“Intelligence is the ability to adapt to change…”

“If there’s a will, there’s a way…”

Stephen Hawking
Patient with Amyotrophic Lateral Sclerosis and a ventilator user. English theoretical physicist and cosmologist, was the Lucasian Professor of Mathematics at the University of Cambridge for thirty years, taking up the post in 1979 and retiring on 1 October 2009, year he was awarded the Presidential Medal of Freedom, the highest civilian award in the United States.
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| Blood Gases | 58 |
| Noninvasive ventilation in stable COPD | 59 |
| Noninvasive ventilation in Restrictive Disorders | 62 |
| Chest wall disorders | 62 |
| Amyotrophic Lateral Sclerosis | 63 |
| Duchenne muscular dystrophy | 65 |
| Manual and Mechanical techniques for secretion management | 68 |
| Rationale | 68 |
| Patient evaluation and monitoring | 71 |
| Pulmonary function and cough tests | 72 |
| Control of Mucus and Airway Clearance Techniques | 74 |
| Chest physical therapy techniques | 75 |
| Manual Assisted Cough techniques | 76 |
| Mechanical Respiratory Muscle Aids for Secretion Management | 78 |
| Intrapulmonary Percussive Ventilation (IPV) | 79 |
| High Frequency Chest Wall Oscillation (HFCWO) | 80 |
| Mechanical Insufflation-Exsufflation | 82 |
| Purpose of the Thesis | 86 |
| Acute Respiratory Failure | 87 |
| Chronic Respiratory Failure | 93 |
| Home mechanical ventilation | 101 |
| Studies and Publications | 109 |
| **Study 1-** Extubation of Patients with Neuromuscular Weakness: A New Management Paradigm | 109 |
| **Study 2-** Noninvasive ventilation associated with mechanical assisted cough for extubation and decannulation in high spinal cord injury patients | 121 |
| **Study 3-** Effects of mechanical insufflation-exasufflation in preventing respiratory failure after extubation: a randomized controlled trial | 147 |
| **Study 4-** A Ventilator Requirement Index | 169 |
| **Study 5-** Expiratory Flow Maneuvers of Patients with Neuromuscular Disease | 179 |
| **Study 6-** Lung Insufflation Capacity in Neuromuscular Disease | 189 |
| **Study 7-** Indications and Compliance of Home Mechanical Insufflation-Exsufflation in Patients with Neuromuscular Diseases | 197 |
| Study 8- | At Home and On Demand Mechanical Cough Assistance Program for Patients with Amyotrophic Lateral Sclerosis | 205 |
| Study 9- | Home mechanical cough assistance for acute exacerbations in neuromuscular disease | 213 |
| Study 10- | Evolution of Noninvasive Management of End-Stage Respiratory Muscle Failure in Neuromuscular disease. | 231 |

**General Discussion**

- Acute Respiratory Failure | 265 |
- Chronic Respiratory Failure | 277 |
- Home mechanical ventilation | 285 |

**Conclusions** | 299 |

**Resumo**

- Objectivos | 302 |
- Resultados | 303 |
- Conclusões | 306 |

**Summary (Abstract)**

- Purpose | 309 |
- Results | 310 |
- Conclusions | 313 |

**References** | 314 |
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INTRODUCTION

Most patients with impairment of pulmonary function can be differentiated into those who have primarily oxygenation impairment due to predominantly intrinsic lung disease, and those with lung ventilation impairment on the basis of respiratory muscle weakness (1). This distinction is important because, although many patients in the former category have been described to benefit from noninvasive ventilation in the acute care setting (2-3), long term use is more controversial (4-8). Patients with primarily ventilatory impairment, on the other hand, can benefit from the use of both inspiratory and expiratory muscle aids and have excellent prognoses with long term home mechanical ventilation (9-17).

One of the most important developments in the field of mechanical ventilation over the past 15 years has been the emergence of noninvasive ventilation (NIV) as an increasing part of the critical care armamentarium (18). Noninvasive positive-pressure ventilation (NPPV) is the delivery of mechanical ventilation to patients with respiratory failure without the requirement of an artificial airway. Although NPPV is often used for long-term nocturnal or continuous support of patients with forms of chronic respiratory failure (19), its use is increasingly popular in varied clinical situations in the intensive care unit (ICU) setting as high level evidence supporting its use continues to accumulate (2, 20-21).

The attraction for NPPV relates primarily to its advantages over invasive mechanical ventilation. It has been shown to comparatively decrease resource utilization and circumvents the myriad of complications associated with invasive mechanical
ventilation such as upper airway trauma, ventilator associated pneumonia, and compromise of speech and swallowing (22-23). NPPV should, however, be considered in some cases an alternative to invasive mechanical ventilation rather than its replacement (24-28). Keys to the success of NPPV and to improving clinical outcomes of patients with acute respiratory failure are careful patient selection and a well designed clinical protocol because failure of NPPV only delays potentially more definitive therapy with invasive ventilation (29). For patients with secretion accumulation or a weak cough reflex, adequate secretion management with manual or mechanical techniques might be advisable before non-invasive ventilation is declared failed or contraindicated (2, 30).

Noninvasive ventilation has been proposed for several other applications, including facilitation of weaning and extubation. One major determinant of weaning failure is an excessive load on the respiratory muscles after disconnection from the ventilator (31-32). In patients who fail a T-piece trial, invasive and noninvasive ventilation are equally effective in reducing inspiratory effort and improving gas exchange, although noninvasive ventilation results in better patient comfort (33). By allowing effective ventilator assistance, while eliminating the risks associated with endotracheal intubation, noninvasive ventilation may be a valuable alternative to the conventional weaning techniques (20). Considering that difficult to wean patients have higher morbidity and mortality and consume a substantial amount of health care resources (34), these results could lead many of those who have so far considered noninvasive ventilation ineffective or unsafe (35) to change their mind and reevaluate its potential.

Although a relatively straightforward technique, noninvasive ventilation has several specific features that must be taken into account to avoid negative and disappointing results (36).
In the intensive care setting very often patients have impaired airway clearance. Endotracheal intubation prevents the patient from closing the glottis, which is necessary for effective coughing (37). Care of the intubated patient includes direct suction applied to the endotracheal tube which clears a small portion of the airway, is ineffective for clearing secretions in the peripheral airways, and the patient is left dependent upon mucociliary clearance rather than cough clearance (38). Conventional techniques for augmenting the normal mucociliary clearance and cough efficacy have been used for many years to treat patients with respiratory disorders from different etiologies. In recent years, new technologies and more advanced techniques have been developed to be more effective in acute respiratory failure. These techniques involve mechanical application of forces to the chest wall (39) or intermittent pressure changes to the airway to assist airway mucus clearance (40-41).

Mechanical insufflation-exsufflation (MI-E) acts directly on the airway to assist or substitute for expiratory muscle function in the elimination of airway secretions. The effective elimination of airway mucus and other debris is one of the most important factor that permits successful use of chronic and acute ventilation support (noninvasive and invasive) for patients with either ventilatory or oxygenation impairment.

Decades of experience during the polio epidemics (42-43) and subsequently (13, 44-45) established that long-term nocturnal noninvasive ventilation stabilizes gas exchange and improves symptoms in patients with chronic respiratory failure. For home mechanical ventilation, noninvasive ventilation has a number of advantages over invasive mechanical ventilation, including greater ease of administration, reduced need for skilled caregivers, elimination of tracheostomy-related complications, enhanced patient comfort, and lower cost (46-47). However, as is the case in the acute setting, not all patients with chronic respiratory failure are good candidates for noninvasive ventilation.
Long term mechanical ventilation at home now incorporate both ventilator dependent (>16 h per day ventilatory support) and ventilator assisted (primarily nocturnal only) individuals, using a variety of devices and interfaces including invasive ventilation and NIV techniques(48). The diversity of conditions and variability in level of care needed by these individuals means that introducing and maintaining long-term ventilation in the home requires skill and experience on the part of the prescribing centre, particularly if the patient is using ventilatory support on a near continuous basis or has a tracheostomy in place for the delivery of ventilation (49-51). Additionally, introducing medical technology into the home raises a number of issues for the patient and caregivers, as well as local health services, which need to be identified on an individual basis (52-53).

Although no controlled trials have evaluated the efficacy of MI-E, significant amount of evidence suggests that it enhances removal of secretions in patients with impaired cough (54-62). It has been particularly useful in patients’ homes to treat episodes of acute bronchitis, permitting avoidance of hospitalization (63). Clinicians caring for patients with severe cough impairment should be familiar with the various techniques available to assist expectoration. These are particularly important with noninvasive ventilation, because there is no direct access to the airway, and secretion retention is a frequent complication and common cause for failure. Although controlled data are lacking, these techniques appear to be helpful in maintaining airway patency in patients with cough impairment during use of noninvasive ventilation in both acute and chronic settings.

Research on a continuum strategy of care, that include NIV therapy coupled with MI-E from acute care to chronic settings in patients with muscle weakness is warranted to support the application of specific protocols that may improve survival in this patient population.
HISTORICAL PERSPECTIVE OF MECHANICAL VENTILATION AND RESPIRATORY MUSCLE AIDS

NIV was first described in Genesis Chapter 2 when the Lord God “breathed into his (Adam’s) nostrils a breath of life”(64). Around 800 BC, mouth to mouth NIV was provided by Elisha to resuscitate a child as he "...went up, and lay upon the child, and put his mouth upon his mouth, and his eyes upon his eyes, and his hands upon his hands; and he stretched himself upon the child; and the flesh of the child waxed warm.

Mechanical ventilatory assistance may have first been attempted by Theophrastus Paracelsus in 1530. Paracelsus used his chimney bellows to ventilate patients' lungs via the mouth (Figure 1). This technique of respiratory resuscitation continued to be used in Europe through the 1830s (65).

Figure 1- Description of mouth ventilation through a chimney bellows as described by Paracelsus in 1530
Thereafter, John Fathergill, and others used pumps and bellows to insufflate patients via upper airway canulas (66). Successful mouth-to-mouth resuscitation was reported in 1744 (67). In 1767, the Dutch Humane Society published guidelines resuscitating drowning victims. A memo from Louis D’Etiolles to the French Academy of Sciences reported that death from drowning was markedly decreased from 1774 to 1829 by mouth-to-mouth and orolaryngeal intubation resuscitation methods (68).

Orolaryngeal intubation actually dates to Hippocrates in the 4th century BC but was apparently dropped until 1800 (69). For the next 30 years 10 to 20 others in France, Germany, England, and Italy developed manual pumps to ventilate via translaryngeal tubes as well as via noninvasive oral and nasal interfaces, and were “strong advocates of insufflation of the lungs for asphyxia, believing this the best method to restore the victims of asphyxia, no matter what the cause (69).

Then in 1893 Dr. George H. Fell of Buffalo, New York presented a hand-operated bellows to deliver air via translaryngeal or tracheotomy tubes at an International Congress in Washington in 1893. He then substituted an oronasal interface for the invasive tubes to ventilate CO2 narcosis patients (not surgical), using a finger as an “exhalation valve (69). Ignez von Hauke of Austria was probably the first person to use NIV via an oronasal interface in the 1870s (70). In 1896 the Fell-O’Dwyer foot operated manual resuscitator bellows made at Columbia Presbyterian Hospital in New York provide ventilation via orolaryngeal tubes to treat CO2 narcosis due to opium (71). In 1898 Matas used these ideas to provide both anesthesia and ventilatory support via an orolaryngeal tube for thoracic surgery. However, the idea of supporting ventilation rather than just providing anesthesia via airway tubes during surgery did not catch on.
Until around 1830, mouth-to-mouth and tranlaryngeal positive pressure methods were used for resuscitation but gradually the paradigm shifted from applying pressures via airways to pressures to the body. In the “Inversion Method” of the 1770s the body was turned upside down and the chest intermittently compressed. In the “Barrel Method,” (1773) the victim was hoisted onto a wine barrel and rolled back and forth to compress the chest. In 1812 Lifeguards hoisted drowning victims onto horses that trotted to bounce the chest. This was banned in 1815 by "Citizens for Clean Beaches". In 1856, Marshall Hall rolled drowning victims 16 times a minute and applied pressure to the back during exhalation when prone and achieved tidal volumes of 300 ml to 500 ml (72).

The first tank ventilator was described by the Scottish physician, John Dalziel, in 1838. The negative pressure was created in the tank by a pair of bellows worked from outside the tank by manually operating a piston rod (73).

In 1931 John Emerson of Cambridge, Massachusetts built a simplified, inexpensive, and more convenient iron lung that operated quietly, permitted speed changes, and could be operated by hand if electricity failed (Figure 2)(74). Then, in 1936 Fred Snite Jr., age 25, son of Colonel Frederick Snite, a prominent Chicago financier, was stricken with poliomyelitis while traveling with his family in Beijing. The Drinker iron lung, one of only 222 iron lungs in the world in 1936, was used by Mr. Snite for 1 year. He then returned to the United States via truck, ocean liner, and train along with a physician, 7 Chinese nurses, a Chinese physiotherapist, two American nurses, and his family(75). The fanfare, including the fact that he married and fathered 3 daughters, stimulated public awareness and resulted in mass production of Emerson iron lungs in time for the poliomyelitis epidemics that were to come (Figure 3) (76). Mr. Snite lived using the iron lung continuously until 1954 when he died from cor pulmonale.
Figure 2- Emerson™ Iron Lung opened for nursing care, while the patient was ventilated through a dome that covered their heads.

Figure 3- Iron lung wards that managed hundreds of patients during the poliomyelitis epidemics

In 1947 Emerson placed transparent glass domes that enclosed the users' heads and sealed at the iron lung's neck collar. The iron lung bellows could create both negative and positive pressure in the cylinder, and after 1947, the bellows could create positive pressure under the dome. Just as the negative tank pressure insufflated the lungs, the
subsequent positive pressure forcibly exsufflated the patient, increasing tidal volumes. When iron lungs had to be opened to permit nurses access to the body, patients with no breathing tolerance received IPPV via the dome (Figure 2) (43, 76).

The Fairchild-Huxley chest respirator (77) and Monaghan Portable (chest shell) Respirator(78) were introduced in 1949 and became the first mass produced chest shells. Emerson came out with a negative pressure cycling generator for chest shells in 1950. Although the shells were portable, the negative pressure generators used for them were not. These devices were built by hand and so were very expensive. There were no filters so that patients inhaled a great deal of dust and particles from the ventilator itself.

Chest shells were used long-term for daytime ventilatory support with the user sitting (Figure 4) as well as for nocturnal support with the user supine. Similar chest shells are manufactured today and are used predominately for nocturnal ventilatory assistance(68).

After successfully resuscitating drowned cats with a negative pressure body jacket, Alexander Graham Bell developed a similar negative pressure jacket to assist ventilation in premature infants in 1881. However, Bell's invention was not picked up by the medical community until the British Tunnicliffe breathing jacket was described.
in 1955 and Jack Emerson put the Poncho "wrap" style ventilator on the market in 1957 (79). These ventilators, and the wrap ventilators that followed them, consist of a firm grid covering at least the thorax and upper abdomen. The grid and the body under it are covered by a wind-proof jacket that is sealed around the neck and extremities. As negative pressure is cycled under the wrap and grid, air enters the upper airway to ventilate the lungs. The only significant changes in modern wrap ventilators from the original designs are the plastics used to fabricate the jacket and grid, and the length and form of the extremity sleeves (Figure 5).

Figure 5- The pneumowrap ventilator used by a patient with late-onset chronic ventilatory failure.

Figure 6- The rocking bed ventilator (J. H. Emerson Company, Cambridge, MA)
The Rocking Bed Ventilator (J. H. Emerson Company, Cambridge, MA) has been used for ventilatory assistance since 1932 (Figure 6). It rocks the patient 15° to 30°, thereby using gravity to cyclically displace abdominal contents for diaphragmatic excursion (80). It was used until the late 1950s by predominantly poliomyelitis and muscular dystrophy patients and is still occasionally used today. This device is generally less effective than other body ventilators but can be adequate for some patients.

The intermittent abdominal pressure ventilator (IAPV) was developed by Alvin Barach in the United States in 1955 where he used a pump made by the Gast Rotary Pump Company to pump air from an air reservoir into the sac inside the belt that was attached to the abdomen (68).

In 1946, after anesthesiologist James Elam had read about mouth-to-mouth NIV in a historical article on resuscitation, a child became apneic on his ward and he “went into total reflex behavior.”...I stepped out in the middle of the corridor, stopped the gurney, grabbed the sheet, wiped the copious mucous off his mouth and face, sealed my lips around his nose and inflated his lungs. In four breaths he was pink...” In 1951, Elam demonstrated that his expired air blown into an endotracheal tube maintained normal oxygen saturation on postoperative patients before ether anesthesia wore off. This was exactly what Elsberg had done in 1910, Paracelsus in 1530, and even Hippocrates. Elam then recruited 31 physicians and medical students, and one nurse to observe ventilation in anaesthetised and curarized patients most of them for several hours each. Blood O2 and CO2 were analyzed. He demonstrated the method to over 100 lay persons who were then asked to perform the method. These dramatic demonstrations along with the lack of iron lungs during a polio epidemic in Denmark in 1952 resulted in a paradigm shift from body ventilator to tracheostomy tubes for ventilatory support (81).
Galen reported using tracheostomies to ventilate animals in the 2nd century. Trendelenburg was the first to describe the use of a tracheostomy tube with an inflated cuff for manual application of positive pressure ventilatory assistance during anesthesia of a human in 1869(43). Tracheostomy was also used for drowning victims from the 17th century through the mid-19th century and tubes were placed into polio iron lung users with severe bulbar-innervated muscle impairment to suction out airway secretions. Noninvasive IPPV had not yet been reported and mechanical forced exsufflation devices to assist cough were not widely available until after 1953(82-84).

Furthermore, during the Danish epidemic the mortality rate was 94% for patients with respiratory paralysis and concomitant bulbar muscle involvement and 28% for those without bulbar involvement. Lassen reported that mortality figures for ventilator supported patients decreased from 80% to 41%, or to about 7% for the entire Danish acute paralytic poliomyelitis population overall(85). This was in part due to more frequent use of tracheostomy, particularly for those with severe bulbar involvement.

In the meantime, specialized centers in the United States were also reporting equally impressive decreases in mortality by "individualizing" patient care. From 1948 to 1952, 3500 patients were treated at Los Angeles General Hospital. Fifteen to 20% required ventilatory support. Acute poliomyelitis mortality decreased from about 15% in 1948 to 2% in 1952 without the use of tracheostomy for ventilatory support(86). Better nursing care and attention to managing airway secretions including the use of devices to help eliminate them were factors in decreasing mortality rates.

A long debate ensued as to whether tracheostomy IPPV or body ventilators were preferable for ventilatory support. In 1955, an International Consensus Symposium defined the indications for tracheostomy as the combination of respiratory insufficiency
with swallowing insufficiency and disturbance in consciousness or vascular disturbances (86).

Tracheostomy ventilation facilitated mobility by permitting patients to leave iron lungs for wheelchairs with positive pressure ventilators rolled behind them, an obvious advantage considering that the iron lungs were very heavy to transport. The switching to tracheostomy spread across the United States where, in 1956, the small, portable, pressure-limited Bantam ventilator came onto the market for positive pressure through the tube. Tracheostomy also provided for a closed system of ventilatory support that was amenable to precise monitoring of ventilatory volumes and pressures, oxygen delivery, and the use of the high technology respirators and alarm systems that were to come (68).

As the use of endotracheal methods became widespread, manually assisted coughing was no longer taught in medical, nursing, and respiratory therapy curricula and clinicians lost familiarity with body ventilators. Noninvasive IPPV methods were not to be described until 1969 and 1973 (43) and their 24 hour use was not reported for a large population until 1993 (87). Further, the only studies of the use of MI-E devices had been for acute poliomyelitis patients and patients with severe intrinsic pulmonary disease (84). The former was felt to be a transient population, and the latter a population for which the use of noninvasive respiratory muscle aids was not ideal. Although MI-E devices went off the market in the 1950s or early 1960s they continued to be used by patients who had access to them. Meanwhile, with widespread use of translaryngeal intubation and tracheostomy, numerous reports of complications appeared.

Ironically, what may now seem like the simplest solution to the problem of providing ventilatory support, that of delivering positive pressure ventilation via a simple mouth
piece, continues to be the last to be considered. In 1953, Dr. John E. Affeldt of Rancho Los Amigos Hospital in Los Angeles reported in a post-polio myelitis respiratory equipment conference that the positive pressure attachment used to deliver the IPPV was the simple mouth piece used for pulmonary function testing. Patients would intermittently block the mouth piece to cycle adequate tidal volumes into their lungs (42).

The ventilator unit of Goldwater Memorial Hospital in New York City was opened in 1955. In a short period of time the 80 bed unit was filled with mostly post-polio myelitis body ventilator users. Most of the patients had been recumbent in iron lungs in their local hospitals since having poliomyelitis. At Goldwater Hospital these patients, often with no breathing tolerance, were encouraged to leave their iron lungs during daytime hours and use the chest shell ventilator or IAPV when sitting. These patients could now be placed in wheelchairs using chest shells, IAPVs, or IPPV via mouth pieces and the "portable" negative-positive pressure ventilators were rolled behind them until the smaller portable machines like the Bantam became available in 1957(68).

Because mouth piece IPPV can provide much greater air volumes directly to the lungs than can IAPV or chest shell use, it became the mode of ventilatory support that the patients used during intercurrent chest infections and other times of stress. Although in centers other than Goldwater Hospital the great majority of ventilator users were switched to tracheostomy IPPV, isolated patients around the country refused tracheotomy and some reported that they themselves had the idea to ventilate their lungs via mouthpieces.

