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Research article

Spinal Muscular Atrophy: Noninvasive Respiratory Management

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ABSTRACT

Introduction: Without effective respiratory management, all patients with SMA type 1 and the 50% with type 2 and paradoxical breathing die in infancy or early childhood. Usually benign Upper Respiratory tract Infections (URIs) typically cause pneumonia and acute respiratory failure. Patients may be intubated, and when unweanable from ventilatory support, tracheotomy is urged for survival. However, up to Continuous Noninvasive Ventilatory Support (CNVS) and Mechanical In-Exsufflation (MIE) permit patients with SMA types 1-4 to live without tracheotomies.

Methods: NVS is provided via oral, nasal, and oronasal interfaces at full ventilatory support settings. Airway debris is expelled by MIE via oronasal interfaces, mouthpieces, and invasive airway tubes, when present, at 40 to 70 cm H2O pressures. Intubated patients are extubated to CNVS and MIE irrespective of extent of dependence on ventilatory support or vital capacity. Patients become CNVS dependent when it cannot be discontinued without immediate dyspnea, O2 desaturation, and severe distress.

Results: 150 patients with SMA type 1 were prescribed sleep NVS as infants and although they became dependent on CNVS and MIE and needed to be extubated to CNVS and MIE for intercurrent episodes of ARF, at least 17 were CNVS dependent for 5 to 25 years. Likewise, 39 of 78 with SMA type 2 depended on NVS at least while sleeping and on CNVS and MIE during URIs with three being CNVS dependent for 11.9±3.98 (range=8-15) years. The success rate for extubating ventilator "unweanable" patients was 150 in 176 attempts (85%) for SMA type 1 and 100% for 13 ventilator unweanable SMA type 2 and 3 patients. Four ventilator dependent SMA type 2 and 3 patients were also decannulated of their tracheostomy tubes.

Conclusion: Patients with SMA types 1-4 can be managed indefinitely without tracheostomy tubes.

INTRODUCTION

Without ventilatory support or new medications, patients with Spinal Muscular Atrophy (SMA) type 1 who have 1 or 2 copies of the SMN2 gene rarely survive 18 months without undergoing tracheotomies [1]. Affected children with SMA types 1 and 2 have ineffective coughs which cause otherwise benign upper respiratory tract infections to develop into pneumonia (URI-pneumonia) and Acute Respiratory Failure (ARF). Consequently, clinicians often offer little hope to families, arguing poor quality of life

even if the child were to survive. Patients with SMA type 1 undergoing Tracheotomies for Mechanical Ventilation (TMV) immediately become continuously dependent on it (CTMV) and do not develop any speech [1]. Most patients with Neuromuscular Disorders (NMDs) dependent on CTMV die because of complications of the tube rather than directly from the disease[1-3]. As an alternative, centers listed in www.breatheNVS.com offer noninvasive respiratory management.

3.1. Respiratory Pathophysiology

There are three respiratory muscle groups, failure of which can result in ARF. They are the inspiratory muscles, expiratory muscles (mainly for coughing), and the Bulbar Innervated Muscles (BIM) for protecting the airways. Respiratory muscle aids that include NVS and Mechanical Insufflation-Exsufflation (MIE) assist or substitute for inspiratory and expiratory muscle function. These aids are devices and techniques that involve the manual or mechanical application of forces to the body or intermittent pressure changes to the airways. The devices that act on the body include intermittent abdominal pressure ventilators operated by positive pressure ventilators [4]. Ventilators can also apply positive or negative pressures directly to the airways to assist the inspiratory and expiratory muscles, respectively. Untreated patients with SMA type 1 and 50% of those with type 2 have paradoxical breathing, and develop pectus excavatum and funnel shaped chests [5]. The NVS prevents chest wall deformities, permits more normal lung and chest wall growth, and maintains lung compliance and lung volume capacities [5]. Depending on the patients' needs, NVS can be provided during sleep, sleep plus part of the day, or continuously as CNVS. Up to CNVS along with MIE can prevent ARF and greatly prolong survival regardless of the patient's Vital Capacity (VC) or extent of ventilatory insufficiency/failure.

