SUPPLEMENT ARTICLE

Special Considerations in the Respiratory Management of Spinal Muscular Atrophy

Mary K. Schroth, MD

Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

The author has indicated she has no financial relationships relevant to this article to disclose.

ABSTRACT

This is a summary of the presentation on special considerations in the respiratory management of spinal muscular atrophy, presented as part of the program on pulmonary management of patients with pediatric neuromuscular disorders at the 30th annual Carrell-Krusen Neuromuscular Symposium on February 20, 2008. *Pediatrics* 2009;123:S245–S249

www.pediatrics.org/cgi/doi/10.1542/peds.2008-2952K

doi:10.1542/peds.2008-2952K

Abbreviations

SMA—spinal muscular atrophy
REM—rapid eye movement
NIV—noninvasive ventilation
VRI—viral respiratory infection
IPAP—inspiratory positive airway pressure

Accepted for publication Jan 5, 2009

Address correspondence to Mary K. Schroth, MD, University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, 600 Highland Ave, K4/938 CSC, Madison, WI 53792-9988. E-mail: mschroth@pediatrics.wisc.edu.

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The figure for this article appears online at: www.pediatrics.org/content/vol123/Supplement_4

SPINAL MUSCULAR ATROPHY (SMA) is an autosomal recessive disorder and the most common lethal disease of children younger than 2 years. The estimated incidence of SMA is 1 in 6000 to 1 in 10 000 live births.[1–4] There is no ethnic predominance and no gender preference. Ninety-five percent of children with SMA can be diagnosed by gene-mutation testing. The phenotypic expression of this disorder is variable. SMA has been classified into 3 childhood types according to the criteria established by the International Spinal Muscular Atrophy Consortium.[5,6] Children with SMA type 1 exhibit hypotonia and diffuse motor weakness before 6 months of age, are unable to sit independently, and, if no intervention is provided, will die by 2 years of age. SMA type 1 is also known as Werdnig-Hoffman disease. Children with SMA type 2 develop symptoms of weakness between 6 and 18 months of age, are able to sit independently, and are not able to stand independently. If no intervention is provided, they may survive into a third decade of life. SMA type 2 is also known as an intermediate form. Children with SMA type 3 are symptomatic after 18 months of age, often present with an abnormal gait, and have a normal life expectancy. SMA type 3 is also known as Kugelberg-Welander disease or juvenile SMA. SMA type 1 is the most frequently occurring form of the disease.

Clinical manifestations of SMA include symmetric muscle weakness and wasting of voluntary muscles. The proximal muscle groups are weaker than distal muscle groups, and the lower extremities are weaker than the upper extremities. In addition, most individuals with SMA have tongue fasciculations and absent deep-tendon reflexes. Intellect is normal, and sensation is intact.

RESPIRATORY COMPLICATIONS

Respiratory muscle function in SMA features very weak intercostal muscles and a relatively stronger diaphragm. The diaphragm is the primary muscle used for breathing in children with SMA type 1 or 2. In the first year of life the chest wall is very compliant. Thus, the chest wall in children with SMA type 1 or 2 often appears collapsed and bell shaped because of a lack of opposition of the intercostal muscles against the function of the diaphragm (see Fig 1 www.pediatrics.org/content/vol123/Supplement_4). The resulting chest wall deformities include a bell-shaped chest and pectus excavatum. The compromised respiratory muscle function results in:

- impaired cough resulting in poor clearance of lower airway secretions;
- hypoventilation during sleep;
- chest wall and lung underdevelopment; and
- recurrent infections that exacerbate muscle weakness and the integrity of the lung parenchyma.[7]

The natural history of SMA pulmonary compromise parallels progressive respiratory failure. Individuals with SMA 1 or 2 develop inspiratory and expiratory respiratory muscle weakness. Individuals with SMA type 1 also develop bulbar muscle weakness and resulting dysphagia. Ineffective cough is a result of respiratory muscle weakness and contributes to repeated respiratory infections. The next phase is development of rapid eye movement (REM)-related sleep-disordered breathing. Gradual progression results in sleep-disordered breathing during REM and non-REM sleep followed by ventilatory failure during the day and at night. Without intervention, respiratory failure will result in death.

