

THE RESPIRATORY MUSCLES OF PATIENTS WITH SPINAL MUSCULAR ATROPHY

The role of fatigability, disease-modifying therapies, and training

Kim Kant-Smits

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The respiratory muscles of patients with spinal muscular atrophy

The role of fatigability, disease-modifying therapies, and training

De ademspieren van patiënten met spinale musculaire atrofie

De rol van vermoeibaarheid, medicatie en training

(met een samenvatting in het Nederlands)

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Kim Smits e/v Kant

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Chapter 1
General Introduction

Part I
Respiratory muscle fatigability



Part II
Disease-modifying therapies

Part III
Respiratory muscle training

Chapter 7+8
General summary and discussion

TABLE OF CONTENTS

Chapter 1	General Introduction	11
Part I: Respiratory muscle fatigability in patients with SMA.		
Chapter 2	Respiratory muscle fatigability in patients with spinal muscular atrophy.	35
Chapter 3	Respiratory muscle activity and fatigue response during respiratory endurance testing in patients with spinal muscular atrophy.	55
Part II: The effect of disease-modifying therapies on lung function and respiratory muscle strength in patients with SMA.		
Chapter 4	The effect of disease-modifying therapies on lung function and respiratory muscle strength in spinal muscular atrophy: systematic review and meta-analysis.	79
Part III: The effect of respiratory muscle training on lung function and respiratory muscle strength in patients with SMA.		
Chapter 5	The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): study protocol for a randomized controlled trial.	119
Chapter 6	The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): results of a randomized controlled trial.	139
Chapter 7	General summary	177
Chapter 8	General discussion	185
Appendices	Nederlandse samenvatting	208
	Abbreviations	214
	List of co-authors	218
	List of publications	220
	Mijn promotie verhaal	221
	Dankwoord	227
	About the author	233



General introduction

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SPINAL MUSCULAR ATROPHY

Epidemiology

Spinal Muscular Atrophy (SMA) is a severe, autosomal recessive neuromuscular disease. SMA is the most common genetic cause of death in children without access to recently introduced disease-modifying therapies. After cystic fibrosis, SMA is humans' second most common autosomal recessive disease.[1] The incidence, i.e., the number of new disease cases in a particular period, is around 1 per 10,000 live births in the Netherlands. This means that each year, approximately 15-20 children are born with SMA.[2] The prevalence, i.e., the number of living individuals with a disease at a given time, is an estimated 1-2 per 100,000 persons.[2] The number of patients with SMA in the Netherlands is probably around 500.[2]

Pathophysiology

SMA is caused by a deletion or mutation of the survival motor neuron (*SMN)* 1 gene.[1] The *SMN1* gene produces the SMN protein. The SMN protein has various functions in all cells. Motor neurons are particularly vulnerable to its deficiency, probably due to their role in cell-specific processes such as development and maturation.[1,3] Humans are unique because they carry a second *SMN* gene, i.e., *SMN2*. Patients with SMA always have one to more than four copies of the *SMN2* gene, in contrast to healthy individuals who may lack the gene without known health consequences. *SMN2* is highly homologous to *SMN1*, but a point mutation causes altered splicing and the exclusion of exon 7 in most transcripts. This causes the production of a mostly shortened and unstable protein. The SMN protein deficiency level and disease severity correlate inversely with *SMN2* copy numbers.[1,3,4] The presence of fewer *SMN2* copies is associated with the most severe phenotypes of SMA.[3]

Phenotype

Decreased SMN protein leads to degeneration of alpha motor neurons in the spinal cord's anterior horns and neuromuscular junction dysfunction, which predominantly appears clinically as proximal muscle weakness, hypotonia, and muscle atrophy.[4] Axial, respiratory, and proximal limb muscles are weakest.[5,6] The severity of the clinical phenotype of SMA is heterogeneous, ranging from a severe to a relatively mild phenotype.[7]

SMA is classified into five types (i.e., types 0-4) based on age at onset and highest acquired motor milestones.[3,8,9] There are additional subclassifications (i.e., 1a, 1b, 1c, 2a, 2b, 3a, and 3b) to capture variability within the phenotypes.[9,10] SMA type 0 is used for infants with prenatal onset, with respiratory insufficiency at or shortly after birth. Without treatment, infants with SMA type 0 will not survive their first months. The onset of SMA type 1 is during the first six months of infancy, and children never learn to

sit. Without treatment, children with SMA type 1 die from respiratory insufficiency on average at the age of 8 months.[10] The onset of SMA type 2 is between 6 and 18 months, and children will learn to sit but not walk independently. Most children with SMA type 2 will experience orthopedic and respiratory complications, but the large majority live into adulthood.[10] The onset in SMA type 3 is after 18 months, with the distinction of SMA type 3a (i.e., onset between 18 months and 3 years) and SMA type 3b (onset after 3 years, but before 18 years). Patients with SMA type 3 can walk unsupported but may lose that ability during adolescence or adulthood. SMA type 4 is generally used for adult onset, and patients have milder motor impairment. Patients with SMA types 3 and 4 have a normal lifespan (**Table 1.1**).[3,8–10] The type of SMA may not be representative of a patient's functional status at a given time. Therefore, patients with SMA are also classified according to their functional abilities, namely non-sitter, sitter, or walker (**Table 1.1**).[9,11]

The first disease-modifying therapy (DMT) for SMA was approved in 2016, and newborn screening for SMA was implemented in the Netherlands in 2022. This changed the SMA landscape significantly. Three different treatment options are available, and infants are now diagnosed and treated before symptoms appear or earlier in the disease course. As a result, individuals achieve more physical milestones and abilities than previously. The traditional classification of SMA can no longer be used for the new generation of (presymptomatic) infants and children.

Symptoms

Muscle weakness

Patients with SMA experience progressive muscle weakness. The proximal and axial muscle groups are weaker than the distal muscle groups.[12–14] Muscle weakness is mostly symmetrical and more pronounced in the triceps, the deltoid, the intercostals, the iliopsoas, and the quadriceps. The strength of the flexors and extensors of the hand and fingers, the biceps, the diaphragm, and the hamstrings is relatively preserved.[14] This distribution of muscle weakness is not fully explained, but some mechanisms are relevant. First, the median motor neuron pools in the cervical and lumbar segments of the spinal cord are more vulnerable to SMN deficiency than the lateral motor neuron pools due to early loss of synaptic connectivity.[13,14] Second, muscles with larger but fewer motor units are probably weaker than those with smaller motor units.[14,15]

Table 1.1: *SMA classification*

SMA phenotype	**0**	**1A**	**1B**	**1C**	**2A**	**2B**	**3A**	**3B**	**4**
Functional classification	Non-sitter								
					Sitter				
							Walker		
Incidence	<1%	50%			30%		10%	9%	<1%
Age at onset	Prenatal	Prenatal	>6 m	>6 m	6-17 m	6-17 m	18-36 m	3-18 y	>18 y
Motor abilities – without DMT	No head control	No head control	No head control or ability to roll	Head control/ ability to roll	May lose sitting ability	Stand or walk with support	Early loss of ambulation	Later loss of ambulation	Walk without support
Survival – without DMT	Few months	Few months	± 8 m	26 m to adulthood	Majority survive into (early) adulthood		Reduced	Not reduced	Not reduced
SMN2 copy number	1	1	2	3	3	3	3-4	3-4	4
Muscle strength and motor function – without DMT	Severely affected, with very limited or no ability to move extremities.				Progressively declines from early childhood. All children become wheelchair-bound and will usually have only some arm/hand functions left during adolescence.		Ambulation usually lost in adolescence or early adulthood.	Median age of loss of ambulation is ≥40 y.	Progressive decline at later ages may occur, but at a very slow speed. Usually stable for decades.
Lung function – without DMT	Paradoxical breathing pattern, tachypnea, weak cough and crying.			Coughing and breathing problems may occur.			Relatively preserved pulmonary function until late into disease course.		
Scoliosis – without DMT	Not present due to short survival.			Presents in nearly all children.			Present in majority of patients.	Present in minority of patients.	Not present.

Abbreviations: DMT: disease-modifying therapy, m: month/months, SMA: spinal muscular atrophy, SMN: survival motor neuron, y: years

Muscle weakness is progressive in all untreated types of SMA; it is not restricted to children or the more severe phenotypes.[14] Muscle strength can be assessed manually, functionally, or mechanically. The strength of muscle groups can be manually evaluated with the Medical Research Council (MRC) sum score, which consists of a 5-point scale and can be used to calculate sum scores.[14] Functional strength can be evaluated with motor function scales, such as the Hammersmith Functional Motor Scale Expanded (HFMSE). This scale consists of 33 items that can be scored from 0 to 2, resulting in a total score ranging from 0 to 66.[14] From natural history studies in untreated patients with SMA, we know that muscle strength declines by an estimated 1 MRC point and 0.5 HFMSE point per year.[14] The effects of losing just a few points on the MRC or the HFMSE each year may not seem important at first, but over time, it impacts a person's ability to do daily activities.

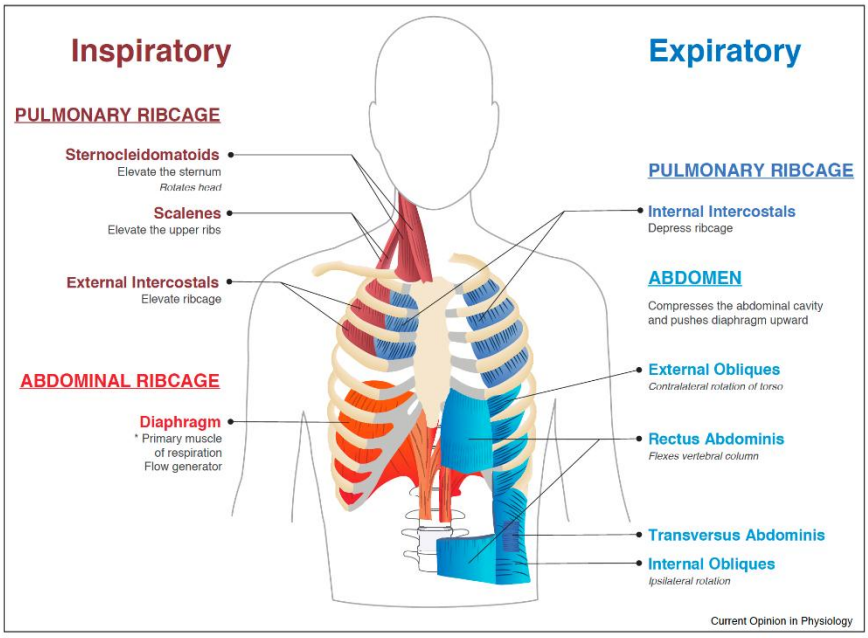


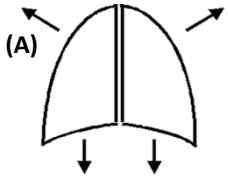
***Figure 1.1**: Respiratory muscles and their function.*[16]

Respiratory function and dysfunction

The respiratory muscles can be categorized into three main groups: the diaphragm, ribcage, and abdominal muscles (**Figure 1.1**).[16–18] During tidal (resting) breathing in an upright position in healthy persons, the diaphragm contributes 70% and the intercostal muscles 30% of the tidal volume.[16,18] During resting inhalation, the diaphragm contracts and moves caudally towards the abdomen. At the same time, the external intercostal muscles raise the anterior chest wall. This creates a negative pressure in the lungs, allowing air to flow into the lungs. The pressure increases to zero as the lungs fill to the

full capacity of the tidal volume.[16] Resting exhalation is a primarily passive process. The diaphragm relaxes and moves cranially towards the chest cavity. The elastic recoil of the chest wall and lung tissue creates a positive pressure, which decreases towards zero as the volume is exhaled.[17,18]

In patients with SMA, respiratory muscle weakness is characterized by a unique pattern of predominant weakness of the expiratory and intercostal muscles, while the diaphragm is relatively spared.[19] Therefore, inhalation relies mainly on the diaphragm. If the diaphragm contracts, it generates a negative intrathoracic pressure. The external intercostal muscles can be too weak to participate in inspiration and counteract the diaphragm's contraction. Because of this, the upper part of the rib cage moves abnormally inwards, creating a paradoxical breathing pattern, a bell-shaped chest, and a pectus excavatum (**Figure 1.2**).[12,20]



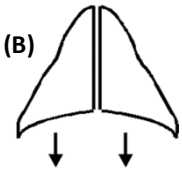


***Figure 1.2**: (A) Normal lungs vs (B) lungs of a patient with SMA.[12]*

Cough is a natural defense mechanism that protects the respiratory tract from inhaling foreign bodies and clears excessive bronchial secretions.[21] The first coughing phase involves a wide opening of the glottis and a deep inhalation. The second phase involves a prompt closure of the glottis and a strong contraction of the abdominal and other expiratory muscles, resulting in an increased intrapulmonary pressure. The third phase involves a sudden opening of the glottis, causing the explosive exhalation of air from the lungs to the outside.[21]

In patients with SMA, respiratory muscle weakness causes three distinct but interrelated problems: inspiratory muscle weakness, expiratory muscle weakness, and upper airway muscle weakness. Combined, this leads to alveolar hypoventilation (**Figure 1.3**).[22]

Inspiratory muscle weakness changes the mechanics of breathing. Inspiratory muscle weakness limits achieving the total lung capacity, which increases the elastic load of the chest and the work of breathing, eventually leading to ventilatory failure. Additionally, disuse of the musculoskeletal system can cause muscle atrophy, osteoporosis, and contractures, all contributing to a stiffened chest wall in adults with neuromuscular diseases.[22] An additional problem is that children with SMA often develop kyphoscoliosis due to axial muscle weakness. Kyphoscoliosis causes chest wall stiffness and, therefore, a mechanical disadvantage. The mechanical disadvantage increases the respiratory load on the already weakened respiratory muscles.[22]

Inspiratory muscle weakness decreases the tidal volume (Vt). To keep the minute volume (the total amount of air breathed in one minute, i.e., Vt times frequency) constant, the patient tries to compensate for this by increasing the breathing frequency. However, as the respiratory muscle weakness progresses, the Vt and the minute volume become insufficient for the patient's needs. This results in the progressive development of alveolar hypoventilation with hypoxemia (low oxygen levels) and hypercapnia (high carbon dioxide levels) (**Figure 1.3**).[20,22]

Upper airway muscle weakness impairs speech and swallowing. Dysfunction of the lips, tongue, pharyngeal, and laryngeal muscles causes drooling and difficulties closing the glottis. These problems together increase the risk of aspiration pneumonia (**Figure 1.3**).[22]

In combination with inspiratory muscle weakness and impaired glottis function, expiratory muscle weakness causes severe impairment of the ability to clear airway secretions.[22,23] The reduced cough strength and poor secretion clearance trigger the vicious circle of 1) recurrent respiratory tract infections, 2) decline of vital capacity and cough strength, 3) alveolar hypoventilation, and 4) further reduction in chest wall and lung compliance (**Figure 1.3**). Eventually, this can lead to respiratory failure and premature death.[24–26]

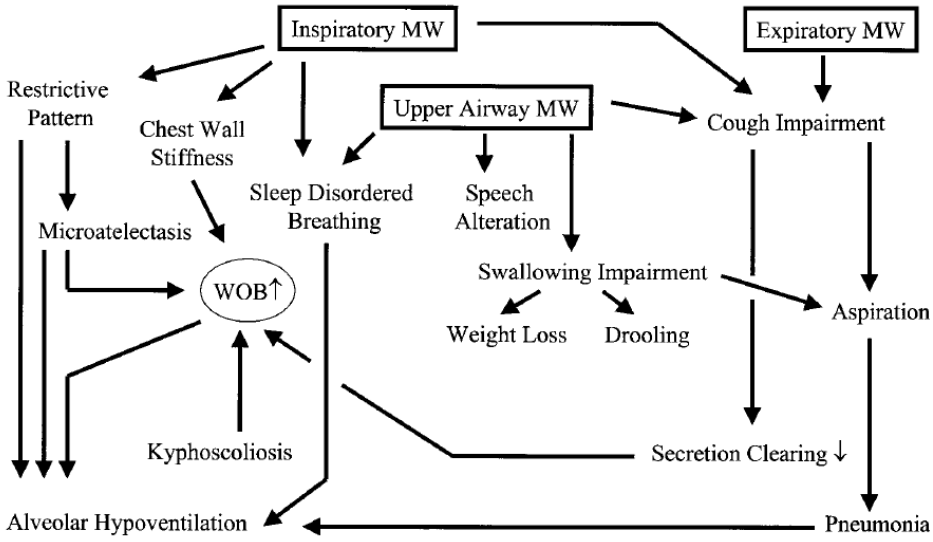


***Figure 1.3**: Schematic representation of the pathologic consequences of progressive respiratory muscle weakness affecting the three major respiratory muscle groups and chest wall.*[22]

Abbreviations: MW: muscle weakness, WOB: work of breathing.

Performance fatigability

In addition to muscle weakness, fatigability is an important impairment of daily life functioning in patients with SMA. Fatigue can be divided into perceptions of fatigue and performance fatigability. Perceptions of fatigue refer to subjective sensations such as feelings of tiredness, a growing sense of effort, a mismatch between the effort put in and actual performance, or feelings of exhaustion.[27] In contrast, fatigability refers to objective changes in performance and is defined as the inability to continue a task at the same intensity, resulting in a decrease in one or more aspects of physical performance, such as peak force and power.[27–29]

Patients with SMA experience performance fatigability during tasks of daily life, such as prolonged (power)wheelchair driving, lifting an arm during eating, chewing food, or walking.[28,29] The factors that cause performance fatigability can be divided into peripheral and central factors.[27] Peripheral factors include changes in the muscle, the neuromuscular junction (NMJ), and peripheral nerves. Peripheral factors can be divided into contractile factors (changes in the muscles) and activating factors (changes in the signal transport system, such as the motor nerves or NMJ).[27,30] Peripheral fatigability is due to a failure of muscle fibers to respond maximally during full activation.[18] Central factors include changes in the brain and nervous system. Central fatigability is due to a failure to recruit all muscle fibers.[18] The pathophysiology of performance fatigability in patients with SMA is complex and can vary between patients. Particularly, the motor unit seems vulnerable to performance fatigability, as abnormalities of the motor neuron, neuromuscular junction, and muscle have been reported in patients with SMA.[31,32] In a previous study, 85% of patients with SMA demonstrated increased fatigability of leg, arm, and hand muscles.[28,33]

In untreated patients with SMA, respiratory failure is the most important cause of morbidity and mortality.[5,34] Respiratory failure is primarily due to respiratory muscle weakness, resulting in impaired cough and poor clearance of the lower airway secretions. However, respiratory muscle fatigability (RMF) may also contribute to the development of respiratory failure.[35] RMF can occur in pathological conditions like chronic obstructive pulmonary disease or amyotrophic lateral sclerosis, as well as in healthy individuals during periods of increased respiratory effort, such as intense physical exercise.[35] RMF has not yet been studied in patients with SMA. More insight into RMF in SMA will facilitate clinical management, aiming to reduce respiratory failure in patients with SMA.

DIAGNOSTICS

Assessment of respiratory (lung) function and respiratory muscle strength

Respiratory function and strength assessment are essential to understand and monitor the involvement of different respiratory muscles in patients with SMA. Early-stage dysfunction of the respiratory muscles can be difficult to detect clinically; therefore, objective measures are essential. The test results and the progression of respiratory muscle function and strength over time can help provide the appropriate treatment.[36]

Respiratory function

Spirometry is the most widely used noninvasive test of respiratory function. Spirometry is the timed measurement of dynamic lung volumes and capacities during forced expiration and inspiration to quantify how effectively and quickly the lungs can be emptied and filled. Often used measurements are the vital capacity (either forced (FVC) or unforced (VC)) and the forced expiratory volume in 1 second (FEV1) (**Figure 1.4**).[37]

FVC is the maximum volume (in liters) forcefully exhaled after maximal inspiration (**Figure 1.4**). A declined FVC is often seen in restrictive lung diseases. Natural history studies in patients with SMA show that FVC in % of predicted shows large variability at the first available measurements of the patients (50% in SMA type 1C, 64% in type 2a, 85% in type 2b, 97% in type 3a, and 109% in type 3b).[34] Most patients with SMA show a decline in FVC with increasing age, with the fastest progression during childhood, followed by a relative stabilization during adulthood in SMA type 1c-3a.[34] The risk of pulmonary complications increases as FVC decreases, with a significant rise in risk for patients with an FVC below 30% of predicted.[38]

Weak patients may be unable to do forced maneuvers. VC is the maximum volume (in liters) slowly exhaled after maximal inspiration and can be reliably measured in almost all weak patients.[19,36,39] A declined VC is often seen in restrictive lung diseases. Significant respiratory muscle weakness can be excluded when VC is within the normal range. In subjects with diaphragm weakness, VC falls when the patient is supine, although this fall must exceed 25% to be abnormal.[36] Natural history studies in patients with SMA show that VC in % of predicted shows similar patterns to FVC.[34]

FEV1 is the maximum volume (in liters) forcefully exhaled during the first second after maximal inspiration (**Figure 1.4**). A declined FEV1 is often seen in obstructive lung diseases. Natural history studies in patients with SMA show that FEV1 in % predicted follows the same pattern as FVC. Significant differences in FEV1 between SMA types are already present at the first available measurements of the patients. Patients with SMA show a yearly decline of 0.2-2% in FEV1 during childhood and adolescence. During adulthood, FEV1 remains relatively stable.[34]

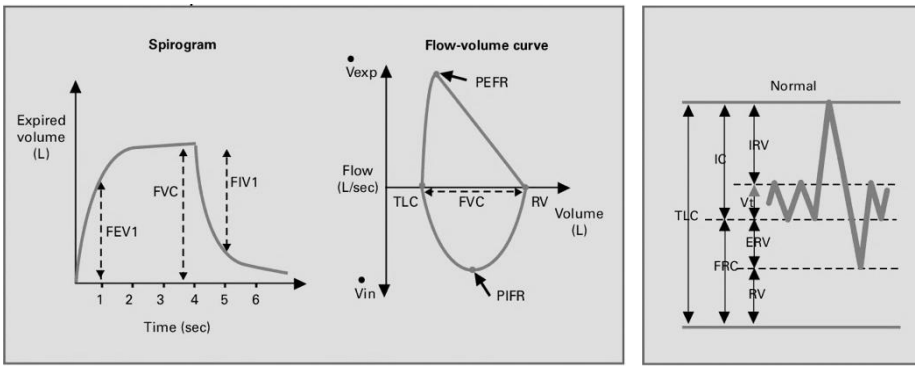


Figure 1.4: *Normal spirogram, flow-volume curve, and lung volumes and capacities showing the conventional measurements made with spirometry.*[37]

Abbreviations: ERV: expiratory residual volume, FEV1: forced expiratory volume in 1 second, FIV1: forced inspiratory volume in 1 second, FRC: functional residual capacity, FVC: forced vital capacity, IC: inspiratory capacity, IRV: inspiratory residual volume, L: liter, PEFR: peak expiratory flow rate, PIFR: peak inspiratory flow rate, sec: seconds, RV: residual volume, TLC: total lung capacity, Vexp: expiratory volume, Vin: inspiratory volume, Vt: tidal volume.

Respiratory muscle strength

Maximum inspiratory mouth pressure (PImax) reflects inspiratory muscle strength and is assessed using a manometer connected to a mouthpiece. The patient is asked to exhale to residual volume and then maximally inhale against an occluded airway. The maximum negative pressure generated after 1 second is recorded as the PImax.[36,39,40] Inspiratory muscle weakness is present in adults if PImax is below 80 centimeters of water pressure (cmH_2O) in men and below 70 cmH_2O in women.[40,41] Natural history studies in patients with SMA showed large intra- and inter-individual differences in PImax, also seen in healthy persons. A sufficient explanation is not yet available, although it is likely that much of the variability reflects the different musculature of individuals.[42] Overall, patients with types 1c and 2a had a PImax below 80 cmH_2O, whereas patients with SMA types 2b, 3a, and 3b mostly had a PImax above 80 cmH_2O.[43]

Maximal expiratory mouth pressure (PEmax) reflects expiratory muscle strength and is assessed using a manometer connected to a mouthpiece. The patient is asked to inhale to total lung capacity and then maximally exhale against an occluded airway. The maximum positive pressure generated after 1 second is recorded as the PEmax.[36,39,40] Expiratory muscle weakness is present in adults if PEmax is below 80 cmH_2O.[41] Natural history studies in patients with SMA show PEmax is more affected than PImax. All patients with SMA had a PEmax below 80 cmH_2O, with the most severely affected patients around 30 cmH_2O and the less affected patients around 60 cmH_2O.[44]

The sniff nasal inspiratory pressure (SNIP) is a more natural maneuver and, therefore, easier to perform than maximal mouth pressures. The SNIP is the nasal

pressure in an occluded nostril during a maximum sniff performed from functional residual capacity through the contralateral nostril.[36,39,40] Values in healthy children aged 6–17 years are similar to those in healthy adults, with a mean SNIP of 104±26 cmH_2O in boys and 93±23 cmH_2O in girls.[36] 75 cmH_2O is considered the lower limit of normal. Natural history studies in patients with SMA show that almost all patients with SMA had an SNIP below 75 cmH_2O.[43]

The ability to cough requires coordinated use of inspiratory, bulbar, and expiratory muscles. Cough effectiveness can be assessed by measuring peak cough flow (PCF). PCF is the maximum flow (liters/minute) produced during a forceful cough.[39,40] Adults, and likely children over 12 years old, with a PCF below 270 l/min, are at risk of respiratory failure during otherwise minor viral respiratory tract infections due to secretion retention. Additionally, adults and children over 12 years old with a PCF below 160 l/min are unable to clear their airway secretions effectively.[19,39,40] Natural history studies in patients with SMA show that PCF was lowest in patients with SMA type 1c, with values <160 l/min throughout life. Patients with SMA type 2a had a PCF of around 160 l/min, while patients with SMA type 2b and 3a had a PCF between 160 and 270 l/min.[43]

Assessment of fatigability

Bartels et al. developed and validated fatigability assessments that can be used across the severity spectrum of SMA.[29] The Endurance Shuttle Walk test was adapted to test leg muscle fatigability, the Endurance Shuttle Box and Block test for upper arm muscles, and the Endurance Shuttle Nine Hole Peg test for lower arm muscles. All tests simulate daily activities, involve submaximal effort with repetitive actions over a longer period, and have a regulated pace. These tests were found to be reliable and valid for documenting fatigability in SMA patients. 73% of ambulatory patients showed increased fatigability in the Endurance Shuttle Walk test, 80% of patients with SMA type 3a in the Endurance Shuttle Box and Block test, and 73% of patients with SMA type 2 in the Endurance Nine Hole Peg test.[29]

Respiratory endurance test (RET)

Respiratory muscle fatigability (RMF) can be measured with a respiratory endurance test (RET), designed using the same construct. The RET is executed at a percentage of the patients' PImax.[35,40,45] RMF is the inability to continue for 60 consecutive breaths, resulting in decreased PImax and increased perceived exertion.[35,45] In patients with Duchenne muscular dystrophy (DMD), RMF could be induced with a RET at 35% of their PImax.[45] The healthy controls in the same study were able to breathe for more than 30 minutes against 35% of their PImax.[45] In healthy individuals, RMF could be induced with a RET at 60-80% of PImax.[35] It is unclear at which percentage of PImax RMF can be induced in patients with SMA.

Surface electromyography (sEMG)

Changes in electromyograms can be used to measure physical fatigability in humans. There are two types of electromyography (EMG): intramuscular EMG and surface EMG (sEMG).[30] The reference standard for measuring the diaphragms' electrical activity is intramuscular EMG.[46] This invasive method causes discomfort and is not suitable for patients with impaired swallowing function or domiciliary ventilation.[46] sEMG is a non-invasive technique to measure the electrical activity of the diaphragm and other respiratory muscles. Electrodes are placed on the skin overlying the muscle of interest. When a muscle contracts, it generates electrical activity known as action potentials. The electrodes capture this activity, which is then amplified and recorded as an EMG signal. The signal reflects the sum of all the action potentials occurring in the muscle fibers beneath the electrode.[47]

sEMG recordings from respiratory muscles during a RET may provide insight into the mechanism underlying performance fatigability.[48] During the early stages of muscle fatigability, the root mean square (RMS) amplitude often increases. This increase reflects greater muscle activation as the nervous system recruits more motor units or increases the firing rate of existing motor units to maintain the required force. The RMS may decrease or plateau if the muscle cannot sustain the required force.[47,48] The median frequency (MF) tends to decrease as the muscle fatigues.[30,47,48] Several factors contribute to this decrease. First, the conduction velocity of action potentials along the muscle fibers decreases, contributing to the lower frequency components of the EMG signal. Second, fatigue can lead to greater synchronization of motor units, which also shifts the power spectrum toward lower frequencies. Third, the accumulation of metabolic byproducts like lactic acid during fatigue can alter muscle fiber properties, further contributing to the frequency shift.[47]

In patients with SMA, sEMG from the upper and lower extremity muscles during endurance tests is used to investigate the availability of motor unit reserve capacity.[48] Decreasing MF and increasing RMS during endurance tests at submaximal performance intensities revealed motor unit reserve capacity in individual patients with SMA.[48] sEMG has not yet been used on the respiratory muscles in patients with SMA. More knowledge of the activation and fatigability response of the respiratory muscles in patients with SMA can provide tools to find the best way to train these muscles.

TREATMENT

Treatment of respiratory problems in patients with SMA aims to normalize gas exchange, improve sleep quality, facilitate home care, reduce hospitalizations and intensive care unit care, and reduce the burden of illness on the patients and their families.[5,12]

Airway clearance techniques

Airway clearance techniques include postural drainage, manually assisted cough, air stacking, mechanical insufflation-exsufflation, and oral suctioning.[5,12,20,22,49] Mechanical insufflation-exsufflation is often initiated when air stacking is impossible, for example, in young children, or when air stacking is no longer effective.[49,50] Air stacking and mechanical insufflation-exsufflation improve FVC immediately after treatment, but it is unclear if using air stacking and mechanical insufflation-exsufflation reduces the number of respiratory tract infections and associated hospital admissions.[49]

(Non)invasive ventilation

Nocturnal hypoventilation, obstructive sleep apnea, respiratory failure during a viral respiratory infection, recurring pneumonia or atelectasis, postoperative care, or a chest wall deformity can be indications for respiratory support. Respiratory support can be noninvasive ventilation or invasive ventilation with tracheostomy. The short-term goals of noninvasive ventilation include respiratory symptom relief, reducing the work of breathing, improving or stabilizing gas exchange, improving sleep quality, enhancing quality of life, and decreasing the risk of pulmonary complications. The long-term goals of noninvasive ventilation include decreasing the number of hospitalizations, postponing the need for a tracheostomy, and prolonging survival.[12,20,22]

Disease-modifying therapies

Since 2016, four important clinical trials have led to the approval of disease-modifying therapies (DMTs): Nusinersen, Onasemnogene abeparvovec, and Risdiplam for the treatment of SMA.[3]

Nusinersen (Spinraza) is an antisense oligonucleotide drug that modifies the splicing of *SMN2* ribonucleic acid. This increases the production of functional SMN protein.[3] Nusinersen is delivered intrathecally at a dose of 12 mg, with a loading scheme of four doses followed by a dose every 4 months. The US Food and Drug Administration (FDA) approved Nusinersen for patients of all ages with SMA in December 2016, and the European Medicines Agency (EMA) in June 2017.[3] In the Netherlands, Nusinersen is reimbursed for patients who are younger than 9.5 years at the start of treatment and conditionally available for older patients. The condition requires patients to participate in an efficacy study of Nusinersen. Clinical trial data and real-world data have shown that treatment with Nusinersen improves motor function and event-free survival (defined as time to death or use of permanent assisted ventilation).[3,51] An early start of treatment results in better outcomes, and the main changes in motor function were observed within the first 14 months of treatment. Data on respiratory and bulbar function have not been documented in detail.[3,51]

Onasemnogene abeparvovec (Zolgensma) is an adeno-associated virus serotype 9-based gene therapy delivering a functional copy of the *SMN1* gene into the

cells of the central nervous system.[3] Onasemnogene abeparvovec is delivered intravenously with a single dose of 1.1 x 10^{14} vector genomes per kg. The FDA approved Onasemnogene abeparvovec as a one-time treatment for patients under 2 years of age with SMA in May 2019. The EMA approved Onasemnogene abeparvovec for all patients with a biallelic mutation in *SMN1* and a clinical diagnosis of SMA type 1 or up to three *SMN2* copies in June 2020.[3] In the Netherlands, Onasemnogene abeparvovec is available for children with SMA type 1 and pre-symptomatic children with up to three copies of the *SMN2* gene. Real-world data indicate that treatment with Onasemnogene abeparvovec improves motor function in children with SMA aged 24 months or younger. Patients with SMA type 1 might still need respiratory and nutritional support after receiving Onasemnogene abeparvovec.[3]

Risdiplam (Evrysdi) is a small-molecule *SMN2* splicing modifier that promotes the inclusion of exon 7 and increases the production of functional SMN protein.[3,52] Risdiplam is administered daily as an oral dose of 5 mg (6.6 ml). The FDA approved Risdiplam for treating patients with SMA older than two months in 2020 and for patients of all ages in 2022. The EMA approved Risdiplam for SMA types 1, 2, or 3 with up to four copies of *SMN2* above the age of two months in 2021 and for people of all ages in 2023.[3] In the Netherlands, Risdiplam is available for patients with SMA type 1, 2, or 3 aged 2 months to 25 years and for presymptomatic children with 1 to 4 copies of the *SMN2* gene. Clinical trial data suggest that Risdiplam is safe, effective, and has the potential to achieve restoration of bulbar and respiratory function.[3]

Commonly used respiratory outcomes to assess the efficacy of DMTs include the need for ventilatory support and the incidence of respiratory failure.[53–56] Although these are important outcome measures of morbidity and mortality in patients with SMA, they also depend on many other factors, such as respiratory tract infections, the absence of criteria for starting or ceasing noninvasive ventilation, and individual treatment center practices. To better understand the effect of DMTs on respiratory outcomes, more direct and standardized outcome measures, such as lung function and respiratory muscle strength, should be evaluated. There is a need to systematically identify, evaluate, and summarize the findings of studies concerning the effect of DMTs on lung function and respiratory muscle strength in patients with SMA.

Pyridostigmine

In addition to DMTs, pyridostigmine can be used to reduce fatigability in patients with SMA.[57] Pyridostigmine is an acetylcholinesterase inhibitor of the natural enzymatic breakdown of acetylcholine and increases its biological availability at the NMJ, enhancing neuromuscular transmission.[6] The effect of pyridostigmine has been examined in a phase 2 study in patients with SMA types 2-4. There was a significant positive effect on experienced endurance performance, and patients showed a 70% reduced risk of endurance shuttle test failure under pyridostigmine.[57] Pyridostigmine is

administered orally four times a day because of the short half-life of pyridostigmine, leading to an effect duration of ~4–6 hours.[57] Pyridostigmine is an FDA and EMA-approved first-line treatment widely used for disorders affecting NMJ transmission, in particular, myasthenia gravis.[57] The effect on the respiratory muscles is still unknown.

Respiratory muscle training

In patients with SMA, the reduced chest wall and pulmonary compliance increase the mechanical load on the weakened respiratory muscles. The imbalance between increased mechanical load and the capacity of the respiratory muscle may lead to fatigue and respiratory failure.[22] Respiratory muscle training (RMT) may be a possible therapy for people with suspected or confirmed respiratory muscle weakness.[58] RMT aims to increase the strength or endurance of respiratory muscles. RMT can be classified into inspiratory muscle training (IMT) and expiratory muscle training (EMT).[58] The respiratory muscles are morphologically and functionally skeletal muscles, so they respond to training in the same way as any muscle of the locomotor system.[59] Thus, the following principles apply to RMT: 1) specificity, 2) intensity, 3) frequency, 4) duration, and 5) reversibility.

1) Specificity means that the training must be specific to the muscles being trained. Training at a high load and with a low speed of muscle contraction is generally used to increase muscle strength. Strength training will increase the number and volume of the muscle fibers (hypertrophy). Training at a low load and with a high speed of muscle contraction is generally used to increase muscle endurance. Endurance training will increase the number of oxidative fibers and capillary density.[58–60]
2) Intensity means that the exercise load must be greater than the current muscular capacity and, therefore, must be adjusted during the training. A training load of >22% of the patients' PImax should be able to improve the inspiratory muscle endurance, while a training load of at least 30% of the patients' PImax should be able to improve the inspiratory muscle strength.[58,60]
3) The frequency and 4) duration of the training sessions determine how much and how quickly the muscles respond to the training.[58,60]
5) Reversibility means that the effect of the training will be lost if the training stops.[58–60] Reducing the training frequency, while keeping the training intensity constant, can help maintain the achieved training effect.[59]

A systematic review in 2019 summarized the known effects of RMT in patients with neuromuscular diseases (NMD).[58] It included 11 studies involving 250 people with NMD. Three trials involved people with amyotrophic lateral sclerosis. Seven trials involved people with myopathies: Duchenne muscular dystrophy, limb-girdle muscular dystrophy, and Becker muscular dystrophy. One trial involved people with myasthenia gravis. Eight

studies assessed IMT, with different training loads and frequencies. Two studies assessed EMT, and one study assessed a combined RMT (strength and endurance training). RMT was compared with sham training, no training, or breathing exercises. The review found low-certainty evidence that RMT may improve lung capacity and respiratory muscle strength in some NMDs. The quality of the current evidence is low, and there is an urgent need for well-conducted randomized controlled trials in people with NMDs that cause impairment of the respiratory muscles (like SMA) to evaluate the clinical benefit of RMT.[58]

Little is known about RMT in patients with SMA. Only one pre-experimental study assessed the safety and feasibility of IMT in eight children with NMD, including three with SMA.[61] This study concluded that IMT (at an intensity of 30% of PImax, twice a day, 5 days a week, 30 breaths per session) was safe, feasible, and acceptable. RMT increased PImax and peak inspiratory flow, and it subjectively improved function and quality of life.[61] RMT can be a promising treatment in patients with SMA, but the effects of RMT in patients with SMA have as yet not been studied systematically.

AIMS AND OUTLINE OF THIS THESIS

In patients with SMA, progressive respiratory muscle weakness is an important cause of morbidity and mortality. However, a great part of the impact of SMA and treatment on the respiratory muscles is still unknown. Fatigability seems to be a major problem in the arm and leg muscles of patients with SMA, but what about fatigability of the respiratory muscles? DMTs appear to positively affect survival, motor function, and functional strength in patients with SMA, but what about their effect on the respiratory muscles? Additionally, respiratory muscle training seems to affect the strength of the respiratory muscles positively, but does that also apply to patients with SMA?

Therefore, the aims of this thesis are:

1. To study **respiratory muscle fatigability** in patients with SMA.
   In **Chapter 2**, we explore respiratory muscle fatigability (RMF) in patients with SMA types 2 and 3. We use a respiratory endurance test (RET) at a percentage of the patients' maximal inspiratory mouth pressure to detect RMF.

   In **Chapter 3**, we explore the muscle activity of the diaphragm, scalene muscles, and intercostal muscles during a RET in patients with SMA types 2, 3a, and 3b. We use surface electromyography on the respiratory muscles to measure the muscle activity at the onset of the RET and the fatigability responses during the RET.

2. To study the effect of **disease-modifying therapies** on lung function and respiratory muscle strength in patients with SMA.

   In **Chapter 4**, we perform a systematic review and meta-analysis of studies that documented the effects of disease-modifying therapies on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, and 4.

3. To study the effect of **respiratory muscle training** on lung function and respiratory muscle strength in patients with SMA.

   In **Chapter 5**, we describe the study protocol of the 'RESISTANT' study (respiratory muscle training in patients with SMA).

   In **Chapter 6**, we describe the results of the RESISTANT study. In this study, we investigate the efficacy and feasibility of respiratory muscle training in patients with SMA types 1, 2, 3, and 4, aged 8 years and older, and with respiratory muscle weakness.

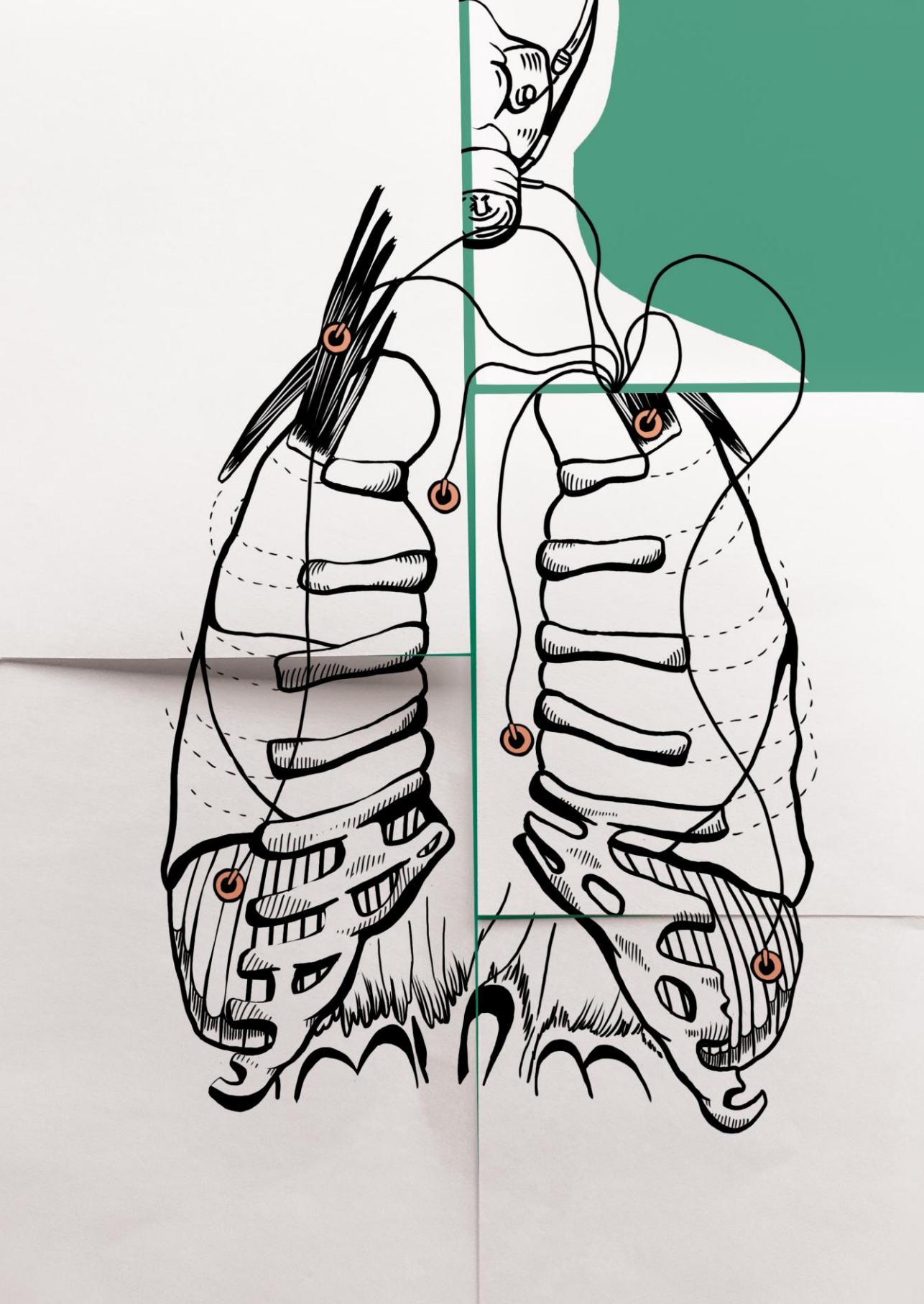
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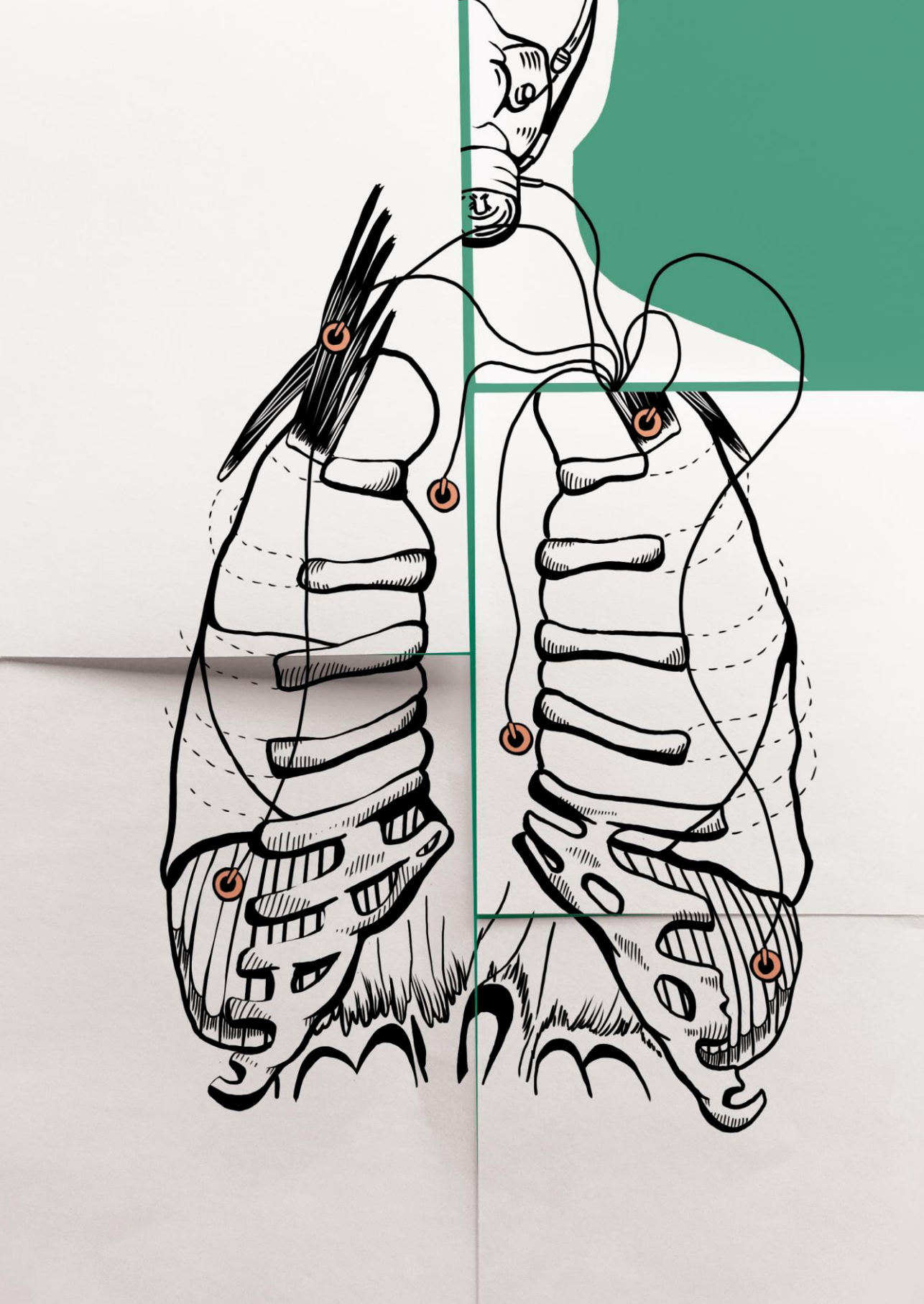
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Part I

Respiratory muscle fatigability in patients with SMA.



Chapter 2

Respiratory muscle fatigability in patients with spinal muscular atrophy.

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ABSTRACT

Background

Respiratory failure is a major cause of morbidity and mortality in patients with spinal muscular atrophy (SMA). Lack of endurance, or "fatigability," is an important symptom of SMA. In addition to respiratory muscle weakness, respiratory function in SMA may be affected by respiratory muscle fatigability (RMF).

Aim

The purpose of this study was to explore RMF in patients with SMA.

Methods

We assessed a respiratory endurance test (RET) in 19 children (median age [years]: 11) and 36 adults (median age [years]: 34) with SMA types 2 and 3. Participants were instructed to breathe against an inspiratory threshold load at either 20%, 35%, 45%, 55%, or 70% of their individual maximal inspiratory mouth pressure (PImax). RMF was defined as the inability to complete 60 consecutive breaths. Respiratory fatigability response was determined by a change in maximal inspiratory mouth pressure (ΔPImax) and perceived fatigue (Δperceived fatigue).