Dr. Augusta Alba took charge of the Goldwater Memorial Hospital ventilator unit in 1956. She encouraged patients to use mouthpiece IPPV for daytime ventilatory support.
Like Dr. Affeldt before her, she soon discovered that mouthpiece IPPV users would nap during the daytime without the mouthpieces falling out of their mouths. This was remarkable because many of these patients had little or no autonomous breathing ability; their ventilators did not have alarms; there was nothing to hold the mouthpiece in the mouth other than the patient's own oropharyngeal muscles and these muscles are not thought to function during REM sleep; and they had little or no extremity function so they could not have put the mouthpieces back into their mouths if they had fallen out. In 1964 she permitted a number of patients to use mouthpiece IPPV overnight rather than return to body ventilators (88). It is remarkable that few if any patients died by losing their mouthpieces during sleep.

No patients were admitted to or managed with tracheostomy tubes on the Goldwater Memorial Hospital ventilator unit until 1968. From the mid-1960s until nocturnal nasal IPPV was described in 1987 (89), simple mouthpiece IPPV was the only method of daytime or nocturnal noninvasive IPPV. It was not until oximeters became widely available in the early 1980s that it was discovered that these patients experienced frequent, and at times, severe SpO2 desaturation associated with periods of leakage of ventilator delivered air (insufflation leakage) during sleep (90).

The Bennett mouth piece with lipseal retention (Mallincriodt, Pleasanton, CA) came onto the market in 1968. It was designed to be used for pulmonary function testing. To prevent the mouthpieces from falling out of the mouths of her IPPV users during sleep, Dr. Alba convinced many of her patients to use mouthpiece IPPV with lipseal retention. Besides mouthpiece retention, by sealing the lips it greatly reduced insufflation leakage out of the mouth (90).
In 1981, as a technical advisor to Professor Yves Rideau of the University of Poitiers, France, Dr. John R. Bach introduced mouthpiece and lipseal IPPV into France. It was in the Winter of 1981-82 that Dr. Rideau suggested to Drs. Delaubier and Bach that ventilation should be tried via nasal access (13). He felt that humidification would be facilitated and the nasal route would prove more physiologic for IPPV. Drs. Bach and Delaubier first used urinary drainage catheters with the cuffs inflated in each nostril to deliver nasal IPPV to themselves and then to French muscular dystrophy patients for daytime and nocturnal ventilatory assistance (91). Nasal IPPV was first used as an alternative to airway intubation for 24 hour ventilatory support in 1984 and it was first reported in 1987 (92). It was in 1984 that nasal CPAP masks became commercially available and could be used as IPPV interfaces (93). This permitted rapidly expanding application of nasal ventilation.

Excessive nasal bridge pressure and insufflation leakage into the eyes were common complaints when using nasal IPPV with the first commercial CPAP "masks". Attempts at customizing nasal interfaces for IPPV were first described in 1987 (92). Custom molded nasal interfaces eventually became available both commercially and individually (94).

In the late 1980s Dr. Adolphe Ratza, a Swedish post-polio myelitis survivor, experimented with the construction of strap-retained custom nasal and oral-nasal interfaces. His oral-nasal interfaces, with strap retention systems much like those used for lipseal and nasal IPPV, were described for long-term supported ventilation in 1989. Over the last 15 years, strap-retained oral-nasal interfaces have been marketed by several ventilatory companies both for chronic and acute care (68).
By 1949 there were over 400 respiratory polio survivors using ventilators in the United States in custodial care at over a hundred hospitals scattered around the country. They were funded by the National Foundation for Infantile Paralysis (March of Dimes) which President Franklin Roosevelt had founded. The hospital charges were so high that the March of Dimes funded a study to find ways to reduce the cost. The study showed that it would be far more economical to move the patients to regional centers with multidisciplinary professional teams. Thus, 16 polio respiratory and rehabilitation centers with 15 to 160 patients were created at the teaching hospitals of 16 medical schools. The March of Dimes paid for the centers’ professional staff, patient care, equipment, research, and ultimately for home care, home modifications, and personal care attendants (95). Interestingly, there were no pulmonologists and respiratory therapy did not exist at that time. The patients' and their families were taught how to ventilate lungs and to facilitate airway secretion elimination and were made key participants in the rehabilitation team.

In 1953 a home care plan was developed at Rancho Los Amigos Hospital in California to save money when it was shown that de-institutionalization with home care by attendants could result in 75% cost savings. The first attendants were trained by the centers but ultimately attendants were hired and trained by the patients and families themselves. In 1953 it was estimated that 1800 post-polio myelitis patients had been respirator (iron lung) supported for one month or more and that 20% of these patients had already been discharged home. Forty-four percent of the home mechanical ventilation users were cared for solely by their families, and 15% of these patients were under 9 years of age. Over 50% of the patients required ventilatory support over 16 hours per day. By 1956, 92% of permanently ventilator dependent individuals had been discharged to their homes (68).
In 1952, Barach and Beck, began applying negative pressure to patient airways via a face mask(84). In May of 1953 Dr. John Affeldt of Rancho Los Amigos noted that he had had his patients try many methods of assisted coughing including Barach's mechanical cough chamber, the suction of vacuum cleaners, manual chest and abdominal compression, and providing maximal insufflation in an iron lung then closing the glottis until positive pressure peaks in the tank to maximize cough flows. He reported being disappointed that he was unable to clear atelectasis in a number of patients with these methods. Mr. Emerson, however, noted that it made much more sense to apply positive and then negative pressure to a face mask to increase cough flows than it did to place patients into the mechanical cough chamber(42). Five months later, Fagin and Barach's brother Edward's company OEM put the Exsufflation-with-Negative Pressure device called a "Cof-flator" (Figure 8) on the market.

Figure 7 - The OEM™ Exsufflation-with-Negative Pressure device called the "Cof-flator®"

In 1954 Beck and Alvin Barach wrote of the Cof-flator, "The life-saving value of exsufflation with negative pressure was made clear through the relief of obstructive
dyspnea as a result of immediate elimination of large amounts of purulent sputum, and, in a second episode, by the substantial clearing of pulmonary atelectasis after 12 hours’ treatment” (83). Although many studies demonstrated its efficacy and no major untoward effects were described with its use, the *Cof-flator* was abandoned with the increasing resort to tracheostomy. However, patients who had access to the original *Cof-flators* kept them and used them effectively as needed. Occasional medical publications continued to refer to its effective use even though it was no longer on the market (81, 88, 96-98).

In February of 1993, a new mechanical insufflator-exsufflator (In-Exsufflator, J. H. Emerson Co., Cambridge, MA) was released onto the market. The In-exsufflator operated like the *Cof-flator* except that cycling between positive and negative pressure had to be done manually. The manual cycling feature facilitated caregiver-patient coordination of inspiration and expiration with insufflation and exsufflation but it required that an additional hand be available to deliver an abdominal thrust (99). Then, in 1995, an automatically cycling device became available. In 2001 it was renamed the "Cough-Assist™".

The creation of the medical specialty of respiratory therapy in 1961 and the training of respiratory therapists has become of paramount importance for the noninvasive management of patients with ventilatory impairment(94). Respiratory therapists have been and continue to be essential for evaluating and training patients in the use of noninvasive ventilation and expiratory muscle aids.

Although NPPV first made its mark in the home environment, as confidence grew, critically ill patients with acute ventilatory failure were ventilated in hospital, and now the noninvasive approach is considered by some to be the treatment of choice for acute
ventilatory failure of whatever etiology (2). Because ventilation can be assisted without the need for paralysing and sedating drugs, patients do not need continuous one-to-one nursing care and assisted ventilation for acute ventilatory failure outside the intensive care unit (ICU) has become a feasible option (19). There is now an ever-growing body of prospective randomized control data to inform medical practice, and it is likely that, just as NPPV has been described as "a new standard of care" in patients admitted to hospital with an acute exacerbation of COPD (18, 100-101), it will assume a still greater role in the management of acutely ill patients with respiratory disease from other etiologies (102-106).
EQUIPMENT AND TECHNIQUES FOR NON INVASIVE POSITIVE PRESSURE VENTILATION

Successful assisted ventilation depends critically upon adapting mechanical ventilation to the patient needs. This is particularly true when the noninvasive mode is used because the patient is conscious and if ventilation is ineffective or uncomfortable the patient may reject it. An understanding of the technical equipment, in particular the modes of ventilation and the potential problems with each, is crucial, as is the selection of an appropriate interface(101)

Characteristics of different modes of ventilation

During noninvasive positive pressure ventilation (NPPV) positive-end expiratory pressure (PEEP) is combined with positive inspiratory pressure. The delivery of positive inspiratory pressure is triggered by the patient’s inspiratory effort, and usually titrated to produce either constant volume (assist volume control; AVC) or constant pressure (pressure-support ventilation; PSV)(107).

Pressure-cycled machines deliver a predetermined pressure and the volume delivered will depend upon the impedance to inflation. If there is a leak in the circuit, flow will increase to compensate, but if there is airway obstruction, tidal volume will be reduced(108). Volume cycled machines deliver a fixed tidal or minute volume and will generate a pressure sufficient to achieve this. If the impedance to inflation is high, pressure will be increased and the targeted tidal volume will be delivered. However, if there is a leak, there will be no increase in flow rate to compensate, a lower pressure will be generated, and the delivered tidal volume will fall(107). Triggering into inspiration and cycling into expiration can be timed by the machine or on the basis of detection of patient initiated changes in flow or pressure(109). Mechanical ventilation
can be "controlled" (i.e. the machine determines respiratory frequency), "assisted" (i.e. the machine augments the patient’s spontaneous breaths), or a combination of the two, "assist/control" (A/C) mode, which is called "spontaneous-timed" (S/T) mode in pressure targeted ventilators. The backup rate is usually set at slightly below the spontaneous breathing rate (110).

In chronic respiratory failure (CRF), timed modes alone may be used in patients with unreliable respiratory effort, unstable ventilatory drive or mechanics, apnoea or hypopneas, massively overloaded respiratory muscles or in patients where the assist mode fails to augment spontaneous breathing. In practice, however, the A/C or S/T has the advantages of the timed mode but allows augmentation of extra spontaneous efforts that may occur with irregular breathing patterns that may be seen at sleep onset or during rapid eye movement (REM) sleep. The proportion of breaths which are assisted and those which are controlled will depend upon the backup rate that is set (111).

**Pressure cycled ventilation.**

In this mode, inspiratory pressure delivered by the ventilator is constant to the preset pressure level, regardless of the magnitude of the patient’s inspiratory effort. It also unloads the fatigued inspiratory muscles by decreasing their inspiratory work of breathing and oxygen consumption(112). For these reasons, it has gained widespread acceptance as a mode of delivering NPPV in both the acute and chronic setting(113). Pressure cycled modes are available on most ventilators designed for use on intubated patients in critical care units. Most such “critical care ventilators” provide pressure support ventilation (PSV) that delivers a preset inspiratory pressure to assist spontaneous breathing efforts and has attained popularity in recent years as a weaning
mode(114). Most such modes also permit patient-triggering with selection of a backup rate. Nomenclature for these modes varies between manufacturers, causing confusion.

For the pressure support mode, some ventilators require selection of a pressure support level that is the amount of inspiratory assistance added to the preset expiratory pressure and is not affected by adjustments in PEEP. Bi-level pressure ventilation requires the selection of inspiratory and expiratory positive airway pressures (IPAP and EPAP) and the difference between the two determines the level of pressure support. It is important to recall that with the latter configuration, alterations in EPAP without parallel changes in IPAP will alter the pressure support level(115).

What distinguishes PSV from other currently available ventilator modes is the ability to vary inspiratory time breath by breath, permitting close matching with the patient’s spontaneous breathing pattern. A sensitive patient-initiated trigger signals the delivery of inspiratory pressure support, and a reduction in inspiratory flow causes the ventilator to cycle into expiration. In this way, PSV allows the patient to control not only breathing rate but also inspiratory duration(116). As shown in patients undergoing weaning from invasive mechanical ventilation, PSV offers the potential of excellent patient-ventilator synchrony, reduced diaphragmatic work, and improved patient comfort. However, PSV may also contribute to patient-ventilator asynchrony, particularly in patients with COPD as brief rapid inhalations that may be seen in these patients with may not permit adequate time for the PSV mode to cycle into expiration, so that the patient’s expiratory effort begins while the ventilator is still delivering inspiratory pressure(117). During NPPV these forms of asynchrony are exacerbated in the presence of air leaks.

Although noninvasive PSV is often administered using standard critical care ventilators, portable devices that deliver pressure-limited ventilation (Figure 8) have also seen
increasing use for both acute and chronic applications. These devices, sometimes referred to as “bi-level” devices because they cycle between two different positive pressures, are lighter and more compact than critical care ventilators, offering greater portability at lower expense.

Some offer not only a spontaneously triggered pressure support mode but also pressure-limited, time-cycled, and assist modes. Some also offer adjustable trigger sensitivities, “rise time” (the time required to reach peak pressure), and inspiratory duration, all features that may enhance patient-ventilator synchrony and comfort(118). Further, the performance characteristics of these ventilators compare favorably with those of critical care ventilators (119). On the other hand, unlike the critical care ventilators, the bi-level are not currently recommended for patients who require high oxygen concentrations or inflation pressures, or are dependent on continuous mechanical ventilation unless appropriate alarm and monitoring systems can be added. Recently, however, new versions of bi-level ventilators (Figure 9) have been introduced that have more sophisticated alarm and monitoring capabilities, graphic displays, and oxygen blenders and are quite suitable for use in the acute care and ICU setting.

Because of their portability, convenience, and low cost, the bi-level devices have proven ideal for home use in patients with chronic respiratory failure requiring only nocturnal
ventilatory assistance. In addition, unlike volume-limited ventilators, they are able to vary and sustain inspiratory airflow to compensate for air leaks, thereby potentially providing better support of gas exchange during leaking(120)

**Figure 9 – V60 acute care bi-level ventilator (Philips Respironics, Inc)**

**Volume cycled ventilation**

In this mode, inspiratory pressure delivered by the ventilator is titrated in order to achieve a preset constant volume target. Most critical care ventilators offer both pressure- and volume-limited modes, either of which can be used for administration of noninvasive ventilation. However, the expiratory volume alarm of intensive care volume ventilators makes them almost impractical to use to deliver NPPV and they are usually not sufficiently portable for home use(121). Portable volume-cycled ventilators, however, are most often conventionally used for providing long-term tracheostomy rather than NPPV, using standard tubing with exhalation valves and humidification as necessary(122). Compared with the portable pressure-limited ventilators described above, the volume-limited portable ventilators are more expensive and heavier. However, they also have more sophisticated alarm systems, the capability to generate higher positive pressures, and built-in backup batteries that power the ventilator for at
least a few hours in the event of power failure(123). These ventilators are usually set in
the assist/control mode to allow for spontaneous patient triggering, and backup rate is
usually set at slightly below the spontaneous patient breathing rate. The only important
difference relative to invasive ventilation is that tidal volume is usually set higher (10 to
15 ml/kg) to compensate for air leaking. Volume cycled ventilators can generally
deliver up to 2500 ml volumes and are well suited for patients in need of continuous
ventilatory support or those with severe chest wall deformity or obesity who need high
inflation pressures(124-125).

The minimum inspiratory effort required by the patient is to trigger the ventilator. The
volumes delivered to the lungs correlate with ventilator gauge pressures. Thus, the
pressures indicated on the volume ventilator pressure gauge vary depending on
ventilator delivered volumes, insufflation leakage, and lung impedance. There are also
low and high pressure alarms, sensitivity controls that permit the patient to trigger
ventilator delivered breaths, and flow rate adjustments. Alternatively, when the patient
increases their inspiratory effort, due to increased ventilatory needs, the inspiratory
pressure delivered by the ventilator will decrease in order to keep the constant volume
target(126). The greater the patient’s inspiratory effort, the lesser the ventilator’s
assistance. The ventilator might even deliver negative inspiratory pressure (i.e. pull air
back), when the patient makes an adequately strong inspiratory effort, in order not to
exceed the preset volume target(125). Additionally, it has been shown that some home
ventilators are inaccurate in delivering the preset VT, especially when faced with
deteriorating structural properties of the lung(107). For this reason, this mode has been
disfavored for use as NPPV in the acute setting(18) and, currently, is used merely for
home NIMV for patients with chronic respiratory failure due to neuromuscular
disease(1, 127).
**Ventilators with mixed pressure and volume -targeted modes.**

In order to make the most of the advantages of pressure and volume ventilators, new machines which combine the two modes have recently been released (Figure 10). These respirators are similar to critical care ventilators and may be useful for difficult-to-adapt patients and those with rapidly changing breathing patterns and mechanics(119). The clinical impact of these "dual mode ventilators" has not been well evaluated and therefore it is not known if they offer important advantages to other respirators in routine practice. In an effort to combine the advantages of pressure- and volume-targeted modes into one ventilation mode, new hybrid modes such as average volume-assured pressure support(128) and adaptive servo ventilation(129-130) have recently been introduced in the NPPV setting.

![Elysée 150 for both pressure and volume targeted ventilation (ResMed, Inc)](image1)

**Figure 10 – Elysée 150 for both pressure and volume targeted ventilation (ResMed, Inc)**
Interfaces for the delivery of NPPV

The major difference between invasive and NPPV is that with the latter, gas is delivered to the airway via a mask or “interface” rather than via an invasive conduit. The open breathing circuit of NPPV permits air leaks around the mask or through the mouth, rendering the success of NPPV critically dependent on ventilator systems designed to deal effectively with air leaks and to optimize patient comfort and acceptance.

Apart from the choice of ventilator type, mode and setting, another crucial issue when starting NIV is to find an optimal interface(131). However, despite a broad variety, until now only little attention has been focused on the choice of interface and no generally accepted consensus has been reached concerning the management of interfaces(21). In general, six different types of interface exist: total face masks, oronasal masks, nasal masks, nasal pillows or plugs, mouthpieces and helmets. Advantages and disadvantages of each interface is listed in figure 11.

Early studies dealing with NIV in ARF used nasal masks(132). The nasal mask adds less dead space, causes less claustrophobia and allows expectoration and oral intake. In order to reduce mouth leaks while wearing a nose mask a chin strap is sometimes required but is rarely effective (119). The improvement in arterial blood gas tensions appear to be slower in some studies using nasal masks compared to face masks (133). Compared to nasal masks, the more common application of full face masks in ARF is also a reflection of better quality of ventilation (at least during the initial phase of the intervention) in terms of minute ventilation and improved blood gases (134). Compared to nasal masks, face masks are generally more claustrophobic, impede communication, limit oral intake and increase the dead space which may cause CO2 rebreathing (135). However, based on practical experience, dead space does not seem to reduce the effectiveness of NIV in ARF. In addition, further types of full face masks both for open
and closed circuits are available. Some of these masks have addressed the issue of dead space and have increased leak rates, which may improve the quality of NIV (136-137).

Reducing the risk of skin damage is one of the major goals. The most common sites of friction and skin damage are the bridge of the nose, the upper lip, the nasal mucosa, and the axillae (with the helmet) (136). The most important strategy to prevent skin damage is to avoid an excessively tight fit. Masks that have angle adjustments between the forehead support and the interface can help prevent pressure and friction against the bridge of the nose (119). Rotating interfaces might reduce the risk of skin damage, by changing the distribution of pressure and friction, especially on the bridge of the nose (138-139).

Air leaks may reduce the efficiency of NIV, reduce patient tolerance, increase patient-ventilator asynchrony (through loss of triggering sensitivity), and cause awakenings and sleep fragmentation (140). During pressure-support ventilation (PSV) leaks can hinder achievement of the inspiration-termination criterion (136). In patients with neuromuscular disorders receiving nocturnal NIV, leaks are associated with daytime hypercapnia (141). In order to compensate for a significant leak a ventilator needs high flows. Pressure-targeted ventilators have leak compensating abilities with peak inspiratory flow rates of 120–180 L/min (142). Modern pressure ventilators can compensate for very large leaks, but if they are allowed, sleep quality may be sacrificed. Recently, respiratory system model studies have been published which investigated mask mechanics and leak dynamics during simulated NIV (143). Leak compensation is much more limited in volume-targeted ventilators; adding a leak to the circuit of these ventilators caused a fall in tidal volume of 50% (125). However, moderate leaks can be compensated for by increasing the tidal volume (124).
<table>
<thead>
<tr>
<th>Interface Type</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| Total face mask | Covers mouth, nose, and eyes | - Minimum airleaks  
- Little cooperation required  
- Easy fitting and application | - Vomiting (risk of aspiration)  
- Claustrophobia  
- Speaking difficult |
| Full face (or oronasal) mask | Covers mouth and nose | - Few airleaks  
- Little cooperation required  
- Can be adjusted for comfort | - Vomiting  
- Claustrophobia  
- Possible nasal skin damage  
- Speaking and coughing difficult |
| Nasal mask | Covers nose and not mouth | - Possibility of speaking and drinking  
- Allinson cough  
- Reduced danger of vomiting  
- Minimum risk of asphyxia | - Air leaks if mouth opens  
- Possible nasal skin damage  
- Needs patent nasal passages |
| Mouthpieces | Placed between lips and held in place by lip seal | - Can be applied as a rotating strategy with other interfaces | - Vomiting and salivation  
- Possible air leaks  
- Gastric distension  
- Speaking difficult |
| Nasal pillows or plugs | Inserted into nostrils | - Can be applied as a rotating strategy with other advantages of nasal masks  
- Absence of nasal skin damage | - Unreliable monitoring of expired tidal volume  
- Inspiratory and expiratory air leaks  
- Nasal irritation |
| Helmet | Covers the whole head and all or part of the neck | - No contact with face | - Minimum airleaks  
- Little cooperation required  
- Absence of nasal or facial skin damage | - Rebreathing  
- Vomiting  
- Noisy  
- Asynchrony with pressure support ventilation  
- Discomfort of axillae (from straps) |

**Figure 11** – Advantages and disadvantages of different types of interfaces (Adapted from Nava and Hill (2))
Humidification during NPPV

Humidification and warming of the inspired gas may be needed to prevent the adverse effects of cool, dry gases on the airway epithelium. Unidirectional inspiratory nasal airflow, which can worsened by mouth air-leak, can dry the nasal mucosa, because the nasal mucosa receives little or none of the moisture it would receive from the exhaled gas(136).

