

Spinal Muscular Atrophy Type 1: Prolongation of Survival by Noninvasive Respiratory Aids

John R. Bach, MD, Kavita Gupta, BS, Michael Reyna, BS, and Alice Hon, BS

Previous reports on spinal muscular atrophy type 1 (SMA-1) underestimate potential survival because of failure to optimally use noninvasive respiratory muscle aids including mechanically assisted coughing and noninvasive ventilation (NIV) at full support settings. We report our center's experience in prolonging survival for these patients. We focus on early initiation of nasal noninvasive ventilation, mechanically assisted coughing, and pulse oximetry monitoring during acute respiratory tract infections to guide use of assistive technologies. Seventeen SMA-1 patients with ventilation via tracheostomy are living, with a mean age of 78.2 (range 65–179) months. Ten died at a mean age of 61.6 (range 16–270) months of age. Twenty five of 27 were not able to regain autonomous breathing ability after the tracheostomy. None of the 21 who had not developed the ability to verbalize before undergoing tracheotomy did so after tracheotomy. Six patients had comprehensible speech at the time of tracheotomy and retained some ability to vocalize subsequently. Seventy-two SMA-1 patients using noninvasive ventilation are alive at mean age 86.1 (range 13–196) months; 13 died at 52.3 (range 13–111) months. Sixty seven of the 75 could communicate verbally. The noninvasive ventilation patients had significantly more hospitalizations than tracheostomy patients until age 3 ($P < 0.001$) but not thereafter. SMA-1 survival past adolescence is possible using both noninvasive ventilation and tracheostomy ventilation. The tracheostomy-ventilated patients had greater levels of ventilator dependence and reduced verbal abilities.

Introduction

SPINAL MUSCULAR ATROPHY (SMA) is the second most common potentially lethal autosomal recessive disorder, affecting 1 per 6,000–8,000 live births, and has a 1 in 34 asymptomatic carrier frequency. The SMAs are anterior horn cell disorders in which deletions at chromosome 5q13 are detectable in 99% of patients and responsible for diminution of survival motor neuron (SMN) protein. The 80% to 90% of SMN protein is derived from the *SMN1* gene with the rest from the adjacent *SMN2* gene. With absence of the *SMN1* gene, severity correlates inversely with the number of copies of *SMN2* such that ≤ 2 copies results in type 1 and ≥ 3 copies results in type 3.^{1,2}

The SMAs range in severity from severe weakness and definitive need for ventilatory support as newborns to muscle weakness first presenting in adults. Patients with SMA type 3 develop the ability to walk independently for some period of time. Patients with SMA type 2 never walk but are able to sit independently for some period of time. Children with

SMA type 1, also known as Werdnig–Hoffmann disease, can never roll, sit, or walk. SMA-1 is the most common neuromuscular disease of the hypotonic newborn.³

SMA-1 can be further subdivided by severity. Children whose Vital Capacity plateaus over 300 mL and who require nonoral nutrition or first develop acute respiratory failure after the second birthday can be considered to have a less severe SMA-1B. Children whose maximum attainable Vital Capacity (or plateau Vital Capacity) never exceeds 300 mL and who, by 24 months of age, have become too weak to take food by mouth and have developed respiratory muscle failure have typical SMA type 1A. The most severe SMA type 1A children become lifetime continuously ventilator-dependent due to severe inspiratory muscle weakness before 6 months of age. Occasionally, they require intubation at birth, undergo tracheotomy, and never wean from full tracheostomy ventilation. Much more often type 1A children develop acute respiratory failure between 6 and 18 months of age either during an intercurrent respiratory tract infection or

Department of Neurosciences and Department of Physical Medicine and Rehabilitation, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey.

This work was performed at University Hospital, Newark, New Jersey.

from aspiration of food or saliva. An ineffective cough leads to ineffective mucus clearance, predisposing to respiratory compromise. Our experience suggests that hospitalizations and acute respiratory failure events can be reduced by the use of continuous noninvasive ventilation and mechanically assisted cough despite plateau and lifetime maximum vital capacities that do not permit autonomous breathing, that is, <100 mL (Fig. 1).

Prognosis of SMA-1 Without Technological Support

Pediatric, neurology, and respiratory textbooks consider SMA-1 a progressive disease,⁴⁻⁶ fatal by 3 years of age,^{4,7} or even by age 1.⁸ We also reported untreated SMA-1A to be uniformly fatal by 2 years of age with 50% mortality by 7 months and 90% mortality by 12 months of age.³ “Symptomatic treatment” has been considered of no value in altering the course of SMA-1.⁴ Although most families of children with SMA-1 report that there is a substantial caregiving effort, their child has a good quality of life and their life is worth living⁹ many physicians have discouraged mechanical respiratory support alleging “poor quality of life.”⁷ A physician’s view of the “prognosis of the disease,”⁶ like the physician’s estimate of a patient’s quality of life,¹⁰ will influence whether or not mechanical ventilation of any kind is offered. For example, expressing therapeutic futility and a hopeless prognosis, Cobben et al. reported a median age at death of 176 days for 34 consecutive cases of SMA type 1 in the Netherlands where these children are not offered mechanical ventilation and are not aggressively treated for intercurrent respiratory tract infections.¹¹

Almost as inadequate as providing no treatment at all is the use of bilevel positive airway pressure (BiPAP) at low pressure spans (<10 cm H₂O between expiratory and inspiratory pressure, subsequently referred to as “low

span”). Lower settings are inadequate for full ventilatory support, inspiratory muscle rest, and reversal of paradoxical chest wall movement to promote lung growth and chest wall compliance.¹² Low levels of respiratory assistance using low-span BiPAP for nasal “noninvasive ventilation” is not sufficient to markedly prolong life for children with SMA-1.¹³

Current Management Strategies

There are 4 management approaches to consider:

1. To “let nature take its course” is to provide palliative care without parenteral nutrition and assisted ventilation and to consider use of narcotics and/or supplemental oxygen to relieve perceived suffering and likely hasten death.
2. To perform elective tracheostomy or tracheostomy following translaryngeal intubation for an intercurrent episode of acute respiratory failure, and provide ventilatory assistance via tracheostomy.
3. To treat SMA-1 like sleep disordered breathing with low-span BiPAP until acute respiratory failure inevitably develops. This approach may not provide sufficient support to facilitate lung and chest wall growth and development and to prevent ankylosis of costovertebral joints.
4. To use a spectrum of noninvasive respiratory muscle aids with sufficient pressures and frequency to assist inspiratory and expiratory muscle function, thereby to avoid or postpone respiratory failure and tracheostomy.

