. This underlines the urgency to increase our understanding how to monitor and treat respiratory problems in NMDs.

Spinal Muscular Atrophy is the first NMD for which genetic therapy became available. At present, several genetic-based therapies are under investigation for other NMDs, such as Duchenne Muscular Atrophy (DMD), Congenital Muscular Dystrophies, Myotonic Dystrophies, Congenital Myopathies, Charcot Marie Tooth and Congenital Myasthenic Syndromes [1]. These new treatments have the potential for significant improvement of morbidity and mortality, and may even have curative potential in some cases [1].

Although the number of challenges is more extensive, I will focus on the following challenges in this discussion:
1/ Lack of natural history data of respiratory (dys)function
2/ Changing phenotypes after the introduction of genetic therapies
3/ The need to change the approach of supportive treatment from reactive to pro-active
4/ Lack of evidence for many supportive respiratory treatments
5/ Individualized treatment

Natural history data of respiratory (dys)function

Chapters 2 to 5 in this thesis describe the natural history of lung function, respiratory muscle strength and carbon dioxide levels in patients with Spinal Muscular Atrophy (SMA). We showed a progressive decline of lung function outcomes in childhood and stabilization in early adulthood. Estimated baseline values were significantly lower in more severely affected patients. In contrast to results of conventional lung function tests (i.e. spirometry), respiratory muscle and cough strength were low from early ages onwards even in milder SMA phenotypes. We observed relative hyperventilation with daytime

carbon dioxide levels in the lower range of normal in most non-ventilated patients with SMA. These carbon dioxide levels increased to or beyond the upper limit of normal in the year prior to initiation of home mechanical ventilation. In contrast, we observed no accelerated decline of lung function outcomes prior to chronic respiratory failure.

As described in the introduction of this thesis, guidelines suggest to measure vital capacity (VC) in patients with NMDs who are capable of performing spirometry as part of the respiratory assessment [2–4], because VC is a valuable predictor of susceptibility to infection, need for respiratory support and survival in children and adolescents with DMD [5]. This thesis suggests that tests of respiratory muscle and cough strength may be an even more appropriate outcome measure. Due to the lack of natural history data, lung function and respiratory muscle strength tests are not used as outcome parameters in trials on new treatments. Also, very young children, who participated in the original trials on new treatments, are unable to perform these tests. For this reason, alternative measures of lung function which predict respiratory morbidity, such as infections and respiratory failure, in young children with NMDs would be useful. Chapter 10 in this thesis explores Oscillometry as a surrogate measure of lung function.

Obtaining natural history data in patients with rare diseases is a challenge. The promise of genetic therapies for SMA has been a motivation for a large number of natural history studies on muscle strength and motor function, which were important outcome measures in pivotal clinical trials. Respiratory function has on the contrary been less well studied. After the introduction of genetic therapies, obtaining robust natural history data in treatment naïve patient populations will become even harder. This implies that we will become more dependent on the historical record for comparisons [6].

Natural history studies are important for several reasons. First, it helps clinicians to give relevant information to parents and patients after diagnosis regarding expected morbidity and mortality. Some of our patients reflected, years after they were counseled, on the discrepancies between the initial message and their lived experience. Children with SMA type 1c-2a often survived longer than counselors predicted after diagnosis. This sometimes resulted in confusion and loss of confidence in the medical team, but also in a delay to visit hospitals to initiate supportive treatment. Wijngaarde et al. reported survival in a Dutch national cohort of treatment-naïve SMA patients [7], extending data from previous studies that mainly reported survival of patients with classical SMA type 1. Although median survival (defined as survival without ≥ 16 hours/day mechanical ventilation) in patients with SMA type 1b was 7.7 months, comparable to previous studies. This study reported a probability of surviving beyond the age of 1 year of 30.6% (95% CI 18.2 - 44), which declined to 6.5% (95% CI 1.8 -14.5) after 2 years and 0.2% (95% CI 0.0-1.7) after 4 years. Patients with SMA type 1c in this national cohort had a significantly longer

median survival of 17.0 years. The probability of surviving beyond the age of 5 years was 85.3% (95% CI 76.8 -91.5), decreasing to 69.3% (95% CI 54.7- 81.1) at age 10, 25.3% (95% CI 10.8 -42.2) at age 30, and 7.9% (95% CI 1.1 -22.7) at age 50 [7]. Survival in severe type 2 (i.e. type 2a) is possibly also better than many counselors thought in the past. This experience clearly indicates the value of reference data for counseling purposes.

Secondly, natural history data can serve as a benchmark to measure effects of recently introduced or future treatment strategies [6,8–10]. As mentioned above, survival, the acquisition of motor milestones and functional motor scores were used as primary outcome measures in clinical trials to assess efficacy of genetic (i.e. RNA and DNA-based) treatments of SMA [11–13]. Since respiratory complications are probably an important factor influencing quality of life, the lack of respiratory function tests as outcome measures in clinical trials seems a clear omission. This is, at least partially, explained by a lack of reference data.

Finally, improved insights into the natural history of respiratory muscle strength could guide therapeutic management [14] and improve timing of supportive care [2]. The studies in this thesis show for instance that respiratory muscle strength and peak cough flow (PCF) is reduced even in the milder phenotypes of SMA throughout life. Awareness of the risk of respiratory failure in case of an initially mild respiratory tract infection, helps to counsel the patient and helps to timely introduce treatments such as airway clearance techniques. On the other hand, being aware that a specific NMD has a slower respiratory deterioration, may change follow up frequency and reduce health care utilization in this group.

For many NMDs there are no data on survival, timing of respiratory failure and other respiratory morbidity such as respiratory tract infections. For the reasons stated above and the development of new therapies for these NMDs description of natural history data should be a research priority.

