Inspiratory muscle training in severe spinal muscular atrophy: a case report

Anri Human, Paediatrics Lecturer[1,*], Engela Honey, Senior Lecturer[2], Brenda Morrow, Paediatric Physiotherapist and Professor[3]

[1]Department of Physiotherapy, Sefako Makgatho Health Sciences University, Pretoria, South Africa

[2]Department of Biochemistry, Genetics and Microbiology, University of Pretoria, Pretoria, South Africa

[3]Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

* Correspondence to: Anri Human. Email: anrihuman@gmail.com

Abstract

Background/Aims

Inspiratory muscle training aims to preserve or improve respiratory muscle strength in children with neuromuscular diseases in order to prevent or minimise pulmonary morbidity. The aim of this study was to determine the effect of inspiratory muscle training on clinical outcomes and health-related quality of life in a child with advanced neuromuscular disease and severe pulmonary restriction.

Methods

A one patient pre-test post-test study design was implemented. General function, spirometry, peak expiratory cough flow and health-related quality of life were measured at baseline and after a 6-week inspiratory muscle training programme. Inspiratory muscle strength (maximal inspiratory mouth pressure and sniff nasal inspiratory pressure) was measured every 2 weeks. The patient used a tapered flow threshold inspiratory training device (POWERbreathe K3) at an intensity of ± 30% of maximal inspiratory mouth pressure twice a day, 5 days per week.

Findings

The non-ambulatory 10-year-old girl with type 2 spinal muscular atrophy initially had a forced vital capacity of 18% predicted and peak expiratory cough flow of 60 litres/minute. A substantial improvement was seen in inspiratory muscle strength between baseline and 4 weeks. Patient health-related quality of life improved and patient satisfaction was high, with a score of 9/10. The patient developed a lower respiratory tract infection towards the end of the inspiratory muscle training period. No other adverse events occurred.

Conclusions

Improved inspiratory muscle strength and health-related quality of life was associated with inspiratory muscle training in a child with advanced spinal muscular atrophy. Controlled clinical trials are recommended to determine the safety and efficacy of inspiratory muscle

training in children with advanced spinal muscular atrophy and severe respiratory muscle weakness to inform clinical practice.

Key words: Health-related quality of life; Inspiratory muscle training; Neuromuscular diseases; Spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy, an autosomal recessive condition, is one of the most common neuromuscular diseases affecting the paediatric population (Gozal, 2000). Spinal muscular atrophy is a neurodegenerative anterior horn cell and brainstem motor nuclei disease that clinically presents with progressive muscle weakness, including respiratory muscle weakness. Spinal muscular atrophy can be categorised into four main types based on the time of onset, severity of the symptoms and clinical picture or functional ability (Ioos et al, 2004; Wang et al, 2007). Spinal muscular atrophy type 2 is the most common, intermediate form, with symptom onset between 6 and 18 months of age (Gozal, 2000; Ioos et al, 2004). Children with spinal muscular atrophy type 2 can usually gain independent sitting but cannot walk unassisted (Wang et al, 2007).

Children and adolescents with spinal muscular atrophy are at high risk of morbidity and mortality as a consequence of inspiratory and expiratory respiratory muscle weakness (with relative diaphragmatic sparing) (Bach et al, 2000; Gozal, 2000; Wang et al, 2007; Park et al, 2010). Respiratory muscle weakness and/or bulbar palsy in neuromuscular diseases reduces the ability to cough effectively, with reduced peak expiratory cough flow leading to chronic secretion retention (Bach et al, 2000; Kang and Bach, 2000; Park et al, 2010; Chatwin et al, 2018). Furthermore, as the condition progresses and children age, the paradoxical intercostal breathing pattern (Wang et al, 2007) caused by intercostal muscle weakness leads to the development of a bell-shaped chest wall deformity (Ioos et al, 2004) and forced vital capacity decreases, increasing the risk of pulmonary complications (Ioos et al, 2004). Low tidal volumes, as a consequence of reduced inspiratory capacity, may also lead to the retention of secretions and alveolar hypoventilation (ventilation/perfusion mismatch), causing airway obstruction, atelectasis, recurrent lower respiratory tract infections, hypoxia, restrictive lung disease and, finally, respiratory failure (McCool and Tzelepis, 1995; Bach et al, 2000; Eagle, 2002; Ioos et al, 2004).

Pulmonary rehabilitation in spinal muscular atrophy aims to slow the progressive decline in general and cardiopulmonary function in order to delay the onset of respiratory failure; reduce pulmonary symptoms; improve airway clearance; optimise ventilation, general function and participation; reduce healthcare costs; and ultimately improve health-related quality of life (DiMarco et al, 1985; Gozal, 2000; Koessler et al, 2001; Eagle, 2002; Nici et al, 2006; Hull et al, 2012). The main components of pulmonary rehabilitation include muscle training, education and airway clearance therapy, adapted according to individual patient presentation (Rous et al, 2014). Pulmonary rehabilitation has both physiological and psychosocial benefits for patients living with chronic disease, but is frequently underutilised (Rochester et al, 2015). Early anticipatory respiratory management implemented shortly after neuromuscular disease diagnosis may reduce pulmonary complications and improve

the child's health-related quality of life, and is recommended as standard of care in spinal muscular atrophy (Ioos et al, 2004; Wang et al, 2007).

As a component of pulmonary rehabilitation in spinal muscular atrophy, inspiratory muscle training may reduce associated morbidity and mortality, thereby improving health-related quality of life (DiMarco et al, 1985; McCool and Tzelepis, 1995; Gozal, 2000). Two controlled studies of children, adolescents and adults living with neuromuscular diseases showed significant improvements in inspiratory muscle strength with twice-daily inspiratory muscle training using a threshold device set at 30% of inspiratory muscle strength (Gozal and Thiriet, 1999; Yeldan et al, 2008). The effect of inspiratory muscle training is likely to vary depending on patient presentation and associated pathophysiology, the degree of respiratory involvement and severity of disease (Eagle, 2002). Besides the variability in outcome (Gozal, 2000), it has been suggested that patients with advanced neuromuscular disease with severe pulmonary restriction, especially those retaining carbon dioxide, will likely not benefit from inspiratory muscle training (Wanke et al, 1994; McCool and Tzelepis, 1995). Inspiratory muscle training may therefore be more effective when commenced early in the disease, when respiratory muscles are relatively stronger and lung volumes, such as vital capacity, are higher (DiMarco et al, 1985; Wanke et al, 1994; McCool and Tzelepis, 1995; Winkler et al, 2000; Eagle, 2002). However, evidence for inspiratory muscle training is limited, as endurance might improve more than strength; there is no strong evidence for improved functional outcomes and the benefits might only last for a short period once training ceases (Eagle, 2002). There is also concern that inspiratory muscle training may accelerate fatigue in neuromuscular diseases as a result of overworking/overexertion (Koessler et al, 2001). The American Thoracic Society and British Thoracic Society suggest that inspiratory muscle training could be considered as a component of pulmonary rehabilitation in respiratory muscle weakness, but this is based on a low level of evidence (Nici et al, 2006; Hull et al, 2012).

A systematic review on inspiratory muscle training among children and adolescents with neuromuscular diseases reported that although inspiratory muscle training might be beneficial for improving inspiratory muscle strength and/or endurance, there was no published, scientifically-rigorous research investigating its effect on morbidity (eg hospitalisation rate, respiratory infection frequency, adverse events and health-related quality of life). The review concluded that there is currently no clear evidence for or against the use of inspiratory muscle training in children and adolescents with neuromuscular diseases. Studies included in this systematic review differed regarding the conditions included, severity of the disease, the inspiratory muscle training protocols followed and the duration of these training programmes (Human et al, 2017).