Problems With Using Polysomnography to Titrate Respiratory Support

Extrapolation from sleep medicine algorithms developed for obstructive sleep apnea can lead to inappropriate ventilatory strategies for children with severe neuromuscular

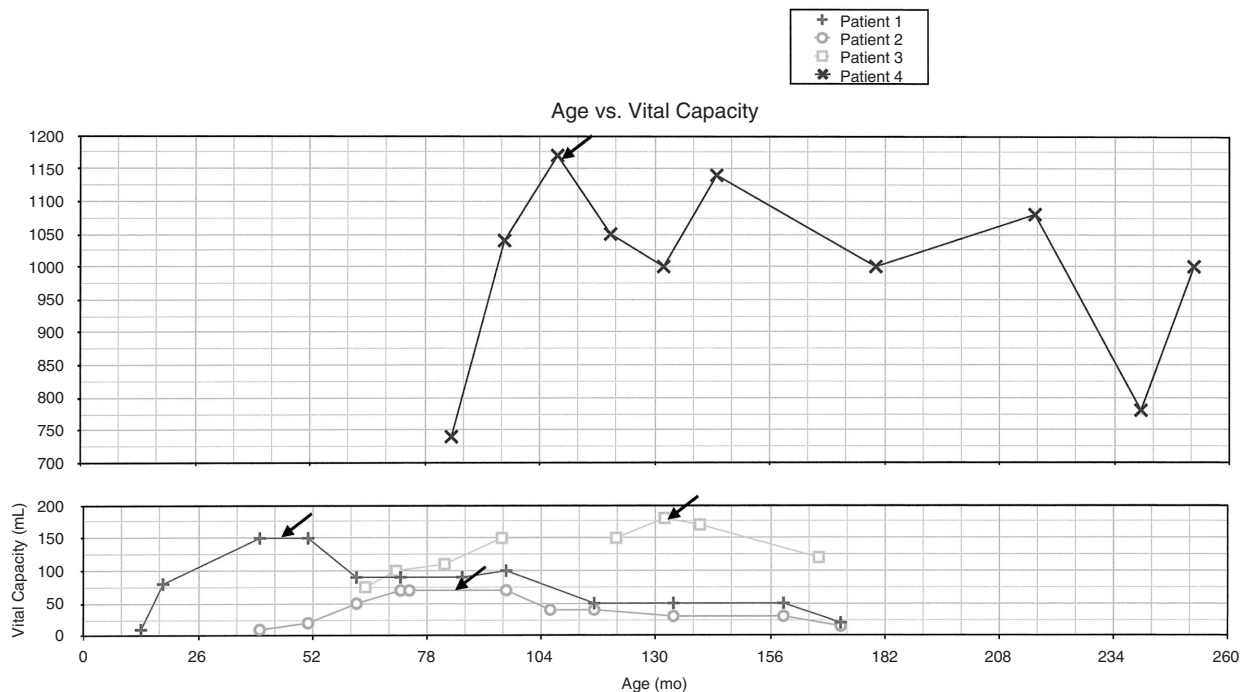


FIG. 1. Graph over time demonstrating plateau (maximum lifetime) vital capacity for 3 typical spinal muscular atrophy (SMA) type 1A patients and 1 type 1B patient.

disease. Polysomnography does not take into account muscle weakness. Paradoxical chest–abdominal movements are interpreted as indicating obstructive events and therefore treated by increasing expiratory pressure, whereas when they are due to muscle weakness the treatment should consist of increasing inspiratory pressure. Whereas continuous positive airway pressure (CPAP) and low-span BiPAP can treat obstructive apneas, they do not treat inspiratory muscle insufficiency for which inspiratory positive pressure is needed. Further, polysomnograms in SMA-1 children can be almost normal with few apneas and hypopneas, normal end expiratory carbon dioxide, and normal oxyhemoglobin saturation (SpO₂) despite severe paradoxical respiration, arousals, nocturnal flushing, and perspiration. Since the goal should be to promote chest wall and lung development and rest inspiratory muscles, polysomnography is not the optimal way to evaluate respiratory muscle weakness and titrate respiratory support for children with SMAs.

Bilevel positive airway pressure devices, which can be used for full ventilatory support, do not permit air stacking (stacking of sequentially delivered volumes of air), generally have no internal batteries, and if a moderate to high expiratory pressure is used will render exhalation uncomfortable and cause patients to breathe at higher than necessary lung volumes. This unnecessarily increased intrathoracic pressure can make it difficult if not impossible for SMA-1 infants to trigger and, therefore, synchronize with the devices. They should only be used for SMA-1 at high (>10 cm H₂O pressure) spans (subsequently referred to as “high span”) and only when a more suitable portable ventilator is unavailable.

Problems With Conventional Critical Care

The typical surviving child with SMA-1 is hospitalized frequently until the third birthday and usually intubated during many of the hospitalizations. Thirty nine of 100 SMA-1 patients followed at our center were intubated during their first hospitalizations and 12 of the patients, none of whom managed by our group, underwent tracheotomy at that time.

When intubated, critical care physicians often set weaning parameters and “spontaneous breathing trials” that must be passed before extubation is conventionally considered. Continuation of supplemental oxygen may suppress respiratory drive (if the patient relies on hypoxemia for respiratory drive due to chronic hypoventilation) and obscures the ability to use oxygen desaturation as a gauge of hypoventilation and extent of airway obstruction with secretions,¹⁴ and thus predisposes to failure of the extubation attempt.¹⁵ Continuous positive airway pressure does not aid weak muscles. Low-span BiPAP is helpful but often insufficient to permit successful extubation. Not surprisingly, in our experience conventional extubation without BiPAP succeeds 6% to 10% of the time, and with BiPAP <50% of the time, leading clinicians to think that tracheostomy is required for survival.¹⁵ Many physicians discourage endotracheal intubation, thinking that extubation will not be possible without tracheostomy, which may worsen quality of life for the patient and caregiver.