METHODS

4.1. Evaluation

Patients are evaluated for symptoms and signs of respiratory muscle dysfunction and hypoventilation. Symptoms for older children and adults can be many but often include morning headaches, fatigue, and hypersomnolence [4]. Signs in infants include paradoxical breathing, nasal flaring, flushing, perspiration, and frequent arousals. Polysomnograms are unnecessary since all infants with paradoxical breathing and symptomatic older patients require at least nocturnal NVS. Routine polysomnography is programmed to attribute apneas and hypopneas to central or obstructive events rather than to hypoventilation from weak muscles [5].

End-tidal CO2, oximetry, assessment of unassisted and assisted Cough Peak Flows (CPF), and spirometry for VC in sitting and supine positions as well as for Lung Volume Recruitment (LVR) should be assessed at every patient visit (see below). End-tidal CO2 and oximetry can also be useful for sleep monitoring. The cry VC was measured for infants and small children too young to cooperate. For SMA type 1, the tidal and cry breaths of tachypneic infants approaches their inspiratory and VCs and is a very useful indication of potential to breathe autonomously. Infants with cry VCs of 50 ml or more can breathe autonomously whereas those with lower VCs cannot [6]. Intubated infants with 50 ml of VC will wean upon extubation to CNVS whereas those with lower VCs, whose VCs do not increase post-extubation to CNVS, may not.

Plateau VC is the lifetime maximum and for some with SMA type 1 is at birth [7]. For example, Case 3 breathed autonomously at birth but the VC was 20 ml by 2 months of age then 0 ml. Thus, the plateau was at birth.

4.2. The Respiratory Muscle Aids

Inspiratory aids, that is, NVS and positive pressure insufflations, are used for LVR as well as for respiratory muscle rest and ventilatory support.

4.3. Lung Volume Recruitment

Lung volume recruitment is a means by which patients with less than normal inspiratory capacities increase lung volume and thereby CPF [4,8,9]. It can be active or passive. Active LVR is done by receiving consecutively delivered volumes of air via manual resuscitator or volume preset ventilation and holding them to deep lung volumes by glottis closure. Cough peak flows are increased by the deep volumes and increased lung recoil pressures [8-10]. The active LVR, or "air stacking," is performed via a mouthpiece, nasal, or oronasal interface or by glossopharyngeal breathing ("frog breathing") [11]. It requires that the patient seal the lips around a mouthpiece, otherwise when performed via a nasal interface, the patient must seal off the oropharynx by moving the soft palate against the tongue or must simply keep the mouth closed. Patients with SMA type 1

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can only receive passive LVR via oronasal interfaces from manual resuscitators with the exhalation valves blocked or from 50+ cm H2O positive pressurefrom a ventilator or MIE device [12].

4.4. Noninvasive Ventilatory Support (NVS)

Infants and small children are placed on nasal pressure control ventilation preferably via active ventilator circuit at the full ventilatory support settings of 17 to 25 cm H2O with physiologic back-up rates and no Positive End-Expiratory Pressure (PEEP). This more fully rests inspiratory muscles during sleep, reverses paradoxing, and greatly relieves the other signs of distress. Portable ventilators and non-vented nasal interfaces are used. Active circuits are preferred to eliminate Expiratory Positive Airway Pressure (EPAP) which, because of excessive leaks and associated auto-triggering, results in increased sympathetic activation, arousals, low to high frequency heart rate variability, and predominance of light non-REM sleep while decreasing N3 sleep [13]. The EPAP also causes a reduction in non-REM stage 2 sleep [14]. Thus, EPAP unnecessarily renders NVS less effective, disrupts sleep, increases sympathetic activation [13-15], and unnecessarily increases intrathoracic pressures and decreases venous return.

Older children and adults often have sufficient lip strength to use mouthpiece NVS. There are 15 mm angled mouthpieces, the 22 mm mouth pieces commonly used for pulmonary function testing, straw-type mouthpieces, and scuba mouthpieces. When unable to use these, nasal prongs are typically used during the daytime and perhaps mask-like interfaces for sleep. Excessive skin pressure is avoided by alternating different nasal interfaces day and night. Since active circuits are used, the interfaces must be non-vented, or if vented, the portals and all leaking surfaces must be covered and sealed. Parents and care providers are educated and trained in the clinic to place interfaces, adjust ventilator settings, evaluate for excessive air leakage, the importance of positive inspiratory pressures, and the correct application of MIE. For babies with SMA type 1 the parents are instructed to place the nasal interface on the sleeping child and gradually increase pressure settings until the child no longer awakens and paradoxical breathing is reversed. Within 1 week, babies are acclimated and tend to avoid sleeping without the nasal NVS. All patients with SMA type 1 and those with SMA type 2 who have paradoxical breathing become CNVS dependent during URIs and, because of ineffective CPF, require frequent MIE along with oximetry feedback during URIs (see the Oximetry CNVS/MIE Protocol below).