If the gas delivered from the ventilator is not humidified, it will have lower than the ambient air, and this is particularly true as the level of inspiratory support increases(140) Humidification can prevent these adverse effects. The 2 types of humidification device, heated humidifier, and heat-and-moisture exchanger (HME), are used both for both short-term and long-term NIV(144). Heat and moisture exchangers (HMEs) are widely used in intubated patients, because HMEs are easy to use and may be less expensive than heated humidifiers(136). However, an HME, which is usually placed between the Y-piece and the interface, can add an important amount of dead-space, compared to a heated humidifier, which is placed in the inspiratory limb(145).
NON INVASIVE VENTILATION IN THE ACUTE CARE SETTING

Rationale

Non-invasive ventilation refers to the delivery of mechanical ventilation with techniques that do not need an invasive endotracheal airway(146). It should not, therefore, be used when patients cannot protect their airway. It is not appropriate for all, and the selection of candidates is important. Compared with invasive mechanical ventilation, this type of ventilation achieves the same physiological benefits of reduced work of breathing and improved gas exchange(22, 33). Furthermore, it avoids the complications of intubation and the increased risks of ventilator-associated pneumonia and sinusitis(103), especially in patients who are immunosuppressed or with co-morbidities(147).

Studies published in the 1990s (132, 148) that evaluated the efficacy of noninvasive positive-pressure ventilation for treatment of diseases such as chronic obstructive pulmonary disease, congestive heart failure and acute respiratory failure have generalized its use in recent years and made a major advance in the management of acute respiratory failure(21). Over the past decade alone, it has been the subject of over 1,500 scientific papers, including 14 meta-analyses(2).

The use of non-invasive ventilation varies greatly between hospitals and geographical regions, and has changed over time. Investigators of a worldwide prospective survey of mechanical ventilation noted that use rose from 4% of all ventilators started in 2001, to 11% in 2004(149). It is increasingly being used in many countries, but frequency of use is highly variable(2)
In 1996, Meduri et al.(150). reported their experience with NPPV in 158 patients with various diagnoses, of whom 65% avoided intubation with NPPV. They suggested that NPPV be first-line therapy for patients with acute hypercapnic and hypoxemic respiratory failure. In parallel with the evolving evidence supporting the use of NPPV for acute respiratory failure, technical advances have increased the variety of interfaces and ventilators for NPPV and facilitated wider application. Surveys have reported the utilization of NPPV in several settings. Carlucci et al.(151) conducted a 3-week observational survey in 42 French intensive care units (ICUs) to evaluate the use of NPPV and to assess its efficacy in everyday practice. NPPV was used in 35% of the patients who were not intubated on admission. This included 14% of patients with hypoxemic respiratory failure, 27% with pulmonary edema, and half of those with hypercapnic respiratory failure, but never in patients with coma.

In a follow-up survey, Demoule et al.(152) reported that NPPV use significantly increased in French ICUs from 1997 to 2002 (up to 24% overall and 52% of patients admitted without prior intubation), and the success rate remained unchanged (47% vs 48%, respectively).

Non-invasive ventilation in acute setting is used mainly for exacerbations of chronic obstructive pulmonary disease (COPD) and for cardiogenic pulmonary oedema(18). Use for hypoxic respiratory failure and facilitation of weaning is still infrequent and is mainly done in specialised centres (153-156).

In patients with ARF due to restrictive disorders the evidence is lower, although published studies demonstrate positive results (157). In fact, randomized clinical trials (RCT) of NIV in ARF tend to exclude patients with restrictive disorders (153-155, 158-161).
Despite these limitations, this technique is increasingly being used outside the traditional and respiratory intensive care units(19), including in emergency departments(29); postsurgical recovery rooms(104); cardiology(162), neurology(163), oncology(164-165) wards; and palliative care units(166-167) Noninvasive ventilation for acute respiratory failure has the potential of reducing hospital morbidity, facilitating the weaning process from mechanical ventilation, shortening length of hospitalization and thereby costs, and improving patient comfort(2). However, patients must be selected carefully (Panel 1) because the risk of complications could be increased if noninvasive ventilation is used inappropriately(156).

**Panel 1: Recommendations for NIV to treat acute respiratory failure**

**Recommendations based on levels of evidence**

**Level 1**  
Systematic reviews (with homogeneity) of RCTs

**Evidence of use (favourable)**
- COPD exacerbations
- Facilitation of weaning/extubation in patients with COPD
- Cardiogenic pulmonary oedema
- Immunosuppressed patients

**Evidence of use (caution)**
- None

**Level 2**  
Systematic reviews (with homogeneity) of cohort studies (including low quality RCTs; eg, <80% follow-up)

**Evidence of use (favourable)**
- Do-not-intubate status
- End-stage patients as palliative measure
- Extubation failure (COPD or congestive heart failure) (prevention)
- Community-acquired pneumonia in COPD
- Postoperative respiratory failure (prevention and treatment)
- Prevention of acute respiratory failure in asthma

**Evidence of use (caution)**
- Severe community acquired pneumonia
- Extubation failure (prevention)
Level 3
Systematic reviews (with homogeneity) of case–control studies, individual case-control study

Evidence of use (favourable)
• Neuromuscular disease/kyphoscoliosis
• Upper airway obstruction (partial)
• Thoracic trauma
• Treatment of acute respiratory failure in asthma

Evidence of use (caution)
• Severe acute respiratory syndrome

Level 4
Case series (and poor quality cohort and case-control studies)

Evidence of use (favourable)
• Very old age, older than age 75 years
• Cystic fibrosis
• Obesity hypoventilation

Evidence of use (caution)
• Idiopathic pulmonary fibrosis

Chronic Obstructive Pulmonary Disease with acute exacerbation

Patients with acute respiratory acidosis caused by an exacerbation of COPD are the group that benefits most from non-invasive ventilation(21). These benefits are because NIPPV is able to decrease work of breathing (WOB) and eliminate diaphragmatic work by unloading the respiratory muscles, lessening diaphragmatic pressure swings, decreasing respiratory rate and counteracting the threshold loading effects of auto-PEEP(168).

In an early study using historically matched control subjects, Brochard and colleagues reported that only 1 of 13 patients with acute exacerbations of COPD treated with face mask NPPV required endotracheal intubation, compared with 11 of 13 control subjects. In addition, patients treated with NPPV were weaned from the ventilator faster and spent less time in the intensive care unit than did the control subjects(169). Individual
trials and meta analyses have confirmed the benefit of NPPV for patients with COPD exacerbation.

Lightowler et al.(170) conducted a meta-analysis of 8 studies restricted to the use of NPPV for COPD exacerbation. NPPV significantly lowered the risk of treatment failure, risk of mortality, the risk of endotracheal intubation, complications of treatment, and hospital stay. NPPV significantly improved pH, PaCO2 and respiratory rate within 1 hour of initiation. Keenan et al.(171) also conducted an updated systematic review and meta-analysis of 15 randomized trials limited to COPD exacerbation. NPPV was associated with significantly lower in-hospital mortality and a significantly lower rate of endotracheal intubation.

Early use in patients with COPD who have with mild respiratory acidosis (as low as pH 7.30) and mild-to-moderate respiratory distress prevents further deterioration, and thus avoids endotracheal intubation and improves survival compared with standard medical therapy. In a large multicentre trial in patients with mild-to-moderate acidotic COPD who were admitted to a respiratory ward, Plant and colleagues noted that intubation and mortality rates were lower with non-invasive ventilation than with standard therapy alone, but subgroup analysis showed that these rates did not differ when pH at enrolment was less than 7.30(172). The investigators surmised that these patients with low pHs might have fared better in an intensive care unit than in the respiratory ward.

Strong evidence of efficacy (from randomised controlled trials and meta-analyses) and low risk of failure (10–20%) means that use of noninvasive ventilation to avoid intubation in patients with mild-to-moderate COPD and acute respiratory failure (pH 7.30–7.34) is regarded as the ventilatory therapy of first choice and can be safely administered in appropriately monitored and staffed areas outside intensive care(173).
Patients with a low pH are still candidates for this technique but transfer to a closely monitored location is strongly advisable(174).

**Acute Cardiogenic Pulmonary Edema**

Non-invasive ventilation has been used to treat acute respiratory failure in patients with cardiogenic pulmonary edema, mainly in emergency departments(175). Investigators of several meta-analyses concluded that this technique, including CPAP, is better than is standard medical therapy for reduction of intubation rate(176-177). This conclusion was not supported in a multicentre trial that compared oxygen therapy alone, CPAP, and non-invasive pressure support ventilation. The physiological improvements were faster with non-invasive ventilation than with oxygen alone but without a statistically significant effect on intubation or mortality rates(178). However, the very low intubation rate (<3%) raises questions as to whether the patients’ population was similar to that of other studies. Studies that compared non-invasive ventilation with CPAP alone in patients with Cardiogenic pulmonary edema showed that intubation and mortality rates did not differ, although investigators of some studies noted more rapid improvements in dyspnea scores, oxygenation, and arterial partial pressure of carbon dioxide (PaCO2) with non-invasive ventilation than with CPAP (179-181). Nonetheless, because of ease of use, some clinicians regard CPAP as first-line treatment for cardiogenic pulmonary oedema. In another meta-analysis, Winck et al.(177) also concluded that robust evidence supports the use of CPAP and NPPV in acute cardiogenic pulmonary edema, and that both techniques decrease the need for endotracheal intubation but only CPAP decreases mortality, compared to standard medical therapy.
Hypoxemic Respiratory Failure

Studies have investigated the use of NPPV in patients with acute hypoxemic respiratory failure (defined as those with a PaO2/FIO2 ratio of < 200, respiratory rate> 35/min from more generalized causes). Antonelli et al.(182) conducted a randomized controlled trial of NPPV in patients with a variety of diagnoses associated with acute hypoxemic respiratory failure. Patients received NPPV or immediate intubation and invasive ventilation. Only 31% of the patients who received NPPV required endotracheal intubation, and more patients in the conventional ventilation group had serious complications (66% vs 38%) and had pneumonia or sinusitis (31% vs 3%). Among the survivors, patients in the NPPV group had shorter periods of ventilation and shorter ICU stays.

Ferrer et al.(154) conducted a randomized controlled trial of NPPV with patients with acute hypoxemic respiratory failure from a variety of diagnoses. NPPV was associated with less need for intubation, lower incidence of septic shock, and lower ICU mortality. The improvement in hypoxemia and tachypnea was more rapid in the NPPV group. Moreover, NPPV was associated with better cumulative 90-day survival.

Keenan et al(183). conducted a meta-analysis of randomized controlled trials of patients who had acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema. The trials compared NPPV plus standard therapy to standard therapy alone, and outcomes included need for endotracheal intubation, ICU and hospital stay, and ICU and hospital survival. They concluded that patients with acute hypoxemic respiratory failure are less likely to require endotracheal intubation when NPPV is added to standard therapy. However, the effect on mortality is less clear, and the heterogeneity found among studies suggests that the effectiveness differs among different settings, patient populations, and diagnostic groups.
Thus, although some studies suggest benefit of NPPV in hypoxemic respiratory failure, its use in acute respiratory distress syndrome or severe community-acquired pneumonia is controversial and not recommended routinely(156). Results of a survey in three intensive care units(184), with staff highly skilled in this technique, showed that only 30% of patients with a diagnosis of acute respiratory distress syndrome met criteria for a trial of this type of ventilation. Of these patients, intubation was avoided in 54%, which was associated with much lowered morbidity (by about 40%) and mortality rates (roughly 30%). This finding suggests that in real-life situations and in expert hands only about 15% of such patients can be treated successfully with this technique; mainly those with a low severity of illness, not in shock, and rapid improvement in oxygenation after therapy is started.

**Immunocompromised Patients**

Acute respiratory failure in patients who are immunocompromised often signals a terminal phase of the underlying disease, with short survival time and high costs of admission to intensive care(105). Early use of non-invasive ventilation could be very helpful, as shown by randomised studies in intensive care units that compared this technique with standard treatment. In patients receiving a solid-organ transplant and who had hypoxaemic acute respiratory failure, such ventilation reduced intubation rate, complications, mortality, and duration of stay in intensive care(185).

In a second study this technique lowered intubation, complication, and mortality rates compared with standard therapy in patients with hypoxaemia and bilateral pulmonary infiltrates and immunosuppression secondary to hematological malignancies(24).

Hilbert et al. (186) conducted a randomized controlled study to compare NPPV with standard medical treatment in 52 patients with immunosuppression from various causes
and acute hypoxemic respiratory failure. In the NPPV group, periods of NPPV of at least 45 min delivered via face mask were alternated with 3-hour periods of spontaneous breathing with supplemental oxygen. Fewer patients in the NPPV group than in the standard treatment group required endotracheal intubation, had serious complications or died in the ICU.

These results support use of NPPV in immunocompromised patients who develop acute hypoxemic respiratory failure. One reason for the better survival in immunosuppressed patients treated with NPPV is their lower likelihood of developing ventilator-associated pneumonia(103, 187)

**Weaning From Invasive Ventilation and Post Extubation Failure**

NPPV may allow earlier extubation and thereby reduce the duration of mechanical ventilation. Several randomized trials showed that non-invasive ventilation can be safely and successfully used to enable weaning from mechanical ventilation in stable patients recovering from an episode of hypercapnic acute respiratory failure (ie, COPD exacerbations)(114, 161) and even in those who previously had an unsuccessful spontaneous breathing trials(153, 188).

This application has been investigated in a meta-analysis. that compared traditional weaning to early extubation with immediate application of NPPV, Burns et al found that extubation to NPPV resulted in favorable outcomes, including lower mortality, lower rate of ventilator-associated pneumonia, and shorter total mechanical ventilation. Burns et al concluded that early extubation to NPPV decreased mortality, and that the use of NPPV to facilitate early extubation is promising(20).

Another related potential application of NPPV in the weaning process is to avoid reintubation in patients who fail extubation. Epstein and colleagues(189) have observed
that such patients have much higher morbidity and mortality rates than do those who are extubated successfully.

Although controversial, accumulating evidence suggests that NIV may have a role in treatment of extubation failure, but mainly in patients with hypercapnic and congestive heart failure who are at high risk for extubation failure (155, 190). Furthermore, patients should be monitored closely to avoid delays in intubation.

**Acute Respiratory Failure in Restrictive Disorders**

International surveys performed in ICU’s around the world in 1996 and 1998, showed that neuromuscular patients correspond to 1.8-10% of patients receiving mechanical ventilation (191-192). An Italian survey of Respiratory Intensive Care Units during 1997-1998 showed that chest wall and neuromuscular disorders accounted for 9% of patients admitted (193).

Restrictive disorders are the most frequent indication for Long-term Home Mechanical Ventilation, with thoracic cage and neuromuscular patients accounting for 65% of patients ventilated at home in Europe (194).

NIV has been shown to be the first line intervention for ARF due to COPD (195). In patients with ARF due to restrictive disorders the evidence is lower, although published studies demonstrate positive results (157). In fact, randomized clinical trials (RCT) of NIV in ARF tend to exclude patients with restrictive disorders. In the only RCT of NIV in ARF that included patients with NMD (n=6) the authors did not discuss those patients because the group was too small for analysis (196).

While Portier et al (197) in a prospective multicentre study of patients with acute-on-chronic respiratory failure (including 16.7% with restrictive disorders) suggested that
the underlying disorder did not influence prognosis, Robino et al (198) in a retrospective study with the larger sample of restrictive patients published to date (mainly with CWD), suggested that effectiveness of NIV was less in this group of patients.

Recently Banfi et al (199) successfully managed at home 7 Kyphoscoliotic patients with infection-related respiratory failure. In fact by increasing daily duration of mechanical ventilation to > 20h, they corrected respiratory acidosis and returned the patients to their baseline condition in 4 weeks.

It seems that Respiratory Failure due to these disorders needs a different approach from the more common obstructive pulmonary diseases (198, 200).

**Acute Respiratory Failure in Chest Wall Disorders**

Patients with severe Kyphoscoliosis (KS) and acute decompensation of respiratory failure, exhibit marked decrease of pulmonary compliance but, contrary to COPD, increase in airway resistance and intrinsic PEEP seem to play only a secondary role (201). Because cough is not impaired like in NMD, secretion management is not so critical in this context, and management of ARF may be easier.

Some case series have shown that ARF occurring in KS can be managed non-invasively, either through negative (202) or positive pressure ventilation (157, 203). Recently Banfi et al (199) have shown reversal of respiratory acidosis in KS patients with ARF, by increasing duration of home mechanical ventilation up to > 20h, both with volume and pressure-cycled ventilators.
Acute Respiratory Failure in Neuromuscular Disorders

In neuromuscular disorders, the normality of the respiratory function requires the integrity of three main respiratory muscles: 1) inspiratory muscles, responsible for ventilation; 2) expiratory muscles, involved in the ability to cough and 3) Bulbar muscles, that protect against the risk of aspiration (204). Laryngeal weakness and swallowing dysfunction can lead to aspiration which is the main reason for failure of non-invasive respiratory aids during ARF in NMD (27).

In patients with previous NMD, respiratory failure is commonly triggered by upper respiratory tract infections (205). These can impair the three muscle components (200, 205). Those patients normally present with rapid shallow breathing, tachycardia, accessory-muscle use, thoraco-abdominal asynchrony, and orthopnea. Blood gases, vital capacity, maximum inspiratory and expiratory pressures and peak cough flow should be evaluated and give useful information about the integrity of the respiratory muscle system. According with the disease and objective parameters need for mechanical ventilation can be predicted. Hypercapnia is a late finding of impending ventilatory failure whereas hypoxemia may suggest atelectasis and secretion encumbrance or pneumonia.

To avoid NMD to be admitted to hospital with ARF, a regular follow-up of all chronic NMD patients with lung function evaluation in order to establish domiciliary non-invasive respiratory aids is fundamental (206). Moreover a pro-active intervention with intensification of home mechanical assisted cough and NIV guided by oxygen saturation has been proposed by some authors (207). In fact this protocol reduces hospitalization in NMD followed in specific outpatient clinics.

However there will always be cases where ARF will be the presentation for NMD, especially those with a rapid evolution like ALS (208-209); apart from those patients,
acute neuromuscular disorders (like Guillain-Barré Syndrome) together with the ICU-acquired neuromuscular disorders are the most frequent NMD associated with ARF (see Table I).

Table I- Major NMD Diseases associated with ARF

<table>
<thead>
<tr>
<th>Motor Nerves</th>
<th>Neuromuscular Junction</th>
<th>Myopathies</th>
<th>Spinal Cord</th>
<th>Acquired NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Myasthenia Gravis</td>
<td>Myotonic dystrophy</td>
<td>Trauma</td>
<td>Critically ill myoneuropathy</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Duchenne Muscular Dystrophy</td>
<td>Transverse myelitis</td>
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**Acute Respiratory Failure in Amyotrophic Lateral Sclerosis**

Analysing a large US database, Lechtzin N et al (210), report that in hospitalized ALS patients mortality is 15%. According with conventional protocols, patients with ALS who present acutely in respiratory failure and require endotracheal intubation and invasive ventilation are rarely weaned and rarely return home (211).

If the cause of ARF is secretions encumbrance, and assisted mucus clearance techniques were unavailable at home, a strict protocol of mechanical in-exsufflation (MI-E) should be implemented (sometimes with a 5 min frequency) together with continuous NIV until blood gases are normalized (212). It should be noted that patients with NMD and excessive secretions/atelectasis may need very frequent assisted cough techniques...
requiring time-consuming care from the nursing and respiratory therapists staffs, making the help of family caregivers essential (213). This will reverse the majority of cases (214); however some patients can be intubated for 24/48 hours to rest and optimize secretion clearance with MI-E through the endotracheal tube (212). Subsequently it might be possible to extubate them directly continuous NIV.

There are not so many studies analysing the role of NIV in ARF due to ALS. In 2000 Vianello et al. (215) published the first paper, prospectively comparing the efficacy of NIV combined with cricothyroid «mini-tracheostomy» and conventional mechanical ventilation via endotracheal tube in 14 patients with ARF and NMD (including 3 ALS). Mean pH was 7.29 in both groups, mortality was lower and ICU stay was shorter in the NIV group compared with controls suggesting their «non-invasive ventilatory approach» could be a first line intervention in this setting.

Five years later Vianello et al. (216) evaluated the short-term outcomes of 11 NMD patients (including 2 ALS), not so severely acidotic (mean pH 7.36), with acute upper respiratory tract infections and tracheobronchial mucous encumbrance. Apart from NIV, they were submitted to MI-E treatment in addition to standard physical therapy. The outcomes were compared with 16 historical matched controls who had received chest physical therapy alone. The treatment failure (defined as the need for cricothyroid “minitracheostomy” or endotracheal intubation, despite treatment) was significantly lower in the MI-E group that in the conventional chest physical treatments group (2/11 vs 10/16 cases). No side effects were related to the use of MI-E alone, while the need of bronchoscopy assisted suctioning was similar in the two groups (5/11 vs 6/16).