The noninvasive strategy

The goals of the noninvasive strategy are to promote lung growth and chest wall compliance, maximize cough flows,

maintain normal alveolar ventilation, and extubate patients recovering from acute respiratory failure to noninvasive aids without resort to tracheotomy.

Promoting Lung Growth and Chest Wall Compliance

Normal babies take deep breaths to fill their lungs with air, expanding both abdomen and chest when crying. When SMA-1 children cry, the paradoxical movements worsen as the upper thoracic wall retracts inward due to weakness of intercostal muscles and the normally hypercompliant thorax of the young infant. Untreated, this paradoxical breathing can result in severe pectus excavatum and a small funnel-shaped chest (Fig. 2). Seventy three of our 75 SMA-1 noninvasive ventilation users presented with paradoxical breathing. It seems reasonable that small children with neuromuscular disease and paradoxical breathing use noninvasive ventilation with sleep from the time of diagnosis to prevent pectus excavatum and to promote lung growth and chest wall compliance (Fig. 3).¹²

Further, the full respiratory effort of normal infants involves the movement of the thorax via the costovertebral joints. Recovery of range of motion is difficult after ankylosis has occurred. We consider this insight as another strong indication for beginning of high-span positive airways pressure early in the course of SMA.

Glottic function does not permit air stacking to achieve greater volumes for children with SMA-1A; the only practical method to achieve maximal lung and chest wall expansion is to supplement full tidal volume noninvasive ventilation with frequent maximal insufflations provided by the insufflations phase of mechanical insufflation–exsufflation

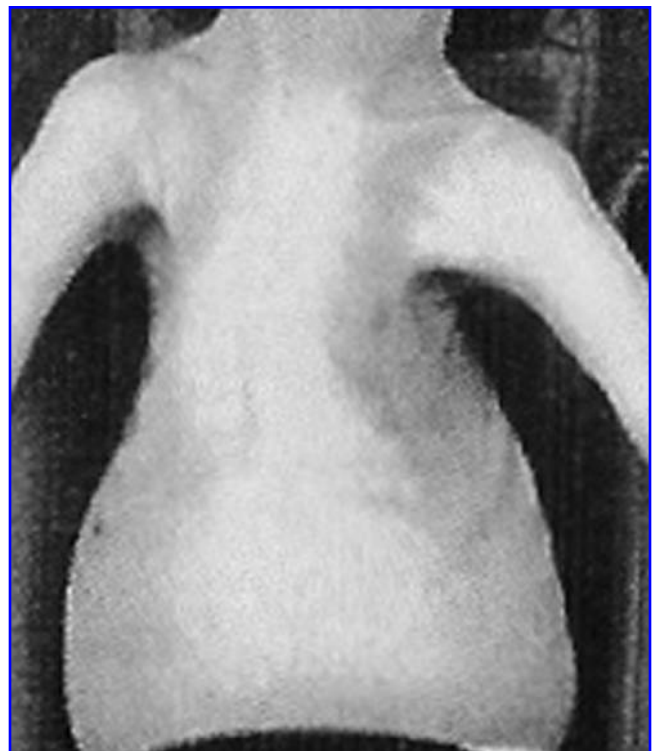


FIG. 2. Typical funnel-shaped chest of an untreated child with spinal muscular atrophy (SMA) type 1.



FIG. 3. Two severe spinal muscular atrophy (SMA) type 1 brothers, continuously noninvasive ventilation (NIV)-dependent since 8 and 4 months of age, respectively, with no pectus and preservation of lung expansion and compliance. Michael, on the left was born in April, 1995, and Danny, on the right, in September, 1997.

(MI-E).¹⁶ Small children can also be insufflated to total lung capacity by a single squeeze from an adult manual resuscitator. The exhalation valve of the manual resuscitator can also be blocked for “artificial” air stacking to allow inflation to total lung capacity for older children and adults. The more often this is done, the better. We recommend at least 3 times daily sessions with 10–15 insufflations each time. The insufflations should be performed as follows: the care provider observes full chest expansion and feels resistance to additional air delivery, without apparent discomfort of the child, and to pressures of 35 cm H₂O or greater. Remarkably, despite thousands of such sessions in our SMA and other neuromuscular patients with some of latter doing this 3 times a day for over 50 years to pressures of over 60 cm H₂O, pneumothorax has been rare.¹⁷

The Maximization of Cough Flows (Expiratory Aids)

The expiratory muscles are critically important for coughing. These muscles can be aided by applying negative pressure to the airways and/or positive pressure to the chest and abdomen during exhalation to increase cough peak flow. A cough involves: (1) a deep inspiration (normal cough volumes in adults are 2,300 mL, far greater than the vital capacities of SMA patients),¹⁸ (2) glottic closure to permit the positive thoracoabdominal pressure, and (3) thoracoabdominal pressure generation to 200 cm H₂O. Since SMA-1 children can neither inspire deeply, generate much thoracoabdominal pressure, nor firmly close the glottis, all 3 elements of an effective cough must be provided by caregivers. By far the easiest way of achieving this is with mechanical insufflation–exsufflation used for mechanically assisted coughing. The mechanical insufflation–exsufflation involves the delivery of a deep lung insufflation to full clinical lung/chest wall expansion immediately followed by a pressure drop from about 40 to –40 cm H₂O to maximally exsufflate the lungs to near residual volume. These pressures or higher can be used for all ages. This pressure drop of 80 or so centimeter H₂O can result in a 10 L/s exhalation flow. An abdominal thrust is delivered, albeit gingerly within 1 h after meals, in conjunction with the

exsufflation to further augment cough peak flow. Mechanical insufflation–exsufflation used with an abdominal thrust is what we call mechanically assisted coughing.