Variability in clinical care between medical centers has resulted in challenges in conducting multicenter clinical trials. The "Consensus Statement for Standard of Care in Spinal Muscular Atrophy" was developed to facilitate

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multicenter clinical trials of SMA by decreasing the variability in outcomes caused by clinical care. The paucity of large clinical trials related to the clinical care of SMA has resulted in a lack of evidence-based data. Therefore, the consensus committee was convened to establish standard-of-care guidelines.[7]

CHRONIC RESPIRATORY CARE MANAGEMENT

Assessment and Pulse Oximetry

Respiratory assessment of SMA includes evaluation of cough effectiveness as identified by the SMA Standard of Care Committee.[7] Pulse oximetry is an important assessment and monitoring tool for SMA types 1 and 2, because the clinical presentation of respiratory distress is muted by the diffuse muscle weakness. Furthermore, the child with SMA type 1 may become visibly cyanotic before changes in respiratory rate and work of breathing. Often, during the early phase of an illness, a child with SMA type 1 or 2 may also be tachycardic. In SMA, an acute drop in pulse oximetry to <95% saturation while in room air and awake is most often a result of atelectasis, mucus plugging, or agitation. An acute decrease in oxygen saturation to <95% while asleep suggests hypoventilation or mucus plugging.

Secretion Mobilization and Clearance

Key to chronic management is discussion with the family regarding goals for care of their child and offering choices for care. Chronic management requires teaching families techniques for supporting their child's breathing. These techniques include methods for airway-secretion mobilization and clearance and respiratory support. Secretion mobilization includes manual or mechanical chest physiotherapy with postural drainage. Other devices for secretion mobilization can be used and do not have proven benefit. Cough techniques include manual cough assistance and mechanical insufflation/exsufflation with the CoughAssist (Respironics, Murrysville, PA) machine.[8–10] Assisted coughing is a critical element of respiratory care for individuals with SMA and may be the only way they can cough and clear secretions. Pressures should be high enough to mobilize secretions (eg, inhale and exhale pressures of at least 30 cm H_2O and ideally up to 40 cm H_2O). The protocol used at the University of Wisconsin is as follows:

1. CoughAssist machine, 4 sets of 5 breaths, followed by oral suctioning of secretions
2. Secretion mobilization with manual or mechanical chest physiotherapy
3. CoughAssist machine, 4 sets of 5 breaths, and oral suctioning
4. Postural drainage (Trendelenburg positioning) for 15 to 20 minutes as tolerated
5. CoughAssist machine, 4 sets of 5 breaths and oral suctioning

Families receive this written guideline for therapy at home. Our guideline for SMA type 1 is to perform airway clearance twice per day when the child is well, and for SMA type 2 our guideline is to perform airway clearance as needed when the child is well. The CoughAssist machine should be used as often as needed. Children with SMA type 3 may need airway clearance postoperatively and with serious illness.

Functional Residual Capacity Relative to Position

SMA results in very weak intercostal muscles and a relatively stronger diaphragm. When positioned upright, the functional residual capacity, or the volume at the end of normal expiration, is increased. The functional residual capacity in SMA is smallest when in the Trendelenburg position. Thus, for SMA types 1 and 2, positioning flat or in the Trendelenburg position during respiratory compromise will benefit diaphragm function. In the upright position, the individual who is diaphragm dependent for breathing is at a mechanical disadvantage.

Respiratory Support

Respiratory support options include (1) noninvasive ventilation (NIV) with bilevel positive airway pressure or a mechanical ventilator and (2) invasive ventilation with tracheotomy. The short-term goals of NIV include respiratory symptom relief, reduced work of breathing, improved or stabilized gas exchange, optimal patient comfort, and good patient-ventilator synchrony while minimizing risk and avoiding intubation.[11] The long-term goals of NIV include improving sleep duration and quality, maximizing quality of life, enhancing functional status, and prolonging survival.[11] Three theories have been proposed to explain the improvement in respiratory status with respiratory assist devices and include resting chronically fatigued respiratory muscles, reversing microatelectasis, and altering the CO_2 set point.[11] In studies of individuals with neuromuscular weakness and chronic respiratory failure, implementation of NIV results in improved P_{CO_2}.[12–14]

Usual indications for NIV at home include hypoventilation, as demonstrated by decreased oxygen saturation by pulse oximetry and increased P_{CO_2} or obstructive sleep apnea. Additional indications for NIV specific to SMA include respiratory failure during a viral respiratory infection (VRI), recurring pneumonia or atelectasis, postoperative care, chest wall deformity, and the diagnosis of SMA type 1 when the family is interested in noninvasive respiratory support. VRIs result in increased neuromuscular weakness.[15] Thus, VRIs exacerbate SMA weakness and when combined with the associated copious respiratory secretion production, VRIs contribute to the risk of respiratory failure.[16] Postoperative complications include upper airway obstruction, transient hypoventilation, and atelectasis, which also increase the risk for respiratory failure.[17]

The natural history of SMA type 1 is respiratory failure and death before the age of 2 years without respiratory intervention.[5] Respiratory support of children with SMA type 1 is a developing area of care resulting from requests by families for choices to support their children and the technologic advances of respiratory