Contrary to the suggestion that inspiratory muscle training in patients with severe disease progression is unlikely to be beneficial (McCool and Tzelepis, 1995; Koessler et al, 2001; Eagle, 2002), we present a case where inspiratory muscle training was associated with clinical benefit in a patient with advanced spinal muscular atrophy type 2. A one patient pre-test post-test study design was implemented.

CASE STUDY

Case history

This is a case report of a 10-year-old African girl diagnosed with spinal muscular atrophy type 2 as a result of a homozygous deletion of the telomeric copy of exon 7 of the *SMN1* gene. She was attending a school for students with special needs in Pretoria, South Africa. A 6-week inspiratory muscle training programme was implemented at the school for all children with neuromuscular diseases.

Over the past few years, the girl had been admitted to hospital two to three times per year. Apart from a nose operation when she was very young, no previous surgeries had been performed; she was not taking any chronic medications and was not on any ventilatory support at the time of the study. Written patient assent and parental consent were obtained to (a) implement the inspiratory muscle training programme, (b) to present her data in this paper and (c) to publish photographs of the child.

The patient received occasional physiotherapy intervention at the school, as needed, according to physiotherapy assessment. This consisted mainly of deep breathing exercises and manual chest physiotherapy (percussions, vibrations and assisted coughing) during intercurrent respiratory infections. The school had no access to cough augmentation devices, such as mechanical insufflation–exsufflation or bag-insufflation kits, and had not been trained in other cough augmentation techniques.

During acute respiratory infections, with the assistance of her mother, the child used a nebuliser (budesonide and saline nebulisations) and applied manual assisted coughing and suctioning every evening. The child's home programme consisted of active upper limb mobility exercises, passive movements to maintain range of motion in the lower limbs (performed by her mother in the morning and sometimes at night), lying in a prone position for 30 minutes, 3 times a week, and occasional swimming and hippotherapy sessions. Her home respiratory exercise programme also included twice-weekly bubble-positive expiratory pressure therapy performed 2–3 times a session. To assist her breathing and prevent pressure sores, the child was turned every 2–3 hours during the night. She complained of difficulty sleeping and the possibility of implementing night time ventilation was being investigated.

Physical examination

The patient's general and respiratory function was determined during a physical assessment conducted by the primary author (AH) and was validated by a research assistant (SF).

The components for the assessment of mobility and general function are outlined in *Figure 1*. At the time of assessment, the patient was non-ambulatory. She made use of an electric wheelchair and used bilateral ankle-foot orthoses to maintain the range of motion in her ankles. She presented with scoliosis, with a last known Cobb angle of 47 degrees. The scoliosis could not be surgically corrected due to the patient's poor respiratory function and progressed in severity by approximately 10 degrees per year. She weighed 28 kg and, due to

her scoliosis, her ulna length was used to estimate her height of 1.54 m. Based on these measures, her body mass index was calculated as 11.8, which is below the fifth percentile for girls her age.

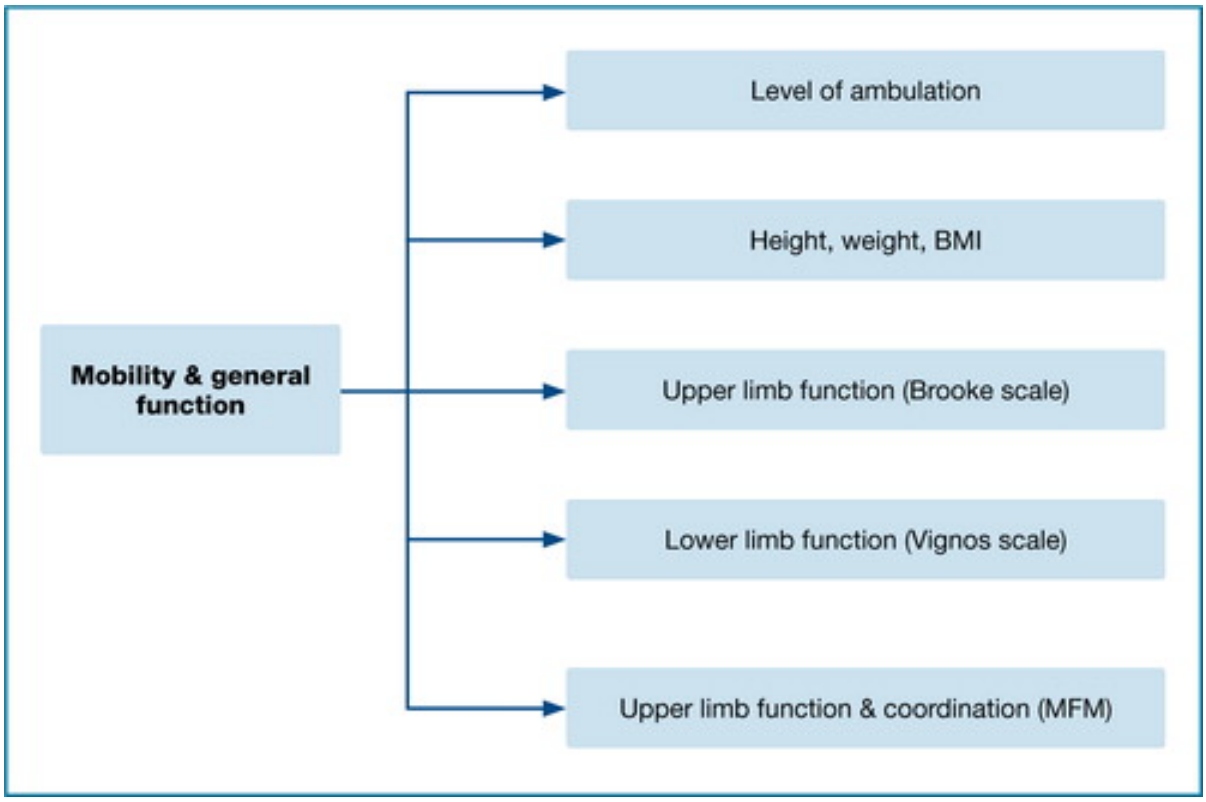

Figure 1. Mobility and function assessment components

The patient scored 4 for upper limb function using the Brooke upper extremity 6-point scale, where 6 is the lowest value and 1 the highest (Lu and Lue, 2012). Her lower limb function score was 9 on the 10-point Vignos scale, where 10 is the lowest possible score (Lu and Lue, 2012). Furthermore, she scored 67% (20/30) on 10 selected Motor Function Measure items (items 14–23) while seated in her wheelchair for baseline assessment of her upper limb, hand function and coordination (Bérard et al, 2005).

The components of pulmonary function assessment are outlined in *Figure 2*. As pulmonary function testing is recommended as part of the complete assessment of patients with spinal muscular atrophy, spirometry, peak expiratory cough flow and inspiratory muscle strength were performed before prescribing a treatment plan (Eagle, 2002).