Most children over age 3 and adults can cooperate nicely with mechanical insufflation–exsufflation so that the machine’s automatic cycling function can be used. Effective use of mechanically assisted cough for babies, however, can only be performed on automatic cycling when the baby is so weak that he or she does not close the glottis or counter the action of the machine. This is usually not the case. Thus, manual cycling should be done with the insufflation phase timed to the baby’s inhalation (the abdomen protruding) and the exsufflation phase timed to exhalation. Because these children can have very high respiratory rates, mechanically assisted cough tends to be inefficient in the very young, which is one of the reasons that respiratory hospitalization rates of infants with SMA-1 remain high until the children are at least 2.5 years, after which full cooperation generally develops.

Humidification should be individually adjusted to prevent inspissation of secretions while avoiding increasing the volume of watery secretions. While chest physical therapy in combination with postural drainage can be very effective in small children, it is not a substitute for effective mechanically assisted cough. Likewise, a normal cough clears airways to the sixth division of the respiratory tree whereas the mucociliary elevator moves debris up to these 6 divisions from the peripheral airways. While chest percussion, vibration, and oscillation may facilitate mucociliary action, they are not necessary when patients are well and not aspirating saliva. They are not a substitute for mechanically assisted coughing.

Noninvasive Ventilation

Parents are trained in how to adjust ventilator settings and how to apply the nasal interface in the clinic and at home. Children are introduced to noninvasive ventilation at home during deep sleep, initially tolerating the nasal interface with minimal inspiratory pressures that are gradually increased to 15–20 cm H₂O. The parents are instructed how to observe for patient-ventilator synchrony by observing the synchrony of abdominal movements with air delivery and ventilator gauge pressures. Parents note that their children quickly adapt to noninvasive ventilation, will not sleep without it, and have fewer arousals and less perspiration and flushing using it. Since BiPAP is suboptimal due to the expiratory positive airway pressure and synchronizing difficulties, these children trigger portable flow sensitive ventilators with backup rates. Thus, our practice is to set the ventilator for infants at 15–20 cm H₂O inspiratory pressure on assist-control mode with an appropriate backup rate for age and sensitivity settings adjusted to facilitate triggering to augment each breath during sleep. We commonly use the LTV-950 (Pulmonetics Systems Inc., Colton, CA). Earlier LTV models like the 800 and 900 do not do both pressure and volume cycling.

Nasal interfaces can be created for children of all sizes and ages including the Fisher–Paykel Bubble CPAP interface for children under 6 months of age. We continue to find the infant CPAP circuits (Hudson 15.0 French CPAP Nasal Prongs) the most practical for this population. These prongs can be taped into the prongs of the small adult Adam circuit (Puritan Bennett, Boulder, CO).¹⁹ The larger prongs of the Adam circuit seal the child’s nostrils and the Adam circuit’s

suspension system retains the interface. Another option for infants under 6 months age is to seal one end of the Hudson Infant Nasal CPAP Adaptor (INCA) and connect the other end to the ventilation circuit using intervening tubing adaptors (Fig. 4). The prongs themselves are passed through foamy material such as the nasal bridge cushions of a Respironics CPAP mask or the center of a Duoderm™ patch (Bristol Myers Squibb Co., New York) that adheres to the nostril linings and seals the nasal orifices.¹⁹ These prongs are designed for infants between 1,500 and 2,000 g. Custom headgear is prepared to secure the interface. We have had success with these prongs in infants and young children up to 2 years of age. The Respironics Small Child Nasal Mask is also very useful for children from 6 months to 4 years of age at which time we often switch to using the Petite Profile Lite Nasal Mask Interface (Respironics International Inc., Murraysville, PA). For continuous noninvasive ventilation users, multiple nasal interfaces are often alternately used to avoid excessive local skin contact and skin breakdown. The exhalation holes of the “CPAP/nasal masks” and prongs need to be sealed when used on a ventilator circuit with an exhalation valve.

The Oximetry/Respiratory Aid Protocol

Care providers are trained and equipped to use pulse oximetry properly. The parents are instructed to use pulse oximetry monitoring at the first sign of an upper respiratory tract infection or cough, and to use noninvasive ventilation



FIG. 4. Child with typical spinal muscular atrophy (SMA) type 1, born in September, 1993, using nasal noninvasive ventilation (NIV) via Hudson CPAP prongs on ventilator circuit (see text for description).

(if not already in use) combined with mechanically assisted coughing to maintain waking $SpO_2 \geq 95\%$. SMA-1 noninvasive ventilation users are instructed to use continuous noninvasive ventilation during these episodes. Every decrease in SpO_2 below 95% first requires an assessment for hypoventilation. The care provider checks to see that targeted airway pressures are being reached; the interface is not leaking; and the ventilator tubing is connected properly and unobstructed. If hypoventilation is not the problem, decreases in SpO_2 are most frequently due to ventilation–perfusion mismatching related to airway secretions. The parents then apply mechanically assisted coughing until the SpO_2 baseline returns to normal. We also recommend a broad spectrum antibiotic to prevent the development of clinically apparent pneumonia during these episodes. If SpO_2 baseline does not return to $\geq 95\%$, then hospitalization is indicated.