Results

The probability of RMF during the RET increased by 59%−69% over 60 breaths with every 10% increase in inspiratory threshold load (%PImax). Fatigability response was characterized by a large variability in ΔPImax (−21% to +16%) and a small increase in perceived fatigue ($p = 0.041$, range 0 to +3).

Conclusion and key findings

Patients with SMA demonstrate a dose-dependent increase in RMF without a severe increase in exercise-induced muscle weakness or perceived fatigue. Inspiratory muscle loading in patients with SMA seems feasible, and its potential to stabilize or improve respiratory function in patients with SMA needs to be determined in further research.

Keywords

fatigue, respiratory endurance test, respiratory muscle strength, SMA

INTRODUCTION

Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by a homozygous deletion of the survival motor neuron-1 gene[1–3], which leads to cellular survival motor neuron (SMN) protein deficiency. SMA has an incidence of about 1 in 6000−12,000 live births.[4] It is characterized by a wide range of disease severity and is classified into 4 types based on age at onset and highest acquired motor milestone.[2,3,5–8] Childhood-onset SMA types 2, 3a, and 3b are characterized by delayed gross motor development and progressive loss of motor function and muscle strength.[3,9–11] SMA type 2 has its onset between 6 and 18 months, and patients acquire the ability to sit, but not to stand or walk. SMA type 3a has its onset between 18 months and 3 years, the ambulation is usually lost in adolescence or early adulthood, whereas patients with SMA type 3b, onset after the age of 3 years, lose their ability to walk at a median age of 40 years.[9,11]

In the last few years, SMN-augmenting genetic therapies have been introduced, including *SMN*-gene therapy and therapies that modify *SMN*2-splicing.[12] Efficacy studies have demonstrated, on average, favorable responses in motor function, survival, and muscle strength, but the respiratory outcomes vary, with most studies showing no significant improvement in lung function parameters in patients with SMA types 2 and 3.[13–16]

Respiratory failure is the most important cause of morbidity and mortality in patients with SMA.[11,17] In SMA, it is primarily due to a decrease in respiratory muscle strength (i.e., muscle weakness), resulting in an impaired cough and poor clearance of lower airway secretions.[11,17] The respiratory muscle weakness is most pronounced in the intercostal muscles, while the diaphragm remains relatively spared.[3]

In addition to respiratory muscle weakness, respiratory dysfunction in SMA may be caused by a lack of endurance of respiratory muscles, also known as increased respiratory muscle fatigability (RMF).[18,19] Fatigability is defined as the inability to continue a task at the same intensity, resulting in a decline in one or more aspects of physical performance, such as peak force and power.[6,20,21] In a previous study, we showed that 85% of patients with SMA demonstrated increased fatigability of leg-, arm-, and hand function.[7,20] Fatigability of the respiratory muscles has not yet been studied in patients with SMA. More insight into respiratory muscle weakness, especially RMF in SMA, will facilitate clinical management with the aim of reducing respiratory failure in patients with SMA.

In this study, we explored the feasibility of inspiratory muscle loading, the dose-response relationship between inspiratory load and RMF, and the fatigability response to RMF in patients with SMA types 2-3.

METHODS

This observational study is part of a large cross-sectional study on fatigability in SMA.[6,7] To ensure an accurate and complete report of our work, we followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[22]

Ethical considerations

The Medical Ethical Committee of the University Medical Centre Utrecht approved the research protocol (NL48715.041.14). The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The criteria of the Dutch Association of Pediatrics concerning research involving children were strictly applied. All participants and all parents or legal guardians of adolescents below the age of 18 years signed informed consent.

Participants

We recruited patients with SMA from the Dutch national SMA registry.[8] Patients aged 8-60 years with a genetically confirmed diagnosis of SMA type 2, 3a, or 3b and the ability to follow test instructions were considered for inclusion. Patients with concomitant medical problems that might have intervened with the outcomes of the testing were excluded. Patients were also excluded if they had a history of neuromuscular diseases or the use of medication that affects neuromuscular junction function, medical conditions incompatible with exercise, or the inability to perform any of the endurance tests. Strenuous physical activities the day before each visit to the hospital were discouraged.

Study procedures

We explored RMF with a respiratory endurance test (RET) executed at a percentage of the patients' maximal inspiratory mouth pressure (PImax). RMF was defined as task failure (TF) on a RET and expressed in the number of breaths until exhaustion.[6,21,23,24] Fatigability response was determined by change in maximal inspiratory mouth pressure (ΔPImax) and change in perceived fatigue (Δperceived fatigue) before and after the RET.[24,25]

Participants were included between March 2015 and March 2018. The measurements were performed at three different visits within approximately six weeks. We obtained demographics and clinical characteristics from the Dutch SMA registry.[8] At the first visit, pulmonary function, including forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV1), was assessed using spirometry (Geratherm, Bad Kissingen, Germany) in accordance with the ERS/ATS recommendations.[26] Global lung function reference equations published in 2012 were used.[27] The motor function

was assessed with the Hammersmith functional motor scale expanded (HFMSE). We determined the individual threshold load of the RET (20%, 35%, or 55% of PImax) and the participant practiced the RET during 10 breaths. Participants performed the RET at visits 2 (RET1) and 3 (RET2), with a minimum of two weeks between the visits. The first 15 participants performed RET1 and RET2 at a 20% threshold load, and then the next participants who completed RET1 (60 breaths) performed RET2 at a higher threshold load (35%, 45%, or 70% of PImax). Participants who only partially completed RET1 performed RET2 at the same inspiratory threshold load as RET1 (**Figure 2.1**).

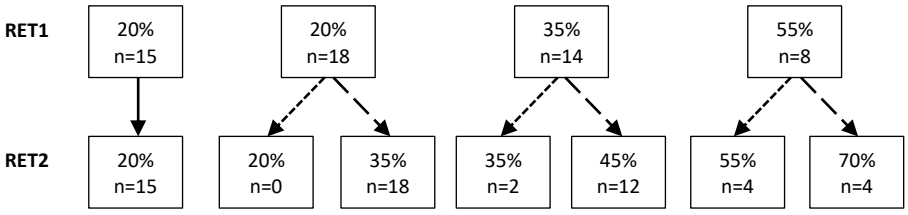


Figure 2.1: *Study procedure: inspiratory threshold load (% of maximal inspiratory mouth pressures [PImax]) of respiratory endurance test (RET) 1 and RET2. n=number of participants.*

The first 15 participants performed RET1 and RET2 at 20%, regardless of whether they completed RET1 (60 breaths) or not.

Participants did not complete 60 breaths at RET1 so they performed RET2 at the same threshold load.

Participants did complete 60 breaths at RET1 so they performed RET2 at a higher threshold load.

The RET

POWERbreathe

The RET was conducted with the POWERbreathe K5, POWERbreathe International Ltd. The POWERbreathe provides immediate feedback on the test execution and applies a patient-friendly gradual increase in resistance up to the threshold load. The POWERbreathe K series device has an electronically tapered flow resistive loading valve. The resistance is constantly monitored and tapered to match the reducing strength throughout the breath, thus allowing greater flow and maximum volume, resulting in a more fulfilling and effective breath, maximum flow and volume, plus more work per breath compared to traditional threshold pressure devices.[28]

Determination of the inspiratory threshold load

At visit 1, we determined the individual maximal inspiratory mouth pressure (PImax in centimeters of water column [cmH_2O]) with the POWERbreathe K5, according to standard procedures.[24,29–31] Participants generated a maximal inspiratory effort from residual volume while breathing through the mouthpiece with the nose occluded. The test was repeated at least 5 times with 30 seconds of rest in between. An additional

repeat was required if the last measurement was the highest. We noted the maximum value of three maneuvers that varied by less than 10%[23] and used that value to calculate the individual inspiratory threshold loads of RET1 and RET2.

Execution of the RET
At visits 2 (RET1) and 3 (RET2), participants performed the RET with the POWERbreathe K5 against an inspiratory threshold load of their PImax (which was determined at visit 1).[23,24] They were instructed to inhale repetitively at approximately 50% of their FVC against the set threshold load until too tired or breathless to continue.[24] Sitting position and encouragement were standardized. RMF was defined as the inability to continue for 60 consecutive breaths (i.e., TF) and the number of breaths until TF was recorded.

Quality of the RET
After each RET, all breaths were checked for quality of performance. An inspiration was performed correctly if a participant had overcome at least 50% of the peak inspiratory load. If the participant failed to do this three consecutive times, all subsequent inhalations were subtracted from the total number of breaths, resulting in a net number of breaths that were used for further quantitative analysis.[24]

Respiratory fatigability response
Respiratory fatigability response was expressed as ΔPImax and Δperceived fatigue. We compared the response in participants with RMF with the response in participants without RMF. We analyzed ΔPImax and Δperceived fatigue for RET1 as well as RET2.

Change in maximal inspiratory mouth pressure (ΔPImax)
ΔPImax in cmH_2O was calculated as the difference between PImax measured immediately after the RET and PImax measured before the RET. We assessed PImax following standard procedures.[23,24] PImax was measured at residual volume with the Micro Respiratory Pressure Monitor, Viasys. Participants generated maximal inspiratory efforts while breathing through the mouthpiece. We noted the highest value of three maneuvers that varied by less than 10%[23] for analysis.

Change in perceived fatigue (Δperceived fatigue)
ΔPerceived fatigue was calculated as the difference between perceived fatigue measured immediately after the RET and perceived fatigue measured before the RET. Perceived fatigue was evaluated with the OMNI scale of perceived exertion (i.e., OMNI Scale), a valid and reliable instrument for measuring perceived fatigue in children and adults.[32,33] The OMNI Scale consists of 11 numbered categories, 0–10, and verbal cues, from “not tired at all” to “very, very tired”.[32] Participants scored their perceived fatigue on an 11-point Likert scale.

Sample size calculation

The sample size was not calculated prospectively because of the novelty of the RET in this population and its unpredictable effect size. The sample size was determined by the number of eligible patients willing to participate.

Statistical analysis

We defined RMF as TF on a RET, executed at a predetermined percentage of the patients' PImax, and expressed in the number of breaths until exhaustion. To explore at which percentage of PImax the chance of RMF was greatest, we compared threshold loads of 20%, 35%, and 45% of PImax for RET1, and for RET2, threshold loads of 20%, 35%, 45%, 55%, and 70% of PImax.

We checked the data for normality and outliers with histograms and Q-Q plots. The continuous variables were presented as the median and interquartile range (M [IQR]). Categorical variables were presented in absolute numbers and percentages (n [%]). We tested differences between groups with the χ^2 test or Fisher's exact test for nominal data. For interval/ratio data, the Mann-Whitney *U* test was used for differences between 2 groups, and the Kruskal-Wallis test for differences between more than two groups.

Kaplan-Meier curves were generated for RET1 and RET2, where the event was defined as TF on the RET. The null hypothesis, that is, there is no difference in the probability of TF during 60 breaths between threshold loads, was tested with the log-rank test. To specify the dose-response relation between %PImax and TF, the Hazard ratio (HR) was computed with Cox Regression with threshold load in %PImax as a continuous variable.

All statistical analyses were performed using SPSS for Windows (version 25.0; SPSS Inc). A $p<0.05$ was considered significant.

RESULTS

Participant characteristics

We included a total of 19 children (median age 11 years [IQR 6 years]; 7 girls) and 36 adults (median age 34 years [IQR 16 years]; 20 women) with SMA. Twenty-nine participants had SMA type 2, 11 type 3a, and 15 type 3b. The median standardized FEV1 was 67.5% (IQR 62.5%). The median standardized FVC was 69% (IQR 62.75%) and the median standardized PImax was 78% (IQR 51%).

RETs characteristics

All 55 participants performed the RET twice, resulting in 110 RETs. There were no dropouts and no adverse events. POWERbreathe data were missing from 8 RETS (RET1:

n=3, RET2: *n*=5), and so the quality of performance could not be checked; they were, therefore, excluded from analysis, resulting in 52 RETs for RET1 and 50 RETs for RET2.

Characteristics per threshold load protocol

First, we analyzed the data per inspiratory threshold load protocol (**Table 2.1** for RET1 and **Table 2.2** for RET2). We compared gender, age, SMA subtype, motor function (HFMSE), and lung function (FEV1 and FVC) between the different threshold loads. For RET1, there were three different threshold loads, namely 20%, 35%, and 55% of patients' PImax. Age was the only statistically significant different characteristic in RET1 (*p*=0.018). For RET2, there were five different threshold loads, namely 20%, 35%, 45%, 55%, and 70% of patients' PImax. There were no statistically significant differences in the patients' characteristics between the different threshold loads of RET2.

Table 2.1: *Characteristics per threshold load protocol for RET1*

Threshold load	**20% of PImax *n*=31 (60%)**	**35% of PImax *n*=13 (25%)**	**55% of PImax *n*=8 (15%)**
Gender, n (%)			
Female	13 (42%)	7 (54%)	6 (75%)
Age (year), M (IQR)	26 (22)*	11 (22)*	38 (24)*
SMA subtype, n (%)			
Type 2	15 (48%)	8 (62%)	5 (63%)
Type 3a	7 (23%)	1 (8%)	2 (25%)
Type 3b	9 (29%)	4 (31%)	1 (13%)
HFMSE, M (IQR)	5 (49)	9 (54) (*n*=11)	4 (34) *(n*=7)
FEV1 (% of predicted), M (IQR)	78 (66.5) (*n*=29)	58.5 (54.5) (*n*=12)	70 (72.5)
FVC (% of predicted), M (IQR)	76 (63.75) (*n*=30)	59 (60)	75 (74)

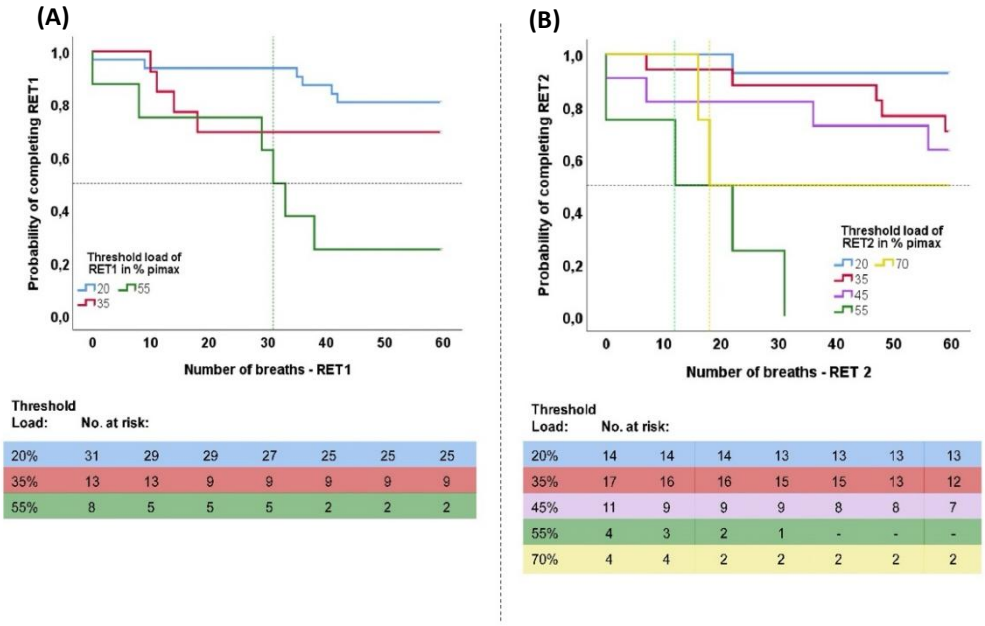
Note: If data were missing, n was expressed by (n=...). The missing data were completely at random. Abbreviations: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, HFMSE: Hammersmith Functional Motor Scale Expanded, M (IQR): median and interquartile range, n (%): number of RETs and percentage, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test, SMA: Spinal Muscular Atrophy.
**Significant differences p<0.05*

TF during RET1

TF during RET1 occurred in 75% (*n*=6) of the RETs, which were executed at 55% of patients' PImax and in 31% (*n*=4) and 19% (*n*=3) of the RETs, which were executed at 35% and 20% of patients' PImax, respectively. With every 10% increase in threshold load (in percentage of PImax), the probability of TF during RET1 increases by 69% (HR 1.69, 95% confidence interval [CI] 1.21-2.36, *p*=0.002).

Figure 2.2A depicts the Kaplan-Meier curves for the different inspiratory threshold loads of RET1. We found that the probability of TF, during RET1 at any point in

time, was significantly different between the different threshold loads (p=0.002). The median number of breaths until TF was 60 at the threshold loads 20% and 35% of PImax. The median number of breaths until TF at the threshold load 55% of PImax was 31 (95% CI 25-37).



Threshold Load:	No. at risk:						
20%	31	29	29	27	25	25	25
35%	13	13	9	9	9	9	9
55%	8	5	5	5	2	2	2

Threshold Load:	No. at risk:						
20%	14	14	14	13	13	13	13
35%	17	16	16	15	15	13	12
45%	11	9	9	9	8	8	7
55%	4	3	2	1	-	-	-
70%	4	4	2	2	2	2	2

Figure 2.2 (A) *Kaplan–Meier curves for each threshold load of RET1.* ***(B)*** *Kaplan–Meier curves for each threshold load of RET2.*

RET: Respiratory Endurance Test. Participants who completed the RET were censored at 60 breaths. The intersection between the horizontal and vertical dashed lines depicts the median time (breath) to TF at the threshold load of 55% of RET1 (green, left curve), 55% of RET2 (green, right curve), and 70% (yellow, right curve). The tables show the number of participants at risk of TF per threshold load per time point (0–60 breaths).

Table 2.2: *Characteristics per threshold load protocol for RET2*

Threshold load	**20% of PImax** ***n*=14 (28%)**	**35% of PImax** ***n*=17 (34%)**	**45% of PImax** ***n*=11 (22%)**	**55% of PImax** ***n*=4 (8%)**	**70% of PImax** ***n*=4 (8%)**
Gender, n (%)					
Female	4 (29%)	8 (47%)	7 (64%)	3 (75%)	3 (75%)
Age (year), M (IQR)	24.5 (26)	26 (19)	19 (26)	47 (34)	34.5 (16)
SMA subtype, n (%)	8 (57%)	8 (47%)	7 (64%)	2 (50%)	3 (75%)
Type 2	4 (29%)	3 (18%)	0 (0%)	1 (25%)	1 (25%)
Type 3a	2 (14%)	6 (35%)	4 (36%)	1 (25%)	0 (0%)
Type 3b					
HFMSE, M (IQR)	4.5 (39)	7 (57)	21 (56) (*n*=9)	9 (28)	4 (*n*=3)
FEV1 (% of predicted), M (IQR)	75 (68.25)	74 (65) (*n*=16)	56 (58.75) (*n*=10)	91.5 (64.25)	49 (60.25)
FVC (% of predicted), M (IQR)	76 (67.75)	79 (64.75) (*n*=16)	59 (68)	97.5 (70.25)	52 (57.75)

Note: If data were missing, n was expressed by (n=...). The missing data were completely at random. Abbreviations: FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, HFMSE: Hammersmith Functional Motor Scale Expanded, M (IQR): median and interquartile range, n (%): number of RETs and percentage, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test, SMA: Spinal Muscular Atrophy.

TF during RET2

TF during RET2 was observed in 50% (*n*=2) of the RETs which were executed at 70% of patients' PImax and in 100% (*n*=4), 36% (*n*=4), 29% (*n*=5), and 7% (*n*=1) of the RETs which were executed at 55%, 45%, 35%, and 20% of patients' PImax, respectively. With every 10% increase in threshold load (in percentage of PImax), the probability of TF during RET2 increases by 59% (HR 1.59, 95% CI 1.18-2.15, *p*=0.003).

Figure 2.2B depicts the Kaplan-Meier curves for the different inspiratory threshold loads of RET2. We found that the probability of TF, during RET2 at any point in time, was significantly different between the different threshold loads (*p*<0.001). The median number of breaths until TF was 60 at the threshold loads 20%, 35%, and 45% of PImax. The median number of breaths until TF at the threshold load 55% of PImax was 12 (95% CI 0-34), and the median number of breaths until TF at the threshold load 70% of PImax was 18 (95% CI?).

Respiratory fatigability response for RET2

Second, we analyzed the data per subgroup RMF (patients with TF) and no RMF (patients with no TF) to determine the respiratory fatigability response (**Table 2.3**). We compared age, SMA subtype, motor function (HFMSE), lung function (FEV1 and FVC), and

inspiratory muscle strength (PImax) between the two subgroups (RMF and no RMF). In addition, we compared respiratory fatigability responses (ΔPImax and Δperceived fatigue). The baseline characteristics and respiratory fatigability response in RET1 were similar to those in RET2 (**Table 2.4 and Appendix 2.A**).

Baseline characteristics per subgroup for RET2

We compared baseline characteristics of the participants with and without RMF on RET2 (**Table 2.3**). There were no statistically significant differences between the characteristics of the two groups for RET2. Notable is the lower median baseline values of PImax % of predicted in the group with RMF compared to the participants without RMF. 56% of the participants with RMF could be classified as inspiratory weak (PImax: <70 cmH_20 for women and <80 cmH_20 for men[23]) as opposed to just 33% of the participants without RMF (*p*=0.215).

Table 2.3: *Characteristics and respiratory fatigability response per subgroup for RET2*

		RMF (TF) ***n*=16 (32%)**	**no RMF (no TF)** ***n*=34 (68%)**
Characteristics	**Age (year), M (IQR)**	29 (32)	25.5 (21)
	SMA subtype, *n* (%)		
	Type 2	10 (63%)	18 (53%)
	Type 3a	3 (19%)	6 (18%)
	Type 3b	3 (19%)	10 (29%)
	HFMSE, M (IQR)	5 (38) (*n*=14)	7 (49) (*n*=33)
	FEV1 % of predicted, M (IQR)	70 (65.25) (*n*=14)	67.5 (63.75)
	FVC % of predicted, M (IQR)	67 (66) (*n*=15)	68.5 (65.25)
	PImax % of predicted[1], M (IQR)	69 (56)	87 (46) *(n*=33)
Respiratory fatigability response	**ΔPImax (cmH_2O), M (IQR)**	-0.5 (5)	1 (8) (*n*=33)
	ΔPImax (%), M (IQR)	-0.64% (7.47%)	1.38% (8.02%) (*n*=33)
	Δperceived fatigue, M (IQR)	0 (1) (*n*=15)	0 (2) (*n*=33)
	+Δperceived fatigue (increase), *n* (%)	5 (33%)	17 (52%)
	No differences in perceived fatigue, *n* (%)	10 (67%)	16 (49%)

Note: If data were missing, n was expressed by (n=...). The missing data were completely at random.
[1]Reference values of Neder et al.[34] were used for ages 20-60 years, and those of Hulzebos et al.[35] for ages 8- 19 years.
Abbreviations: Δ: post RET–pre RET, cmH_2O: centimeters of water column, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, HFMSE: Hammersmith Functional Motor Scale Expanded, M (IQR): median and interquartile range, n (%): number of RETs and percentage, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test, RMF: Respiratory Muscle Fatigability, SMA: Spinal Muscular Atrophy, TF: Task Failure.

Respiratory fatigability response: ΔPImax per subgroup for RET2

We found no statistically significant differences in ΔPImax between the two subgroups (**Table 2.3**). The median change in PImax in the group with RMF for RET2 was -0.5 cmH_2O

(p=0.22), with a large variability in individual response. Eight participants with RMF (50%) showed a decrease in ΔPImax, ranging from -1% to -21%. 5 participants with RMF (31%) showed an increase in ΔPImax ranging from +2% to +16%. 12 participants (36%) without RMF showed a decrease in ΔPImax, ranging from -1% to -10%, compared to an increase in 19 participants (58%) in this group, ranging from +1% to +32%.

To gain some more insight, we divided PImax and age into quartiles so we could see if the youngest/weakest patients showed the most increase in ΔPImax. We found no statistically significant differences in age groups (p=0.243). We did find statistically significant differences between the PImax groups (p=0.048). However, this was not a clinically relevant difference. The median ΔPImax was 1 cmH_2O in the weakest group, -0.5 cmH_2O in the Q2 group, -2 cmH_2O in the Q3 group, and 1 cmH_2O in the strongest group.

Respiratory fatigability response: Δperceived fatigue for RET2

Both groups, participants with and without RMF, demonstrated a small, significant increase in Δperceived fatigue after RET2 (RMF: p=0.041, no RMF: p<0.001) (**Table 2.3**). We found a similar response in Δperceived fatigue ranging from 0 to +3 in both groups. We found no statistically significant differences in Δperceived fatigue between the two subgroups.

DISCUSSION

In this study, we explored RMF in patients with SMA. Patients with SMA demonstrate a dose-dependent increase in RMF with a large individual variation in fatigability response.

The probability of experiencing RMF in our study was the highest at an inspiratory threshold load of 55% of their individual PImax, which is similar to the probability in healthy individuals[25] and 20% higher than in patients with Duchenne muscular dystrophy (DMD).[24] In a recent study on fatigability of arm and leg muscles, patients with SMA showed increased fatigability compared to patients with DMD, despite similar levels of muscle weakness.[7,20,36] Therefore, we expected patients with SMA to show RMF at a similar or even lower inspiratory threshold load compared to patients with DMD.[24]

The diaphragm acts as the primary inspiratory muscle and accounts for 70% of the inspired air volume during regular breathing.[37] In patients with SMA, the diaphragm is relatively spared, while in DMD, it is one of the most severely affected respiratory muscles.[10,38,39] This might explain why patients with DMD experience RMF at a lower inspiratory threshold load than patients with SMA.

A decrease in ΔPImax of 9.3%-50% after a RET as a response to RMF was reported by Janssens et al. in healthy individuals[25], while Matecki et al.[24] reported a mean decrease of 22% in ΔPImax in children with DMD. In contrast, we found no

statistically significant decrease in PImax after the RET in patients with SMA. Interestingly, we observed large interindividual differences in ΔPImax, ranging from a decrease of 21% to an increase of 16% in PImax as a response to RMF. We suggest that the observed increase in inspiratory muscle strength after the RET in some patients might be due to a learning effect, similar to what was previously observed during endurance testing of the upper and lower extremities.[7] Intramuscular coordination generally improves after repeated performance of a new motor task. We expected that the learning effect would be greatest in the youngest or weakest patients, but sub-analysis showed no association between age, strength (PImax), and ΔPImax. The variability in age and subtypes of SMA and the fast recovery of fatigability in patients with SMA may also have contributed to a blunted response in PImax.[6,7] To provide insight into the underlying mechanism of RMF during a RET, and to better understand variable responses in ΔPImax, we suggest the use of surface electromyography (sEMG) in future studies.[40]

There was a small but significant increase in perceived exertion in both patients with and without RMF. However, these results should be interpreted with some caution. The OMNI scale, used to measure perceived exertion, has only been validated in children and adults during motor activities.[32,33] Unfortunately, no validated scale was available for perceived exertion of the respiratory muscles in SMA or other neuromuscular diseases. Further research is needed to determine the validity of the OMNI scale to detect perceived exertion in neuromuscular diseases. To objectify RMF and validate the OMNI scale, we suggest comparing scores to objective outcome measures such as sEMG.[40] Until then, other parameters indicative of exercise intensity will have to be included to monitor the response to respiratory muscle loading, such as the experienced intensity of the training and perceived dyspnea measured with a Borg scale.[41] In addition to subjective measurements, objective measurements, for example, breathing frequency, use of accessory inspiratory muscles, and retractions, can be used as indicators of increased work of breathing.

The results of our study show that RMF in patients with SMA is observed at a similar percentage of the individual PImax compared to healthy individuals. The probability of RMF in patients with SMA seems to be highest at a threshold load of 55% of PImax; in healthy individuals, RMF is induced at a threshold load of 60% of PImax.[25] Inspiratory loading appears feasible in patients with SMA, and they are capable of breathing against a high inspiratory threshold load, which provides opportunities for respiratory training. This study shows that respiratory muscle endurance seems adequate in patients with SMA, but the low baseline levels of PImax suggest a therapeutic window for respiratory muscle strength training. Furthermore, compared to core and limb muscles relevant for motor function tests, respiratory muscles may be less responsive to SMN-augmenting therapies. Respiratory muscle training could, therefore,

be a complementary therapy to the treatment strategies that have now become increasingly available for patients with SMA.[13,14]

Due to a lack of knowledge on the feasibility of inspiratory muscle loading in patients with SMA, we decided to use a dose escalation method starting at a low intensity. After 15 patients, we noticed that almost all patients completed the RET, and we decided to gradually increase the intensity of the RET. This resulted in relatively small numbers of participants in each subgroup, which requires the results to be interpreted with some caution. Our findings do confirm that fatigability in the respiratory muscles seems less prominent than fatigability of the muscles in arms and legs.[7,20] Further research in a larger group of patients with SMA is necessary to validate the RMF threshold and further explore the variability in fatigability response. Also, further research is needed to investigate the feasibility and effectiveness of respiratory muscle training in patients with SMA.

CONCLUSION

Patients with SMA types 2 and 3 demonstrate a dose-dependent increase in RMF without a severe increase in exercise-induced muscle weakness or perceived fatigue. Inspiratory muscle loading in patients with SMA seems feasible, and its potential to stabilize or improve respiratory function in patients with SMA needs to be determined in further research.

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APPENDIX 2.A

Respiratory fatigability response for respiratory endurance test 1 (RET1)

For RET1, we analyzed the data per subgroup respiratory muscle fatigability (RMF) (patients with task failure [TF]) and no RMF (patients with no TF) to determine the respiratory fatigability response (**Table 2.4**). We compared age, spinal muscular atrophy (SMA) subtype, motor function (Hammersmith functional motor scale expanded [HMFSE]), lung function (forced expiratory volume in the 1s and forced vital capacity), and inspiratory muscle strength (maximal inspiratory mouth pressure [PImax]) between the two subgroups (RMF and no RMF). In addition, we compared fatigability responses (change in maximal inspiratory mouth pressure [ΔPImax] and change in perceived fatigue [Δperceived fatigue]).

Table 2.4: *Characteristics and respiratory fatigability response per subgroup for RET1*

		RMF (TF) ***n*=16 (31%)**	**no RMF (no TF)** ***n*=36 (69%)**
Characteristics	**Age (year), M (IQR)**	21.5 (35)	26 (22)
	SMA subtype, *n* (%)		
	Type 2	10 (63%)	18 (50%)
	Type 3a	4 (25%)	6 (17%)
	Type 3b	2 (13%)	12 (33%)
	HFMSE, M (IQR)	4 (13) (*n*=15)	8.5 (54) (*n*=34)
	FEV1 % of predicted, M (IQR)	56.5 (71.75) (*n*=14)	78 (62) (*n*=35)
	FVC % of predicted, M (IQR)	60 (72) (*n*=15)	76 (60.75)
	PImax % of predicted[1], M (IQR)	60 (47)	85.5 (50)
Respiratory fatigability response	**ΔPImax (cmH_2O), M (IQR)**	1.5 (14.75)	0 (7.75)
	ΔPImax (%), M (IQR)	3.17% (17.01%)	0% (10.27%)
	Δperceived fatigue, M (IQR)	0.5 (2) (*n*=14)	0 (2) (*n*=33)
	-Δ perceived fatigue (decrease), *n* (%)	1 (7%)	3 (9%)
	+Δperceived fatigue (increase), *n* (%)	7 (50%)	16 (49%)
	No differences in perceived fatigue, *n* (%)	6 (43%)	14 (42%)

Note: If data were missing, n was expressed by (n=...). The missing data were completely at random.
[1]Reference values of Neder et al.[34] were used for ages 20-60 years, and those of Hulzebos et al.[35] for ages 8- 19 years.
Abbreviations: Δ: post RET – pre RET, cmH_2O: centimeters of water column, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, HFMSE: Hammersmith Functional Motor Scale Expanded, M (IQR): median and interquartile range, n (%): number of RETs and percentage, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test, RMF: Respiratory Muscle Fatigability, SMA: Spinal Muscular Atrophy, TF: Task Failure.

Baseline characteristics per subgroup for RET1

We compared baseline characteristics of the participants with and without RMF on RET1 (**Table 2.4**). There were no statistically significant differences between the characteristics of the two groups for RET1. Notable is the lower mean baseline values of PImax % of

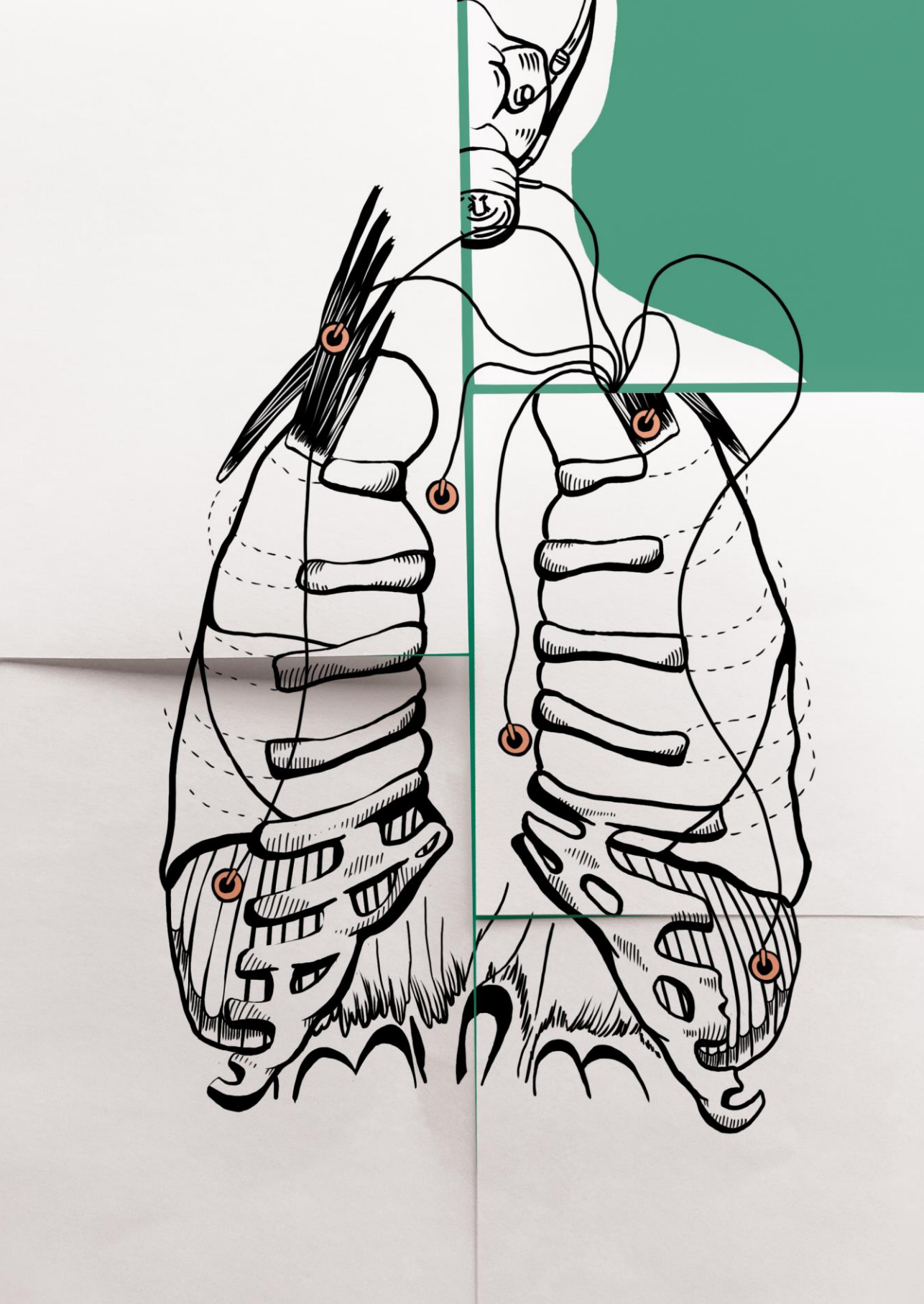
predicted in the group with RMF compared to the participants without RMF. 63% of the participants with RMF could be classified as inspiratory weak (PImax % of predicted: <70 cmH_20 for women and <80 cmH_20 for men[23]) as opposed to just 36% of the participants without RMF (p=0.129).

Respiratory fatigability response: ΔPImax per subgroup for RET1

We found no statistically significant differences in ΔPImax between the two subgroups (**Table 2.4**). The median change in PImax in the group with RMF for RET1 was 1.5 cmH_2O (p=0.35) with a large variability in individual response. Six participants with RMF (38%) showed a decrease in ΔPImax, ranging from -1% to -24%. Nine participants with RMF (56%) showed an increase in ΔPImax ranging from +3% to +29%. 16 participants (44%) without RMF showed a decrease in ΔPImax, ranging from -1% to -18%, compared to an increase in 17 participants (47%) in this group, ranging from +1% to +36%.

Respiratory fatigability response: Δperceived fatigue for RET1

Both groups, participants with and without RMF, demonstrated a small, significant increase in Δperceived fatigue after RET1 (RMF: p=0.024, no RMF: p=0.005) (**Table 2.4**). We found a similar response in Δperceived fatigue in both groups. In the group with RMF, Δperceived fatigue ranged from -1 to +4; in the group without RMF, Δperceived fatigue ranged from -3 to +8. We found no statistically significant differences in Δperceived fatigue between the two subgroups.



Chapter 3

Respiratory muscle activity and fatigue response during respiratory endurance testing in patients with spinal muscular atrophy.

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ABSTRACT

Objective
To explore respiratory muscle activity and fatigue response during a respiratory endurance test (RET) in patients with spinal muscular atrophy (SMA).

Methods
Fifty-five participants with SMA types 2 and 3 performed a respiratory endurance test (RET) at 20%-70% of their maximum inspiratory mouth pressure (PImax). We recorded surface electromyography (sEMG) of the diaphragm, intercostal, and scalene muscles and evaluated muscle activity at onset and during the test. Respiratory muscle fatigability (RMF) was the inability to complete 60 consecutive breaths during the RET.

Results
The diaphragm showed a significantly lower variance in activity at onset of the test compared to the intercostal and scalene muscles (p=0.002). Participants with RMF showed fatigue of the diaphragm, indicated by a significant decrease in root mean square amplitude (p=0.012) and median frequency (p<0.001), compared to those without RMF.

Conclusion
The relative activity of the diaphragm at onset of a RET remained stable at higher intensity levels, while the activity of the intercostal and scalene muscles became more variable. The diaphragm showed significant signs of fatigue, while accessory inspiratory muscles showed no clear fatigue signs.

Significance
The results of this study provide more insight into respiratory muscle function and fatigability in patients with SMA.

Keywords
spinal muscular atrophy, respiratory muscles, surface electromyography, muscle activity, fatigability, fatigue responses

Highlights
- It is possible to assess the muscle activity of different respiratory muscles in patients with SMA using sEMG.
- Intercostal and scalene muscle activity at onset of a respiratory endurance test is more variable than diaphragm activity.

- Surface EMG captures fatigue responses of the diaphragm in patients with SMA during respiratory endurance testing.

INTRODUCTION

Spinal muscular atrophy (SMA) is a severe, autosomal recessive neuromuscular disease caused by the loss of function of the survival motor neuron 1 (*SMN1)* gene.[1] SMA has a large variability of disease severity, ranging from neonatal respiratory insufficiency and death (type 1), inability to walk independently (type 2), and problems with or loss of ambulation (type 3) to mild impairments in adults (type 4).[2,3] The most prominent clinical characteristic of SMA is progressive muscle weakness, particularly of axial, proximal, bulbar, and respiratory muscles.[3,4] Fatigability, defined as the inability to sustain a functional task at any desired intensity, is a common (>85%) additional symptom of impaired motor function in patients with SMA. Fatigability has a major impact on activities of daily living, such as difficulties with or the inability to manually operate a power-driven wheelchair, to drink from a glass, or to walk.[5–7]

Respiratory muscle weakness is an important cause of morbidity and mortality in patients with SMA. Reduced cough strength and poor secretion clearance cause frequent respiratory tract infections and alveolar hypoventilation.[8,9] Respiratory muscle weakness is most pronounced in the intercostal muscles, while the diaphragm is relatively spared.[2]

Recent advances in genetic disease-modifying therapies (DMTs) have improved survival, acquisition of motor milestones in young patients, and motor function in subgroups of older patients.[10,11] However, current DMTs do not cure symptomatic patients, and various health problems need to be addressed.[12–14] Most importantly, DMTs have a limited effect on respiratory function and respiratory muscle strength in patients with SMA.[15] New approaches to supplement the recommended airway clearance techniques to combat respiratory tract infections are therefore needed.[14]

We previously investigated respiratory muscle fatigability (RMF) in patients with SMA using a newly developed respiratory endurance test (RET).[16] Most patients with SMA showed a normal respiratory muscle fatigue threshold, but this was not accompanied by other expected physiological fatigue responses, such as increased perceived fatigue and transient respiratory muscle weakness. The cause of this abnormal fatigue response is unclear, but the altered breathing pattern in SMA may play a role.[17] More insight into the mechanisms underlying respiratory fatigue responses can help develop and evaluate respiratory function treatment strategies. We therefore explored individual respiratory muscle activity and fatigue response of the diaphragm, scalene muscles, and intercostal muscles during a RET in patients with SMA types 2, 3a, and 3b using surface electromyography (sEMG).

sEMG captures the sum of motor unit action potentials of multiple active motor units and informs on the recruitment of muscle fibers and the onset of muscle fatigue based on the dynamics of two parameters: the root mean square (RMS) amplitude and the median frequency (MF) of the signal.[18–22] Higher muscle activity is defined as a higher

amount of motor units being recruited or an increase in the firing rate in the respiratory muscle, following Henneman's size principle.[18,23,24]

Muscle fatigue during RET manifested either as an initial increase in RMS amplitude, often followed by a decrease reflecting additional motor unit recruitment and failure, respectively, or as a decrease in MF reflecting a lower firing rate of current motor units due to reduced conduction velocity of action potentials.[18,21]

We hypothesized that:

1) A higher RET resistance level is associated with higher muscle activity of the diaphragm, intercostal, and scalene muscles.
2) Patients with SMA with RMF show fatigue responses in all respiratory muscles over time during the RET.[18,23,24]

METHODS

This study is part of a larger cross-sectional study on fatigability in SMA.[7,16,20,25] To ensure an accurate and complete report of our work, we followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[26]

Standard protocol approvals, registrations, and patient consent

The study was conducted according to the principles of the Declaration of Helsinki, the code of conduct, and the national rules of the Dutch Association of Pediatrics for the protection of minor study participants. The Medical Research Ethics Committee Utrecht (METC Utrecht) approved this study based on the requirements of the WMO (NL48715.041.14). All participants and all parents or legal guardians of children below the age of 18 years signed informed consent. We included participants between March 2015 and March 2018. None of the participants received disease-modifying therapies before or during the study period.

Participants

We recruited patients from the Dutch National SMA Registry.[4] Patients aged 8 to 60 with a genetically confirmed diagnosis of SMA type 2, 3a, or 3b and who could follow test instructions were considered for inclusion. We used the SMA classification system to define types. In short, patients with SMA type 2 had a disease onset between 6 and 18 months and had learned to sit independently but not to walk. Patients with SMA type 3a experienced their first symptoms before 3 years of age and learned to walk. In SMA type 3b, the onset of symptoms was between 3 and 30 years of age.[27] Exclusion criteria were a history of other neuromuscular diseases or the use of medication that could affect neuromuscular junction function, medical conditions incompatible with exercise, or the

inability to perform endurance tests.[16] We discouraged strenuous physical activities the day before each visit to the hospital.

Study procedures

The study consisted of three visits within approximately six weeks. At the first visit, we documented baseline characteristics and determined the individual resistance of the RET, after which the participant practiced for 10 breaths. Participants performed the RET at visits 2 and 3, with a minimum of two weeks between the visits. We collected sEMG data during visit 3.

Respiratory endurance test (RET)

Details about the RET have been published previously.[16] In short, participants performed the RET at a preset percentage of the participant's maximum inspiratory mouth pressure (PImax) (i.e., resistance levels: 20%, 35%, 45%, 55%, or 70%) with a POWERbreathe K5 (with advanced Breathe-Link® software, n.d.). Participants inhaled repetitively at 50% of their forced vital capacity against the set resistance.[16,28] Respiratory muscle fatigability (RMF) was defined as the inability to complete 60 consecutive breaths. After each RET, we checked the performance quality of all inspirations. An inspiration was performed correctly if a participant had overcome at least 50% of the peak inspiratory load. If the participant failed to do this three successive times, the following inhalations were subtracted from the total number of breaths, resulting in a net number of breaths.[16,28] The resistance gradually increased during the first six inspirations until the intended resistance was reached. From the seventh inspiration onward, the resistance remained constant.

Maximal voluntary contractions

We followed standard procedures to measure maximal voluntary contraction (MVC) of the inspiratory muscles (i.e., PImax).[28,29] We measured PImax at residual volume with the Micro-Respiratory Pressure Monitor, before and immediately after the RET.

sEMG registration

During the two MVC assessments (prior and post-RET) and the RET, we measured the electrical muscle activity of the various respiratory muscles using wireless Bio Radio (Great Lakes Neurotechnologies, Cleveland, Ohio, USA) bipolar four-channel sEMG electrodes. Each breath during RET was manually marked in the sEMG signal recordings.

Electrode placement

We prepared the skin by removing hair and rubbing and cleaning the skin with alcohol (70% denatured ethanol incl. 5% isopropanol). We used Philips Neonatal/pediatric disposable cloth snap electrodes (Ag/AgCl sensor with solid gel, 22mm x 22mm) for the

scalene and intercostal muscles. To measure the signals of the scalene muscles, we placed two electrodes 2 cm apart on a slightly oblique angle just above the clavicle in the hollow triangle so that they run parallel to the muscle fibers (**Figure 3.1**).[30] To measure the signals of the external intercostal muscles, we placed two electrodes in the second intercostal space at the mid-clavicular line (**Figure 3.1**).[31] We used 3M™ Red Dot™ disposable foam snap electrodes (Ag/AgCl sensor with solid gel, diameter 51mm) for the diaphragm. To measure the signals of the diaphragm, we placed one electrode 5 cm superior to the tip of the xiphoid process and a second electrode at the costal margin (seventh intercostal space) on the right side with an inter-electrode distance of 16 cm (**Figure 3.1**).[31] The reference electrode was placed on the sternum. All electrodes were fastened using surgical tape.

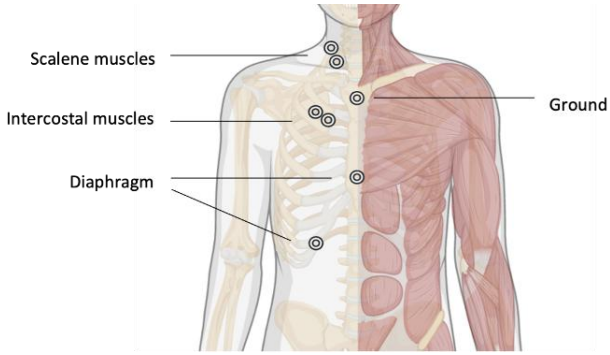


Figure 3.1. *Electrode placement locations of the diaphragm, intercostal muscles, and scalene muscles. Image created in BioRender. Pomp, L. (2025). https://BioRender.com/d73u244.*

Signal acquisition and processing

We used Biocapture software to measure real-time muscle electrical activation at a sampling frequency of 1000 samples/s and amplified with a gain of 1000. The sampling resolution was 6 microvolts (μV) per least significant bit. An anti-aliasing filter, set to 250 hertz (Hz), was implemented in the recording system. We processed raw sEMG data with MATLAB R2023a (Mathworks, Natick, Massachusetts, USA). We filtered the signals using a high-pass 4th-order Butterworth filter at 20 Hz, a low-pass 4th-order Butterworth filter at 450 Hz, and a 50 Hz notch filter to remove power line noise. We detected electrocardiogram (ECG) complexes in the diaphragm lead and removed the ECG by gating. We excluded a window of 150 ms around each R-peak of the ECG wave in all diaphragm leads.[19] The analyses were performed from the 7th to the last inspiration because the first 6 breaths were used to gradually build up resistance. We manually checked the markers for each breath for presence and position. We calculated the RMS amplitude per breath over an overlapping moving window of 100 samples. We calculated the MF of the power spectrum per breath using the Fast Fourier Transformation.[20]

Statistical analysis

We present continuous variables as mean and standard deviation (m±SD) or mean and 95% confidence interval (95%CI), or as median and interquartile range (M [IQR]). We present categorical variables in absolute numbers and percentages (n [%]). We tested if there were statistically significant differences in baseline variables between the different resistances with a chi-square test for categorical data and a Kruskal-Wallis test for continuous data.