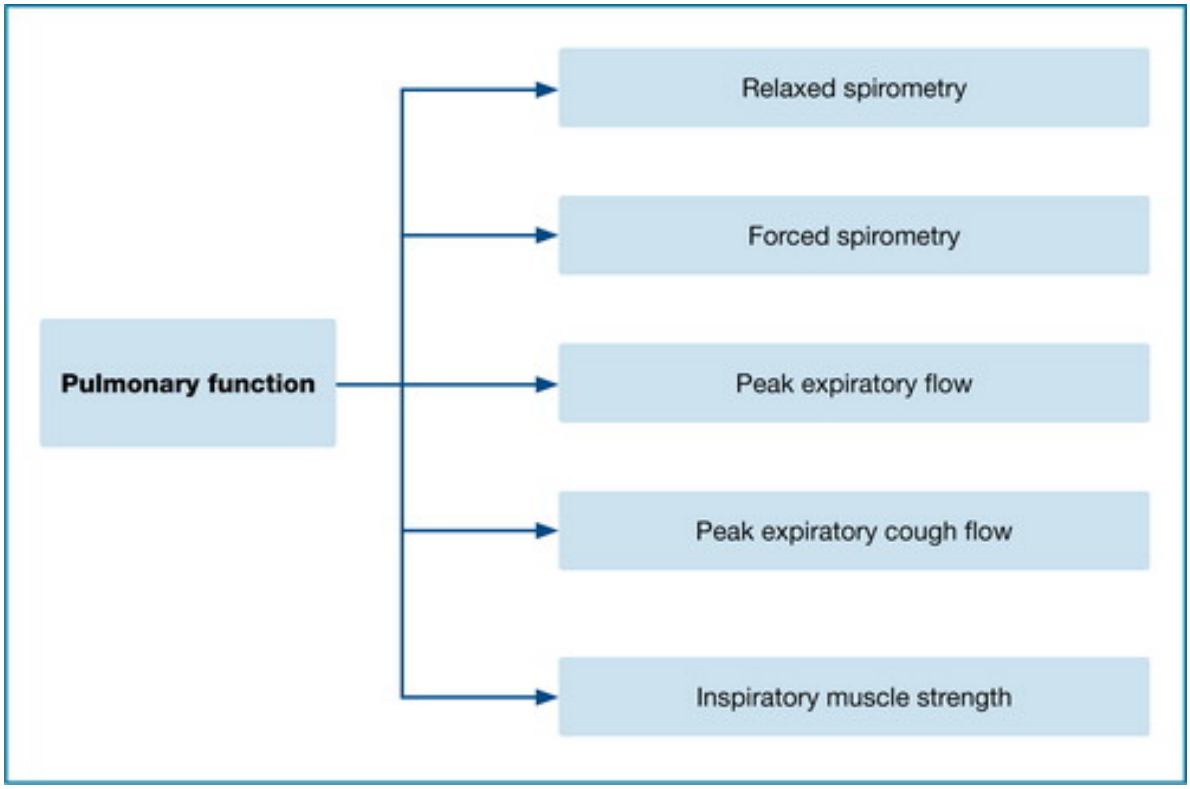

Figure 2. Pulmonary function assessment components

Spontaneous/relaxed and forced spirometry (CareFusion, MicroLoop spirometer, Vyaire Medical, Mettawa, IL) measures were recorded at baseline and after the 6-week intervention. These measures were performed in a sitting position and based on the American Thoracic Society/European Respiratory Society task force guidelines for the standardisation of lung function testing (Miller et al, 2005). An open circuit method, as described by Miller et al (2005), was used for all manoeuvres. The patient was able to maintain good mouth closure with assistance and did not tolerate the nose clip, so a closed circuit manoeuvre with a nose clip to ensure adequate closure and pressure was not used. Although the patient presented with a moderate decrease in oral control, a mouthpiece was used as the interface for all pulmonary function tests. To ensure a complete seal, the researchers manually assisted the patient to obtain adequate lip closure.

During relaxed spirometry the patient was asked to perform a slow vital capacity manoeuvre by breathing out for as long as possible after a full inspiration. Relaxed spirometry measures, such as a slow vital capacity test, might be more appropriate in patients with spinal muscular atrophy as they have difficulty in performing forced spirometry manoeuvres owing to their underlying respiratory muscle weakness (Hull et al, 2012). The patient executed good effort blows, and the British Thoracic Society criteria were met (British Thoracic Society, 1994).

Forced spirometry was performed by asking the patient to exhale as forcefully (hard and fast) as she could after a maximum inhalation. The ‘bubble blowing’ function on the MicroLoop spirometer was used as a visual incentive during forced spirometry. The qualities of the blows were good and the British Thoracic Society criteria were met, but the American

Thoracic Society interpretation indicated severe obstruction (Miller et al, 2005; Nici et al, 2006).

While the spirometry tests were being performed, the researcher observed that the patient presented with a poor sitting posture and made use of accessory muscles of respiration and compensatory mechanisms. After three spirometry attempts, she was short of breath and had to rest for a few minutes before performing the peak expiratory cough flow and inspiratory muscle strength tests.

Unassisted cough ability was determined by means of peak expiratory cough flow, measured in a sitting position with a Mini-Wright AFS Low range peak flow meter (HS Clement Clarke International Ltd; Essex, UK) (*Figure 3*), similar to the technique described by Park et al (2010). These values provided an indication of the patient's disease progression, ability to clear secretions and the risk for developing respiratory complications (Kang and Bach, 2000; Bianchi and Baiardi, 2008). The patient was asked to perform three efforts. The best value was used for analysis, similar to previous studies and as recommended by spirometry guidelines (Wanke et al, 1994; Miller et al, 2005; Park et al, 2010). To minimise variation between the spirometry efforts, three satisfactory efforts were sought with acceptable variation <20% between efforts. The patient's baseline pulmonary function measurements are given in *Table 1*.

Figure 3. Peak expiratory cough flow measurement

Table 1. Pulmonary function at baseline

Pulmonary measurement	Patient values	Percentage predicted
Peak expiratory cough flow, litres/minute	60	–
Peak expiratory flow, litres/minute	76	20
Vital capacity (slow vital capacity), litres	0.45	18
Forced vital capacity, litres	0.45	18
FEV_1, litres/second	0.38	18
FEV_1/forced vital capacity	84	100
Maximal inspiratory pressure, cmH_2O	23	–
Sniff nasal inspiratory pressure, cmH_2O	6	–

FEV_1: forced expiratory volume in one second

Inspiratory muscle strength was measured in the sitting position using an electronic mouth pressure meter (MicroRPM, Vyaire Medical, Mettawa, IL), similar to the technique described by Park et al (2010). The maximal inspiratory mouth pressure was measured after full expiration (residual volume) and performing a maximum inspiratory effort maintained for at least 1 second without a nose clip (Park et al, 2010) (*Figure 4*). Fauroux and Aubertin (2007) agree that a nose clip is not needed when testing maximal inspiratory mouth pressure, but it should be measured with the child seated and maximal inspiratory pressure maintained for an adequate duration, as was the case in this study. The researcher assisted the patient to obtain a good seal when performing the test. To address the possibility that her weak oral control could have influenced the validity of the maximal inspiratory mouth pressure values, sniff nasal inspiratory pressure was also measured. For sniff nasal inspiratory pressure, the right nostril was occluded with a nasal probe (size 1) and a sniff manoeuvre performed at the end of tidal volume (functional residual capacity) with the mouth closed, see *Figure 5*. Although this test is usually easier to perform than the maximal inspiratory mouth pressure, the patient's values were very low (Wanke et al, 1994; Fauroux and Aubertin, 2007).