As noted by Gonçalves and Bach in the commentary accompanying the paper (213), some mistakes concerning the use of the MI-E probably compromised the final results. Setting the machine at a very low insufflation and exsufflation pressures (less than 30
cmH20), and forgetting the abdominal thrust during the exsufflation phase were reasons for sub-optimal results. These low pressures have been shown not to be effective in lung models (217) as well as in clinical studies (218-219) and accordingly did not effectively avert bronchoscopy-assisted aspiration. Moreover, using the MI-E 2.7 times a day as described in this paper may be insufficient. In fact as mentioned before, during an acute episode of respiratory tract infection, MI-E may have to be applied very frequently and the only way to solve this problem is allowing the primary care providers or relatives to stay at the bedside to use it anytime is required (220).

Servera et al (27) in a non-intensive care setting prospectively evaluated the efficacy of continuous NIV together with coughing aids (including MI-E) to avoid endotracheal intubation for 17 patients with NMD during ARF. The studied group had a mean pH of 7.38 and included 11 patients with ALS (5 of which with Bulbar dysfunction). There was treatment failure in 20.8% and mortality in 8.3% cases, significantly related with patients with severe bulbar impairment. Those patients (in which NIV and assisted coughing may be unsuccessful) and those who cannot cooperate, may have a more invasive approach: endotracheal intubation and mechanical ventilation followed by tracheostomy (221) or as Vianello (222) proposes minitracheostomy.

However, even in Bulbar ALS patients, MI-E should be tried, since Hanayama et al (223) described an ALS woman with immeasurable CPF, already with a gastrostomy, in which MI-E was able to clear bronchial secretions and reverse ARF.

In our experience with 11 consecutive non bulbar ALS with ARF, non invasive respiratory aids (continuous NIV and high-intensity mechanical assisted cough) had a success rate of 100%, with resolution of respiratory failure and discharge after 8 days (214) (Figure12). With this protocol, MI-E resolved atelectasis and none of those
patients needed endotracheal intubation or fiberoptic bronchoscopy-assisted aspiration (Figure 13).

**Figure 12**-Outcomes of 11 patients with non-bulbar ALS and ARF

<p>| | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>LOS</td>
<td>7.9 ± 8.9 days</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 1.3</td>
</tr>
<tr>
<td>PaO2</td>
<td>57.8 ± 8.4 mmHg</td>
</tr>
<tr>
<td>PaCO2</td>
<td>64.7 ± 26.1 mmHg</td>
</tr>
<tr>
<td>Tt Failure</td>
<td>0</td>
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Legend: LOS-Length of stay; Tt Failure-Treatment Failure; CPF-Peak Cough Flow (L/min)

**Figure 13**-Resolution of Left lower lobe atelectasis in one patient ALS with MI-E (Left before; right After MI-E)
Concerning the mode of non-invasive ventilation, it is preferable to use volume-cycled ventilators in assist control with high tidal volumes, for sufficient lung expansion and to allow air-stacking for coughing (27, 214). This can be done during the day through mouthpiece and at night with a nasal or oral interface. As soon as the patient learns to air-stack and can autonomously produce CPF above 160L/min, assisted coughing can be reduced in frequency, provided that oxygen saturation levels on the ventilator are above 95% (224). In the beginning the patient will need continuous NIV but at discharge will return to the previous duration of home NIV (27, 214).

When patients with ALS under home mechanical ventilation need to be hospitalized due to ARF there are some technical as well some ethical aspects that need to be considered. We need to confirm if all non-invasive respiratory aids were optimized at home, if the patient has refused tracheostomy, if bulbar impairment is severe and the risk of aspiration is high. Lung function status previous to the decompensation can help in the decision making. Discussions about aggressiveness of resuscitation should have been carried out with the family and patient in a stable state (225).

Another different issue is when patients with non-bulbar NMD are intubated because of failure of NIV or due to a more conventional approach. In this context, it is a common attitude to gradually reduce the support of the ventilator until the patient is weaned. Unfortunately NMD patients with a pre-existing respiratory dysfunction often fail to wean from invasive ventilation and almost invariably are tracheostomized. MI-E in these cases can be really successful to help clearing secretions first via the tube, and then, after the tube is removed, via an oronasal mask while the ventilation is delivered through non-invasive interfaces. MI-E, applied in this circumstance, avoid mucus encumbrance, the need of blind suctioning through the nose and definitely tracheostomy, also for patients 24 hours ventilator dependent.
Acute Respiratory Failure in Guillain-Barré Syndrome and in Myasthenia Gravis

In the developed world Guillain-Barré Syndrome (GBS) and Myasthenia Gravis (MG) account for the majority of cases of respiratory failure associated with NMD. Although the use of NIV in this setting has not been extensively evaluated (226-228), it should be always tried unless there is significant bulbar dysfunction. In fact, GBS and MG are not so different diseases from other NMD where a non-invasive respiratory aids protocol has avoided endotracheal intubation (27, 214, 216). The only difference is that contrary to the majority of ALS and DMD patients with ARF, those patients are naïve to NIV.

According with the literature, between 25-50% of GBS patients and 15-27% MG gravis patients require mechanical ventilation (229-230). A practical rule (the «20/30/40 rule») proposed by Lawn et al (231) in which a VC<20ml/kg, Pimax<-30cmH20, Pemax<40cmH20 were associated with progression to respiratory failure, may be useful in deciding to initiate ventilatory support. These simple bed-side tests of respiratory function may be clinically generalizable to other neuromuscular conditions.

Acute Respiratory Failure in Spinal Cord Injury

Demographic data form the US Spinal Cord Injury (SCI) data base between 1973 and 2003 show a significant increase in the percentage of cervical injuries and of ventilator-dependent cases, with 6.8% of SCI patients requiring ventilation on discharge between 2000 and 2003 (232). Most SCI patients who require ventilatory support undergo tracheostomy during their acute hospitalization (233). Despite improvements in SCI medical management, re-hospitalization rates remain high, associated with respiratory complications (234). Cervical spine injuries can be separated into higher cervical cord
injuries (levels C1 and C2) and mid and lower cervical cord injuries (C3 to C8). The former produce almost total respiratory muscle paralysis, while the latter have limited expiratory function. Lesions from C3-C5 cause also significant compromise of inspiration (233).

During the 80’s, survival for ventilatory dependent tetraplegic patients ranged from 63% at 3 years (235) to 33% at 5 years (236). In those times, only 51% of SCI patients with C3 injury levels were able to be weaned (236). Life expectancy was considerably improved in those successfully weaned (237).

Because of their youth, intact mental status and bulbar musculature, high level tetraplegic patients are perfect candidates for non invasive ventilatory assistance (238). In fact, Bach et al suggest that patients with lesions under C1 level, can be managed by using noninvasive respiratory aids (up to continuous noninvasive IPPV and manually and mechanically assisted coughing) provided that they are able to generate assisted peak cough flow >160 L/min (239).

It is recommended that all patients with acute SCI have their Vital Capacity measured every 6h during the first few days of admission. If symptoms or signs of impending ventilatory failure develop or VC decreases < 1500ml, the patient should be placed on continuous oximetry monitoring and trained in using MIV and Manually and mechanically assisted coughing (240).

When patients with SCI are tracheostomized, there will always be the potential for decannulation. Although this topic his beyond the scope of this chapter, it must be emphasized that even in patients with little ventilator-free breathing ability, switch to NIV and «aggressive» mechanical insufflation-exsufflation can lead to successful decannulation (241).
Critical-illness myoneuropathy

ICU-acquired NMD is reported in 25% of patients who have been ventilated for ≥ 7 days (242). This figure increases in patients with sepsis and severe acute asthma (243). Normally patients present with diffuse skeletal-muscle weakness and difficult weaning. ICU-acquired NMD is associated with longer duration of mechanical ventilation, longer ICU stay and increased mortality (243). Cough inefficacy and reduction in maximal respiratory pressures have been reported in these patients (244), suggesting the implementation of secretion clearance techniques together with non invasive ventilatory support can have a role (200). Although studies reporting application of Non-invasive Respiratory aids in this context are lacking, in the authors’ experience, application of this protocol in ICU-acquired NMD has allowed decannulation and weaning in a significant number of patients (data not published).

Critical-illness myoneuropathy have been also implicated in respiratory failure that develops after discharge from the ICU (244). Recovery of peripheral and respiratory muscle function is highly variable, with some patients having persisting weakness at 2 years of follow-up.

Contraindications to Noninvasive Positive Pressure Ventilation in acute care

There are few absolute contraindications to NPPV, the majority of which assume that endotracheal intubation (ETI) is an immediate option(174). The need for a secure airway contraindicates use of NPPV, as do severe facial trauma or burns and an ongoing need to clear airway secretions that cannot be cleared by noninvasive means (including mechanical assisted cough)(245-246). Altered mental status not due to CO2 retention is a commonly cited contraindication, as are nausea and vomiting.Most studies have
excluded patients with significant hypotension and/or recent gastric surgery (within one week). An uncooperative or combative patient is unlikely to benefit from NPPV(36). Light sedation or analgesia may aid in the control of the latter type of patient. The exclusion of patients with acute apnea, active cardiac ischemia, or ongoing arrhythmia seems reasonable.

Panel II: Contraindications for NPPV in ARF:

The contraindications to NIPPV include (18, 21):

- severe hypoxemia (PaO$_2$/FiO$_2$ < 75mmHg)
- severe acidemia
- multi-organ failure or slowly reversible disease
- upper airway obstruction
- anatomic abnormalities that interfere with gas delivery (i.e., facial burns, trauma)
- respiratory arrest/apnea
- cardiac arrest and hemodynamic or cardiac instability
- unconscious / uncooperative patient
- encephalopathy with the inability to protect the airway
- increased risk of aspiration (copious secretions, vomiting)
- severe Gastro-intestinal(GI) bleeding
- recent airway or GI surgery
NON INVASIVE VENTILATION IN THE CHRONIC CARE SETTING

Rationale

Noninvasive ventilation (NIV) constitutes one of the major advances in pulmonary medicine in recent times, having assumed an important role in the therapy of respiratory failure in chronic settings (46). Long term NIV in the chronic setting refers to the provision of NIV mainly at night during sleep, usually for 12 to 24 h, although some NMD patients gradually extend hours of use to continuous as their disease progresses (1).

From the 1950s through to the early 1990s, home mechanical ventilation (HMV) was limited to a relatively small number of individuals using negative pressure devices or receiving positive pressure ventilation through a tracheostomy (247). More recently, noninvasive ventilation (NIV) has emerged as an effective and acceptable approach to managing chronic respiratory failure (CRF) patients outside of the hospital setting (48). The significant benefits of this therapy have been widely documented, and include relief of symptoms, improved quality of life, reduced need for unplanned hospitalisation and improved survival. Consequently, over the past 20 years a dramatic increase in the number of individuals using HMV has occurred (248).

Before starting respiratory support, it is essential to ask three main questions: 1) Does the patient have a disease known to cause ventilatory failure? 2) Does the patient have symptoms suggesting hypoventilation? 3) Does the patient have physiological abnormalities confirming hypoventilation? Sometimes, due to disease progression,
ventilatory dependency can increase and ventilatory support must be adapted accordingly(249).

**Indications of Noninvasive ventilatory support**

**Disease categories** (table 1)

A large number of conditions can result in chronic ventilatory failure and benefit from home ventilation. Typically, patients with restrictive disorders have decreased compliance of the chest wall, resulting from thoracic cage deformity or respiratory muscles involvement (250). In patients with severe Obstructive Pulmonary Disorders, respiratory muscle fatigue and sleep hypoventilation are thought to contribute to respiratory failure (251-252).

It is useful to define disease category in order to predict natural history and specific intervention. It is well known that patients with primarily restrictive disorders can have both inspiratory and expiratory muscle weakness and so apart from non-invasive ventilatory support they also need cough assistance (207, 219). On the other hand, patients with obstructive disorders rarely need mechanical expiratory aids except for severe acute infectious exacerbations when difficulties in clearing copious secretions can ensure (219, 253-254).

Some neuromuscular diseases, for example Guillain-Barre syndrome, may only require temporary ventilatory support(255) while other, such as post-polio syndrome requires lifelong noninvasive ventilatory support (45). Amyotrophic lateral sclerosis, an example of a rapidly evolving disease, needs a specific approach particularly for the bulbar involvement which may render noninvasive ventilatory support less effective (221).
Table II- Indications for Non-invasive ventilatory support

<table>
<thead>
<tr>
<th>Restrictive disorders</th>
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</thead>
<tbody>
<tr>
<td>Chest wall disorders</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
</tr>
<tr>
<td>Thoracoplasty</td>
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<tr>
<td>Fibrothorax</td>
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<tr>
<td>Obesity-hypoventilation syndrome</td>
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<tr>
<td>Stable Neuromuscular Disorders</td>
</tr>
<tr>
<td>Old polyomyelitis</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
<tr>
<td>Progressive Neuromuscular Disorders</td>
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<tr>
<td>Amyotrophic Lateral Sclerosis</td>
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<tr>
<td>Duchenne Muscular Dystrophy</td>
</tr>
<tr>
<td>Other Neurological Disorders</td>
</tr>
<tr>
<td>Cervical Spinal Cord Injury</td>
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<tr>
<td>Phrenic nerve lesions</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Obstructive disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>Bronchiectasis and Cystic Fibrosis</td>
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</tbody>
</table>

**Patient selection**

**Symptoms of nocturnal hypoventilation**

Every consensus statement reinforces the importance of detecting symptoms of nocturnal hypoventilation(252, 256-259). However, symptoms may be subtle due to the variability of patient sensitivity and sometimes it is difficult for the patient to establish
differences between fatigue, dyspnea, and sleepiness. So, carefully designed questionnaires that assess symptoms systematically may be very useful. Jackson et al (260) have described a pulmonary symptom scale consisting of 14 questions, answered on a scale from 1-7. Others evaluated by simple questionnaires the positive and negative effects of ventilation(261). Although symptom questionnaire are insensitive in identifying patients with SDB and nocturnal hypercapnic hypoventilation (260, 262) their systematic evaluation is useful in evaluating response to NIV, as compliance to it is strongly correlated with patients symptoms (263).

Using rating scales for different symptoms has been also recommended. Dougan et al (264) developed a useful tool (the MND dyspnoea rating scale) consisting of 16 questions each rated on a five-point likert scale that allows the patients with ALS to quantify how dyspnea affects their daily life. This specific questionnaire may be more appropriate to quantify dyspnea in neuromuscular patients compared with other existing measures such as the Medical Research Council (MRC) dyspnea scale (265).

Moreover, one of the most common used sleepiness scales, the Epworth Sleepiness scale, may not be as reliable in NMD like Myotonic Dystrophy (266).

**Physiologic evaluations**

Together with the careful evaluation of symptoms, monitoring of respiratory function should be evaluated routinely. Vital Capacity (VC) is one of the most reproducible tests of lung function. Although it may not fall below normal limits until there is a 50% reduction in muscle strength (267), its rate of decline has been shown to predict survival (268). Although no consensus exist as to how often pulmonary function should be
evaluated, some authors propose that if VC is > 60% predicted it should be performed every 6 months while if under 60% every 3-4 months (269).

Measurement of the VC in the supine position gives an index of weakness of the diaphragm. A fall of more than 15% indicates diaphragmatic dysfunction and correlates with complaints of orthopnea (270) and a supine FVC under 75% was highly sensitive and specific of low transdiaphragmatic pressure (271).

Muscle strength

Like VC, testing for respiratory muscle strength should be obtained periodically. Maximal inspiratory mouth pressure (MIP) values > 80cmH20 exclude clinically relevant respiratory muscle weakness (267). A low MIP with a normal MEP suggests isolated diaphragmatic weakness. Sniff nasal inspiratory pressure (SNIP) is a more natural and easier to perform manoeuvre than MIP (272). Values greater than -70cmH20 (for males) and -60cmH2O (for females) exclude significant inspiratory muscle weakness (273). Moreover a SNIP < 40cmH20 was associated with nocturnal hypoxemia and predicted median survival at 6 months (273). Chaudri et al (274) also recommend that patients with SNIP < 30% of predicted are at risk of developing hypercapnia and should have their ABG measured. Some authors advise that in patients with moderate to severe restrictive defect MIP is higher than SNIP so suggesting that the latter may overestimate the level of inspiratory weakness in this context (275).

Transdiaphragmatic pressures and nonvolitional tests of respiratory muscle strength are more accurate and may be indicated when others tests are difficult to interpret or in the context of clinical trials (268).


**Blood Gases**

Once the VC drops below 50% of predicted or MIP (or SNIP) below 30% predicted, daytime arterial blood gases (ABG) should be checked (276). However, performance of ABG analysis at every clinic attendance is uncomfortable for patients. Accurate devices for measuring PaO2/PaCO2 non-invasively are becoming available and will become standard practice in the future.

Daytime oxygen saturation (SpO2) measurement by pulse oximetry can be routinely used as screening tool. If SpO2 is under 95% it can either be caused by inspiratory, expiratory of bulbar dysfunction (221). In ALS, when SpO2 can not be normalized by NIV and mechanical assisted cough tracheostomy needs to be considered due to severe bulbar dysfunction (221).

Capnography as been recommended as ideal for measuring carbon dioxide tensions(277). It measures end-tidal CO2 and can be performed during daytime evaluations and continuously during sleep (278-279). According to recent data, measuring ETCO2 by a VC maneuver provides a more accurate estimate of PaCO2 and can be very useful for check-point determinations in hospital or at home (278).

Transcutaneous CO2 (TcCO2) has been widely used for long-term measurement during sleep and after NIV (280-282). TcCO2 measurements require more time and its levels are normally 3-12 mmHg higher and more accurate than ETCO2 (283-284). However some authors advise that the accuracy of TcCO2 seems to be restricted to patients with PaCO2 values <56mmHg (285).
Noninvasive methods of CO2 monitoring normally tend to give a slightly higher PaCO2 level, so a normal reading can exclude hypercapnia (267).

More recently combined TcCO2-SpO2 single sensors have been investigated, and seem valid in various settings (286-288).

Noninvasive ventilation support in stable COPD

Long term NIV in COPD remains an area of controversy. The central conundrum is that while there are have been no randomised trials which demonstrate a major impact on survival or quality of life, the use of home NIV in COPD is a major growth area. A European survey (194) has shown that in some countries far more obstructive lung disease patients then restrictive patients are long term NIV recipients, even adjusted for prevalence.

It is interesting to observe that early studies showed very mixed results. Case series (8, 289) from the early 1990s indicated that a possible target group for home NIV might be those COPD patients that developed hypercapnia on long term oxygen therapy (LTOT). Several uncontrolled (290) or retrospective studies (291) suggested significant improvement in arterial blood gas tensions, and a possible reduction in hospital admissions and General Practitioner consultation rates (292). In a cross over study of LTOT v. NIV plus LTOT Meecham Jones and colleagues (293) demonstrated improvements in nocturnal and arterial blood gas tensions on NIV and enhanced sleep quality and improvement in quality of life. These results are offset by another crossover study (294) that showed worse sleep quality using NIV v.LTOT, and two
small randomised trials (295-296) which showed no significant improvement in physiological measures. In the RCT by Gay et al (296) bilevel pressure support was compared to sham NIV. Poor tolerance of NIV was noted in both RCTs. A number of messages emerge from this early work – firstly a suggestion that more hypercapnic subgroups of patients may be more likely to benefit, and secondly in some studies relatively low level of inspiratory positive pressure support were applied which may not have been effective.

Finally it seems that acclimatisation to NIV may be slower in some COPD patients than in those with restrictive disorders, therefore trials lasting only a few weeks may be insufficient to gauge the impact of the intervention, even on physiological endpoints.

Clearly, longer trials are also required to investigate effects on the key outcomes of frequency of exacerbations, quality of life and survival. More recently there have been two longer term randomised controlled trials. Casanova et al in a one year study (297) randomised 52 COPD patients to standard care or standard care plus NIV. Outcomes included rate of acute exacerbations, hospital admissions, need for intubation and mortality at 3, 6 and 12 months. For the NIV group, ventilation was initiated as an inpatient using a bilevel positive pressure system in spontaneous mode. The authors targeted an expiratory positive airway pressure (EPAP) level of 4 cmH2O and an inspiratory positive airway pressure (IPAP) level of at least 12 cmH2O. Pressures were adjusted to decrease perception of dyspnoea and accessory muscle use, and oxygen delivered to the mask to achieve a SaO2 > 90%. Five of the NIV group (total n=26) did not tolerate NIV. Average ventilation in the remainder was 6.2 hours per 24 hours and marginally decreased to 5.9 hours/24 hours at 9 months. Eleven percent used NIV for less than 3 hrs/day.
One year survival was similar in both groups. The number of acute exacerbations did not differ between standard and NIV groups at all time points. However, the frequency of admissions was decreased at 3 months in the NIV group (5% versus 15%, p<0.05), although this difference was not sustained at 6 months. Borg breathlessness scores decreased in the NIV group, but only one psychomotor test improved. The authors carried out a subgroup analysis to see if any clinical or functional variables were predictive of benefit, but in this study there was no evidence that more hypercapnic patients (PaCO2 >7.3 kPa versus PaCO2< 7.3Kpa), or those that used NIV for >5 hours per 24 hours did better than standard group.

