Inspiratory muscle training in a child with nemaline myopathy and organ transplantation

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Objective: To report the use of inspiratory muscle strength training to treat repeated ventilatory insufficiency in a child with nemaline myopathy who underwent cardiac and renal transplantation.

Design: Case report.

Setting: Pediatric intensive care unit of a tertiary care university teaching hospital.

Patient: A 16-yr-old female with nemaline myopathy affecting cardiorespiratory function, recent organ transplantation, and delayed postoperative ventilatory recovery.

Intervention: Inspiratory muscle strength training was provided 5 days weekly for 2 wks, accompanied by progressive weaning from noninvasive ventilation.

Nemaline myopathy (NM) is a congenital muscular disease characterized by cytosolic accumulation of thin-filament protein aggregates, resulting in the appearance of electron-dense rods in affected sarcomeres (1). Thin-filament myopathies, such as NM, have been associated with impaired myofiber regeneration, disrupted calcium homeostasis, and altered contraction speed (2, 3). Clinically, symptoms of NM include stable or slowly progressive weakness of the facial, respiratory, and proximal appendicular muscles (3). The type of genetic variation does not reliably predict disease course (4). Disease presentation may vary from a severe congenital form, marked by lack of spontaneous movement, respiratory failure, and early mortality to adult-onset disease, with comparatively mild proximal and respiratory weakness (5).

In patients with NM, respiratory muscle weakness can lead to symptoms, including impaired central respiratory drive leading to sleep apnea (6), pulmonary restriction due to chest wall defects, progressive scoliosis, and inspiratory muscle weakness, or a combination of deficits (5). Greater numbers of nemaline rods in the diaphragm and accessory respiratory muscles have been reported in patients with ventilatory insufficiency (4). Progressive ventilatory insufficiency has been associated with early mortality (5). Despite the presence of histologic and functional adaptations of respiratory muscle in NM, specific inspiratory strength training strategies have not been previously reported.

The purpose of this case report is to illustrate the use of inspiratory muscle strength training (IMST) to increase inspiratory performance in an adolescent with NM affecting cardiorespiratory function, recent organ transplantation, and delayed postoperative ventilatory recovery. We present this case as evidence that children with NM may be able to improve inspiratory performance with moderate-intensity training.

CASE REPORT

The patient was a 16-yr-old female diagnosed with NM as a young child, with moderate impairment of respiratory, trunk, and proximal extremity muscle strength. Before organ transplantation, the child was ambulatory throughout the community. In addition to NM, her medical history included end-stage dilated cardiomyopathy, severe restrictive lung disease, secondary to focal segmental glomerulosclerosis. She required hemodialysis for 2 yrs before transplantation. The girl was admitted to the hospital for orthotopic heart transplantation and concurrent cadaveric renal transplantation. The postoperative clinical course was remarkable for acute tubular necrosis of the donor kidney necessitating temporary renal replacement therapy, and recurrent episodes of ventilatory failure. Although the patient was extubated on postoperative day (POD) 1, she required use of continuous BiPAP ventilation to maintain ventilatory homeostasis. Her initial physical therapy evaluation on POD 2 revealed moderate generalized weakness. The patient devel-
oped recurrent ventilatory failure and required intubation during the first 2 postoperative weeks. Arterial blood gas analyses revealed repeated episodes of respiratory acidosis, and she required mechanical ventilation for 8 of the first 17 postoperative days. Ventilator weaning was accomplished through gradual reduction of rate and pressure support. By POD 18, she was extubated but needed continuous intensive care unit monitoring and used BiPAP ventilation 24 hrs per day. At this time, she was referred for IMST.

It was determined that the patient would be a good candidate for IMST because she experienced repeated hypercapnic respiratory failure (resting arterial blood gases: pH 7.37; PaCO2, 57 torr [70 kPa], PaO2, 85 torr [112 kPa], SaO2, 99%; HCO3−, 33 mEq/L), accompanied by a decline from her baseline respiratory function. In addition, she took immunosuppressant medications that may alter striated muscle performance, including 20 mg of prednisone (7) and 6 mg of tacrolimus daily. The patient and her parents consented to our assessment and intervention, and initial consultation occurred on POD 20. At this academic medical center, Institutional Review Board approval was not required for case reports.