Figure 4. Maximal pressure at the mouth

Figure 5. Sniff nasal inspiratory pressure

The patient and her mother were asked to complete the Pediatric Quality of Life Inventory (PedsQL Generic Score Scale) form for children between 8 and 12 years of age (patient and proxy), at baseline and post intervention (Iannaccone et al, 2009). The questionnaire consists of four domains: physical, emotional, social and school functioning. The first two

questions under the physical domain were not applicable, as the patient was non-ambulant, therefore the total score was calculated based on 21 items instead of 23.

The omnibus (OMNI) scale (a visual representation of a figure moving up a hill in a wheelchair, *Figure 6*) was implemented before and after each training session, and as a measure of how tired the patient felt on average when performing inspiratory muscle training over every 2-week period. This scale was used to provide subjective, visual feedback on her perceived level of exertion after inspiratory muscle training (Utter et al, 2002). The OMNI scale is an adaption of the Borg scale, which provides subjective information on how tired the child felt in order to avoid overexertion. The scale ranges from 0 to 10, where 0 represents not tired at all and 10 extremely exhausted.

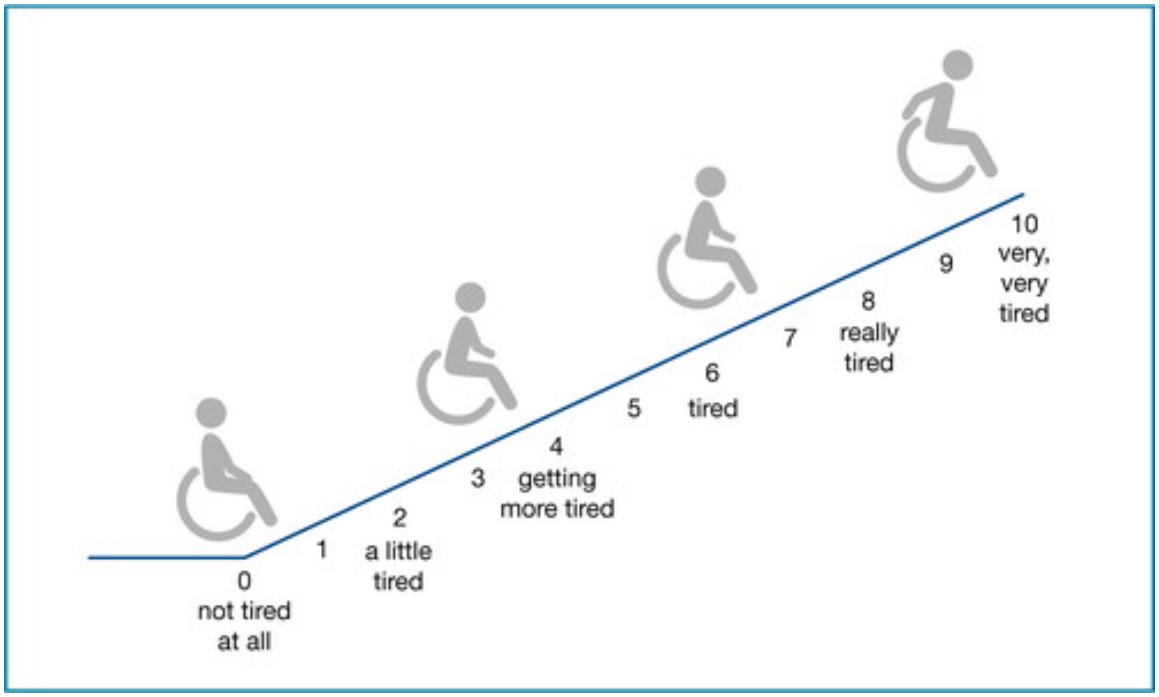

Figure 6. The OMNI scale, which indicates the patient's perceived level of exertion before and after inspiratory muscle training

Intervention

Despite her predicted forced vital capacity of 18% (based on the European Community for Coal and Steel normal values for spirometry (Quanjer et al, 1993) and against commonly accepted but scientifically unsupported recommendations (Wanke et al, 1994; Koessler et al, 2001), the researchers hypothesised that this patient may clinically benefit from inspiratory muscle training, as she had never previously done any respiratory muscle training. Furthermore, she and her mother were eager to attempt inspiratory muscle training.

Inspiratory muscle training was performed with an electronic handheld tapered-flow threshold device (POWERbreathe K3, HaB International Ltd, Southam, UK), see *Figure 7*, which provides visual stimulus and emits an audible beep every time the patient needs to take another breath (pacing). The intensity for training was set at ± 30% of her best maximal

inspiratory mouth pressure value, as the literature (Lötters et al, 2002) and manufacturer guidelines suggest this is the minimum value required for improved clinical effect, and we wished to avoid over-exerting the patient. The baseline training intensity was set at 7 centimetres of water (cmH_2O). She performed three sets of five breaths, with a rest interval of 20 seconds between sets. These sets were performed twice a day, 5 days a week, except during periods of absence from school. Her training sessions were monitored and noted by independent physiotherapists working at the school. The primary investigator and research assistant performed the follow-up assessments. The patient completed 48 inspiratory muscle training sessions in total over the 6-week period.

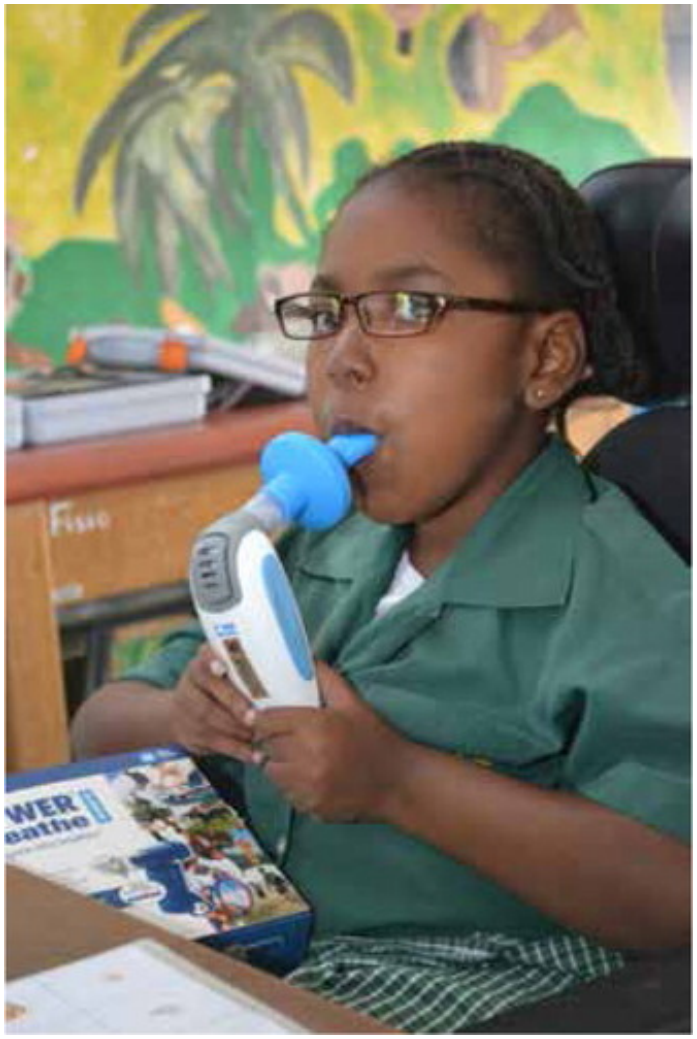

Figure 7. Training with the tapered-flow threshold inspiratory muscle training device.