In an Italian multicentre trial (298) which has furthered the debate, 122 stable hypercapnic COPD patients on LTOT for > 6 months were randomised to continue LTOT alone, or LTOT plus NIV using a bilevel positive pressure device over a 2 year period. The study was powered to assess reduction in daytime PaCO2 rather than mortality. Drop out rates were similar in both groups, and compliance with NIV was impressive at 9 hours/24 hours.

The authors showed no significant difference in hospital or ICU admissions, although there was a trend to fewer admissions in the NIV group (compared to the previous year admissions decreased by 45% in NIV group and increased by 27% in LTOT group). Mortality did not differ. PaCO2 was slightly reduced in NIV patients using LTOT and there was also a reduction in dyspnoea and increase in heath related quality of life scores in NIV group. Potential criticisms of the study are that the IPAP levels used were low, it is difficult to know whether nocturnal hypoventilation was corrected by nighttime NIV, and it is possible that some quality of life and symptomatic improvements might be related to a placebo effect. A reasonable riposte to this last point is that although short term trials using sham CPAP and sham NIV have been
performed, it would be difficult practically and ethically to carry out a randomised trial of NV over several years with a sham NIV limb.

It is evident therefore that widespread use of long term NIV across the board in COPD patient cannot be justified on the evidence presented above. The studies do however suggest that primary end points of number of acute exacerbations and hospital admissions may be a more sensitive measure than mortality. The frequency of acute exacerbations of course has economic implications. On that point Tuggey et al (299) examined the economic impact of home NIV in a selected group of COPD with recurrent exacerbations who had responded well to NIV during these acute episodes. In this group, preselected because of good tolerance, provision of home NIV resulted in a mean cost saving of 11720 euros (5698-17,743 euros) per patient year. The number of hospital admissions in the year on NIV compared to the year pre NIV was reduced from 5 to 3, mean hospital days decreased from a mean (SD) of 78 (51) to 25 (25) p=0.004, and ICU days fell from 25 to 4 (p=0.24). Outpatient visits also decreased.

Noninvasive ventilation support in restrictive disorders

Chest wall disorders

Patients with untreated scoliosis have an increased risk of developing respiratory failure (300). The larger the scoliotic angle, the lower the vital capacity and the younger the age of scoliosis onset, the greater is the risk (301). Patients who have reached skeletal maturity and have a vital capacity below 45% of predicted value the risk of developing respiratory failure increases with age (301). Symptoms of cardio-respiratory failure
generally appear between the fourth and sixth decade of life, however some patients survive into the seventh decade without experiencing cardio-respiratory problems (302). It is well known that severe kyphoscoliosis may induce sleep-related respiratory abnormalities (303) and retrospective long-term studies of nocturnal NIV have shown a better prognosis of those patients compared with neuromuscular and obstructive disorders (8, 289). In fact, in prospective studies, NIV improves hypoventilation-based symptoms, muscle function and nocturnal oxygenation in patients with daytime hypercapnia and FVC< 50% (304-305). In patients with less severe respiratory impairment, nocturnal NIV improves significantly exercise capacity and there is a trend for an increase in daytime PaO2 (306). Data from a large French observatory (307) and a recent prospective study (308) clearly show that kyphoscoliotic patients treated by home mechanical ventilation experience a better survival than those treated by oxygen therapy alone. Moreover, Masa et al have shown that NIV but not oxygen improved nocturnal hypoventilation in 7 patients with Kyphoscoliosis and normal daytime ABG (309). So, in symptomatic patients with daytime normocapnia but significant nocturnal desaturation (according with Masa (309) > 10% of Total sleep time with <90% SpO2 or mean REM SpO2 <90% and minimum SpO2<90% and according with the consensus conference (252) SpO2≤ 88% for 5 consecutive minutes) NIV is warranted (252).

Amyotrophic Lateral Sclerosis

Although initially regarded as controversial because of fear that it would simply delay death without improving quality of life, NIV has become the standard of care for patients with symptoms and evidence of respiratory involvement (310). In fact, NIV improves symptoms, quality of life (260, 311) and survival (312).
Because ALS patients eventually become quadriplegic, they require a high level of assistance from caregivers (313). In one study, one of the best predictors of success of NIV was a good caregiver support (314).

Although there is no clear evidence regarding timing for NIV, it seems reasonable to start in symptomatic patients (table II) with signs of respiratory muscle weakness (FVC<80% or SNIP<40cmH20) and evidence of significant nocturnal desaturation or PaCO2>49mmHg (310). Bourke et al suggest that ortopnea was the most useful criterion for benefit and compliance with NIV (311), and Sivak (315) that there was a lack of correlation between VC at the institution of NIV and the duration of its successful use.

In a small prospective study Jackson et al (260) suggest that early intervention, based on nocturnal oximetry criteria (SpO2<90% form 1 cumulative minute), may result in improved quality of life with NIV.

For most patients, NIV begins at night but may rapidly develop 24h ventilator dependence (316). If bulbar function is well preserved, continuous NIV (daytime mouth-piece and nocturnal oro-nasal NIV) may manage up to 20% of ALS patients safely for long years (221, 239, 316), avoiding tracheostomy.

Unlike patients with Duchenne Muscle Dystrophy, Post-Poliomyelitis Syndrome, and most other NMD, ALS may have bulbar muscle dysfunction, carrying a high risk of aspirating saliva and not being able to clear airways secretions (316).

Bulbar muscles involvement carries a worse prognosis (317) and in those patients, NIV may be less tolerated (318-319). However the recent RCT found that patients with moderate to severe bulbar impairment gained a smaller, although clinically significant quality of life benefit from NIV (312).
Bulbar muscle dysfunction should be evaluated in patients with ALS. Apart from rating scales like the ALSFRS (320) one of the best ways to measure it objectively is by comparing the MIC with the VC and the PEF with the CPF. The wider the gradient, the better the bulbar function (321-322). Bach has shown that in ALS, that the ability to generate assisted CPF>180L/min and to have an high MIC VC difference is associated with the capacity to use continuous NIV (224). However, when strictly tailored NIV and Mechanical Assisted Cough does not prevent oxygen desaturation below 95%, saliva aspiration is likely and tracheostomy should be offered (221).

Care should also be put into secretion management since Mechanical Assisted Cough to prevent airway encumbrance is an essential complement to NIV and a key to successful full-time NIV (316)

**Duchenne muscular dystrophy**

Duchenne Muscular dystrophy (DMD) has an X-linked recessive pattern of inheritance and affects up to 1 in 3300 live male births. (323) Affected patients typically become wheelchair dependent by the age 10-12 years at which VC plateaus. With the development of respiratory muscle weakness and skeletal deformity, VC starts to fall (324). The patients usually remain asymptomatic until VC decreases below 450ml and begin daytime hypercapnia (212). Hukins et al suggest that once FEV1 falls below 40% predicted, arterial blood gases should be performed (325) and Hahn et al report that hypercapnia appears in patients with MIP lower than 30cmH2O or 30% of predicted normal (326).

The first signs of respiratory involvement occur during sleep. Obstructive sleep apnea is very frequent in DMD, with some authors reporting a prevalence of 57% (327), and
occurring more commonly in younger children (328). Hypoventilation was the major abnormality in older children (early second decade) (328).

By the time patients become hypercapnic, nocturnal NIV is clearly indicated. Vianello et al (329) have shown that life expectancy is <1 year once diurnal hypercapnia develops and compared with a non-ventilated control group, NIV significantly prolonged survival in DMD patients with symptomatic daytime hypercapnia. In fact the majority of published studies using NIV in DMD included patients with symptoms and diurnal hypercapnia (17, 324, 330). In a UK study that followed a cohort of 23 severely hypercapnic patients with DMD, the use of NIV has increased median survival, with a 5 year survival of 73% (17).

In a randomised controlled trial, including normocapnic, essentially asymptomatic patients with VC between 20-50%, Raphael et al did not show any improvement in survival (331). However this study should not be viewed as definitive as their findings may have been caused by a lack of standardized ventilator and mask use between investigators (332). In addition it may be argued that for NIV to be effective longterm, the implementation of assisted cough techniques are critical a intervention that was not considered in this trial, in which the main causes of death in the NIV group were due to infection with retention of tracheobronchial secretions.

Although some authors suggest that once the VC is <1L the 5 year survival rate is 8% (333) with inspiratory and expiratory non-invasive respiratory aids, 10 year survival can be up to 93.3% (212). In fact, compared with a conventional approach before 1993, with a proactive protocol that included NIV (up to full time) together with Mechanical In-Exsufflation guided by home oximetry, the New Jersey University Hospital has
managed to significantly extend survival and avoid respiratory mortality in patients with DMD(63).

More recently several groups in Europe have shown that once nocturnal hypercapnia (measured by transcutaneous CO2) is present treatment with NIV should be implemented (334-336). Others, in the absence of nocturnal CO2 measurements, suggest that symptomatic patients with mean nocturnal SpO2 below 94% should be encouraged to use NIV, especially if they had symptomatic relieve or correction of nocturnal desaturation (207).

According with the ATS consensus statement daytime ventilation should be considered when measured waking PaCO2 exceeds 50mmHg or when haemoglobin saturation remains <92% while awake (277). The most commonly used noninvasive technique is mouth-piece intermittent positive pressure ventilation (M-IPPV), which was first reported in 1969 (337). Since then the New Jersey University Hospital has extensively reported their experience with M-IPPV for continuous NIV as an alternative to tracheostomy (338-340). Others centers from the US have also described their successful experience (330, 341-344). In Europe, although an expert group report recommended its use in 1993 (345), it was not until very recently that diurnal ventilation via mouthpiece was described in end-stage DMD patients (335). In this prospective study, Toussaint et al have shown that a simple angled mouthpiece held stable near the mouth could confortably deliver volume cycled ventilation during the daytime, stabilising VC, decreasing symptoms, daytime hypercapnia and extending survival up to 7 years in 51% of 42 M-IPPV users(335).

Death from cardiomyopathy is significant in patients with DMD, so regular cardiac assessment and adequate medication should be implemented (346)
A recent study has shown that although patients with DMD are severely disabled they still perceive a high quality of life, not correlated with physical impairment nor the need of NIV (347).

MANUAL AND MECHANICAL TECHNIQUES FOR SECRETION MANAGEMENT

Rational

In healthy individuals, mucociliary clearance and cough mechanisms are normally effective and efficient for defence on secretion encumbrance, but may become ineffective if these systems malfunction and in the presence of excessive bronchial secretions. Mucus secretion and clearance are extremely important for airway integrity and pulmonary defence. It has been estimated that mucus secretion volume is between 10 and 100ml per day in healthy subjects (348).

Mucus is transported from the lower respiratory tract into the pharynx by airflow and mucociliary clearance. Overload of normal secretion or mucociliary clearance impairs pulmonary function and increases risk of infection. When there is extensive ciliary damage and secretion encumbrance, coughing becomes critically important for airway hygiene (349). Airflow dependent clearance can also be increased by moving secretions from the periphery of the lung to the more proximal airways, were greater secretion depth and higher expiratory air flow can improve expectoration. This is why cough is generally incorporated into most chest physical therapy techniques (350).
Cough and expectoration of mucus are the best-known symptoms in patients with pulmonary impairment disorders. Airway clearance may be impaired in disorders associated with abnormal cough mechanics, altered mucus rheology, altered mucociliary clearance, or structural airway defects. A variety of interventions are used to enhance airway clearance with the goal of improving lung mechanics and gas exchange, and preventing atelectasis and infection (351).

Techniques for augmenting the normal mucociliary clearance and cough efficacy have been used for many years to treat patients with respiratory disorders from different etiologies. In recent years, new technologies and more advanced techniques have been developed to be more comfortable and effective for the majority of patients. Postural drainage with manual chest percussion and shaking has, in most parts of the world, been replaced by more independent and effective techniques such as the active cycle of breathing, autogenic drainage, R-C Cornet®, Flutter®, positive expiratory pressure mask, high frequency chest wall oscillation, intrapulmonary percussive ventilation and mechanical insufflation-exsufflation (349). The evidence in support of these techniques is variable and the literature is confusing and sometimes conflicting, regarding the clinical indication for each technique. This fact may be related to the intensity, duration and frequency being different between physiotherapists in different parts of the world, and have changed over the years (352). Moreover, it can be confusing for health care professionals, patients and their caregivers when it comes to choosing and utilizing the most appropriate airway clearance techniques and products.

Patients who require mechanical breathing assistance or pharmaceutical intervention, often also need assistance to mobilize and clear secretions from their airways and lungs. It is critically important for these patients to keep their airways clear of secretions to avoid the risk of atelectasis caused by mucus plugs and infections, including
pneumonia, which can often lead to numerous hospitalizations and even premature death. Patients with chronic lung disease, such as chronic obstructive pulmonary disease (COPD) and Cystic Fibrosis (CF), those that have neuromuscular disorders such as muscular dystrophy (MD), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), post-polio syndrome, and those paralyzed due to Spinal Cord Injury (SCI), are at the greatest risk of developing such infections.

The effective elimination of airway mucus and other debris is one of the most important factor that permits successful use of chronic and acute ventilation support (noninvasive and invasive) for patients with either ventilatory or oxygenation impairment. In ventilatory dependent patients, the goals of intervention are to maintain lung compliance and normal alveolar ventilation at all times and to maximize cough flows for adequate bronchopulmonary secretion clearance (353).

In patients with primarily ventilatory impairment, such as neuromuscular disease, 90% of episodes of respiratory failure are a result of inability to effectively clear airway mucus during intercurrent chest colds (354). Although the use of respiratory muscle aids is the single most important intervention for eliminating airway secretions for patients with inspiratory and expiratory muscle weakness, as for normal coughing these aids may not adequately expulse secretions from the very small peripheral airways more than 6 divisions from the trachea, the flows they create may not be sufficient to eliminate secretions that are obstructing the smaller airways (355). In these situations, it is important to consider secretion mobilization techniques to gradually loosen and mobilize secretions to assist mucociliary clearance from the lower airway into the upper airway where they then need to be cleared by either assisted coughing techniques or the patient’s natural cough.
A great majority of episodes of secretion encumbrance develop in acute respiratory failure and it has been demonstrated that in even acute episodes of respiratory failure morbidity and mortality can be avoided without hospitalisations with a correct and effective secretion management protocol (356). Moreover, it has been reported that conventional chest physical therapy for secretion management does not increase the chances of weaning and extubation success in critical ill patients (357). However, some of these patients may have normal mucociliary clearance but ineffective peak cough flows (CPF) which itself has been associated with extubation failure (37, 358). A protocol that includes assisting coughing techniques as adjunct to a efficient NIV application may increase the success rates of extubation in difficult to wean patients.

**Patient evaluation and monitoring**

The respiratory patient evaluation includes a survey for symptoms of chronic and/or acute alveolar hypoventilation, medical history, physical examination, cough evaluation and simple pulmonary function tests. Measurement of mucous transport through the bronchial tree by radiolabeled tracers is a technique that has been used above all to study mucociliary clearance, as well as the measurement of the volume of expectorated mucous (359).

Respiratory physiotherapy interventions can be evaluated using different outcome variables, such as bronchial mucus transport measurement, measurement of the amount of expectorated mucus, pulmonary function, medication use, frequency of acute exacerbations and quality of life(349, 352, 360).
**Pulmonary function and cough tests**

Evaluation of respiratory physiotherapy interventions only with pulmonary function tests appears to be inadequate for significant conclusions. However it is knowned that mucus retention has a strong impact on pulmonary function and gas exchange. Severe mucus retention can cause an acute decrease in vital capacity (VC), forced VC, flow rates, as well as SpO₂. Patients with severe airway obstruction have more difficulties expectorating mucus. Patients with ineffective cough and low VC’s are in extreme respiratory distress in the presence of secretion accumulation. A correct evaluation of pulmonary function and cough parameters may predict a successful respiratory physiotherapy treatment.

Poponick et al. (361) demonstrated that acute viral illness was associated with a reduction in vital capacity (VC) due to a reduction in inspiratory and expiratory respiratory muscle strength (by 10–15% of baseline values), which causes a decline in CPF to the critical level of 160 L·min⁻¹.

A spirometer is used to measure VC in sitting, recumbent, and sidelying positions. The spirometer is also used to measure the maximal insufflation capacity (MIC) for patients with VCs at least 30% less than predicted normal levels who are trained in air stacking (362). Usually a manual resuscitator is used for the patient to air stack via a mouthpiece for the MIC measurements (Figure 14).
Figure 14: Air stacking with manual resuscitator via a mouthpiece in a DMD patient with low vital capacity and suboptimal peak cough flow.

An effective CPF requires a pulmonary inspiration or insufflations until 85-90% of the vital capacity, and the generation of high intratoracic pressure so as to expel 2.3-2.5 L of air at a CPF of 6-20 L/sec. In order for an effective cough to occur, the Peak Cough Flow (CPF) must be higher than 270 L/min (363)

Unassisted cough peak flows (CPF) are measured by having the patient cough as hard as possible through a peak flow meter to get a baseline value. Kang and Bach (364) proved that the CPF value could be even higher if it is performed through the Maximum Insufflation Capacity (MIC). The MIC is related to the pulmonary compliance and with the pharyngeal and oropharangeal muscles function. After a deep inspiration the subject makes an apnoea and receives an extra air volume of air (through a manual resuscitator or volume ventilator) via a mouthpiece, nasal interface. This extra air volume will produce the lung distension, allowing a cough at a higher volume, and therefore more effective. The patient coughs via an oronasal interface if there is a tendency for insufflated air to leak out of the nose.
Finally, (fully) assisted CPF are measured from the MIC with an abdominal thrust timed to glottic opening. The most important CPF measurement is usually the latter because it is the manually assisted cough from the MIC that the patient must often use to clear airway secretions to avoid respiratory failure. The inability to generate a CPF greater than 2.7 L/s even when MIC exceeds 1 L, generally indicates the existence of fixed upper airway obstruction or significant bulbar impairment, with hypopharyngeal collapse during mechanical assistance to aid cough (60, 365-366).

Control of Mucus and Airway Clearance Techniques

Airway clearance refers to two separate, but connected, mechanisms: mucociliary clearance and cough clearance. Techniques for controlling and assisting the mobilization of secretions from the airways have long been advocated for use in the patient with impairment in mucociliary clearance or an ineffective cough mechanism. The goals of this therapy are to reduce airway obstruction, improve mucociliary clearance and ventilation and optimise gas exchange.

Approaches to preventing airway secretion retention include pharmacotherapy to reduce mucus hypersecretion or to liquefy secretions, and the application of chest physiotherapy techniques. Chest physiotherapy (CPT) can be defined as the external application of a combination of forces to increase mucus transport that include postural drainage positions, special breathing exercises, manual chest vibration and percussion, autonomous instrumental techniques and manual assisted coughing.

Research studying the results of airway clearance are often difficult to evaluate because the components of a given treatment have not been standardized. Availability of equipment or education about a technique as well cultural differences in its application confounds the results. CPT does not appear to benefit patients during recovery from
acute exacerbations of COPD or pneumonia. These conditions are characterized by interstitial pathology, which cannot be influenced by physical interventions in the airways (367-369). Further studies are needed to identify the patients and more circumstances, which are at risk from complications or adverse effects of chest physiotherapy.

Chest physical therapy techniques

Approaches to preventing retention of airway secretions include the use of medication to reduce mucus hypersecretion or to liquefy secretions and the facilitation of mucus mobilization. To complement this objective, chest physiotherapy techniques (CPT) are shown to be very effective in preventing pulmonary complications in infant and adult patients with bronchopulmonary secretion accumulation. The principles of manual chest physiotherapy techniques consists in the application of external forces in the thoracic cage that have direct effect on mucus mobilization.

Manual chest percussion, sometimes referred to as chest clapping, is very well knowned in the respiratory physiotherapy community. Some authors demonstrated an increase in airflow obstruction when chest clapping was included in an airway clearance regimen (370). Chest clapping has also been shown to cause an increase in hypoxemia, but when short periods of chest clapping have been combined with three or four thoracic expansion exercises, no fall in oxygen saturation has been seen(349). Some patients with severe lung disease demonstrate oxygen desaturation with self-chest clapping. This may be due to the work of the additional upper limb activity. On the basis of three randomised, controlled trials of chest physiotherapy and one observational study, manual chest percussion as applied by physical or respiratory therapists is ineffective
and perhaps even detrimental in the treatment of patients with acute exacerbations of COPD(371).

Another manual chest physical therapy technique is vibration applied throughout exhalation concurrently with mild compression of the patient’s chest wall. Vibration is proposed to enhance mucociliary transport from the peripheral of the lungs fields to the larger airways.

Manual thoracic techniques are effective in removing pulmonary secretions, facilitating inspiration and improving alveolar ventilation. Guidebooks have been published that demonstrates the hand placements and thrusting techniques in children and adults (372).

**Manual assisted coughing techniques**

Cough is the primary defense mechanism against foreign bodies in the lower airways. Any stimulation of the pharyngeal, laryngeal, tracheal or bronchial receptors can create a cough. When this mechanism is not functioning correctly mucus restrain will occur, as bronchial obstruction. This problem may be due to the fact that the subject cannot make a deep inspiration, or incapable of glottis closure, or incapable of rising intra abdominal and intra thoracic pressure.

An effective cough is based of expiratory muscles force, capable of producing effective CPF´s. The CPF is a routine measure in the evaluation of neuromuscular patients (373) and clinical investigations such suggest that it should be used in spinal cord patients as well (88, 97).

The patient with partial or complete abdominal muscle paralysis is unable to produce an effective cough. Manually assisted cough is the external application of pressure to the
thoracic cage or epigastric area, coordinated with a forced exhalation. This action serves to simulate the normal cough mechanism by generating an increase in the velocity of the expired air and may be helpful in moving secretions toward the trachea, where they can be removed by nasotracheal suctioning.