4.5. Dependence on Continuous Noninvasive Ventilatory Support (CNVS)

For SMA type 1, transition from sleep-only NVS to CNVS is complicated by the fact that these patients typically recline for months or years without assuming the sitting position, often because of lack of ability to breathe autonomously when seated. Indeed, their VCs are almost always greater when supine than when sitting, sometimes by more than 70%. Thus, they may have little dyspnea when supine yet require NVS to reverse paradoxing, but have little or no autonomous ability to breathe in the seated position. Parents tend to avoid the children assuming the seated position rather than place them on NVS when seated but this is a mistake. Excessive reclining can diminish intravascular blood volumes and autonomic tone for sitting, a position necessary for quality of life. Thus, many if not most of these children, if assuming a seated position, are in a sense CNVS dependent although they may have significant ventilator free breathing ability when supine. Thus, sleep nasal NVS must be prescribed to reverse paradoxing and thereby promote lung growth despite the fact that about 85% of these infants with typical rather than severe SMA type 1 can breathe autonomously when beginning NVS for sleep. Therefore, children using sleep NVS for paradoxical breathing are nasal CNVS dependent from the time that they have no autonomous ability to breathe in the seated position. About one half of children with SMA type 1, untreated by oligonucleotides or gene therapies, become CNVS dependent before age 10 and one-half after age 10. Virtually all patients with SMA type 1 and those with type 2 and paradoxical breathing, who are otherwise free of daytime NVS, become CNVS dependent during intercurrent URIs when they also require frequent MIE. For patients with SMA types 2-4 the transition from sleep NVS into daytime hours and sometimes to CNVS is far more gradual and most patients never depend on CNVS with no autonomous ability to breathe until old age.

4.6. Expiratory Aids or Mechanical Insufflation Exsufflation (MIE) for Secretion Mobilization

Conventional approaches for airway secretion mobilization include chest physical therapy with percussion, vibration, and postural drainage along with administration of bronchodilators and nebulization for medication administration and humidification. However, these methods are directed at facilitating mucociliary function rather than increasing cough flows. These patients have normal airways so there is no evidence that bronchodilators or chest percussion is beneficial and it certainly does not replace the need for effective cough flows to expulse debris and maintain normal room air O2 saturation. Humidification needs to be sufficient for mucus to remain loose but when excessive only increases airway secretions that line the airways and are more difficult to expel.

Mechanical insufflation-exsufflation substitutes for an ineffective cough by generating effective cough flows. It is triggered by having small children use the CoughTrak™ of the CoughAssist™ MIE device (Respironics Inc., Murrysville, Pa). Manual cycling, timing the insufflation to the child's inhalation and the exsufflation to the exhalation can be used if the device is not triggerable. Manual cycling is also important early-on to determine the insufflation times to full clinical lung expansion and the subsequent exsufflation time to full clinical lung emptying before automatic cycling times are set up [12,16]. Pressure is maintained between 40 and 60 cm H2O via oronasal or mouthpiece interfaces and 60 to 70 cm H2O via invasive airway tubes. The MIE generates about 10 liters per second of expiratory flows (MIE-EF) for effective mechanically assisted coughing. The MIE-EF can sometimes be further enhanced by applying an abdominal thrust concomitant with exhalation [12]. Typically, MIE-EF are only 50 to 70 L/m for babies with SMA type 1 but increase to 250 to 380 L/m when they are over 20 years of age.