Although the patient's maximal inspiratory mouth pressure values improved after 2 weeks, the training intensity was not increased to 10 cmH_2O but kept at 7 cmH_2O, as she had difficulty with the quality of breaths and was unable to reach the threshold with every breath. At 4 weeks, the patient reported having had a dry cough for a few days and feeling tired when training (5 on the OMNI scale). For this reason, despite the improvement in maximal inspiratory mouth pressure, the researcher decreased her training intensity to 5 cmH_2O. At this intensity, she could reach the threshold more effectively during her 15 breaths and the effort of breathing was decreased.

Results

The patient showed substantial improvement in inspiratory muscle strength (change of 10 cmH_2O) until week 4. She contracted a lower respiratory tract infection towards the end of week 5. She continued with inspiratory muscle training during this time, but had difficulty with the quality of breaths and reported increased perceived exertion. Post-intervention assessment was conducted after 6 weeks as initially planned, despite her respiratory tract infection and associated shortness of breath.

The patient's spirometry results are presented in *Figure 8*. During relaxed spirometry at 6 weeks, the quality of blows was good but the British Thoracic Society quality criteria were not met. When she performed the forced manoeuvres, the blows were of good quality and British Thoracic Society criteria were met, but the American Thoracic Society interpretation indicated very severe obstruction. There was a slight decrease in vital capacity of 0.04 litre (from 18% to 16% predicted) and forced expiratory volume in one second (FEV_1) decreased by 0.06 litres per second (from 18% to 15% predicted), while forced vital capacity improved by 0.05 litre (from 18% to 20% predicted).

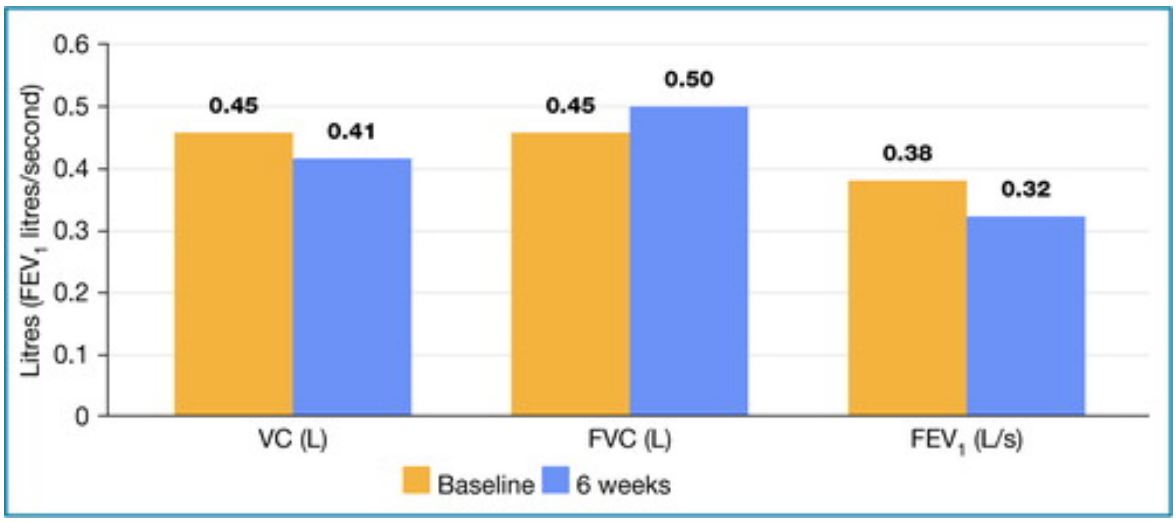

Figure 8. Spirometry measurements pre- and post-intervention

Due to her disease progression she presented with very low baseline values, but her peak expiratory flow was higher than her peak expiratory cough flow (*Figure 9*). She showed a 20 litres/minute decrease in cough ability (peak expiratory cough flow) and 22 litres/minute reduction in peak expiratory flow from baseline.

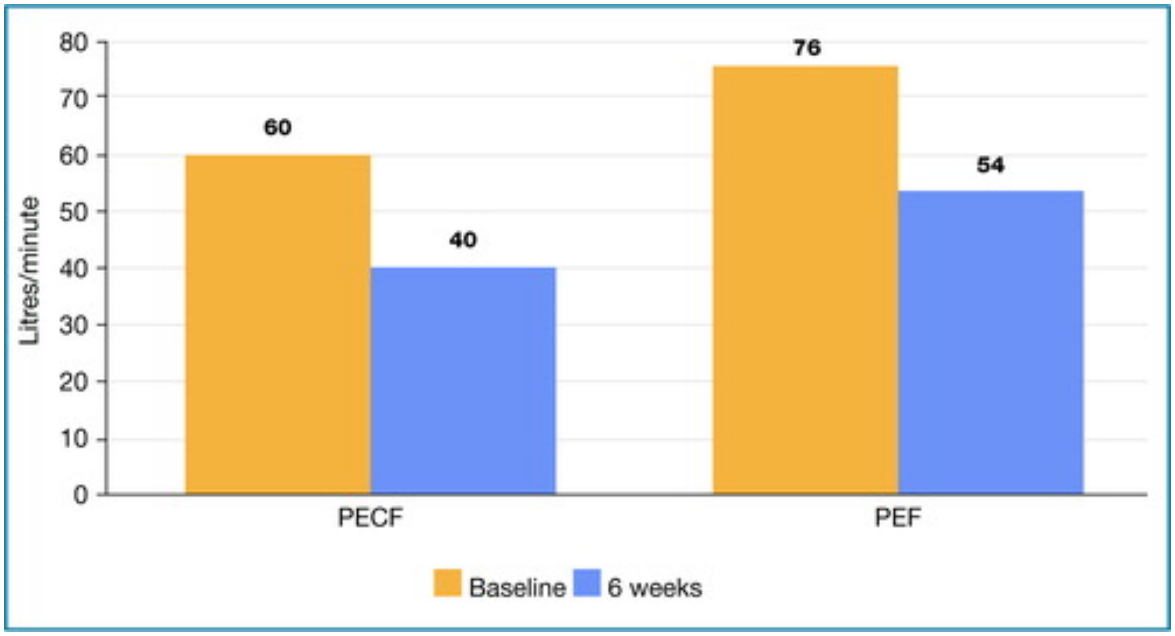

Figure 9. Peak expiratory flows pre- and post-intervention

The maximal inspiratory mouth pressure and sniff nasal inspiratory pressure values during the intervention are depicted in *Figure 10*. Her maximal inspiratory mouth pressure increased by 10 cmH_2O and her sniff nasal inspiratory pressure by 15 cmH_2O in the first 4 weeks, after which there was a major decline in both values. The OMNI scale indicated an increased level of perceived exertion (dyspnoea) from week 2 onwards (from two to seven out of 10 at the end of the intervention).