The abdominal thrust is an assisted coughing technique which consists of the association of two techniques: the costo-phrenic compression and the Heimlich manoeuvre. The combination of deep lung insufflations to the MIC followed by manual assisted cough with abdominal thrust (Figure 15) has been shown to increase significantly CPF’s values in restrictive patients (366, 374).

Although an optimal insufflation followed by an abdominal thrust provides the greatest increase in CPF, it can also be significantly increased by providing only a maximal insufflation or providing only an abdominal thrust without a preceding maximal insufflation. Interestingly, CPF are increased significantly more by the maximal insufflation than by the abdominal thrust (375-376).

Manually assisted coughing and MIC maneuver requires a cooperative patient, good coordination between the patient and care giver), and adequate physical effort and often frequent application by the family care giver (Figure 2). It is usually ineffective in the presence of severe scoliosis because of a combination of restricted lung capacity and the inability to effect diaphragm movement by abdominal thrusting because of severe rib cage and diaphragm deformity.
Abdominal compressions should not be used for 1 to 1.5 hours following a meal, however, chest compressions can be used to augment CPF. Chest thrusting techniques must be performed with caution in the presence of an osteoporotic rib cage. Unfortunately, since it is not widely taught to health care professionals manually assisted coughing is under utilized (377).

**Mechanical Respiratory Muscle Aids for Secretion Management**

Respiratory muscle aids for secretion management are devices and techniques that involve mechanical application of forces to the body or intermittent pressure changes to the airway to assist expiratory muscle function and airway mucus clearance. The devices that act on the body include high frequency chest wall oscillators that create atmospheric pressure changes with oscillations around the thorax and abdomen, intrapulmonary percussive ventilators that create a rapid frequency adjusted for internal percussion for mucus progression to the large airways, and insufflation- exsufflation devices that apply force and pressure changes directly to the airway to assist the
expiratory muscles for cough augmentation and the inspiratory muscles for lung expansion.

Intrapulmonary Percussive Ventilation (IPV)

The intrapulmonary percussive ventilator is an airway clearance device that simultaneously delivers aerosolized solution and intrathoracic percussion. This modified method of intermittent positive-pressure breathing imposes high-frequency minibursts of gas (at 50–550 cycles/min) on the patient’s own respiration. This creates a global effect of internal percussion of the lungs, which could promote clearance of the peripheral bronchial tree.

IPV devices include: Im®-F00012, IPV1C®-F00001-C, IPV2C®-F00002-C (Percussionaire® Corporation, ID, USA); and IMP II (Breas Medical, Sweden). The percussions (sub-tidal-volume) are delivered continuously through a sliding air-entrainment device (called Phasitron) powered by compressed gas at 20–40 psi. The high frequency gas pulses expand the lungs, vibrate and enlarge the airways, and deliver gas into distal lung units, beyond accumulated mucus (378-380). Treatment with IPV is titrated for patient comfort and visible thoracic movement. The patient initiates the flow of gas and during inspiration the pulsatile flow results in an internal percussion. Interruption of the inspiratory flow allows for passive expiration.

This technique has been shown to be as effective as a standard chest physiotherapy and to assist mucus clearance in patients with secretion encumbrance from different etiologies, such as cystic fibrosis (381), acute exacerbations of COPD (41) and Duchenne muscle dystrophy (378). In cystic fibrosis IPV was shown to be as effective
as the other methods of airway clearance in sputum mobilization, when the amount of sputum produced was assessed by dry weight(382).

IPV can be delivered through a mouthpiece, a facial mask and also through an endotracheal and tracheostomy tube (383). The primary aims of this technique are to reduce secretion viscosity, promote deep lung recruitment, improve gas exchange, deliver a vascular “massage”, and protect the airway against barotrauma. The main contraindication is the presence of diffuse alveolar haemorrhage with homodynamic instability. Relative contraindications include active or recent gross haemoptysis, pulmonary embolism, subcutaneous emphysema, bronchopleural fistula, esophageal surgery, recent spinal infusion, spinal anesthesia or acute spinal injury, presence of a transvenous or subcutaneous pacemaker, increased intracranial pressures, uncontrolled hypertension, suspected or confirmed pulmonary tuberculosis, bronchospasm, empyema or large pleural effusion and acute cardiogenic pulmonary edema(384).

**High-frequency chest wall oscillation (HFCWO)**

In 1939 it was recognized that alveolar ventilation and blood circulation could be assisted by rapidly alternating negative and positive pressure under a chest shell. J. H. Emerson developed the first high frequency chest wall oscillation jacket, the Ucyclist-B Vest, to facilitate bronchial secretion clearance in the early 1950s but he provided oscillation only during part of the breathing cycle. Barach described use of a similar unit by patients with chronic bronchial asthma and emphysema in 1966 (385).

During HFCWO, positive pressure air pulses are applied to the chest wall. Oscillation and vibration can be applied externally to the chest wall or abdomen by rapidly oscillating pressure changes in a vest that include the SmartVest® (Electromed Inc,
MN, USA), The Vest® (Hill-Rom, MN, USA) and the ThAIRapy Vest™, (American Biosystems, Inc., St. Paul, MN), or by cycling oscillating pressures under a chest shell (Hayek™ oscillator, Breasy Medical Equipment Inc., Stanford, CN).

This technique provides oscillation at 5 to 25 Hz. Mechanical vibration is performed at frequencies up to 40 Hz. Vibration is applied during the entire breathing cycle or during expiration only. The adjustable I/E ratio permits asymmetric inspiratory and expiratory pressure changes (for example +3 to -6 cm H₂O), which favor higher exsufflation flow velocities to mobilize secretions. Baseline pressures can be set at negative, atmospheric, or positive values thus commencing oscillation above, at, or below the functional residual capacity (FRC) (39, 353). The average length of time spent in each treatment session will vary according to patient tolerance, amount and consistency of secretions, and the phase of the patient’s illness (acute or chronic)(380). Simultaneous use of an aerosolized medication or saline is recommended throughout the treatment. This humidifies the air to counteract the drying effect of the increased airflow (41).

HFCWO may act like a physical mucolytic, reducing both the spinability and viscoelasticity of mucus and enhancing clearance by coughing (353, 379, 386). High frequency chest wall oscillation (HFCWO) has demonstrated efficacy in assisting mucus clearance in patients with disorders associated with mucus hyper-secretion but preserved muscle function such as cystic fibrosis (CF) (386). HFCWO is an external non-invasive respiratory modality proven effective in mobilizing airway secretions from the small peripheral airways and improving mucus rheology in patients with CF and has become an important modality in the airway clearance techniques of this group of patients (387-389). High frequency oscillation to the airways has also been reported to increase mucus transport in healthy subjects (390).
These beneficial effects upon both mucus clearance and clinical parameters are not so evident in other groups of patients such as COPD. Moreover, side effects of percussion and vibration include increasing obstruction to airflow for patients with COPD. (369, 391-392). The proven value of HFCWO in patients with relatively normal mucus composition and characteristics but neuromuscular weakness is still under investigation, especially as a long-term treatment modality. In one study, the addition of HFCWO to randomly selected patients with ALS failed to achieve any significant clinical benefits in relation to the time of death (survival days). In addition, HFCWO failed to modify the rate of decline in FVC given the progressive nature of this chronic neurodegenerative disease process. There were no significant differences concerning the frequency of atelectasis, pneumonia and number of hospitalisations for a respiratory related abnormality, or requirement for tracheostomy and mechanical ventilation (39).

On another hand, Lange et al (393) also compared lung function parameters in ALS patients who were randomized to 12 weeks of HFCWO or no treatment. Results showed maintenance of FVC and decreased fatigue and dyspnoea in HFCWO group compared to the untreated group.

Contraindications for HFCWO are mostly the same as for IPV, plus head or neck injury not yet stabilized, burns, open wounds, infection or recent thoracic skin grafts, osteoporosis, osteomyelitis, coagulopathy, rib fracture, lung contusion, distended abdomen, and chest wall pain (353, 388).

**Mechanical Insufflation-Exsufflation (MI-E).**

Mechanical insufflator-exsufflators (Cough Assist\textsuperscript{tm}, Philips Respironics, Inc) deliver deep insufflations (at positive pressures of 30 to 60cmH2O) followed immediately by deep exsufflations (at negative pressures of -30 to -60cmH2O). The insufflation and
Exsufflation pressures and delivery times are independently adjustable (55). With an inspiratory time of 2 seconds and an expiratory time of 3 seconds, there exists a very good correlation between the pressures used and the flows obtained (56) (394).

Except after a meal, an abdominal thrust is applied in conjunction with the exsufflation (MAC) (376). Mechanical in-exsufflation can be provided via an oral-nasal mask a simple mouthpiece, or via a translaryngeal or tracheostomy tube. When delivered via the latter, the cuff, when present, should be inflated (395).

MI-E applied with an oronasal mask can generate CPFs greater than 2.7 L/s in motor neuron disease patients, with the exception of those with very acute bulbar dysfunction (396), in whom there exists great instability of the upper airways (60). If, in normal subjects, the sudden application of negative pressure at this level produces reflex activation of the genioglossus to maintain permeability, in those patients with diminished strength and speed of the pharyngeal muscles there will be obstruction during the expiratory phase (363).

The Cough Assist™ can be manually or automatically cycled. Manual cycling facilitates care giver-patient coordination of inspiration and expiration with insufflation and exsufflation, but it requires hands to deliver an abdominal thrust, to hold the mask on the patient, and to cycle the machine. One treatment consists of about five cycles of MI-E or MAC followed by a short period of normal breathing or ventilator use to avoid hyperventilation (62). Insufflation and exsufflation pressures are almost always from +35 to +60 cm H2O to -35 to -60 cm H2O. Most patients use 35 to 45 cm H2O pressures for insufflations and exsufflations. In experimental models, +40 to -40 cm H2O pressures have been shown to provide maximum forced deflation VCs and flows (365, 375, 394). Multiple treatments are given in one sitting until no further secretions
are expulsed and any secretion or mucus induced desaturations are reversed. Use can be required as frequently as every few minutes around the clock during chest infections(58). Although no medications are usually required for effective MI-E in neuromuscular ventilator users, liquefaction of sputum using heated aerosol treatments may facilitate exsufflation when secretions are inspissated.

The use of MI-E via the upper airway can be effective for children as young as 11 months of age. Patients this young can become accustomed to MI-E and permit its effective use by not crying or closing their glottises. Between 2 1/2 and 5 years of age most children become able to cooperate and cough on queue with MI-E. Exsufflation timed abdominal thrusts are also used for infants (397-398).

Whether via the upper airway or via indwelling airway tubes, routine airway suctioning misses the left main stem bronchus about 90% of the time. MI-E, on the other hand, provides the same exsufflation flows in both left and right airways without the discomfort or airway trauma of tracheal suctioning and it can be effective when suctioning isn't. Patients almost invariably prefer MI-E to suctioning for comfort and effectiveness and they find it less tiring (399-400).

When mucous plugs are eliminated in acute episodes in ventilated neuromuscular patients, MI-E may attain 300% improvement in VC as well as normalization of oxygen saturation (401). Contraindications of the technique include previous barotrauma, the existence of bullae, emphysema, or bronchial hyperreactivity (402). There continue to be no publications contradicting the reports of effectiveness or describing significant complications of MI-E. Even when used following abdominal surgery and following extensive chest wall surgery no disruption of recently sutured wounds was noted (403-404). Secondary effects, such as pneumothorax, aspiration, or coughing up blood are
reduced considerably by treating the mentioned contraindications. On the other hand, gurgling noises and abdominal distension are rare and can be eliminated by lowering the insufflation pressure. The significant increase of forced expiratory flows in periods immediately following post-exsufflation indicates that MI-E does not provoke obstruction of the airways. As patients with spinal shock can present bradycardias, MIE should be carried out with cautious in them, with gradual increase in pressures or premedication with anticholinergics (405). In patients with very low VC who have not previously received maximum insufflations, the use of high pressures may cause thoracic muscle discomfort; thus, progressive increase is also indicated.

The use of MI-E has been demonstrated to be very important in extubating NMD patients following general anesthesia despite their lack of any breathing tolerance, and to manage them with noninvasive ventilation (355-356, 373). It has also permitted to avoid intubation or to quickly extubate NMD patients in acute ventilatory failure with no breathing tolerance and profuse airway secretions due to intercurrent chest infections (27, 406-407). MI-E in a protocol with manually assisted coughing, oximetry feedback, and home use of noninvasive IPPV was shown to effectively decrease hospitalizations and respiratory complications and mortality for patients with NMD (354, 408).
PURPOSE OF THE THESIS

Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or intermittent pressure changes to the airway to assist inspiratory or expiratory muscle function. Noninvasive ventilation (NIV) and mechanical assisted cough (MAC) are techniques that may have a role in different phases of both acute and chronic respiratory failure. In fact, there is sufficient evidence that support the physiological benefits of these techniques in aiding both inspiratory (NIV) and expiratory muscle function (MAC) in different patient populations.

Patients with impaired respiratory muscle function from different etiologies may be at risk of developing ventilatory failure during an acute exacerbation or during the primary disease progression in a chronic setting. Protocols and timing of NIV and MAC application have to be adjusted according to the different clinical scenarios and treatment goals should be based on a continuous level of care from acute to long term management. In this patient population, primary treatment goals in acute care are reversion of the episode of acute respiratory failure (ARF), avoid (when possible) or minimize the time on invasive ventilation, prevent and reduce complications of treatment and promote a safe hospital discharge to the community. In the chronic care setting, the main treatment goals are to prevent complications with close follow up, reduce hospitalizations due to ARF, prolong survival and enhance quality of life.

The main purpose of this thesis is to describe the efficacy of NIV and MAC in the different “windows of opportunity” set to achieve specific goals from acute to chronic
care, and present new management and evaluation paradigms in patients with muscle weakness from different etiologies. Methodological design of the thesis goals is presented in Figure 16.

**Figure 16:** Methodological design of the thesis studies (1 to 10) according to the different settings.

**Acute Respiratory Failure**

Mechanical ventilation using an artificial airway is probably the most frequently life-saving procedure used in the management of critically ill patients with severe respiratory failure(35). However, it is associated with multiple complications, primarily increased risk of pneumonia(409) with a high mortality rate, but also generalized myopathy, possibly related to the sedation or curarization necessary for invasive mechanical ventilation(410). In the majority of cases, mechanical ventilation can be withdrawn after resolution or significant improvement of the underlying indication for mechanical ventilation. However, it is estimated that 20 to 30% of patients require gradual withdrawal of ventilatory support, namely weaning(411).
A distinction must be made between dependence on the ventilator and an ongoing need for endotracheal intubation. When there is no need for an artificial airway, conventional extubation attempts follow successful “spontaneous breathing trials (SBTs) and the passing of ventilator weaning parameters that include respiratory rate less than 38 per minute and a rapid shallow breathing index below 100 breaths/min/L (412). This presupposes that ventilator weaning is mandatory before a patient can be safely extubated, otherwise patients are extubated only after tracheotomy. However, even for patients who satisfy weaning criteria and pass ventilator weaning trials, there is an extubation failure rate of 10 to 20% (413). The reasons given for extubation failure include lack of improvement in work of breathing, hypoxemia, respiratory acidosis, retained secretions, and decreased consciousness (414).

The process of discontinuing mechanical ventilation may be a major challenge, especially in patients with chronic respiratory disorders, in whom weaning is particularly difficult (415). Patients that develop acute respiratory failure that could result in prolonged invasive ventilation include COPD, spinal cord injury, neuromuscular disease (NMD), chest wall disease, and primary central nervous system disease.

The process of weaning from mechanical ventilation must balance the risk of complications due to unnecessary delays in extubation with the risk of complications due to early discontinuation and the need of reintubation(411). Patients who require reintubation have been noted to have a significantly higher mortality rate than those who are successfully extubated on the first attempt(416).

While studies have reported that NIV has been used in the emergency setting to avert intubation (21, 29, 417), and to facilitate extubation and weaning in the critical care
setting (114, 153, 158) in patients with lung/airways diseases (primarily oxygenation impairment) (155, 161, 418), the studies either report very few patients with primarily ventilatory impairment (unable to sustain spontaneous breathing) due to neuromuscular weakness i.e. 18 of 162 (155), 17 of 900 (413) or they completely exclude these patients when weaning is considered unlikely (357) or the risk of post-extubation failure is considered high (160). This is true despite the fact that neither adequate ventilator settings for full continuous noninvasive ventilatory support nor mechanically assisted coughing (MAC) were used in any of the studies on adult patients (419). Some studies do not even report the NIV settings (413).

Patients with pre-existing NMD are relatively infrequently in critical care (420), about 4 to 12.5% of cases (34, 156) (up to 25% in weaning centers) (421), and are seldom included in randomized critical care controlled trials of NIV (422). On the other hand, acquired critical care NMD is common yet often unrecognized (410, 423). Controlled invasive mechanical ventilation can induce diaphragmatic dysfunction (424) and becomes part of a positive feedback loop leading to respiratory muscle failure (425). In multicenter prospective studies 25.3% of patients who underwent invasive mechanical ventilation for more than 7 days developed acquired NMD (410). Risk factors include malnutrition (423), corticosteroids (424), neuromuscular blocking agents (426), aminoglycosides, hyperglycemia, sepsis (425, 427), and “prolonged” invasive mechanical ventilation (428-429). These patients commonly fail extubation by conventional approaches and are considered “unweanable” (188, 430-431).

Ventilatory insufficiency and impaired airway secretion clearance are common acute care complications of NMDs and high level spinal cord injury patients (SCI) and can lead to prolonged ventilation(415) with very difficult weaning (429, 432). Since the extubation failure risk is very high in this patient population, they are also considered
“unweanable” (411, 431, 433). Standard invasive ventilatory management options such as early intubation and tracheostomy for long term care have been described as alternatives to minimize respiratory complications in these patients (434-437).

Although it might be presumed that self-directed adult unweanable muscle weakness patients who have failed multiple ventilator weaning trials can cooperate with the use of NIV and MAC, there are no critical care publications that have reported the use of those methods to extubate them. We hypothesized that, since there is no chronic lung disease in these totally ventilator dependent patients, and if at extubation the lungs are healthy with SpO2>95% in ambient air, ventilation could be fully maintained noninvasively even with no ventilatory autonomy (Study nr 1).

It has also been described that decannulation and conversion to NIV can facilitate weaning in patients with no ventilator-free breathing ability (438), and that MAC can be used for effective secretion clearance as an alternative to bronchoscopy to relieve atelectasis and normalize SpO2 (358). Further, patients almost invariably prefer noninvasive aids over tracheostomy for safety, convenience, appearance, comfort, facilitating effect on speech, sleep, and swallowing, and general acceptability (439).

However, respiratory complications are highly prevalent in ASIA A SCI patients with 84% of patients with C1-C4 and 60% of those with C5-C7 injury levels present severe ventilatory failure (440). Such patients are conventionally managed by translaryngeal intubation and mechanical ventilatory support (441) and the overall incidence of tracheostomy in these cases was between 81 and 83% (442-443). The number of respiratory complications during this acute phase contributes significantly to both hospital length of stay and costs (444).
Following the line of research of this thesis, we hypothesized that noninvasive methods of assisted ventilation and coughing may facilitate both extubation and decannulation with significant improvement on ventilatory dependence and pulmonary function in totally ventilator dependent patients with high level SCI. We also questioned if early intervention in extubation can produce better outcomes than late decannulation (study nr 2).

It has been reported that conventional chest physical therapy for secretion management does not increase the chances of weaning and extubation success (357). However, critically ill patients may have normal mucociliary clearance but ineffective cough peak flows (CPF) which itself has been associated with extubation failure (37, 358) due to airway secretion accumulation (37, 358) but very few studies reported CPF at extubation. (37, 445)

Early extubation, coupled with the use of noninvasive ventilatory support has been used effectively in several critical ill populations to facilitate weaning(20, 114, 155), improve survival(161), decrease the incidence of ventilator-associated pneumonia(103, 153) and reduce ICU length of stay(153, 161). However there is a higher risk of NIV failure when applied in patients that develop ARF after extubation and the evidence that supports its application is controversial (159-160, 446).

Despite a great interest in this field, it is still not clear the role of impaired airway secretion clearance on the outcome of post-extubation respiratory failure in critical ill ventilator dependent patient treated with non-invasive ventilation. Airway clearance may be impaired in disorders associated with abnormal cough mechanics, altered mucus rheology, altered mucociliary clearance, or structural airway defects. A variety of interventions are used to enhance airway clearance with the goal of improving lung
mechanics and gas exchange, and preventing atelectasis and infection (351). We hypothesized that the inclusion in a weaning protocol of mechanical insufflation-exsufflation (MI-E) device for mechanical cough assistance may prevent the development of respiratory failure after extubation in patients that successfully pass the SBT and may reduce the incidence of NIV failure in those who develop ARF after extubation. We also questioned if this technique has a role in reducing both re-intubation rates and ICU length of stay (study nr 3).