The following measures were recorded: maximal inspiratory pressure (MIP), respiratory parameters at rest and with extrinsic loads, and rate of pressure development at standard inspiratory threshold loads (5 cm H2O, 10 cm H2O, and 15 cm H2O). Respiratory testing was conducted with a respiratory monitor (COP2SMO Plus, Novametrix, Murrysville, PA) connected to a digital pressure manometer (Sper Scientific, Scottsdale, AZ). The subject could tolerate and consistently open, according to the following guidelines: the patient could generate an inspiratory volume >50% of her unloaded resting inspirations; vital signs were stable with perceived exertion <7 on the modified Borg 10-point scale (11); and valve opening occurred in 100% of threshold breaths.

During the IMST, the load on the training device increased from 7 cm H2O on the first training day (19% of MIP) to 18 cm H2O on day 15 (23% of MIP). The patient demonstrated consistent weekly gains in MIP. After 1 wk, MIP increased from −36.7 cm H2O to −61.1 cm H2O (66% increase). By the end of wk 2, MIP improved to −77.8 cm H2O (112% increase from baseline). Functionally, the patient progressed from 1 hr of unassisted ventilation before training to 11–13 hrs daily, and she used BiPAP ventilation only when asleep (Fig. 2).

Ventilatory parameters improved during maximal-effort, threshold-loaded breathing (Table 1). Initially, the patient was able to complete the inspiratory performance tests at each load. However, PIF, VT, and Pact decreased progressively at the higher loads, accompanied by a prolonged inspiratory time and shortened expiratory time. After training, both inspiratory time and expiratory time de-

Figure 1. Image of the inspiratory muscle strength training apparatus used to administer training and test muscle performance during standardized breathing loads.

In addition to MIP, we evaluated inspiratory performance during maximal-effort breathing against standardized inspiratory threshold loads (5 cm H2O, 10 cm H2O, and 15 cm H2O). At each threshold load, an average value was obtained for the following ventilatory parameters: inspiratory tidal volume (VT), peak inspiratory flow (PIF), inspiratory and expiratory times, and the peak inspiratory pressure achieved during the threshold breaths. The imposed work of breathing (VT × peak inspiratory pressure) and imposed power of breathing (POBi) (VT × peak inspiratory pressure/inspiratory time) were calculated to quantify the work and power of breathing produced by the inspiratory pump in response to the loaded breaths. In addition, inspiratory pressure activation (Pact) was assessed during the loaded breaths, defined as the negative pressure generated 100 msecs into the inspiratory effort. Pact reflected the patient’s ability to generate pressure quickly against the graded threshold loads. The Pact was used to reflect the ability of the inspiratory muscles to dynamically generate pressure during a concentric contraction and, thus, was not considered to be equivalent to the static occlusion pressure (P0.1) used to estimate neural drive. Finally, we recorded the number of hours of BiPAP used daily, arterial blood gases when available, and experienced exertion and vital signs during training.

The patient completed IMST 5 days per week for 2 wks. IMST was conducted, using a Threshold PEP trainer (HS735, Phillips Respironics). The opening of the Threshold PEP device contained a poppet valve occluded by a spring, and the spring tension was adjusted to modify the pressure required to open the valve. The PEP device was inverted to deliver inspiratory threshold training loads (Fig. 1). The patient completed four sets of 10 threshold-loaded breaths per training session, and rested for 2 mins between exercise sets. The intensity of the training device was set at the highest inspiratory load that the subject could tolerate and consistently open, according to the following guidelines: the patient could generate an inspiratory volume >50% of her unloaded resting inspirations; vital signs were stable with perceived exertion <7 on the modified Borg 10-point scale (11); and valve opening occurred in 100% of threshold breaths.

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increased during threshold-loaded breaths, accompanied by increased VT [scap] and PIF. The largest training-induced gains occurred in measures of muscle power: PIF, POBi, and P_act. Because threshold devices provide consistent pressure loads that are independent of inspiratory flow under most conditions (12), it was not surprising that the threshold breaths measured during the loaded breaths did not increase appreciably after training.