4.7. The Oximetry CNVS/MIE Protocol

Patients and families are instructed to administer continuous pulse oximetry at the first sign of a URI and to use NVS and MIE for any O2 desaturation below 95%, on patient demand, or with sounds of airway congestion upon auscultation. If the baseline O2 sat decreases and remains below 95% and they become dyspneic, intubation for acute lung disease may be required. Once the lungs are made healthy again, in large part by using MIE hourly at 60 to 70 cm H2O pressures via the translaryngeal tube, and all extubation criteria have been met, they are extubated back to their usual NVS settings whether ventilator weanable or not (Table 1). These patients virtually never require tracheotomy for extubation failure even though a second or third attempt may be necessary for infants and children under age 3.

4.8. Extubation and Decannulation

The steps for successful extubation of ventilator unweanable patients with SMA who pass no spontaneous breathing trials or ventilator weaning parameters are noted in Table 1 [17,18]. Any oro- or nasogastric tube is first removed to facilitate nasal NVS. For adolescents and adults extubation is to nasal CNVS at volumes set between 800-1500 mL, rate 10-14 breaths per minute in ambient air for patients who can air stack, and at pressure control 18 to 25 cm H2O for infants and small children who cannot air stack. A key for infants is getting them in synchrony with the nasal NVS. This can sometimes be facilitated for these very tachypneic infants by setting a back-up rate to slightly over one-half the respiratory rate and capturing every other breath, then decreasing the rate as the child's deeper tidal volumes ease the tachypnea. After comfortably ventilating the lungs via a nasal interface, older patients are educated on how to use NVS via 15 mm angled mouthpieces. Family members and other care providers must be present in critical care to provide MIE up to every 20 minutes for any O2 desaturations below 95% for the first 24 to 36 hours post-extubation. This protocol renders tracheotomies unnecessary [17-20].

For children dependent on more than sleep NVS, decannulation is deferred until at least 12 years of age at which point they have full understanding and can cooperate fully on how to achieve this. Small children using only sleep NVS can only be decannulated if they can be counted on to cooperate with nasal NVS. Ventilator weaned patients can be decannulated at any age provided that the trachea and adjacent airways have not been severely damaged by the presence of the tube. The steps for decannulating motivated and cooperative older patients are similar to those for extubation [21].

Table 1: Intubation Management and Extubation Protocol.

While intubated:
1. Conventional management of infectious disease, nutrition, and other supportive medical care.
2. Limit oxygen delivery for O2 saturation of 94%–95%.
3. Use MIE via the tube at 60 to 70 cm H2O to -60 to -70 cm H2O pressures for 3 to 5 cycles multiple times.
To up to every 60 min until O2 saturation becomes and/or remains normal. Endotracheal tube and upper airways are suctioned after MIE.
4. Attempt to wean from ventilation without permitting hypercapnia.
5. Extubate the patient even if the patient cannot pass spontaneous breathing trials when meeting the following criteria:

a) Afebrile and normal white blood cell count;
b) Medically stable;
c) O2 saturation ≥95% at room air for over 12 h;
d) Chest radiograph abnormalities are clear or clearing;
e) Fully alert mental status
f) Airway suctioning is required only 1-2 times every 8 h or airway secretions are no longer decreasing;
g) Coryza is diminished sufficiently so that suctioning of the nasal orifices is required less than once every 8 h to permit post-intubation nasal NVS.

Extubation:
1. Remove naso/orogastric tube if present.
2. Extubate to continuous full-setting NVS using pressure control ventilation via active ventilator circuit with no supplemental oxygen for small children and possibly volume preset ventilation for older patients.
3. Use oximetry feedback to guide the use of NVS, MIE, postural drainage, and chest physical therapy to reverse any desaturations due to airway mucus buildup/plugging or underventilation.
4. With CO2 retention or ventilator dyssynchrony, eliminate any nasal air leaks and adjust settings to capture every or every other breath at full NVS. Continuous desaturation despite normal CO2 levels and aggressive use of MIE indicates impending respiratory failure and need for re-intubation.
5. After re-intubation, repeat protocol for a second extubation to nasal NVS or after successful extubation,
the patient may wean to nocturnal nasal NVS in 3–21 days depending on extent of vital capacity, can be accomplished at home.
6. May discharge patient if O2 saturation ≥ 95% for 24–48 h

Table 2: Types of SMA patients and their ventilatory management.