Extubation of “Unweanable” Children

The use of noninvasive ventilation, mechanically assisted coughing, and antibiotics are not always successful in averting pneumonia and acute respiratory failure, especially for children under 3 years of age. Although intercurrent respiratory tract infections often necessitate intensive care and intubation, tracheotomy can be avoided for most SMA-1 children by a short-term intubation followed by timely extubation to noninvasive ventilation following the indications and protocol noted in Table 1.²⁰

While intubated, patients are managed conventionally except for the frequent use of mechanical insufflation–exsufflation via the endotracheal tube. Because of pressure drop-off due to resistance, small gauge infant tubes render mechanical insufflation–exsufflation much less effective. Mechanical insufflation–exsufflation use via endotracheal tubes, however, can be very effective for older patients with larger endotracheal tubes. Once the patients satisfy extubation criteria (Table 1), they are extubated to full noninvasive ventilatory support, that is, inspiratory pressures of 15–22 cm H_2O with an age appropriate backup rate, as noted in Table 1. Extubation is usually successful irrespective of the extent of ventilator dependence without post-extubation supplemental oxygen.^{20,21}

Ideally, the children are extubated to noninvasive ventilation at the full ventilatory support settings they had been using before they were intubated. Patient-ventilator synchrony should be optimized. Acutely ill infants with respiratory rates over 50 breaths per minute may initially have a backup rate set to capture every other breath until the spontaneous rate decreases with the augmented assisted volumes and minute ventilation. The great majority of postextubation episodes of hypoxemia (decreases in SpO_2 below 95%) are due to airway secretions, which can be mobilized by mechanically assisted coughing used up to every 20 min. In our institution, committed family members and care providers in the critical care unit perform this frequent care around-the-clock for at least the first 2–3 days postextubation. We consider extubation to be successful when re-intubation is not required during the same hospitalization.^{20,21}

Outcomes Using This Strategy

Continuous noninvasive ventilation-dependent patients with Duchenne muscular dystrophy,²² bulbar amyotrophic

TABLE 1. INDICATIONS AND SMA-1 EXTUBATION PROTOCOL

While intubated:

1. Conventional management of infectious disease, nutrition, and other supportive medical care.
2. Oxygen administration limited to maintain SpO₂ 94%–95%.
3. Mechanical insufflation–exsufflation used via the tube at 40–60 cm H₂O to 40 to –60 cm H₂O pressures, 15–20 cycles, along with exsufflation-timed abdominal thrusts up to every 60 min as needed when there is auscultatory evidence of airway secretion accumulation and especially to reverse oxyhemoglobin desaturations due to airway mucus accumulation. Endotracheal tube and upper airway are suctioned after mechanically assisted coughing.
4. Ventilator weaning attempted without permitting hypercapnia.
5. Extubation done whether or not the patient can pass spontaneous breathing trials when meeting the following conditions:
 - A) A febrile and normal white blood cell count;
 - B) SpO₂ ≥95% in ambient air for over 12 h;
 - C) Chest radiograph abnormalities cleared or clearing;
 - D) Fully alert mental status, no sedative medications;
 - E) Airway suctioning required only 1 or 2 times during 8 h or airway secretions no longer decreasing;
 - F) Coryza diminished sufficiently so that suctioning of the nasal orifices is required less than once every 8 h (for postextubation nasal ventilation).

Extubation

1. Nasogastric tube, if present, removed.
2. Extubation to continuous full-setting nasal ventilation using portable volume/pressure ventilator and no supplemental oxygen.
3. Oximetry feedback used to guide in the need for mechanically assisted coughing, postural drainage, and chest physical therapy to reverse any desaturations due to airway mucus accumulation.
4. With CO₂ retention or ventilator dyssynchrony nasal interface leaks should be eliminated and settings adjusted to capture every or every other breath at full ventilatory support settings. Persistent oxyhemoglobin desaturation despite eucapnia and aggressive mechanically assisted coughing indicates impending respiratory failure and the need to re-intubate.
5. After re-intubation the protocol is repeated for a second extubation to nasal ventilation, or after successful extubation, the patient may wean to nocturnal nasal ventilation in 3–21 days, usually accomplished at home.
6. Discharge home after the SpO₂ remains ≥95% for 24–48 h.

Abbreviation: SMA, spinal muscular atrophy.

lateral sclerosis (ALS),²³ post-polio,²⁴ high-level tetraplegia,²⁵ and other conditions with respiratory muscle paralysis can avoid tracheostomy.²⁶ Thus, older children and adults with little or no vital capacity can be managed without tracheostomy provided that bulbar-innervated muscle dysfunction is not to the degree that continuous saliva aspiration causes SpO₂ baseline to decrease below 95%.²³ This rarely happens in any neuromuscular condition other than advanced bulbar ALS. Since dysfunction of SMA-1 children's bulbar-innervated musculature appears to be similar to that of bulbar ALS patients, like other physicians we recommended tracheotomy and considered it essential for survival in SMA-1 until 1995.

In 1995, the parents of 2 children with typical SMA type 1 (Figs. 3 and 4), refused tracheotomies despite being informed by us that their children would probably not survive 1 year. One of the 2 SMA-1 patients became continuously noninvasive ventilation-dependent at 8 months of age. His vital capacity plateaued at 150 mL at age 4 (Fig. 3). With severe bulbar-innervated muscle failure, the patient could never speak and required nutrition via nasogastric tube by 4 months of age. The second child's vital capacity plateaued at 190 mL at age 10. These children, now 14 and 16 years old, respectively, still have no tracheostomy tubes (Figs. 5 and 6), and one has a brother with the same condition 2 years younger with a vital capacity plateau of 70 mL (Fig. 1) at age 6 years (Figs. 3 and 5). The 2 brothers now have vital capacities of 20 and

15 mL, respectively (Fig. 1). Because, despite absence of any autonomous ability to breathe, these first 2 children did so well without tracheostomy tubes, in 1996 we began to discourage tracheotomy and promote noninvasive ventilation and mechanically assisted coughing for these patients.

We reviewed the status of all SMA-1 patients who visited our neuromuscular disease clinic from March 1996 through 2009. We have previously reported outcomes on 80 of these patients including 21 who did not use mechanical ventilation, through June 2006.¹⁵ These 21 patients died from respiratory failure at mean (SD) age 9.4 ± 4.1 months of age. For 20 of these patients, noninvasive ventilation, mechanically assisted coughing, and invasive tubes were refused. One patient died before insurance company approval for the respiratory support equipment.