Changing phenotypes after the introduction of genetic therapies

The introduction of new genetic-based therapies for SMA has taught us that clinical phenotypes of NMDs change with treatment. However, it is unlikely that all muscles weakened by SMA associated disease processes respond to the same extent to treatment. Disease trajectories in patients receiving genetic-based treatment such as intrathecal Nusinersen injections differ significantly from the known natural history of the disease [15]. This is illustrated by the patients who -against the expectations of natural history- learned to sit, stand or even walk, but still required a feeding tube [16] or mechanical ventilation because of bulbar weakness or chronic respiratory failure due to respiratory muscle weakness. This stands in contrast with the 'walker' (i.e. type 3) phenotype from the pre-treatment era: children able to walk do not generally suffer from respiratory failure. This is

further illustrated in a French [17] and German [18] cohort of patients with SMA type 1 treated with Spinraza in an Expanded Access Program. A significant proportion of patients with SMA type 1 who initially showed motor function improvement required permanent ventilation or underwent tracheostomy during 6 months follow up. It is unclear whether this reflects a poor treatment effect on respiratory function, or a more proactive approach in the participating centers to initiate mechanical ventilation in treated patients.

These experiences may paint a picture in which genetic treatments may mitigate disease course by prolonging life and improving motor function at the expense of more intensive respiratory treatment. However, many patients in both our and published cohorts had chronic respiratory failure at initiation of treatment, i.e. were supported by non-invasive or invasive ventilation. It is not known whether effects of systemic treatment such as gene therapy on respiratory function are superior to localized intrathecal treatment. Although the first pilot trial of 12 patients with gene therapy suggested that effects on respiratory function might be better than the experience with Nusinersen, follow-up trials including 63 patients with SMA type 1 painted a more nuanced picture [19,20]. Optimizing treatment effects probably depends primarily on early treatment. The most impressive results have been observed in pre-symptomatic patients [15,21] and this is why an increasing number of countries explores the possibility to include SMA in newborn screening programs (NBS). In the Netherlands NBS for SMA was implemented in June 2022.

The importance of NBS is further illustrated by the diagnostic delay observed in young children. A systematic review of the literature confirms this delay. The mean age of diagnosis of SMA type 1 was at the age of 6.3 months with a delay of 3.6 months between onset of symptoms and diagnosis [22]. This delay in diagnosis reduces the odds of effectiveness dramatically [21]. Although NBS will probably improve treatment efficacy, this will be restricted to children with 2 and 3 copies. The discussion when treatment should be initiated in patients with 4 (or more) SMN2 copy numbers will continue, despite the fact that a significant percentage of patients with 4 copies has symptom onset before the age of 3 years. Important questions remain: Will treatment of asymptomatic patients result in reduction of respiratory problems? Or will effects of presymptomatic treatment on respiratory muscle function be less pronounced compared to effects on skeletal muscle, as suggested by the first results of presymptomatic treatment with Nusinersen? The changing phenotype will be most pronounced in children with SMA type 1, but may also be present to a lesser extent in milder phenotypes, as the NBS will allow treatment of asymptomatic patients having 3 SMN2 copy numbers, which are mainly patients with SMA type 2 [23]. In children with SMA type 2, treatment reduces progression of the disease compared with the natural history. For patients with mild SMA type 2, developing the ability to walk is a possibility, although with different gait due to compensation of the impaired muscles by the relatively spared hip girdle muscles [19].

The new phenotype is not only represented in changed motor skills. Treated SMA type 1 patients may be able to sit unsupported and, therefore, with the effect of gravity, they exhibit a higher rate of scoliosis with often severe kyphoscoliosis in the first years of life [24]. Severe scoliosis decreases the compliance of the chest wall, thereby restricting VC [25] and increasing respiratory morbidity.

The increase in muscle strength promotes the worsening of contractures [24], requiring multidisciplinary care by physiotherapists, rehabilitation specialist and orthopedic surgeons [26].

A recent systematic review suggested that children with SMA type 1 are more likely to have cognitive impairment (attention and executive function) [27]. With prolonged survival due to new therapies, this cognitive impairment may become more apparent.

Finally, SMA is a multisystem disease with dysfunction in skeletal muscle, heart, kidney, liver, pancreas, spleen, bone, connective tissues, and immune systems. New or more significant comorbidities may become clear as these patients survive into childhood and adulthood [28]. This requires intensive monitoring and awareness of the possibility of new, previously unknown symptoms in these patients.

The need to change the approach of supportive treatment from reactive to pro-active

The development of disease-modifying therapies requires the continued acceleration of improvements in supportive care and more specific guidelines regarding the management of patients with the long-term impact of novel therapies not being known [29].

This supportive treatment involves a multidisciplinary approach with for instance respiratory support, nutritional support, immunizations, physiotherapy etc. New emerging genetic therapies and better multidisciplinary management are prolonging the survival of children with SMA. This requires strategies to help patients with SMA navigate the transition from adolescence to adult life [29].

In this discussion I will focus on the respiratory supportive treatment.
Before the introduction of genetic therapies, attitudes and approaches towards respiratory support by mechanical ventilation or cough augmenting therapies showed large international differences. In the United States, respiratory support of patients with SMA type 1 was not uncommon. For instance, Bach described a cohort of 65 patients with SMA type 1 of which 89% (n = 58) started mechanical ventilation since the late 1990s, either invasive via tracheostomy (n = 16) or non-invasive (n = 33) [30]. From the 1980s, one center in the UK considered initiation of non-invasive ventilation in children with SMA

type 1 to palliate respiratory symptoms and facilitate care at home [31]. In contrast, it was uncommon in 2017 in the Netherlands to support children with SMA type 1 with home mechanical ventilation (Dutch SMA type 1 guideline, 2018). There was consensus among Dutch respiratory care professionals not to initiate chronic invasive ventilation via tracheostomy.