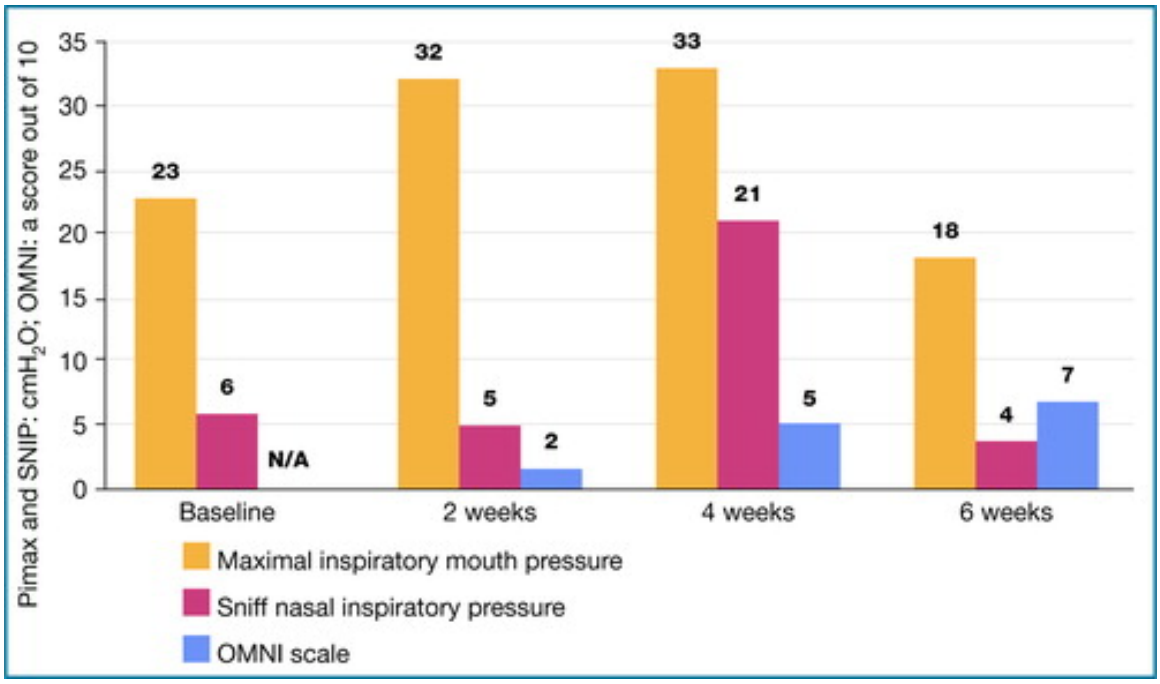

Figure 10. Inspiratory muscle strength and perceived exertion during training

There was no change in functional ability for the upper limbs (Brooke) or lower limbs (Vignos scale) during the study period and just a one-point improvement on the Motor Function Measure (21/30) post intervention.

The patient reported an 8% improvement in her overall health-related quality of life score (69%) at the end of the intervention; this improvement related to reported increases of 10%, 17% and 20% in the school, physical and social function domains, respectively (*Figure 11*). Contrary to the patient's improved total score, the proxy total score as reported by her mother decreased from 73% to 49%, with a 50% reduction in physical function, 30% reduction in emotional function and 15% reduction in the social function. In line with the patient, her mother indicated a perceived improvement (5%) in the school function domain.

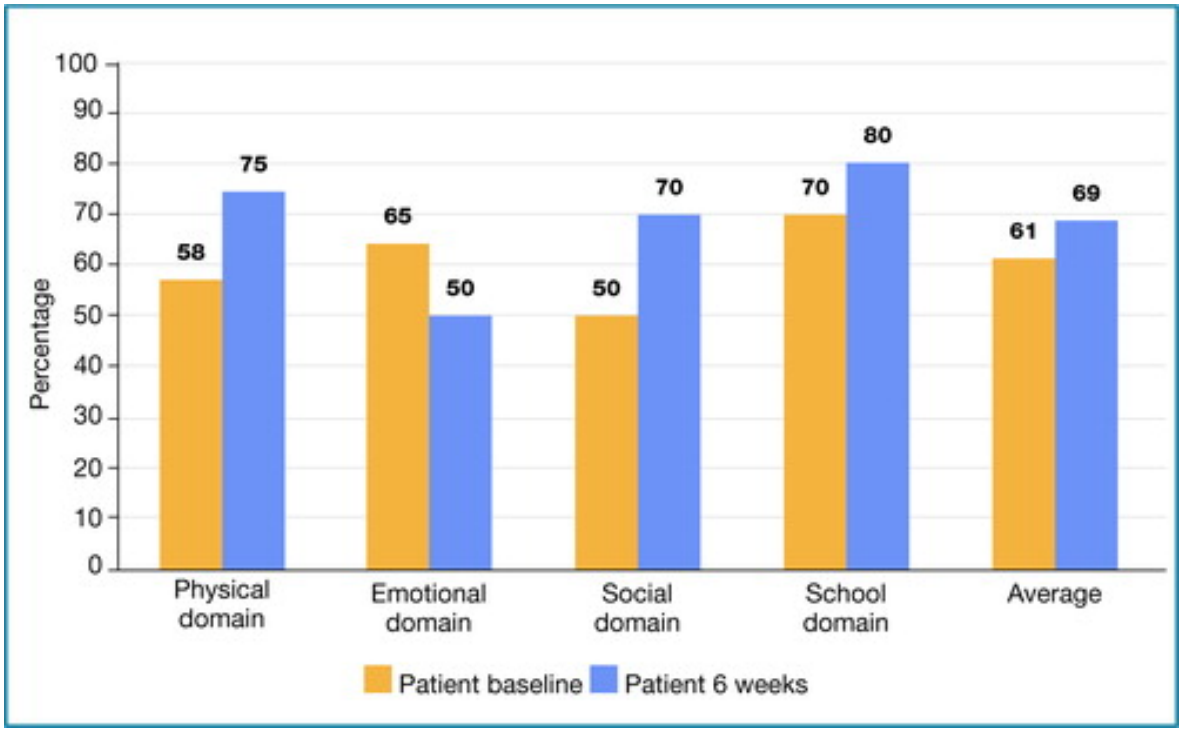

Figure 11. Self-reported health-related quality of life scores pre- and post-intervention

Overall patient satisfaction with the use of inspiratory muscle training was high; she rated her satisfaction as 9/10 on a visual analogue scale. She indicated that she would like to continue with the use of inspiratory muscle training as 'it helps me to breathe better during the day'. No adverse events related to the intervention were reported.

DISCUSSION

In this case report, a child with spinal muscular atrophy type 2 and severe pulmonary restriction presented with improved inspiratory muscle strength and patient-reported health-related quality of life following a 6-week inspiratory muscle training programme using a tapered-flow device set at low intensity. Spirometry showed minimal decline over the inspiratory muscle training period, while her upper limb function and coordination improved slightly. Patient satisfaction with the intervention was high.

Spirometry and peak expiratory cough flow

Lung volumes, including forced vital capacity and FEV_1, are significantly lower in children with neuromuscular diseases compared to typically healthy children (P<0.01) (Anderson et al, 2012). This patient's forced vital capacity (0.45–0.5 litre), FEV_1 (0.32–0.38 litres per second) and FEV_1/forced vital capacity ranged from 84–100% of the predicted values (the proportion was 71–84), which were similar to those reported in children with neuromuscular diseases (including spinal muscular atrophy), namely 0.7 ± 0.5 litre; 0.5 ± 0.4 litres per second and 76.4 ± 23.6%, respectively (Chatwin et al, 2003).

The case patient's pulmonary function, based on inspiratory muscle strength, improved notably during the first 4 weeks of inspiratory muscle training, after which she developed a lower respiratory tract infection. Despite the acute infection, her forced vital capacity remained higher than baseline after 6 weeks, although other measures such as vital capacity, FEV_1 and peak expiratory flow declined. This is interesting, as a significant positive correlation has been demonstrated between sniff nasal inspiratory pressure and forced vital capacity (r=0.46; P=0.02) as well as sniff nasal inspiratory pressure and FEV_1 (r=0.55; P=0.01) in children with neuromuscular diseases (Anderson et al, 2012). The improvement in inspiratory muscle strength (sniff nasal inspiratory pressure) could result in improvement in forced vital capacity, while the presence of obstructive secretions and expiratory muscle weakness can lead to a lower FEV_1. The improved forced vital capacity in this case study could also be attributed to improved sitting posture, improved performance (coordination) of breathing manoeuvres and increased chest and lung compliance.