Hypothesis 1: muscle activity

To determine the relative muscle activity (nRMS) of each muscle at onset of the RET, we used the following equation: (RMS_{RET}/RMS_{MVC}) * 100%. We performed an analysis of variance to test whether the relative muscle activity differed between the different resistance levels (20%, 35%, 45%, 55%, 70%). We analyzed the variance between individual muscles irrespective of intensity level with Levene's test.

Hypothesis 2: fatigue response

We used the natural logarithm-transformed RMS (lnRMS) amplitudes and MF during the RET to analyze the change over the breath numbers of each muscle. We transformed the RMS with a natural logarithm to increase the normality and decrease the heteroskedasticity for robust statistical analysis. We used linear mixed-effects models with group (RMF *vs.* No RMF), breath numbers, and the interaction between breath numbers by group as fixed effects and a random intercept per individual to account for the dependencies within the data. Significance was based on a likelihood ratio test to evaluate the time-by-group interaction term. From the model, we extracted the population average rate of change over breath numbers for the RMF and No RMF groups, together with their 95% CI. We estimated the change in lnRMS amplitudes and MF with and without correction for the different resistance levels of the RET as an additional fixed effect. All statistical analyses were performed using RStudio version 2024.09.0+375. A p-value below 0.05 was considered significant.

RESULTS

Participant characteristics

We included a total of 55 participants. Data from nine participants were missing due to technical problems with the POWERbreathe device (n=5) and Bioradio system (n=4). We analyzed data from 46 participants, 23 men, and 23 women, with a median age of 26 years. A total of 26 participants had SMA type 2, nine type 3a, and 11 type 3b. A total of 14 participants performed the RET with a resistance of 20% of their PImax, 13 with a resistance of 35%, 11 with a resistance of 45%, four with a resistance of 55%, and four with a resistance of 70% (**Table 3.1**). A total of 16 participants showed RMF on the RET.

One (7%) at a resistance level of 20%, five (38%) at 35%, four (36%) at 45%, four (100%) at 55%, and two (50%) at 70%.[16] Baseline characteristics did not significantly differ between the sub-groups.

Table 3.1: *Participant characteristics per resistance level*

Resistance level of the RET (% of PImax)	**20% n=14 (30%)**	**35% n=13 (28%)**	**45% n=11 (24%)**	**55% n=4 (9%)**	**70% n=4 (9%)**	**All n=46 (100%)**
Gender, n (%)						
Female	4 (29%)	6 (46%)	7 (64%)	3 (75%)	3 (75%)	23 (50%)
Male	10 (71%)	7 (54%)	4 (36%)	1 (25%)	1 (25%)	23 (50%)
Age (year), M (IQR)	24.5 (26)	26.0 (22)	19.0 (26)	47.0 (34)	34.5 (16)	26.0 (27)
SMA subtype, n (%)	8 (57%)	6 (46%)	7 (64%)	2 (50%)	3 (75%)	26 (56%)
Type 2	4 (29%)	3 (23%)	0 (0%)	1 (25%)	1 (25%)	9 (20%)
Type 3a	2 (14%)	4 (31%)	4 (36%)	1 (25%)	0 (0%)	11 (24%)
Type 3b						
HFMSE, M (IQR)	4.5 (39)	7 (53)	21 (56) (n=9)	9 (28)	4 (n=3)	6 (42) (n=43)
PImax (cmH_2O), m±SD	101.8±40.6	77.5±36.9	71.3±32.6	84.3±54.4	90.3±33.2	85.1±38.7
PImax (%pred), m±SD	89.6±33.2	70.0±28.0	70.7±24.8	83.3±43.2	86.3±23.6	78.7±30.1

Abbreviations: %pred: percentage of predicted, cmH_2O: centimeters of water column, HFMSE: Hammersmith Functional Motor Scale Expanded, m±SD: mean and standard deviation, M (IQR): median and interquartile range, n (%): number and percentage, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test, SMA: Spinal Muscular Atrophy.

Respiratory muscle activity at onset of the RET

The mean nRMS amplitude of the diaphragm, intercostal, and scalene muscles did not significantly differ between resistance levels (*p*-values all >0.1) (**Figure 3.2, Appendix 3.A**). Overall variability was significantly different between the diaphragm (mean: 35.1, 95% CI: 30.8-39.2, variance: 201), intercostal muscles (mean: 46.1, 95% CI: 37.9-54.3, variance: 766), and scalene muscles (mean: 41.2, 95% CI: 32.1-50.3 variance: 943) (*p*=0.002) (**Appendix 3.B**).

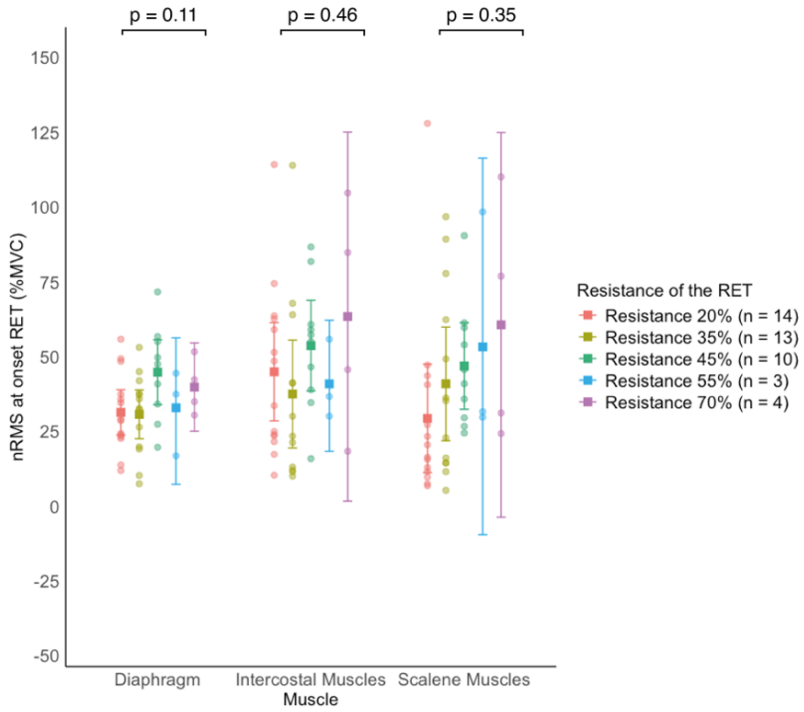


Figure 3.2. *Mean, 95% confidence intervals, and individual data points of the normalized root mean square (nRMS) amplitude of the diaphragm, intercostal muscles, and scalene muscles at onset (breath 7) of the respiratory endurance test (RET).*
Resistance levels are indicated in colors.

Fatigue responses during RET
Different resistance levels were not associated with differences in the slopes of the lnRMS amplitudes and MF (**Appendix 3.C and 3.D**).

Diaphragm
Participants with and without RMF had significantly different slopes of the lnRMS amplitudes of the diaphragm (p=0.01). While participants without RMF showed a non-significant increase in lnRMS amplitude of the diaphragm, participants with RMF showed a significant decrease (**Figure 3.3A** and **Appendix 3.C)**. The slopes of the MF of the diaphragm significantly differed between participants without and with RMF (p<0.001), with a significant decrease among participants with RMF (**Figure 3.3B** and **Appendix 3.C**).

Intercostal muscles
The slopes of the lnRMS amplitudes and MF of the intercostal muscles did not differ between participants without RMF and with RMF (both p=0.07) (**Figure 3.3A, 3.3B,** and **Appendix 3.C**).

Scalene muscles

The slopes of the lnRMS amplitudes and MF of the scalene muscles did not differ between participants without RMF and with RMF (p=0.57 and p=0.16, respectively) (**Figure 3.3A, 3.3B,** and **Appendix 3.C**).

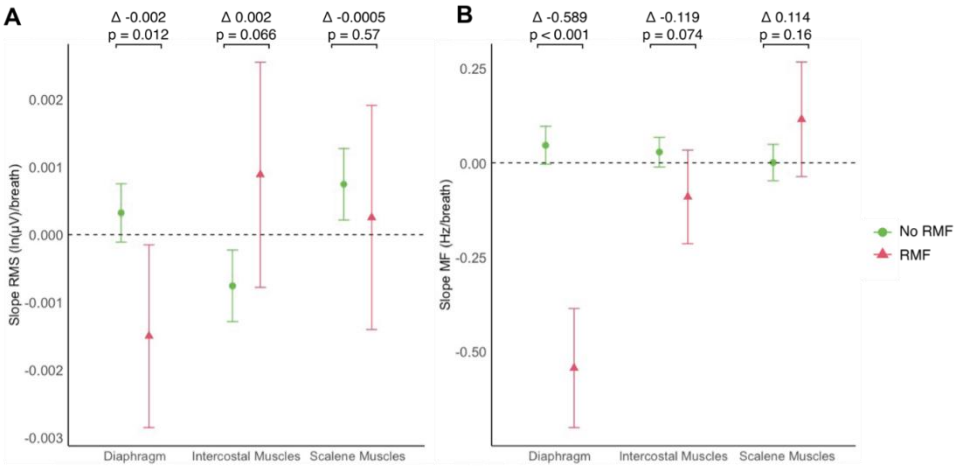


Figure 3.3A: *Mean and 95% confidence interval (corrected for resistance level) of the slope of the natural logarithm of the root mean square (lnRMS) amplitude of the diaphragm, intercostal, and scalene muscles of participants without and with respiratory muscle fatigability (RMF).* ***3.3B:*** *Mean and 95% confidence interval (corrected for resistance level) of the slope of the median frequency (MF) of the diaphragm, intercostal, and scalene muscles of participants without and with RMF.*

Abbreviations: Δ: Mean differences in slope between participants without and with RMF. p: significance level of the mean differences in slope.

DISCUSSION

We explored individual muscle activity and fatigue response of the diaphragm, intercostal, and scalene muscles during a respiratory endurance test with different inspiratory resistance levels in patients with SMA types 2 and 3 using surface EMG recordings. The activity level of the individual respiratory muscles at onset was generally not significantly associated with the level of inspiratory resistance, although the diaphragm muscle did show significantly lower variance in activity at onset of the RET compared to the intercostal and scalene muscles. Participants with respiratory muscle fatigue (RMF) showed a significant fatigue response of the diaphragm during the RET.

At the onset of the RET, the relative activity of the diaphragm remained stable at higher RET intensity levels, while the activity of the intercostal and scalene muscles was much more variable. This suggests that the load of breathing against resistance is

shared amongst different respiratory muscles according to their biomechanical and morphological specificities.[32,33] The large variation in the activity of the scalene muscles and intercostal muscles may be explained by the mechanical disadvantage that patients with a more severe phenotype experience due to the typical alterations of thoraco-abdominal volumes and asynchronies. The activation of inspiratory costal muscles is closely related to the muscle fiber orientation at the ribcage, known as neuromechanical matching.[34,35] Lo Mauro et al. showed that in contrast to healthy subjects and SMA type 3b, patients with SMA type 2-3a demonstrate poor pulmonary rib cage expansion, a higher degree of within-rib cage asynchrony, and high abdominal contribution.[17] In the case that any capacity to recruit the accessory respiratory muscles at higher breathing work intensities is limited, excessive demand may be placed on the relatively spared diaphragm. Therefore, we propose that, before setting any inspiratory loading level, the breathing pattern and the actively involved respiratory muscles should be analyzed to prevent excessive demand on one muscle group.

The results of this study also suggest that assessment of fatigue parameters during inspiratory loading is essential to adjust intensity and prevent overloading appropriately. Participants with SMA and RMF showed fatigue of the diaphragm muscle but not of the scalene and intercostal muscles. As reported previously, participants with RMF showed no functional signs of fatigue, such as increased perceived fatigue or transient muscle weakness.[16] Basoudan et al. studied scalene and sternocleidomastoid activation during normoxic and hypoxic incremental inspiratory threshold loading in thirteen healthy adults and found a similar pattern of increases in respiratory muscle activity without changes in EMG-frequency or maximal inspiratory mouth pressure.[36] However, they found a significant increase in perceived dyspnea. Further research on the use of perceived dyspnea to monitor exercise intensity in patients with SMA is needed.

The application of sEMG allowed us to study individual respiratory muscles in depth. sEMG is easy to apply, safe, non-invasive, and patient-friendly.[19] We followed standard guidelines and 'best practices' for the correct placement of the electrodes and data analysis, as correct signal acquisition and processing can be difficult due to variable measurement setups and strong crosstalk from the heart and adjacent muscles.[18,19,21,24,30,31,37] We normalized the RMS amplitudes, as normalization improves the interpretability and comparability.[19] A limitation of sEMG is that it was not possible to compare the level of activity of different muscles because of the anatomical and physiological variations, electrode placement, and thickness of subcutaneous tissues.[18] As such, the relative contribution of each muscle to the force generated to overcome the resistance of the RET could not be determined. In this study, the registration of muscle activity was limited to the diaphragm, intercostal, and scalene muscles, leaving the response of other inspiratory accessory muscles, such as the sternocleidomastoid and trapezius, undetermined. Analyzing muscle activation patterns may offer valuable insights into RMF. Specifically, studying changes in relative timing between the

diaphragm and accessory muscles could be a promising biomarker for treatment response, as patients may be able to shift their respiratory drive to accessory muscles before neuromuscular fatigue of the diaphragm becomes evident.[19,33] Relative recruitment measured by the latency to onset of EMG activity during an isometric contraction may be an interesting alternative to compare the involvement of different respiratory muscles in patients with SMA.[38]

Some of our recordings resulted in nRMS amplitudes above 100% MVC. This could be explained by enhanced inter-neuromuscular coordination elicited by repeated inspiratory muscle loading during the determination of the PImax before the RET.[39] In future studies, this may be prevented by applying a short period of submaximal inspiratory loading before the MVC determination.[19,33]

Lastly, we recommend that, if possible, patients should be tested at all resistance levels of the RET at multiple time points to compare the muscle activity at different resistance levels. This would further increase the power and interpretability of the study.

CONCLUSION

In this study, we explored the muscle activity and fatigue response of respiratory muscles during a respiratory endurance test using sEMG in patients with SMA. The relative activity of the diaphragm at onset of a respiratory endurance test remained stable at higher intensity levels, while the activity of the intercostal and scalene muscles became more variable. The diaphragm showed the most significant signs of fatigue, while accessory inspiratory muscles like the scalene muscles showed no clear fatigue signs. This suggests that the load of breathing against resistance is shared amongst different respiratory muscles according to their biomechanical and morphological specificities.

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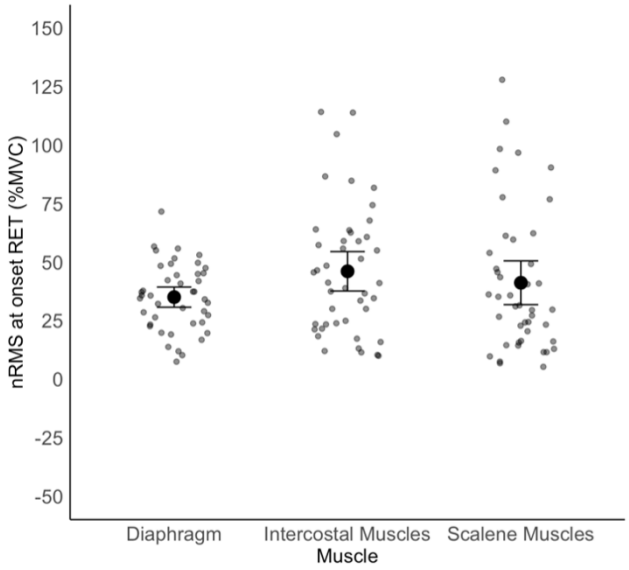
APPENDIX 3.A: nRMS amplitudes at onset of the RET per resistance level

Resistance level of the RET (% of PImax)	**20% n=14 (32%)**	**35% n=13 (29%)**	**45% n=10 (23%)**	**55% n=3 (7%)**	**70% n=4 (9%)**	***p*-value**
nRMS amplitude Diaphragm in %MVC, mean (95%CI)	31.3 (23.8-38.9)	30.7 (22.5-38.8)	44.8 (34.6-54.9)	32.9 (10.0-55.7)*	39.8 (25.0-54.5)*	0.11
nRMS amplitude Intercostal muscles in %MVC, mean (95%CI)	44.9 (28.5- 61.3)	37.4 (19.4-55.5)	53.6 (39.4-67.8)	40.8 (19.5-62.1)*	63.3 (1.8-125.0)*	0.46
nRMS amplitude Scalene muscles in %MVC, mean (95%CI)	29.3 (11.2-47.4)	40.9 (21.9-59.9)	46.8 (33.2-60.4)	53.2 (-9.0, 115.0)*	60.6 (-3.7, 125,0)*	0.36

*Note: *The reliability of the calculated 95% CI is limited due to the low sample size.*

Abbreviations: %MVC: percentage of the root mean square amplitude during a maximal voluntary contraction, CI: confidence interval, Hz: hertz, n: number of participants, nRMS: normalized root mean square, PImax: maximal inspiratory mouth pressure, RET: Respiratory Endurance Test.

APPENDIX 3.B: Variance between the nRMS of the diaphragm, intercostal muscles, and scalene muscles at onset (breath 7) of the respiratory endurance test (RET).



Note: Boxplots with the individual data points of all RET resistances are visualized, with their mean and 95% confidence intervals. The variance of the normalized root mean square (nRMS) between the muscles was significantly different (p=0.002).

APPENDIX 3.C: results of the linear mixed model analyses, slopes of the lnRMS amplitudes and MF, corrected for the different resistance levels of the RET.

	noRMF n=30	RMF n=16	Δslope	*p*-value
Slope lnRMS amplitude Diaphragm in ln(mV)/breath, mean (95%CI)	0.00032 (-0.00011 - 0.00075)	-0.00150 (-0.00285 - -0.00015)	-0.00182 (-0.00324 - -0.00040)	**0.012**
Slope lnRMS amplitude Intercostal muscles in ln(mV)/breath, mean (95%CI)	-0.00076 (-0.00129 - -0.00023)	0.00089 (-0.00078 - 0.00255)	0.00164 (-0.00010 - 0.00339)	0.065
Slope lnRMS amplitude Scalene muscles in ln(mV)/breath, mean (95%CI)	0.00074 (0.00022 - 0.00127)	0.00025 (-0.00140 - 0.00191)	-0.00049 (-0.00223 - 0.00125)	0.58
Slope MF Diaphragm in Hz/breath, mean (95%CI)	0.04662 (-0.00366 - 0.09689)	-0.54343 (-0.70118 - -0.38559)	-0.59005 (-0.75561 - -0.42439)	**<0.0001**
Slope MF intercostal in Hz/breath, mean (95%CI)	0.02869 (-0.01076 - 0.06813)	-0.08990 (-0.21400 - 0.03390)	-0.11859 (-0.24881 - 0.01134)	0.074
Slope MF Scalene muscles in Hz/breath, mean (95%CI)	0.00095 (-0.04738 - 0.04928)	0.11546 (-0.03628 - 0.26733)	0.1145 (-0.04474 - 0.27388)	0.16

Abbreviations: Δ: differences between the slopes of the noRMF group and the RMF group, μV: microvolt, CI: confidence interval, Hz: hertz, ln: natural logarithm, MF: median frequency, n: number of participants, RMF: respiratory muscle fatigability, lnRMS: natural logarithm-transformed root mean square.

APPENDIX 3.D: results of the linear mixed model analyses, slopes of the lnRMS amplitudes and MF, not corrected for the different resistance levels of the RET.

	noRMF n=30	**RMF n=16**	**Δslope**	***p*-value**
Slope lnRMS amplitudes Diaphragm in ln(μV)/breath, mean (95%CI)	0.00032 (-0.00011 - 0.00075)	-0.00151 (-0.00286 - -0.00016)	-0.00183 (-0.00324 - -0.00041)	**0.012**
Slope lnRMS amplitudes Intercostal muscles in ln(μV)/breath, mean (95%CI)	-0.00076 (-0.00129 - -0.00023)	0.00088 (-0.00079 - 0.00254)	0.00164 (-0.00011 - 0.00338)	0.066
Slope lnRMS amplitudes Scalene muscles in ln(μV)/breath, mean (95%CI)	0.00074 (0.00022 - 0.00127)	0.00024 (-0.00141 - 0.00190)	-0.00050 (-0.00224 - 0.00124)	0.57
Slope MF Diaphragm in Hz/breath, mean (95%CI)	0.04663 (-0.00365 - 0.09691)	-0.54214 (-0.69986 - -0.38424)	-0.58878 (-0.75430 - -0.42306)	**<0.0001**
Slope MF intercostal in Hz/breath, mean (95%CI)	0.02869 (-0.01076 - 0.06813)	-0.09001 (-0.21407 - 0.03383)	-0.11870 (-0.24888 - 0.01127)	0.074
Slope MF Scalene muscles in Hz/breath, mean (95%CI)	0.00095 (-0.04738 - 0.04928)	0.11538 (-0.03638 - 0.26721)	0.11442 (-0.04484 - 0.27377)	0.16

Abbreviations: Δ: differences between the slopes of the noRMF group and the RMF group, μV: microvolt, CI: confidence interval, Hz: hertz, ln: natural logarithm, MF: median frequency, n: number of participants, RMF: respiratory muscle fatigability, lnRMS: natural logarithm-transformed root mean square.



Part II

The effect of disease-modifying therapies on lung function and respiratory muscle strength in patients with SMA.





Chapter 4

The effect of disease-modifying therapies on lung function and respiratory muscle strength in spinal muscular atrophy: systematic review and meta-analysis.

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ABSTRACT

Background

Spinal muscular atrophy (SMA) is often complicated by respiratory problems. The disease-modifying therapies (DMTs) (Nusinersen, Onasemnogene abeparvovec, and Risdiplam) have improved survival, motor function, and functional muscle strength in patients with SMA, but their effects on lung function and respiratory muscle strength need further clarification. Therefore, we performed a systematic review of studies that documented the effects of DMTs on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, and 4.

Methods

We searched the electronic databases PubMed/Medline, CINAHL, Embase, and Web of Science up to December 2023. We included pre-post studies that determined the effect of DMTs for SMA on lung function or respiratory muscle strength in patients with SMA. Where possible, we performed a meta-analysis using a random-effects model with generic inverse variance weighing.

Results

We included 19 studies out of 376 identified records (16 longitudinal cohort studies and three case series) with 384 participants. Seventeen studies investigated the effect of Nusinersen, and two studies investigated the effect of Risdiplam. Seventeen studies had a moderate, and two had a high risk of bias. Most of these studies did not report statistically significant improvement in lung function or respiratory muscle strength after treatment with Nusinersen or Risdiplam. A meta-analysis of 13 studies showed no statistically significant improvement in FVC after two, six, 10, and >12 months of treatment with Nusinersen.

Conclusion

The findings of this review indicate that there is moderate evidence that Nusinersen does not improve FVC, FEV1, peak expiratory flow, or maximum inspiratory pressure in patients with SMA types 1, 2, 3, or 4. There was no statistically significant decline in lung function and respiratory muscle strength after treatment. This may suggest that Nusinersen may have stabilized lung function and respiratory muscle strength.

Keywords

spinal muscular atrophy, disease-modifying therapies, Nusinersen, Risdiplam, lung function, respiratory muscle strength, systematic review, meta-analysis

INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) has an estimated incidence of 1 in 6,000-12,000 live births.[1] SMA is caused by the loss of function of both alleles of the survival motor neuron 1 gene (*SMN1*). This causes a deficiency of intracellular SMN protein and degeneration of alpha motor neurons in the spinal cord.[2–4] Ultimately, this leads to progressive weakness of axial, respiratory, and proximal limb muscles.[5,6]

SMA has a wide range of severity that is categorized into four SMA types based on the age at onset and the highest acquired motor milestone.[3,4,7–10] Progressive weakness of respiratory muscles is an important characteristic of SMA.[11,12] Respiratory muscle weakness is associated with a decreased ability to cough, leading to a vicious cycle of recurrent (lower) respiratory tract infections and finally respiratory failure.[12] Natural history studies have shown that respiratory muscle strength and lung function deteriorate without treatment in patients with early-onset SMA, i.e., SMA types 1, 2, and 3a.[11,12] The majority of treatment-naïve patients with SMA type 1 or 2 eventually require mechanical ventilation.[13]

To address the deficiency of SMN protein and potentially enhance muscle strength, the disease-modifying therapies (DMTs) Nusinersen (Spinraza®, Biogen, Cambridge, Massachusetts, United States of America), Onasemnogene abeparvovec (Zolgensma®, Novartis, Dallas, Texas, United States of America), and Risdiplam (Evrysdi®, Genentech, South San Francisco, California, United States of America) were introduced between 2016 and 2021. These therapies have improved survival, motor function, and functional muscle strength in patients with SMA types 1, 2, and 3.[14] Commonly used respiratory outcomes to assess the efficacy of DMTs include the need for ventilatory support and the incidence of respiratory failure.[14–17] Although these are important outcome measures of morbidity and mortality in patients with SMA, they also depend on many other factors, such as respiratory tract infections, the absence of criteria for starting or ceasing noninvasive ventilation (NIV), and individual treatment center practices. To better understand the effect of DMTs on respiratory outcomes, more direct and standardized outcome measures, such as lung function and respiratory muscle strength, should be evaluated.

Therefore, we performed a systematic review to identify, evaluate, and summarize the findings of studies concerning the effect of DMTs (Nusinersen, Onasemnogene abeparvovec, and Risdiplam) on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, or 4.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[18] to ensure an accurate and complete report of our work.

Search strategy

We searched the electronic databases PubMed/Medline, CINAHL, Embase, and Web of Science for eligible articles until December 7th, 2023. We used the following MeSH terms and Emtree: *"Muscular Atrophy, Spinal", "Spinal Muscular Atrophies of Childhood", "Oligonucleotides, Antisense", "Nusinersen", "Onasemnogene abeparvovec", "Risdiplam", "Respiratory Muscle Strength", "Maximal Inspiratory Mouth Pressure", "Maximal Expiratory Mouth Pressure", "Respiratory Muscle Function", "Vital Capacity", "Forced Expiratory volume in 1 second", "Peak Cough Flow", "Peak Expiratory Flow", "Sniff Nasal Inspiratory Pressure"* and *"Airway Occlusion Pressure"*. **Appendix 4.A** shows the complete search strategy.

Inclusion and exclusion of studies

We defined the eligibility criteria a priori. We included articles if they met the following inclusion criteria:

1) Genetically proven SMA as defined by homozygous *SMN1* deletion or compound heterozygous alterations (mutation and deletion) on chromosome 5q13;
2) Clinical SMA types 1, 2, 3, or 4;
3) Treatment with disease-modifying therapies for SMA (Nusinersen, Onasemnogene abeparvovec, or Risdiplam);
4) Assessment of lung function or respiratory muscle strength:
    a. Slow/forced vital capacity ([S/F]VC): maximum amount of air gradually or forcefully exhaled after maximum inspiration.
    b. Forced expiratory volume in 1 second (FEV1): volume of air forcefully exhaled in the first second of an FVC test.
    c. Total lung capacity (TLC): maximum volume of air in the lungs after maximum inspiration.
    d. Peak cough flow (PCF): maximum speed of airflow generated during a forceful cough.
    e. Peak expiratory flow (PEF): maximum speed of expiration.
    f. Maximum inspiratory pressure (PImax): highest negative pressure generated during a forceful inhalation against an occluded airway, reflecting inspiratory muscle strength.
    g. Maximum expiratory pressure (PEmax): highest positive pressure generated during a forceful exhalation against an occluded airway, reflecting expiratory muscle strength.

h. Sniff nasal inspiratory pressure (SNIP): highest negative pressure generated during a rapid sniff through the nose against an occluded airway, reflecting inspiratory muscle strength.

5) Longitudinal study design, including at least data from a baseline measurement and one post-treatment measurement.

We excluded articles if they were not available in full text (even after contacting the authors); written in a language other than English, Dutch, or German; classified as protocols and abstracts; or case reports (case series were included because they often provide a larger number of cases compared to case reports and are frequently utilized to report the outcomes of new treatments or interventions, which is relevant to the research question).

Study selection

Two reviewers (KKS and LvdH) independently screened the articles for eligibility based on their titles and abstracts. We read the full text of studies that were potentially eligible to decide on inclusion/exclusion. If there was any doubt concerning the articles, we discussed the article inclusion with a third assessor until we reached consensus. Additionally, we performed reference tracking and snowballing of all included articles to ensure a comprehensive search. The PRISMA flowchart displays the process of study selection (**Figure 4.1**).

Data extraction and management

We extracted the characteristics of the included studies using a standard extraction form. The extracted data were: 1) first author, publication year, and the study site; 2) used DMT and SMA type; 3) study design; 4) number and age of participants; 5) mean age at onset and disease duration; 6) timing of assessment of lung function/respiratory muscle strength; 7) study results of the effect of DMT on lung function/respiratory muscle strength; 8) overall conclusion regarding the effect of DMT on lung function/respiratory muscle strength.

Assessment of the risk of bias

Two reviewers (KKS and LvdH) independently scored the study's risk of bias (ROB) with the 'Quality Assessment Tool for Before-After (Pre-Post) studies with No Control Group' from the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, Accessed July 5, 2023) (**Appendix 4.B**). The tool evaluates the internal validity of a study with 12 questions. The questions can be answered with yes, no, cannot determine, not applicable, or not reported. We calculated the total yes scores and divided this total by the number of applicable questions to determine the ROB. Scores between 75% and 100% indicated a low ROB, scores between

25% and 75% indicated a moderate ROB, and scores between 0% and 25% indicated a high ROB. The strength of interrater agreement after the first scoring was measured by Cohen's Kappa (K) coefficient, with K=0.41-0.60 indicating moderate agreement, K=0.61-0.80 indicating good agreement, and K≥0.81 indicating very good agreement. Disagreements were resolved in a consensus meeting between the raters.

Data synthesis

We performed a meta-analysis with Review Manager 5.4 software[19] (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) if outcome data were available in three studies or more. We generated a standardized mean difference (SMD) with a 95% confidence interval (CI) using the generic inverse variance method in a random-effects model. We used mean and standard deviation (SD) at baseline and follow-up measurements for continuous outcomes. We evaluated heterogeneity using the *p*-value of the chi-square test, I^2, Tau^2, and visual inspection following the Grading of Recommendations Assessment, Development, and Evaluation handbook (https://gdt.gradepro.org/app/handbook/ handbook.html, Accessed July 5, 2023). If studies reported change from baseline without SD or if they reported median outcome measures, we requested raw data from the authors of the studies. We conducted subgroup analysis for short-term (≤ 12 months) and long-term (> 12 months) follow-up.

When we could not perform a meta-analysis, we summarized the evidence with a best-evidence synthesis based on the system of the Cochrane Collaboration Back Review Group.[20] This system is a method to summarize evidence in observational studies in which the study population, the assessment of exposure and outcomes, and the data analyses are heterogenic. It has five levels of evidence:

1) Strong evidence: consistent findings in multiple cohort studies with low ROB;
2) Moderate evidence: consistent findings in one cohort study with a low ROB and/or multiple cohort studies with a moderate ROB;
3) Limited evidence: consistent findings in one cohort study/case-series study with a moderate ROB and/or multiple cohort studies/case-series studies with a high ROB;
4) Conflicting evidence: consistent findings in less than 75% of the studies;
5) No evidence: findings in one cohort study/case-series study with a high ROB or no studies available.

RESULTS

Study selection

The search strategy produced 376 hits, including 106 duplicate studies. After excluding duplicates and screening titles and abstracts, we identified 55 studies as possibly relevant. Thirty-four studies were only available in (conference) abstract and therefore excluded. We excluded four additional studies after full-text screening based on specific

criteria outlined in the PRISMA flow diagram (**Figure 4.1**), leading to a final number of 17 studies.[21–37] We found two extra studies using backward snowballing.[38,39] We requested and received raw baseline data or follow-up data from the authors of five included studies.[21,27,28,33,35]

Characteristics of included studies

Characteristics of the included studies are presented in **Table 4.1**. Of the 19 included studies, 16 studies were observational cohort studies, of which 12 had a prospective design[21–29,33,35,36] and four a retrospective design.[30,32,37,39] Three studies had a case series design.[31,34,38] One study included a control group[21] and two studies compared results before treatment with results during treatment.[23,24] The two observational cohort studies from de Wel et al. used the same cohort; in the first study, they reported the results after six and 14 months of treatment[24] and in the second study, they reported the results after 22 months of treatment.[25]

In total, the included studies enrolled 499 patients; 25 patients had SMA type 1, 163 patients had SMA type 2, 306 patients had SMA type 3, and five patients had SMA type 4. Three studies included children (n=88)[23,30,37], two studies included both children and adults (n=50)[21,22], and 14 studies included adults only (n=361).[24–29,31–36,38,39] Not all of the enrolled patients assessed lung function or respiratory muscle strength, leading to a total of 384 patients with data on lung function or respiratory muscle strength.

Seventeen studies investigated the effect of Nusinersen and two the effect of Risdiplam.[34,38] Seventeen studies assessed FVC[21–28,30,31,33–39], one VC[32], six FEV1[29,34–37,39], one TLC[22], two PCF[23,33], and four PEF[24,25,35,36] (**Appendix 4.C and 4.E**). Four studies assessed PImax and PEmax[22,23,26,32] and two SNIP[23,32] (**Appendix 4.D**).

In addition to results for the entire group of included patients, a few studies also showed results per subgroup. Four studies reported results per SMA type.[23,26,29,39] One study reported results stratified according to the number of *SMN*2 copies, functional status (nonsitter/sitter/walker), and scoliosis surgery status (no spinal fusion/spinal fusion).[26] One study reported results stratified according to ambulatory status (ambulatory/non-ambulatory) and fatigue status (with fatigue/without fatigue).[35] One study reported results stratified for functional scores, i.e., </≥15.6% on the 32-item Motor Function Measurement (MFM-32).[32]

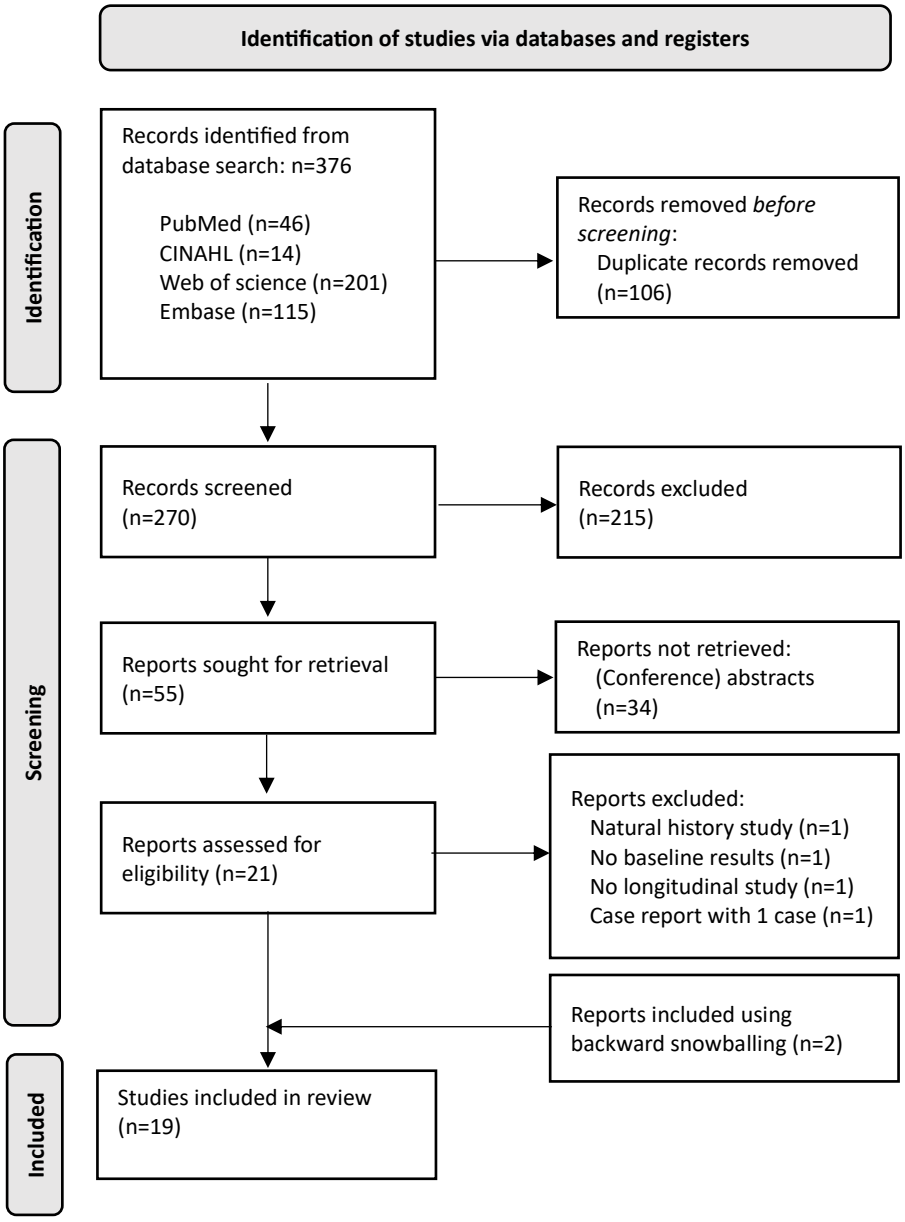


Figure 4.1: *PRISMA flow diagram*
Abbreviation: n: number

Table 4.1: *Descriptives and characteristics of the included articles*

First author Year[ref] Location	*Study type*	*Number of participants (% male)*	*SMA type*	*Ambulant*	*Mean age, years (range)*	*Mean age at onset (range)*	*Disease duration (range)*	*Outcomes*	*Measurement moments*	*Main results, mean difference [95% CI], p-value*	*ROB*
NUSINERSEN											
Bjelica 2023[35] Germany	Pro-spective cohort study	38* (61.4) *Adults*	1 (n=1) 2 (n=14) 3 (n=21) 4 (n=2)	28.9%	38.4	NR	32.5y (SD: 13.5y)	FVC (l) FEV1 (l) PEF (l/sec)	T0, M10, M22, M30	- n.s. results in FVC, FEV1, and PEF. - PEF sign ↑ in subgroup ambulatory vs non-ambulatory at M30: +0.8 vs -0.0, p<.05. - PEF sign ↑ in subgroup fatigue vs no fatigue at M10: +0.6 vs -0.4, p<.05.	**M**
Carson 2022[22] USA	Pro-spective cohort study	11 (45) *Children + adults*	2	0%	18.1 (7.9-31.5)	NR	NR	FVC (l) TLC (l) PImax (cmH_20) PEmax (cmH_20)	T0, M1, M6, M14, M22, M30, M34	- n.s. results in FVC, TLC, PImax, and PEmax.	**M**
Chacko 2022[23] Australia	Pro-spective cohort study	28* (53.6) *Children*	1 (n=7) 2 (n=12) 3 (n=9)	NR	8.71† (0.08-18.58)	NR	NR	FVC (%pred) PCF (l/min) PImax (z-score) PEmax (z-score) SNIP (cmH_20)	2 years before T0, T0, D29, D64, D183, D302, D365	- Slower rate of decline py in FVC in SMA type 2. Difference between pretreatment – posttreatment rate of decline: 4.83 %pred [1.20, 8.47], p=.009. - n.s. results in PImax, PEmax, SNIP, PCF.	**M**
De Wel 2021[24] Belgium	Pro-spective cohort study	16 (63) *Adults*	3 (n=14) 4 (n=2)	43.7%	37.5 (22-66)	6.5y (1-30y)	NR	FVC (l) PEF (l/sec)	T0, M6, M14	- FVC sign ↑ at M6: +0.12l [0.03, 0.21], p=.01. - n.s. results in PEF.	**M**

De Wel 2022[25] Belgium	Pro-spective cohort study	16 (63) *Adults*	3 (n=14) 4 (n=2)	43.7%	37.5 (22-66)	6.5y (1-30y)	30.5y (8-60y)	FVC (l) PEF (l/sec)	T0, M22	- PEF sign ↑at M22: +0.41L, p=.011. - n.s. results in FVC.	**M**
Duong 2021[26] USA	Pro-spective cohort study	42* (57.1) *Adults*	2 (n=18) 3 (n=24)	26.2%	33.7 (17.7-66.1)	18M† (3-18M)	30.9y (12.1-60.6y)	FVC (%pred) PImax (cmH_2O) PEmax (cmH_2O)	T0, every 4M after (range 3-24M)	- FVC sign ↑ in subgroup spinal fusion: +5.31 %pred py [0.36, 10.25]. - n.s. results in FVC in the whole group/other subgroups. - PEmax sign ↑ in whole group: +6.38 cmH_2O py [2.52, 10.25], subgroup walkers: +18.25 cmH_2O py [6.87, 29.64], subgroup no spinal fusion: +7.68 cmH2O py [2.23, 13.12]. - n.s. results in PEmax in other subgroups. - n.s. results in PImax.	**M**
Elsheikh 2021-04[27] USA	Pro-spective open-label study	19 (36.8) *Adults*	2 (n=9) 3 (n=10)	0%	39.7 (21.3-64.8)	27M (2-156M)	NR	FVC (l)	T0, M2, M6, M10, M14	- n.s. results in FVC.	**M**
Elsheikh 2021-05[28] USA	Pro-spective open-label study	13 (53.8) *Adults*	3 (n=12) 4 (n=1)	100%	36.6 (18-59)	NR	NR	FVC (l)	T0, M2, M6, M10, M14	- FVC sign ↑ at M6: +0.16 l [0.04, 0.27], *p*=.008, M10: +0.12 l [0.01, 0.24], *p*=.0332) and M14: +0.17 l [0.05, 0.3], *p*=.007.	**M**
Fainmesser 2022[29] Israel	Pro-spective cohort study	37* (54) *Adults*	2 (n=15) 3 (n=22)	18.9%	38† (21-64)	2y† (0.5-33y)	NR	FEV1 (%pred)	T0, M6, M14, M26	- n.s. results in FEV_1.	**M**
Freigang 2023[36] Germany	Pro-spective study	24* (46) *Adults*	2 (n=10) 3 (n=14)	20.8%	37.2 (17-57)	1.5y† (0.15-15y)	34y (15-54y)	FVC (%pred) FEV1 (%pred) PEF (%pred)	T0, M26	- n.s. results in FVC, FEV_1, PEF.	**M**

Gonski 2023[37] Australia	Retro-spective cohort study	48* (52) *Children*	1 (n=10) 2 (n=23) 3 (n=15)	16.7%	6.98 (SD: 5.25)	NR	NR	FVC (l, %pred, z-score) FEV1 (l, %pred, z-score)	Pre: 0-2 years before start - Post: 0-2 years after start	- FVC in l sign ↑ post: +0.21 l [0.06, 0.37], p=.01. - FVC in %pred lower post: -6.28% [-13.9, 0.52], p=.07 - FEV1 in l sign ↑ post: +0.20 l [0.07, 0.34], p=.005 - FEV1 in %pred lower post: -4.57% [-10.95, 1.81], p=.15	**M**
Heitschmidt 2021[30] Germany	Retro-spective study	12 (66.7) *Children*	2 (n=3) 3 (n=9)	58.3%	NR (4-12.5)	NR	NR	FVC (%pred)	T0, D180, D300	- n.s. results in FVC.	**M**
Jochmann 2020[31] Germany	Case series	7* (71.4) *Adults*	2 (n=4) 3 (n=3)	14.3%	45† (20-68)	1.3y† (9M-14y)	NR	FVC (%pred)	T0, M2, M6, M10	- n.s. results in FVC.	**H**
Lefeuvre 2022[32] France	Retro-spective cohort study	18 (66.7) *Adults*	1 (n=7) 2 (n=9) 3 (n=2)	NR	28 (21-39)	NR	NR	VC (l) PImax (cmH_20) PEmax (cmH_20) SNIP (cmH_20)	D0 , D63, D183, D303	- n.s. results in VC, PImax, PEmax, SNIP.	**M**
Maggi 2020 [39] Italy	Retro-spective cohort study	116* (58.6) *Adults*	2 (n=13) 3 (n=103)	44.8%	34† (18-72)	3y† (0-17y)	29y† (3-63y)	FVC (%pred) FEV1 (%pred)	T0, M6, M10, M14	- FVC sign ↑in subgroup SMA type 3 'walker' at M14: +9 %pred, *p*=.031. - FEV_1 sign ↑ in subgroup SMA type 3 at M14: +5.86 %pred, *p*=.0499.	**M**
Vazquez-Costa 2022[21] Spain	Pro-spective cohort study	39* (51.3) *>15 year*	2 (n=10) 3 (n=29)	33.3%	33.35 (SD: 13.35)	NR	28.84y (SD: 13.53y)	FVC (%pred)	T0, M6, last visit (mean M16.06)	- n.s. results in FVC.	**M**
Walter 2019[33] Germany	Pro-spective cohort study	19 (63.2) *Adults*	3	63.2%	35.11 (18-59)	10.79y (1-40y)	24.32y (6-53y)	FVC (%pred) PCF (l/min)	T0, D63, D180, D300	- n.s. results in FVC. - PCF sign ↑ at D180: moderate effect size: d=0.5, r=0.25, *p*= .044.	**M**

RISDIPLAM											
Mccluskey 2022[34] UK	Case series	6 (16.7) *Adults*	2	0%	33† (26-44)	6-12M† (6-12M - 12-18M)	NR	FVC (%pred) FEV1 (%pred)	T0, M3, M6, M9	- n.s. results in FVC, FEV1.	**M**
Ñungo Garzón 2023[38] Spain	Case series	6* (50) *Adults*	2	0%	35.5† (17-46)	NR	NR	FVC (%pred)	12 months before T0, T0, M6, M12	- No clinically meaningful changes in FVC at M12.	**H**

*Notes: †: median, *: no respiratory test data available from all included patients, ↑ : improved*
*Abbreviations: %pred: percentage of predicted, cmH_20: centimeter of water column, CI: confidence interval, d: Cohen's d, D: day, D…: after … days of treatment, (F)VC: (forced) vital capacity, FEV1: forced expiratory volume in one second, **H**: high risk of bias, l: liter, l/min: liter per minute, **M**: moderate risk of bias, M: months, M…: after … months of treatment, NR: not reported, n.s.: no statistically significant, PEmax: maximal expiratory pressure, PImax: maximal inspiratory pressure, n: number of patients, NR: not reported, p: probability value, PCF: peak cough flow, PEF: peak expiratory flow, py: per year, r: effect size, ROB: Risk of bias, SD: standard deviation, sign: significant, SMA: spinal muscular atrophy, SNIP: sniff nasal inspiratory pressure, T: time, T0: before start Nusinersen/Risdiplam, TLC: total lung capacity, y: year, Z-score: A standardized score indicating the deviation from the mean in units of standard deviation.*

Risk of bias (ROB)
Seventeen studies had a moderate ROB[21–30,32–37,39] and two studies had a high ROB.[31,38] See **Table 4.1** for the conclusion of the ROB assessment and **Appendix 4.B** for a more detailed ROB summary. The Cohen's K coefficient was 0.79 for the interrater reliability, representing good agreement.

Results of individual studies and syntheses
Table 4.1 shows the main results of the individual studies. **Appendix 4.C** (effect of Nusinersen on lung function), **Appendix 4.D** (effect of Nusinersen on respiratory muscle strength), and **Appendix 4.E** (effect of Risdiplam on lung function) show the results of all measurement outcomes at baseline, short-term follow-up (≤ 12 months), and long-term follow-up (> 12 months). **Table 4.2** shows the summary of the levels of evidence per lung function/respiratory muscle strength measure.