Provision of care varies from region to region and from specialty to specialty [31]. Cultural standards, but also disparities in family resources and medical practitioners' knowledge probably underlie these big differences in respiratory care. This sometimes resulted in attempts by parents to obtain expert care abroad, albeit in a costly and inefficient manner [32]. These international differences in care were also reflected in the first consensus statement on the treatment of SMA that was published in 2007 by a group of experts from both the United States and Europe. This statement, published at a time when genetic therapies were not yet available, states the following: "*In non-sitters, care without ventilation support is an option if the burden of treatment outweighs benefit. Noninvasive ventilation can be used palliatively to facilitate discharge to home from a hospital and reduce work of breathing…. Tracheotomy for chronic ventilation is a decision that needs to be carefully discussed if requested by parents. In non-sitters, this is controversial and an ethical dilemma*." [32]. Ten years later the updated consensus statement contained a pro-active approach instead of purely reactive approach on the respiratory management in patients with SMA type 1. It contained advise "*to use non-invasive ventilation in all symptomatic infants prior to respiratory failure to be "prepared" for respiratory failure, minimize chest wall distortion and palliate dyspnea*". Moreover, tracheotomy was considered in selected patients in whom non-invasive ventilation failed or if there was no suitable mask for effective non-invasive ventilation [2].

Dutch respiratory care practice for SMA has generally followed suit after genetic treatment became available in 2017. The rationale for this policy change is that in order to optimize the odds of efficacy of these treatments, optimal supportive treatment, such as nutritional and respiratory support, is a requirement. Cough augmenting techniques and mechanical ventilation are currently being offered with lower thresholds than previously. Genetic treatment is offered to children with SMA type 1 in a relatively good condition and a fair chance of treatment response. Although this may reduce the chance of children who survive without relevant motor function gains, a more pro-active attitude towards respiratory care may pose new (ethical) challenges and questions.

Studies suggest that home mechanical ventilation can have significant impact on patient, parents and siblings, and may result in parent job loss, financial struggles, depression, and burnout [33]. The comprehensive care of a patient with SMA and his family is not complete without the surveillance and management of their psychosocial wellbeing [29].

Not all patients are offered genetic and supportive treatment after diagnosis. Sometimes parents prefer a palliative treatment for their child, after extensive counselling about (uncertainty) of expected results of treatment. A palliative approach continues to be chosen in severe forms. The choice of palliative care versus supportive care has to be respected in emergency care. Discussions with families about options for acute illnesses should take place as early as possible. Individualized anticipatory care plans can be developed and regularly updated by a multidisciplinary team and families [29].

The NBS probably creates a stressful situation for parents to receive a severe diagnosis in an apparently healthy baby. This requires not only qualified genetic counselling and psychological support [24], but also counselling by neurologists and pediatricians about the respiratory problems their newborn baby will probably suffer from in the future.

Finally, ethical discussions do not only involve the individual patient. There is a public debate on the economic burden of these new expensive genetic therapies. There is an increasing importance of economic considerations in healthcare decision-making. A recent review on the economic burden concludes that there is a need for further prospective and independent economic studies, in patients treated after symptom onset and in patients who are benefiting from pre-symptomatic treatment [34].

Lack of evidence for supportive respiratory treatments

Although supportive care for NMDs includes more than respiratory care, i.e. nutritional support, orthopedic treatment and rehabilitation care [2,4,26,35], this thesis focusses on respiratory support, covering both cough augmenting techniques or airway clearance techniques as well as mechanical ventilation.

Not surprisingly, supporting patients with severe NMDs with mechanical ventilation probably prolongs their survival. There is a huge number of uncontrolled trials claiming beneficial effect of nocturnal mechanical ventilation, but a limited number of randomized studies. An available Cochrane review concluded that evidence about the therapeutic benefit of mechanical ventilation is, although of very low quality, consistent in its suggestion of alleviation of the symptoms of chronic hypoventilation in the short term. The authors conclude that, with the exception of motor neuron disease and DMD for which the natural history support improved survival after the start of mechanical ventilation, further larger randomized trials should assess the long-term benefit of different types and modes of nocturnal mechanical ventilation on quality of life, morbidity and mortality, and its cost-benefit ratio in NMDs [36].

This a recurring theme in treatment efficacy studies in rare disorders. It is doubtful whether further resources should be spent to gather further evidence on efficacy of treatments

that have been proven in clinical practice, such as effect of mechanical ventilation on survival. Small scale studies have a risk of inclusion bias [37]. I consider it unethical to set up a randomized controlled trial to study the effect of mechanical ventilation on survival and thereby withholding some children with a NMD support with mechanical ventilation.

In the Netherlands mechanical ventilation is initiated when there is evidence for nocturnal hypoventilation with hypercapnia; in some centers respiratory support is initiated prior to that. The consensus statement on treatment of patients with SMA advises to "*use mechanical ventilation in all symptomatic infants with SMA type 1 and prior to respiratory failure to be "prepared" for respiratory failure, minimize chest wall distortion and palliate dyspnea*" [2]. Evidence for this consensus statement is lacking: case reports suggest that the use of non-invasive ventilation helps to prevent chest wall distortion [31], which could be explained by effect on compliance, but randomized studies have not been performed. Moreover, children may not accept non-invasive ventilation if initiated before respiratory failure. It is unknown whether less invasive treatments, such as airway clearance techniques (ACTs) or application of regular positive expiratory pressure (pep), may prevent chest wall distortion with beneficial effect on progression of restrictive lung function decline. Further research is therefore required on timing of initiation of mechanical ventilation, prevention of chest wall distortion and improvement of chest wall and lung compliance.

Although widely applied as standard care and recommended in the consensus statement, there is even less evidence on beneficial effects of ACT. A recently published Cochrane review concludes that there is no evidence of effect on hospital admissions and insufficient evidence of beneficial effects on gaseous exchange, pulmonary function, quality of life, patient preference and satisfaction. Although the available studies may suggest that a range of ACTs may increase peak cough flow compared to unassisted cough, even this is far from certain. It is unknown which ACT works best [38]. We specifically focused on mechanical insufflation-exsufflation and our systematic review, which was not limited by only including randomized controlled trials, confirmed the immediate effect on peak cough flow when compared to unassisted cough. Further research is required to establish the safety and efficacy of ACTs in patients with NMDs, for both long-term maintenance use, and during respiratory exacerbations for 'rescue' use. We need future studies to measure longer-term, clinically relevant outcomes, such as respiratory tract infections and hospital admissions and compare the value of the available techniques. Such future studies should include systematic analysis of adverse events to assess safety. Cost-effectiveness analyses are also needed. Finally, studies are required to compare settings and frequency of these treatments.