In addition to IMST, the patient received routine physical therapy 3 days per week while hospitalized, with an emphasis on upright mobilization and walking endurance. The patient’s functional mobility improved during the hospitalization. On POD 20 (IMT day 1), she was able to transfer to a chair with minimal assistance and sit upright for 1 hr. On POD 28 (IMT 9), she could walk approximately 1000 feet at a self-selected pace. The strength of 12 extremity muscle groups was scored bimonthly by clinical therapists, using the Medical Research Council (MRC) (Table 2) 6-point ordinal scale (13). The MRC sum score can be completed at the bedside, and benefits include rapidity of testing and low within-subject variance (14). Prior reports (13, 15) suggested that a score of < 48 of 60 indicates clinically significant weakness. The patient’s MRC sum score was 46 of 60 on POD 2 and the score remained unchanged at the time of the monthly therapy reassessment (POD 32).

The girl’s medical condition was upgraded on POD 31 (IMST day 12), and she was transferred from intensive care to a regular pediatric nursing unit. By POD 34 (IMST day 15), the patient reached her preoperative ventilatory function and demonstrated MIP within an expected age and gender-predicted range (10). IMST was discontinued at that time. Six days later, she was discharged to home.

**DISCUSSION**

This report describes the effect of IMST on inspiratory strength and function in a 16-yr-old girl with NM and persistent postoperative ventilatory insufficiency. After 2 wks of IMST, the patient made significant gains in inspiratory performance, accompanied by improvements in resting ventilation. Gains in strength seemed to be most evident in the inspiratory muscles. A robust recovery of gender- and age-predicted MIP indicated that IMST increased the perfor-

**Table 2.** The Medical Research Council sum score provides a noninvasive estimate of generalized extremity muscle strength that can be used in bed-bound, critically ill patients.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Muscle State</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No contraction</td>
</tr>
<tr>
<td>1</td>
<td>Flicker or trace contraction</td>
</tr>
<tr>
<td>2</td>
<td>Active movement with gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>Active movement against gravity</td>
</tr>
<tr>
<td>4</td>
<td>Active movement against gravity and some resistance</td>
</tr>
<tr>
<td>5</td>
<td>Normal muscle power</td>
</tr>
</tbody>
</table>

Testers rate the strength of shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion in all extremities, using standard testing positions. Each plane of movement receives a 0- to 5-point ordinal score, for a total possible sum score of 60.

**Table 1.** Average ventilatory parameters achieved during maximal-effort threshold-loaded breathing at standardized loads, before and after inspiratory muscle strength training.

<table>
<thead>
<tr>
<th>Threshold Breathing Parameters</th>
<th>5 cm H2O Load-Baseline</th>
<th>5 cm H2O Load-wk 2</th>
<th>% Change</th>
<th>10 cm H2O Load-Baseline</th>
<th>10 cm H2O Load-wk 2</th>
<th>% Change</th>
<th>15 cm H2O Load-Baseline</th>
<th>15 cm H2O Load-wk 2</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIF (L/min)</td>
<td>46.83</td>
<td>93.77</td>
<td>100</td>
<td>40.90</td>
<td>82.45</td>
<td>102</td>
<td>22.68</td>
<td>60.83</td>
<td>168</td>
</tr>
<tr>
<td>TI (sec)</td>
<td>0.88</td>
<td>0.73</td>
<td>-17</td>
<td>1.03</td>
<td>0.67</td>
<td>-35</td>
<td>1.48</td>
<td>0.63</td>
<td>-57</td>
</tr>
<tr>
<td>TE (sec)</td>
<td>0.98</td>
<td>0.65</td>
<td>-34</td>
<td>0.68</td>
<td>0.52</td>
<td>-24</td>
<td>0.58</td>
<td>0.35</td>
<td>-40</td>
</tr>
<tr>
<td>VT (mL)</td>
<td>356</td>
<td>582</td>
<td>63</td>
<td>288</td>
<td>484</td>
<td>68</td>
<td>213</td>
<td>325</td>
<td>53</td>
</tr>
<tr>
<td>PI (cm H2O)</td>
<td>-5.62</td>
<td>-7.53</td>
<td>34</td>
<td>-10.78</td>
<td>-13.87</td>
<td>29</td>
<td>-15.75</td>
<td>-17.18</td>
<td>9</td>
</tr>
<tr>
<td>P_act (cm H2O)</td>
<td>-2.50</td>
<td>-4.63</td>
<td>85</td>
<td>-2.25</td>
<td>-8.45</td>
<td>276</td>
<td>-1.28</td>
<td>-13.56</td>
<td>959</td>
</tr>
<tr>
<td>WOBi (J)</td>
<td>0.20</td>
<td>0.43</td>
<td>115</td>
<td>0.30</td>
<td>0.66</td>
<td>120</td>
<td>0.33</td>
<td>0.55</td>
<td>67</td>
</tr>
<tr>
<td>POBi (W)</td>
<td>0.22</td>
<td>0.59</td>
<td>168</td>
<td>0.30</td>
<td>1.00</td>
<td>233</td>
<td>0.23</td>
<td>0.87</td>
<td>278</td>
</tr>
</tbody>
</table>