Effect of Nusinersen on lung function

Forced Vital Capacity (FVC)
Fifteen studies, 14 with a moderate ROB[21–28,30,33,35–37,39] and one with a high ROB[31], assessed FVC in patients with SMA type 1, 2, 3, or 4. Five studies reported statistically significant improvement in FVC after different durations of treatment[24,28,37,39] or in a subgroup[26], while nine studies did not.[21,22,25,27,30,31,33,35,36] One study[23] reported no statistically significant improvement in FVC %pred after one year of treatment with Nusinersen; however, they reported a statistically significant slower rate of annual decline in FVC %pred in 12 children with SMA type 2 under treatment, compared to pre-treatment.

Thirteen studies were eligible for statistical pooling using meta-analysis.[21–25,27,28,31,33,35–37,39] All studies assessed FVC in patients with multiple types of SMA in the same study. Meta-analysis was performed on three short-term follow-up moments: after two months of Nusinersen treatment (four studies[27,28,31,33], **Figure 4.2a**), after six months of Nusinersen treatment (six studies[24,27,28,31,33,39], **Figure 4.2b**), and after 10 months of Nusinersen treatment (six studies[27,28,31,33,35,39], **Figure 4.2c**). Meta-analysis was also performed on 10 studies[21–23,25,27,28,35–37,39] with a long-term follow-up moment (>12 months) (**Figure 4.2d**). All meta-analyses failed to show statistically significant improvements in FVC after treatment with Nusinersen. Therefore, there is moderate evidence that Nusinersen does not improve FVC in patients with SMA type 1, 2, 3, or 4 after two, six, 10, or >12 months of treatment.

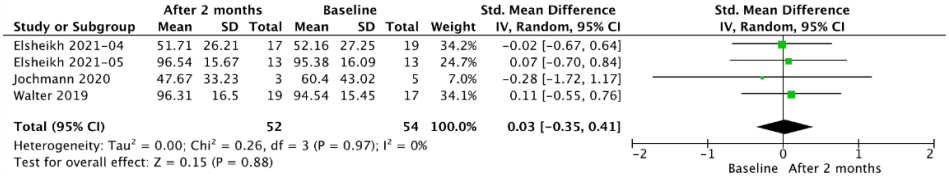


Figure 4.2a: *Forest plot presenting the pooled analysis of the four studies comparing FVC between baseline and after two months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

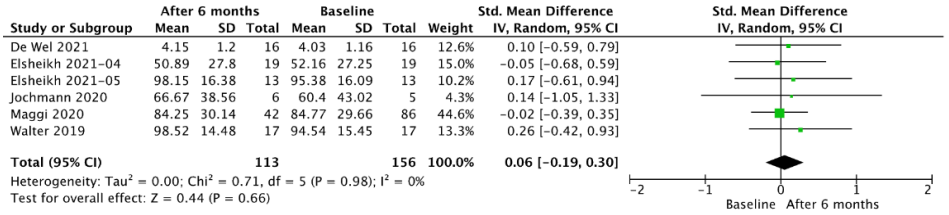


Figure 4.2b: *Forest plot presenting the pooled analysis of the six studies comparing FVC between baseline and after six months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

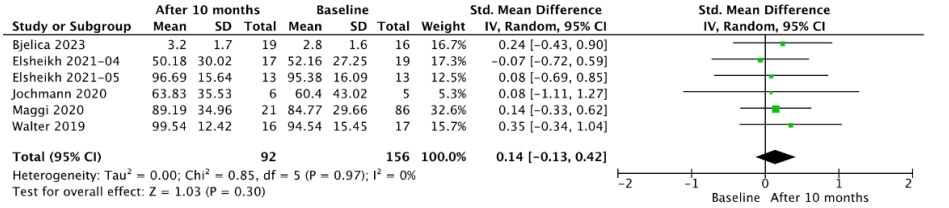


Figure 4.2c: *Forest plot presenting the pooled analysis of the six studies comparing FVC between baseline and after 10 months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

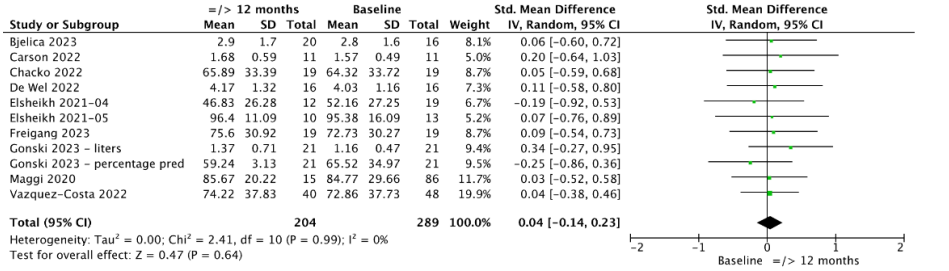


Figure 4.2d: *Forest plot presenting the pooled analysis of the 10 studies comparing FVC between baseline and after >12 months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

Vital Capacity (VC)

One study, with a moderate ROB[32], reported no statistically significant improvement in VC after 63, 183, or 303 days of treatment in 18 patients with SMA type 1, 2, or 3. Therefore, there is limited evidence that Nusinersen does not improve VC in patients with SMA type 1, 2, or 3. There is no evidence about the efficacy of Nusinersen on VC in patients with SMA type 4.

Forced Expiratory Volume in 1 second (FEV1)

Five studies, with a moderate ROB[29,35–37,39], assessed FEV1 in patients with SMA type 1, 2, 3, or 4. One study (in 21 children with SMA type 2 or 3) reported a statistically significant improvement in FEV1 in liters, but not in FEV1 in percentage of predicted.[37] One study reported a statistically significant improvement in FEV1 in 15 patients with SMA type 3 after 14 months of treatment[39], while three studies reported no statistically significant improvement in FEV1.[29,35,36]

Four studies, with a long-term follow-up moment, were eligible for statistical pooling using meta-analysis[35–37,39] (**Figure 4.3)**. The meta-analysis failed to show statistically significant improvement in FEV1 after treatment with Nusinersen. Therefore, there is moderate evidence that Nusinersen does not improve FEV1 in patients with SMA type 1, 2, 3, or 4.

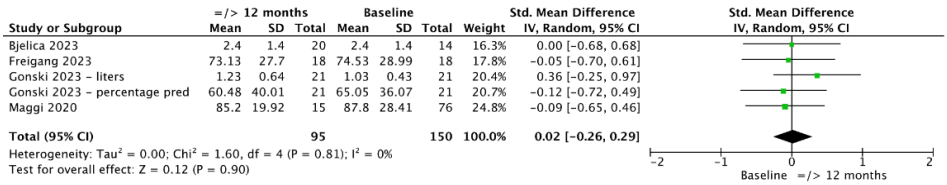


Figure 4.3*: Forest plot presenting the pooled analysis of the four studies comparing FEV1 between baseline and after >12 months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

Total Lung Capacity (TLC)

One study, with a moderate ROB[22], reported no statistically significant improvement in TLC after 22-34 months of treatment in 11 patients with SMA type 2. Therefore, there is limited evidence that Nusinersen does not improve TLC in patients with SMA type 2. There is no evidence about the efficacy of Nusinersen on TLC in patients with SMA type 1, 3, or 4.

Peak Cough Flow (PCF)

Two studies, with a moderate ROB[23,33], assessed PCF. One study[23] reported no statistically significant improvement in PCF after 12 months of treatment in 28 patients with SMA type 2 or 3. One study[33] reported a statistically significant improvement in PCF

after 180 days of treatment in 13 patients with SMA type 3. However, this effect disappeared after 300 days of treatment. Therefore, there is limited evidence that Nusinersen does not improve PCF in patients with SMA type 2, and there is conflicting evidence about the effect of Nusinersen on PCF in patients with SMA type 3. There is no evidence about the efficacy of Nusinersen on PCF in patients with SMA type 1 or 4.

Peak Expiratory Flow (PEF)

Four studies (two with the same cohort), with a moderate ROB[24,25,35,36], assessed PEF in patients with SMA type 1, 2, 3, or 4. One study reported a statistically significant improvement in PEF in the subgroups of ambulatory patients (n=4, after 30 months of treatment) and patients with fatigue (n=6, after 10 months of treatment)[35], but not in the whole group (n=20, SMA type 1, 2, 3, or 4) or the subgroups at other time points.[35] The studies with the same cohort[24,25] reported no significant improvements in 16 patients with SMA type 3 or 4 after six or 14 months of treatment[24], but they did report a statistically significant improvement in PEF after 22 months of treatment.[25] One study reported no statistically significant improvement in PEF in 18 patients with SMA type 2 or 3 after 26 months of treatment.[36]

Three studies, with a long-term follow-up moment, were eligible for statistical pooling using meta-analysis[25,35,36] **(Figure 4.4)**. The meta-analyses failed to show statistically significant improvement in PEF after treatment with Nusinersen. Therefore, there is moderate evidence that Nusinersen does not improve PEF in patients with SMA type 1, 2, 3, or 4.

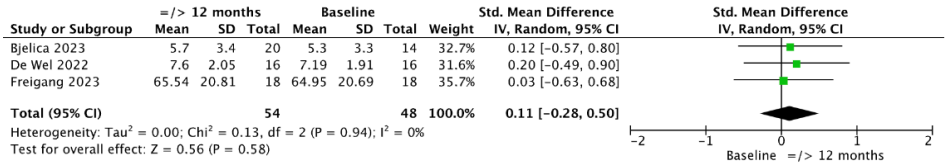


Figure 4.4: *Forest plot presenting the pooled analysis of the three studies comparing PEF between baseline and after >12 months of treatment with Nusinersen.*

Abbreviations: CI: confidence interval, df: degrees of freedom, I^2: level of heterogeneity, P: probability value, SD: standard deviation, Tau^2: between-study variance.

Effect of Nusinersen on respiratory muscle strength

Maximal Inspiratory Pressure (PImax)
Four studies, with a moderate ROB[22,23,26,32], assessed PImax in patients with SMA type 1, 2, or 3. None of them reported statistically significant improvements in PImax after treatment with Nusinersen. Therefore, there is moderate evidence that Nusinersen does not improve PImax in patients with SMA type 1, 2, or 3. There is no evidence about the efficacy of Nusinersen on PImax in patients with SMA type 4.

Maximal Expiratory Pressure (PEmax)
Four studies, with a moderate ROB[22,23,26,32], assessed PEmax in patients with SMA type 1, 2, or 3. One study[26] reported an average rate of change per year of 6.38 cmH_2O [95%CI: 2.52 to 10.25] in PEmax in 25 treated patients with SMA type 2 or 3, most prominently in the subgroup walkers (n=5) and the subgroup no spinal fusion (n=16). One study[22] reported no statistically significant improvement in PEmax after 22-34 months of treatment in 11 patients with SMA type 2. One study[23] reported no statistically significant improvement in PEmax after 12 months of treatment in 13 patients with SMA type 2 or 3. One study[32] reported no statistically significant improvement in PEmax after 63, 183, or 303 days of treatment in 18 patients with SMA type 1, 2, or 3. Therefore, there is limited evidence that Nusinersen does not improve PEmax in patients with SMA type 1. There is moderate evidence that Nusinersen does not improve PEmax in patients with SMA type 2. There is conflicting evidence about the effect of Nusinersen on PEmax in patients with SMA type 3. There is no evidence about the efficacy of Nusinersen on PEmax in patients with SMA type 4.

Sniff Nasal Inspiratory Pressure (SNIP)
Two studies, with a moderate ROB[23,32], assessed SNIP in patients with SMA type 1, 2, or 3. Both reported no statistically significant improvement in SNIP after treatment with Nusinersen. Therefore, there is limited evidence that Nusinersen does not improve SNIP in patients with SMA type 1, 2, or 3. There is no evidence about the efficacy of Nusinersen on SNIP in patients with SMA type 4.

Effect of Risdiplam on lung function and respiratory muscle strength
Two studies, one with a moderate ROB[34] and one with a high ROB[38], assessed FVC in nine patients with SMA type 2. Both reported no statistically significant improvement after nine or 12 months of treatment. Therefore, there is limited evidence that Risdiplam does not improve FVC in patients with SMA type 2.

One study, with a moderate ROB[34], assessed FEV1 in six patients with SMA type 2. They reported no statistically significant improvement after nine months of treatment. Therefore, there is limited evidence that Risdiplam does not improve FEV1 in patients

with SMA type 2. There is no evidence about the efficacy of Risdiplam on FVC and FEV1 in patients with SMA type 1, 3, or 4. There is also no evidence about the efficacy of Risdiplam on VC, TLC, PCF, PEF, PEmax, PImax, or SNIP in patients with SMA type 1, 2, 3, or 4.

Table 4.2: *Summary of the level of evidence per lung function/respiratory muscle strength measure per SMA subtype for the effect of Nusinersen.*

	SMA type 2	**SMA type 2**	**SMA type 3**	**SMA type 4**
FVC	Moderate evidence	Moderate evidence	Moderate evidence	Moderate evidence
	No improvement	No improvement	No improvement	No improvement
VC	Limited evidence	Limited evidence	Limited evidence	No evidence
	No improvement	No improvement	No improvement	
FEV1	Moderate evidence	Moderate evidence	Moderate evidence	Moderate evidence
	No improvement	No improvement	No improvement	No improvement
TLC	No evidence	Limited evidence	No evidence	No evidence
		No improvement		
PCF	No evidence	Limited evidence	Conflicting evidence	No evidence
		No improvement	No/yes improvement	
PEF	Moderate evidence	Moderate evidence	Moderate evidence	Moderate evidence
	No improvement	No improvement	No improvement	No improvement
PImax	Moderate evidence	Moderate evidence	Moderate evidence	No evidence
	No improvement	No improvement	No improvement	
PEmax	Limited evidence	Moderate evidence	Conflicting evidence	No evidence
	No improvement	No improvement	No/yes improvement	
SNIP	Limited evidence	Limited evidence	Limited evidence	No evidence
	No improvement	No improvement	No improvement	

Abbreviations: (F)VC: (forced) vital capacity, FEV1: forced expiratory volume in one second, PEmax: maximal expiratory pressure, PImax: maximal inspiratory pressure, PCF: peak cough flow, PEF: peak expiratory flow, SMA: spinal muscular atrophy, SNIP: sniff nasal inspiratory pressure.

DISCUSSION

In this systematic review, we explored the effect of the DMTs (Nusinersen and Risdiplam) on lung function and respiratory muscle strength in patients with SMA type 1, 2, 3, or 4. Most of the included studies reported no statistically significant improvement in lung function or respiratory muscle strength after treatment with Nusinersen or Risdiplam. Furthermore, a meta-analysis of 13 included studies showed no statistically significant improvement in FVC after two, six, 10, or >12 months of treatment with Nusinersen. At this stage, available evidence suggests that treatment of SMA with Nusinersen or Risdiplam does not lead to improved lung function or respiratory muscle strength.

The results of our review are similar to the results of less comprehensive reviews. A review of the therapeutic effects of Nusinersen[40] included three studies and concluded that Nusinersen did not statistically significantly improve FVC %pred in

patients with SMA type 2 or 3. Similarly, a review of the therapeutic effects of Risdiplam[41] included six studies and concluded that FVC tended to decrease by −2.34% (95% CI: −7.93, 3.24) and −5.18% (95% CI: −10.47, 0.11) after 12 and 24 months of treatment, while FEV1 decreased by −4.88% (95% CI: −8.87, −0.89) after 24 months. Conversely, PCF remained stable and SNIP improved by 4.41% (95% CI: 1.63, 7.19).[41] Four of the six included studies could not be included in our review because they did not report baseline data.

From natural history data, we know that (F)VC and FEV1 %pred decline during early life in most types of SMA.[11,12] We also know that the earlier the treatment with DMTs, the better the outcomes. Therefore, the effects of Nusinersen are expected to differ between children and adults with a similar SMA type. Three of the 19 studies included only children. Two studies included both children and adults but did not differentiate between them when presenting the results. The three studies that included only children report no statistically significant improvements in FVC and FEV %pred.[23,30,37] Real-world evidence has shown that treatment with Nusinersen improves motor function and survival in children with early-onset spinal muscular atrophy, however, bulbar and respiratory function might not improve as much as motor function.[42]

Natural history studies have shown a progressive decline in lung function and respiratory muscle strength in young treatment-naïve patients with SMA type 1, 2, or 3a.[11,12] Also, retrospective parts of two included studies[23,28] show a statistically significant decline in lung function in 28 patients with SMA type 2 or 3 in the years before treatment. Most of the included studies reported no statistically significant improvement in lung function or respiratory muscle strength after a period of treatment with Nusinersen or Risdiplam. They also did not report a statistically significant decline, which may suggest that Nusinersen or Risdiplam may have halted the expected decline in lung function and respiratory muscle strength. However, another explanation is that lung function and respiratory muscle strength tend to stabilize in patients with SMA after the first 20 years of life.[11,12] Since most studies included adult patients with SMA, stabilization may also be part of the natural course rather than the effect of Nusinersen or Risdiplam.

Treatment beyond the window of opportunity could be a reason for the lack of improvement in lung function and respiratory muscle strength. In most of the included studies, Nusinersen was started relatively late in the disease course. In the course of the disease, the combination of fibrotic, shortened, and stiffened muscles and reduced movement of the chest wall results in articular contractures.[23,30,41] The start of treatment may have been in a context of a respiratory system beyond repair.[30]

In this review, we searched across multiple generic databases, which enhances the representativeness of the included studies. Two assessors independently performed the screening procedure and qualitative assessment, which reduced the ROB and

increased the reliability of the review findings. Our review has limitations. First, no randomized controlled trials could be included, since we could not find any with respiratory muscle strength or lung function as an outcome measure. Second, the intrinsic limitations of the included studies are the small number of participants, the differences in disease duration, combinations of children and adults, ambulatory and non-ambulatory patients, and patients with different SMA types. The patient heterogeneity obviously limits conclusions. Third, the results of the effect of Risdiplam on lung function and respiratory muscle strength are based on only two studies.

CONCLUSION

The findings of this review indicate that there is moderate evidence that Nusinersen does not improve FVC, FEV1, PEF, or PImax in patients with SMA type 1, 2, 3, or 4. For the other outcome measures on lung function and respiratory muscle strength, there is insufficient evidence regarding the efficacy of Nusinersen in patients with SMA type 1, 2, 3, or 4. Although no improvements were found, there was no statistically significant decline in lung function or respiratory muscle strength. This may suggest that Nusinersen may have halted the expected decline in lung function and respiratory muscle strength, as seen in natural history studies. The effect of Risdiplam on lung function and respiratory muscle strength has so far been studied only in patients with SMA type 2 and in very small groups. We could not identify studies reporting the effect of Onasemnogene abeparvovec. Studies on the effects of DMTs suggest that they are effective in improving survival, motor function, and functional muscle strength, but this is less obvious in respiratory function or respiratory muscle strength. This indicates that respiratory care professionals may need to prepare for a larger population of individuals with SMA who require specialized respiratory care expertise.

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APPENDIX 4.A: Search strategy

Pubmed 6-12-2023

Search#	*Query*	*Results*
#1	“Muscular Atrophy, Spinal”[MeSH]	6.531
#2	“Spinal Muscular Atrophies of Childhood”[MeSH]	1.741
#3	“muscular Atrophy, Spinal” [Title/Abstract]	16
#4	“Spinal Muscular Atrophies of Childhood”[Title/Abstract]	9
#5	"spinal muscular atrophy"[Title/Abstract]	6.699
#6	"SMA"[Title/Abstract]	29.189
#7	“SMA type 1”[Title/Abstract]	200
#8	"SMA type 2"[Title/Abstract]	113
#9	“SMA type 3”[Title/Abstract]	54
#10	“SMA type 4”[Title/Abstract]	6
#11	5q	3696
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 ((((((((((Muscular Atrophy, Spinal[MeSH Terms]) OR (Spinal Muscular Atrophies of Childhood[MeSH Terms])) OR (muscular Atrophy, Spinal[Title/Abstract])) OR (Spinal Muscular Atrophies of Childhood[Title/Abstract])) OR (spinal muscular atrophy[Title/Abstract])) OR (SMA[Title/Abstract])) OR (SMA type 1[Title/Abstract])) OR (SMA type 2[Title/Abstract])) OR (SMA type 3[Title/Abstract])) OR (SMA type 4[Title/Abstract])) OR (5q[Title/Abstract])	37.642
#13	"Oligonucleotides, Antisense"[Mesh]	16.876
#14	"Oligonucleotides, Antisense"[Title/Abstract]	78
#15	"nusinersen" [Supplementary Concept]	369
#16	“nusinersen”[Title/Abstract]	688
#17	“Spinraza”[Title/Abstract]	132
#18	“ASO-10-27”[Title/Abstract]	3
#19	"Risdiplam" [Supplementary Concept]	50
#20	"Risdiplam"[Title/Abstract]	140
#21	"Evrysdi"[Title/Abstract]	26
#22	"rna splicing modifier"[Title/Abstract]	3
#23	"smn2 splicing"[Title/Abstract]	90
#24	“Zolgensma”[Title/Abstract]	93
#25	“onasemnogene abeparvovec”[Title/Abstract]	185
#26	“AVXS-101”[Title/Abstract]	37
#27	"Genetic Therapy"[MeSH]	54.150
#28	"Genetic Therapy"[Title/Abstract]	653
#29	“gene therapy”[Title abstract]	56.195
#30	"Gene based therapy”[Title/Abstract]	218

#31	#13 OR #14 OR #15OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 ((((((((((((((((((Oligonucleotides, Antisense[MeSH Terms]) OR (Oligonucleotides, Antisense[Title/Abstract])) OR (nusinersen[Title/Abstract])) OR (nusinersen[Supplementary Concept])) OR (risdiplam[Supplementary Concept])) OR (spinraza[Title/Abstract])) OR (ASO-10-27[Title/Abstract])) OR (risdiplam[Title/Abstract])) OR (Evrysdi[Title/Abstract])) OR (rna splicing modifier[Title/Abstract])))) OR (smn2 splicing[Title/Abstract])) OR (Zolgensma[Title/Abstract])) OR (onasemnogene abeparvovec[Title/Abstract])) OR (AVXS-101[Title/Abstract])) OR (Genetic Therapy[Title/Abstract])) OR (Genetic Therapy[MeSH Terms])) OR (gene therapy[Title/Abstract])) OR (Gene based therapy[Title/Abstract])	97.906
#32	"maximal inspiratory mouth pressure"[Title/Abstract]	123
#33	"MIP"[Title/Abstract]	18.357
#34	"pimax"[Title/Abstract]	785
#35	"respiratory muscle strength"[Title/Abstract]	1.628
#36	"inspiratory muscle strength"[Title/Abstract]	697
#37	“expiratory muscle strength"[Title/Abstract]	281
#38	"maximal expiratory mouth pressure"[Title/Abstract]	25
#39	"MEP"[Title/Abstract]	9.260
#40	"pemax"[Title/Abstract]	395
#41	"SVC"[Title/Abstract]	3.597
#42	"IVC"[Title/Abstract]	9.655
#43	"inspiratory capacity"[Title/Abstract]	1159
#44	"expiratory capacity"[Title/Abstract]	43
#45	"EC"[Title/Abstract]	110.637
#46	"EVC"[Title/Abstract]	514
#47	"FVC"[Title/Abstract]	17.810
#48	"vital capacity"[Title/Abstract]	20.514
#49	"VC"[Title/Abstract]	13.034
#50	"total lung capacity"[Title/Abstract]	3.955
#51	"TLC"[Title/Abstract]	15.972
#52	"forced expiratory volume in 1 second"[Title/Abstract]	5.974
#53	"FEV1"[Title/Abstract]	35.910
#54	"peak expiratory flow"[Title/Abstract]	7.573
#55	"PEF"[Title/Abstract]	6.081
#56	"cough strength"[Title/Abstract]	117
#57	"sniff nasal inspiratory pressure"[Title/Abstract]	156
#58	"SNIP"[Title/Abstract]	848
#59	"airway occlusion pressure"[Title/Abstract]	149
#60	"p01"[Title/Abstract]	229
#61	"p0.1"[Title/Abstract]	592

#62	"pulmonary function"[Title/Abstract]	36.919
#63	"lung function"[Title/Abstract]	41.979
#64	"respiratory function"[Title/Abstract]	16.180
#65	"spirometry"[Title/Abstract]	21.294
#66	"lung volume"[Title/Abstract]	9.889
#67	"respiratory drive"[Title/Abstract]	1.676
#68	"respiratory effort"[Title/Abstract]	1.198
#69	"work of breathing"[Title/Abstract]	2.129
#70	"WOB"[Title/Abstract]	358
#71	"transdiaphragmatic pressure"[Title/Abstract]	889
#72	"PDI"[Title/Abstract]	9728
#73	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 ((maximal inspiratory mouth pressure[Title/Abstract]) OR (MIP[Title/Abstract])) OR (pimax[Title/Abstract])) OR (respiratory muscle strength[Title/Abstract])) OR (inspiratory muscle strength[Title/Abstract])) OR (expiratory muscle strength[Title/Abstract])) OR (maximal expiratory mouth pressure[Title/Abstract])) OR (MEP[Title/Abstract])) OR (pemax[Title/Abstract])) OR (SVC[Title/Abstract])) OR (IVC[Title/Abstract])) OR (inspiratory capacity[Title/Abstract])) OR (expiratory capacity[Title/Abstract])) OR (Ec[Title/Abstract])) OR (EVC[Title/Abstract])) OR (FVC[Title/Abstract])) OR (vital capacity[Title/Abstract])) OR (VC[Title/Abstract])) OR (total lung capacity[Title/Abstract])) OR (TLC[Title/Abstract])) OR (forced expiratory volume in 1 second[Title/Abstract])) OR (FEV1[Title/Abstract])) OR (peak expiratory flow[Title/Abstract])) OR (PEF[Title/Abstract])) OR (cough strength[Title/Abstract])) OR (sniff nasal inspiratory pressure[Title/Abstract])) OR (SNIP[Title/Abstract])) OR (airway occlusion pressure[Title/Abstract])) OR (p01[Title/Abstract])) OR (p0.1[Title/Abstract])) OR (pulmonary function[Title/Abstract])) OR (lung function[Title/Abstract])) OR (respiratory function[Title/Abstract])) OR (spirometry[Title/Abstract])) OR (lung volume[Title/Abstract])) OR (respiratory drive[Title/Abstract])) OR (respiratory effort[Title/Abstract])) OR (work of breathing[Title/Abstract])) OR (WOB[Title/Abstract])) OR (transdiaphragmatic pressure[Title/Abstract])) OR (PDI[Title/Abstract])	321.451
#74	#12 AND #31 AND #73	46

Cinahl 7-12-2023

#Search	*Query*	*Results*
#1	TI (Spinal Muscular Atrophies of Childhood OR muscular Atrophy, Spinal OR SMA type 1 OR SMA type 2 OR SMA type 3 OR Spinal Amyotroph*) OR AB (Spinal Muscular Atrophies of Childhood OR muscular Atrophy, Spinal OR SMA type 1 OR SMA type 2 OR SMA type 3 OR SMA type 4 OR Spinal Amyotroph*)	1.762
#2	TI (Oligonucleotides, Antisense OR nusinersen OR spinraza OR ASO-10-27 OR Risdiplam OR Evrysdi OR rna splicing modifier OR SMN augmenting genetic therapy OR smn2 splicing OR Zolgensma OR onasemnogene abeparvovec OR AVXS-101 OR genetic therapy OR gene therapy OR gene-based therapy) OR AB (Oligonucleotides, Antisense OR nusinersen OR spinraza OR ASO-10-27 OR Risdiplam OR Evrysdi OR rna splicing modifier OR SMN augmenting genetic therapy OR smn2 splicing OR Zolgensma OR onasemnogene abeparvovec OR AVXS-101 OR genetic therapy OR gene therapy OR gene-based therapy)	10.194
#3	TI (maximal inspiratory mouth pressure OR MIP OR pimax OR respiratory muscle strength OR inspiratory muscle strength OR maximal expiratory mouth pressure OR MEP OR pemax OR exhalation muscle strength OR expiratory muscle strength OR Slow vital capacity OR inspiratory vital capacity OR SVC OR IVC OR inspiratory capacity OR expiratory vital capacity OR EVC OR expiratory capacity OR EC OR forced vital capacity OR FVC OR vital capacity OR VC OR total lung capacity OR tlc OR forced expiratory volume in 1 second OR FEV1 OR peak expiratory flow OR PEF OR cough strength OR sniff nasal inspiratory pressure OR SNIP OR airway occlusion pressure OR p01 OR p0.1 OR pulmonary function OR lung function OR respiratory function OR spirometry OR lung volume OR respiratory drive OR respiratory effort OR work of breathing OR wob OR transdiaphragmatic pressure OR PDI) OR AB (maximal inspiratory mouth pressure OR MIP OR pimax OR respiratory muscle strength OR inspiratory muscle strength OR maximal expiratory mouth pressure OR MEP OR pemax OR exhalation muscle strength OR expiratory muscle strength OR Slow vital capacity OR inspiratory vital capacity OR SVC OR IVC OR inspiratory capacity OR expiratory vital capacity OR EVC OR expiratory capacity OR EC OR forced vital capacity OR FVC OR vital capacity OR VC OR total lung capacity OR tlc OR forced expiratory volume in 1 second OR FEV1 OR peak expiratory flow OR PEF OR cough strength OR sniff nasal inspiratory pressure OR SNIP OR airway occlusion pressure OR p01 OR p0.1 OR pulmonary function OR lung function OR respiratory function OR spirometry OR lung	66.867

	volume OR respiratory drive OR respiratory effort OR work of breathing OR wob OR transdiaphragmatic pressure OR PDI)	
#4	#1 AND #2 AND #3 ((Spinal Muscular Atrophies of Childhood OR muscular Atrophy, Spinal OR SMA type 1 OR SMA type 2 OR SMA type 3 OR Spinal Amyotroph*) OR AB (Spinal Muscular Atrophies of Childhood OR muscular Atrophy, Spinal OR SMA type 1 OR SMA type 2 OR SMA type 3 OR SMA type 4 OR Spinal Amyotroph*)) AND ((Oligonucleotides, Antisense OR nusinersen OR spinraza OR ASO-10-27 OR Risdiplam OR Evrysdi OR rna splicing modifier OR SMN augmenting genetic therapy OR smn2 splicing OR Zolgensma OR onasemnogene abeparvovec OR AVXS-101 OR genetic therapy OR gene therapy OR gene-based therapy) OR AB (Oligonucleotides, Antisense OR nusinersen OR spinraza OR ASO-10-27 OR Risdiplam OR Evrysdi OR rna splicing modifier OR SMN augmenting genetic therapy OR smn2 splicing OR Zolgensma OR onasemnogene abeparvovec OR AVXS-101 OR genetic therapy OR gene therapy OR gene-based therapy)) AND ((maximal inspiratory mouth pressure OR MIP OR pimax OR respiratory muscle strength OR inspiratory muscle strength OR maximal expiratory mouth pressure OR MEP OR pemax OR exhalation muscle strength OR expiratory muscle strength OR Slow vital capacity OR inspiratory vital capacity OR SVC OR IVC OR inspiratory capacity OR expiratory vital capacity OR EVC OR expiratory capacity OR EC OR forced vital capacity OR FVC OR vital capacity OR VC OR total lung capacity OR tlc OR forced expiratory volume in 1 second OR FEV1 OR peak expiratory flow OR PEF OR cough strength OR sniff nasal inspiratory pressure OR SNIP OR airway occlusion pressure OR p01 OR p0.1 OR pulmonary function OR lung function OR respiratory function OR spirometry OR lung volume OR respiratory drive OR respiratory effort OR work of breathing OR wob OR transdiaphragmatic pressure OR PDI) OR AB (maximal inspiratory mouth pressure OR MIP OR pimax OR respiratory muscle strength OR inspiratory muscle strength OR maximal expiratory mouth pressure OR MEP OR pemax OR exhalation muscle strength OR expiratory muscle strength OR Slow vital capacity OR inspiratory vital capacity OR SVC OR IVC OR inspiratory capacity OR expiratory vital capacity OR EVC OR expiratory capacity OR EC OR forced vital capacity OR FVC OR vital capacity OR VC OR total lung capacity OR tlc OR forced expiratory volume in 1 second OR FEV1 OR peak expiratory flow OR PEF OR cough strength OR sniff nasal inspiratory pressure OR SNIP OR airway occlusion pressure OR p01 OR p0.1 OR pulmonary function OR lung function OR respiratory function OR spirometry OR lung	14

	volume OR respiratory drive OR respiratory effort OR work of breathing OR wob OR transdiaphragmatic pressure OR PDI))	

Web of Science 7-12-2023

Search	*Query*	*Results*
#1	(((((((TS=(Spinal Muscular Atrophies of Childhood)) OR TS=(muscular Atrophy, Spinal)) OR TS=(SMA type 1)) OR TS=(SMA type 2)) OR TS=(SMA type 3))OR TS=(SMA)) OR TS=(SMA type 4)) OR TS=(spinal muscular atrophy)) OR TS=(5q)	50.245
#2	((((((((((((TS=(Oligonucleotides, Antisense)) OR TS=(nusinersen)) OR TS=(spinraza)) OR TS=(ASO-10-27)) OR TS=(risdiplam)) OR TS=(evrysdi)) OR TS=(rna splicing modifier)) OR TS=(smn2 splicing)) OR TS=(zolgensma)) OR TS=(onasemnogene abeparvovec)) OR TS=(AVXS-101)) OR TS=(Genetic Therapy)) OR TS=(gene therapy)) OR TS=(Gene based therapy)	385.043
#3	((TS=(maximal inspiratory mouth pressure)) OR TS=(MIP)) OR TS=(pimax)) OR TS=(respiratory muscle strength)) OR TS=(inspiratory muscle strength)) OR TS=(expiratory muscle strength)) OR TS=(maximal expiratory mouth pressure)) OR TS=(mep)) OR TS=(pemax)) OR TS=(scv)) OR TS=(ivc)) OR TS=(inspiratory capacity)) OR TS=(expiratory capacity)) OR TS=(EC)) OR TS=(EVC)) OR TS=(FVC)) OR TS=(vital capacity)) OR TS=(VC)) OR TS=(total lung capacity)) OR TS=(tlc)) OR TS=(forced expiratory volume in 1 second)) OR TS=(fev1)) OR TS=(peak expiratory flow)) OR TS=(pef)) OR TS=(cough strength)) OR TS=(sniff nasal inspiratory pressure)) OR TS=(snip)) OR TS=(airway occlusion pressure)) OR TS=(p01)) OR TS=(p0.1)) OR TS=(pulmonary function)) OR TS=(lung function)) OR TS=(respiratory function)) OR TS=(spirometry)) OR TS=(lung volume)) OR TS=(respiratory drive)) OR TS=(respiratory effort)) OR TS=(work of breathing)) OR TS=(wob)) OR TS=(transdiaphragmatic pressure)) OR TS=(pdi)	599.438
#4	#1 AND #2 AND #3	201

Embase 7-12-2023

Search	*Query*	*Results*
#1	('spinal muscular atrophy'):ti,ab,kw OR (('spinal amyotrophy'):ti,ab,kw)	10.220
#2	(nusinersen):ti,ab,kw OR (('antisense oligonucleotide'):ti,ab,kw) OR ((aso-10-27):ti,ab,kw) OR ((risdiplam):ti,ab,kw) OR (('rna splicing modifier'):ti,ab,kw) OR (('smn2 splicing'):ti,ab,kw) OR	92.214

	(('onasemnogene abeparvovec'):ti,ab,kw) OR (('gene therapy'):ti,ab,kw) OR (('gene based therapy'):ti,ab,kw)	
#3	(mip):ti,ab,kw OR (('maximal inspiratory mouth pressure'):ti,ab,kw) OR (('respiratory muscle strength'):ti,ab,kw) OR (('inspiratory muscle strength'):ti,ab,kw) OR (('expiratory muscle strength'):ti,ab,kw) OR (('maximal expiratory mouth pressure'):ti,ab,kw) OR ((mep):ti,ab,kw) OR ((pemax):ti,ab,kw) OR ((pimax):ti,ab,kw) OR (('slow vital capacity'):ti,ab,kw) OR ((ivc):ti,ab,kw) OR (('inspiratory capacity'):ti,ab,kw) OR (('expiratory capacity'):ti,ab,kw) OR (('forced vital capacity'):ti,ab,kw) OR (('vital capacity'):ti,ab,kw) OR (('total lung capacity'):ti,ab,kw) OR (('forced expiratory volume'):ti,ab,kw) OR (('peak expiratory flow'):ti,ab,kw) OR (('cough strength'):ti,ab,kw) OR (('sniff nasal inspiratory pressure'):ti,ab,kw) OR (('airway occlusion pressure'):ti,ab,kw) OR (('lung function'):ti,ab,kw) OR (('respiratory function'):ti,ab,kw) OR ((spirometry):ti,ab,kw) OR (('lung volume'):ti,ab,kw) OR (('respiratory effort'):ti,ab,kw) OR (('work of breathing'):ti,ab,kw) OR (('transdiaphragmatic pressure'):ti,ab,kw) OR (('tidal volume'):ab,ti)	239.535
#4	#1 AND #2 AND #3 (mip):ti,ab,kw OR (('maximal inspiratory mouth pressure'):ti,ab,kw) OR (('respiratory muscle strength'):ti,ab,kw) OR (('inspiratory muscle strength'):ti,ab,kw) OR (('expiratory muscle strength'):ti,ab,kw) OR (('maximal expiratory mouth pressure'):ti,ab,kw) OR ((mep):ti,ab,kw) OR ((pemax):ti,ab,kw) OR ((pimax):ti,ab,kw) OR (('slow vital capacity'):ti,ab,kw) OR ((ivc):ti,ab,kw) OR (('inspiratory capacity'):ti,ab,kw) OR (('expiratory capacity'):ti,ab,kw) OR (('forced vital capacity'):ti,ab,kw) OR (('vital capacity'):ti,ab,kw) OR (('total lung capacity'):ti,ab,kw) OR (('forced expiratory volume'):ti,ab,kw) OR (('peak expiratory flow'):ti,ab,kw) OR (('cough strength'):ti,ab,kw) OR (('sniff nasal inspiratory pressure'):ti,ab,kw) OR (('airway occlusion pressure'):ti,ab,kw) OR (('lung function'):ti,ab,kw) OR (('respiratory function'):ti,ab,kw) OR ((spirometry):ti,ab,kw) OR (('lung volume'):ti,ab,kw) OR (('respiratory effort'):ti,ab,kw) OR (('work of breathing'):ti,ab,kw) OR (('transdiaphragmatic pressure'):ti,ab,kw) OR (('tidal volume'):ab,ti) AND ((nusinersen):ti,ab,kw OR (('antisense oligonucleotide'):ti,ab,kw) OR ((aso-10-27):ti,ab,kw) OR ((risdiplam):ti,ab,kw) OR (('rna splicing modifier'):ti,ab,kw) OR (('smn2 splicing'):ti,ab,kw) OR (('onasemnogene abeparvovec'):ti,ab,kw) OR (('gene therapy'):ti,ab,kw) OR (('gene based therapy'):ti,ab,kw)) AND (('spinal muscular atrophy'):ti,ab,kw OR (('spinal amyotrophy'):ti,ab,kw))	115

APPENDIX 4.B: Quality Assessment

'Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group' from the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, Accessed July 5, 2023).

First author, year[ref]	1. Question clear?	2. Selection criteria clear?	3. Participants representative?	4. All eligible participants enrolled?	5. Sample size sufficiently large?	6. Intervention clearly described?	7. Outcome measure accurate?	8. Assessors blinded?	9. Lost to follow-up 20% or less?	10. Statistical methods accurate?	11. Interrupted time-series design?	12. Individual-level data used?	Total score
Bjelica, 2023[35]	Y	Y	N	N	N	Y	Y	NR	Y	Y	N	NA	55% ◯
Carson, 2022[22]	Y	Y	N	Y	N	N	Y	NR	Y	Y	N	NA	55% ◯
Chacko, 2022[23]	Y	Y	N	N	N	N	Y	NR	Y	Y	Y	NA	55% ◯
De Wel, 2021[24]	Y	Y	N	N	N	Y	Y	NR	Y	Y	Y	NA	64% ◯
De Wel, 2022[25]	Y	Y	N	N	N	Y	NR	NR	Y	Y	CD	NA	45% ◯
Duong, 2021[26]	Y	Y	N	N	N	Y	N	NR	Y	Y	N	NA	45% ◯
Elsheikh, 4-2021[27]	Y	Y	N	CD	N	Y	NR	NR	N	Y	N	NA	36% ◯
Elsheikh, 5-2021[28]	Y	Y	N	CD	N	Y	NR	NR	N	Y	Y	NA	45% ◯
Fainmesser, 2022[29]	Y	Y	N	CD	N	Y	N	NR	N	Y	N	NA	36% ◯
Freigang, 2023[36]	Y	Y	N	CD	N	Y	NR	NR	N	Y	N	NA	36% ◯
Gonski, 2023[37]	Y	Y	N	Y	N	N	Y	NR	CD	Y	Y	NA	55% ◯
Heitschmidt, 2021[30]	Y	N	N	CD	N	N	Y	NR	N	Y	N	NA	27% ◯
Jochmann, 2020[31]	N	N	N	CD	N	Y	N	NR	Y	N	N	NA	18% ●
Lefeuvre, 2022[32]	Y	Y	N	CD	N	Y	NR	NR	Y	Y	N	NA	45% ◯
Maggi, 2020[39]	Y	Y	N	Y	N	Y	NR	NR	N	Y	N	NA	45% ◯

McCluskey, 2022[34]	Y	Y	N	CD	N	N	NR	NR	Y	Y	N	NA	36% ◯
Ñungo Garzón, 2023[38]	N	N	N	CD	N	Y	N	NR	Y	N	CD	NA	18% ●
Vazquez-Costa, 2022[21]	Y	Y	N	CD	N	Y	N	NR	Y	Y	N	NA	45% ◯
Walter, 2019[33]	Y	Y	N	CD	N	Y	Y	NR	N	Y	N	NA	45% ◯

Abbreviations: CD: cannot determine, NA: not applicable, N: no, NR: not reported, ref: reference, Y: yes, ◯: moderate risk of bias. (25-75%), ●: high risk of bias (0-25%)

APPENDIX 4.C: Effect of Nusinersen on lung function

First author Year[ref]	*SMA type (n)*	*Baseline mean (±SD)[95% CI]*	*Follow-up mean (±SD)[95% CI]*	*p-value*
Forced Vital Capacity				
Bjelica 2023[35]	1+2+3+4 (n=16)	2.8 l (1.6)	S (M10), n=19: 3.2 l (1.7) L (M22), n=16: 3.2 l (1.7) L (M30), n=20: 2.9 l (1.7)	>.05 >.05 >.05
Carson 2022[22]	2 (n=11)	1.6 l (0.5)	L (M22-34): 1.7 l (0.6)	.063
Chacko 2022[23]	2 (n=12) 3 (n=7) 2+3 (n=19)	45 %pred (23) 98 %pred (18) 64 %pred (34)	S (M12), n=11: 45 %pred (24) S (M12), n=8: 5 %pred (19) S (M12), n=19: 66 %pred (33)	.88 .73 1.0
De Wel 2021[24], 2022[25]	3+4 (n=16)	4.3 l (1.2)	S (M6): 4.2 l (1.2) L (M14): 4.1 l (1.2) L (M22): 4.2 l (1.3)	**.01** .11 .087
Duong 2021[26]	 2 (n=11) 3 (n=16) 2+3 (n=27)	 NR NR 61.5 %pred (33)	Average change per year: 2.6 %pred [-1.7, 6.9] -0.3 %pred [-3.7, 3.0] 0.8 %pred [-1.9, 3.4]	 NR NR NR
Elsheikh 2021-04[27]	2+3 (n=19) Non-ambulant	1.9 l [1.3, 2.6]	Change from baseline: S (M2), n=17: -0.0 l [-0.1, 0.1] S (M6), n=19: -0.0 l [-0.1, 0.1] S (M10), n=17: -0.0 l [-0.1, 0.1] L (M14), n=12: 0.0 l [-0.1, 0.1]	 .73 .66 .68 .77
Elsheikh 2021-05[28]	3+4 (n=13) Ambulant	4.1 l [3.4, 4.8]	Change from baseline: S (M2), n=13: 0.1 l [-0.0, 0.2] S (M6), n=13: 0.2 l [0.0, 0.3] S (M10), n=13: 0.1 l [0.0, 0.3] L (M14), n=10: 0.2 l [0.1, 0.3]	 .22 **.008** **.033** **.007**
Freigang 2023[36]	2+3 (n=19)	73 %pred (30)	L (M26): 76 %pred (31)	.14
Gonski 2023[37]	 2+3 (n=21) 2+3 (n=21)	Pre Nusinersen: 1.2 l (0.5) 66 %pred (35)	Post Nusinersen (M?): 1.4 l (0.7) 59 %pred (3)	 **.01** .07
Heitschmidt 2021[30]	B-D180: 2+3 (n=6)	93 %pred (53-113)*	S (D180): 91 %pred (57-126)*	1.00
	B-D300: 3 (n=6)	96 %pred (85-113)*	S (D300): 90 %pred (78-100)*	1.00
	D180-D300: 2+3 (n=9)	D180: 95 %pred (53-126)*	S (D300): 90 %pred (67-114)*	.65
Jochmann 2020[31]	2+3 (n=5)	60 %pred (43)	S (M2), n=3: 48 %pred (33) S (M6), n=6: 67%pred (39) S (M10), n=6: 64 %pred (36)	NR NR NR
Maggi 2020[39]	2 (n=7) 3 (n=79)	32 %pred (24) 89 %pred (25)	S (M6), n=4: 26 %pred (21) S (M10), n=4: 32 %pred (19) S (M6), n=38: 90 %pred (24)	n.s. n.s. n.s.