Respiratory muscle training is increasingly used by patients with NMDs, although it is not a standard treatment in the Netherlands. A recent Cochrane review found low evidence that respiratory muscle training may improve lung capacity and respiratory muscle

strength in some NMDs, although findings were not consistent [39]. Randomized controlled trials are needed to assess training effects on inspiratory and expiratory muscle function. This should ideally include an assessment of optimal intensity of training [39]. We recently started a randomized controlled trial comparing sham to combined inspiratory and expiratory respiratory muscle training in patients with SMA. If successful, this approach could be used for other NMDs.

The challenge in all these studies on supportive care in NMDs remains the heterogeneity of patients with different stages of disease and different ages and disease duration.

Individualized treatment

The large variability among patients with rare NMDs implies that 'one approach fits all' may turn out to be unsuccessful. Supportive treatment for both treatment-naïve and treated patients with NMDs should be individualized.

As outlined in the introduction of this thesis, neuromuscular respiratory morbidity is not a uniform concept. Not only the pattern of respiratory muscle involvement varies within a specific NMD, but also the severity of the respiratory muscle weakness. This obviously suggests different supportive treatment requirements for different NMDs at different disease stages. Moreover, physicians and patients should find the balance between burden and benefits of treatments and this should be regularly evaluated as this may change over time.

New genetic-based treatments will result in different phenotypes of NMDs. At initiation of these genetic-based therapies, the expected outcome and respiratory course cannot be predicted, which complicates counseling and follow up. In case of SMA, different treatment options are available and at present it is unclear which treatment has the best changes of greatest effect. This complicates balanced and shared decision of the risks and benefits of genetic treatment [40].

In rare NMDs, predictive biomarkers are extremely useful to highlight the different outcomes of a particular treatment, discriminating between patient categories based on their response [41]. Ideally, these parameters should be able to show a significant change within a short time period and at an early stage of the disease. This is particularly relevant in young children, in whom performing lung function tests and respiratory muscle tests is not possible. In older children and adults with NMDs who are able to perform these tests, the minimum clinically meaningful difference for these lung and respiratory muscle function tests are unknown. Consequently, we do not know which tests are the most appropriate for clinical trials [14].

These examples illustrate the need for simple, non-invasive and reproducible respiratory muscle tests, which require minimal cooperation of children [14]. We therefore performed a pilot study on oscillometry, which is easy to perform even in infants, as a surrogate measure of lung function. Currently, follow up data are collected to study if this technique can be used to monitor the course of lung function decline in NMDs. However, non-invasive tests which directly measure involvement of respiratory muscles, lung and chest wall compliance or lung volumes and work of breathing may be preferred over surrogate measures such as oscillometry. Possible options are (a combination of) ultrasound of respiratory muscles, multiple breath washout tests and respiratory inductance plethysmography.

Finally, it is important to associate the respiratory muscle parameters to the skeletal muscle parameters as there is not always a parallel between the involvement of these muscle types [14].

This may help in the prediction of treatment effect on respiratory morbidity by the effect on motor scores.

What do we need to overcome these challenges?

National and international collaboration is required to overcome the challenges outlined above. One of the reasons for lack of knowledge is that different types of NMDs are rare, and care for these patients is often not centralized. This results in lack of power to accurately describe natural history and gather evidence on effects of different treatments.

This is further complicated by an important heterogeneity in type and frequency of collected data. Despite consensus statements on standards of care, there are still important differences in the supportive treatments offered to patients.

Collection of real-world data on standardized outcome measures, including respiratory outcome measures, will be essential to improve the understanding of treatment effects of new treatments in NMDs and will ultimately be the basis for clinical decision-making and individualized treatment [15]. This requires international databases with systematic measurements at clearly defined time intervals and preferably international treatment protocols.

Randomized controlled trials are not always possible to study effect of treatments which are already widely introduced in standard clinical care. A randomized controlled trial comparing airway clearance techniques to a sham-treated group, is in my opinion unethical as some evidence is available that these techniques improve peak cough flow compared to unassisted cough in patients with NMDs and this treatment is already

incorporated in the standards of care. However, a randomized controlled trial (RCT) comparing two different types of airway clearance techniques is certainly useful.

Long-term parallel-group RCTs, for instance comparing the number of respiratory tract infections in two groups using different airway clearance techniques provide the best evidence, but NMDs are rare and attaining sufficient sample size is difficult. Multisite collaborative studies are necessary to reach sufficient sample sizes for adequate power and allow meaningful subgroup analyses. For short- and medium-term outcomes, such as immediate change in PCF after applying airway clearance, cross-over trials may be useful, as smaller samples may yield equivalent power to a parallel-group RCT [38]. International collaboration will certainly facilitate answering many questions and unresolved dilemmas.

I am a strong supporter of centralization of care for patients suffering from rare diseases, such as NMDs, especially in a small country like the Netherlands and in care which mainly involves outpatients care. I realize this is a sensitive topic, because it usually involves the loss of patients in one center in favor of another center [42].

Although SMA is a rare disease, I personally experienced that pattern recognition occurs with higher patient load. Our chapter on relative hyperventilation in patients with SMA is an example of this. Studies on beneficial effect of centralization of care, are mainly studies on surgical and acute care and suggest better outcomes in larger-volume hospitals [43–48]. There is limited evidence on centralization of care for patients with NMDs [49–51].