PIF, peak inspiratory flow; TI, inspiratory time; TE, expiratory time; VT, tidal volume; PI, peak inspiratory pressure; P_act, inspiratory pressure activation; WOBi, imposed work of breathing; POBi, imposed power of breathing.

After 2 wks of training, the child generated large gains in tidal volume, peak inspiratory flow, imposed work of breathing, imposed power of breathing, and inspiratory pressure activation.

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mance of the inspiratory muscles. Functionally, the patient was able to meet her ventilatory requirements with a reduced perception of respiratory effort. During our initial examination, her perceived exertion was 5 of 10 after 1 hr of unassisted ventilation. Upon completion of IMST, she reported no detectable exertion with tidal breathing on room air. Consequently, she regained her preoperative baseline function and used BiPAP ventilation only when asleep.

Although IMST conferred specific respiratory performance benefits, we cannot state whether it facilitated improvements in generalized strength or mobility. We report that walking distance increased during the hospitalization without an apparent change in lower extremity strength. Although the patient’s extremity strength scores did not change appreciably, the sensitivity of the MRC scale decreases at higher scores (13). Thus, the MRC sum score may not have detected clinically meaningful limb strength changes. On the other hand, walking tolerance remained below normal, suggesting persistent lower extremity deconditioning. Due to vigorous increases in respiratory performance, it is doubtful that inspiratory weakness impeded the reported gains in walking distance.

The function of related organ systems has been shown to affect respiratory muscle strength, namely, cardiac (16) and renal (17) function. On POD 2, an echocardiogram revealed that the girl’s ejection fraction was 62%. Cardiac biopsy on POD 28 (IMST day 9) confirmed an absence of organ rejection. The child received temporary renal replacement therapy when a biopsy on POD 3 indicated acute tubular necrosis. A repeat biopsy on POD 15 showed improvement of renal function and no evidence of rejection. The patient did not undergo daily weights, but daily fluid intake and output was recorded. During wk 1 of IMST, her average daily fluid balance was +175 mL, and the daily fluid balance averaged +204 mL during wk 2 of IMST. Furthermore, her blood urea nitrogen and creatinine were stable. Daily blood urea nitrogen was 28 mg/dL on IMST day 1 and 32 mg/dL on IMST day 15; creatinine was 1.46 mg/dL on IMST day 1 and 0.92 mg/dL on IMST day 15. Therefore, we concluded that changes in the patient’s cardiac or renal function were unlikely to have significantly influenced the respiratory performance gains observed during the training period. In addition, liver function tests did not change appreciably from preoperative values and remained largely within normal limits during the IMST period. At a routine follow-up, the patient’s restrictive pulmonary disease had increased marginally 2 months after transplant (FEV1 36% predicted, FVC 33% predicted).