			S (M10), n=17: 103 %pred (21)	n.s.
			L (M14), n=15: 86 %pred (20)	**.02**
	2+3 (n=86)	85 %pred (30)	S (M6), n=42: 84 %pred (30)	n.s.
			S (M10), n=21: 89 %pred (35)	.099
			L (M14), n=15: 86 %pred (20)	**.02**
Vazquez-Costa 2022[21]	2+3 (n=39)	73 %pred (38)	Change from baseline: S (M6): +3 %pred (8)	.14
Walter 2019[33]	3 (n=17)	95 %pred (15)	S (D63), n=19: 96 %pred (17)	.32
			S (D180), n=17: 98 %pred (14)	.33
			S (D300), n=16: 100 %pred (12)	.34
Vital capacity				
Lefeuvre 2022[32]	1+2+3 (n=18)	1.0 l (0.5, 1.4)†	S (D63): 1.0 l (0.5, 1.8)†	NR
			S (D183): 1.0 l (0.5, 1.3)†	NR
			S (D303): 0.9 l (0.5, 1.7)†	NR
Forced expiratory volume in 1 sec				
Bjelica 2023[35]	1+2+3+4 (n=14)	2.4 l (1.4)	S (M10), n=19: 2.7 l (1.4)	>.05
			L (M22), n=16: 2.7 l (1.3)	>.05
			L (M30), n=20: 2.4 l (1.4)	>.05
Fainmesser 2022[29]	2 (n=13)	55 %pred (27-88)*	S (M6): 56 %pred (27-82)*	.83
	3 (n=18)	97 %pred (83-107)*	S (M6): 93 %pred (785-104)*	.11
	2+3 (n=31)	89 %pred (62-101)*	S (M6): 79 %pred (64-96)*	.23
	2 (n=6)	71 %pred (35-88)*	L (M14): 72 %pred (38-84)*	.91
	3 (n=15)	96 %pred (83-105)*	L (M14): 96 %pred (85-107)*	.26
	2+3 (n=21)	90 %pred (77-101)*	L (M14): 90 %pred (78-100)*	.23
	2 (n=1)	25 %pred*	L (M26): 29 %pred*	NA
	3 (n=6)	97 %pred (91 -104)*	L (M26): 90 %pred (85-109)*	.91
	2+3 (n=7)	96 %pred (83-101)*	L (M26): 87 %pred (79-105)*	.95
Freigang 2023[36]	2+3 (n=18)	75 %pred (29)	L (M26): 73 %pred (28)	.52
Gonski 2023[37]		Pre Nusinersen:	Post Nusinersen (M?):	
	2+3 (n=21)	1.0 l (0.4)	1.2 l (0.6)	**.005**
	2+3 (n=21)	65 %pred (36)	60 %pred (40)	.15
Maggi 2020[39]	2 (n=5)	28 %pred (16)	S (M6), n=4: 26 %pred (19)	n.s.
			S (M10), n=3: 30 %pred (22)	n.s.
	3 (n=71)	92 %pred (24)	S (M6), n=37: 93 %pred (21)	n.s.
			S (M10), n=17: 102.%pred (20)	n.s.
			L (M14), n=15: 85 %pred (20)	**.0499**
	2+3 (n=76)	88 %pred (28)	S (M6), n=41: 86 %pred (29)	n.s.
			S (M10), n=20: 91 %pred (32)	n.s.
			L (M14), n=15: 85 %pred (20)	**.0499**

Total lung capacity				
Carson 2022[22]	2 (n=11)	2.7 l (1.0)	L (M22-34): 2.9 l (1.0)	.15
Peak cough flow				
Chacko 2022[23]	2 (n=8)	156.9 l/min (116.7-216.3)†	S (M12): 128.7 l/min (111.9-177.9)†	.43
	3 (n=5)	242.4 l/min (237.0-322.3)†	S (M12): 242.4 l/min (237.0-353.4)†	.17
	2+3 (n=13)	215.4 l/min (147.6, 242.4)†	S (M12): 208.8 l/min (119.4, 254.4)†	1.00
Walter 2019[33]	3 (n=14)	376.1 l/min (183.1)	S (D63), n=14: 430.0 l/min (160.5) S (D180), n=13: 461.5 l/min (147.2) S (D300), n=8: 435.6 l/min (125.2)	.31 **.044** .29
Peak expiratory flow				
Bjelica 2023[35]	1+2+3+4 (n=14)	5.3 l/sec (3.3)	S (M10), n=19: 6.2 l/sec (3.3) L (M22), n=16: 6.3 l/sec (3.3) L (M30), n=20: 5.7 l/sec (3.4)	>.05 >.05 >.05
Freigang 2023[36]	2+3 (n=18)	65 %pred (20.69)	L (M26): 66 %pred (20.81)	.81
De Wel 2021[24], *2022*[25]	3+4 (n=16)	7.2 l/sec (1.9)	S (M6): 7.3 l/sec (1.9) L (M14): 7.3 l/sec (1.9) L (M22): 7.6 l/sec (2.1)	.52 .39 **.011**

*Notes: *: Median (range),†: Median (interquartile range),* ***p-values in bold are significant: p<.05.***
Abbreviations: %pred: percentage of predicted, B: baseline, CI: confidence interval, D: day, L: long-term follow-up (>12 months), l: liter, l/min: liter per minute, M: months, n: number of patients, NA: not applicable, NR: not reported, n.s.: not statistically significant, p-value: probability value, ref: reference, S: short-term follow-up (≤12 months), SD: standard deviation, SMA: spinal muscular atrophy, Z-score: standardized score indicating the deviation from the mean units of standard deviation.

APPENDIX 4.D: Effect of Nusinersen on respiratory muscle strength

First author Year[ref]	*SMA type (n)*	*Baseline mean (±SD)[95% CI]*	*Follow-up mean (±SD)[95% CI]*	*p-value*
Maximal inspiratory pressure				
Carson 2022[22]	2 (n=11)	58 cmH_2O (13)	L (M22-34): 71 cmH_2O (16)	.30
Chacko 2022[23]	2 (n=8)	Z-score: -1.1 (1.2)	S (M12): Z-score: -1.2 (1.2)	.49
	3 (n=5)	Z-score: 0.0 (0.8)	S (M12): Z-score: 0.0 (1.0)	.92
	2+3 (n=13)	Z-score: -0.7 (1.2)	S (M12): Z-score: -0.8 (1.5)	.64
Duong 2021[26]			Average change per year:	
	2 (n=11)	NR	4.3 cmH_2O [-5.0, 13.7]	NR
	3 (n=15)	NR	6.3 cmH_2O [-1.3, 13.8]	NR
	2+3 (n=26)	80 cmH_2O (44)	5.5 cmH_2O [-0.5, 11.5]	NR
Lefeuvre 2022[32]	1+2+3 (n=18)	47 cmH_2O (26, 60)*	S (D63): 55cmH_2O (30, 62)*	NR
			S (D183): 46 cmH_2O (22, 54)*	NR
			S (D303): 44 cmH_2O (24, 51)*	NR
Maximal expiratory pressure				
Carson 2022[22]	2 (n=11)	38 cmH_2O (13)	L (M22-34): 41 cmH_2O (14)	.63
Chacko 2022[23]	2 (n=8)	Z-score: -2.6 (1.1)	S (M12): Z-score: -3.2 (0.4)	.49
	3 (n=5)	Z-score: -1.3 (0.9)	S (M12): Z-score: -0.9 (1.2)	.25
	2+3 (n=13)	Z-score: -2.1 (1.2)	S (M12): Z-score: -2.3 (1.4)	.78
Duong 2021[26]			Average change per year:	
	2+3 (n=25)	51 cmH_2O (27)	6.4 cmH_2O [2.5, 10]	NR
Lefeuvre 2022[32]	1+2+3 (n=18)	23 cmH_2O (15, 34)*	S (D63): 24 cmH_2O (18, 32)*	NR
			S (D183): 21 cmH_2O (12, 30)*	NR
			S (D303): 23 cmH_2O (14, 29)*	NR
Sniff nasal inspiratory pressure				
Chacko 2022[23]	2 (n=9)	41 cmH_2O (27, 73)*	S (M12), n=7: 44 cmH_2O (28, 73)*	.74
	3 (n=5)	77 cmH_2O (57, 83)*	S (M12): 83 cmH_2O (68, 92)*	.61
	2+3 (n=14)	57 cmH_2O (28, 73)*	S (M12), n=12: 68 cmH_2O (44, 86)*	.51
Lefeuvre 2022[32]	1+2+3 (n=18)	36 cmH_2O (24, 52)*	S (D63): 45 cmH_2O (23, 56)*	NR
			S (D183): 42 cmH_2O (23, 54)*	NR
			S (D303): 43 cmH_2O (31, 59)*	NR

*Note: *: Median (interquartile range).*

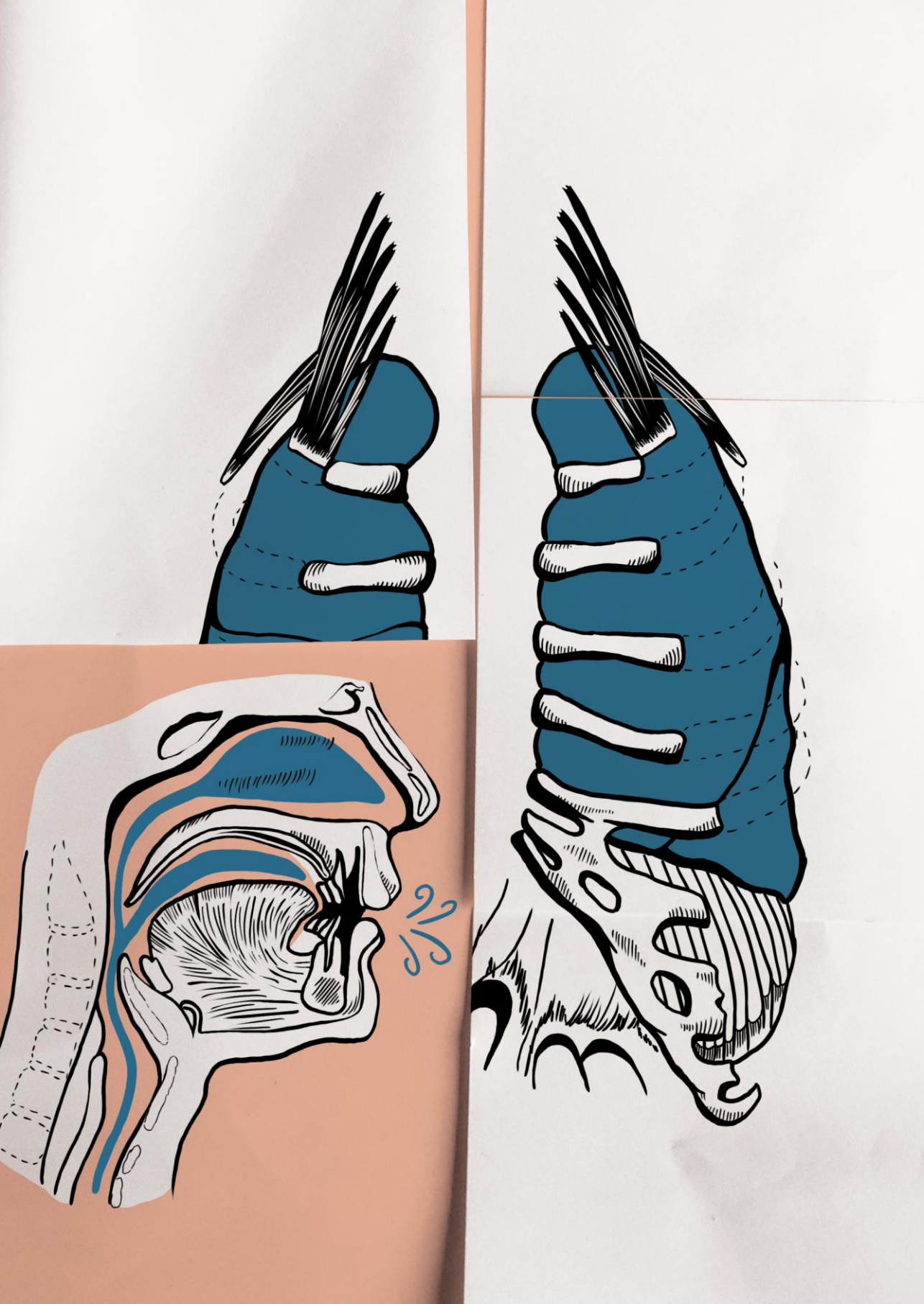
Abbreviations: %pred: percentage of predicted, CI: confidence interval, cmH_2O: centimeter of water column, D: day, L: long-term follow-up (>12 months), l: liter, l/min: liter per minute, l/sec: liter per second M: months, n: number of patients, NR: not reported, p-value: probability value, S: short-term follow-up (≤12 months), SD: standard deviation, SMA: spinal muscular atrophy, Z-score: standardized score indicating the deviation from the mean units of standard deviation.

APPENDIX 4.E: Effect of Risdiplam on lung function

First author Year[ref]	*SMA type (n)*	*Baseline mean (±SD)[95% CI]*	*Follow-up mean (±SD)[95% CI]*	*p-value*
Forced Vital Capacity				
McCluskey 2022[34]	2 (n=6)	45 %pred	S (M9): 48 %pred	.06
Ñungo Garzón, 2023[38]	2 (n=3)	18 %pred (16-34)*	S (M12): 18 %pred (16-36)*	NR
Forced expiratory volume in 1 sec				
McCluskey 2022[34]	2 (n=6)	46 %pred	S (M9): 47 %pred	.52

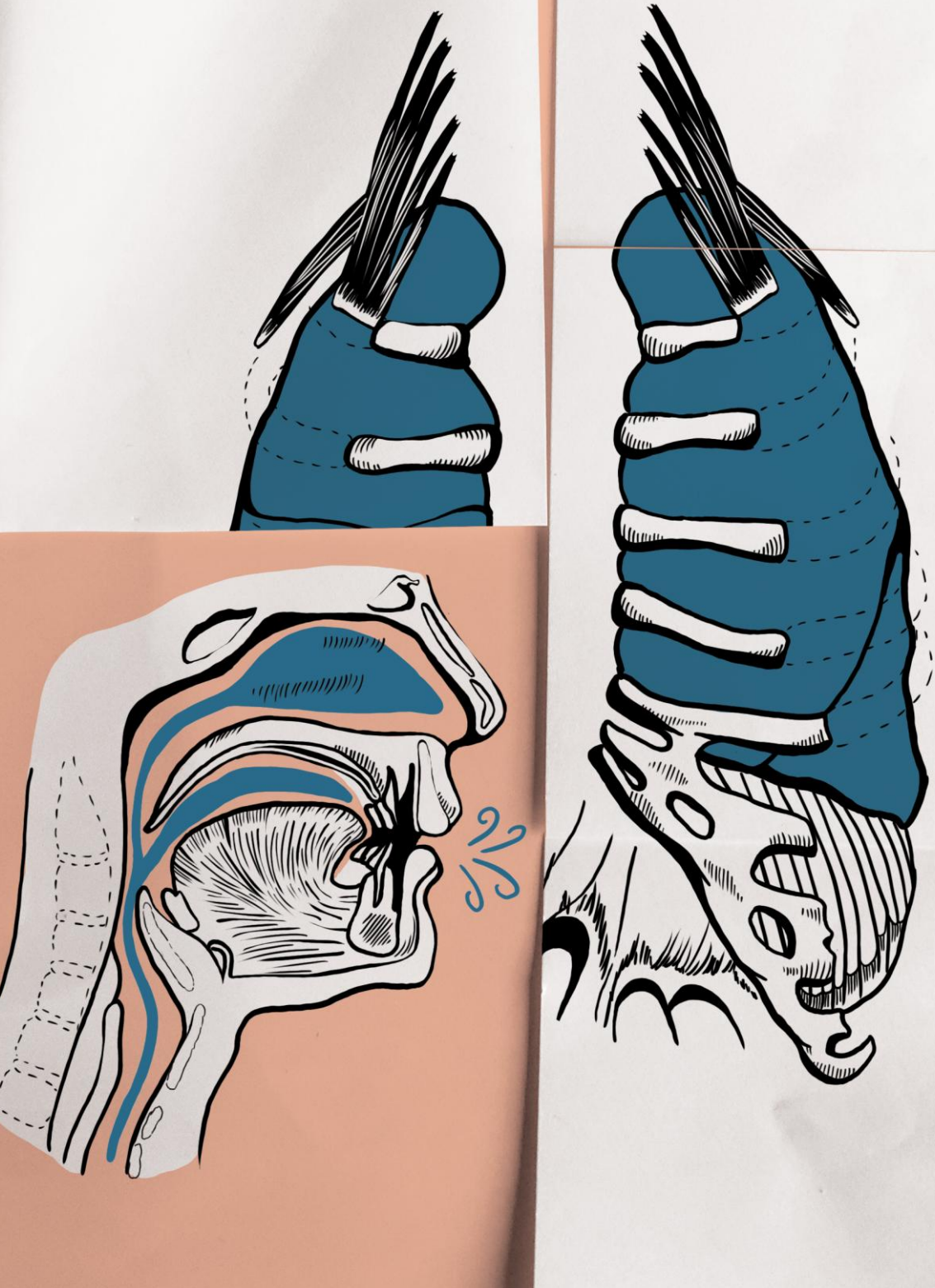
*Note: *: Median (range).*

Abbreviations: %pred: percentage of predicted, CI: confidence interval, M: month, n: number of patients, NR: not reported, p-value: probability value, ref: reference, S: short-term follow-up (≤12 months), SD: standard deviation, SMA: spinal muscular atrophy.



Part III

The effect of respiratory muscle training on lung function and respiratory muscle strength in patients with SMA.



Chapter 5

The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): study protocol for a randomized controlled trial.

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ABSTRACT

Background

Spinal Muscular Atrophy (SMA) is characterized by progressive and predominantly proximal and axial muscle atrophy and weakness. Respiratory muscle weakness results in impaired cough with recurrent respiratory tract infections, nocturnal hypoventilation, and may ultimately lead to fatal respiratory failure in the most severely affected patients. Treatment strategies to either slow down the decline or improve respiratory muscle function are needed.

Objective

This study aims to assess the feasibility and efficacy of respiratory muscle training (RMT) in patients with SMA and respiratory muscle weakness.

Methods

The effect of RMT in patients with SMA, aged ≥8 years with respiratory muscle weakness (maximum inspiratory mouth pressure [PImax] ≤80 Centimeters of Water Column [cmH_2O]), will be investigated with a single-blinded randomized sham-controlled trial consisting of a 4-month training period followed by an 8-month open-label extension phase.

Intervention

The RMT program will consist of a home-based, individualized training program involving 30 breathing cycles through an inspiratory and expiratory muscle training device. Patients will be instructed to perform 10 training sessions over 5-7 days per week. In the active training group, the inspiratory and expiratory threshold will be adjusted to perceived exertion (measured on a Borg scale). The sham-control group will initially receive RMT at the same frequency but against a constant, non-therapeutic resistance. After 4 months, the sham-control group will undergo the same intervention as the active training group (i.e., delayed intervention). Individual adherence to the RMT protocol will be reviewed every 2 weeks by telephone/video call with a physiotherapist.

Main study parameters/endpoints

We hypothesize that the RMT program will be feasible (good adherence and good acceptability) and improve inspiratory muscle strength (primary outcome measure) and expiratory muscle strength (key secondary outcome measure), as well as lung function, patient-reported breathing difficulties, respiratory infections, and health-related quality of life (additional secondary outcome measures, respectively) in patients with SMA.

Discussion

RMT is expected to have positive effects on respiratory muscle strength in patients with SMA. Integrating RMT with recently introduced genetic therapies for SMA may improve respiratory muscle strength in this patient population.

Keywords

expiratory muscle training, inspiratory muscle training, maximum expiratory mouth pressure, maximum inspiratory mouth pressure, spinal muscular atrophy.

BACKGROUND

Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by a homozygous deletion of the survival motor neuron-1 (*SMN*) gene[1–4], which leads to cellular *SMN* protein deficiency. SMA has an incidence of 1 in 6000-12,000 live births.[5] The main characteristic of SMA is the degeneration of alpha motor neurons in the anterior horns of the spinal cord, resulting in progressive muscle weakness of axial muscles and muscles of the arms and legs, with a mild to severely reduced life expectancy in the majority of patients.[6,7] SMA is classified into 4 types based on age at onset and highest acquired motor milestone.[2,4,8–11] In the last few years, *SMN*-augmenting genetic therapies have been introduced, including *SMN*-gene therapy (Onasemnogene abeparvovec) and therapies that modify *SMN2*-splicing (Nusinersen and Risdiplam).[12] Efficacy studies have demonstrated, on average, improved motor function, survival, and overall muscle strength, but the respiratory outcomes vary, with most studies showing no significant improvement in lung function parameters in patients with SMA types 2 and 3.[13–16]

Respiratory problems are among the principal challenges in clinical care for patients with SMA.[6] Weakness of respiratory muscles requires daily interventions and thereby profoundly affects the quality of life.[8,17–19] Progressive decline of vital capacity (VC) and cough strength causes respiratory failure in virtually all children with SMA type 1.[20–22] In the more chronic types of SMA (type 2 and type 3), weakness or dysfunction of the respiratory musculature leads to severe respiratory complications.[20–22] These include reduced cough strength and poor secretion clearance resulting in recurrent respiratory tract infections, reduced chest wall, and pulmonary compliance with restrictive lung function decline, alveolar hypoventilation, and, finally, chronic respiratory failure leading to premature death.[20–22]

In healthy subjects and patients with pulmonary diseases, kyphoscoliosis, or Duchenne's muscular dystrophy, respiratory muscle training (RMT) has been shown to improve respiratory muscle strength as well as endurance.[23–26] However, little is known about the therapeutic benefits of RMT in patients with SMA. A pre-experimental study in three children with SMA showed that inspiratory muscle training was safe, feasible, and acceptable, and improved inspiratory muscle strength and peak inspiratory flow.[27] Importantly, none of these children had received any form of SMN-augmenting therapy, which has also been shown to exert positive effects on overall muscle strength in some patients with SMA.[27]

To further investigate the treatment efficacy of RMT in SMA, we have designed a randomized controlled trial to study the efficacy of a 4-month home-based RMT program in patients with SMA, including patients who were recently started on SMN-augmenting therapy.

METHODS

Aim

The aim of this study is to assess the feasibility and efficacy of respiratory muscle training (RMT) in patients with SMA and respiratory muscle weakness. We hypothesize that an individualized incremental home-based RMT program will be feasible and may improve inspiratory muscle strength, expiratory muscle strength, lung function, and patient-reported breathing difficulties in patients with SMA.

Study setting

We will conduct this study at the outpatient department of the Netherlands SMA Center and the Child Development and Exercise Center at the University Medical Center Utrecht (UMCU), the Netherlands. All members of the study team, consisting of physicians, physiotherapists, lung function technicians, clinical exercise physiologists, and nurses, have broad experience with SMA due to the national cohort study that has been carried out in this center since 2010.[28]

Study design

The study protocol was designed using the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[29] The RESISTANT study is an investigator-initiated, monocenter study consisting of two parts (**Figure 5.1**).

Part 1 (0-4 months): a single-blinded randomized sham-controlled trial (RCT)

In the first part of the study, we will determine the feasibility and efficacy of respiratory muscle training (RMT) in patients with SMA. The active treatment group will receive inspiratory muscle training starting at a therapeutic intensity of 30% of maximum inspiratory mouth pressure (PImax) and expiratory muscle training starting at a therapeutic intensity of 30% of maximum expiratory mouth pressure (PEmax) for 4 months [30]. The sham-control group will receive the same training protocol but with a low (10% of PImax and PEmax) non-therapeutic intensity. Both groups will receive supervision through two-weekly telephone/video calls with a physiotherapist.

Patients will be stratified before randomization based on PImax (group 1: PImax <60 centimeters of water column [cmH_2O], group 2: PImax ≥60 cmH_2O, 60 cmH_2O was the median PImax in the group of patients used for the natural history study[31]) and then randomly allocated to the intervention or sham-control group. We will use a variable block randomization method with allocation concealment in a centralized system for randomization. The lung function analyst is blinded for treatment allocation. A data analyst (RvE) will design and sign the data analysis plan in advance. The data will be analyzed according to the analysis plan by a physiotherapist (KK) who is not blinded for treatment allocation. The physiotherapists who will perform the two-weekly telephone

calls (KK and EH) are not blinded for treatment allocation. Patients will know that there are two treatment groups, and they are informed that it is not yet known which treatment is most effective.

Part 2 (5-12 months): open-label extension phase

In the second part of the study, the sham-control group will be provided with a supervised RMT at a therapeutic intensity of 30% of PImax and PEmax, and we will explore the long-term effects of RMT on the occurrence of respiratory infections, health-related quality of life, and feasibility in the active treatment and sham-controlled groups.

Participants will visit our outpatient department every 4 months for 12 months after inclusion for assessment of primary and secondary outcome measures. This study is currently ongoing; the first participant was included on 2-2-2021. We expect study completion in the first quarter of 2023.

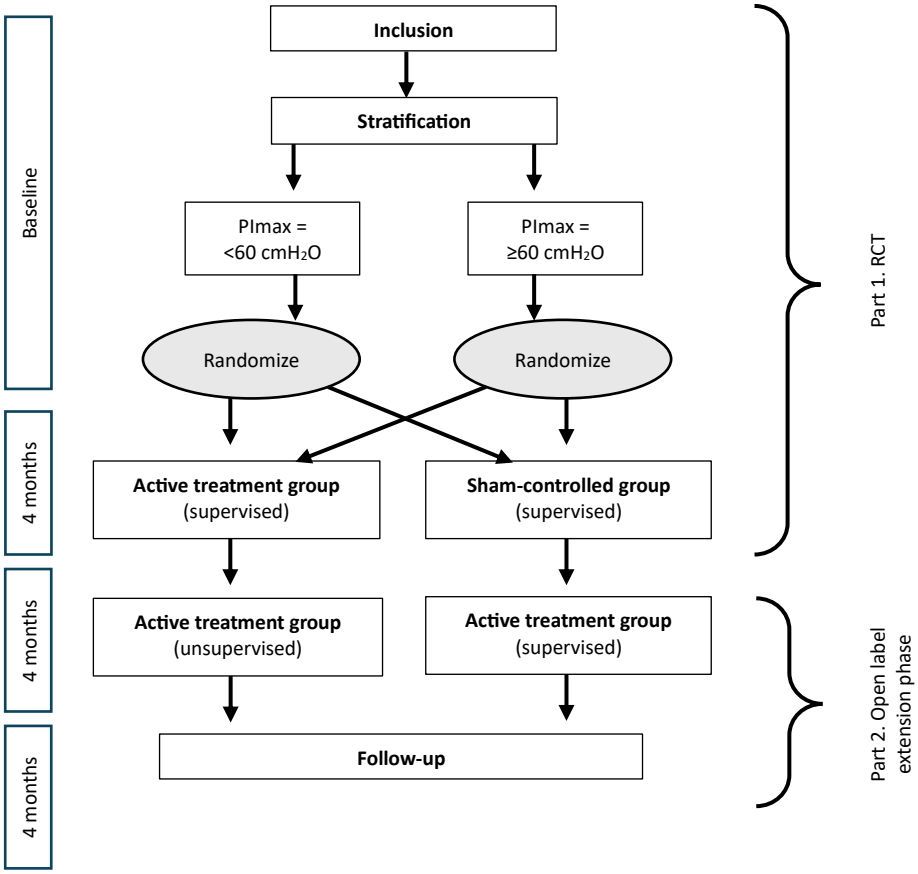


Figure 5.1 *Study design.*

Abbreviations: cmH_2O: centimeter of water column, PImax: maximal inspiratory mouth pressure.

Participants

Recruitment
We will recruit patients with SMA from the Dutch national SMA registry, which contains detailed clinical data of more than 400 patients.[11]

Eligibility criteria
Patients with SMA (any type) will be invited to participate. The inclusion criteria are:

- Age ≥8 years;
- Respiratory muscle weakness (PImax ≤80 cmH_2O[32]);
- Maintenance dose (≥2 months) Spinraza or (≥2 months) Risdiplam, or no treatment;
- Given oral and written informed consent when ≥16 years old and additional informed consent by the parents or legal representative if the participant is <16 years old.

The exclusion criteria are:

- Inability to perform respiratory and/or lung-function testing;
- Inability to understand Dutch or English;
- A history of pneumothorax or symptomatic low cardiac output syndrome;
- Treatment period <2 months of Spinraza or Risdiplam.

Sample size
Based on a previous report on inspiratory muscle training in patients with neuromuscular diseases (n=27, 18 patients with Duchenne muscular dystrophy [DMD] and nine patients with SMA)[17] indicating a mean improvement in PImax of 28 cmH_2O difference (Standard Deviation [SD] ±26.27), we assume a mean difference between active and sham-treated patients after 4 months of 20 cmH_2O (SD 25.0). To detect this effect size with 80% power and a two-sided alpha of 5%, 50 patients are needed (25 per group).

Intervention
Inspiratory muscle training
For the inspiratory muscle training (IMT), we use the POWERbreathe KHP2.[33] Clinical research has shown high participant motivation and adherence to training with the POWERbreathe KHP2 thanks to the on-screen feedback.[34] Furthermore, healthcare professionals can review participant progress by tracking up to 30 of the participants' training sessions, which the KHP2 can store. This data can be scrolled through to monitor progress. The electronic, variable, tapered flow valve ensures maximum training benefits. It is easy to use, easy to clean, and training improvements can be easily monitored.[33]

Expiratory muscle training

For the expiratory muscle training (EMT), we use the Threshold Inspiratory Muscle Trainer (IMT) (Philips Respironics) in reverse. Use of the Threshold Positive Expiratory Pressure (PEP) (Philips Respironics) is one method to perform EMT. However, the maximal expiratory resistance of the Threshold PEP is limited to 20 cmH_20.[35] To overcome this limitation in expiratory resistance, we chose the reverse use of the Threshold IMT.[35–37] This device contains, at its end, a valve closed by the positive pressure of a spring, which can be graded from 9 to 42 cmH_2O and allows resistance changes by 1 cmH_2O increments. The reverse Threshold IMT has a one-way spring-loaded valve that closes during expiration and requires that participants exhale hard enough to open the valve and let the air go out. This device provides constant pressure for expiratory muscle training, regardless of how quickly or slowly the participant breathes, and the optimal loading pressure can be adjusted based on the individual characteristics of the participant.[35,37,38]

Participant timeline

The study schedule is presented in **Table 5.1**. Before the first visit, participants will be recruited for enrollment by a research nurse. Patients who express interest in participating receive a patient information letter and an appointment with the physiotherapist. At the first visit (month [M] 0), the physiotherapist further determines whether patients are eligible for participation. After signing the informed consent form, participants are weighed and their length is determined, followed by lung function tests. If PImax >80 cmH_2O, participants are excluded from the study. If PImax ≤80 cmH_2O, participants will be stratified (group 1 <60 cmH_2O, group 2 ≥60 cmH_2O) and then randomly allocated to either the active treatment group or the sham-controlled group.

All participants (and parents) will be instructed by a trained physiotherapist on the use of both devices at the first visit (M0). Participants are instructed to aim for 10 training sessions per week, divided over 5 to 7 days. A minimum of 6 hours in between training sessions is recommended. Per training session, the participant breathes 30 times through the POWERbreathe and 30 times through the reverse Threshold IMT. If necessary, the participant may take a break, with a maximum of 60 seconds after 10 or 15 breaths. After each session, they fill in a diary, which contains information about the intensity of the training and the perceived exertion (Borg scale 0-10).

In the active treatment group, the intensity of the training is set at M0 at 30% of PImax and PEmax and will be increased or decreased based on the level of perceived exertion. Participants are instructed to increase the intensity by 1-5 cmH_2O if they score a perceived exertion of 0-4 and decrease the intensity if they score a perceived exertion of 7-10. If they score a perceived exertion of 5 or 6, the intensity will not be adjusted. The intensity of the training in the sham-controlled group will be set at M0 at 10% of PImax and PEmax and will remain the same during the first 4 months of training. After 4

months, we will provide the sham-controlled group with the same training regimen as the active treatment group.

Data collection

Baseline measures

We will record the following baseline data: gender, age, SMA type, number of *SMN2* copies, type of SMN-augmenting therapy, use of other medication, co-morbidities, ambulatory level according to the modified Hoffer classification[39], use of ventilatory support, and use of Airway Clearance Techniques (ACT) (Airstacking [AS] or Mechanical insufflation-exsufflation [MI-E]).

Outcome measures

This study investigates the feasibility and efficacy of respiratory muscle training in patients with SMA. The lung function analysts, who are blinded for treatment allocation, administer the questionnaires (health-related quality of life, Medical Research Council [MRC] dyspnea, and dyspnea immediately after lung function measure), perform lung function tests, and measure respiratory muscle strength, in a fixed order.

Feasibility

Feasibility will be determined based on adherence and acceptability. Adherence is defined as the completion rate of the estimated number of training sessions over 4 months (≥ 80% of the participants have fulfilled the prescribed treatment = good adherence). Adherence will be monitored by a patient diary, two weekly telephone or video calls with a physiotherapist, and the number of training sessions in the POWERbreathe KHP2. Acceptability is defined as the willingness to continue the training (≥5 = good acceptability) and will be assessed with a Borg Scale (0-10) at M4, M8, and M12 by the physiotherapist.

Efficacy: Primary and key secondary outcome measure

- *PImax and PEmax:* To measure the efficacy, we will examine changes in respiratory performance over time in both groups. Measurements of PImax and PEmax are a simple assessment of global respiratory muscle strength in a clinical setting, and the test is responsive to evaluate changes within subjects. PImax and PEmax in kiloPascal (kPa) are assessed conform the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations.[32] PImax and PEmax will be converted to cmH_2O by multiplying the value in kPa by 10.197. Reference values of Wilson et al.[40] will be used to calculate % of predicted.

Table 5.1: *Study schedule of enrolment, interventions, and assessments*

	Study Period			
	Allocation	**Post allocation**		**Closeout**
Time point	M0	M4	M8	M12
Enrolment:				
Eligibility screen	X			
Informed consent	X			
Stratification	X			
Randomization	X			
Part 1 Randomized Controlled Trial:				
Active treatment group (supervised)	X ———	X		
Sham-controlled group (supervised)	X ———	X		
Part 2 Delayed intervention:				
Active treatment group (unsupervised)		X ———	X	
Active treatment group (supervised)		X ———	X	
Part 2 Follow-up:				
Active treatment group (unsupervised)			X ———	X
Active treatment group (unsupervised)			X ———	X
Assessments:				
Feasibility		X	X	X
PImax	X	X	X	X
PEmax	X	X	X	X
MRC Dyspnea	X	X	X	X
Lung function	X	X	X	X
SF-36 or PedsQL	X	X	X	X
Infections	X	X	X	X

Abbreviations: M: month, MRC: Medical Research Council, PEmax: maximum expiratory mouth pressure, PedsQL: Pediatric Quality of Life Inventory, PImax: maximum inspiratory mouth pressure, SF-36: 36-item Short Form Health Survey

Efficacy: secondary outcome measures

To additionally investigate the effect of respiratory muscle training on daily life functioning, lung function, and respiratory infections, we use the following measures:

- *Health-related quality of life:* Health-related quality of life will be measured with the 36-item short-form health survey (SF-36) for adults and the pediatric quality of life inventory (PedsQL) for children. The SF-36 Health Survey is composed of 36 questions and standardized response choices, organized into eight multi-item scales: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH). All raw scale scores are linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of functioning or well-being.[41] The scores of the different scales will be summarized into a physical component summary (PCS) and a mental component summary (MCS).[42] The PedsQL generic score scale consists

of 23 items and has a child self-report format for ages 5–7, 8–12, and 13–18 years. The items are scored on a five-point Likert scale, ranging from 'never a problem' to 'almost always a problem' (corresponding scores 100, 75, 50, 25, or 0) and are organized into four multidimensional scales: physical functioning, emotional functioning, social functioning, and school functioning and three summary scores: total scale score, physical health summary score, and psychosocial health summary score. A higher PedsQL score indicates a better quality of life.[43]

- *Lung function:* Lung function testing includes spirometry with measurements of upright (forced) vital capacity ([F]VC) in liters, peak expiratory flow (PEF) in liters per second, forced expiratory volume in 1 second (FEV1) in liters, peak cough flow (PCF) in liters per second, sniff nasal inspiratory pressure (SNIP) in cmH_2O, and mouth occlusion pressure at 100ms during quiet breathing (P0.1) in kPa. P0.1 is intended to measure the actual central respiratory drive.[44] P0.1/PImax is the ratio between the respiratory drive and the capacity of the inspiratory muscles and has been suggested as an important predictor of impending respiratory muscle fatigue (work of breathing).[44] Lung function is assessed conform the ERS/ATS recommendations.[32] Global lung function reference equations for VC[45], FVC and FEV1[46], PEF[47,48], and P0.1[44,49] will be used to calculate % of predicted.
- For the use of the reference equations, height in centimeters and weight in kilograms will be needed. Height is assessed using the ulna method.[50] This method is useful for determining the height of wheelchair-bound patients and those with curvature of the spine. Weight will be measured with a passive floor lift (Maxi Move, type Arjo).
- *Patient-reported breathing difficulties:* Patient-reported impact of breathing difficulties will be measured with the Medical Research Council (MRC) dyspnea scale. The dyspnea scale has been in use for many years for grading the effect of breathlessness on daily activities. This scale measures perceived respiratory disability. The MRC dyspnea scale is simple to administer as it allows the patients to indicate the extent to which their breathlessness affects their mobility.[51,52] Dyspnea immediately after lung function measure and after each training session is measured with a Borg scale ranging from 0 to 10.
- *Respiratory infections:* Respiratory infection frequency (based on the need for antibiotics and/or hospitalization) will be assessed during the two weekly telephone consultations and each visit by the physiotherapist. In case of uncertainties, the general practitioner, the neurologist, or the patient's pharmacy will be consulted.
- *Adverse Events (AEs): A*ll AEs that are reported spontaneously by the participant or observed by the investigator or study staff members are recorded, and if necessary, appropriate measures are taken.

Statistical analysis

Continuous variables will be expressed as means with standard deviations or medians with interquartile ranges (whichever is more appropriate), and discrete variables will be expressed as numbers with percentages. The main efficacy population will consist of all patients being randomized and analyzed according to their original treatment allocation, irrespective of actual received treatment or follow-up (intention-to-treat). The primary comparison will be the mean difference in PImax % of predicted at month 4. For the secondary outcome measures, we will compare the mean difference in health-related quality of life, PEmax % of predicted, VC % of predicted, FVC % of predicted, FEV1 % of predicted, PEF % of predicted, P0.1 % of predicted, PCF, SNIP, P0.1/PImax, and patient-reported breathing difficulties. An ANCOVA model will be used to analyze the differences between groups, adjusting for baseline values. Missing data in the outcomes at month 4 will be imputed by the baseline-observation-carried-forward (BOCF) approach. This will be a conservative method because we expect patients' PImax will improve after training. For the longitudinal data, we will use a mixed model for repeated measurements, including a term for visit, treatment, their interaction, and baseline PImax to account for the correlation within subjects. Similar models will be used for the secondary endpoints. We will summarize the incidence of respiratory infections and other AEs by treatment group and in all treatment groups combined in frequency tables, coded according to the introductory guide Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.[53]

Data management

The following measures will be taken to assure the confidentiality and anonymity of the participants' data or documents collected in Castor: a) each participant will be identified in an electronic database by a unique six-digit code; b) the list of participant names corresponding to the codes will be stored in a separate encrypted electronic database, safeguarded by the principal investigator; c) only study investigators will have access to the databases and examine individual data or documents; d) all logins will be recorded; e) adopt strict precautions to prevent access to the data or documents by non-authorized persons; f) the handling of data and documents will comply with the General data protection regulation (GDPR) and is further described in the Data Monitoring Plan.

Ethics, dissemination, and safety monitoring

The study is registered in The Overview of Medical Research in the Netherlands (OMON): NL73280.041.20, registration date: August 10, 2020; https://onderzoekmetmensen.nl/en/trial/52847. This study is also registered in the American Registry for Clinical Studies and Trials (NCT05632666; https://clinicaltrials.gov). The investigator obtains written informed consent before study participation from participants and parents if the participant is <16 years old.

The trial is monitored by an external independent party (Julius Clinical). Because of the negligible risk classification, minimal monitoring will be necessary. All participants are insured by the sponsor in case of harm due to study participation.

The study will be conducted according to the principles of the Declaration of Helsinki, adapted 19-10-2013, and in accordance with the Medical Research Involving Human Subjects Act (WMO). The Code of Conduct, as agreed upon 2001 by the Dutch organization of Pediatrics, will be used. The study is partly done by minors, which means that in any case of resistance, the test and research protocol will be terminated. Resistance means that the participant's behavior obviously differs from or is more excessive compared to the participant's normal behavior. The national rules of the Dutch Association of Pediatrics for the protection of minor study participants are followed during the entire study. The results of this study will be publicly disclosed in several publications in peer-reviewed scientific journals related to the topic of this study and orally at conferences concerning this theme.

DISCUSSION

Most studies on the effect of SMN-augmenting genetic therapies on respiratory outcomes do not show significant improvement in lung function parameters in patients with SMA types 2 and 3.[13–16] Respiratory muscle training (RMT) has been shown to be effective in patients with pulmonary diseases, kyphoscoliosis, or DMD.[23–26] Two studies included patients with SMA; however, the groups of patients with SMA were small (*n*=9, 33% of the total number of patients[17] and *n*=3, 37% of the total number of patients[27]) and a distinction was not made between the results for the patients with DMD and SMA. None of these patients with SMA received any form of SMN-augmenting therapy. To further study the efficacy of a 4-month home-based RMT program in patients with SMA, we designed a randomized controlled trial.

The diaphragm acts as the primary inspiratory muscle and accounts for 70% of the inspired air volume during regular breathing.[54] In patients with SMA, intercostal respiratory muscles are weak, while the diaphragm is relatively spared[55,56] resulting in lower expiratory muscle strength (PEmax) compared to inspiratory muscle strength (PImax).[31] Therefore, RMT may perhaps be expected to particularly benefit the rescue of expiratory muscle function. Here, however, we chose PImax as the primary outcome measure for the following specific reason: it turned out that reference values to identify patients with respiratory muscle weakness and calculate the required sample size are only available for this particular outcome measure (i.e., PImax ≤ 80 cmH_2O[32]). As a result, it may be difficult to reach the primary endpoint of this study.

Training intensities of at least 30% of PImax and PEmax are necessary to increase the strength of the inspiratory and expiratory muscles, respectively.[30] RMT has been studied before in patients with neuromuscular diseases[30,57]; however, almost all

these studies were conducted in patients with amyotrophic lateral sclerosis (ALS) or myopathies, such as DMD.[30,57] The frequency of training, duration of the interventions, and the intensity of the training programs varied considerably.[30,57] Only a few studies included patients with SMA, and none of the studies provided separate data for patients with SMA.[30] In a pre-experimental study with eight participants, including three patients with SMA, participants performed inspiratory muscle training twice a day, 5 days a week, 30 breaths per session, for 6 weeks.[27] Here, we chose to copy the training intensity and frequency used in this study.[27]

Studies suggest that an IMT protocol of training twice a day with PImax as guidance of resistance over a period of 3 to 6 months can have a positive effect on inspiratory muscle strength in patients with neuromuscular diseases.[57] Patients who are treated with the *SMN2*-splicing-modifying drugs Spinraza or Risdiplam have their follow-up visits in our center every 4 months. To minimize patient burden, we have opted to combine visits for the RESISTANT trial with these therapy follow-up visits, and we have chosen a training period of 4 months.

Lastly, a recent study on fatigability of respiratory muscles in patients with SMA observed that perceived exertion, measured with an OMNI scale, did not correlate with objective exertion.[58] The OMNI scale has only been validated in children and adults during motor activities[59,60] and may not detect exertion of the respiratory muscles. Here, we have therefore chosen to monitor the response to respiratory muscle loading with the experienced intensity of the training and perceived dyspnea measured with a Borg scale.[61]

In conclusion, we will conduct a single-blinded randomized sham-controlled trial to investigate the feasibility and efficacy of respiratory muscle training in patients with SMA and respiratory muscle weakness. We hypothesize that RMT is feasible and that it will improve inspiratory and expiratory muscle strength.

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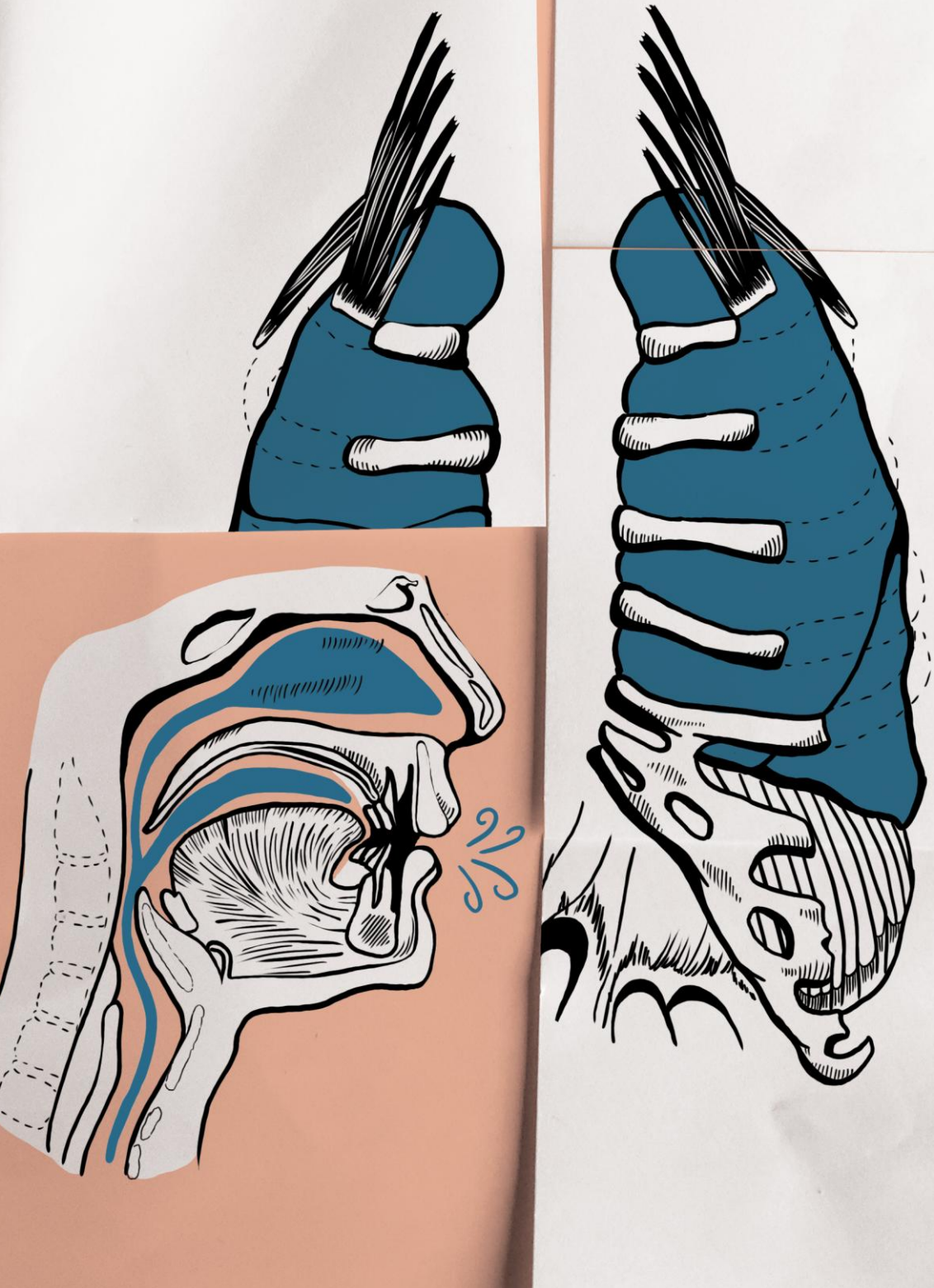
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Chapter 6

The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): results of a randomized controlled trial.

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ABSTRACT

Objectives

To investigate the efficacy and feasibility of respiratory muscle training (RMT) in patients with spinal muscular atrophy (SMA) and respiratory muscle weakness.

Design

A 4-month, single-blinded, randomized controlled trial (RCT), followed by an 8-month extension phase.

Setting

The outpatient clinic of the Neurology department and the Child Development and Exercise Center at the University Medical Center Utrecht (UMCU), the Netherlands.

Participants

30 participants, ≥ eight years, SMA type 1, 2, 3, or 4, and respiratory muscle weakness.

Interventions

The training group started RMT at 30% of their maximum inspiratory (PImax) and expiratory mouth pressure (PEmax) and adjusted their training intensity based on perceived exertion. The control group started and continued RMT at 10% of PImax and PEmax. After four months, the control group received the same RMT as the training group.

Main outcome measures

The primary outcome was the between-group difference in PImax after the RCT phase. Additionally, we explored the association between training volume (i.e., number of training sessions x training intensity) and the increase in PImax over 1 year.

Results

25 participants completed the study. Mean PImax after four months (corrected for baseline value) training group: 61.1 cmH_2O, control group: 54.3 cmH_2O, mean difference in PImax: 6.8 cmH_2O [95% CI: -2.0 to 15.6]. Despite the study being underpowered, we did find a strong association between training volume and an increase in PImax (R^2=0.531).

Conclusion

There was a small between-group difference in PImax after the RCT phase. The training was safe, but the feasibility of the training needs further improvement.

Clinical Trial Registration Number: NL73280.041.20.

Contribution of the paper

- There was a small difference in PImax improvement between training at different intensities (10% vs 30% of PImax).
- Higher training volume (frequency times intensity) is strongly associated with improvement of inspiratory muscle strength.
- Adherence to respiratory muscle training can be improved by supervision from physiotherapists.

Keywords

muscular atrophy spinal, respiratory muscle training, maximum inspiratory mouth pressure, maximum expiratory mouth pressure

INTRODUCTION

Spinal muscular atrophy (SMA) is a severe neuromuscular disease with an incidence of 1 in 6,000-12,000 live births.[1] The SMA classification system captures the wide range of disease severity and traditionally distinguishes four types (i.e., types 1-4) based on age at onset and the highest acquired motor milestone.[2,3]

SMA is caused by the loss of function of the survival motor neuron 1 gene (*SMN1*), leading to cellular SMN protein deficiency.[4] Although SMN is expressed by all human cells, alpha motor neurons in the spinal cord's anterior horns are the most sensitive to this deficiency, and their degeneration results in progressive muscle weakness of axial, respiratory, and proximal limb muscles.[5]

In patients with SMA, the progressive decline of respiratory muscle strength is the main cause of respiratory complications. The reduced cough strength and poor secretion clearance trigger the vicious circle of 1) recurrent respiratory tract infections, 2) further reduction in chest wall and lung compliance, 3) alveolar hypoventilation, and 4) further decline of vital capacity and cough strength. Eventually, this can lead to respiratory failure and premature death.[6–8]

The available disease-modifying therapies (DMTs) (Nusinersen, Onasemnogene abeparvovec, and Risdiplam) increase SMN protein levels and improve survival, motor function, and muscle strength in patients with SMA.[7] However, they do not appear to significantly improve respiratory muscle strength.[7,9] Therefore, we need other strategies to prevent respiratory complications.