A survey by the Dutch Neuromuscular Diseases Association (VSN) questioned adult patients with NMDs on the perceived medical care and showed that patients have better experiences with the different components of hospital care when this was received in university hospitals where they have more expertise with diagnosis and treatment of NMDs. High quality of care for adult patients with NMDs can be obtained by regionalization and concentration of care in a few university hospitals with specialized neuromuscular centers [50]. In the UK a neuromuscular center for adult NMD patients was opened a few years ago which aims to provide high-quality multidisciplinary and multispecialty care that is pre-emptive, cost-effective and accessible for all patients [51].

Quality improvement may be even more pronounced with centralization of care for pediatric NMDs, as the number of pediatric patients is even smaller. Both parents of children with NMDs, patients association and physicians involved in the care should support each other to discuss the need for centralization and create real plans to centralize care and research for pediatric NMD patients. Arguments against centralization are the travel time and a lack of competition and no chance for a second opinion in the country. Patients who already come to our center for treatment of SMA do not experience travel time as a huge

problem. Competition or rather collaboration to improve care for rare disease should be worldwide and not only national [42].

Conclusion

This thesis compiles studies on the natural history of respiratory function in patients with SMA, the effect of ACTs in NMDs and the effect of scoliosis surgery on lung function in patients with NMDs. I also presented some pilot data on a surrogate measure of lung function. The results presented in this thesis may help to provide some answers to clinical dilemmas and to identify remaining unresolved questions in the treatment of respiratory problems in children with NMDs.

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APPENDIX

A

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

Publications

Nederlandse samenvatting

Spierziekten zijn een heterogene groep van ziekten van het motorische neuron, de neuromusculaire overgang en spiervezels, met wisselende debuutsleeftijd, presentatie, natuurlijk beloop en prognose. Er bestaan naar schatting 500 tot 600 spierziekten, waarbij iedere individuele spierziekte zeldzaam is.

Tot recent bestond er geen behandeling voor spierziekten en hadden spierziekten op de kinderleeftijd vaak een slechte prognose. Dit verandert langzaam door zowel symptomatische, ondersteunende behandeling als ziekte-specifieke behandelingen, zoals steroïden bij de ziekte van Duchenne en de genetische behandelingen bij Spinale Spier Atrofie.

Naast motorische betrokkenheid, zijn bij veel spierziekten de ademspieren ook in meer of mindere mate aangedaan. Ademspierzwakte is een belangrijke oorzaak van morbiditeit en mortaliteit bij patiënten met spierziekten. Ademspierzwakte met hierbij verstijving van de borstkas resulteert in hypercapnisch falen van de ademhaling. Dit wordt vaak versterkt door hypoxisch falen van de ademhaling, door parenchymschade ten gevolge van luchtweginfecties en/of aspiratie bij verminderde hoestkracht en bulbaire dysfunctie.

Ondanks de vooruitgang in ondersteunende behandeling van het falen van de ademhaling, zijn er nog veel onbeantwoorde vragen. Behandelingen zijn vaker gebaseerd op ervaringen van een behandelteam of de mening van experts en minder vaak op basis van bewijzen voortvloeiend uit wetenschappelijk onderzoek. De beperkte evidence die beschikbaar is, is in elk geval deels te verklaren door de heterogene groep patiënten met zeldzame ziekten.

Ondanks (inter)nationale richtlijnen en consensus statements, zijn er nog steeds grote verschillen in de behandeling van ademhalingsproblemen bij spierziekten.

Deze thesis heeft als doel een aantal van deze vragen te beantwoorden, maar heeft vooral een zaadje geplant voor nog veel meer vragen.

Doelstellingen van deze thesis:

1/ Het vastleggen van het natuurlijk beloop van respiratoire problemen bij SMA (Deel 1, Hoofstuk 2-5).
2/ Evidence verzamelen voor ondersteunende behandelingen bij patiënten met spierziekten, zoals hoestondersteunende technieken en chirurgische correctie van een scoliose (Deel 2, Hoofdstuk 6-9).

3/ Exploratie van haalbaarheid en betrouwbaarheid van een alternatieve methode om de longfunctie te meten (Deel 3, Hoofdstuk 10).

Deel 1: Natuurlijk beloop van respiratoire problemen bij SMA

Spinale Spier Atrofie, ofwel SMA (Spinal Muscular Atrophy), wordt gekarakteriseerd door verlies van motorische neuronen in het ruggenmerg met daarbij progressieve spierzwakte en spieratrofie. SMA wordt veroorzaakt door een homozygote deletie van het survival motor neuron 1 (*SMN1)* gen. SMA wordt gekenmerkt door een grote variabiliteit in ziekte-ernst en wordt traditioneel ingedeeld in verschillende typen op basis van debuut van klachten en hoogst behaalde motorische mijlpaal (Tabel 1, Introduction). SMA type 1 is de meest ernstige variant met presentatie voor de leeftijd van 6 maanden, het niet zelfstandig kunnen zitten en een beperkte overleving zonder behandeling. Patiënten met SMA type 2 presenteren zich tussen de 6 en 18 maanden en deze kinderen leren nooit zelfstandig lopen. SMA type 3 is een mildere vorm waarbij de eerste symptomen op latere kinderleeftijd ontstaan en waarbij het los lopen de hoogst behaalde motorische mijlpaal is. SMA type 4 is een zeldzame vorm van SMA, waarbij klachten pas op volwassen leeftijd ontstaan.

In 2017 werd een grote wetenschappelijke doorbraak bereikt en de eerste SMA-specifieke behandeling goedgekeurd, namelijk intrathecale toediening van de antisense oligo-nucleotide (ASO) Nusinersen (Spinraza®). Recent is ook hier *SMN1*-gentherapie (Onasemnogene abeparvovec-xioi, Zolgensma®) en orale risdiplam (Evrysdi®) bijgekomen. In de diverse studies naar het effect van deze nieuwe behandelingen is voornamelijk gekeken naar overleving en het effect op de motorische functie en niet of nauwelijks naar respiratoire verbetering. Dit wordt in elk geval deels verklaard door het gebrek aan gegevens over het natuurlijk beloop van de respiratoire problemen bij SMA.