There were 95 with typical, severe SMA type 1A and 7 with SMA-1B who have received assisted ventilation at our center. SMA-1 was diagnosed on the basis of DNA evidence of chromosome 5 exons 7 and 8 deletion in 95 of 102 children, affected siblings with genetically confirmed disease in 5 patients, and characteristic laboratory, muscle biopsy, and electromyography results in 2 children who did not undergo DNA testing. Inclusion criteria for "typical" SMA type 1A, besides inability to roll or sit unsupported at any time, included plateau vital capacity never exceeding 300 mL, and respiratory muscle failure and loss of ability to receive any nutrition by mouth before 24 months of age. By 18 months



FIG. 5. Brothers with spinal muscular atrophy (SMA) type 1 seen in Figure 3 are now 14 and 12 years of age. Remarkably, unlike all 100 other patients, these boys have received all nutrition via nasogastric tubes since 8 and 4 months of age, respectively, without episodes of sinusitis or other untoward effects.

of age all of the patients had little more than residual finger, toe, and facial movements. SMA-1 patients whose vital capacities ever exceeded 300 mL or who were able to take food by mouth and did not develop respiratory failure until age 2 or later are considered type 1B.

The 27 of 95 type 1A patients who had tracheostomy tubes included 14 who had the tubes placed at mean (SD) 7.6 ± 3.3 months of age, before referral to our clinic. Three others underwent tracheotomy because of acute respiratory failure before being able to procure prescribed equipment for noninvasive ventilation because of medical insurance delays. Seven of 27 were type 1A patients who were initially managed using noninvasive ventilation until a mean (SD) age of 41.5 ± 18.3 (range 24–71) months and a 1B patient on continuous noninvasive ventilation who underwent tracheostomy at 20 years of age due to upper airway obstruction. Two other patients underwent tracheostomy at mean (SD) 12.0 ± 6.6 months of age because of congenital bronchomalacia and anoxic encephalopathy, respectively.

Ten of 27 tracheostomy ventilation users died at mean (SD) 61.6 ± 72.2 (range 16–270) months of age, 5 suddenly either from mucus plugging or bradycardia, 2 from accidental disconnections, and 1 each from sepsis, cerebral hemorrhage, and complications of bronchiectasis. One patient died at 270 months of age from bradycardia after continuous respiratory support via tracheostomy tube since 2 months of age. Two who died suddenly had chronic purulent bronchitis, which is likely a complication related to the artificial airway. One patient died suddenly due to persistent whole lung atelectasis from congenital bronchomalacia 6 months after tracheotomy and one died 2 weeks after tracheotomy because of anoxic encephalopathy that occurred during a cardiopulmonary arrest from airway mucus plugging before undergoing tracheotomy. Seventeen are still alive at mean (SD) 78.2 ± 36.1 (range 65–179) months of age.

Six patients had comprehensible speech at the time of tracheotomy and retained some verbalization afterward. None of the 21 patients who had not developed speech before tracheotomy did so after it. Twenty five of 27 lost all autonomous breathing ability immediately after tracheotomy, whereas 2 patients temporarily weaned to nocturnal-only ventilation.

Of the 75 remaining SMA-1 patients on noninvasive ventilation, 68 are type 1A and 7 are type 1B. Of the 68 type 1A patients using noninvasive ventilation, 56 are still alive at a



FIG. 6. Child seen in Figure 4 is now 16 years of age with a vital capacity plateau of 190 mL at age 14.

TABLE 2. RESPIRATORY HOSPITALIZATIONS PER YEAR

Patient #	Year																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
SMA Type 1A																						
1	—	1	—	→																		
2	1	1→*																				
3	—	1	1	—	→																	
4	2	—	↓																			
5	1	—	—	—	—	—	—	↓														
6	1	—	—	—	—	→																
7	1	—	—	—	—	↓																
8	1	1	—	—	—	—	—	—	→													
9	1	—	1	—	—	—	—	—	—	—	—	—	→									
10	1	1	→																			
11	1	—	1	—	—	—	—	—	→													
12	1	1	—	—	1	—	→															
13	1	4	1	2	2	1	—	—	—	→												
14	1	1	1	—	—	—	—	↓														
15	2	1	—	—	—	—	—	—	—	1	—	—	→									
16	2	1	—	—	1	—	—	→														
17	1	3	—	—	→*																	
18	—	4	1	↓																		
19	1	↓																				
20	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
21	1	1↓																				
22	2	2	1	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	→
23	—	4	3	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	→
24	2	—	—	—	—	—	—	↓														
25	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	→
26	—	—	—	—	—	—	1	—	—	—	—	—	→									
27	2	2	—	—	—	—	—	—	—	—	—	→										
28	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
29	3	2	1	—	—	1↓																
30	1	—	—	—	5	↓																
31	3	1	—	—	—	—	—	—	1	1	—	—	→									
32	—	2	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
33	—	1	3	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	→
34	1	1	7	2	1	—	—	—	—	—	—	—	→									
35	4	4	4	—	—	—	—	—	—	↓												
36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
37	1	1	1	→																		
38	—	3	2	—	—	2	2	1	1→													
39	—	6	2↓																			
40	→																					
41	2	8	—	—	—	—	→															
42	—	1	→																			
43	1	2→																				
44	1	—	→																			
45	1	—	—	—	→																	
46	—	↓																				
47	2	—	—	→*																		
48	2	1	—	—	→																	
49	1	1																				
50	3	2	—	1	→																	
51	—	1→																				
52	1→*																					
53	1	—	—	—	→																	
54	3	3	1→																			
55	1	→																				

(Continued)

TABLE 2. (CONTINUED)

Patient #	Year																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
56	2	1	2→																			
57	2	—	1	→																		
58	1	—	1	—	→																	
59	1	2	—	—	—	1	—	→														
60	2	1→																				
61	—	1→*																				
62	1	→																				
63	—	—	1	—	—	→																
64	1	3	—	→*																		
65	1→*																					
66	1	2	2	3	2↓																	
67	—	3	—	—	2	3	—	—	→													
68	1	1	—	—	—	→																
Total Hosp	75	84	38	9	16	8	3	2	2	3	0	1	0	0	0	1	0					
Total Pts	68	66	55	48	41	33	27	23	19	15	13	13	12	7	6	2	1					
SMA Type 1B																						
1	3	5	1	—	—	—	—	—	—	—	—	→										
2	—	2	—	—	—	—	—	→														
3	—	1	1	—	—	1	—	—	1	1	1	—	—	—	—	—	—	—	—	1	—	→*
4	—	—	1	—	—	—	1	—	1	—	—	→										
5	—	—	—	—	—	9	→															
6	—	—	—	—	—	—	↓															
7	—	1	—	—	—	—	—	—	—	—	1	—	—	—	→							
Total Hosp	3	9	3	0	0	10	1	0	2	1	2	0	0	0	0	0	0	0	0	1	0	0
Total Pts	7	7	7	7	7	7	7	5	4	4	4	4	2	2	2	2	2	2	2	2	1	1