Respiratory muscle training (RMT) is an intervention that may stabilize the progression of respiratory weakness in SMA. Silva et al.[10] concluded that there was low-certainty evidence that RMT may improve lung function and respiratory muscle strength in neuromuscular diseases, such as Duchenne muscular dystrophy and amyotrophic lateral sclerosis. The effects of RMT in patients with SMA have not been systematically studied. Therefore, we performed a randomized controlled trial (RCT) to investigate the efficacy and feasibility of a 4-month individualized, incremental, and home-based RMT in patients with SMA.

METHODS

Participants

We have described the study protocol in detail in a recent publication.[11] In short, participants 1) were ≥8 years old, 2) had SMA type 1, 2, 3, or 4, and 3) had respiratory muscle weakness (maximum inspiratory mouth pressure [PImax] ≤80 centimeters of water column [cmH_2O]).[12] Participants either did not use DMTs or had started Nusinersen or Risdiplam at least two months before inclusion. We excluded patients if

they 1) were unable to perform lung function testing, 2) had a history of pneumothorax, or 3) had symptomatic low cardiac output syndrome.

Standard protocol approvals, registrations, and patient consent

This RCT is an investigator-initiated, monocenter, single-blinded study with a delayed start design. We performed the study at the outpatient clinic of the Department of Neurology and Neurosurgery and the Child Development and Exercise Center at the University Medical Center Utrecht (UMCU), the Netherlands. We conducted the study according to the principles of the Declaration of Helsinki, the code of conduct, and the national rules of the Dutch Association of Pediatrics for the protection of minor study participants. The Medical Research Ethics Committee Utrecht (METC Utrecht) approved this study based on the requirements of the Dutch law (WMO, NL73280.041.20). An external independent party (Julius Clinical, Zeist, the Netherlands) monitored the study for accuracy, integrity, and safety. The study was registered in The Overview of Medical Research in the Netherlands (OMON): NL73280.041.20, registration date: August 10, 2020; https://onderzoekmetmensen.nl/en/trial/52847.

Participants and parents, if the participant was <16 years old, gave written informed consent. The first participant was included on February 2, 2021. A unique six-digit code was assigned to each participant to ensure the confidentiality and anonymity of the participants' data or documents.

We followed the Consolidated Standards of Reporting Trials (CONSORT) checklist to ensure an accurate and complete report of our work (**Appendix 6.A**).

Study procedures

Participants visited our outpatient clinic every 4 months for 1 year (M0, M4, M8, and M12). The lung function analysts, blinded to treatment allocation, administered the questionnaires, performed lung function tests[12], and assessed respiratory muscle strength.[12] The physiotherapists (KKS, EH), not blinded to treatment allocation, registered the adverse events (AEs) and adherence during the telephone/video calls (once every 2 weeks) and at each visit.

The delayed start study consisted of two parts (**Figure 6.1**): the RCT phase (M0-M4) and the extension phase (M4-M12). At M0, we stratified participants based on PImax and allocated them randomly to the training or control group.[11] We described the intervention in the protocol[11] and provide a summary in **Table 6.1**. At M4, the training group continued the RMT unsupervised. The control group then received the same supervised RMT that the training group had received in the RCT phase. At M8, both groups continued the RMT unsupervised.

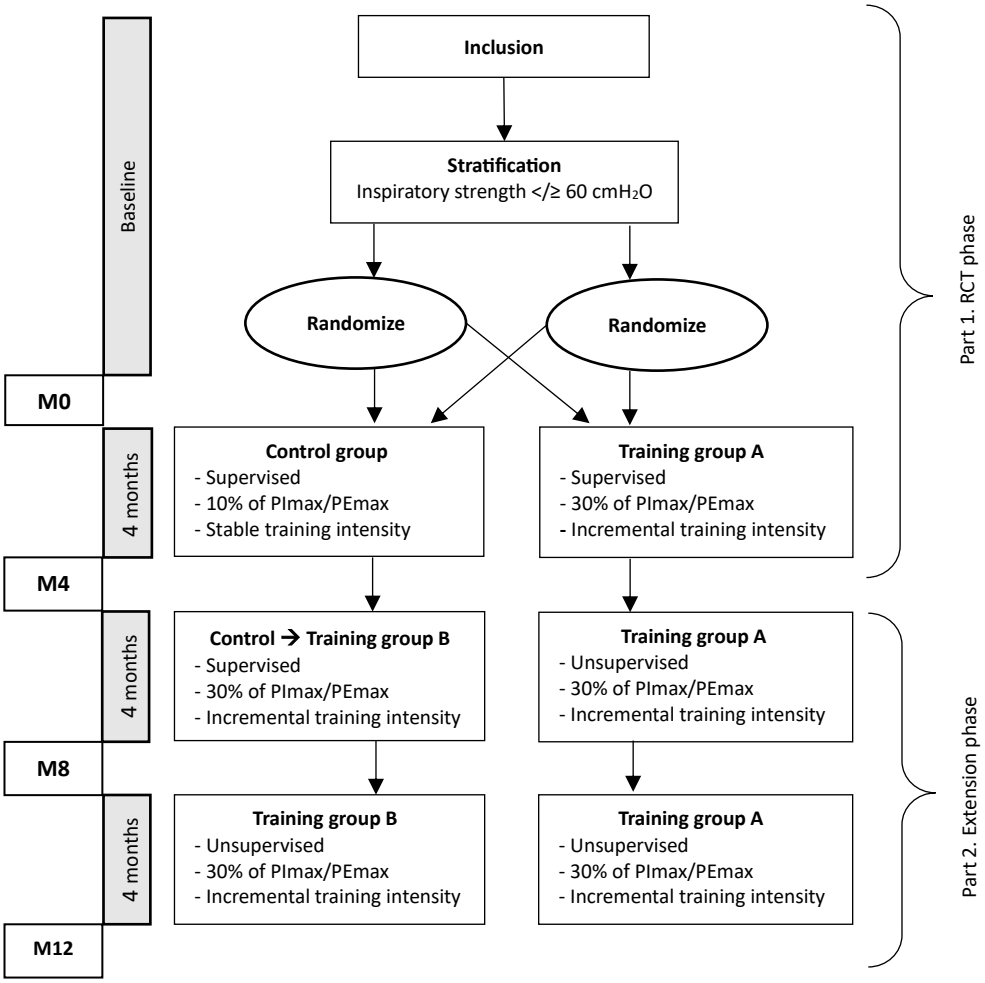


Figure 6.1: *Study protocol*

Abbreviations: cmH_2O: centimeters of water column, Incremental training intensity: participants adjusted training intensity based on their perceived exertion (Borg score <5: increase the intensity with 1 or 2 cmH_2O, Borg score 5 or 6: good intensity, Borg score >6: decrease the intensity with 1 or 2 cmH_2O), M: month, PEmax: maximum expiratory mouth pressure, PImax: maximum inspiratory mouth pressure.

Table 6.1: *Intervention description of the first 4 months using the template for intervention description and replication (TIDieR) checklist.*[13]

Checklist item	Experimental group	Control Group
Brief name	Training group	Control group
What Materials	IMT: POWERbreathe KHP2.[14] EMT: reversed Threshold Inspiratory Muscle Trainer (Philips Respironics).[15]	IMT: POWERbreathe KHP2.[14] EMT: reversed Threshold Inspiratory Muscle Trainer (Philips Respironics).[15]
What procedures	IMT: 30% of PImax. EMT: 30% of PEmax.	IMT: 10% of PImax. EMT: 10% of PEmax.
Who provided	A trained physiotherapist. Supervision via telephone/video calls, once every 2 weeks (**Appendix 6.B**).	A trained physiotherapist. Supervision via telephone/video calls, once every 2 weeks (**Appendix 6.B**).
Where	Visits: outpatient clinic of the Wilhelmina Children's Hospital. Training: participant's home.	Visits: outpatient clinic of the Wilhelmina Children's Hospital. Training: participant's home.
When and How Much	10 training sessions per week, in 5 to 7 days. IMT: 30 breaths. EMT: 30 breaths.	10 training sessions per week, in 5 to 7 days. IMT: 30 breaths. EMT: 30 breaths.
Tailoring	Patient adjusted training intensity based on perceived exertion (Borg scale from 0-10[16]), scored after each training. Aim for a Borg of 5-6, perceived as heavy but not exhausting. If Borg <5 → increase intensity with 1 or 2 cmH_2O. If Borg >6 → decrease intensity with 1 or 2 cmH_2O.	Training intensity remained stable.

Abbreviations: cmH_2O: centimeters of water column, EMT: expiratory muscle training, IMT: inspiratory muscle training, PEmax: maximum expiratory mouth pressure, PImax: maximum inspiratory mouth pressure.

Outcome measures

Table 6.2 summarizes the outcome measures. We refer to the published protocol for a detailed description of all outcome measures.[11]

Table 6.2: *Outcome measures*

PRIMARY OUTCOME MEASURE	
Inspiratory muscle strength	Between-group difference in maximum inspiratory mouth pressure (PImax) in cmH_2O (and %pred[17]) after the 4-month RCT phase.
KEY SECONDARY OUTCOME MEASURE	
Expiratory muscle strength	Between-group difference in maximum expiratory mouth pressure (PEmax) in cmH_2O (and %pred[17]) after the 4-month RCT phase.
SECONDARY OUTCOME MEASURES	
Lung function	Slow/forced vital capacity ([S/F]VC) in %pred.[18,19] Forced expiratory volume in 1 second (FEV1) in %pred.[19] Peak expiratory flow (PEF) in %pred.[20,21] Peak cough flow (PCF) in l/s. Sniff nasal inspiratory pressure (SNIP) in cmH_2O. Mouth occlusion pressure at 100ms during quiet breathing (P0.1) in %pred.[22] Ratio between P0.1 and PImax.
Health-related quality of life	Pediatric Quality of Life Inventory (PedsQL) for children. The 36-item Short Form Health Survey (SF-36) for adults.
Dyspnea	Borg scale (0=no dyspnea, 10=very dyspneic). Immediately after lung function tests and after each training session.
Respiratory infection frequency	Symptoms of respiratory tract infection requiring antibiotics and/or hospitalization. Assessed during telephone/video calls and at each visit.
FEASIBILITY	
Safety	Related (serious) adverse events. Assessed during telephone/video calls and at each visit.
Adherence	The completion rate of the prescribed number of training sessions over 4 months. Monitored with diaries, during the telephone/video calls, and at each visit.
Acceptability	Question: How willing are you to continue the training? Answer: 0=not willing at all to 10=very willing. A score of ≥5 was considered acceptable.

Abbreviations: %pred: percentage of predicted, cmH_2O: centimeters of water column, l: liters, RMT: respiratory muscle training, s: seconds.

Training volume

To analyze whether the number of training sessions and/or training intensity was related to the change in PImax or PEmax, we calculated the number of executed training sessions per participant and the training intensity per executed training session (percentage of the last measured PImax and PEmax). We defined the total training volume of inspiratory muscle training (IMT) and expiratory muscle training (EMT) as the sum of all training intensities (i.e., the average training intensity times the number of executed training sessions).

Semi-structured interview month (M)12

At M12, we conducted a semi-structured interview consisting of closed-ended (where we asked the participant to give a score on a 10-point scale) and open-ended questions that addressed the participant's experiences with the training devices, the frequency and subjective effects of the training, and the frequency of the video calls **(Appendix 6.C)**.

ANALYSES

Based on a previous report on inspiratory muscle training in patients with neuromuscular diseases[23] indicating a mean improvement in PImax of 28 cmH_2O (standard deviation (SD) ± 26.27), we assumed a mean difference between active and sham-treated patients after 4 months of 20 cmH_2O (SD 25.0). To detect this effect size with 80% power and a two-sided alpha of 5%, 50 patients were needed (25 per group). All participants were analyzed according to their randomized treatment allocation, irrespective of actual received treatment or follow-up. The primary endpoint was the mean difference in PImax between randomized arms after 4 months. Missing data at M4 were imputed by the baseline-observation-carried-forward (BOCF) approach. The between-group differences adjusted for baseline values were calculated with an ANCOVA model. We recorded and coded (S)AEs according to the introductory guide Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.[24] We used IBM SPSS Statistics 29.0 for all calculations and analyses.

To investigate the effect of training volume on PImax and PEmax, we performed regression analysis with the percentage change from baseline in PImax or PEmax as the dependent variable and training volume of IMT or EMT as the independent variable.

RESULTS

Participants

Between October 2020 and November 2021, we informed 123 patients with SMA included in the Netherlands SMA registry (59 children, 64 adults) about the study. Eighty-nine patients did not want to participate, mainly because they thought the training would be too time-consuming. Therefore, we were not able to reach the calculated sample size. We screened 34 participants for eligibility and randomized 30 participants for participation (**Figure 6.2** and **Table 6.3**).

Table 6.3: *Baseline characteristics*

	Training group (n=15)	**Control Group (n=15)**	**All (n=30)**
Female, n (%)	8 (53)	10 (67)	18 (60)
Age in years, mean (SD)	36.9 (14.9)	38.2 (17.6)	37.5 (16.1)
Child (<18 years), n (%)	0 (0)	3 (20)	3 (10)
Adult (≥18 years), n (%)	15 (100)	12 (80)	27 (90)
SMA subtype, n (%)			
Type 1c	2 (13)	1 (67)	3 (10)
Type 2a	6 (40)	6 (40)	12 (40)
Type 2b	3 (20)	4 (27)	7 (23)
Type 3a	3 (20)	3 (20)	6 (20)
Type 3b	0	1 (7)	1 (3)
Type 4	1 (7)	0	1 (3)
SMN2 copies, n (%)			
3 copies	12 (80)	14 (93)	26 (87)
4 copies	3 (20)	1 (67)	4 (13)
SMN therapy, n (%)			
Nusinersen	2 (13)	4 (27)	6 (20)
Risdiplam	9 (60)	8 (53)	17 (57)
No SMN-augmenting therapy	4 (27)	3 (20)	7 (23)
Ambulatory level, n (%)			
Non-ambulant	14 (93)	15 (100)	29 (97)
Household ambulant	1 (7)		1 (3)
Use of ventilatory support, n (%)			
Yes	9 (60)	8 (53)	17 (57)
No	4 (27)	4 (27)	8 (27)
Only airstacking	2 (13)	3 (20)	5 (17)
PImax (cmH_2O), mean (SD)	50.4 (18.5)	47.1 (19.7)	48.7 (18.9)
PImax (%pred), mean (SD)	58.1 (20.5)	62.5 (25.2)	60.3 (22.6)
PEmax (cmH_2O), mean (SD)	29.9 (19.0)	30.7 (13.1)	30.3 (16.0)
PEmax (%pred), mean (SD)	26.1 (15.2)	30.0 (12.9)	28.0 (14.0)

Abbreviations: %pred: percentage of predicted, cmH_2O: centimeters of water column, n: number, PEmax: maximum expiratory mouth pressure, PImax: maximum inspiratory mouth pressure, SD: standard deviation, SMA: spinal muscular atrophy, SMN: survival motor neuron.

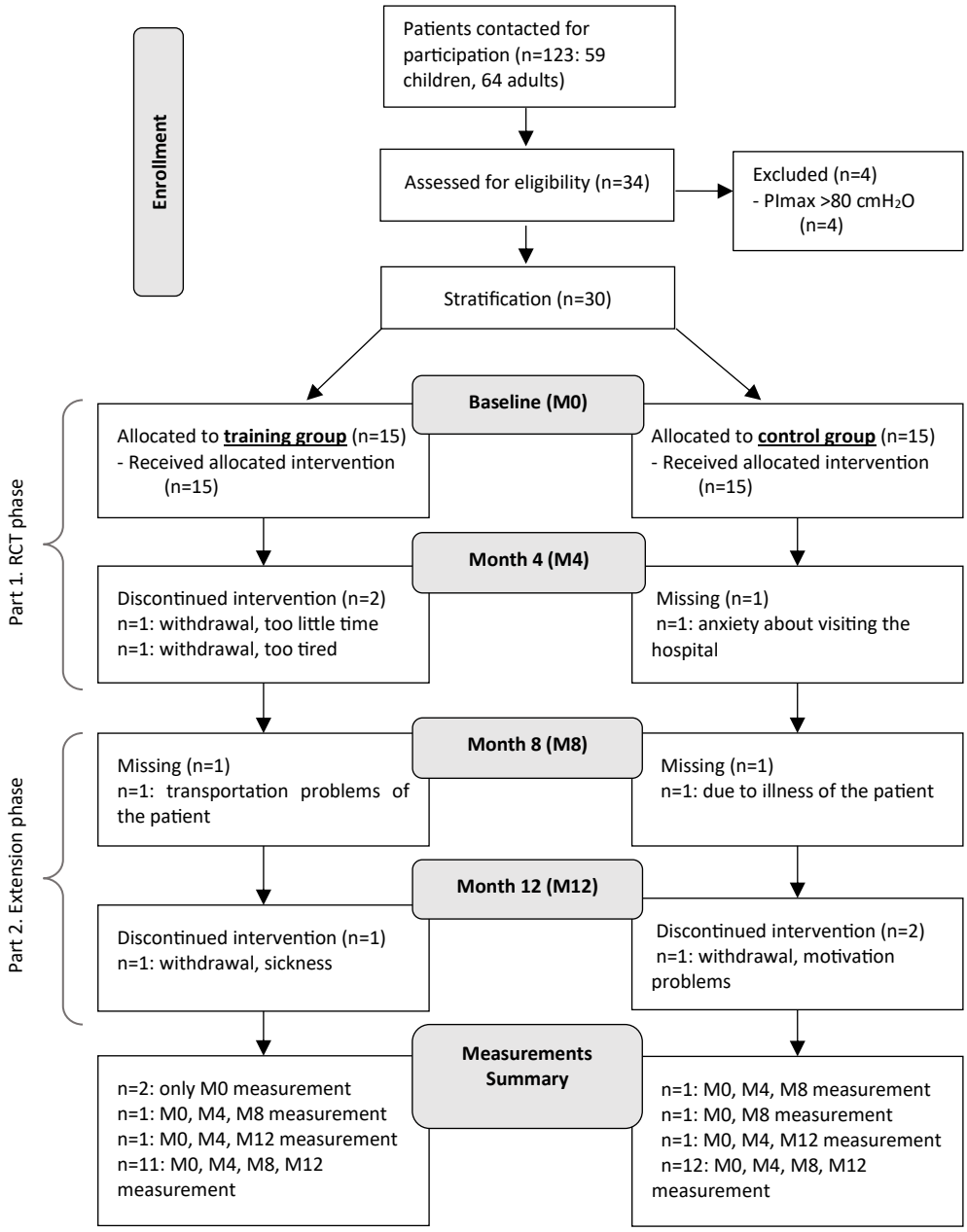


Figure 6.2: *Patient flow diagram*

Abbreviations: cmH₂O: centimeters of water column, M: month, n: number of participants, PImax: maximum inspiratory mouth pressure, RCT: randomized controlled trial.

PART 1: RCT phase (0-4 months)

At M4, data was missing and therefore imputed with the baseline value from three participants (training group: n=2, control group: n=1) (**Figure 6.2**).

Table 6.4: *Summary of Primary and Secondary Outcome Measures at M4*

	Adjusted means Training group M4 (n=15)	**Adjusted means Control group M4 (n=15)**	**Mean difference**	**95% CI**
Primary outcome measure				
PImax (cmH₂O)	61.1	54.3	+6.8	-2.0 to15.6
PImax (%pred)	74	70	+4	-9 to 16
Key secondary outcome measure				
PEmax (cmH₂O)	36.1	32.8	+3.3	-6.3 to 13.0
PEmax (%pred)	33	32	+1	-7 to 9
Secondary outcome measure				
SVC (%pred)	34	37[1]	-3	-5 to -0
FVC (%pred)	34	38	-4	-7 to -1
FEV1 (%pred)	35	40	-4	-8 to -1
PEF (%pred)	40	41	0	-3 to 3
SNIP (cmH₂O)	48.8	54.1[1]	-5.2	-15.7 to 5.2
P0.1 (%pred)	185	225[1]	-40	-106 to 26
P0.1/PImax	5.4	6.4[1]	-1.0	-2.5 to 0.5
Dyspnea with Borg	2.1[2]	1.6[2]	+0.6	-0.8 to 1.9
PedsQL-PhHSS	-	17.7[4]	-	-
PedsQL-PsHSS	-	62.2[4]	-	-
SF-36-PCS	28.7[1]	32.0[3]	-3.6	-7.3 to 0.2
SF-36-MCS	61.9[1]	61.6[3]	+0.2	-5.2 to 5.7

Note: if data were missing, n was expressed by: [1]n=14, [2]n=13, [3]n=12, [4]n=3.

Abbreviations: %pred: percentage of predicted, adjusted: corrected for baseline value, CI: confidence interval cmH₂O: centimeters of water column, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, M4: after 4 months of training, MCS: mental component summary, n: number of participants, P0.1: mouth occlusion pressure at 100ms during quiet breathing, PCF: peak cough flow, PCS: physical component summary, PedsQL: pediatric quality of life inventory, PEF: peak expiratory flow, PEmax: maximum expiratory mouth pressure, PhHSS: physical health summary score, PImax: maximum inspiratory mouth pressure, PsHSS: psychosocial health summary score, SF-36: 36-item short-form health survey, SNIP: sniff nasal inspiratory pressure, SVC: slow vital capacity.

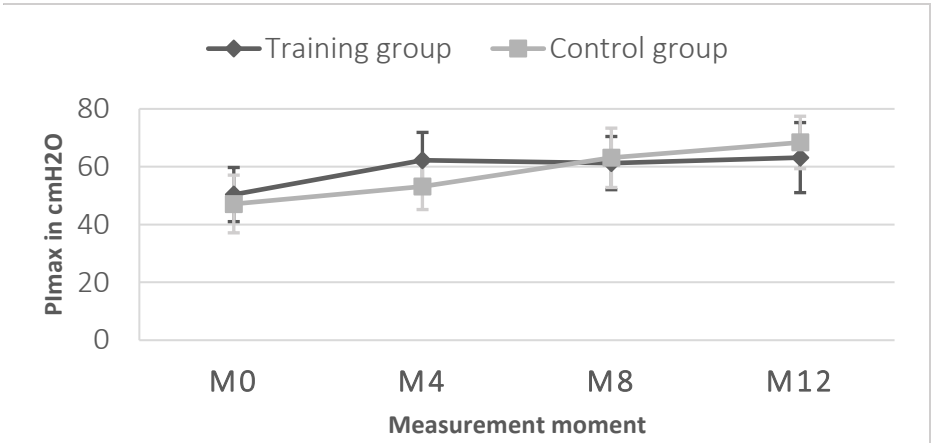
Efficacy M0-M4

Primary outcome measure: PImax

The mean PImax at M4 (corrected for baseline value) in the training group was 61.1 cmH_2O, and in the control group, it was 54.3 cmH_2O. Between the training and control group, the mean difference in PImax was 6.8 cmH_2O [95% CI: -2.0 to 15.6] (**Table 6.4**).

Within the training group, PImax increased by 11.8 cmH_2O. Within the control group, PImax increased by 6.1 cmH_2O (**Figure 6.3**).

Figure 6.3: *Means and 95% CI of PImax in cmH_2O*



	M0	M4	M8	M12
Mean PImax Training group	50.4 (n=15)	62.2 (n=15)	63.3 (n=12)	63.9 (n=12)
Mean PImax Control group	47.1 (n=15)	53.2 (n=15)	64.9 (n=14)	66.1 (n=13)
Adjusted mean difference [95%CI]	-	6.8 [-2.0 to 15.6]	-3.5 [-12.3 to 5.4]	-5.3 [-17.3 to 6.6]

	M0-M4	M4-M8	M8-M12
M (IQR) number of IMT sessions: Training group	115 (62-154)	20 (1-102)	5 (0-127)
M (IQR) number of IMT sessions: Control group	173 (115-194)	155 (71-185)	118 (13-163)
M (IQR) intensity of IMT (% of PImax): Training group	40 (31-50)	32 (0-42)	38 (0-44)
M (IQR) intensity of IMT (% of PImax): Control group	13 (9-18)	46 (33-61)	53 (41-77)
M (IQR) IMT volume: Training group	3549 (2465-6450)	345 (0-4360)	202 (0-5959)
M (IQR) IMT volume: Control group	1761 (1374-3019)	5215 (2924-8446)	1573 (661-10293)

Abbreviations: Adjusted: corrected for baseline value, CI: confidence interval, cmH_2O: centimeters of water pressure, IMT: inspiratory muscle training, M: month, M (IQR): median and interquartile range (lower quartile-upper quartile), n: number of participants, PImax: maximum inspiratory mouth pressure.

Key secondary outcome measure: PEmax

The mean PEmax at M4 (corrected for baseline value) in the training group was 36.1 cmH_2O, and in the control group, it was 32.8 cmH_2O. Between the training and control group, the mean difference in PEmax was 3.3 cmH_2O [95% CI: -6.3 to 13.0] (**Table 6.4**). Within the training group, PEmax increased by 5.9 cmH_2O. Within the control group, PEmax increased by 2.4 cmH_2O (**Appendix 6.D**).

Other secondary outcome measures

There were no clinically relevant differences (all <10%) in lung function measures, dyspnea, and quality of life between the training and the control group (**Table 6.4**).

Related adverse events (safety) and respiratory infections

Fourteen participants (training group n=7, control group n=7) reported dizziness, nausea, or headache during or after training. All complaints were resolved after advising the participant to breathe more slowly through the devices. Five participants (training group n=2, control group n=3) experienced muscle aches or tiredness after the training, which resolved spontaneously. Between M0-M4, two participants of the training group developed a respiratory tract infection, for which they needed antibiotics and hospitalization (**Appendix 6.Ea**).

Feasibility M0-M4

Adherence

The participants in the training group fulfilled 62% of the prescribed training sessions, and the participants in the control group fulfilled 91% of the prescribed training sessions.

Acceptability

At M4, the median score for acceptability was 8 (interquartile range: lower quartile-upper quartile) (IQR: 7-9) in the training group and 9.5 (IQR: 8-10) in the control group.

Training volume M0-M4

The training group had a median IMT volume of 3549 (IQR: 2465-6450). The control group had a median IMT volume of 1761 (IQR: 1374-3019) (**Figure 6.3**).

The training group had a median EMT volume of 5585 (IQR: 4655-11185). The control group had a median EMT volume of 4181 (IQR: 3260-6116) (**Appendix 6.D**).

PART 2: RCT + extension phase (0-12 months)

Efficacy M0-M12

Primary outcome measure: PImax

Within the training group, PImax increased in 1 year by 13.5 cmH_2O. Within the control group, PImax increased by 19.0 cmH_2O (**Figure 6.3**).

Key secondary outcome measure: PEmax

Within the training group, PEmax increased in 1 year by 6.0 cmH_2O. Within the control group, PEmax increased by 3.0 cmH_2O (**Appendix 6.D**).

Training volume M0-M12

Overall, there was a very strong association between total IMT volume (M0-M12) and percentage change from baseline in PImax (R^2=0.531). With every 1000 increase in IMT volume (for example, +50 training sessions at an intensity of 20% of PImax), PImax increased by 3% (**Figure 6.4**). There was a weak association between total EMT volume (M0-M12) and percentage change from baseline in PEmax (R^2=0.017) (**Appendix 6.F**).

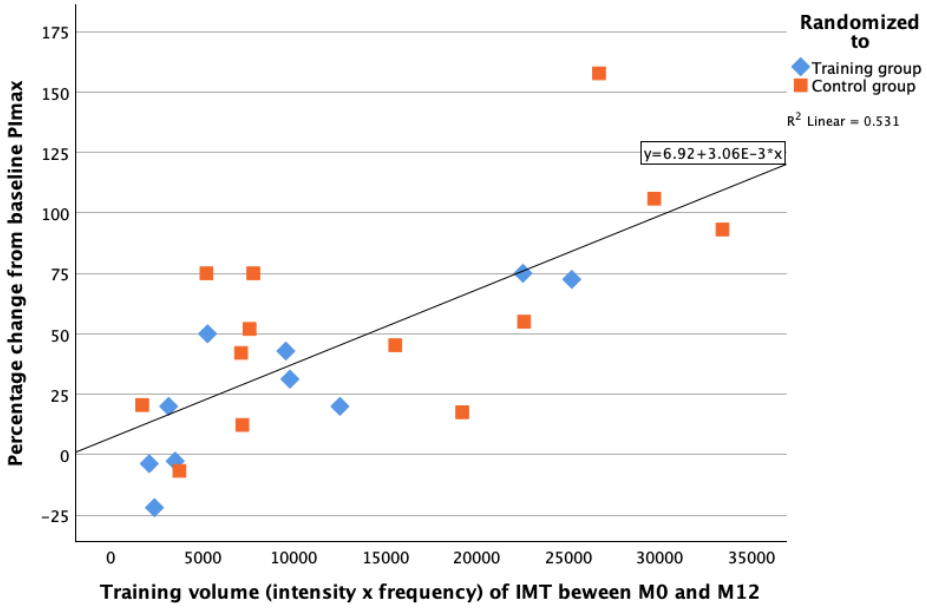


Figure 6.4: *Scatterplot IMT volume vs percentage change from baseline in PImax.*

Abbreviations: IMT: inspiratory muscle training, M: month, PImax: inspiratory mouth pressure, R^2: coefficient of determination.

Semi-structured interview M12

We interviewed 25 participants (training group n=12, control group n=13). The training group benefited from the training (0=not at all, 10=very much) with an average score of 7.3, while the control group scored 8.2 (mean difference: -0.90 [95% CI: -2.615 to 0.820]). Participants from both groups reported the following benefits: improved lung function measurements, easier and more powerful cough, deeper breathing, more energy during the day, more confidence in their own body, using longer sentences, and speaking louder. The following disadvantages were reported: fatigue, muscle pain, shortness of breath during or after the training, and the training being another thing the participants needed help with.

80% of all the participants reported that the video consultations contributed to their motivation to train. 67% of the participants in the training group and 54% in the control group felt that the training frequency of 10 times a week was too much. For 64% of all the participants, the ideal training frequency would be once a day for 5-7 days per week. 28% would like to train twice a day for 4-7 days per week. For 8%, the ideal frequency would vary depending on the week.

DISCUSSION

We investigated the efficacy and feasibility of an individualized, incremental, and home-based RMT in patients with SMA and respiratory muscle weakness. We did not reach the sample size that would have ensured adequate power, mainly because patients thought the training would be too time-consuming. We, therefore, could not perform inferential analysis. Both groups increased in the primary outcome measure (i.e., PImax) after 4 months of training, but the training group improved more. After 1 year of training, the control group improved the most in PImax. Overall, higher IMT volume (M0-M12) was very strongly associated with improvement of PImax. PEmax, lung function, quality of life, or perceived dyspnea remained stable over 1 year of training. RMT was safe (there were no related SAEs) and acceptable, but adherence to the training needs further improvement.

Aslan et al.[6] investigated, with a similar training protocol as ours, the efficacy of an 8-week IMT and EMT program in 24 ambulatory patients with slowly progressive NMDs, such as myotonic dystrophy. The training group started IMT and EMT at 30% of PImax and PEmax and adjusted the intensity weekly. The control group trained at the lowest possible intensity of the training devices: 9 cmH_2O for IMT and 5 cmH_2O for EMT. They also found an increase in PImax in both groups, but the increase was significantly higher in the training group. The training group also showed significant increases in PEmax and SNIP compared to the control group.[6] Human et al.[25] investigated the safety, feasibility, and efficacy of an IMT program in eight children with various neuromuscular diseases (NMDs), including three with SMA, in a pre-experimental observational study.

They concluded that IMT (at an intensity of 30% of PImax) appears safe, feasible, and acceptable. PImax %pred improved significantly after 6 weeks of IMT.[25] The training was performed twice a day, five days a week, at school, with daily supervision by a physiotherapist, unlike in our study. We saw a drop in adherence when the supervision stopped.

Poor adherence to exercise programs is a well-known phenomenon.[26] Low levels of adherence may even cause some randomized controlled trials aimed at assessing the benefits of exercise to not achieve significant results.[26] Moreover, although most people know that an active life is important for a healthy lifestyle, inactivity is still a major concern worldwide. Collado-Mateo et al. reviewed key factors influencing adherence to physical exercise in chronic patients and older adults. In summary, patient-tailored exercise programs, supervised by qualified exercise professionals, can significantly improve adherence, while technology can be beneficial if participants are willing to use it.[26]

In our study, lung volume measurements remained stable over 1 year. This may be an important finding since natural history studies have shown declining lung volumes of most patients with SMA type 2 (for example, FVC declined between 1-2% per year).[3] Since participants in this study mainly had SMA type 2 and their lung function test results did not decline, this may indicate a stabilizing effect of RMT.[6,23]

PEmax showed minor improvements during training. A training protocol of 30 repetitions at 30% of PEmax appears to be suboptimal for improving expiratory muscle strength. Because the expiratory muscles are more active in phasic activities, such as coughing, they might need to be loaded at a higher % of a patient's PEmax with fewer repetitions. An alternative explanation is that in patients with SMA, intercostal and abdominal muscles are more difficult to train because they are relatively weak compared with the diaphragm.[27,28]

Our study has limitations, primarily related to the challenges of adherence to the training protocol. Although the expected time investment initially raised concerns among patients and parents, the actual duration of the protocol was not perceived as the main issue. Instead, most patients required assistance from others to complete the training due to reduced hand function. Additionally, individuals with physical disabilities often spend significantly more time on daily activities, such as self-care, moving indoors and outdoors, eating, and drinking, compared to healthy individuals. Introducing an extra task, such as RMT, can lead to time or energy constraints. This issue was compounded by the high training frequency of 10 sessions per week, which reduced its feasibility. To improve adherence, practical support from others, physiotherapists, or the use of assistive devices (e.g., a tablet holder) could be beneficial.

The lowest possible resistance of the Threshold was 9 cmH_2O, which was, in most cases, more than 10% of the participants' PEmax. This means that the control group trained at a higher EMT resistance than planned (median intensity of EMT

between M0-M4 training group: 56%, control group: 30%, **Appendix 6.D**). Finally, participants felt that the test position differed from their training position, possibly leading to an underestimation of the results. Especially of PEmax, since most participants trained at higher resistances than the measured PEmax.

RMT in patients with SMA has been identified by patient representatives as an important topic for research. We think that RMT is a promising intervention in patients with SMA. We found a major increase in PImax in both groups after 1 year of training, and we found a very strong association between IMT volume (M0-M12) and improvement of PImax. The control group eventually increased more in PImax, possibly because the adherence in the control group was better than in the training group. Starting with a lower training resistance might be more feasible, leading to better adherence and more increase in inspiratory muscle strength. How adherence to RMT can be further improved should be discussed with patients and their representatives. This will allow us to identify patient-related issues and better tailor the training to the intended target group. As a result, patient inclusion will improve, which will hopefully enable us to demonstrate effectiveness in a larger study. Future research should also focus on finding the optimal dose-response relation between RMT and increase in respiratory strength. Furthermore, the minimal clinically important difference in PImax and PEmax in patients with SMA should be determined.

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APPENDIX 6.A: CONSORT Checklist 2010

Section/topic	Item No	Checklist item	Reported on page No
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	139
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	140-141
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	142
Background and objectives	#2b	Specific objectives or hypothesis	142
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	143 + [11]
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	#4a	Eligibility criteria for participants	142-143 + [11]
Participants	#4b	Settings and locations where the data were collected	142-143 + [11]
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	143-145 + [11]
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	146-147 + [11]
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	#7a	How sample size was determined.	147 + [11]
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	[11]
Randomization – Sequence generation	#8a	Method used to generate the random allocation sequence.	[11]
Randomization – Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	143-144 + [11]
Randomization – Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	[11]

Randomization – Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	143 + [11]
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	143 + [11]
Blinding	#11b	If relevant, description of the similarity of interventions	143-145 + [11]
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	147
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	147
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Figure 6.1+6.2
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 6.2
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	147 + Figure 6.2
Recruitment	#14b	Why the trial ended or was stopped	147
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	148
Numbers analyzed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	148 + Figure 6.2
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	150-154
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	150-154
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	150-154 +174
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	152, Appendices 6.Ea, 6.Eb, 6.Ec
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	154-156
Generalizability	#21	Generalizability (external validity, applicability) of the trial findings	154-156
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	154-156

Registration	#23	Registration number and name of trial registry	143
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	154-156
Registration	#23	Registration number and name of trial registry	143
Protocol	#24	Where the full trial protocol can be accessed, if available	[11]
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	-

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APPENDIX 6.B: Structure of the telephone/video calls

- How are you doing?
- How did you experience the training in the past two weeks?
- How difficult/heavy did you find the training the past two weeks?
- Do you feel like it's making a difference?
- Have you experienced any complaints during or after the training in the past two weeks?
- Are you managing to fill in the diary?

- Has anything changed in your medication over the past two weeks?
- Have you had a respiratory infection in the past two weeks?
- Have you had to take antibiotics in the past two weeks? If so, for what?
- Have you been hospitalized in the past two weeks? If so, for what?
- Has there been any change in your respiratory support in the past two weeks?

- Adherence: How often have you trained in the past two weeks? Can you show this in the diary? What was the reason if it didn't work out?

APPENDIX 6.C: Topic guide semi-structured interview RESISTANT study M12

Participants' research number:

Date:

1. I liked the inhalation training (with the POWERbreathe).

Not at all										Very much
0	1	2	3	4	5	6	7	8	9	10

1.1 What did you like:

1.2 What did you not like:

2. **I liked the exhalation training (with the threshold).**

Not at all										Very much
0	1	2	3	4	5	6	7	8	9	10

2.1 What did you like:

2.2 What did you not like:

3. **I benefited from the training.**

No benefit at all										Very beneficial
0	1	2	3	4	5	6	7	8	9	10

3.1 What positive effects do you notice/have you noticed from the training:

3.2 What negative effects do you notice/have you noticed from training:

4. **Which device did you find most comfortable to train with?**

- ☐ POWERbreathe (electric device for inhalation)
- ☐ Threshold (horn for exhalation)
- ☐ Both/no difference

4.1 Why do you feel that way?

5. **What did you think of the 2-weekly video consultations?**

Not enjoyable at all										Very enjoyable
0	1	2	3	4	5	6	7	8	9	10

5.1 Why do you feel that way*?*

5.2 Did these conversations/consultations contribute to your motivation to train?

- ☐ Yes
- ☐ No
- ☐ No opinion

5.3 Why yes/no/no opinion?

5.4 Did you miss these conversations during the months they didn't take place*?*

- ☐ Yes
- ☐ No

6. What did you think of the frequency of training 10 times per week?

Too little					Just right					Too much
0	1	2	3	4	5	6	7	8	9	10

6.1 Why do you feel that way*?*

6.2 Did you achieve this frequency (training 10 times per week)?

- ☐ Yes
- ☐ No

6.3 If not, why not:

6.4 What would be the ideal frequency for you?

……. times per day
……. times per week

7. Are you willing to continue training?

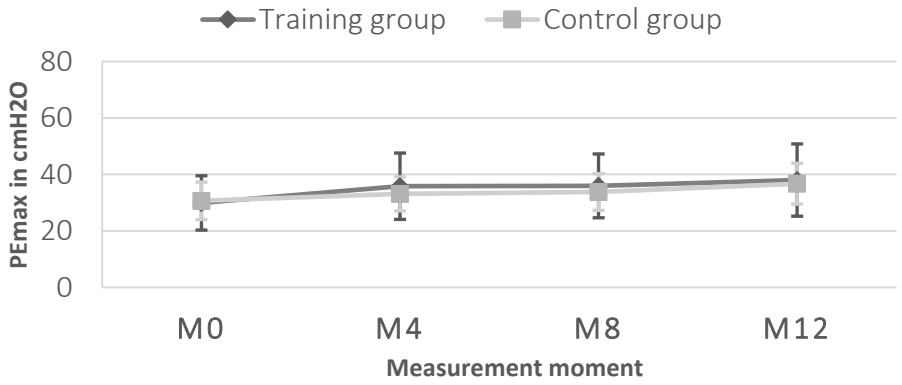
Not willing at all										Very willing
0	1	2	3	4	5	6	7	8	9	10

7.1 Why are you or are you not willing to continue?

8. What did you like about the study?

9. Do you have any tips for us?

APPENDIX 6.D: Means and 95% CI of PEmax in cmH_2O



	M0	M4	M8	M12
Mean PEmax Training group	29.9 (n=15)	35.8 (n=15)	33.6 (n=12)	35.9 (n=12)
Mean PEmax Control group	30.7 (n=15)	33.1 (n=15)	33.9 (n=14)	33.7 (n=13)
Adjusted mean difference [95%CI]	-	3.3 [-6.3 to 13.0]	2.7 [-7.0 to 12.4]	2.8 [-11.8 to 17.5]

	M0-M4	M4-M8	M8-M12
M (IQR) number of EMT sessions: Training group	115 (56-154)	21 (0-102)	13 (1-127)
M (IQR) number of EMT sessions: Control group	157 (108-184)	137 (72-174)	108 (13-163)
M (IQR) intensity of EMT (% of PEmax): Training group	56 (42-88)	58 (0-74)	81 (34-121)
M (IQR) intensity of EMT (% of PEmax): Control group	30 (21-44)	87 (60-99)	102 (86-130)
M (IQR) EMT volume: Training group	5585 (4655-11185)	1400 (0-8196)	914 (154-6959)
M (IQR) EMT volume: Control group	4181 (3260-6116)	9523 (5348-13972)	9981 (1145-15422)

Abbreviations: Adjusted: corrected for baseline value, CI: confidence interval, cmH_2O: centimeters of water pressure, EMT: expiratory muscle training, M: month, M (IQR): median and interquartile range (lower quartile-upper quartile), n: number of participants, PEmax: maximum expiratory mouth pressure.