De tot nu toe gebruikte uitkomstmaten zijn bovendien minder geschikt bij de mildere fenotypen waar de motoriek minder snel achteruitgaat en de overleving niet of beperkt is aangedaan.

De aanwezigheid van het SMA-expertise centrum in het UMC Utrecht en de beschikbare gegevens uit de landelijke database maakte het mogelijk het natuurlijk beloop van de ademhalingsproblemen bij SMA te analyseren.

In Hoofdstuk 2 beschrijven we het natuurlijk beloop van de uitslagen van de conventionele longfunctietesten, verkregen middels spirometrie. Hiervoor werden bijna 2100 longfunctieuitslagen geanalyseerd van 170 patiënten met SMA type 1c-4 tussen de 4 en

74 jaar, die nog geen SMA-specifieke behandeling hadden gehad. Bij patiënten met SMA type 1c-3 werd een progressieve achteruitgang van de FEV_1 (geforceerd expiratoir volume na 1 seconde) en de (F)VC ((geforceerde) vitale capaciteit) op jonge leeftijd gezien, met een relatieve stabilisatie op volwassen leeftijd. De geschatte uitgangswaarden waren duidelijk lager bij de meer ernstige fenotypes, met bijvoorbeeld een VC van 44% bij patiënten met type 1c en een normale VC bij patiënten met type 3b. De gemiddelde jaarlijkse afname van de gemeten uitkomstmaten varieerde ook duidelijk bij vergelijking van de verschillende fenotypes. De beperkte hoeveelheid beschikbare data beschikbaar van patiënten met een mild fenotype (SMA type 3b en 4) toonde in de meeste gevallen een normale longfunctie.

Het probleem bij SMA en andere spierziekten is niet primair pulmonaal, maar is zwakte van de ademspieren. In hoofdstuk 3 beschrijven we daarom specifiek het natuurlijk beloop van de inspiratoire en expiratoire spierkracht, door middel van het meten van de maximale inspiratoire en expiratoire drukken (MIP en MEP; ofwel PImax en PEmax) en de SNIP (snif nasale inspiratoire druk). Recidiverende luchtweginfecties door verminderde hoestkracht is vaak de eerste presentatie van ademspierzwakte bij patiënten met SMA. Om deze reden onderzochten we ook het natuurlijk beloop van de hoestkracht (PCF, peak cough flow) en piek expiratoire flow (PEF). PEF nam lineair af en was verlaagd (< 80% van voorspeld) vroeg op de kinderleeftijd bij patiënten met SMA type1c-2 en tijdens de adolescentie in patiënten met SMA type 3a. We zagen dat de metingen van de ademspierkracht vroeger in het ziektebeloop verlaagd waren, vergeleken met uitslagen van het conventionele longfunctie onderzoek. Bovendien was de ademspierkracht ook verlaagd bij de mildere fenotypes. Alle patiënten, behalve patiënten met SMA type 3b, hadden een verminderde hoestkracht. Hoe ernstiger het fenotype, hoe zwakker de hoestkracht (type 1c: PCF << 160 L/min, type 2a: PCF 160 L/min, types 2b en 3a: PCF 160 - 270L/min). De SNIP was laag bij bijna alle patiënten.

MIP en MEP waren laag in bijna alle patiënten, waarbij de expiratoire spierkracht meer was aangedaan, met een MEP/MIP ratio onder de 1 in alle SMA types op alle leeftijden. Overigens hebben we in Hoofdstuk 1 gekeken naar het verschil tussen uitslagen van de spirometrie in liggende en zittende positie, aangezien bij spierziekten vaak geadviseerd wordt om onderzoek in beide posities te doen, om hiermee een idee te krijgen over de diafragmafunctie, een inspiratoire spier. Bij patiënten met SMA werden geen belangrijke verschillen gevonden in de metingen in verschillende posities, wat bevestigt dat het diafragma relatief gespaard is bij SMA.

Doordat we veel patiënten met SMA op onze polikliniek zagen, viel het ons op dat veel patiënten die nog geen chronische beademing gebruikten een laag-normaal capillair gemeten koolstofdioxide hadden. Dit in tegenstelling tot patiënten met andere

spierziekten. Deze observatie werd bevestigd door retrospectief alle capillaire bloedgassen te analyseren die waren afgenomen tijdens poliklinisch bezoek van SMA patiënten zonder beademing of intercurrente infectie (Hoofdstuk 5). Hierbij zagen we een versnelde stijging naar hoog-normale of verhoogde koolzuur waarden het jaar voorafgaand aan de start van nachtelijke non-invasieve beademing.
In Hoofdstuk 4 hebben we onderzocht of er ook een versnelde achteruitgang van de longfunctie en expiratoire ademspierkracht wordt gezien bij patiënten met SMA kort voor het ontstaan van chronische respiratoire insufficiëntie. Ondersteuning met beademing was nodig bij patiënten met SMA met een ernstige restrictieve longfunctie beperking met een gemiddelde FVC, FEV_1 en PEF van 29-30% van de voorspelde waarden. Gemiddelde jaarlijkse achteruitgang van deze gestandardiseerde longfunctie waarden was 1.7% en er was geen versnelde achteruitgang voorafgaand aan de respiratoire insufficiëntie. MEP was gemiddeld 35 cmH_2O bij start van nachtelijke beademing en relatief stabiel de jaren voorafgaand aan de respiratoire insufficiëntie.