SMA Type	Number NVS	Duration NVS* (years)	VC NVS plateau or maximum observed (ml)	Number CNVS	Duration CNVS (years)	VC CNVS (ml)	Current Age (years)	Extubations/Attempts	Air Stack	Number nNVS
1	61	10.7±1.9	328±321	17*	12.0±1.9	0-40 ml	17.5±3.1	147/173	U	0
2	106	16.2±6.02 Range: 3-30	587±371	5	11.9±3.98 Range: 8-15	135±71.9	23.9±13.1 Range:0.4-76	13/13	55	29
3	23	12.3±7.08 Range:1-22	1741±1395	1?	?	?	43.8±16.4 Range:29-91	3/3	22	61
4	1	4.19	3110	0	0	0	66	5/5	-	3

SMA Type – Spinal Muscular Atrophy type; NVS – Noninvasive Ventilatory Support (see text); Number NVS – number of patients using NVS <23 hr/day; Duration NVS-Duration of dependence on NVS; VC NVS – Average maximum observed or plateau vital capacity of the 61 NVS users; Number CNVS - number of patients using continuous noninvasive ventilator support; Duration CNVS - Average duration of dependence on CNVS with no autonomous breathing ability; VC CNVS – Average vital capacity of CNVS patients; Current Age – Average age currently or at last visit; Number of successful extubations/attempts of "unweanable" patients to CNVS; Air Stack – Number of patients capable of air-stacking and performing it regularly; Number nNVS – Number of patients not using NVS; U – Unable

*Although 150 patients with SMA type 1 were prescribed NVS and all would have been dependent on CNVS during URIs to prevent acute respiratory failure, 61 were documented to have used NVS for at least sleep. Although these patients used NVS during sleep to reverse signs of distress (see text), they could generally not tolerate upright (seated) positioning without using NVS. Since they were able to breathe autonomously supine for over 1 hour despite paradoxing, they were not considered CNVS dependent by our definition until having lost all autonomous breathing ability. Thus, the 61 began NVS at 6.3±4.5 months of age and the 17 who used CNVS with no autonomous breathing ability for at least 5 years used it for sleep and when sitting for 5.1 years before becoming CNVS dependent with no autonomous breathing ability for 12.0±1.9 years to a mean age of 17.6±3.1 years.

RESULTS AND OUTCOMES

Table 1 denotes criteria for extubation and the steps of the extubation protocol. (Table 2) notes patients by SMA type, extent of need for and duration of use of NVS, as well as protocol extubation success rates. All patients were placed on NIV/NVS from time of diagnosis from 2 to 18 months of age. There were 150 patients with SMA type 1 prescribed NVS or switched from NIV to NVS. However, 23 of 30 (77%) local patients but only 38 of 120 (32%) out-of-state patients came for repeated annual visits. A follow up telephone call was made to those who stopped coming. It is unclear whether or not the 68% of 1-visit out-of-state patients' children were ever set up using NVS. Almost invariably the respiratory therapists of home care companies have no understanding of using active ventilator circuits for pressure control via non-vented nasal interfaces or bi-level PAP at NVS settings so only inadequate low span bi-level PAP (NIV) is generally used, irrespective of what I prescribe, until the children develop ARF and die or undergo tracheotomy. Most of our 23 multi-visit local patients, however, were managed by local home care companies with respiratory therapists specifically educated and trained in NVS and the oximetry CNVS/MIE protocol. Thus, at least eight have so far survived over 20 years using nasal CNVS and were extubated by us to CNVS and MIE despite none having more than 40 ml of VC or any autonomous ability to breathe.

From (Table 3), 17 of the 61 patients with SMA type 1 having multiple visits were so far documented to depend on CNVS for >5 years with no autonomous breathing ability. Of the 17, 9 (53%), were local. None of these local patients have died despite dependence on NVS/CNVS for 16.1 (range 5 to 25.3) years and their current average age is 20.5 (range=5.9-26) years (Figure 1). Only three non-local patients have thus far survived over 10 years using CNVS. Although none of these local patients have died, four non-local patients died, in 2 cases during sleep, and in two cases due to intensivists not extubating them to CNVS and MIE. One was extubated to death and the other underwent tracheotomy then died from a tracheal bleed. Besides having no VC, two of the local patients, Cases 6 and 10, have absolutely no volitional or BIM movement other than for several millimeters of eye excursion. They have never been able to make any vowel or consonant sounds nor have they been able to take any nutrition by mouth since 4 months of age but both are high school graduates. They became CNVS dependent by 4 and 6 months of age, respectively, in both cases without hospitalization. They were hospitalized and intubated for pneumonias for the first and only times at 8 and 12 years of age then extubated back to CNVS and MIE. Six of these 17 patients became CNVS dependent without being hospitalized.