Similar results, with improvement in forced vital capacity after resistive respiratory muscle training, have been reported in patients with motor neuron disease, myoneural junction and progressive muscular disease (Gross and Meiner, 1993). This is in contrast with other studies on respiratory muscle training in neuromuscular diseases that report changes in respiratory muscle strength and/or endurance with unchanged lung volumes (DiMarco et al, 1985; Vilozni et al, 1994; Winkler et al, 2000). Most studies included in a systematic review on inspiratory muscle training in children and adolescents with neuromuscular diseases reported no statistically significant differences in pulmonary function tests, such as vital capacity, FEV_1, forced vital capacity, functional residual capacity and total lung capacity, between experimental (respiratory muscle training) and control groups (Human et al, 2017). None of the studies reported in the British Thoracic Society guideline on respiratory management in children with neuromuscular weakness reported an improvement in lung volumes associated with respiratory muscle training (Hull et al, 2012). Because of the sigmoid shape of the pressure–volume curve, it would be expected that a patient with decreased vital capacity, despite an increase in maximal inspiratory mouth pressure, will not show a change in lung volume. Once vital capacity and respiratory muscle strength are below the 50% predicted value, the patient is at risk of hypoventilation, even during a minor respiratory tract infection (Bianchi and Baiardi, 2008), as seen in our patient. It is possible that the long-term effect of respiratory muscle training might not be sufficient to counterbalance the natural decline of pulmonary function in patients with neuromuscular diseases.

At baseline the case patient's peak expiratory flow was higher than her peak expiratory cough flow values. A possible explanation for this phenomenon could be that peak expiratory cough flow requires glottis closure and good oral control, and this patient presented with moderately decreased oral control; therefore the performance of peak expiratory flow (54–76 litres/minute) could have been easier than peak expiratory cough flow. Her peak expiratory flow values pre- and post-intervention were below normative values reported for girls between the ages of 4 to 18 (80–576 litres/minute) (Bianchi and Baiardi, 2008). Due to bulbar involvement, many patients with neuromuscular diseases have difficulty with glottis closure, which can increase the risk of aspiration, retention of secretions and pulmonary morbidity (Wang et al, 2007; Bianchi and Baiardi, 2008). Normative values for peak expiratory cough flow in children and adolescents with neuromuscular diseases are limited. A study conducted by Bianchi and Baiardi (2008) in 649 normal children reported a normative median peak expiratory cough flow range of 147–488 litres/minute for girls aged 4–18 years. The patient's peak expiratory cough flow values (40–60 litres/minute) were much lower than expected for girls her age, and even lower than the unassisted cough of children and adults with neuromuscular diseases (including spinal muscular atrophy), of 169 litres/minute (range: 129–209 litres/minute) (Chatwin et al, 2003). When patients with neuromuscular diseases present with peak expiratory cough flow <270 litres/minute, cough augmentation techniques are recommended to assist with airway clearance as patients are at a high risk of respiratory failure during superadded respiratory tract infections, which are associated with further declines in peak expiratory cough flow (Bach et al, 1997).

Inspiratory muscle strength

Besides peak expiratory cough flow, respiratory muscle strength is an important part of the clinical assessment of patients with neuromuscular diseases (Gozal, 2000). Inspiratory muscle training in neuromuscular diseases remains controversial due to contradictory findings in the literature and concern about potential muscle damage, especially in the dystrophinopathies (Vilozni et al, 1994; Wanke et al, 1994; Winkler et al, 2000; Koessler et al, 2001; Eagle, 2002). In patients with Duchenne muscular dystrophy (DMD) and spinal muscular atrophy presenting with progressed disease, namely vital capacity <25% predicted value or $PaCO_2$ >45 mmHg, no benefit with inspiratory muscle training has been reported (Wanke et al, 1994; Koessler et al, 2001). It has therefore been suggested that greater benefit might be seen with inspiratory muscle training in slowly progressive disease with lung volume preservation (Winkler et al, 2000; Eagle, 2002). Patients with severe disease progression not only have decreased respiratory muscle capacity but also decreased chest wall and lung compliance (Kang and Bach, 2000; Winkler et al, 2000; Bianchi and Baiardi, 2008), causing the already weakened respiratory muscles to work beyond their capacity. In spite of these suggestions, in this case study we noted marked increases in maximal inspiratory mouth pressure and sniff nasal inspiratory pressure following the inspiratory muscle training programme, especially over the first 4 weeks of intervention.

It could be argued that the initial improvement in maximal inspiratory mouth pressure and sniff nasal inspiratory pressure was the result of a ‘learning effect’ (Eagle, 2002) due to improved respiratory muscle action coordination when training with a threshold device (Estrup et al, 1986; Winkler et al, 2000; Tomalak et al, 2002). Inspiratory muscle training

manoeuvres as well as maximal inspiratory mouth pressure measurements were performed at residual volume, which might explain an improvement in maximal inspiratory mouth pressure values. Sniff nasal inspiratory pressure measurements, however, were assessed at functional residual capacity and not at residual volume. In addition, the improvements in inspiratory muscle strength continued between weeks 2 and 4 (especially sniff nasal inspiratory pressure), suggesting possible true inspiratory muscle strength improvement. These findings are similar to an 8-week study that reported a significant improvement in inspiratory (maximal inspiratory mouth pressure and sniff nasal inspiratory pressure) and expiratory (maximal expiratory pressure) muscle strength in adults with slowly progressive neuromuscular diseases who performed inspiratory and expiratory muscle training (Aslan et al, 2013). A study among children with DMD and spinal muscular atrophy type 3 patients concurred: a 6-month respiratory training programme was associated with a significant improvement in inspiratory (P<0.02) and expiratory muscle strength (P<0.004) compared to the control group (Gozal and Thiriet, 1999).

Although children tend to generate lower pressures with maximal inspiratory mouth pressure and sniff nasal inspiratory pressure than adolescents and adults (Tomalak et al, 2002), and children with neuromuscular diseases present with lower values than their peers (Anderson et al, 2012), this patient's maximal inspiratory mouth pressure values were far below normative values for 10-year-old girls (71±29 cmH_2O) (Fauroux and Aubertin, 2007), even after 4 weeks of intervention. Her maximal inspiratory mouth pressure values were similar to previous reports in patients with DMD and amyotrophic lateral sclerosis (64.5±24.7 cmH_2O) (Suárez et al, 2002); children, adolescents and adults with a variety of neuromuscular diseases (50±26 cmH_2O) (Stefanutti et al, 2000); and children with neuromuscular diseases (including spinal muscular atrophy) (22.7±14.3 cmH_2O) (Chatwin et al, 2003). Similarly, this patient's sniff nasal inspiratory pressure values (4–21 cmH_2O) were much lower than the normal mean values in healthy girls (93 ± 23 cmH_2O) (Maillard et al, 1998; Fauroux and Aubertin, 2007); in children, adolescents and adults with neuromuscular diseases (56 ± 26 cmH_2O) (Stefanutti et al, 2000); and in children with general neuromuscular diseases (including spinal muscular atrophy) (43.6 ± 26 cmH_2O (24.8±9.5)) (Chatwin et al, 2003; Anderson et al, 2012). Low sniff nasal inspiratory pressure values can be attributed to severe ventilatory restriction caused by respiratory muscle weakness and atrophy (Fauroux and Aubertin, 2007) as well as fibrotic changes and tightness of the lungs and chest wall (Gozal, 2000). The clinical relevance of sniff nasal inspiratory pressure values can unfortunately also be limited if the patient already presents with severe respiratory muscle weakness, as with this patient (maximal inspiratory mouth pressure 18–33 cmH_2O; forced vital capacity 18–20% predicted). Alternative measures of diaphragmatic strength, such as magnetic phrenic nerve stimulation, transdiaphragmatic pressures and non-volitional tests such as twitch mouth pressure, could be considered in future studies (Winkler et al, 2000; Hull et al, 2012).