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support devices. The benefits of initiating NIV for children with SMA type 1 include the potential for prolonging life without a surgical intervention and facilitating caring for the child at home.[18] In addition, NIV has been shown to alter the chest wall deformity in SMA and may improve lung development[19,20] and, potentially, lung function. The limitations are difficulty identifying a well-fitting interface and the complications of applying an interface for long periods of time (>16 hours/day), including skin irritation and breakdown and midface hypoplasia. Gastric distention and emesis are also potential complications and can result in aspiration, pneumonia, and possibly death. Chronic care of children with SMA type 1 includes consideration of palliative care. Palliative care can include the techniques discussed above, including secretion mobilization, airway clearance, and NIV. These techniques may facilitate discharge to home[7] and may allow families to care for their child at home for longer periods of time. Application of these techniques may also decrease respiratory symptoms, improve quality of life and comfort by avoiding PICU stays and tracheotomy, and provide psychological, social, and spiritual support for the family and individual with SMA.

Children with SMA type 2 may require NIV support depending on the severity of weakness. They rarely need a tracheotomy. Children with SMA type 2 are at risk for hypoventilation, especially during sleep, and this is exacerbated during VRIs and postoperatively. Chest wall deformity and lung development may also be improved in children with SMA type 2. Children and adults with SMA type 3 generally have normal lung function and respiratory muscle strength measurements and rarely require noninvasive respiratory techniques. However, during times of illness and postoperatively, NIV and airway-secretion mobilization and clearance techniques may be necessary. Adults with SMA type 3 may need NIV as they age and are at risk for the development of obstructive sleep apnea and hypoventilation that may be unrecognized.

NIV use in SMA requires consideration of respiratory pathophysiology. Individuals with SMA maintain minute ventilation with a high respiratory rate and small tidal volume. Because of neuromuscular weakness and small tidal volumes, individuals with neuromuscular weakness are at risk for not being able to trigger an NIV support device. Therefore, a device with a backup rate is recommended; in general, these devices are bilevel positive airway pressure devices with a spontaneous timed (ST) mode. These devices have multiple settings including inspiratory positive airway pressure (IPAP), expiratory positive airway pressure, respiratory rate, inspiratory time, and rise time. Bach et al[21] have demonstrated that individuals with SMA type 1 who used high-span bilevel positive airway pressure with an inspiratory and expiratory pressure difference of at least 10 cm H_2O had decreased hospitalizations after 5 years of age and were able to tolerate time off NIV compared with similar children who had a tracheotomy and ventilator. The NIV settings used were high enough to ventilate the children. A similar experience was observed at the University of Wisconsin. Therefore, in weaker individuals with SMA, one approach to NIV management is to set the IPAP at a pressure high enough to ventilate the individual and set the expiratory positive airway pressure at the lowest level possible to facilitate passive exhalation from low tidal volumes. In the weakest patients, setting the respiratory rate high enough to capture the respiratory effort will result in resting the respiratory muscles. The highest setting is 30 breaths per minute for home bilevel positive airway pressure units, which is lower than the baseline respiratory rate for most infants with SMA type 1. The inspiratory time setting is the length of the breath and may be set on the basis of the age and respiratory rate of the user. The rise time is the time to peak inspiratory pressure and ideally may be set at a level that is comfortable for the user. Mechanical ventilators can also be used for NIV, and several modes can be used, including synchronous intermittent mandatory ventilation with pressure- or volume-control settings.

The greatest obstacle for applying NIV successfully in young children is availability of an appropriate interface. Respironics, Inc (Murraysville, PA) and SleepNet Corporation (Hampton, NH) offer the smallest nasal masks available to date. Respironics, Inc offers the small child nasal mask with comfort flap and small child headgear. SleepNet Corporation offers the MiniMe nasal mask with 3 sizes of headgear: small (infant), medium (older infant through toddler), and large (adult). Bilevel positive airway pressure devices are single-limb circuits, and interfaces require exhalation ports or valves. In contrast, mechanical ventilators use double-limb closed circuits, and the nasal interfaces must be sealed.