Figure 1: 24 year old with spinal muscular atrophy type 0 with 0 ml of vital capacity, dependent on continuous nasal noninvasive ventilatory support since 4 months of age [37]. He has also received all nutrition via an indwelling nasogastric tube since 4 months of age.

While using domiciliary NVS/CNVS and MIE, the 61 patients with SMA type 1 required intubation one or more times for ARF but were extubated to CNVS and MIE despite multiple extubation failures elsewhere (Table 2). Three cases of ventilator unweanable patients with SMA type 1 remained intubated for as long as 5½ months and failed 5 to 6 extubation attempts while awaiting insurance coverage for transfer for successful extubation to CNVS and MIE in each case in under 48 hours.

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Table 3: Patients with SMA type 1 with 2 Copies of SMN 2 Dependent on CNVS for Over 5 Years.

		VC(ml)							Age (years)
		Plateau	Plateau	Last	years		Intubations		
Patient	Local	VC	VC	VC	CNVS	Hosp	<age 5	>age 5	
1	yes	5.4y	110	0	13.1	6	2	0	16.6
2	no	2.3y	40	10	10.1	3	3	0	11.4†
3	no	0.0y	65	0	5.4	4	2	0	6.9†
4	yes	5.0y	140	0	17.7	2	3	1	20.1
5	no	5.5y	300	40	7.9	3	1	0	22.2
6	yes	4.0y	40	0	23.3	1		1	23.7
7	yes	4.1y	70	0	25.3	1		1	25.9
8	yes	8.8y	100	0	16.6	3	3	1	17.3
9	no	4.0y	300	20	13.2	3	3	0	24.4
10	yes	3.3y	150	0	23.9	1	0	1	24.5
11	no	5y	130	0	8.5	3	1	0	10.1
12	no	5y	100	0	18.3	7	5	0	20.3
13	yes	11y	170	20	12.8	7	3	1	25.1
14	yes	14.1y	270	40	7.3	8	10	1	26.0‡
15	no	¿	¿	-	5.5	2	1	1	6.7†
16	yes	3.5	140	30	5.0	1	0	0	5.9
17	no	¿	¿	0	7.4	0	0	0	10.7

VC-(cry) vital capacity; plateau-lifetime máximum; CNVS-continuous noninvasive ventilatory support with no autonomous ability to breathe and VC less than 50 ml; hosp-respiratory hospitalizations; intubations-intubations for acute respiratory failure resulting in extubations to CNVS and mechanical insufflation-exsufflation (MIE) without resort to tracheotomy, all extubations of patients over age 5 were to CNVS and MIE as were 21 of the extubations before age 5; † died; ‡ 3 copies of SMN2.

Causes of death: #2 unknown, #3 underwent tracheotomy and died from tracheal bleed 3 months later, #15 extubated to death by a Parisian pediatric intensivist with no knowledge of extubation to CNVS and MIE.

The VCs of SMA types 2 and 3 patients are also typically greater in the supine position. These patients can require sleep NVS to relieve hypoventilation symptoms and normalize daytime blood gases for years before requiring and/or becoming dependent on daytime NVS or CNVS. Of 222 patients with SMA type 2 currently a mean 41.8±8.9 years of age, 106 (48%) had paradoxical breathing and were placed on sleep NVS as small children. Virtually all of the 106 eventually extended sleep NVS into daytime hours once their VCs decreased below 300 ml. They used sleep NVS for a mean 16.2±6.0 (range: 3-30) years and sleep plus some daytime NVS for a total of at least 11.9±4.0 years. Four were known to have died from non-respiratory causes. Only four of these patients have thus far become CNVS dependent with no autonomous breathing ability and VCs less than 120 ml. All of the 106 patients required CNVS during intercurrent URIs along with MIE and the oximetry CNVS/MIE protocol to avoid URI-pneumonias and ARF. However, 29 of the 109 patients had URI-pneumonias for which they not only required intubation but were ventilator unwinnable and failed conventional extubation attempts, refused tracheotomies, and were transferred to our center for successful extubation to CNVS and MIE. For one patients with SMA type 2 this occurred twice at ages 3 and 29 years. These 106 patients with SMA type 2 are currently 23.9±13.1 (range=0.4 to 76) years of age.