Considering the incidence of mortality and respiratory morbidity in “high risk” critical ill patients with severe inspiratory and expiratory muscle weakness managed by standard ventilatory invasive techniques, we question if NIV coupled with MAC is efficient in treating post-extubation respiratory failure and can facilitate both extubation and decannulation in “unweanable” patients with significant improvement on ventilatory dependence and pulmonary function

Questions:

- **Question 1** – Is it possible to extubate and prevent post-extubation failure in cooperative, totally ventilator dependent (unweanable) neuromuscular weakness patients without tracheotomy using a protocol that include full, continuous NIV and MAC? **Answer described in study nr 1.**

- **Question 2** – Can totally ventilator dependent neuromuscular weakness patients wean from ventilatory support, with significant improvement in Vital Capacity
(VC) and CPF after being submitted to an extubation protocol that include full, continuous NIV and MAC. **Answer described in study nr 1**

- **Question 3** – Is it possible to extubate and decanulate totally ventilator dependent ASIA A SCI patients with a protocol that include full and continuous NIV and MAC? **Answer described in study nr 2**

- **Question 4** - Does a protocol that include full and continuous NIV and MAC produce better outcomes when applied during extubation rather than in decannulation of ASIA A SCI patients? **Answer described in study nr 2**

- **Question 5** – Can totally ventilator dependent ASIA A SCI patients wean from ventilatory support, with significant improvement in Vital Capacity (VC) and CPF after being submitted to an extubation or a decannulation protocol that include full, continuous NIV and MAC. **Answer described in study nr 2**

- **Question 6** - Is the inclusion of MI-E in weaning protocol effective in reducing NIV failure and re-intubation rates in patients that successfully pass SBT’s, but develop respiratory failure after extubation? Does it have any impact on ICU length of stay? **Answer described in study nr 3**

**Chronic Respiratory Failure**

Chronic respiratory patients with primarily ventilatory impairment such as NMD and other restrictive syndromes benefit significantly with the use of long term noninvasive ventilation (8, 15, 447-449). In this line of research, noninvasive ventilation (NIV) refers only to devices aimed to assist inspiratory muscles (CPAP excluded) through bi-
level positive airway pressure ventilation or volume cycled intermittent positive pressure ventilation.

Standardized protocols for managing and monitoring NIV at home are lacking, and depend on organizational, administrative and funding structures not only between countries but often within different regions of the same country (248). Before starting a patient on long term NIV(450), it is essential to ask three main questions: 1) Does the patient have a disease known to cause ventilatory failure? 2) Does the patient have symptoms suggesting hypoventilation? 3) Does the patient have physiological abnormalities confirming hypoventilation? (249).

Ventilatory insufficiency progresses insidiously in most of restrictive muscle weakness patients and NIV typically relieves fatigue and other daytime symptoms of which patients may have been unaware (309, 451-453). Every consensus statement reinforces the importance of detecting symptoms of nocturnal hypoventilation (252, 256-259). However, symptoms may be subtle due to the variability of patient sensitivity and sometimes it is difficult for the patient to establish differences between fatigue, dyspnea, and sleepiness. So, carefully designed questionnaires that assess symptoms systematically may be very useful. Jackson et al (260) have described a pulmonary symptom scale consisting of 14 questions, answered on a scale from 1-7. Others evaluated by simple questionnaires the positive and negative effects of ventilation(261). Although symptom questionnaire are insensitive in identifying patients with nocturnal hypercapnic hypoventilation (260, 262) their systematic evaluation is useful in evaluating response to NIV, as compliance to it is strongly correlated with patients symptoms (263).
Since 1993, different consensus conferences and guidelines have proposed indications for initiating ventilatory support in patients with chronic respiratory failure (252, 256-259, 277, 345, 454). Initially, criteria for beginning ventilatory support have relied on abnormal awake blood gases (PaO2 < 60mmHg and PaCO2 ≥ 45mmHg) or significant nocturnal desaturation (SpO2 below 90% for ≥ 20% recorded time) (345), then on Forced Vital Capacity (FVC) impairment (under 50% of predicted (256) or under 1L(258)) or mouth pressures (maximum inspiratory pressure under 60cmH2O(252)). More recently more sensitive parameters have also been included and nocturnal hypercapnia (transcutaneous CO2 of 50 mmHg for more than 50% of sleep time(258)) and Sniff nasal pressure (SNP under 40cmH2O(259, 310)) may be better in assessing the need for ventilatory support.

Vital Capacity (VC) is one of the most reproducible tests of lung function in restrictive patients. Although it may not fall below normal limits until there is a 50% reduction in muscle strength (267), its rate of decline has been shown to predict survival (268). Although no consensus exists as to how often pulmonary function should be evaluated, some authors propose that if VC is > 60% predicted it should be performed every 6 months while if under 60% every 3-4 months (269). Measurement of the VC in the supine position gives an index of weakness of the diaphragm. A fall of more than 15% indicates diaphragmatic dysfunction and correlates with complaints of orthopnea (270) and a supine FVC under 75% was highly sensitive and specific of low transdiaphragmatic pressure (271).

Bellemare and Grassino demonstrated a relationship between tension time index of the diaphragm (TTIdi) and diaphragm endurance or limitation time (Tlim)(455). TTIdi signals the extent to which diaphragm action can continue unabated or fail due to muscular fatigue. However, because of its invasive nature and the difficulties in its
interpretation in seriously compromised patients, TTIdi is neither practical for the acute care nor for outpatient settings.

The TTIdi is the product of the fraction of time that the diaphragm spends in contraction \((Ti/Ttot)\) and the ratio of the tension generated at each contraction \((Pdi)\) to the maximal \(Pdi\) that can be achieved voluntarily during a near isometric contraction \((PdiMax)\). Bellemare and Grassino reported that this index correlates significantly with extent of respiratory impairment in lung disease patients(456).

We hypothesized that the ratio of tidal volume to vital capacity \((Vt/VC)\) could substitute for the \(Pdi/PdiMax\) in the Bellemare and Grassino equation. A validated noninvasive measurement of TTIdi (457) in NMD patients could play a role in the decision to initiate ventilator use (458). We realized if this index would probably better correlate with symptomatic inspiratory muscle dysfunction if it reflects ongoing inspiratory muscle action rather than effort over only one breath cycle. Thus we proposed a Ventilator Requirement Index (VRI) were we multiplied the \(Ti/Ttot \times Vt/VC \times \text{respiratory rate (RR)}\), to determine whether this index could distinguish patients with NMDs with various levels of inspiratory muscle dysfunction and need for ventilator use and if such an index could add to the diagnostic efficiency of simple VC measurement in determining need for ventilator use (study nr 4).

The main cause of morbidity and mortality in patients with NMD is respiratory failure and, in particular, cough dysfunction (447, 459-460). Inspiratory, expiratory, and bulbar innervated musculature are required for effective coughing (461-462). Normal precough inspiration is to 85-90% of total lung capacity(463). Thus, cough flows are diminished for patients who have VCs less than 1500 ml (460).
Both, peak expiratory flows (PEF) and cough peak flows (CPF) have been described as useful clinical parameters of respiratory muscle function (364). “Dart flows” (DF) are generated by creating pressure behind the lips and tongue with the mouth closed. As the lips open in a maneuver like spitting or projecting a dart through a narrow tube, the flows can also be measured by peak flow meter. These flows can be confused with PEF and CPF and cause the latter to be overestimated. They are largely a function of the ability to seal the lips and control the tongue and buccal muscles.

To optimize CPF for patients with low VCs, particularly for those with VCs below 1000 ml, coughing needs to be preceded by the delivery of maximal insufflations or maximum air stacking(462). The delivered air should be to the maximum insufflation capacity (MIC)(362) which, even when not greater than 1500 ml, can greatly increase the pressure of the lung’s recoil once the glottis is opened during the cough(364). This can dramatically increase CPF even without applying an abdominal thrust to manually augment the flows(464).

Expiratory muscles can be manually assisted by providing thoracoabdominal thrusts(465). The combination of applying an abdominal thrust to a maximally inflated lung is an assisted cough (54, 464, 466). While unassisted cough flows depend on inspiratory, expiratory, and bulbar-innervated musculature, air stacking ability and, therefore, assisted cough flows depend only on glottic control or on bulbar-innervated muscle function alone. Thus, the greater the difference between the MIC and the VC and the difference between assisted and unassisted cough peak flows (CPF), the greater is bulbar-innervated muscle function by comparison to inspiratory muscle function(10, 396, 460). Patients who cannot close the glottis cannot air stack. They may “huff” but cannot cough. CPF better reflect the capacity to expulse debris from the airways than do peak expiratory flows (PEF) which occur without glottic closure (461).
There are no standard normal values for CPF or DF but PEF range from 500 to 700 L/min for men and from 380 to 500 L/min for women, and from 150 to 840 L/sec for children and adolescents with variations due to age, race, gender, and height(467).

We proposed to describe and compare the CPF, PEF, and DF in NMD patients, whose VCs were less than normal, and question if they correlate with VC or MIC, to consider their use in the evaluation of the respiratory muscles and to justify the indication of inspiratory and expiratory muscle aids (study nr 5).

As VC decreases markedly, the largest breath that one can take can only expand a small portion of the lungs. Use of incentive spirometry or deep breathing can expand the lungs no greater than the VC. Although possibly useful, manual chest wall stretching and rocking the pelvis onto the chest to decrease costovertebral tightness has not been shown to increase lung volumes. As has been recognized since at least 1952, this can only be achieved by air stacking, by providing deep insufflations (via the upper airway or by "sighs" for patients using invasive mechanical ventilation), or by nocturnal noninvasive ventilation for patients who can not cooperate with air stacking or insufflation therapy(468).

A patient's maximum insufflation capacity (MIC) is determined by measuring spirometrically the largest volume of air that a patient can hold with a closed glottis(362). The patient air stacks via a mouth piece consecutively delivered volumes from a volume-cycled ventilator or a manual resuscitator. This is performed multiple times three times daily. The patient stacks the consecutively delivered volumes with a closed glottis until the lungs are maximally expanded(469). If the lips or cheeks are too weak to permit air stacking, stacking is done via a nasal interface or lipseal.
The extent to which the MIC is greater than the VC predicts the capacity of the patient to be maintained by noninvasive rather than tracheostomy ventilatory support. This is because the MIC/VC difference, like the extent of assisted CPF, is a function of bulbar muscle integrity (470-471).

With complete loss of glottic closure, MIC no longer exceeds VC; the NMD patient can no longer air stack or cough, and both the glottis, and many bulbar-innervated muscles, are extremely impaired. In this case, lung insufflation can only be provided by bypassing glottic function. This can be done by using a manual resuscitator with a closed expiratory valve mimicking glottic closure and insufflate to the approached predicted maximum insufflation.

We proposed that the maximum passive lung insufflation volume achieved in this manner is defined as the lung insufflation capacity (LIC). We questioned if passively insufflating the patient to the maximum LIC could be efficient for chest wall ROM when bulbar muscle impairment is present. We hypothesized that LIC could be compared with MIC (lung inflation by air stacking) and with vital capacity (VC) and that relationships between these variables could correlate with glottic function and CPF (study nr 6).

Questions:

- **Question 7** – Can the measurement of a new proposed ventilator requirement index (VRI) distinguish patients with NMDs according to various levels of inspiratory muscle dysfunction and need for ventilator use? **Answer described in study nr 4**
- **Question 8** – Does the VRI add new findings to the diagnostic efficiency of simple VC measurement for determining the need and the extent for ventilator use? *Answer described in study nr 4.*

- **Question 8** – Can a simulation expiratory flow maneuver like the DF overestimate PEF and CPF in NMD patients? *Answer described in study nr 5.*

- **Question 9** – Is there any correlation between CPF and PEF with VC or MIC, for evaluation of bulbar muscle function and how can it influence the efficacy of inspiratory and expiratory muscle aids? *Answer described in study nr 5.*

- **Question 10** – Will lung volumes be significantly greater by passive insufflation than by air stacking, especially in patients with severe bulbar innervated muscle dysfunction, and will both LIC and MIC significantly exceed VC and increase CPF? *Answer described in study nr 6.*

- **Question 11** – Will LIC-MIC correlate inversely with MIC-VC and, therefore, correlate inversely with glottic integrity? *Answer described in study nr 6.*

- **Question 12** – Can LIC and MIC increase with practice were the greatest increases will be for the most severely affected patients, that is, with the lowest VC? *Answer described in study nr 6.*
Home mechanical ventilation

Preparing the patient for discharge on home mechanical ventilation requires planning. Most respiratory patients are discharged home with a simple bi-level device for nocturnal use only. Those patients have normally sleep disorder breathing defined as nocturnal hypoventilation during sleep due to several causes that include either obstructive lung/airways disease or mild to moderate restrictive syndromes (472). However, there are an increasing number of individuals on HMV that are continuous ventilator dependent through either noninvasive interfaces or tracheostomy. Those patients normally have severe muscle weakness associated in the majority of cases to NMD that may include patients with severe bulbar muscle dysfunction, such as ALS. Training, organizing and funding appropriate equipment and resources for such individuals is more complex and time consuming (49, 473-476).

In patients with neuromuscular disorders with severe ventilatory impairment, instigating a secretion-management protocol is an essential component of any home management programme (46), and this needs to be carried out on a regular basis. Approaches to preventing peripheral airway secretion retention at home for patients with NMD include the use of medications to liquefy secretions and manual techniques of mucus mobilization to transport mucus from the peripheral to the central airways from where it can more easily be eliminated. As already described in the line of research of this thesis, an optimal insufflation to the MIC followed by an abdominal thrust provides the greatest increase in CPF in NMD patients with intact bulbar function. When these techniques alone are no longer effective, MAC defined as the use of mechanical insufflation-exsufflation (MI-E) (62) with an exsufflation-timed abdominal thrust can be
applied at home both through a oronasal interface or through a tracheostomy tube with cuff inflated (61).

An optimal home management of both ventilatory failure and profuse secretion retention should be guided by an oximetry feedback protocol. Since supplemental oxygen is avoided for NMD patients, once artifact is ruled out, SpO₂ below 95% is due to one of three causes: hypercapnia (hypoventilation), airway encumberment (secretions), and if these are not managed properly, intrinsic lung disease, usually gross atelectasis or pneumonia (127). This protocol consists of using an oximeter for feedback to maintain SpO₂ greater than 94% by maintaining effective alveolar ventilation and airway secretion elimination. However, application of these techniques and protocols at home require skill and coordination if they are to be performed effectively (63). Therefore, not only do the techniques need to be taught initially, periodic assessment of the caregivers skills in performing the technique is required.

Despite increasing experience and published results concerning this technique as a first-line intervention for hospitalized patients with ALS and others with neuromuscular diseases (58-59, 61, 127, 246, 401, 477-478), there are limited data related to its indications for home care use. We aimed at describing the indications of home MAC use with oximetry feedback and questioned its safety and compliance in NMD patients, under continuous mechanical ventilation either through noninvasive or tracheostomy ventilation, when centred in non-professional caregivers, with the support of a trained health care professional in a home on-call regime (study nr 7).

Particularly in patients with Amyotrophic Lateral Sclerosis (ALS), secretion encumbrance episodes often result in acute respiratory failure especially during acute chest infections (401, 460, 479). Moreover, in case of severe bulbar-innervated muscle
dysfunction with inability to protect the airways both manual assisted coughing with lung insufflation and MAC may be ineffective(10, 60, 480) and result in hospitalization and need for tracheotomy(481).

Organization of home care programs that include the use of MAC in this population with severe ventilatory impairment requires more study. While effective when continuously available at home(63, 127), expense can be mitigated by on-demand rather than continuous access of MAC if on-demand use can be demonstrated to be effective.

In Europe, home respiratory care is often inadequate because home care companies provide only equipment, not assistance, instruction, or expertise for which the patient must depend on emergency services(476), and there is great burden on caregivers(482). Thus, hospitalization rates and lengths of stay in this patient population are high, especially when ARF and intubation result in tracheotomy. It has been reported that the mean acute hospitalization for patients undergoing tracheotomy is 72 days, mostly in intensive care(483) at a very high cost per day.

To help reduce hospitalizations costs and establish an optimal MI-E provision regimen at home, we studied a telephone accessed integrated care (TAIC)(53) program with oximetry feedback, that provided equipment and professional home care services on an “as needed basis” to treat clinical exacerbations due to secretion encumbrance and related respiratory problems in ALS patients (study nr 8).

For the great majority of NMD patients, up to continuous use of noninvasive ventilation (NIV) can maintain quality of life,(484) and markedly prolong a survival(10) that is, nevertheless, punctuated by respiratory tract infections (RTIs). Intercurrent RTIs are the main cause of morbidity, prolonged hospitalizations, acute respiratory failure (ARF), intensive care admissions, and mortality (47, 63, 127, 460). When MAC is used for
airway secretion clearance, multiple treatments are given until no further secretions are expelled and any secretion or mucus induced O2 desaturations are reversed. Use can be required as frequently as every few minutes around-the-clock during intercurrent RTIs(58, 127, 485). Because respiratory muscles are weakened and bronchial secretions are profuse during RTI’s patients often need to NIV continuously at these times both to maintain alveolar ventilation and for air stacking to increase CPF (246, 363). If, when using NIV at adequate delivered volumes the SpO\textsubscript{2} is not above 94%, the desaturation is not due to hypoventilation but to mucus accumulation especially during chest infections and ARF(27, 47).

In hospital application, MAC has been described an effective first-line intervention for NMD patients with ARF,(61, 246, 401, 478, 486-487). However, similar immediate effects of this technique when applied at home during ARF have not been widely explored. We hypothesized that MAC when applied at home, according to previous protocols included in this thesis, can be efficient in treating NMD patients with acute exacerbations due to secretion encumbrance. We questioned if MAC could normalize SpO2 in time to avoid hospitalizations and reduce the number of deep airway suctions in patients under continuous ventilatory support either by NIV or tracheostomy (study nr 9).

Respiratory insufficiency appears in the course of NMD patients first during sleep and then at a later stage during the day. Nocturnal only NIV produces 24-h effective blood-gas improvement and symptom control for several years(15). However, in end-stage respiratory muscle failure patients such as Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy type 1 (SMA 1), nocturnal NIV needs to be progressively extended during the day as increasing ventilatory dependency develops(11, 16, 447, 488-489). Mouthpiece intermittent
positive pressure ventilation (IPPV) is the most important method of daytime
ventilatory support for patients who need ventilatory support continuously since
continuous NIV with a nasal or oronasal mask may create skin breakdown or may even
interfere with the patient’s social activity (87, 490-491).

Although mouthpiece IPPV is being used for ventilatory support since 1953 (42) very
few studies reported its use for long-term management(1, 87, 90, 491-492). Since
ventilatory support delivered noninvasively is the single most important inspiratory muscle
aid in patients with NMD routine evaluations are recommended to predict its
application and monitor its efficacy both for nocturnal only and continuous use(9).
Although nocturnal only NIV can benefit mildly affected patients, instead of increasing
the spans or switching to the use of volume-cycled ventilators for daytime mouthpiece
IPPV, when low span pressure assistance is no longer adequate and ventilator
dependence progresses to daytime use, clinicians conventionally recommend
tracheotomy(15, 493-496).

For the final work of this thesis and to conclude this line of research, we proposed to
analyse the historical evolution of practice regarding the use of noninvasive mechanical
ventilation (NIV) and complementary interventions for long-term full-time noninvasive
ventilatory support of patients with neuromuscular diseases (NMDs) with primary focus
on the three most common and severe disorders, that is, Duchenne muscular dystrophy
(DMD), amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy type 1 (SMA
1). To reinforce the argument that noninvasive alternatives for ventilatory support and
secretion management are feasible and efficient, we aimed to analyze data from
different international centers that provide continuous NIV for this patient population as
an alternative to tracheostomy to prolong survival and develop conclusions and
recommendations that may permit its widespread use (study nr 10).
Questions

- **Question 13** – Is home based MAC with oximetry feedback effective and can it be safely applied by trained non professional caregivers in continuous ventilator dependent NMD patients, according to specific indications? **Answer described in study nr 7**

- **Question 14** – What is the frequency use of home MAC in NMD patients? Do patients under tracheostomy ventilation used it more than patients under NIV? **Answer described in study nr 7**

- **Question 15** – Is a telephone accessed integrated care, that include on-demand consult and MI-E device rapid access, efficient and feasible for ALS patients? **Answer described in study nr 8**

- **Question 16** – Is a home on-demand MAC program cost effective and can it produce significant cost savings when compared to continuous home MAC prescription in ALS patients? **Answer described in study nr 8.**

- **Question 17** – Can home MAC with oximetry feed-back be efficient in reverting O2 desaturations related to secretion encumbrance during an acute exacerbation in NMD patients under continuous ventilatory support either by NIV or tracheostomy? **Answer described in study nr 9.**

- **Question 18** – Are the effects of home MAC sufficient to avoid hospitalizations for ARF episodes related to secretion encumbrance in NMD patients under continuous ventilatory support either by NIV or tracheostomy? **Answer described in study nr 9.**
- **Question 19** – During the last two decades, has there been an evolution of practice, regarding the recommendations of continuous full time NIV and MAC for patients with NMD? **Answer described in study nr 10.**

- **Question 20** – What are the outcomes from international centers that provide continuous full time NIV and MAC for patients with NMD? **Answer described in study nr 10.**

Analyzing the body of works that support the line of research of this thesis, our main goal was to achieve a continuum of care for patients with respiratory muscle weakness, that, due to their severe ventilatory impairment, can benefit either in acute or chronic settings, from specific evaluation protocols and management paradigms that include NIV for ventilatory assistance and MAC for secretion management.
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
Study 1

Extubation of Patients with Neuromuscular Weakness: A New Management Paradigm

John R. Bach, Miguel R. Gonçalves, Irram Hamandi, João Carlos Winck
Extubation of Patients With Neuromuscular Weakness: A New Management Paradigm

John Robert Bach, Miguel R. Gonçalves, Irram Hamdani and Joao Carlos Winck

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Background: Successful extubation conventionally necessitates the passing of spontaneous breathing trials (SBTs) and ventilator weaning parameters. We report successful extubation of patients with neuromuscular disease (NMD) and weakness who could not pass them.