Invasive ventilation refers to the placement of a tracheostomy tube and use of mechanical ventilation. Tracheotomy is not an acute intervention and is controversial for SMA type 1. Tracheotomy is not indicated in SMA type 2.[7] Some children with SMA type 1 require full-time NIV, have airway instability when they are well, and frequent episodes of respiratory instability when off NIV and may benefit from tracheostomy and mechanical ventilation. For some with SMA type 1, without tracheostomy tube placement and mechanical ventilation, they would not survive. Placement of a tracheostomy tube and mechanical ventilation in children with SMA type 1 typically results in the inability of the child to tolerate time off mechanical ventilation and lack of vocalization.[21]

ACUTE RESPIRATORY CARE MANAGEMENT

VRIs result in increased respiratory muscle weakness, increased airway secretions, and more difficulty in breathing.[16] Hypoxemia may be the presenting symptom. The goal of treatment is to normalize gas exchange by decreasing atelectasis and optimizing airway clearance. Supplemental oxygen is not the first line of treatment. Supplemental oxygen results in improved oxygen saturation but does not improve ventilation or treat the underlying cause. If airway clearance and respiratory support are not initiated in a timely way, respiratory failure is inevitable for individuals with SMA type 1 or 2. The first intervention is mechanical airway-secretion mobilization and clearance with assisted coughing, either manual or mechanical insufflation/exsufflation. As

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described previously, the protocol used at the University of Wisconsin is to use the CoughAssist machine (4 sets of 5 breaths), followed by oral suctioning of secretions, followed by secretion mobilization, followed by using the CoughAssist machine (4 sets of 5 breaths) and oral suctioning, followed by postural drainage for 15 to 20 minutes as tolerated, and followed again by using the CoughAssist machine (4 sets of 5 breaths) and oral suctioning. During acute illness this is performed at home every 4 hours. If the individual with SMA is hospitalized, he or she may receive this respiratory care protocol every 2 hours depending on severity of illness, chest radiograph changes, and respiratory support needs. Our success is based on providing families with the tools to care for their child at home and providing a consistent plan of care. The CoughAssist machine should be used as often as needed, and pulse oximetry should be used to guide intervention. If pulse oxygen saturation is $<94\%$, assisted coughing should be used. If there is no improvement, an airway-clearance treatment should be initiated, and the individual should be placed on his or her respiratory support device. Assisted coughing techniques are preferred over deep suctioning and bronchoscopy.[7]

Increased NIV should be initiated early during acute illness. Bilevel positive airway pressure provides greater respiratory muscle rest compared with continuous positive airway pressure.[11] Bilevel positive airway pressure also decreases respiratory muscle work by increasing tidal volume and decreasing respiratory rate, and it improves gas exchange.[11] The use of NIV with aggressive airway clearance may decrease the need for intubation. In addition, NIV can be used while awake to relieve fatigue. During acute illness, intubation and mechanical ventilation may be needed and transient. Oxygen therapy is not first-line therapy; however, if airway clearance and respiratory support is maximized and hypoxemia continues, supplemental oxygen should be used. During acute illness, hydration should be maintained, and fasting for >6 hours should be avoided. Continued enteral feeding or intravenous caloric feeding should be implemented to avoid metabolic decompensation in the setting of a catabolic state.[7] During recovery, extubation should be considered when the individual is afebrile and does not require supplemental oxygen, a chest radiograph shows no atelectasis or infiltrates, airway secretions are significantly reduced, and respiratory depressants have been minimized. Extubation should occur to a respiratory assist device with a backup respiratory rate. Before extubation, ventilator settings can be weaned to settings that approximate the bilevel positive airway pressure respiratory rate and IPAP. Ventilator weaning to determine whether a patient with SMA can breathe above the ventilator should occur only while awake. Pressure support and continuous positive airway pressure trials while intubated are not indicated and generally result in atelectasis and fatigue in SMA.

CONCLUSIONS

SMA 1 and 2 result in diffuse respiratory muscle weakness with greater weakness of the intercostal muscles compared with the diaphragm. SMA respiratory muscle weakness results in increased difficulty clearing lower respiratory secretions and hypoventilation during sleep, especially during VRIs. Interventions include airway-secretion mobilization and clearance techniques and respiratory support with NIV. During acute illnesses, airway-clearance techniques and NIV are increased. In addition, nutrition and hydration should be maintained, and there is a low threshold for antibiotic administration. Important to the success of home management is education of families to provide respiratory care to their child on a chronic basis and with acute illness. Individuals with SMA type 3 typically have normal lung function and respiratory muscle strength. However, they may be at risk for obstructive sleep apnea and may require respiratory support and airway-secretion mobilization and clearance during acute illness or postoperatively. They may also develop hypoventilation during adulthood.

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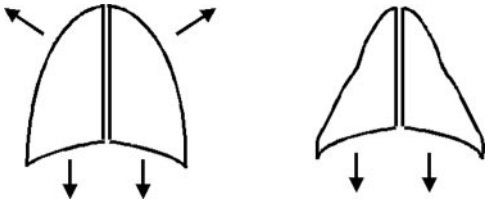


FIGURE 1
Chest wall changes. Left, Normal lungs; right, lungs of a patient with SMA.

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DOI: 10.1542/peds.2008-2952K

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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