Abbreviations: Pt(s), Patient(s); Hosp, Hospitalizations.
 — Indicates no hospitalizations in a given year.
 → Indicates that the patient is still alive.
 ↓ Indicates when the patient died.
 * Indicates that the patient underwent tracheotomy.

mean age of 80.3 (range 13–196) months. Twelve died at 52.1 (range 13–111) months of age. Eight died suddenly at home from probable mucus plugs or bradycardias. One died from an intracranial hemorrhage while intubated for respiratory failure. Two died from mucus plugs during respiratory tract infections when intubation was unsuccessful. Another died from a pulmonary embolism.

Sixty of the 68 individuals on chronic noninvasive ventilation could communicate verbally and 19 were continuously dependent on noninvasive ventilation with no ventilator-free breathing ability. Thirty-four users of nocturnal noninvasive ventilation extended its use through daytime hours, including all 15 who are over age 10 and all 6 who are over age 15. Except for 3 whose vital capacities plateaued at 210, 270, and 300 mL, respectively, all others' vital capacities never attained 200 mL.

The 7 SMA type 1B patients' mean age is 11.6 (range 6–21) years. They have a mean (SD) maximum (plateau) vital capacity mean (SD) of 816 ± 354 mL with their vital capacity plateaus occurring between ages 5 and 12 years. Their initial episodes of respiratory failure occurred at 9, 13, 15, 24, 31, 41, and 55 months of age and gastrostomy tubes were placed at 16, 41, 72, and 179 months of age, except for 3 patients who did not require them. The 22-year-old patient with the highest plateau vital capacity of 1,170 mL has been a 24 h/day

ventilator user for 9 years. Three require continuous noninvasive ventilation. The other 4 require only nocturnal noninvasive ventilation. This group has had 32 respiratory hospitalizations in 87 patient-years. One died at 78 months of age from sepsis.

Fifty nine of the 75 SMA-1 patients have been intubated at least once for respiratory failure before 1 year of age and 287 times in all. The success rate extubating SMA-1 patients, most of whom could not pass spontaneous breathing trials either before or after extubation using the Table 1 protocol, is 121 of 143 or 85%. Eighty eight of the 121 extubations were performed on SMA-1 patients who had failed extubation in other facilities and were transferred to us after persistently refusing tracheotomy. This included 6 patients who had failed post-gastrostomy extubation.

The 27 patients with tracheostomy tubes had 31 respiratory hospitalizations in 69 patient-years (0.4 ± 0.8/patient-year) in their first 3 years with the tubes, then 23 hospitalizations in the 109 patient-years (0.2 ± 0.7/patient-year) subsequently. This compared with 197 hospitalizations over 189 patient-years for the SMA-1A group (1.1 ± 1.3/patient-year) and 15 hospitalizations over 21 patient-years (0.7 ± 1.3/patient-year) for the SMA-1B group's first 3 years, then 45 hospitalizations over 260 patient-years (0.2 ± 0.6/patient-year) for the SMA-1A group and 17 hospitalizations over 66 patient-years

(0.3 ± 1.2 /patient-year) for the SMA-1B group's years subsequent to the third birthday. While the tracheostomy patients had significantly fewer hospitalizations over the first 3 years ($P = 0.0003$) than both 1A and 1B noninvasive ventilation groups, there was no difference subsequently ($P = 0.86$). Hospitalizations per patient-year for the noninvasive ventilation users are noted in Table 2. The noninvasively ventilated patients' parents also reported hundreds of avoided hospitalizations defined as episodes of continuous respirator dependence with oxyhemoglobin desaturations below 95% that were reversed by mechanically assisted coughing without hospitalization.¹⁵ Mechanically assisted coughing use by tracheostomy ventilation users also appeared to result in a drop-off of hospitalization rates for individual patients, for example, one patient had 4 respiratory hospitalizations in 4 years post-tracheostomy versus none in 9 years subsequent to initiation of mechanically assisted coughing.

Eight noninvasive ventilation users underwent tracheostomy. The 4 who had tracheostomy for severe airway secretion management difficulties were felt by their parents to be better off with the tracheostomy. The 4 patients who underwent tracheostomy for extubation failure later regretted it. Since most health care providers are familiar with tracheostomy tubes, parents tend to be spared from having to provide continuous care when the patient has a tracheostomy tube.

While the ages of the tracheostomy patients are greater than those of the noninvasive ventilation users, the data are skewed by the fact that the 27 tracheostomy patients were referred to our center at 25.7 ± 44.3 months of age as opposed to 9.1 ± 10.7 months of age for noninvasive ventilation users and, in most cases, after undergoing tracheostomy. For example, in one case, a tracheostomy ventilation user who subsequently died at 22 years of age first visited us at age 19.

Conclusions

Following our protocols for assisted ventilation using volume or pressure-control intermittent positive pressure ventilation, mechanically assisted coughing, and home pulse oximetry monitoring to identify need for escalation of noninvasive ventilation and mechanically assisted coughing, prolonged survival is possible for patients with SMA type 1, with survival to 17 years for SMA-1A and 22 years for SMA-1B documented so far. Patients managed with tracheostomy had fewer hospitalizations prior to age 3 compared with those managed with the noninvasive ventilation approach. Post-tracheostomy, patients did not regain the ability to breathe spontaneously and did not develop the ability to verbalize.²⁷

Our experience demonstrates that "unweanable" SMA-1 patients can be successfully extubated to noninvasive ventilation, which allows these patients prolonged survival without tracheostomy, far beyond the survival described in textbooks and the medical literature. Hospitalization rates diminish to levels equal to those of patients with tracheostomy tubes after age 3 when children can fully cooperate with mechanically assisted coughing. Routine nocturnal use of noninvasive ventilation from diagnosis facilitates future extubations besides its other benefits. The current paradigm of not extubating patients until ventilator

weaned, extubating without full noninvasive ventilation support, using airway and chest vibration methods rather than mechanically assisted coughing to expulse secretions, and routinely administering oxygen rather than using full-setting noninvasive ventilation and mechanically assisted coughing with oximetry feedback must be re-thought to permit long-term survival without tracheostomy.