APPENDIX 6.Ea: Adverse Events M0-M4

	Training group						Control group					
System Organ class	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**
Blood disorders	12	abnormal blood gas	mild	unrelated	none	unknown	34	protein loss, higher B2M in blood	mild	unrelated	none	unknown
Cardiac disorders	19	palpitations	mild	unrelated	none	recovered						
Ear disorders							29	Earache	mild	unrelated	temporarily paused	recovered
Endocrine disorders	33	high HCG in blood	mild	unrelated	none	unknown						
Gastrointestinal disorders	5	nausea, diarrhea, no appetite	intermediate	unrelated	none	recovered	6	nausea during training once	mild	possibly	paused that training	recovered
	8	stomach complaints (due to antibiotics)	mild	unrelated	none	recovered	15	sometimes nausea during/after training	mild	possibly	slower breathing	recovered
	12	stomach flu	intermediate	unrelated	temporarily paused	recovered	28	irritated and full bowels	mild	unrelated	none	unknown
							30	nausea when training after eating	mild	possibly	training before eating	recovered
General disorders	1	tiredness, poor sleep, unwell	mild	possibly	stop	unknown	4	poor sleep	mild	unrelated	none	unknown
	1	extreme tiredness, unwell, headache, feverish	intermediate	possibly	stop	unknown	4	tiredness because of poor sleep and stress	mild	unrelated	none	unknown
	10	tiredness due to new work	mild	unrelated	none	ongoing	13	unwanted weight loss	mild	unrelated	none	ongoing
	10	tiredness, poor sleep possible due to problems with the NIV	mild	unlikely	none	recovered	30	unwanted weight loss	mild	unrelated	none	ongoing
	11	overall tiredness	mild	unrelated	none	ongoing	30	poor sleep	intermedi ate	unrelated	none	unknown
	11	more tiredness at the end of a training	mild	possibly	temporarily lowered frequency	recovered	30	unwell, back pain, tiredness and nausea	intermedi ate	unrelated	temporarily paused	recovered
	12	positive test on Pfeiffer disease	intermediate	unrelated	none	unknown						
	12	tiredness, feverish, poor sleep	intermediate	unlikely	none	ongoing						

	18	frequent choking while eating	mild	unrelated	none	unknown						
	18	poor sleep	mild	unrelated	none	unknown						
	18	overall tiredness	intermediate	unlikely	none	unknown						
	19	tiredness	mild	unrelated	none	recovered						
	26	weight loss	mild	unrelated	none	unknown						
	33	unwell	mild	unrelated	none	recovered						
Infections and infestations	12	laryngitis	intermediate	unrelated	temporarily paused	recovered	23	Covid-19 infection	mild	unrelated	temporarily paused	recovered
	33	shingles and erysipelas	intermediate	unrelated	temporarily paused	recovered	29	Covid-19 infection	mild	unrelated	temporarily paused	recovered
							29	fever without further complaints	mild	unrelated	none	recovered
Injury, poisoning and procedural complications	12	swollen throat, fatigue, high blood pressure, laryngitis, headache. (Presumably due to allergic reaction to Risdiplam)	intermediate	unrelated	temporarily paused	recovered						
Metabolism and nutrition disorders	10	vitamin d deficiency	mild	unrelated	none	recovered						
Musculoskeletal and connective tissue disorders	1	pain sternum/ intercostals during training	mild	possibly	slower breathing	recovered	4	pain sternum/ intercostals during training	mild	possibly	slower breathing	recovered
	5	phantom pain	intermediate	unrelated	medication	ongoing	13	pain sternum/ intercostals during training	mild	possibly	slower breathing	recovered
	5	strained intercostals (due to phantom pain attack)	mild	unrelated	temporarily calmer trained	recovered	14	tiredness in jaw muscles (due to clamping device between teeth)	mild	possibly	none	recovered
	10	cold hands	mild	unrelated	none	recovered	14	cramps in tongue	mild	possibly	none	ongoing
	18	painful hip and back	intermediate	unrelated	none	unknown	30	pain in hip, neck, shoulders	mild	unrelated	none	ongoing
	18	lame feeling in arms	mild	unrelated	none	unknown	30	flexion contracture of the hips	mild	unrelated	none	ongoing
	32	hip pain	mild	unrelated	none	unknown						
Neoplasms benign, malignant and unspecified	12	nodule on thyroid discovered	intermediate	unrelated	none	unknown						

Nervous system disorders	1	dizziness during training	mild	possibly	slower breathing	recovered	3	dizziness during training	mild	possibly	slower breathing	recovered
	5	dizziness during training	mild	possibly	slower breathing	recovered	6	dizziness during training	mild	possibly	slower breathing	recovered
	10	headache	intermediate	unrelated	none	recovered	9	dizziness during training	mild	possibly	slower breathing	recovered
	12	dizziness and headache	mild	possibly	slower breathing	unknown	13	hyperventilation-like symptoms	intermediate	possibly	slower breathing	recovered
	18	headache after rapid breathing during training	mild	possibly	slower breathing	recovered	29	dizziness during training	mild	possibly	slower breathing	recovered
	18	numb feet, especially at night	mild	unrelated	none	unknown	30	dizziness during training	mild	possibly	slower breathing	recovered
	18	headache after rapid breathing during training	mild	possibly	slower breathing	recovered	34	dizziness during training	mild	possibly	slower breathing	recovered
	24	dizziness during training	mild	possibly	slower breathing	recovered						
Psychiatric disorders	5	emotional lability	intermediate	unrelated	temporarily paused	unknown	9	stress because of results device	mild	possibly	stopped filling in the diary	unknown
	19	mental problems	mild	unrelated	none	unknown						
	33	mental problems, overall tiredness	intermediate	unrelated	temporarily paused	unknown						
Renal and urinary disorders	12	bladder infection	mild	unrelated	none	recovered						
	16	bladder infection	mild	unrelated	none	recovered						
	18	extremely low ureum and creatine	intermediate	unrelated	none	unknown						
	18	fluid retention	intermediate	unrelated	none	unknown						
	24	bladder infection	mild	unrelated	none	recovered						
	33	high microalbumin in urine	mild	unrelated	none	unknown						
Respiratory, thoracic and mediastinal disorders	7	settings NIV changed (based on measurement before start)	mild	unrelated	none	recovered	9	symptoms of a cold	mild	unrelated	none	recovered
	8	symptoms of a cold	mild	unrelated	none	recovered	15	settings NIV changed (based on measurement before start)	mild	unrelated	none	recovered

	8	aspiration pneumonia (due to frequent vomiting) Hospitalization	serious	unrelated	temporarily paused	recovered	30	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	10	feelings of dyspnea during training	mild	possibly	slower breathing	Recovered	31	chest pain during cold and more mucus	mild	unlikely	none	recovered
	10	symptoms of a cold	intermediate	unrelated	none	recovered	31	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	10	symptoms of a cold	mild	unrelated	none	recovered	31	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	16	symptoms of a cold	intermediate	unrelated	none	Recovered						
	16	bilateral pneumonia, hospitalization	serious	unlikely	temporarily paused	recovered						
	26	symptoms of a cold	mild	unrelated	none	recovered						
	27	dyspnea after training	mild	possibly	slower breathing	Recovered						
Skin disorders	24	sweating during training	mild	possibly	none	recovered						
Surgical and medical procedures							6	wisdom tooth extraction	intermediate	unrelated	none	recovered

APPENDIX 6.Eb: Adverse Events M4-M8

	Training group					Control group					
System Organ class	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**
Cardiac disorders	7	high blood pressure	mild	unrelated	none	unknown	21	high blood pressure	mild	unrelated	none	unknown
	12	sinus rhythm with arrhythmia, QTc 500-550, abnormal repolarization and tremor	intermediate	unrelated	none	unknown						
Gastrointestinal disorders							28	complicated diverticulitis, hospitalization	serious	unrelated	temporarily paused	recovered
General disorders	18	swallowing complaints. Jaw opening is getting smaller.	intermediate	unrelated	none	unknown	13	tiredness during training	mild	possibly	none	recovered
							28	general tiredness	mild	possibly	none	unknown
							29	Tiredness	mild	possibly	none	unknown
Hepatobiliary disorders	7	higher amylase in blood	mild	unrelated	none	unknown						
Infections and infestations	12	laryngitis	intermediate	unrelated	temporarily paused	recovered	28	bowel infection, hospitalization	serious	unrelated	temporarily paused	recovered
	12	Covid-19 infection	intermediate	unrelated	temporarily paused	recovered	30	Covid-19 infection	mild	unrelated	none	recovered
	18	fever in the morning	mild	unrelated	none	unknown	34	Covid-19 infection	mild	unrelated	none	recovered
	32	Covid-19 infection	mild	unrelated	none	recovered						
	33	erysipelas infection, hospitalization	serious	unrelated	temporarily paused	recovered						
	33	pseudomonas bacteria suprapubic catheter insertion	mild	unrelated	none	recovered						
Injury, poisoning and procedural complications	24	toothache after filling a cavity	mild	unrelated	none	recovered	34	allergic reaction to antibiotics	intermediate	unrelated	none	unknown
Metabolism and nutrition disorders	5	hyperglycemia, diabetes type 2	mild	unrelated	none	ongoing	21	Hypokalemia	mild	unrelated	none	unknown
	10	mild hypokalemia	mild	unrelated	none	recovered	28	Hypokalemia	mild	unrelated	none	unknown

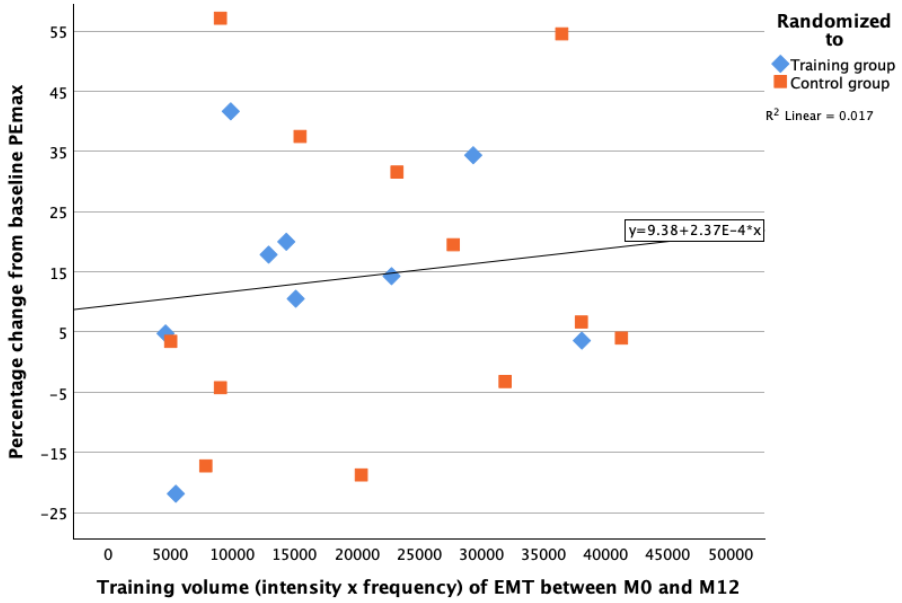
	11	iron and vitamin D deficiency	mild	unrelated	none	ongoing						
Musculoskeletal and connective tissue disorders	12	fractured tibia due to fall	serious	unrelated	temporarily paused	recovered	4	muscle spasm of neck muscles	mild	unrelated	none	recovered
	18	occasional jaw cramp	mild	unrelated	none	unknown	4	less strength in limbs (due to the cold)	mild	unrelated	none	recovered
	24	tiredness in the arms	mild	unrelated	none	unknown	22	muscle ache	mild	possibly	none	recovered
							22	strained ribs (due to heavy coughing)	mild	possibly	temporarily paused	recovered
							22	stiff hands	mild	unrelated	none	unknown
							30	severe bruise on calf and cheek (bumped into pole with wheelchair)	intermediate	unrelated	none	recovered
							31	chest pain/muscle ache during training	mild	possibly	slower breathing	recovered
							34	thrombotic right arm, loss of muscle strength in that arm	intermediate	unrelated	none	recovered
Nervous system disorders	5	ulnaropathie	mild	unrelated	none	unknown	13	dizziness during training	mild	possibly	temporarily trained with lower resistance	recovered
	12	concussion (due to fall)	intermediate	unrelated	temporarily paused	recovered	15	loss of strength in right hand, slow progression	intermediate	unrelated	none	unknown
	16	tingling in hand and brief periods of passing out	intermediate	unrelated	none	unknown						
	19	loss of strength in right arm and chewing muscles, slow progression	intermediate	unrelated	none	unknown						
Renal and urinary disorders	5	renal function disorder (due to diabetes type 2)	mild	unrelated	none	ongoing	13	difficulties urinating after bladder examination	intermediate	unrelated	none	recovered
	10	initial renal impairment	mild	unrelated	none	ongoing						
	10	increased protein in urine	mild	unrelated	none	ongoing						
	12	bladder infection	intermediate	unrelated	none	recovered						
	27	mild proteinuria	mild	unrelated	none	unknown						

Respiratory, thoracic and mediastinal disorders	5	symptoms of a cold	mild	unrelated	none	recovered	4	settings NIV changed	mild	possibly	none	recovered
	7	symptoms of a cold	mild	unrelated	temporarily paused	recovered	6	more mucus in the morning	mild	unlikely	none	recovered
	11	pneumonia	intermediate	unrelated	temporarily paused	recovered	21	hay fever	mild	unrelated	none	recovered
	16	pneumonia	intermediate	unlikely	temporarily paused	recovered	28	symptoms of a cold	mild	unrelated	none	recovered
	18	symptoms of heavy cold	intermediate	unrelated	temporarily paused	Recovered	29	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	24	irritated nasal passages	mild	unlikely	none	unknown	30	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	26	more mucus and coughing	mild	possibly	none	recovered	31	respiratory tract infection	intermediate	unlikely	temporarily paused	recovered
	27	respiratory tract infection	intermediate	unlikely	temporarily paused	recovered	31	symptoms of a cold	mild	unrelated	temporarily paused	recovered
	27	respiratory tract infection	intermediate	unlikely	temporarily paused	Recovered						
Skin and subcutaneous tissue disorders	24	sensitive skin, eczema in face and blemishes under the armpits	mild	unrelated	none	unknown						
	26	peeling of the skin (without sun exposure)	mild	unrelated	none	unknown						
Surgical and medical procedures	16	placement gastrostoma	serious	unrelated	temporarily paused	recovered						

APPENDIX 6.Ec: Adverse Events M8-M12

	Training group						Control group					
System Organ class	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**	**pt no**	**description**	**severity**	**related to intervention**	**intervention action?**	**outcome**
Blood and lymphatic system disorders	16	anemia	mild	unrelated	none	unknown	23	Low vWF (without a tendency to bleed)	mild	unrelated	none	ongoing
Infections and infestations	18	Covid-19 infection	intermediate	unrelated	temporarily paused	recovered	28	Covid-19 infection	mild	unrelated	temporarily paused	recovered
	18	inflammation in the foot	intermediate	unrelated	none	recovered						
Metabolism and nutrition disorders	16	hypokalemia	mild	unrelated	none	unknown						
Musculoskeletal and connective tissue disorders	10	decrease in hand function	intermediate	unrelated	none	ongoing						
Nervous system disorders	18	loss of strength in right hand, slow progression	intermediate	unrelated	none	unknown	3	loss of strength in arms and shoulders, slow progression	intermediate	unrelated	none	ongoing
							3	fast progression of SMA	serious	unrelated		death
Renal and urinary disorders							23	Slow rise in cyst c without changes in creat/urine	mild	unrelated	none	ongoing
Respiratory, thoracic and mediastinal disorders	10	decrease in lung function	intermediate	unrelated	none	ongoing	28	very severely impaired lung function	intermediate	unrelated	none	ongoing
	24	respiratory tract infection	intermediate	unlikely	temporarily paused	recovered	31	pneumonia, hospitalization	serious	unrelated	temporarily paused	recovered
							31	symptoms of a cold, fever	mild	unrelated	temporarily paused	recovered
							34	pneumonia, hospitalization	serious	unrelated	temporarily paused	recovered

APPENDIX 6.F: Scatterplot EMT volume vs percentage change from baseline in PEmax



Abbreviations: EMT: expiratory muscle training, M: month, PEmax: expiratory mouth pressure, R^2: coefficient of determination.



Chapter 7

General summary

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BACKGROUND

Spinal muscular atrophy (SMA) is a severe, autosomal recessive neuromuscular disease. It is the most common genetic cause of death in children without access to recently introduced disease-modifying therapies and has an incidence of around 1 per 10,000 live births.[1,2] In the Netherlands, the number of patients with SMA is probably around 500, and 15-20 children are born with SMA each year.[2] SMA is caused by a homozygous deletion or a heterozygous deletion in combination with a mutation of the second allele of the survival motor neuron (*SMN*) 1 gene. Patients with SMA typically have one or more copies of the second *SMN* (*SMN2)* gene, which is highly homologous to the *SMN1* gene but produces less functional SMN protein.[1,3] The clinical phenotype of SMA is heterogeneous, ranging from a severe form (type 0) to a milder adult-onset phenotype (type 4). Fewer copies of *SMN2* (i.e., 2 or 3) are associated with the most severe phenotypes of SMA; however, even with 4 copies, early onset of weakness is common.[3] The recent introduction of disease-modifying therapies (DMTs), including Nusinersen (Spinraza), Onasemnogene abeparvovec (Zolgensma), and Risdiplam (Evrysdi), is likely to attenuate its natural history, which is characterized by deterioration of motor function. Combining DMTs with newborn screening is expected to have the most significant impact by enabling (semi-)normal gross motor development in many children who would otherwise be unable to learn to crawl, stand, or walk.

SMA is characterized by progressive axial, respiratory, and proximal limb muscle weakness. Respiratory failure is the most important cause of morbidity and mortality in patients with SMA.[4] This is primarily due to muscle weakness, most pronounced in the intercostal muscles, while the diaphragm remains relatively spared.[5] The respiratory muscle weakness results in impaired cough and poor clearance of lower airway secretions.[5] In addition to respiratory muscle weakness, respiratory dysfunction in SMA may be caused by a lack of endurance of respiratory muscles, also known as increased respiratory muscle fatigability (RMF).

AIM THESIS

The main aim of this thesis was to gain more knowledge of and insight into the function of respiratory muscles in patients with SMA. This information is necessary to design the best possible supportive treatment for patients with SMA.

Chapter 1 presents a general introduction to SMA, the respiratory problems in patients with SMA, the available diagnostics of the respiratory problems, and the available treatment options.

Part I of this thesis focuses on RMF in patients with SMA types 2 and 3. We explored RMF with a respiratory endurance test (**Chapter 2**) and investigated the muscle activity of the diaphragm, scalene muscles, and intercostal muscles during the test with surface electromyography (**Chapter 3**).

- *Respiratory muscle fatigability in patients with SMA. Pediatr Pulmonol 2022;1-10. Doi:10.1002/ppul.26133*
- *Respiratory muscle activity and fatigue response during respiratory endurance testing in patients with spinal muscular atrophy. Clinical Neurophysiology, submitted.*

Part II of this thesis focuses on the effect of disease-modifying therapies on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, and 4 (**Chapter 4**).

- *The effect of disease-modifying therapies on lung function and respiratory muscle strength in spinal muscular atrophy: systematic review and meta-analysis. Respiratory care 2025 Mar;70(3):337-348. Doi: https://doi.org/10.4187/respcare.12378*

Part III of this thesis focuses on the effect of respiratory muscle training on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, and 4 and respiratory muscle weakness. I described the protocol in **Chapter 5** and the results in **Chapter 6.**

- *The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): study protocol for a randomized controlled trial. BMC Neurology 2023 Mar;23(1):118. Doi: 10.1186/s12883-023-03136-3*
- *The RESISTANT study (respiratory muscle training in patients with spinal muscular atrophy): results of a randomized controlled trial. Physiotherapy, In Press 2025. Doi: 10.1016/j.physio.2025.101842*

Here, I will summarize the main findings of all studies (**Chapter 7**). In **Chapter 8**, I will provide an in-depth general discussion of the outcomes, implications for clinical practice, and recommendations for future research.

SUMMARY Part I: Respiratory muscle fatigability in patients with SMA.

In **Chapter 2**, we explored the feasibility of inspiratory muscle loading, the dose-response relationship between inspiratory load and RMF, and the fatigability response to RMF in participants with SMA types 2-3. Respiratory fatigability response was determined by a change in PImax (ΔPImax) and perceived fatigue (Δperceived fatigue). Participants performed a respiratory endurance test (RET) against an inspiratory threshold load at either 20%, 35%, 45%, 55%, or 70% of their individual maximal

inspiratory mouth pressure (PImax). RMF was defined as the inability to complete 60 consecutive breaths.

The probability of RMF during the RET increased by 59%−69% over 60 breaths with every 10% increase in inspiratory threshold load (%PImax). The probability of experiencing RMF in our study was the highest at an inspiratory threshold load of 55% of participants' individual PImax, which is similar to the probability in healthy individuals[6] and 20% higher than in patients with Duchenne muscular dystrophy (DMD).[7] Fatigability response was characterized by a large variability in ΔPImax (−21% to +16%) and a small increase in perceived fatigue (p=0.041, range 0 to +3).

Participants with SMA types 2 and 3 demonstrated a "normal" dose-dependent increase in RMF without the expected physiological fatigue responses (transient respiratory muscle weakness and increased perceived fatigue). This study showed that respiratory muscle endurance seems adequate in patients with SMA, but the low baseline levels of PImax suggested a therapeutic window for respiratory muscle strength training. To provide insight into the underlying mechanism of RMF during a RET, and to better understand variable responses in ΔPImax, we suggested the use of surface electromyography (sEMG) in future studies.

In line with our suggestion, we explored in **Chapter 3** the muscle activity and fatigue response of the diaphragm, intercostal muscles, and scalene muscles during the RET (as described in **Chapter 2**) in participants with SMA types 2 and 3 using sEMG. We recorded sEMG of the diaphragm, intercostal, and scalene muscles and evaluated muscle activity at onset (in root mean square (RMS) amplitude) and during the test (change in RMS amplitude and median frequency over time).

The activity level at onset of the individual respiratory muscles did not correlate with the level of inspiratory resistance. Overall, the diaphragm showed a significantly lower variance in activity compared to the intercostal and scalene muscles (p=0.002). Participants with RMF showed fatigue of the diaphragm, indicated by a significant decrease in RMS amplitude (p=0.012) and median frequency (p<0.001), compared to those without RMF.

The relative activity of the diaphragm at onset of a respiratory endurance test remained stable at higher intensity levels, while the activity of the intercostal and scalene muscles became more variable. The diaphragm showed the most significant signs of fatigue in participants with RMF, while accessory inspiratory muscles like the scalene muscles showed no clear fatigue signs. This suggests that the load of breathing against resistance is shared amongst different respiratory muscles according to their biomechanical and morphological specificities.

SUMMARY Part II: The effect of disease-modifying therapies on lung function and respiratory muscle strength in patients with SMA.

In **Chapter 4,** we performed a systematic review to identify, evaluate, and summarize the findings of studies concerning the effect of disease-modifying therapies (DMTs) (Nusinersen, Onasemnogene abeparvovec, and Risdiplam) on lung function and respiratory muscle strength in patients with SMA types 1, 2, 3, or 4.

We included 19 studies out of 376 identified records (16 longitudinal cohort studies and three case series) with 384 participants. Seventeen studies investigated the effect of Nusinersen and two of Risdiplam. Seventeen studies had a moderate and two had a high risk of bias. Most of these studies did not report statistically significant improvement in lung function or respiratory muscle strength after treatment with Nusinersen or Risdiplam. Furthermore, a meta-analysis of 13 included studies showed no statistically significant improvement in forced vital capacity after two, six, 10, and >12 months of treatment with Nusinersen.

Although there was no improvement in lung function, there was also no statistically significant decline in lung function or respiratory muscle strength. This may suggest that Nusinersen may have halted the expected decline in lung function and respiratory muscle strength, as seen in natural history studies. The effect of Risdiplam on lung function and respiratory muscle strength has so far been studied only in patients with SMA type 2 and in very small groups. We could not identify studies reporting the effect of Onasemnogene abeparvovec. Studies on the effects of DMTs suggest that they are effective in improving survival, motor function, and functional muscle strength, but this is less obvious in respiratory function or respiratory muscle strength. This means that a potentially large group of patients with SMA may live longer and achieve more motor milestones, but will still require specialized respiratory care. It also implies that we need additional strategies to prevent respiratory complications.

SUMMARY Part III: The effect of respiratory muscle training on lung function and respiratory muscle strength in patients with SMA.

In **Chapter 5,** we described the study protocol of the 4-month, single-blinded, randomized controlled trial, followed by an 8-month extension phase, called the RESISTANT-study (Respiratory Muscle Training in Patients with Spinal Muscular Atrophy). This study aimed to investigate the efficacy and feasibility of respiratory muscle training (RMT) in patients with SMA and respiratory muscle weakness. The RMT program consisted of a home-based, individualized training program involving 30 breathing cycles through an inspiratory and expiratory muscle training device. Participants were instructed to perform 10 training sessions over 5-7 days per week. Participants were randomized in either the training or the control group. The training group started RMT

at 30% of their maximum inspiratory (PImax) and expiratory mouth pressure (PEmax) and adjusted their training intensity based on perceived exertion. The control group started and continued RMT at 10% of PImax and PEmax. A physiotherapist supervised the participants via video/telephone calls once every two weeks. After four months, the control group received the same RMT as the training group (delayed intervention), while the training group continued the training unsupervised.

In **Chapter 6,** we described the results of this study. Thirty participants were included in the study, 15 in the training group and 15 in the control group. After four months of training, the mean PImax (corrected for baseline value) in the training group was 61.1 cmH_2O and 54.3 cmH_2O in the control group (mean difference: 6.8 cmH_2O, 95% CI: -2.0 to 15.6). Within the training group, PImax increased by 11.8 cmH_2O. Within the control group, PImax increased by 6.1 cmH_2O.

The mean PEmax at M4 (corrected for baseline value) in the training group was 36.1 cmH_2O and 32.8 cmH_2O in the control group (mean difference: 3.3 cmH_2O, 95% CI: -6.3 to 13.0). Within the training group, PEmax increased by 5.9 cmH_2O. Within the control group, PEmax increased by 2.4 cmH_2O.

In 1 year, PImax increased 13.5 cmH_2O in the training group and 19.0 cmH_2O in the control group. Overall, there was a very strong association between the total volume of the inspiratory muscle training (frequency × intensity) and the percentage change from baseline in PImax (R^2: 0.531). With every 1000 increase in volume (for example, +50 training sessions at an intensity of 20% of PImax), PImax increased by 3%.

PEmax, lung function, quality of life, or perceived dyspnea remained stable over 1 year of training. RMT was safe (there were no related serious adverse events) and acceptable, but adherence to the training needs further improvement. The control group eventually increased more in PImax, possibly because the adherence in the control group was better than in the training group. Starting with a lower training resistance might be more feasible, leading to better adherence and more increase in inspiratory muscle strength.

Summary of the main findings of this thesis:

- Individuals with SMA types 2 and 3 exhibit normal fatigability of the inspiratory muscles without an exercise-induced increase in perceived fatigue and muscle weakness.
- Diaphragmatic muscle activity at the start of a respiratory endurance test remained stable at higher resistance levels, whereas intercostal and scalene muscle activity became more variable.
- The diaphragm shows the most signs of fatigue in individuals with SMA and fatigability.

- The disease-modifying therapies Spinraza and Evrysdi do not appear to improve lung function and respiratory muscle strength in individuals with SMA types 1, 2, 3, and 4.
- Spinraza may have a stabilizing effect on lung function and respiratory muscle strength in individuals with SMA types 1, 2, 3, and 4.
- Respiratory muscle training is safe to perform in individuals with SMA.
- Starting training at low training resistance (10% of maximal inspiratory pressure) and subsequently increasing the resistance based on perceived fatigue appears to be the most effective approach to improving inspiratory muscle strength in individuals with SMA.
- Supervision of individuals with SMA during respiratory muscle training improves therapy adherence.

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Chapter 8

General discussion

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The central aim of this thesis was to advance our understanding of the (patho)physiology of the respiratory muscles in individuals with spinal muscular atrophy (SMA). This knowledge and experience are necessary to provide the best possible (respiratory) treatment to patients with SMA. A key observation from this thesis is that the respiratory muscles in patients with SMA behave differently from skeletal limb muscles. Both respiratory muscles (which control breathing) and skeletal muscles (which enable movement) share fundamental structural components. However, respiratory muscles have specialized roles in ventilation and respond to autonomic and voluntary control. Respiratory muscles, like other skeletal muscles, can experience fatigue when subjected to prolonged or excessive workload. However, they are normally highly resistant to fatigue due to their continuous function in breathing. The differences between respiratory muscles and limb muscles in patients with SMA are particularly evident in fatigability and response to treatment and training.

1. Fatigability

In patients with SMA, respiratory muscles show "normal" fatigability (**Chapter 2**) and significantly less fatigability compared to the limb muscles. The respiratory muscles may have a distinct endurance profile compared to the limb muscles in patients with SMA.

2. Treatment Response

The effect of disease-modifying therapies (DMTs) is more evident in improving limb function and motor strength than in lung function and respiratory muscle strength[1] (**Chapter 4**). This discrepancy suggests that the respiratory muscles may respond differently to DMTs than the limb muscles.

3. Training Response

Patients with SMA show improvement in inspiratory muscle strength with training intensities as low as 10% of their maximum inspiratory mouth pressure (PImax), an intensity level generally considered insufficient for therapeutic purposes in limb muscles (**Chapter 6**). This finding suggests that respiratory muscles, particularly the diaphragm, retain better endurance and are more responsive to low-resistance training compared to limb muscles.

1. FATIGABILITY

Strength vs Endurance

Respiratory dysfunction in patients with neuromuscular disorders can be caused by muscle weakness (reduced strength) or muscle fatigability (reduced endurance). Fatigability leads to a progressive decline in performance, while weakness is a constant and immediate inability to produce normal force.[2–4] One can exist without the other.[5] In patients with SMA, respiratory dysfunction is likely the result of a combination of both, varying by muscle group.[6] Understanding this imbalance provides insight into the unique challenges patients with SMA face and can help develop targeted interventions to optimize respiratory function in patients with SMA.

Fatigability and weakness of the inspiratory muscles

During resting inhalation, the primary inspiratory muscles are active; the diaphragm contracts and moves caudally toward the abdomen, while the external intercostal muscles elevate the anterior chest wall. The accessory inspiratory muscles (such as the sternocleidomastoid and scalene muscles) activate only in situations requiring increased respiratory effort, such as during exercise or respiratory distress. The primary inspiratory muscles remain continuously active and must resist fatigue to maintain effective ventilation.

The inspiratory muscles of patients with SMA demonstrate "normal" fatigability (**Chapter 2**) and significantly less fatigability compared to those with Duchenne muscular dystrophy (DMD). In contrast to DMD, diaphragm strength is relatively preserved in patients with SMA. Interestingly, **Chapter 3** highlights that during endurance testing, the diaphragm showed the most significant signs of fatigue, whereas accessory inspiratory muscles like the scalene muscles exhibited no clear signs of fatigue. Furthermore, the relative activity of the diaphragm at the onset of an endurance test remained stable at higher intensity levels, while the activity of the accessory muscles became more variable. This suggests that the load of breathing against resistance is distributed among different inspiratory muscles according to their biomechanical and morphological specificities.

The large variation in the activity of the accessory muscles may be explained by the mechanical disadvantages that patients with a more severe phenotype face due to typical alterations in thoracoabdominal volumes and asynchronies.[12,13]

Interestingly, patients who exhibited fatigability during endurance tests had lower baseline PImax values compared to those who did not (**Chapter 2**). PImax is a maximal inspiratory pressure test that primarily reflects the strength of the accessory muscles rather than the diaphragm. This suggests that the accessory muscles were weak and, therefore, unable to adequately support the diaphragm during the RET, leading to task failure. The absence of visible signs of fatigue in these muscles during the RET could be because we measured relative rather than absolute muscle activity. If the accessory

muscles are weak, even a high percentage of their maximal capacity may still represent a low absolute output.

Altogether, this raises the question of whether inspiratory muscle fatigability is more closely linked to underlying inspiratory muscle weakness than previously thought. The findings from **Chapters 2 and 3** at least underscore that breathing—particularly in patients with SMA—is a complex interplay of various muscles, each with distinct functions and limitations.

Inspiratory muscle adaptations

In contrast to the inspiratory muscles in patients with SMA, the arm and leg muscles do show increased fatigability, even more so than in patients with DMD.[3,14,15] While inspiratory muscles share the basic structure and function of other skeletal muscles, they serve the vital, life-sustaining function of breathing.[8] Healthy individuals have specific characteristics in their inspiratory muscles that differ from those in limb muscles, owing to the continuous nature of breathing.[8,9] Given the fact that the diaphragm in patients with SMA is relatively spared, the following key distinctions might also explain the fatigability differences between the inspiratory muscles and the limb muscles in patients with SMA:

1) The diaphragm contains ~55% slow fibers (type 1), ~21% fast oxidative fibers (type 2A), and ~24% fast glycolytic fibers (type 2X). This fiber composition ensures both endurance (from slow fibers) and force production when needed during heavy respiratory loads (from fast fibers). In contrast, limb muscles show variable distributions of fiber types, depending on their specific functional roles. For example, postural muscles contain more slow fibers, whereas locomotor muscles contain more fast fibers for quick and powerful movements.[9]
2) Diaphragm fibers generally have a smaller cross-sectional area compared to limb muscles. The diaphragm fibers are also surrounded by a denser capillary network. This smaller fiber size, combined with an efficient oxygen supply, enhances the diaphragm's ability to resist fatigue compared to limb muscles.[8,9]
3) The respiratory muscles can adapt to increased respiratory loads, hypoxia, and certain diseases by modifying fiber-type proportions and enzyme activities. For example, in patients with chronic obstructive pulmonary disease, the diaphragm shows an increased proportion of slow fibers and enhanced oxidative capacity, likely as an adaptation to chronic higher respiratory demands.[9]
4) While training typically leads to fiber-type transitions in limb muscles (for example, from type 2X to type 2A with endurance training), respiratory muscles like the diaphragm show limited fiber-type changes in response to training. This suggests that the respiratory muscles' adaptation to training is less pronounced than in limb muscles.[9]

5) Disuse of limb muscles leads to significant atrophy and a shift towards faster fiber types, which is less pronounced in respiratory muscles due to their continuous activity.[9]
6) The diaphragm uniquely expresses two isoforms of calcium release channels, enhancing its responsiveness to calcium release and caffeine stimulation. Limb muscles lack these specific molecular adaptations, reflecting their primary role in movement rather than continuous activity.[9]

Future directions

Future research should aim to validate the observed "normal" fatigability of the respiratory muscles in a larger cohort of patients with SMA and further investigate the variability in fatigability responses. In-depth analysis of muscle activation patterns, including timing and relative contribution, using advanced sEMG techniques and additional muscles (for example, the sternocleidomastoid and trapezius) may provide insights into respiratory muscle fatigability mechanisms and serve as biomarkers for treatment response. Finally, optimizing test protocols, such as standardized inspiratory loading intensities and a short period of submaximal inspiratory loading before determining the maximal voluntary contraction, will improve the interpretability and reliability of future studies. Studies should explore the feasibility and effectiveness of respiratory muscle training as a complementary therapy, particularly given the relatively spared diaphragm and potential limitations in recruiting accessory muscles.

2. TREATMENT RESPONSE

Disease-modifying therapies (DMTs)

Until 2016, SMA was an untreatable disease and a leading inherited cause of infant mortality.[16] Today, three DMTs (Nusinersen, Onasemnogene abeparvovec, and Risdiplam) can at least partially compensate for deficient survival motor neuron protein, significantly improving life expectancy, limb function, motor strength, and quality of life.[1,17]

Our systematic review (**Chapter 4**) analyzed 19 studies on the effects of Nusinersen and Risdiplam on lung function and respiratory muscle strength in patients with SMA, with most research focusing on Nusinersen since this was the first drug that was approved by the FDA and EMA. While these treatments appear to slow the expected decline, no significant improvements in lung function were observed. Consequently, many patients still require respiratory support, which limits their social and educational participation.[18] Early treatment, especially in pre-symptomatic patients, may reduce respiratory complications, but long-term effects remain uncertain. Some patients, particularly those with two *SMN2* copies, treated from birth, show improved motor function but still rely on ventilation and airway clearance techniques.[19] The varying

impact of DMTs on different muscle groups remains to be fully documented, as does the potential superior efficacy of one treatment over another.

The included studies in the review were highly heterogeneous, using different outcome measures, follow-up periods, SMA types, and disease duration, making summarization difficult. Few studies prioritized respiratory outcomes, highlighting the need for standardized assessments in patient follow-ups.

Assessment of respiratory function and strength

Systematic and regular monitoring of respiratory muscle function and strength in patients with SMA is essential to prevent and treat acute and chronic respiratory failure.[20] Monitoring is crucial to determine the start of an intervention, assess the effect of the intervention, evaluate disease progression, counsel patients, and evaluate the effectiveness of new treatments in patients with SMA. However, proving the benefits of treatment, particularly in patients with SMA, is challenging. Capturing meaningful stabilization or improvement often requires long-term observation, given the significant individual variability in disease progression. This variability complicates translating clinically meaningful changes observed in individual patients into trends applicable to a larger cohort. Furthermore, currently available assessment tools are limited in detecting improvements in severely or mildly affected patients with SMA.

Noninvasive vs invasive assessments

Assessments evaluating respiratory muscles are broadly categorized as "volitional" or "nonvolitional" and as "noninvasive" or "invasive." In clinical practice, volitional and noninvasive assessments, such as forced vital capacity (FVC) and PImax, are most commonly used due to their simplicity, availability, and ease of use.[20,21] However, the limitations of these assessments are their reliance on patient cooperation and the inability to detect small changes.[18–20,22–24]

In contrast, invasive assessments, such as trans diaphragmatic pressure measurements, directly assess respiratory muscle function and are more sensitive in detecting early changes. However, these require the placement of esophageal and gastric balloons or pressure transducers, as well as specialized equipment and trained personnel.[20,24,25] Given the increasing evidence that early intervention improves outcomes,[18,26,27] there is a pressing need for respiratory assessments to detect and quantify early respiratory muscle involvement, particularly in young children.[25]

Objective assessments used in this thesis

In this thesis, we used several assessments to evaluate lung function, respiratory muscle strength, and respiratory muscle endurance in patients with SMA.

The respiratory endurance test (RET) executed at a percentage of the participant's PImax was feasible in measuring respiratory muscle fatigability (RMF) in

patients with SMA. We expected physiological fatigue responses, such as transient respiratory muscle weakness and increased perceived fatigue. However, we observed substantial interindividual variability, which may be explained by differences in learning effects (since intramuscular coordination generally, but not always, improves after repeated performance of a new motor task) or by variations in age and SMA subtype (since mechanical disadvantages are associated with older patients and patients with more severe phenotypes).

Surface electromyography (sEMG) was a feasible, safe, and non-invasive method to explore respiratory muscle activity and fatigue during a RET.[28] However, its accuracy is challenged by variability in electrode placement, anatomical differences, and signal contamination from adjacent muscles and cardiac activity.[28–34] Consequently, we were unable to compare the activity of different respiratory muscles or determine their relative contributions to overcoming the resistance of the RET (**Chapter 3**).

The standardized assessments for lung function and respiratory muscle strength, included in **Chapter 4** and **Chapter 6**, to assess the effects of DMTs and respiratory muscle training (RMT), have the advantage that they directly measure respiratory muscle function. However, these assessments require active patient participation, limiting their applicability to younger children, individuals with severe respiratory muscle weakness, and those with limited cooperation. Therefore, no conclusions can be drawn about the effect of DMTs or RMT on respiratory muscle function in children below approximately six years or very weak patients.

Suggestions for objective assessments

Ideally, reliable and objective respiratory assessments should exhibit minimal or no variation upon repetition, should not be influenced by fatigue, and should be independent of patient effort. Respiratory assessments must be applicable across all age groups, have established normative values, require minimal instructions, be easy to use, and be capable of detecting small changes in respiratory muscle function and strength. This latter applies to severely affected patients and those in the early stages of disease progression. Additionally, these assessments should be clinically relevant and contribute to decision-making in patient care. **Table 8.1** summarizes possible respiratory muscle function and strength assessments in young children, individuals with limited cooperation, or those with severe respiratory muscle weakness. The table is not comprehensive but provides several suggestions that should be further investigated for their use in assessing lung function and respiratory muscle strength in patients with SMA.

***Table 8.1**: Summary of possible respiratory muscle function and strength assessments in young children, individuals with limited cooperation, or those with severe respiratory muscle weakness.*

Assessments	Volitional (V) / non-volitional (NV)	Specific muscle tested?	Advantages (+) / disadvantages (-)
NON-INVASIVE			
Sniff nasal inspiratory pressure[21,23,24,35,36]	V	Inspiratory	+ Natural maneuver, easy to perform, for children aged >2 years. - Requires cooperation, not reliable in case of nose obstruction.
Crying mouth pressure[21]	V	Inspiratory and expiratory	+ Easy to perform in newborns. - High variability; glottic closure should be prevented.
Mouth whistle pressure[21,37]	V	Expiratory	+ Easy to perform, natural maneuver, for children aged >2 years, playful, audible feedback. - Requires cooperation, no reference values in children.
Forced oscillation technique[6,38,39]	V	No	+ Minimal cooperation is required, during quiet breathing, detects early changes, gives comprehensive information on central and peripheral airway function. - Accuracy influenced by artifacts from the extra thoracic upper airway, interpretation complex, lack of standardized reference values and guidelines.
Breathing pattern[21]	NV	No	+ Can be performed at any age. - Requires quiet breathing, does not test a specific muscle.
Diaphragm ultrasound[24,36,40]	NV	Diaphragm	+ Radiation-free, common equipment necessary, reference values available. - Operator-dependent method, difficult to measure in obese patients.
Optoelectronic plethysmography[36,41,42]	NV	Inspiratory and expiratory	+ Accurate and validated method of measuring lung volumes and chest wall movements during quiet breathing, can be performed in newborns, gives specific information on inspiratory ribcage muscles status. - Large number of markers necessary, placement of markers time-consuming and complicated.
Lung Clearance Index[43]	NV	No	+ Detects early and subtle changes, during quiet breathing, feasible for all ages, sensitive for small airway dysfunction. - Very young children might require sedation, total test takes 15-30 minutes, specialized equipment and expertise necessary, lack of standardized reference values and guidelines.
Great Ormond Street Respiratory score[44]	NV	No	+ Objective tool, aids clinicians in making informed decisions about respiratory interventions and management strategies, able to distinguish between SMA type 1 subtypes. - New tool, need for validation of its reliability and generalizability, specifically developed for SMA type 1.

Surface electromyography[22,24,36]	*NV*	*Inspiratory and expiratory*	*+ Easy to use, useful for continuous monitoring, extremely sensitive for detecting muscle contractions.* *- Cross-talk, limited standardization for analysis of the signal.*
INVASIVE			
Electromyography with intramuscular electrode[22,24,36]	NV	Inspiratory and expiratory	+ Minimally invasive, mildly painful, less cross-talk than sEMG, single motor unit recordings possible. - Discomfort, difficult to place, small pneumothorax risk.
Breathing pattern with Poes and Pgas[21]	NV	Diaphragm	+ Can be performed at any age. - Mildly uncomfortable, requires quiet breathing.
Pgas during a maximal cough[21,24,37]	V	Expiratory	+ Natural maneuver, easy to perform, can be performed in children aged >2 years. - Mildly uncomfortable, requires cooperation, no reference values in young children.
Poes and Pgas during a maximal whistle[37]	V	Expiratory	+ Natural maneuver, easy to perform, can be performed in children aged >2 years, playful, audible feedback. - Mildly uncomfortable, requires cooperation, no reference values in young children.
Pdi[24]	V	Diaphragm	+ Specific for the diaphragm, reference values available. - Materials are not readily available in most public hospitals, require experienced examiners.
Crying Pdi[21]	V	Diaphragm	+ Can be performed in newborns. - Mildly uncomfortable, high variability.

Abbreviations: Pdi: trans diaphragmatic pressure, Pgas: gastric pressure, Poes: esophageal pressure, NV: non-volitional, V: volitional.

Subjective assessments used in this thesis

In addition to objective physiological assessments, we evaluated subjective experiences of fatigue and quality of life. In **Chapter 2**, we assessed perceived fatigue using the OMNI scale. The OMNI scale is a valid way to assess perceived fatigue across different populations and exercise modalities. However, it has only been validated in children and adults for motor activities, which may limit its accuracy in assessing respiratory fatigue.[45,46]

In **Chapter 6**, we assessed health-related quality of life (HRQoL) using the 36-item Short-Form Health Survey and the Pediatric Quality of Life Inventory. These questionnaires are standardized, widely used, and validated to assess HRQoL across various populations. Despite one year of RMT, no measurable improvements in HRQoL were detected. However, semi-structured interviews provided important insights that were not captured by standardized questionnaires. Participants reported subjective benefits, including deeper breathing, more effective coughing, improved voice projection, increased confidence in bodily function, and higher energy levels. For example, not needing to be lifted out of a chair to cough effectively was an important improvement for one participant, which was not captured by standard questionnaires or objective assessments. These findings suggest that traditional HRQoL tools may not be sensitive enough to detect subtle functional improvements, while patient-reported experiences highlight meaningful benefits of respiratory training.

Suggestions for subjective assessments

Understanding the different impacts of disease on a patient's life is essential to providing optimal care.[47] Patient-reported outcome measures (PROMs) can objectively quantify patient experiences.[47] PROMs are standardized, validated survey tools used to assess health outcomes directly reported by patients. PROMs can be administered during an illness or treatment and capture patient changes that may otherwise be missed.[47,48] Although it is becoming increasingly clear that the regular measurement instruments used to assess treatment effects in patients with SMA do not always capture the patient-reported positive effects, PROMs are not yet routinely implemented for patients with SMA.[47] A scoping review highlighted that, despite the potential benefits of PROMs in monitoring and assessing adults with SMA, additional validation studies are necessary before they can be used for clinical decision-making.[47]

Another method for evaluating interventions is Goal Attainment Scaling (GAS), where individualized goals are set and tailored to a person's specific needs and circumstances. Progress is assessed on a 5-point scale, ranging from much worse than expected (-2) to much better than expected (+2), with "0" representing the expected outcome. GAS provides a flexible and person-centered approach to follow meaningful improvements, even in small but impactful steps.[49]

Qualitative studies are another approach to gain more insight into patient-reported outcomes. Conducting a qualitative study in patients with SMA can offer several significant benefits. It can provide an in-depth understanding of patients' experiences, identify meaningful changes, and help develop relevant assessment tools.[50,51]

Future research directions

Regular assessment of lung function and respiratory muscle strength in patients with SMA is crucial for preventing and managing respiratory failure. Additionally, detecting even small changes in lung function and respiratory muscle strength is essential for evaluating treatment effectiveness. Forced oscillation techniques and the lung clearance index are promising tools for detecting early and subtle changes in lung function. However, specialized equipment and expertise are necessary, and there is a lack of standardized reference values and guidelines. The sniff nasal inspiratory pressure and the mouth whistle pressure seem the easiest inspiratory and expiratory muscle strength assessments. However, they still require some cooperation. Therefore, future research should focus on developing a comprehensive assessment kit to assess lung function and respiratory muscle strength in all patients with SMA. Patient-reported outcome measures will also need to be added to monitor outcomes that are important to the patient.

3. THERAPY RESPONSE

Inspiratory muscle training – optimal training intensity

In the RESISTANT study (**Chapter 6**), we randomized patients into a control and a training group. The participants in the control group started their training with a training intensity of 10% of PImax. After 4 months, they increased the training intensity based on their level of perceived exertion. The average training intensity in the control group was 14% in the first four months, 46% in the second four months, and 57% in the last four months. The participants in the training group started their training with a training intensity of 30% of PImax and could immediately increase their intensity based on their level of perceived exertion. The average training intensity in the training group was 41% in the first four months, 28% in the second four months, and 26% in the last four months. The results of this study revealed that participants initially assigned to the control group ultimately showed greater improvements in PImax than those who started in the training group. This unexpected outcome could be explained by higher adherence in the control group, suggesting that starting with low-intensity training and gradually increasing intensity may lead to better adherence and greater long-term strength gains. Or it could be explained by the higher average training intensities in the second and last four months, suggesting that training intensities below 30% are less effective in improving PImax.[52]

In **Chapter 6**, a very strong association was observed between inspiratory muscle training (IMT) volume and PImax improvement. IMT volume reflects both the intensity of the training and the number of training sessions. Increasing either the intensity of the training or the number of training sessions can result in better PImax outcomes. However, we found that smaller training volumes also led to measurable gains in PImax. This suggests that daily training may not always be necessary; less frequent sessions could still yield clinically meaningful improvements while being easier to sustain long-term. During the first four months, the control group also showed modest improvements in PImax. This suggests that even minimal activity can be better than none.

Expiratory muscle training and/or cough training

Expiratory muscles, such as the abdominal and intercostal muscles, are primarily involved in active expiration tasks like coughing.[9] These muscles require high absolute strength rather than endurance. Expiratory muscle weakness is evident in SMA: maximum expiratory mouth pressure (PEmax) is significantly lower than PImax (**Chapter 6**), impairing cough effectiveness.[6,35]

We only found a small increase in PEmax after training the expiratory muscles (**Chapter 6**). Unlike the strong association between IMT volume and PImax improvement, no association was found between expiratory muscle training (EMT) volume and PEmax improvement. This may suggest that the training volume for expiratory muscles was insufficient to produce noticeable improvements in PEmax.

Both muscle groups were trained using the same protocol, yet they serve different physiological purposes. Inspiratory muscles primarily function to sustain prolonged activity, requiring endurance, whereas expiratory muscles are tasked with generating absolute force, such as during coughing.[9] The training protocol, which was more endurance-focused, might have been better suited to the needs of inspiratory muscles. For expiratory muscles, a training regime with higher resistance and fewer repetitions might be more effective for improving absolute strength.[53,54]

In patients with SMA, difficulty clearing mucus often leads to sputum retention in the airways and increases the risk of respiratory infections.[6,35] Effective coughing relies not only on the strength of expiratory muscles but also on the ability to maximize lung volume during inspiration and closing the glottis to increase intrathoracic pressure.[6] Cough strength did not improve after RMT (**Chapter 6**), possibly indicating that the training lacked specificity for improving cough function. A more targeted approach, such as resistance-based cough training challenging both inspiratory and expiratory muscles, could be beneficial. Enhanced cough ability could significantly reduce respiratory complications in patients with SMA, potentially having a greater impact on their quality of life than improvements in inspiratory or expiratory muscle strength only. This

highlights the importance of tailoring training protocols to match the specific functional demands of different respiratory muscles in patients with SMA.

Adherence to training

The adherence to the training protocol used in the RESISTANT study was lower than we aimed for (**Chapters 5** and **6**). There were two notable findings: adherence was better in the control group than in the training group, and adherence was better with supervision than without supervision. Additionally, participants experienced difficulties in getting assistance during training, leading to lower adherence than participants wanted. Problems with the POWERbreathe device also caused frustration among participants, resulting in reduced adherence.

Poor adherence to exercise programs is a well-known phenomenon.[55] Low levels of adherence may even cause some randomized controlled trials aimed to assess the benefits of exercise not to achieve significant results.[55] Moreover, although most people know that an active life is important for a healthy lifestyle, inactivity is still a major concern worldwide. Collado-Mateo et al. reviewed key factors influencing adherence to physical exercise in chronic patients and older adults.[55] In summary, patient-tailored fun exercise programs supervised by qualified exercise professionals can significantly improve adherence, while technology can be beneficial if participants are willing to use it.[55]

Since the control group in the RESISTANT study (**Chapter 6**) had better adherence to the training than the training group, starting with low-intensity training may have contributed to better adherence. Starting with low-intensity training allows patients to adapt physically and neurologically. It also builds familiarity and confidence with the training. Gradually increasing intensity makes it easier to embed the training into daily routines, enhancing adherence. Conversely, high-intensity training from the beginning may feel overwhelming, leading to reduced motivation and lower adherence.

Respiratory muscle training: future steps

When looking at the results of the RESISTANT study (**Chapter 6**), RMT appears to be effective, at least in improving PImax. A complicating factor in performing respiratory training (studies) in the Netherlands is that many eligible patients also wanted to participate in conditional reimbursement programs for DMTs. These studies typically mandate that patients only receive standard care as described in current guidelines, which do not yet include RMT. We feel that the design of future conditional reimbursement programs for neuromuscular and other rare diseases should somehow provide room for studies or new interventions that aim to improve supportive care, including RMT.

Future studies on the effect of RMT in patients with SMA should determine the minimum effective training volume required to achieve meaningful benefits. In addition,

studies need to assess whether higher training intensities provide additional advantages in daily life. Understanding the differences in adaptation between respiratory and limb muscles in patients with SMA could further refine training protocols. Additionally, research should focus on optimizing expiratory muscle and cough function training.