Deel 2: Ondersteunende behandelingen bij patiënten met spierziekten, zoals hoest-ondersteunende technieken en chirurgische correctie van een scoliose

Multidisciplinaire, ondersteunende behandeling is van essentieel belang voor patiënten met spierziekten. Dit omvat onder andere de behandeling van luchtweginfecties, hoest-ondersteunende technieken, adequate voeding en behandeling van deformaties van het skelet zoals scoliose. Internationale richtlijnen adviseren hoest-ondersteunende technieken te starten bij een PCF < 270 L/min of een FVC <50%, maar er wordt geen uitspraak gedaan over keuze van de diverse technieken. Er bestaan verschillende technieken die ofwel de expiratie (manuele compressie), ofwel de inspiratie (bijvoorbeeld air stacken) ofwel beiden ondersteunen (hoestmachine). Deze laatste techniek is veel duurder en wordt in Nederland niet vergoed door de zorgverzekering. De hoestmachine wordt meestal ingezet als andere technieken niet mogelijk zijn of niet het gewenste effect hebben. Hoofdstuk 6 van deze PhD thesis beschrijft in een systematische review de evidence voor dagelijks gebruik van hoestmachine in patiënten met spierziekten. Totaal werden 25 studies geïncludeerd. Studies over het effect op de belangrijkste uitkomstmaat, namelijk het aantal en de ernst van luchtweginfecties, waren zeer beperkt. Er was slechts 1 randomized controlled trial, die de hoestmachine vergeleek met airstacken en geen significnt verschil aantoonde tussen deze technieken, mogelijk door te weinig power en omdat deze studie werd gedaan bij patiënten met ALS. In andere studies werd namelijk gezien dat patiënten met ALS regelmatig averechts reageren op behandeling met een hoestmachine door samenvallen van de luchtweg. De andere 3 studies waren observationele studies die luchtweginfecties de periode voor en na start

van de hoestmachine vergeleken. Hiervan werd bij 1 studie eem significante afname van het aantal opnames in verband met luchtwegifnecties gezien na start van dagelijks hoestmachine gebruik. Bij 2 studies werd een kortere opnameduur gezien in de periode na start van regelmatig hoestmachine gebruik. De meeste studies hadden uitslagen van longfunctie onderzoek als uitkomstmaat. Slechts 2 studies keken naar het effect op de longfunctie op lange termijn. De eerder genoemde randomized controlled trial toonde geen verschil in longfunctie verandering aan tussen de 2 groepen. Een retrospectieve observationele studie in een heterogene groep patiënten toonde een gunstig effect aan op de vitale capaciteit in de periode na het starten van de dagelijkse hoestmachine behandeling.

De meeste studies beschreven echter het onmiddellijke effect (dat wil zeggen direct na hoestmachine behandeling) op diverse longfunctie uitkomstmaten, waarbij dit vaak vergeleken werd met andere technieken of combinaties van technieken. Meta-analyse was alleen mogelijk op het vergelijken van de PCF voor en direct na behandeling met hoestmachine. Dit toonde, zoals verwacht een verbetering van de PCF aan. Of dit effect anders zou zijn indien de patiënten behandeld zouden zijn met air stacken is niet bekend. Resultaten van studies over effect op respiratoire parameters varieerden enorm. Tenslotte beschreven de kwalitatieve studies meest positieve resultaten, wat in elk geval deels beïnvloed wordt door belangrijke bias.

De studies in deze systematic review waren extreem heterogeen qua patiënten, instellingen van de hoestmachine en studie-opzet. De verzamelde evidence voor dagelijks gebruik van de hoestmachine was zeer beperkt.

In de studies naar het onmiddellijke effect van de hoestmachine uit de systematic review, werd niet onderzocht hoe lang een verbetering van de longfunctie aanhield. Om deze reden beschrijven wij in Hoofdstuk 7 het effect tot twee uur na gebruik van de hoestmachine of na het air stacken in patiënten zonder luchtweginfectie, die één van deze technieken dagelijks gebruiken. We zagen een verbetering van FVC en FEV_1 onmiddellijk na gebruik van de hoestmachine of na het air stacken. In de patiënten die de hoestmachine gebruikten, hield dit effect nog een uur nadien aan. Het effect was meer uitgesproken in patiënten met SMA dan in patiënten met Duchenne Spierdystrofie.

Omdat er in de systematische review weinig studies waren over het effect van de hoestmachine op het aantal en de ernst van luchtweginfecties en pediatrische studies sowieso weinig gedaan waren, beschrijven we in Hoofdstuk 8 alle 37 kinderen in ons centrum die dagelijks de hoestmachine gebruik(t)en. Het gemiddelde aantal luchtweginfecties 3 jaar voor inzet van de hoestmachine was hoger dan 3 jaar na inzet van de hoestmachine (3,7 versus 0,9 luchtweginfecties per 1000 bestudeerde dagen).

Nog opvallender was dat het aantal opname-dagen duidelijk minder was in de jaren dat de hoestmachine werd gebruikt, namelijk gemiddeld 2,7 versus 33,6 opname-dagen per 1000 bestudeerde dagen. Patiënten waren erg tevreden met de hoestmachine, hadden het gevoel dat deze infecties voorkomt en raadden deze behandeling andere patiënten aan.

Patiënten met een spierziekte ontwikkelen vaak een scoliose, waarvoor een operatie wordt gedaan om progressie te verminderen, pijnklachten te voorkomen, verzorgbaarheid en zitfunctie te stabiliseren. Conflicterende resultaten worden in de literatuur beschreven over het effect van een scoliose-operatie op de longfunctie. Dit is wel een vraag die we vaak van (ouders van) patiënten in ons spreekuur krijgen. Om deze reden hebben we in Hoofdstuk 9 een prospectieve studie beschreven, waarbij we het effect op de longfunctie beschrijven van een operatie voor een niet-idiopathische scoliose bij 23 kinderen met spierziekten en 20 kinderen met syndromale aandoeningen. Hierbij werd een longfunctie onderzoek gedaan voor de operatie en tijdens de post-operatieve poliklinische controle 3-4 maanden na de operatie. We zagen geen stabilisatie en we konden op basis van deze studie geen uitspraak doen over het effect op de mate van jaarlijkse achteruitgang van de longfunctie.