References

- Ogino S, Wilson RB. Spinal muscular atrophy: molecular genetics and diagnostics. *Expert Rev Mol Diagn* 2004; 4:15–29.
- Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, Bromberg MB. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol* 2005; 57:704–712.
- Niranjan V, Bach JR. Noninvasive management of pediatric neuromuscular ventilatory failure. *Crit Care Med* 1998; 26:2061–2065.
- Menkes JH, Harvey B, Sarnat HB, Bernard L. Diseases of the motor unit. In: Menkes JH, Haftrvey B, Sarnat HB, Bernard L, eds. *Child neurology*, 7th ed., Philadelphia: Lippincott Williams & Wilkins, 2006, pp. 972–978.
- Kang PB. Spinal muscular atrophy. In: Schwartz MW, ed. *The 5-minute pediatric consult*, 5th ed. Philadelphia: Walters Kluwer, Lippincott Williams & Wilkins, 2008, pp. 796–797.
- Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Disorders of neuromuscular transmission and of motor neurons: Nelson textbook of pediatrics, 18th ed. Philadelphia: Saunders, 2007, pp. 2557–2559.
- Parke JT. Disorders of the anterior horn cell. In: McMillan JA, Feigin RD, DeAngelis CD, Jones MD, Jr., eds. *Oski's pediatrics principles & practice*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2006, pp. 2307–2309.
- Hughes MI. Neuromuscular disease. In: McIntosh N, Helms P, Smyth R, Logan S, eds. *Forfar et Arneil's textbook of pediatrics*, 7th ed., Philadelphia: Elsevier, 2008, pp. 916–917.
- Bach JR, Vega J, Majors J, Friedman A. Spinal muscular atrophy type 1 quality of life. *Am J Phys Med Rehabil* 2003; 82:137–142.
- Bach JR. Quality of life and ethical issues. In: Bach JR, ed. *The management of patients with neuromuscular disease*. Philadelphia: Hanley & Belfus, 2004, pp. 331–354.
- Cobben JM, Lemmink HH, Snoeck I, Barth PA, van der Lee JH, de Visser M. Survival in SMA type I: a prospective analysis of 34 consecutive cases. *Neuromuscul Disord* 2008; 18:541–544.
- Bach JR, Bianchi C. Prevention of pectus excavatum for children with spinal muscular atrophy type 1. *Am J Phys Med Rehabil* 2003; 82:815–819.
- Birnkrant DJ, Pope JF, Martin JE, Repucci AH, Eiben RM. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. *Pediatr Neurol* 1998; 18:407–410.
- Bach JR. Physiology and pathophysiology of hypoventilation: ventilatory vs. oxygenation impairment. In: Bach JR, ed. *Noninvasive mechanical ventilation*. Philadelphia: Hanley & Belfus, 2002, pp. 25–45.
- Bach JR, Saltstein K, Sinqee D, Weaver B, Komaroff E. Long-term survival in Werdnig-Hoffmann disease. *Am J Phys Med Rehabil* 2007; 86:339–345 quiz 346.
- Kang SW, Bach JR. Maximum insufflation capacity. *Chest* 2000; 118:61–65.
- Suri P, Burns SP, Bach JR. Pneumothorax associated with mechanical insufflation-exsufflation and related factors. *Am J Phys Med Rehabil* 2008; 87:951–955.
- Leith DE. Lung biology in health and disease: respiratory defense mechanisms, part 2. In: Brain JD, Proctor D, Reid L, eds. *Cough*. New York: Marcel Dekker, 1977, pp. 545–592.

19. Bach JR. Pediatric respiratory management. In: Bach JR, ed. The management of patients with neuromuscular disease. Philadelphia: Hanley & Belfus, 2004, pp. 309–330.
20. Bach JR, Niranjana V, Weaver B. Spinal muscular atrophy type 1: A noninvasive respiratory management approach. *Chest* 2000; 117:1100–1105.
21. Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: management and outcomes. *Pediatr Pulmonol* 2002; 34:16–22.
22. Gomez-Merino E, Bach JR. Duchenne muscular dystrophy: prolongation of life by noninvasive ventilation and mechanically assisted coughing. *Am J Phys Med Rehabil* 2002; 81:411–415.
23. Bach JR, Bianchi C, Aufiero E. Oximetry and indications for tracheotomy for amyotrophic lateral sclerosis. *Chest* 2004; 126:1502–1507.
24. Bach JR, Alba AS. Sleep and nocturnal mouthpiece IPPV efficiency in postpoliomyelitis ventilator users. *Chest* 1994; 106:1705–1710.
25. Bach JR, Alba AS. Noninvasive options for ventilatory support of the traumatic high level quadriplegic patient. *Chest* 1990; 98:613–619.
26. Bach JR. The management of patients with neuromuscular disease. Philadelphia: Elsevier 2004, p. 414.
27. Bach JR, Rogers B, King A. Noninvasive respiratory muscle aids: Intervention goals, and mechanisms of action. In: Bach JR, ed. The management of patients with neuromuscular disease. Philadelphia: Hanley & Belfus, 2004, pp. 211–270.

Address correspondence to:

John R. Bach, MD
Department of Physical Medicine and Rehabilitation
University Hospital B-403
150 Bergen Street
Newark, NJ 07871

E-mail: bachjr@umdnj.edu

Received for publication February 1, 2010; accepted after revision February 1, 2010.