As acute respiratory infection can affect a patient's respiratory muscle strength, lung volumes and cough ability, it is likely that the deterioration in inspiratory muscle strength values seen at 6 weeks were related to the child's intercurrent pulmonary infection. However, it is suggested that future controlled studies consider the potential effect of inspiratory muscle training on respiratory exacerbations, in order to ascertain safety of the intervention.

Function, health-related quality of life and adverse events

There was no change in the patient's level of mobility, lower or upper limb function, and a slight improvement in her upper limb coordination. This lack of change was expected, as the duration of intervention was only 6 weeks. The slight improvement in upper limb coordination could be attributed to improved sitting posture in the wheelchair, as the patient was reminded of her posture while training, or to increased proximal stability due to stronger inspiratory muscles (especially the diaphragm), which stabilise the trunk.

Very limited evidence is available regarding the effect of exercise and/or respiratory muscle training on functional ability and health-related quality of life in patients with neuromuscular diseases (Vilozni et al, 1994; Eagle, 2002). In this case there were contradictory results for the PedsQL child report and proxy version. Such discrepancies have previously been reported (Varni et al, 2002; Hull et al, 2012). The patient's decreased emotional domain score reflected the sad and angry feelings she sometimes experienced over the 6 weeks before reassessment. This change in emotional wellbeing could have been a consequence of the acute respiratory infection, which caused difficulty in breathing at night as well as feelings of anxiety. Other than this, the patient reported an improved overall health-related quality of life, which could be related to social interaction with the other children participating in the inspiratory muscle training programme. Furthermore, she reported that inspiratory muscle training made her 'breathe better', which could contribute to improved feelings of wellbeing. It is thought that the major decrease in the proxy score is related to the mother's anxiety about her child's respiratory infection and troubled breathing at night. Early proactive respiratory management, including cough augmentation, may reduce pulmonary complications and improve patient and caregiver health-related quality of life (Ioos et al, 2004; Wang et al, 2007).

No adverse events related to inspiratory muscle training were reported during this study. However, the patient's average perceived exertion increased between week 4 and week 6. This could be attributed to the acute respiratory infection, as the intensity of training was kept at lower levels (<30% maximal inspiratory mouth pressure) to improve the quality of breaths while she was training with the device, not breathing in general. Furthermore, to prevent overexertion, the patient was provided with a rest interval of 20 seconds after each set of five breaths. No adverse effects were reported by a review conducted to determine the effect of inspiratory muscle training on patients with neuromuscular diseases (McCool and Tzelepis, 1995) or an inspiratory muscle training study conducted among patients with DMD (Wanke et al, 1994). Similar to our patient's case, patients with severe disease progression (based on their vital capacity) did not present with any adverse events on lung function parameters due to inspiratory muscle training (Winkler et al, 2000).

Strengths and recommendations

The use of inspiratory muscle strength measures such as maximal inspiratory mouth pressure and sniff nasal inspiratory pressure seem to be feasible, simple and accurate, even in children with advanced neuromuscular diseases and severe pulmonary restriction. Forced vital capacity and maximal inspiratory mouth pressure are measures of pulmonary function that correlate with nocturnal hypoventilation, but performing these volitional tests might be

difficult for children with neuromuscular diseases (Fauroux et al, 2009). Therefore studies could consider including other pulmonary function tests, such as total lung capacity, total lung capacity/residual volume and maximal expiratory pressure, as well as indicators of respiratory muscle fatigue and endurance, such as tension time index and diaphragmatic strength measured by magnetic stimulation of the phrenic nerves. Although phrenic nerve stimulation is non-volitional, it remains invasive (Fauroux et al, 2009), which might not be ideal for children. Instead, the non-invasive tension time index of the respiratory muscles (TTmus) could be used (Mulreany et al, 2003). The value of tension time indices in the neuromuscular disease population is that it can assist in decision making regarding ventilatory support, as it indicates nocturnal and diurnal hypoventilation and can also be a predictor of extubation outcomes (within an acute setting) (Mulreany et al, 2003; Stehling et al, 2016). Face mask interfaces should be considered as standard practice when measuring peak expiratory cough flow in children with and without oral control, as recently recommended for patients with neuromuscular diseases (Chatwin et al, 2018).

Additional interventions for cough augmentation, such as assisted inspiration/insufflation (including single breath, air-stacking and glossopharyngeal breathing) – which are effective in improving chest wall and lung compliance, maintaining lung volumes and improving peak expiratory cough flow in children with neuromuscular diseases – should be included in the management of patients with neuromuscular diseases (Kang and Bach, 2000; Marques et al, 2014; Chatwin et al, 2018). The school the patient was attending did not have access to bagging kits to assist with lung volume recruitment (insufflation), and therapists lacked training and experience in other cough augmentation techniques. Following this and related on-going studies (unpublished), recommendations will be made to the Departments of Health and Education to supply bag-insufflation kits to special-needs schools in the region and school physiotherapists will receive training to improve their knowledge and skills in the respiratory management of children with neuromuscular diseases. Furthermore, it will be recommended that patients with neuromuscular diseases receive regular monitoring of pulmonary function, including peak expiratory cough flow, so physiotherapists can implement early proactive respiratory management strategies.

Limitations

This single case study suggested potential benefit of inspiratory muscle training in a child with advanced spinal muscular atrophy type 2, but the results cannot be generalised to other patients or contexts and causality cannot be determined on the basis of this study design. Further appropriately-powered research is recommended to confirm these findings. The long-term effect of inspiratory muscle training on morbidity and health-related quality of life should also be investigated.

Another limitation of this case study was that the assessors were not blinded to the intervention and outcomes; and some spirometric values, such as total lung capacity, could not be measured due to resource limitations. Maximal expiratory pressure was not assessed, as the intervention was specific in training inspiratory muscles, but could be considered as an additional outcome measure for future research.

CONCLUSIONS

The implementation of a 6-week inspiratory muscle training programme in a child with advanced spinal muscular atrophy and severe respiratory muscle weakness resulted in observed improvement in inspiratory muscle strength and self-reported health-related quality of life. The patient developed a lower respiratory tract infection towards the end of the intervention period, but it is unclear whether this was related to the intervention. No other adverse events were reported, and patient satisfaction with inspiratory muscle training was very high. On the basis of this case report, it is recommended that longer-term, sufficiently powered, randomised controlled trials be conducted to determine the safety and efficacy of inspiratory muscle training in children with advanced spinal muscular atrophy and severe respiratory muscle weakness in order to inform clinical practice.

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Notes

Anri Human is also a PhD Student at the University of Cape Town, Cape Town, South Africa. Engela Honey is also a Paediatrician at the Dr George Mukhari Academic and Steve Biko Academic Hospitals, South Africa.

Conflict of interest

The authors declare no conflict of interest.

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