Deel 3: Exploratie van haalbaarheid en betrouwbaarheid van een alternatieve methode om de longfunctie te meten

Longfunctie onderzoek is belangrijk in de follow-up en behandeling van patiënten met spierziekten. In de toekomst is er mogelijk ook een rol voor longfunctie onderzoek als uitkomstmaat of zelfs voorspeller van het effect van (nieuwe) behandelingen. Conventioneel longfunctie onderzoek middels spirometrie is echter niet mogelijk in jonge kinderen, of in patiënten met een zeer ernstige restrictieve longfunctie beperking. Om deze reden zijn we begonnen om andere technieken te exploreren, die een mogelijk alternatief zijn voor de spirometrie, toepasbaar zijn bij alle patiënten en bij voorkeur niet belastend voor de patiënt zijn. In het laatste hoofdstuk van deze PhD thesis (Hoofdstuk 10) beschrijven we onze eerste ervaringen met het gebruik van oscillometrie. Bij kinderen met spierziekten die in staat waren een betrouwbaar conventioneel longfunctie onderzoek te doen, werd ook oscillometrisch onderzoek verricht. Oscillometrie is een gemakkelijke, niet invasieve techniek waarbij een weerstand R en reactantie X wordt gemeten. Onze hypothese was dat we een hogere R en een lagere X zouden observeren bij meer restrictieve longfunctie beperking. In totaal werden 148 patiënten geïncludeerd. Onze hypothese werd bevestigd met een negatieve correlatie tussen R en de uitslagen van spirometrie, en een positieve correlatie tussen X (dwz minder negatief) en uitslagen van de spirometrie. De relatie tussen oscillometrie en spirometrie was niet linear. Overigens

wordt deze studie op dit moment vervolgd door de patiënten met meerdere metingen over de tijd te vervolgen.

Conclusies van dit proefschrift:

- SMA is een spierziekte, waarbij de expiratoire spieren meer zijn aangedaan dan de inspiratoire spieren.
- Hoe ernstiger het SMA fenotype hoe meer de longfunctie is aangedaan. De geschatte uitgangswaarden waren duidelijk lager bij de meer ernstige fenotypes.
- Bij patiënten met SMA type 1c-3 bestaat een progressieve achteruitgang van longfunctie op jonge leeftijd, met een relatieve stabilisatie op volwassen leeftijd.
- Afname van de ademspierkracht bij patiënten met SMA wordt vroeger in het ziektebeloop geobserveerd dan afname van de conventionele longfunctie uitslagen, gemeten middels spirometrie.
- Ademspier- en hoestkracht is ook verlaagd bij patiënten met mildere SMA fenotypes.
- Patiënten met SMA die nog geen beademing gebruiken hebben een laag-normaal capillair gemeten CO_2. Toename tot hoog-normale waarden kan een waarschuwing zijn voor naderende respiratoire insufficiëntie.
- Op het moment van optreden van chronische respiratoire insufficiëntie waarvoor beademing nodig is hebben patiënten met SMA een ernstig restrictieve longfunctie beperking met een gemiddelde FVC van 29% van voorspeld. Hieraan voorafgaand neemt deze gestandardiseerde FVC jaarlijks 1,8% af, zonder een versnelde afname net voor start beademing.
- Studies naar het effect van de hoestmachine zijn erg heterogeen. De enige evidence die er bestaat is een onmiddellijke verbetering van de PCF na inzet van de hoestmachine.
- De FVC neemt toe onmiddellijk na gebruik van de hoestmachine of na het air stacken bij patiënten die deze behandeling dagelijks gebruiken. Bij patiënten die de hoestmachine gebruiken houdt dit effect nog een uur aan.
- Het effect van air stacken lijkt meer uitgesproken in patiënten met SMA dan in patiënten met Duchenne Spierdystrofie.
- Een afname van het aantal luchtweginfecties en opnameduur wordt gezien bij een cohort kinderen uit ons centrum in de jaren na start van dagelijks hoestmachine gebruik.
- Er werd geen stabilisatie van de longfunctie beperking gezien 3-4 maanden na de operatie van een niet-idopathische scoliose bij kinderen met spierziekten of een syndromale aandoening. Er kan geen uitspraak gedaan worden over het effect van de operatie op de snelheid van achteruitgang van de longfunctie.

- Oscillometrie is mogelijk bij kinderen met spierziekten en er bestaat een niet-lineair verband tussen de uitslagen van de oscillometrie en het conventionele longfunctie onderzoek middels spirometrie: hoe meer restrictieve longfunctie beperking hoe hoger de weerstand R en hoe lager de reactantie X.

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Curriculum vitae

Esther Veldhoen was born on the 22nd of April 1972 in Deventer, The Netherlands.
After graduating from Florens Radewijns College in 1990, she attended Medical School at the KU Leuven in Belgium and obtained her medical degree in 1997 (with distinction).

She started a pediatric training rotation in the United Kingdom (Hull, Birmingham, Manchester) and obtained her Membership of the Royal College of Paediatrics and Childhealth (MRCPCH) in 2000.

She continued her pediatric training in the Sophia Children's Hospital, Erasmus MC under supervision of Prof. dr. A.J. van der Heijden. From 2005 till 2008 she combined a fellowhip pediatric intensive care in the Wilhelmina Children's Hospital under supervision of Prof. dr. A.J. van Vught† and dr. N.J. G. Jansen, with her work as consultant general pediatrics in the same hospital. She started working as a consultant pediatric intensivist in Utrecht in 2009.
In 2014 she obtained her Master Degree in Epidemiology at VU Amsterdam.
Since 2012 she is involved in the care for children with (pending) chronic respiratory failure.

Because of her special interest in this patient group and because a PhD thesis is still required to be able to be responsible for the postgraduate training, she started working on this PhD thesis in 2018.

After obtaining her PhD degree, she will continue her research activities, with the aim to delay chronic respiratory failure in children with neuromuscular diseases.

Esther is married to Uday Sonker and they have 2 children: Juliette (2012) and Christophe (2014).

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