The child achieved the greatest performance improvement in POB1 and Pact during maximal ventilatory efforts with high extrinsic loads. POB1 and Pact specify the velocity-dependent characteristics of ventilatory muscle performance. The Pact estimated the maximal pressure activation the patient could generate in a dynamic fashion during threshold breathing challenges. In people with respiratory weakness, estimates of inspiratory drive (P01) may be normal or slightly elevated, but they do not sufficiently increase with added extrinsic demands (10). After IMST, the dynamic range of pressure development (Pact) was increased during loaded inspirations. As a result, the patient quickly overcame the threshold pressure settings of the device, opened the poppet valve, and generated rapid inspiratory flow. Power is necessary to produce pressure quickly throughout the inspiration. Because POB1 reflects pressure-time performance, it may describe dynamic inspiratory function to a greater degree than static performance measures, such as MIP. Recovery of POB1 and Pact indicate that IMST enhanced the patient’s respiratory pump reserve and thereby increased her capacity to compensate rapidly to increased ventilatory loads.

The present case is unique in two aspects. To our knowledge, this is the first clinical report that describes a respiratory strengthening benefit for NM. The advantages of inspiratory training exercises have been described in children with other neuromuscular diseases, namely Duchenne muscular dystrophy (18–20). These investigations conclude that respiratory muscle performance can increase in children with mild-to-moderate disability (18), but children with severe dystrophic changes may experience no benefit (19). Animal research revealed that training adaptations may differ between dystrophies and myopathies. In contrast to progressive degeneration associated with many dystrophies, muscle loading does not seem to worsen disease activity in less severe NM gene variants (2, 21). Thus, it is feasible that some patients with childhood- or adult-onset NM may benefit from IMST.

This account illustrates that some children who meet IMST criteria (Table 3) may be able to achieve inspiratory

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Table 3. Clinical indications and contraindications for inspiratory muscle strength training

<table>
<thead>
<tr>
<th>Clinical Indications for Inspiratory Muscle Strength Training</th>
<th>Contraindications for Inspiratory Muscle Strength Training</th>
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</thead>
<tbody>
<tr>
<td>Inspiratory strength below age and gender-predicted normal values</td>
<td>Hemodynamic instability (systolic BP &lt;90 mm Hg, or resting HR &gt;110 beats/min) or requirement of continuous vasopressor medications</td>
</tr>
<tr>
<td>Decline from premorbid level of ventilatory function—acute requirement for assisted ventilation</td>
<td>Evidence of uncontrolled infection (temperature &gt;36.0°C or &gt;38.5°C, WBC &gt;19/mm³)</td>
</tr>
<tr>
<td>Failure to wean with routine clinical methods (i.e., reduced IMV, pressure support, lengthening spontaneous breathing trials)</td>
<td>Acute pulmonary instability: untreated hemothorax or pneumothorax, unstable fractures</td>
</tr>
<tr>
<td>Gas exchange maintained with minimal ventilatory support (i.e., Fio2 &lt;0.6, IMV &lt;8, PS &lt;15, PEEP &lt;8)</td>
<td>Presence of seizure activity, ventriculostomy, or evolving neurological injury</td>
</tr>
<tr>
<td>Current or previously prescribed medication known to impair skeletal muscle excitation-contraction coupling (such as corticosteroids, β blockers, neuromuscular blockade, aminoglycoside antibiotics, immunosuppressants)</td>
<td>Inability to follow commands</td>
</tr>
</tbody>
</table>

IMV, intermittent mandatory ventilation; PS, pressure support; PEEP, positive end-expiratory pressure; BP, blood pressure; HR, heart rate; WBC, white blood cell count.
strength gains in a monitored, critical care environment. Most published inspiratory training reports (18) utilized low pressure loads over a sustained duration, designed to increase endurance. In contrast, our training regime consisted of higher loads delivered for a limited number of repetitions, more closely resembling strength training. However, it should be noted that targeted IMST exertion levels were achieved, using relatively modest threshold loads (19% to 23% of MIP). This observation may reflect underlying excitation-contraction coupling impairments associated with NM.

CONCLUSIONS

This report describes an IMST performance benefit in a child with NM and postoperative ventilatory insufficiency, and it corroborates the respiratory training effects identified in other neuromuscular diseases (18). Respiratory complications of NM have been associated with a more negative clinical prognosis (5, 6). Although other clinical reports (6, 22, 23) illustrated that acute ventilatory insufficiency in NM can cause life-threatening medical complications, ours is the first to document specific respiratory performance and functional gains with IMST. IMST may be beneficial for some patients with NM who experience symptomatic respiratory muscle weakness and a decline from baseline ventilatory function.

REFERENCES