Likewise, 23 SMA type 3 patients extended sleep NVS into daytime hours after 12.3±7.08 (range: 1-22) years with three intubated and ventilator unweanable patients requiring transfer to us for extubation to CNVS and MIE.

All SMA 1-4 patients wean back to pre-intubation ventilator use regimens within 1 month following extubation. This is in contrast to patients undergoing tracheotomies who, especially for SMA type 1, almost invariably remain CTMV dependent for life with little to no autonomous ability to breathe. Indeed, while 85% of our extubation attempts on ventilator unweanable patients with SMA type 1 are successful and virtually all patients are successfully extubated without undergoing tracheotomy, the conventional extubation success rate for SMA type 1 is only 6% [19,20]. While 80% of patients with SMA type 1 managed with NVS/CNVS develop and retain functional speech, patients with SMA type 1 undergoing tracheotomies do not develop speech.

DISCUSSION

These outcomes data demonstrate that virtually all patients with SMA, other than those few with severe bradycardia's and cardiovascular instability, can be managed indefinitely without resort to tracheotomies. Patients with SMA type 1A who are CNVS dependent before 6 months of age are surviving over 25 years despite having no skeletal or BIM function at all. Virtually all SMA patients who experience URI-pneumonias or who require surgical procedures under general anesthesia can be extubated to CNVS and MIE without resort to tracheotomy. We had only one typical SMA type 1 patient fail 3 protocol extubation attempts and undergo tracheotomy only to greatly regret this when observing the functional gains he has been subsequently making by nusinersen administration. Two others underwent tracheotomies due to severe autonomic dysfunction and bradycardias causing loss of consciousness and severe O2 desaturation.

Considering out-of-state patients with SMA type 1, only three of 38 have thus far become CNVS dependent for over 10 years by comparison to seven of 23 local patients so far. Whereas local patients were cared for by NVS/MIE expert

home care respiratory therapists, this was not the case for most out-of-state patients. This demonstrates the need for all SMA treatment centers to have respiratory therapists and that they be expertly trained. The local patients with more frequent routine clinic visits were better primed to use the oximetry CNVS/MIE protocol to prevent URI-pneumonias and ARF and so to avoid the pressure to undergo tracheotomies by the critical care specialists of other institutions. When hospitalized out-of-state conventional management includes supplemental O2 rather than CNVS and MIE so ARF and tracheotomy or death is almost inevitable since only 6% of conventional extubation attempts of SMA type 1 patients are successful and only some www.breatheNVS.com centers have intensivists who extubate ventilator unweanable patients to CNVS and MIE.

Tracheostomy tubes can cause mediastinitis, pneumonia, tracheitis, sternoclavicular osteomyelitis, tracheoesophageal fistulae, thyroid injury, bleeding, infection, cannula/tube displacement, trachiectasis, tracheomalacia, cardiopulmonary arrest and mortality from other causes [22]. As noted, tracheostomy can also prevent speech to develop and result in immediate and permanent loss of any ability to breathe autonomously. In a 2009 study of 27 CTMV dependent children with SMA, 93% lost their autonomous breathing ability immediately after tracheotomy. Six with comprehensible speech retained partial verbalization after tracheostomy and the other 21 did not develop speech at all [1]. With NVS, patients wean back to pre-intubation NVS regimens and speech typically develops.

One of the key objectives of NVS is to promote lung growth and maintain lung and chest wall compliance by reversing paradoxical breathing [4,23]. Polysomnographic titrations of bi-level PAP do not accomplish this. The lungs of sleep NVS SMA 1 users can receive > 2 L of air by passive LVR by adolescence even when having 0 ml of VC [24]. Both MIE and NVS are useful for lung and chest wall expansion [12,24].