Key recommendations for future training protocols

RMT in patients with SMA has been identified by patient representatives as an important topic for research. We think that RMT is a promising intervention in patients with SMA. However, the protocol needs some adjustments. How adherence to RMT can be further improved should be discussed with patients and their representatives. This will allow us to identify patient-related issues and better tailor the training to the intended target group. For now, we suggest the following adjustments based on insights from the studies in this thesis and findings in other studies.[53,55]

1) Replace flow-dependent devices: In the RESISTANT study, the flow-dependent resistance of the POWERbreathe often malfunctioned due to participants' low vital capacity, causing frustration and reduced adherence. Alternative devices with consistent resistance or new app-connected tools could address this issue.
2) Incorporate visual feedback: Participants of the RESISTANT study expressed a desire for feedback on their performance. Devices offering visual metrics or progress tracking could improve adherence.[55]
3) Inform patients about the benefits of training, the risks of doing nothing, and common sensations during and after training (like muscle soreness).[55]
4) Gradual introduction to IMT: Since the control group of the RESISTANT study eventually increased more in PImax, beginning with 1 to 2 months of stable, low-resistance training before increasing resistance based on perceived exertion seems the best way to train the inspiratory muscles of patients with SMA. Final resistance should target 30-45% of PImax to ensure effective diaphragm training without overrecruiting accessory muscles.[56,57]
5) Give the participant simple diaphragmatic breathing instructions to increase the activity of the diaphragm during IMT.[58]
6) Modify EMT protocol: Since PEmax showed only minor improvements after the EMT used in the RESISTANT study, focusing on fewer repetitions at higher resistance might better align with the strength-oriented function of expiratory muscles.
7) Provide supervised support: Regular (video) consultations enhanced adherence in the RESISTANT study. The consultations allow participants to access the professional's knowledge, feedback, and support, which may increase self-efficacy and reduce discouraging feelings.[55]
8) Incorporate patient-reported outcomes: Goal-setting tools or patient-reported outcome measures could capture individual benefits beyond strength improvements.[47]

EFFECT OF SINGLE VS. COMBINED TREATMENTS

Disease-modifying therapy and respiratory muscle training

Our review (**Chapter 5**) suggests that Nusinersen may have a stabilizing effect on patients with SMA. In addition, our randomized controlled trial (**Chapter 6**) indicates that RMT may stabilize lung function and expiratory muscle strength. The RESISTANT study included 30 patients: six were treated with Nusinersen, 17 with Risdiplam, and seven received no DMT. While we acknowledge that the stabilization of lung function and muscle strength could be attributed to Nusinersen or Risdiplam, we were unable to conduct subgroup analyses due to small group sizes. Further research is needed to distinguish the effects of DMTs from RMT, allowing both to be used effectively, potentially enhancing each other's benefits.

Pyridostigmine and respiratory training

We previously investigated the efficacy of pyridostigmine, an acetylcholinesterase inhibitor, in diminishing fatigability experienced by patients with SMA. By inhibiting the breakdown of acetylcholine, pyridostigmine enhances neuromuscular transmission, improving muscle function.[59] A phase 2 study showed that pyridostigmine significantly improved endurance, as measured with validated endurance tests used as a secondary outcome measure, in patients with SMA types 2-4 by up to 70%.[60] The diaphragm, the primary inspiratory muscle, is naturally well-suited for sustained activity. However, it is susceptible to fatigue, as discussed in **Chapter 3**. A RET conducted with and without pyridostigmine can help us determine if pyridostigmine enhances respiratory muscle endurance.

Combining DMTs or RMT with other treatment options

Respiratory muscle weakness limits the ability to achieve total lung capacity in patients with SMA.[35,61] Disuse of the musculoskeletal system can lead to muscle atrophy, osteoporosis, and contractures, all contributing to a stiffened chest wall in adults with neuromuscular diseases.[35] In children with SMA, axial muscle weakness often leads to kyphoscoliosis, which further restricts chest wall movement and creates a mechanical disadvantage.[35]

One reason for the lack of improvement in lung function and respiratory muscle strength in patients treated with DMTs or training may be that treatment was initiated too late. In many of the studies included in our review (**Chapter 4**), treatment with DMTs was started relatively late in the disease course. Similarly, most participants in the RESISTANT study (**Chapter 6**) were adults with long disease durations. Over time, the combination of fibrotic, shortened, and stiffened muscles, along with reduced chest wall movement, leads to joint contractures.[62–64] As a result, starting treatment or training may have occurred when the respiratory system was already beyond repair.

Physiotherapy and respiratory therapy aimed at promoting the use of total lung capacity, performing breathing exercises, and preventing contractures could enhance the effects of DMTs and RMT.[65] These interventions are likely to be most beneficial when introduced early, before significant damage occurs. In the past decade, the approach to managing the pulmonary aspects of SMA has shifted from a reactive model, where treatment is initiated only when airway clearance or ventilation becomes necessary, to a more proactive model, where these therapies are introduced earlier in the disease process.[65] DMTs or RMT may have a greater impact when applied to muscles and lungs that have not yet suffered significant damage. Determining the optimal time to start therapy remains a challenge. However, starting treatment as early as possible is likely to yield the best results.[66] That said, we also know that young children can develop resistance to therapy over time, making it difficult for them to accept therapy when they truly need it.

CONCLUSION

This thesis compiles studies on fatigability of the respiratory muscles in patients with SMA, the effect of DMTs on lung function and respiratory muscle strength, and the effect of inspiratory and expiratory muscle training on inspiratory and expiratory muscle strength in patients with SMA. The results of this thesis will hopefully increase the knowledge of the respiratory muscles in patients with SMA among all healthcare professionals working with these patients, as well as among the patients themselves. It has become clear that the respiratory muscles of patients with SMA respond differently to fatigability, treatment with DMTs, and training compared to the limb muscles. Although the diaphragm remains relatively spared in patients with SMA, we still observe signs of fatigue in this muscle. From the RESISTANT study, we now know that inspiratory muscle strength can be effectively trained, and patients report subjective improvements in their breathing and cough strength. Importantly, respiratory muscle training can be performed safely in this patient group. Although we have taken a step forward in understanding the respiratory muscles of patients with SMA, many questions remain unanswered. Overall, more homogeneous cohorts with longer follow-ups are needed to distinguish the specific effects of DMTs versus RMT versus pyridostigmine and clarify their individual and combined contributions to respiratory function and muscle strength improvement. Clinical relevance should be evaluated using comprehensive objective assessment kits and subjective assessments such as PROMs, GAS, and respiratory-specific quality-of-life measures. The respiratory muscle training also needs improvement. It should be more tailored to the individual patient and specific muscles, and strategies to enhance adherence should be considered.

For now, healthcare professionals working with patients with SMA should be alert to the limited effects of DMTs on the respiratory muscles and the possibility of training these muscles!

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Appendices

Nederlandse samenvatting
Abbreviations
List of co-authors
List of publications
Mijn promotie verhaal
Dankwoord
About the author

NEDERLANDSE SAMENVATTING

Spinale musculaire atrofie

Spinale Musculaire Atrofie (SMA) is een ernstige, erfelijke spierziekte. Het is de meest voorkomende genetische oorzaak van overlijden bij kinderen die niet behandeld worden. SMA komt voor bij 1-2 op de 100.000 mensen. In Nederland zijn er naar schatting op dit moment tussen de 450 en 700 mensen met SMA. Ieder jaar worden er 15-20 kinderen geboren met SMA. SMA wordt veroorzaakt door een fout in het survival motor neuron (*SMN*) 1-gen, dat het SMN-eiwit produceert. Dit eiwit speelt een belangrijke rol bij de ontwikkeling en rijping van motorische (bewegings) zenuwcellen. Mensen met SMA hebben één of meer kopieën van het reserve-gen *SMN2*. Het *SMN2*-gen lijkt op het *SMN1*-gen, maar het produceert een kwalitatief minder SMN-eiwit. Hierdoor ontstaat er een tekort aan SMN-eiwit, wat leidt tot het afsterven van motorische zenuwcellen in het ruggenmerg. Het gevolg is steeds erger wordende spierzwakte, vooral in de spieren van de romp, armen en benen en de ademspieren. SMA wordt gekenmerkt door een grote variatie in ziekte-ernst. Hoe minder kopieën van het *SMN2*-gen iemand heeft, hoe ernstiger de ziekte meestal is.

SMA wordt ingedeeld in vijf typen (typen 0-4) op basis van de leeftijd van eerste symptomen en de hoogste verworven motorische mijlpaal:

- **Type 0**: De symptomen beginnen voor de geboorte, en baby's hebben onmiddellijk adem ondersteuning nodig. Ze overleven vaak niet lang zonder behandeling.
- **Type 1**: De symptomen beginnen in de eerste 6 levensmaanden van een kind. Kinderen kunnen nooit zelfstandig zitten en overleven meestal niet hun eerste levensjaar zonder behandeling.
- **Type 2**: De symptomen beginnen tussen de leeftijd van 6 tot 18 maanden. Kinderen kunnen zitten, maar niet lopen. De meesten overleven tot de volwassenheid, ondanks orthopedische- en ademhalingsproblemen.
- **Type 3a en 3b**: De symptomen beginnen tussen de 18 maanden en 3 jaar bij type 3a en tussen de 3 en 18 jaar bij type 3b. Kinderen kunnen zelfstandig lopen, maar verliezen deze mogelijkheid vaak in de adolescentie of volwassenheid. Mensen met dit type hebben vaak een normale levensduur.
- **Type 4**: De symptomen beginnen op volwassen leeftijd en de motorische problemen zijn milder. Mensen met dit type hebben vaak een normale levensduur.

De indeling in types is niet altijd representatief voor wat een persoon op een bepaald moment kan. Daarom worden mensen met SMA ook ingedeeld op basis van hun functionele vaardigheden: ‘niet-zitters’, ‘zitters’ of ‘lopers’.

Sinds 2016 zijn er drie medicijnen tegen SMA in Europa op de markt gekomen. Alle drie zijn ze gericht op het verhogen van de hoeveelheid SMN-eiwit. In 2022 is SMA

toegevoegd aan de hielprikscreening. Hierdoor kunnen kinderen soms al behandeld worden voor de eerste symptomen. Mensen met SMA bereiken hierdoor meer motorische mijlpalen dan voor de komst van deze medicijnen. De traditionele classificatie van SMA sluit daarom niet meer aan bij de nieuwe generatie mensen die vroeg worden behandeld.

Symptomen van SMA

Bij mensen met SMA is steeds erger wordende zwakte van de ademspieren een belangrijke oorzaak van ziekte en sterfte. Deze zwakte is overwegend aanwezig in de uitademspieren en de tussenribspieren, terwijl het middenrif relatief gespaard blijft. Zwakte van de ademspieren kan leiden tot een verminderde hoestkracht en daardoor moeite met het ophoesten van slijm uit de longen. Dit resulteert in steeds terugkerende luchtweginfecties en kan uiteindelijk leiden tot ademfalen en een vroegtijdige dood. Naast spierzwakte is ook vermoeibaarheid van de spieren een groot probleem bij mensen met SMA. Vermoeibaarheid betekent dat iemand niet langdurig een handeling op eenzelfde intensiteit kan volhouden, terwijl men fysiek wel in staat is om deze handeling uit te voeren. Mensen met SMA ervaren bijvoorbeeld vermoeibaarheid tijdens het lopen, schrijven, kauwen of haren kammen.

Meten van vermoeibaarheid van de inademspieren

De vermoeibaarheid van de inademspieren kan worden gemeten met een adem-uithoudingstest. De test wordt uitgevoerd met een bepaalde weerstand. Deze weerstand is een percentage van de maximale kracht van de inademspieren. Als iemand niet 60 keer achter elkaar tegen deze weerstand kan inademen, is er sprake van testfalen en dus van vermoeibaarheid van de inademspieren. In **hoofdstuk 2** beschrijven we de resultaten van het onderzoek naar de vermoeibaarheid van de inademspieren. 19 kinderen en 36 volwassenen met SMA types 2 en 3 hebben hiervoor een adem-uithoudingstest uitgevoerd. De deelnemers moesten door een apparaatje inademen dat was ingesteld op een weerstand van 20%, 35%, 45%, 55% of 70% van hun maximale inademkracht.

De resultaten lieten zien dat de kans op vermoeibaarheid van de ademspieren het grootst was bij de test waarbij men moest inademen tegen een weerstand van 55%. Bij gezonde mensen was dit bij een test waarbij men moest inademen tegen een weerstand van 60%, min of meer vergelijkbaar dus. Bij mensen met een andere spierziekte, de ziekte van Duchenne, was dit bij een test met een weerstand van 35%. Mensen met SMA laten dus een normale vermoeibaarheid zien.

Als iemand vermoeibaar is, zien we ook vaak een toename van de ervaren vermoeidheid (hoe moe iemand zich voelt). Ook zien we dat de maximale kracht van de spieren die we testen na de test vaak lager is dan voor de test. Dat noemen ze door inspanning veroorzaakte toename van ervaren vermoeidheid en spierzwakte. Bij de

mensen met SMA die de adem-uithoudingstest niet konden volhouden en dus vermoeibaarheid van de inademspieren lieten zien, vonden we echter geen toename in ervaren vermoeidheid of spierzwakte. De spierkracht nam bij sommige mensen met 21% af, terwijl deze bij anderen juist met 16% toenam. De conclusie van dit onderzoek was dat mensen met SMA types 2 en 3 een normale vermoeibaarheid van de inademspieren lieten zien, maar zonder een door inspanning veroorzaakte toename van ervaren vermoeidheid en spierzwakte.

Elektrische activiteit van de inademspieren

Tijdens de adem-uithoudingstest van **hoofdstuk 2** hebben we de spieractiviteit van verschillende ademspieren onderzocht met oppervlakte-elektromyografie (sEMG). sEMG meet de elektrische activiteit van spieren met elektroden die op de huid worden geplakt. Het laat zien hoe sterk en hoe vaak een spier actief is, bijvoorbeeld tijdens beweging of vermoeidheid. Door het plaatsen van elektroden op de scalenusspieren (hulpademspieren in de nek), de tussenribspieren en het middenrif (belangrijkste inademspier), hebben we de activiteit van iedere spier kunnen meten tijdens de test. Het doel van dit onderzoek was het verkennen van de activiteit en de reactie op vermoeibaarheid van de inademspieren tijdens het uitvoeren van een adem-uithoudingstest. We bekeken hoe actief de spieren waren aan het begin van de test en hoe dit veranderde tijdens de test. In **hoofdstuk 3** beschrijven we de resultaten van dit onderzoek.

De spieractiviteit van de ademspieren aan het begin van de test had geen duidelijke relatie met hoe zwaar de weerstand was. We hadden verwacht dat hoe zwaarder de test zou zijn, hoe meer spieractiviteit de spieren zouden laten zien. Ook zagen we dat het middenrif bij verschillende weerstanden een stabiele spieractiviteit had, terwijl de tussenrib- en scalenusspieren veel meer variatie in spieractiviteit lieten zien.

Tijdens de test kregen mensen met vermoeibaarheid (uitval op de test) een vermoeid middenrif, wat te zien was aan een afname van spieractiviteit en spierfrequentie. Mensen zonder vermoeibaarheid lieten deze afname niet zien. We zagen deze afname ook niet in de tussenrib- en scalenusspieren.

We konden hieruit opmaken dat bij hogere weerstanden de activiteit van het middenrif stabiel bleef, terwijl de tussenrib- en scalenusspieren meer schommelingen lieten zien. Dit zou kunnen beteken dat de inademspieren samenwerken om een test tegen een hogere weerstand vol te kunnen houden. Het middenrif was de spier die het meest vermoeid raakte, terwijl de andere ademspieren minder duidelijke tekenen van vermoeidheid lieten zien. Deze studie helpt om beter te begrijpen hoe de ademspieren werken bij mensen met SMA en hoe snel deze spieren moe worden.

Effect van medicatie op de ademspieren

Zoals hierboven beschreven zijn tussen 2016 en 2021 drie medicijnen tegen SMA in Europa op de markt gekomen: Spinraza® (Nusinersen), Zolgensma® (Onasemnogene abeparvovec) en Evrysdi® (Risdiplam). Alle drie zijn ze gericht op het verhogen van de hoeveelheid SMN-eiwit. Uit onderzoek naar deze medicijnen is gebleken dat ze de overleving, motorische functie en functionele spierkracht verbeteren bij mensen met SMA. Veelgebruikte uitkomstmaten om de effectiviteit van deze medicijnen op de ademspieren te beoordelen, zijn de behoefte aan ademondersteuning en het optreden van ademfalen. Hoewel dit belangrijke uitkomstmaten zijn voor ziekte en sterfte bij mensen met SMA, zijn ze ook afhankelijk van andere factoren. Voorbeelden van deze factoren zijn: luchtweginfecties, timing van het starten of stoppen van hoestondersteuning of beademing en operaties voor bijvoorbeeld een scoliose (scheve rug). We wilden graag weten wat het effect van deze medicijnen was op de longfunctie en ademspierkracht van mensen met SMA. Daarom hebben we in **hoofdstuk 4** een systematisch literatuuronderzoek uitgevoerd. We vatten hierin de resultaten samen van studies naar het effect van Spinraza, Zolgensma en Evrysdi op longfunctie en ademspierkracht bij mensen met SMA type 1, 2, 3 en 4. We vonden 19 studies met in het totaal 384 deelnemers. 17 studies onderzochten het effect van Spinraza en twee studies onderzochten het effect van Evrysdi. We vonden geen studies die het effect van Zolgensma onderzochten. De meeste studies lieten geen significante verbetering (dus de resultaten zouden toeval kunnen zijn) in longfunctie of ademspierkracht zien na 2 tot >12 maanden behandeling met Spinraza of Evrysdi. Samenvattend konden we zeggen dat Spinraza mogelijk een stabiliserend effect heeft op longfunctie en ademspierkracht bij mensen met SMA type 1, 2, 3 en 4. Stabilisatie is bij mensen met SMA ook een belangrijk effect, omdat zonder behandeling de longfunctie en ademspierkracht geleidelijk achteruitgaat.

Trainen van de ademspieren – protocol van de studie

Bij mensen met SMA verhoogt de verminderde beweeglijkheid van de borstkas en de longen de belasting op de al verzwakte ademspieren. De disbalans tussen de verhoogde belasting en de verminderde kracht van de ademspieren kan leiden tot vermoeidheid en ademfalen.

Training van de ademspieren kan een mogelijke therapie zijn voor mensen met zwakte van de ademspieren. In **hoofdstuk 5** beschrijven we het protocol van de RESISTANT-studie (Respiratory Muscle Training in Patients with Spinal Muscular Atrophy). In deze studie onderzochten we het effect van training op de kracht van de ademspieren van mensen met SMA. Mensen met SMA en ademspierzwakte (kracht van de inademspieren van <80 cmH_2O, cmH_2O betekent centimeters of water en is een eenheid om kracht van de ademspieren aan te geven) werden bij de start van de studie (M0) in twee groepen gedeeld, de trainingsgroep en de controlegroep. Beide groepen

trainden hun inadem- en uitademspieren door 10 keer per week 30 inademingen en 30 uitademingen te doen door een apparaatje dat weerstand geeft tijdens het ademen. De apparaatjes waren ingesteld op een percentage van ieders maximale kracht.

De deelnemers in de trainingsgroep startten hun training met een hogere weerstand (30% van hun maximale kracht) dan de controlegroep (10% van hun maximale kracht). Daarnaast mochten de deelnemers in de trainingsgroep de weerstand verhogen op basis van hun ervaren vermoeidheid (zie tabel 1). De deelnemers in de controlegroep trainden de eerste vier maanden met een stabiele weerstand.

***Tabel 1**: scoren van de ervaren zwaarte/vermoeidheid van/na de training*

Ervaren zwaarte/vermoeidheid		**Advies**
0	Niet voelbaar	
1	Erg licht	Te licht, verhoog de
2	Licht	weerstand met 1 a 2 cmH_2O
3	Matig	
4	Redelijk zwaar	
5	Zwaar	Precies goed
6	Zwaar	
7	Erg zwaar	
8	Erg zwaar	Te zwaar, verlaag de
9	Heel, heel zwaar	weerstand
10	Maximaal	

Alle deelnemers werden eens per twee weken gesuperviseerd door een fysiotherapeut via een telefonisch- of videoconsult. Na vier maanden (M4) ging de trainingsgroep verder met trainen zonder supervisie, de controlegroep kreeg na vier maanden dezelfde training aangeboden als de trainingsgroep had gehad in de eerste vier maanden. Na acht maanden trainen (M8) gingen de deelnemers in beide groepen nog vier maanden verder met trainen zonder supervisie (tot M12).

Trainen van de ademspieren – resultaten van de studie

In **hoofdstuk 6** bespreken we de resultaten van de RESISTANT-studie. In totaal deden er 30 mensen met SMA mee aan de studie. Na vier maanden (op M4) was de inademkracht bij deelnemers in beide groepen verbeterd (training groep +11.8 cmH_2O, controlegroep +6.1 cmH_2O). Na 1 jaar trainen was de inademkracht van deelnemers in beide groepen nog meer verbeterd (training groep +13.5 cmH_2O, controlegroep +19 cmH_2O). We zagen een sterke relatie tussen het trainingsvolume (aantal keer trainen x trainingsweerstand) en de verbetering van inademkracht; hoe meer men trainde, hoe meer men vooruitging in kracht. De kracht van de uitademspieren, longfunctie en kwaliteit van leven bleef stabiel gedurende het jaar. Er waren geen ernstige aan de training gerelateerde

bijwerkingen, dus de training was veilig. De deelnemers wilden ook graag doorgaan met de training, maar de therapietrouw was matig. 10 keer in de week trainen was voor veel deelnemers een uitdaging, voornamelijk omdat ze hulp nodig hadden bij de training. De supervisie was voor veel deelnemers een stok achter de deur, waardoor de therapietrouw bij deelnemers met supervisie hoger was dan bij deelnemers zonder supervisie.

Samenvattend zijn de belangrijkste bevindingen van dit proefschrift:

- Mensen met SMA types 2 en 3 laten een normale vermoeibaarheid van de inademspieren zien zonder een 'normale' door inspanning veroorzaakte toename van ervaren vermoeidheid en spierzwakte.
- De spieractiviteit van het middenrif bij het begin van een adem-uithoudingstest bleef stabiel bij hogere weerstandsniveaus, terwijl de spieractiviteit van de tussenribspieren en de scalenusspieren variabeler werd.
- Het middenrif laat bij mensen met SMA en vermoeibaarheid de meeste tekenen van vermoeidheid zien.
- De medicijnen Spinraza en Evrysdi lijken de longfunctie en ademspierkracht van mensen met SMA types 1, 2, 3 en 4 niet te verbeteren.
- Het medicijn Spinraza heeft mogelijk een stabiliserend effect op de longfunctie en ademspierkracht van mensen met SMA types 1, 2, 3 en 4.
- Ademspiertraining is veilig uit te voeren bij mensen met SMA.
- Op een lage weerstand (10% van de maximale inademkracht) starten met trainen en daarna de weerstand ophogen op basis van de ervaren vermoeidheid lijkt de meest effectieve manier om de inademkracht te verbeteren bij mensen met SMA.
- Supervisie van mensen met SMA die ademspiertraining doen, zorgt voor een betere therapietrouw.

ABBREVIATIONS

ΔPImax	change in maximal inspiratory mouth pressure
Δperceived fatigue	change in perceived fatigue
Δslope	differences between the slopes of the noRMF group and the RMF group
%pred	percentage of predicted
ACTs	airway clearance techniques
AE(s)	adverse event(s)
ALS	amyotrophic lateral sclerosis
AS	airstacking
B	baseline
BOCF	baseline-observation-carried-forward
CD	cannot determine
CI	confidence interval
cmH_2O	centimeters of water column
CONSORT	Consolidated Standards of Reporting Trials
d	Cohen's d
D	day
D…	after … days of treatment
df	degrees of freedom
DMD	Duchenne muscular dystrophy
DMT(s)	disease-modifying therapy (therapies)
EMA	European medicines agency
EMG	electromyography
EMT	expiratory muscle training
ERS/ATS	European respiratory society/ American thoracic society
ERV	expiratory residual volume
FDA	US food and drug administration
FEV1	forced expiratory volume in 1 second
FIV1	forced inspiratory volume in 1 second
FRC	functional residual capacity
FVC	forced vital capacity
GDPR	general data protection regulation
H	high risk of bias
HFMSE	hammersmith functional motor scale expanded
HR	hazard ratio
Hz	hertz
I^2	level of heterogeneity
IC	inspiratory capacity

i.e.	id est (that is)
IMT	inspiratory muscle training
IRV	inspiratory residual volume
IQR	Interquartile range
K	Kappa
kPa	kilopascal
L/l	liter
l/min	liter per minute
l/sec	liter per second
L	long-term follow-up (>12 months)
ln	natural logarithm
lnRMS	natural logarithm-transformed root mean square
m/M	month(s)
M	moderate risk of bias
M…	after … months of treatment
MAC	manually assisted cough
MedRA	medical dictionary for regulatory activities
METC	Medical Ethics Research Committee
MF	median frequency
MFM	motor function measurement
MI-E	mechanical insufflation-exsufflation
M (IQR)	median and interquartile range
MRC	medical research council
MVC	maximal voluntary contraction
MW	muscle weakness
n	number
n.s.	not statistically significant
N	no
NA	not applicable
NIV	noninvasive ventilation
NMD(s)	neuromuscular disease(s)
NMJ	neuromuscular junction
NR	not reported
nRMS	normalized root mean square
NRS	numeric rating scale
OMNI	OMNI scale of perceived exertion
***p*/*P*/*p*-value**	probability value
P0.1	mouth occlusion pressure at 100ms during quiet breathing
PCF	peak cough flow
PedsQL	Pediatric Quality of Life inventory

	PhHSS: physical health summary score
	PsHSS: psychosocial health summary score
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PEmax	maximum expiratory mouth pressure
PEP	positive expiratory pressure
PIFR	peak inspiratory flow rate
PImax	maximum inspiratory mouth pressure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
py	per year
r	effect size
r	Spearman's correlation coefficient
R^2	coefficient of determination
RCT	randomized controlled trial
ref	reference
RESISTANT	Respiratory Muscle Training in Patients with Spinal Muscular Atrophy
RET	respiratory endurance test
RMF	respiratory muscle fatigability
RMS	root mean square
RMT	respiratory muscle training
ROB	risk of bias
RV	residual volume
s/sec	second
S	short-term follow-up (≤12 months)
SAE	serious adverse event
SD	standard deviation
sEMG	surface electromyography
Sign	significant
SF-36	36-item short-form health survey
	PF: physical functioning
	RP: role limitations due to physical health problems
	BP: bodily pain
	GH: general health perceptions
	VT: vitality
	SF: social functioning
	RE: role limitations due to emotional problems
	MH: general mental health
	PCS: physical component scale

	MCS: mental component scale
SMA	spinal muscular atrophy
SMD	standardized mean difference
SMN	survival motor neuron
SPIRIT	standard protocol items: recommendations for interventional trials
SNIP	sniff nasal inspiratory pressure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVC	slow vital capacity
T	time
T0	before start Nusinersen/Risdiplam
Tau^2	between study variance
TF	task failure
TIDieR	the template for intervention description and replication
TLC	total lung capacity
μV	microvolt
UMCU	University Medical Center Utrecht
VC	vital capacity
Vexp	expiratory volume
Vin	inspiratory volume
Vt	tidal volume
WOB	work of breathing
WMO	Medical Research Involving Human Subjects Act
y	year/years
Y	yes
Z-score	A standardized score indicating the deviation from the mean in units of standard deviation
◯	moderate risk of bias
●	high risk of bias

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Part of this thesis

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MIJN PROMOTIE VERHAAL

Ik heb lang getwijfeld over of ik dit verhaal wel in mijn proefschrift wil zetten. Maar uiteindelijk heb ik toch besloten om het te doen, omdat dit het verhaal is over hoe dit proefschrift tot stand gekomen is. En dat is geen standaard promotie verhaal (voor zover er standaard promotieverhalen zijn). Ik geloof niet dat er veel mensen zijn die borstkanker en promoveren gecombineerd hebben. Het promoveren en de behandelingen voor de borstkanker zijn met elkaar verweven tot de moeilijkste vijf jaar van mijn leven. Maar mogelijk ook wel tot de mooiste vijf jaar van mijn leven. En daarom wil ik dit verhaal delen. Misschien kan ik mensen inspireren met mijn verhaal, misschien ook niet. Het opschrijven van dit verhaal heeft in ieder geval een therapeutisch effect gehad op mij en ik hoop dat ik, met het behalen van mijn PhD, de afgelopen vijf jaar op een spectaculaire manier kan afsluiten!

Aanloop promotie

In september 2017 begon ik aan de master Klinische Gezondheidswetenschappen aan de Universiteit Utrecht. Ik werkte al een tijdje als kinderfysiotherapeut in een particuliere praktijk en ik wilde graag naast iets betekenen voor de kinderen die ik behandelde, ook iets betekenen voor mijn collega's en het vak kinderfysiotherapie. Daarnaast was het mijn droom om in een academisch ziekenhuis te kunnen werken. Zorg, onderzoek en misschien ook wel onderwijs combineren, leek me fantastisch! De opleiding ging me goed af, al verliep deze niet zonder slag of stoot. Tijdens de pre-master viel ik op mijn hoofd tijdens het skiën in Italië. Ik weet niets meer van die dag en ik hield er een flinke hersenschudding aan over, waarvan ik drie maanden moest herstellen. Tijdens het eerste jaar van de master overleed mijn moeder na een ziekbed van 10 jaar aan borstkanker. Uiteraard was ik intens verdrietig, maar het was ook goed zo. Mijn moeder heeft me altijd in alles aangemoedigd, ze wist van mijn ambities en was mijn steun en toeverlaat. Ze heeft me dan ook tot op het laatste moment gemotiveerd om mijn dromen na te jagen.

Een half jaar na het overlijden van mijn moeder komt mijn droom uit, ik word aangenomen in het Wilhelmina Kinderziekenhuis (WKZ) en mag gaan deelnemen aan een onderzoek naar ademspiertraining bij patiënten met spinale musculaire atrofie (de RESISTANT-studie)! Ook mijn afstudeeropdracht van de Klinische Gezondheids-wetenschappen mag ik in het WKZ uitvoeren. Hieruit komt mijn eerste publicatie die uiteindelijk hoofdstuk 2 van dit proefschrift vormt.

Covid-19 en uitstel studie

In maart 2020 breekt het Covid-19 virus uit. Ik woon dan nog in 's-Hertogenbosch en omdat ze nog even denken dat ze het virus wel onder de rivieren kunnen houden, moet ik als eerste van ons team thuis gaan werken. Al snel bereikt het virus echter ook de rest

van Nederland en mogen we maar met een beperkt aantal mensen op de afdeling zijn. In de tweede week van maart horen we dat vanwege Covid de METC-procedures in het UMCU voorlopig stil komen te liggen, helaas moeten we de start van de RESISTANT-studie dus uitstellen. Uiteindelijk krijgen we op 10 augustus groen licht van de METC. De RESISTANT-studie kan eindelijk beginnen!

Borstkanker diagnose en behandeling

Terwijl de wereld in de greep is van het Covid virus, ontdek ik op 8 april 2020 een knobbeltje in mijn linkerborst. Het voordeel van Covid is dat alleen acute zorg door mag gaan en dat er daardoor nauwelijks wachttijden zijn. Een groot nadeel is dat je niemand mee mag nemen bij de afspraken. Op 16 april krijgen we de uitslag. Mijn man, Wilco, mag in eerste instantie niet mee het ziekenhuis in. Als we vertellen waarvoor we komen, maken ze een uitzondering. Als de oncoloog bij binnenkomst vraagt of we het gesprek willen opnemen, weet ik al dat het foute boel is. Er is een tumor ontdekt, vooralsnog klein en mogelijk valt het mee. Maar toch, borstkanker. Dit verschrikkelijke nieuws aan mijn vader te moeten vertellen, iets meer dan een jaar nadat hij zijn vrouw aan borstkanker heeft verloren, is het moeilijkste wat ik ooit heb moeten doen.

In de weken na de uitslag wordt het scenario steeds zwarter. De tumor is groter dan gedacht, er zit een uitzaaiing in mijn lymfeklier en ik heb het CHEK2 gen, waardoor de kans op recidief erg groot is. Uiteindelijk gaan we qua behandelplan voor het volledige pakket aan behandelingen: dubbele borstamputatie en reconstructie, 15 bestralingen, 16 chemobehandelingen en nog minstens vijf jaar anti hormonale therapie. Op 27 mei 2020 vindt de grote operatie plaats. Die valt tegen. Ik heb veel pijn en de wonden stoppen maar niet met bloeden. Het herstel gaat langzaam. Twee weken na de operatie doe ik liggend vanaf de bank via Zoom mijn afstudeerpresentatie voor de opleiding Klinische Gezondheidswetenschappen. Toch een voordeel van Covid, ik hoef niet helemaal naar Utrecht toe hiervoor.

Anderhalve maand na de operatie krijgen we de sleutel van ons nieuwe huis. Ik kan je vertellen dat vier grote life events in een half jaar (nieuwe baan, ziek worden, afstuderen en verhuizen) niet echt een aanrader is. Tussen het klussen in ons nieuwe huis door, begin ik aan de bestralingen. Drie weken lang elke werkdag op en neer naar het UMCU.

Na de bestralingen start de volgende behandelfase, de chemotherapieën. Eerst vier zware kuren en daarna 12 lichtere. Ondanks dat ze me hebben verzekerd dat overgeven na chemotherapie niet meer van deze tijd is, omdat je tegenwoordig hele goede antimisselijkheidmedicatie hebt, begin ik er ’s nachts toch mee en stopt het pas als ik 24 uur later aan het infuus in het UMCU lig. Na twee nachten ziekenhuis mag ik weer naar huis en na ruim een week voel ik me pas weer een beetje mens. Helaas staat een week later de volgende chemo alweer op het programma. Ze passen de medicatie aan en ik word uit voorzorg opgenomen. Deze keer gaat het gelukkig beter. De laatste

zware chemo valt echter weer niet goed. Terwijl de Covid-cijfers oplopen en ik amper meer naar buiten durf, krijg ik steeds meer klachten. Een week na de chemo krijg ik koorts en dat is foute boel tijdens chemo's. Er volgt een ziekenhuis opname, een flinke dosis antibiotica, thuisquarantaine en een extra week herstel voordat de 'lichtere' chemo's starten. Ook de lichtere chemo's vallen niet goed bij me. Deze zijn wekelijks en ik kom amper bij tussen twee chemo's. Bij de derde gaat het al mis. Ik moet een dag van tevoren bloed prikken en ik heb 0.0 neutrofielen (witte bloedcellen). Nummer 3 kan dus niet doorgaan. Ondertussen word ik steeds zieker. Het wordt langzaam duidelijk dat ik niet 'normaal' reageer op de chemotherapie en daarom wordt de dosis gehalveerd. De chemo's daarna kom ik gelukkig wat beter door.

Revalidatie en re-integratie

Twee weken na de laatste chemotherapie (februari 2021) krijg ik van de bedrijfsarts groen licht om weer wat meer te gaan werken. Ook mag ik, in plaats van alleen maar thuis, weer in het WKZ gaan werken en dus ga ik voor het eerst sinds acht maanden weer naar het WKZ om de eerste patiënt van de RESISTANT-studie te zien. Ik ben zo blij dat ik weer mag werken en mijn uren kan opbouwen, eindelijk weer terug naar normaal!

Helaas loopt ook dat anders dan gepland. Een maand na de laatste chemotherapie start ik met anti hormonale therapie. Omdat ik een hormoongevoelige tumor had, zouden eventuele onzichtbare uitzaaiingen kunnen groeien onder invloed van hormonen. Daarom mag mijn lichaam geen hormonen meer aanmaken. Hierdoor kom ik van de ene op de andere dag in de overgang, met alle gevolgen van dien. Opvliegers, gewrichtsstijfheid, peesklachten, hoofdpijn, slechter slapen, maar ook vermoeidheid. En die vermoeidheid lijkt zelfs nog erger te zijn dan tijdens de chemo's. Om hiermee om te leren gaan, start ik met een intensief revalidatietraject van drie maanden in het UMCU. Daarnaast probeer ik te werken. Ik zit echt al veel te lang thuis en ben er helemaal klaar mee.

In mei 2021 ben ik voor de wet één jaar ziek. Helaas maakt het niet uit wat voor ziekte je hebt en of je nog volop in behandeling bent of niet, maar na je eerste ziektejaar gaan er 'UWV-radartjes' lopen. Ik heb me hier erg over verbaasd. Het is totaal geen maatwerk en met al hun rechten en plichten houden ze totaal geen rekening met de aard van de ziekte. Hoe vaak ik niet heb moeten uitleggen dat ik niet 'ziek' was toen ik me ziekmeldde, maar dat ik in het jaar daarna 'ziek ben gemaakt'. Het is dan ook totaal niet logisch dat je na een jaar al wordt aangemeld voor een re-integratietraject op een andere werkplek dan je eigen werkplek. Ik ben op dat moment nog volop aan het re-integreren op mijn eigen werkplek en dat gaat prima, maar daarnaast moet ik op zoek naar een eventuele andere plek om te re-integreren zowel binnen als buiten het WKZ/UMCU. Hiervoor moet ik tig gesprekken voeren met allerlei verschillende mensen en dit kost bakken met energie. Energie die ik veel liever gewoon in mijn eigen werk stop. In

september 2021 word ik ook nog een paar stappen teruggeworpen in mijn herstel, omdat ik opnieuw geopereerd word en mijn definitieve borstprotheses krijg.

Eind december 2021 loopt mijn oorspronkelijke contract van twee jaar af. Eigenlijk zou de RESITANT-studie nu klaar moeten zijn, maar door alle omstandigheden is dat natuurlijk niet het geval. Gelukkig mag ik door met de studie! Ik krijg een contract van 16 uur per week om de RESISTANT-studie af te maken. Dit maakt de verdere re-integratie nogal ingewikkeld, omdat ik eigenlijk moet re-integreren naar mijn oorspronkelijke aantal uren (28.8 uur). Daardoor ga ik deels ziek uit dienst en snapt niemand precies hoe het nu verder moet. Er volgen weer vele gesprekken en uiteindelijk moet ik zelfs een WIA-aanvraag doen terwijl het re-integreren best voorspoedig loopt en alle betrokkenen verwachten dat ik volledig herstel binnen twee jaar. Gelukkig heb ik de WIA-uitkering niet nodig en kan ik me op 15 april 2022, na bijna twee jaar ziekte, eindelijk volledig beter melden!

Promotie struggles

Begin 2023 krijg ik officieel te horen dat ik mag promoveren. Ik vind dit een hele eer en ben ontzettend blij dat ik deze kans krijg. Ik weet dat struggles horen bij het promotietraject, maar toch heb ik me ook verbaasd over bepaalde zaken. Wie heeft bijvoorbeeld verzonnen dat ieder wetenschappelijk tijdschrift andere eisen heeft ten aanzien van de opbouw en opmaak van artikelen? Wat dus betekent dat wanneer je een artikel opnieuw moet indienen bij een ander tijdschrift je vervolgens zeker twee volle dagen bezig bent met het herstructureren van je artikel, alvorens je het opnieuw kan indienen. Ik pleit voor eerst een algemene versie indienen en pas bij goedkeuring je artikel opmaken volgens de eisen van het tijdschrift, dit zou heel veel mensen heel veel tijd schelen!

Wat ik ook lastig vind, is hoe de resultaten van een onderzoek door verschillende mensen op verschillende manieren geïnterpreteerd worden. De resultaten van de RESISTANT-studie zijn eigenlijk heel positief. De patiënten lieten bijna allemaal een verbetering zien in ademspierkracht na een periode van training. Het ‘probleem’ is dat de mensen in de controlegroep ook een verbetering lieten zien en daardoor kan je niet met zekerheid zeggen dat de training werkt. Het kan ook iets anders zijn geweest wat voor de verbetering heeft gezorgd. Dit zorgt voor een lastige situatie. Als clinicus heb ik gezien dat ademspiertraining werkt, maar als onderzoeker mag ik dat eigenlijk niet met zoveel zekerheid zeggen. Hierdoor is het artikel ook minder interessant voor tijdschriften. Ook is ademspiertraining nog geen standaard zorg bij patiënten met SMA en daardoor mogen patiënten niet trainen als ze aan andere onderzoeken meedoen. Ik vind dit lastig omdat ik graag alle patiënten met SMA zou willen helpen met ademspiertraining. Maar voordat ik dat kan en mag gaan doen, moet ademspiertraining eerst onderdeel gaan worden van de standaard zorg bij patiënten met SMA.

Ooit ben ik aan het doen van onderzoek begonnen om mensen daarmee te kunnen helpen, maar als je, vooral aan het einde, alleen nog maar letters en cijfers ziet, dan weet je op een gegeven moment niet meer welke mensen daar ook alweer achter zaten en voor welke mensen je dit ook alweer deed.

Ondanks deze struggles is het me toch gelukt om voor ogen te houden wat me ooit trok in het doen van onderzoek, namelijk iets kunnen betekenen voor mijn vak en de patiënten die ik behandel. Het heeft uiteindelijk geleid tot dit mooie proefschrift en daar ben ik maar wat trots op!

5 jaar later

Inmiddels ben ik 5 jaar verder. Vijf jaar schijnt een belangrijke mijlpaal te zijn in oncologie-land, maar ik voel hem nog niet helemaal. Het lastige van twee geamputeerde borsten, is dat ik geen borstweefsel meer heb om te onderzoeken of de kanker terug is gekomen of niet. Ook kunnen ze geen bloedonderzoek doen en een scan maken doen ze niet zomaar. Het vervelende van borstkanker is namelijk dat als het terug komt en uitgezaaid is, het niet meer te genezen is. En dus redeneert de medische wereld als volgt: als het terugkomt, kunnen we het toch niet meer genezen en dus maakt het niet uit of we het nu ontdekken of over een jaar. Hierdoor moet ik er maar op vertrouwen dat het goed gaat. En dat is lastig als je lijf je al eens zo in de steek heeft gelaten. Nog steeds denk ik bij ieder gek pijntje dat de kanker terug is. In februari 2026 moet of mag ik met de anti hormonale therapie stoppen. Ik ervaar nog dagelijks de gevolgen van deze behandeling. De opvliegers vliegen me zo'n 10-15 keer per dag om de oren (en dat is op goede dagen, het kan ook zomaar ineens het dubbele zijn). Mijn lijf voelt als dat van een oude dame: stijf, snel overbelast en onrustig. De vermoeidheid is nog altijd aanwezig en kan me zomaar ineens knock-out slaan. Over een jaar kan mijn lijf hopelijk hier ook nog een beetje van herstellen. Spannend wordt het dan wel, want dan is er niets meer wat me beschermt. En dan is het hopen dat alle behandelingen niet voor niets zijn geweest, dat ze ieder kanker celletje de nek om hebben gedraaid en dat er niet een eigenwijs celletje tussendoor is geglipt.

Samenvattend

De afgelopen 5 jaar gingen met vallen en opstaan. Alles bij elkaar heeft het me veel tranen en veel energie gekost. Maar ik heb ook veel geleerd en heel veel mooie momenten meegemaakt! Over mezelf heb ik geleerd dat ik oneindig veel geduld, veerkracht en doorzettingsvermogen bezit. Ik heb onwijs veel geleerd over SMA, over ademen en over hoe je een onderzoek uitvoert. Daarnaast heb ik geleerd dat je andere mensen nodig hebt om het leven lichter en leuker te maken. De afgelopen 5 jaar heb ik ook hele toffe dingen mee mogen maken. Ik mocht presenteren voor allerlei nationale én internationale gezelschappen, 'online' op het Amerikaanse SMA congres en fysiek op het Europese SMA congres. Ik mocht een fietstocht mede organiseren van Utrecht naar

Gent om aandacht te vragen voor kinderen met een spierziekte. Ik mocht een workshop geven op het kinderfysiotherapie congres en een filmpje over ademspiertraining opnemen voor spierziekten Nederland. Daarnaast mocht ik met het Scapino ballet Rotterdam, de F|Fort Foundation en lotgenoten een dansvoorstelling maken over jong zijn en leven met en na kanker. Deze voorstelling heeft enorme indruk gemaakt op familie en vrienden, maar ook op volslagen onbekenden tijdens twee internationale dansfestivals en een congres voor oncologisch verpleegkundigen. Er is een documentaire over gemaakt en deze is zelfs uitgezonden op tv! En als kers op de taart mocht ik de Prinses Beatrix Spierfonds Impact Award 2024 in ontvangst nemen! Met de RESISTANT-studie hebben we impact gemaakt voor patiënten en dat is uiteindelijk waarom ik dit hele traject ben begonnen!

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Lieve **mama,** ook al ben je fysiek niet meer hier, ik weet en voel dat je trots op me bent. Je hebt me altijd in alles gesteund en ik kon altijd bij je terecht. Ik heb je ontzettend gemist de afgelopen jaren - ik had je graag als ervaringsdeskundige aan mijn zijde gehad toen ik ziek was. Je was mijn voorbeeld in hoe om te gaan met een ziekte waar niet tegen te strijden valt. Ook miste ik je lieve briefjes, zoals je die vroeger schreef om me door de proefwerkweek heen te helpen. 'Niet te hard leren, schat', schreef je dan, maar tegelijkertijd stimuleerde je me ook om te komen waar ik nu ben. Je kende mijn ambities en dromen, en je zou maar wat trots zijn geweest om te zien dat ik ze heb kunnen waarmaken. Ook al dacht jij van niet: dat doorzettingsvermogen, dat heb ik toch echt van jou!

Lieve **papa,** wat ben ik blij dat onze band de laatste jaren zoveel sterker is geworden. Je bent er voor me, en ik hoef je maar te bellen of je staat al voor me klaar. We hebben fijne gesprekken over van alles en nog wat: jij leert me wat harder te zijn en meer aan mezelf te denken, en ik leer jou wat minder zwart-wit te kijken. Ook al heb je soms geen idee van wat ik precies aan het doen ben, je bent altijd geïnteresseerd en steunt me in alles! Bedankt voor alles, pap!

En dan, last but not least: lieve **Wilco,** wat ben ik ongelofelijk trots en blij met jou aan mijn zijde. Ik heb het je al eerder gezegd, maar nog steeds ben jij de stabiele boei in mijn onstuimige hoofd én leven! Door jou kan ik alle stormen aan die op ons pad komen. Ze zeggen wel eens: 'Achter elke sterke man, staat een sterke vrouw', maar bij ons is dat zéker andersom! Mijn succes hangt af van jouw steun en inzet. Je zegt wel eens dat jij op de wereld bent om mij gelukkig te maken - waarop ik altijd roep dat je niet zo gek moet doen - maar dat jij dat zegt, vind ik zó ongelofelijk lief! Zonder jouw onvoorwaardelijke steun was ik nooit zo ver gekomen! Laten we vooral blijven genieten van het leven: van de mooie reizen die we maken, onze kneuterige momenten en de tijd met onze steunkinderen. Schat, ik hou van je!

ABOUT THE AUTHOR



Kim Kant-Smits was born on August 1, 1984, in Eindhoven, the Netherlands. She spent her childhood in Eindhoven with her parents and sister. She attended secondary school at Stedelijk College Eindhoven and received her VWO diploma in 2002. In 2006, Kim obtained her Bachelor of Health Science degree in Physiotherapy from Fontys University of Applied Sciences in Eindhoven. In 2007, she worked for four months as a physiotherapist at Jumba Special School for mentally disabled children in Tamale, Ghana.

Her interest in child development and her love for working with children motivated her to start a master's program in pediatric physical therapy at Utrecht University of Applied Sciences in 2008. After earning her Master of Science degree in 2011, she worked for several years as a pediatric physical therapist in primary care practices. While working there, she increasingly felt the desire to make a greater impact on her field and support her colleagues. She also dreamed of one day working in an academic children's hospital. To further her development, she began a pre-master's program in Clinical Health Sciences at Utrecht University in 2017.

In 2019, during her master's in Clinical Health Sciences, she had the opportunity to write a systematic review under the guidance of Janjaap van der Net, who was then head of the Child Development and Exercise Center at the Wilhelmina Children's Hospital (WKZ). In 2020, her dream came true: she was able to work as a pediatric physical therapist and junior researcher at WKZ. Her master's thesis in Clinical Health Sciences, which focused on respiratory muscle fatigability in patients with SMA, became the foundation for her eventual PhD trajectory.

As a junior researcher, Kim began working on the RESISTANT study (Respiratory Muscle Training in Patients with Spinal Muscular Atrophy) under the supervision of Erik Hulzebos and Bart Bartels. However, in March 2020, COVID-19 gripped the world, and in April 2020, she herself was diagnosed with breast cancer. The RESISTANT study was delayed by a year but was successfully completed in January 2023. In January 2023, Kim officially secured a PhD position within the SMA research team under the supervision of Prof. Dr. W. Ludo van der Pol. With Bart Bartels and Erik Hulzebos as co-supervisors and Prof. Dr. Kors van der Ent as second supervisor, her PhD supervisory team was complete. Her doctoral research focused on the respiratory muscles in patients with spinal muscular atrophy.

Kim is married to Wilco Kant and lives in Vianen. Together with her husband, she is a part-time foster parent to an 11-year-old girl and a 6-year-old boy. She enjoys traveling, dancing, doing puzzles, sports, and hiking in her free time. She is also creative and makes her own jewelry and birthday cards. In addition to the foster children, she often has her nieces and nephews over as well.