While the hospitalization/intubation rate for SMA type 1 is 0.7 per year until the 3rd birthday and 0.3/year from then to the 5th birthday it is far less than 0.1 per year subsequently as the patients cooperate better with MIE [1]. Avoidance of hospitalizations and ARF maintains quality of life and greatly reduces cost. Noninvasive management is, therefore, the desired option for quality of life, cost, and survival. In addition, there are third party payers who refuse to pay for Nusinersen therapy for SMA patients with tracheostomy tubes.

Considering the CNVS MIE protocol extubations, the often need for very frequent MIE for the first few post-extubation days and having the parents or other care providers administer it in the intensive care unit not only facilitates successful extubations and relieves hospital staff burden but facilitates the care providers' education and training in how to provide CNVS and MIE. This tends to decrease the likelihood of future respiratory complications and hospitalizations.12 Relying only on chest physiotherapy and suctioning rather than MIE is often ineffective and tiring [25].

6.1. Quality of Life: "Terminal illness" is a Self-Fulfilling Prophesy

In 2017, 64 families with children with SMA type 1 were asked to participate in a survey to gauge their child's quality of life. Healthcare providers were asked to participate for comparison. A t-test demonstrated a statistically significant difference between the two groups. The 104 care providers had a more positive perception of patients' quality of life, 7.8±0.2, compared to 67 clinicians' 2.9±0.2, $p<0.0001$ [26]. The parents and other care providers noted that the children were very happy and their lives very worthwhile despite a relatively high effort to raise them. The ongoing use of NVS was clearly not considered an intolerable burden for these children or their care providers [26].

Other surveys have also demonstrated the extent to which health care professionals underestimate severely disabled ventilator users' satisfaction with life [27,28] Unfortunately, physicians' inaccurate assessment of patients' quality of life affect the likelihood of administering therapeutic interventions. Physicians consider patients' quality of life to justify withholding therapy rather than to administer it in the form of mechanical ventilation ($p<0.01$) [29,30]. Physicians often intentionally withhold information on ventilator use thinking that the quality of life of these children does not warrant them surviving and their parents cannot make the "appropriate" decision to "let them go". This has been told to parents by physicians of affected children at "Families of SMA (CureSMA)" annual conferences before nusinersen became available.

The emotional status of the children with SMA also needs to be assessed. It was reported that five SMA type 2 and 3 patients

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had intense and recurrent anguish about death [31]. The paper reported SMA as "a terminal disease." Thus, a large part of the anguish can be explained by the physicians' opinions and lack of knowledge of how NVS and MIE can avert respiratory morbidity and mortality, essentially indefinitely. Now that even severe SMA type 1 patients can live into adulthood without tracheotomy tubes and there are an ever increasing number of effective medications for them, more needs to be done to keep their throats free of invasive airway tubes and to evaluate their emotional needs.

People with all severities of SMA have gone to college and achieved meaningful social relationships even with virtually no residual volitional muscle weakness. In a study of SMA ventilator users, of 10 over 18 years of age, 3 had college degrees, 2 were college students, 3 graduated from high school, and 2 completed eleventh grade. Two patients are mothers of healthy children including a 29-year-old woman with SMA type 1. Patients are also employed and do volunteer work [32]. Purtilo noted that misconceptions about the undesirability of "'going on a respirator' have far reaching negative effects for persons now happily being supported on a respirator, and mitigate the positive effects it could have for some types of chronically impaired persons whose quality of life also could be enhanced by the use of a ventilator" [33]. Clearly, health care professionals should cease to impose their own concepts, values, and judgments onto the disabled [34]. Noninvasive management should always take precedence over using invasive airway tubes. New medical treatments can only further improve the prognoses of these patients [35,36].

Clearly, it is far more likely that patients can survive without tracheostomy tubes if their local physicians learn how to accomplish this and have specifically trained respiratory therapists in the clinics to educate, train, and set up and monitor the patient's use of NVS in their homes. When patients require intubation for URI-pneumonias or surgical procedures the cooperation of critical care personnel is also required to extubate them back to CNVS and MIE and to permit the family's care providers to administer MIE post-extubation. In many cases, the parents of non-local SMA NVS/CNVS users are unable to muster up resources to transfer their children to our center for extubation to CNVS. They may acquiesce to the intense pressure from their local physicians to consent to the tracheotomies. However, since many, if not most children with SMA type 1, can be definitively managed without tracheostomy tubes, it stands to reason that virtually no one with and SMA should require them either.

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