Methods: NMD-specific extubation criteria and a new extubation protocol were developed. Data were collected on 157 consecutive “unweanable” patients, including 83 transferred from other hospitals who refused tracheotomies. They could not pass the SBTs before or after extubation. Once the pulse oxymoglobin saturation ($SpO_2$) was maintained at $\geq 95\%$ in ambient air, patients were extubated to full noninvasive mechanical ventilation (NIV) support and aggressive mechanically assisted coughing (MAC). Rather than oxygen, NIV and MAC were used to maintain or return the $SpO_2$ to $\geq 95\%$. Extubation success was defined as not requiring reintubation during the hospitalization and was considered as a function of diagnosis, preintubation NIV experience, and vital capacity and assisted cough peak flows (CPF) at extubation.

Results: Before hospitalization 96 (61\%) patients had no experience with NIV, 41 (26\%) used it $< 24$ h per day, and 20 (13\%) were continuously NIV dependent. The first-attempt protocol extubation success rate was 95\% (149 patients). All 98 extubation attempts on patients with assisted CPF $\geq 160$ L/min were successful. The dependence on continuous NIV and the duration of dependence prior to intubation correlated with extubation success ($P < .005$). Six of eight patients who initially failed extubation succeeded on subsequent attempts, so only two with no measurable assisted CPF underwent tracheotomy.

Conclusions: Continuous volume-cycled NIV via oral interfaces and masks and MAC with oximetry feedback in ambient air can permit safe extubation of unweanable patients with NMD.

CHEST 2010; 137(5):1033–1039

Abbreviations: ALS = amyotrophic lateral sclerosis; CCM = critical care myopathy; CPF = cough peak flows; IPPV = intermittent positive pressure ventilation; MAC = mechanically assisted coughing; NIV = noninvasive mechanical ventilation; NMD = neuromuscular disease; PAP = positive airway pressure; SBT = spontaneous breathing trial; SMA 1 = spinal muscular atrophy type 1; $SpO_2$ = pulse oxymoglobin saturation; VC = vital capacity

Conventional extubation attempts follow successful “spontaneous breathing trials” (SBTs) and the passing of ventilator weaning parameters, otherwise patients undergo tracheotomy. Patients are often extubated to supplemental oxygen and bilevel positive airway pressure (PAP), but settings are infrequently reported, and extubation studies report very few if any patients with neuromuscular disease (NMD) (eg, 18 of 162, 17 of 900) and completely exclude unweanable patients.

Patients with preexisting NMD make up only 4\% to 12.5\% of cases in critical care, but about 25\% in weaning centers. While acquired critical care myopathy (CCM) is common, it is an often unrecognized cause of extubation failure by conventional approaches.

There are no guidelines for extubating unweanable patients with NMD and CCM. Many are dependent on noninvasive mechanical ventilation (NIV) with no autonomous breathing ability for years before being intubated, and they refuse tracheotomy. Further, these patients can have ineffective cough peak flows (CPFs), which can result in extubation failure due to airway secretion accumulation, but very few studies...
have reported CPF\textsuperscript{2,21} and none systematically used mechanically assisted coughing (mechanical insufflation-exsufflation with exsufflation-timed abdominal thrust) (MAC).\textsuperscript{4,42} There are no “ventilator weaning parameters” that address the ability to expel secretions. With success in decannulating unweanable patients with traumatic tetraplegia and others to continuous MAC and NIV, which includes noninvasive intermittent positive pressure ventilation (IPPV) and high-span bilevel PAP,\textsuperscript{20,25,27} we used similar criteria to exsufflate unweanable patients with NMD and CCM and report the success rates.

**Materials and Methods**

The data were gathered in two centers, with 113 patients in New Jersey and 44 in Portugal, using the inclusion criteria described in Table 1. The study was approved by the institutions’ review boards. All intubated patients were treated conventionally except for the use of MAC via the tube. Although virtually unknown in critical care, MAC has been instrumental in avoiding pneumonia, respiratory failure, and hospitalizations for NIV-dependent patients with NMD.\textsuperscript{26-30} Vital capacities (VCs) (Wright Mark 3 spirometer; Ferraris Ltd; London, England) and unassisted and assisted CPFs (Access Peak Flowmeter; Health Scan Products Inc.; Cedar Grove, NJ) were measured within 12 months before intubation for the local patients (group 1). The other 53 intubated patients were transferred intubated from other hospitals after one to four failed extubation attempts (group 2) or after failing multiple SBTs (group 3).

VC was measured via the tube with the cuff inflated following clearing of the airways by MAC just prior to extubation. Patients were ready for extubation and inclusion in this study only when all Table 1 criteria were satisfied and SBTs failed, as described.\textsuperscript{31-33} Patients had to experience immediate distress, precipitous oxygen desaturation, and hypercapnia without stabilization before return to full ventilatory support both before and immediately postextubation. Local patients were considered to be group 1 because their greater experience with NIV and MAC could have affected outcomes. All transferred patients had been told that extubation and survival were not possible without tracheotomy.

We reported that the risk for extubation failure is high when assisted CPF cannot attain 160 L/m.\textsuperscript{2} Considering that patients with advanced avarial bulbar amyotrophic lateral sclerosis (ALS) can rarely attain a CPF of 160 L/m.\textsuperscript{34,35} we generally did not accept such patients for transfer (exclusion criteria). Local patients with a CPF < 160 L/m were offered extubation if acknowledging that three extubation failures would necessitate tracheotomy. Other, at least temporary, exclusion criteria were medical instability, inadequate cooperation, and imminent surgery.\textsuperscript{20,27}

### Protocol

While intubated, sufficient ventilatory support was used to maintain normocapnia and normal respiratory rates. MAC (CoughAssist; Respertronics, Inc.; Murrysville, PA) was used at 40 to 40 cm H\textsubscript{2}O to greater than achieve clinically full chest expansion to clinically complete emptying of the lungs, with exsufflation-timed abdominal thrusts. The MAC sessions were up to every 20 min to maintain the pulse oxygen desaturation (Sp\textsubscript{o2}%) of ≥ 95% in ambient air. Tracheotomy would have been recommended if the Table 1 criteria could not be met within 2 weeks of transfer.

Once the Table 1 criteria were met, the orogastric or nasogastric tube was removed to facilitate postextubation nasal NIV. The patient was then extubated directly to NIV on assist/control of 500 to 1,500 mL, at a rate of 10 to 14 min in ambient air. Pressure control of at least 18 cm H\textsubscript{2}O was used if abdominal distension developed. The NIV was provided via a combination of nasal, oro-nasal, and mouthpiece interfaces.\textsuperscript{16} Assisted CPF and CPF obtained by abdominal thrust following “air stacking” were measured within 3 h as the patient received full-volume-cycled NIV support.

Patients kept 15-mmangled mouthpieces accessible (Fig 1), and weaned themselves, when possible, by taking fewer and fewer IPPVs as tolerated. Diurnal nasal IPPV was used for those who could not secure the mouthpiece. Patients took as much of the delivered volumes as desired. They used nasal or oronasal interfaces (Figs 2, 3) for nighttime ventilation. For episodes of Sp\textsubscript{o2} < 95%, ventilator positive inspiratory pressure, interface or tubing air leakage, CO\textsubscript{2} retention, ventilator settings, and MAC were considered.

Patients were taught to maximally expand their lungs by air stacking (retaining consecutive) ventilator delivered volumes to the largest volume the glottis could hold.\textsuperscript{37} Once the lungs were air stacked, an abdominal thrust was provided to manually assist the cough,\textsuperscript{20,37} and these assisted CPFs were measured. For patients using pressure-cycling, air stacking volumes were provided by manual resuscitator. The therapists, nurses, and in particular, the family and personal care attendants provided MAC via oronasal interfaces up to every 20 min until the Sp\textsubscript{o2}, no longer dipped below 95% and the patients felt clear of secretions. In seven cases, the postextubation oral intake was considered unsafe, so open

### Table 1—Exsufflation Criteria for Unweanable Ventilator-Dependent Patients

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Aged 4 y and older</td>
</tr>
<tr>
<td>Ventilator-Free Breathing</td>
<td>No ventilator-free breathing tolerance with 7-cm pressure support in ambient air on the basis of NMD or CCM</td>
</tr>
<tr>
<td>VC</td>
<td>VC &lt; 20% of normal</td>
</tr>
<tr>
<td>PaSO\textsubscript{2}</td>
<td>PaSO\textsubscript{2} ≥ 40 mm H\textsubscript{2}O at peak inspiratory pressures ≤ 35 cm H\textsubscript{2}O on full-setting assist/control mode at a rate of 10-13/min</td>
</tr>
<tr>
<td>Sp\textsubscript{o2}</td>
<td>Sp\textsubscript{o2} ≥ 95% for 12 h or more in ambient air</td>
</tr>
<tr>
<td>Oxygen Desaturation</td>
<td>All oxyhemoglobin desaturations &lt; 95% reversed by MAC and suctioning via transaryngeal tube</td>
</tr>
<tr>
<td>Air Leaks</td>
<td>Fully alert and cooperative, receiving no sedative medications</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Chest radiograph abnormalities cleared or clearing</td>
</tr>
<tr>
<td>Airway</td>
<td>Air leakage via upper airway sufficient for vocalization upon cuff deflation</td>
</tr>
</tbody>
</table>

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Miguel Ramalho do Souto Gonçalves 113
in means were compared using the Wilcoxon rank test. A \( P \) value \( \leq 0.05 \) was considered significant. Univariate comparisons of potential predictive factors for failure or success were run with the Fisher exact test for categorical variables and the Wilcoxon rank-sums test for continuous variables.

### Results

The 157 patients, mean age 37 ± 21 years, included 139 (89%) with NMD who were intubated for acute respiratory failure and compromise due to pneumonia and/or surgery and 18 patients with CCM (11%). The 74 local patients (group 1) were intubated at our institutions, and 83 others were intubated elsewhere. Demographic data are in Table 2. VC and CPF data are in Table 3. Twenty (13%) of the 157 patients had been continuously NIV dependent for 12.2 years (range 5-47) before being intubated. Forty-one (26%) used NIV part-time (<24 h/d), and 96 (61%) used no NIV before intubation. All patients satisfied the Table 1 criteria in <2 weeks.

Univariate comparisons of potential predictive factors for extubation success yielded significant differences for continuous NIV use (\( P < .0001 \)) and for the duration of continuous NIV use and MAC use prior to intubation (\( P = .0038 \)), indicating that experience with NIV and MAC was significant in predicting success. Given only 15 failures in eight patients, it was not possible to run multivariable logistic regression models considering diagnosis, patient group, VC, and CPF.

Of 172 extubations on 157 patients, all 98 on patients with assisted CPF \( \geq 160 \) L/m were successful. Fifty-nine of 74 attempts (80%) on patients with CPF < 160 L/m were successful, including 52 of 60 (87%) at first extubation. Six patients who initially failed, succeeded on second (four patients) and third (three patients) attempts. One with advanced bulbar ALS and one with facioscapulohumeral muscular dystrophy, both with no measurable assisted CPF, failed a total of five extubations and underwent tracheotomy. Only one of the eight who failed any extubation attempt had reintubation experience with NIV and MAC; but she and several others had suboptimal postextubation care provider support for aggressive MAC. She and eight patients with bulbar ALS with little residual bulbar-innervated muscle function required oro-nasal interfaces for a closed system of postextubation NIV (Hybrid NE; Teleflex Medical; Research Triangle Park, NC) (Fig 2). All nine had gastrostomy tubes for total enteral nutrition. One lip-seal nocturnal NIV user for 28 years prior to intubation was extubated back to lip-seal NIV (Fig 3).

Data on VC, CPF, and duration of NIV use as a function of postextubation weaning capacity are included in Table 4. Weaning from full-time to part-time
NIV took 3 to 21 days and was usually accomplished at home. As supine VC increased to approach 1,000 mL, we encouraged patients to sleep without NIV but with SpO₂ and end-tidal CO₂ monitoring, and when these remained stable for 2 weeks to discontinue NIV. The mean extubation VCs and assisted CPFs for the 29 patients ≥18 years of age who were successfully extubated at first attempt despite assisted CPF < 160 L/m were 245 ± 114 mL (range 120-620) and 97 ± 39 L/m (range 0-150), respectively. No clinically or radiographically apparent barotrauma was noted for any patients.

The 83 patients in groups 2 and 3 had been intubated for 11.6 ± 9.1 days (range 5-1-80) before transfer and 2.6 ± 1 days (range 1-11) on our units before extubation (P < .005). Upon admission, 21% fraction of inspired O₂, 71 (85%) of the patients’ SpO₂ levels settled below 95%. Increased NIV support to normalize CO₂ and especially MAC normalized SpO₂ generally within 24 to 48 h to satisfy a criterion for extubation.

The intensivists and respiratory therapists estimated that noninvasive treatment necessitated more time than invasive respiratory treatment. The extubation itself required about 1.5 h for a specifically trained respiratory therapist to train the patients and care providers in NIV and MAC. In part because only one local nursing/rehabilitation facility would accept NIV users, all except one patient who had a tracheostomy were discharged home. One hundred thirty-one patients are alive using NIV (Table 4). Nine patients (6%) died of cardiac failure, six (4%) from lung disease/respiratory failure, two (2%) with bulbar ALS died after tracheotomy from sepsis and decubiti, and nine (6%) died of unknown causes. Although offered, no patients accepted tracheotomy following successful extubation.

**Discussion**
There are no extubation studies on continuously NIV-dependent patients with NMD. A recent controlled

### Table 2—Demographic Data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No. (%)</td>
<td>74 (47)</td>
<td>45 (29)</td>
<td>38 (24)</td>
<td>157 (100)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>52 male (70)</td>
<td>28 male (62)</td>
<td>17 male (45)</td>
<td>97 male (62)</td>
</tr>
<tr>
<td>22 female (30)</td>
<td>17 female (38)</td>
<td>21 female (55)</td>
<td>60 female (38)</td>
<td></td>
</tr>
<tr>
<td>Diagnoses, No. (%)</td>
<td>ICU/M, 15 (20)</td>
<td>SMA, 10 (22)</td>
<td>SMA, 10 (26)</td>
<td>SMA, 25 (16)</td>
</tr>
<tr>
<td>SCI, 13 (18)</td>
<td>MD, 9 (20)</td>
<td>DMD, 9 (24)</td>
<td>MD, 9 (24)</td>
<td>MD, 22 (14)</td>
</tr>
<tr>
<td>ALS, 11 (15)</td>
<td>MG, 9 (12)</td>
<td>PPS, 5 (13)</td>
<td>SCI, 17 (11)</td>
<td></td>
</tr>
<tr>
<td>MG, 9 (11)</td>
<td>MD, 9 (11)</td>
<td>PPS, 4 (9)</td>
<td>oNMD, 4 (9)</td>
<td>oNMD, 10 (10)</td>
</tr>
<tr>
<td>oNMD, 8 (11)</td>
<td>oNMD, 4 (9)</td>
<td>SCI, 3 (8)</td>
<td>oNMD, 16 (10)</td>
<td></td>
</tr>
<tr>
<td>SMA, 5 (7)</td>
<td>ALS, 3 (7)</td>
<td>ALS, 2 (5)</td>
<td>ICU/M, 15 (10)</td>
<td></td>
</tr>
<tr>
<td>DMD, 3 (4)</td>
<td>SCI, 1 (2)</td>
<td>...</td>
<td>MG, 15 (10)</td>
<td></td>
</tr>
<tr>
<td>Cont, 10 (14)</td>
<td>No NIV, 51 (69)</td>
<td>Cont, 10 (14)</td>
<td>No NIV, 51 (69)</td>
<td>No NIV, 51 (69)</td>
</tr>
<tr>
<td>Noct, 15 (17)</td>
<td>Cont, 10 (14)</td>
<td>Cont, 10 (14)</td>
<td>No NIV, 51 (69)</td>
<td>No NIV, 51 (69)</td>
</tr>
</tbody>
</table>

ALS = amyotrophic lateral sclerosis; Cont = continuous noninvasive ventilation; DMD = Duchenne muscular dystrophy; ICU/M = ICU-acquired neuromuscular disease; MD = muscular dystrophy; MG = myasthenia gravis; NIV = noninvasive ventilation; Noct = nocturnal noninvasive ventilation; oNMD = other neuromuscular disease; PPS = postpolio syndrome; SCI = spinal cord injury; SMA = spinal muscular atrophy, including types 1, 2, and 3, and other neuromuscular disease.

*Local patients.

*Patients transferred after failing extubations in other institutions.

*Patients transferred after failing multiple spontaneous breathing trials in other institutions.
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves

Duration ventilator use, mo (range) . . . 48
CPF at extubation, L/min 204
VC at extubation, mL 423
Subjects, n 23
Characteristics Weaned in 1 wk Weaned to Part-Time NIV Unweanable

CPF 3-6 mo postextubation, mL 1,121
VC 6 mo postextubation, mL 1,797
Assisted CPF at extubation, L/min 187
VC at extubation, mL 355
Subjects, n (%) 74 (47%) 45 (29) 37 (24%) 157
Characteristics Group 1

VC 3-6 mo postextubation, mL 1,797
Assisted CPF at extubation, L/min 187
VC at extubation, mL 355
Subjects, n 23

Table 3—Pulmonary Function

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>74 (47%)</td>
<td>45 (29%)</td>
<td>37 (24%)</td>
<td>157</td>
</tr>
<tr>
<td>Assisted CPF at extubation, L/min</td>
<td>187 ± 85</td>
<td>162 ± 86</td>
<td>178 ± 62</td>
<td>177 ± 77</td>
</tr>
<tr>
<td>VC at extubation, mL</td>
<td>335 ± 171</td>
<td>273 ± 180</td>
<td>295 ± 185</td>
<td>315 ± 173</td>
</tr>
<tr>
<td>VC 3-6 mo postextubation, mL</td>
<td>1,121 ± 748</td>
<td>709 ± 679</td>
<td>617 ± 412</td>
<td>877 ± 698</td>
</tr>
</tbody>
</table>

Intergroup differences were not statistically significantly different except for postextubation VC, with that of group 1 being greater than for groups 2 and 3 (P < .05). CPF = cough peak flows. See Table 1 for expansion of the other abbreviation.

*Local patients.
+Patients transferred after failing extubations in other institutions.
++Patients transferred after failing multiple spontaneous breathing trials in other institutions.

Postextubation respiratory failure study of 106 patients included only two with restrictive syndromes, but none with NMD, and all had passed SBTs. They were extubated to supplemental O₂ alone or in conjunction with bilevel PAP at spans up to 14 cm H₂O, pressures inadequate for normal alveolar ventilation for our patients. A metaanalysis of 12 extubation studies to bilevel PAP demonstrated decreased mortality, ventilator-associated pneumonia, length of stay, and resort to tracheotomy, but unweanable patients with NMD were uniformly excluded. Eligibility for extubation was based on “readiness for weaning” and failure of SBTs after 30 min or more. While this justifies extubation to NIV for patients who primarily have lung/airways disease with some autonomous breathing ability and for whom SpO₂ > 90% may be acceptable with or without supplemental O₂, our patients had no ability to sustain breathing before or after extubation with VCs as low as 0 mL. Thus, no control group extubation to O₂ or less than full NIV would be possible, ethical, or permissible by any review board. While there are always limitations of uncontrolled studies when comparing two approaches, this was a study of only one approach to extubate patients not previously considered extubatable. For our long-term NIV users, aspiration causing persistent SpO₂ < 95% despite continuous NIV and MAC in ambient air is the indication for tracheotomy.

Besides hypoventilation, ineffective CPF have been associated with extubation failure. MAC is essentially noninvasive suctioning via noninvasive or invasive interfaces. It can clear the left airways that are often not cleared by invasive suctioning and can acutely increase VC and SpO₂. Our success stemmed not only from providing continuous full-setting NIV via a variety of interfaces but also from frequent and aggressive MAC to expel secretions and maintain or return SpO₂ > 95%.

In our earlier study of extubation/decannulation to NIV, considering the extent of need for NIV, age, VC, and maximum assisted CPF, only assisted CPF ≥ 160 L/m predicted success in 62 extubation/decannulation attempts on 49 consecutive patients, including 34 with no ventilator-free breathing ability. None of the 15 attempts on those with maximum CPF < 160 L/m succeeded, as opposed to an 87% first-attempt extubation success rate in this study. The most likely reasons for the difference between then and now are: baseline SpO₂ criterion for extubation of 92% vs 95%, and thus the earlier patients had more residual airway secretions or lung disease at extubation; 5% vs 39% of patients with pre-extubation experience with NIV and MAC; less hospital staff experience with NIV and MAC; less hospital staff experience with NIV and MAC; 50 of 62 patients were decanulated, not extubated; the patients were in various hospital locations; and MAC was used less often and without family involvement.

The 87% first-attempt extubation success rate on patients with maximum CPF < 160 L/m in this study is greater than the 82.4% (61 of 74) success rate reported for extubating NIV-dependent infants with spinal muscular atrophy type 1 (SMA 1), according to an almost identical protocol. The difference may be the result of the ability of these patients, as opposed to babies, to cooperate with NIV and MAC. The SMA 1 infants may have also had more severe bulbar-innervated muscle dysfunction. Thus, while higher than those

Table 4—Postextubation Long-Term Noninvasive Ventilation Use for 155 Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Weaned in 1 wk</th>
<th>Weaned to Part-Time NIV</th>
<th>Unweanable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>23</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>VC at extubation, mL</td>
<td>423 ± 157</td>
<td>344 ± 152</td>
<td>259 ± 179</td>
</tr>
<tr>
<td>CPF at extubation, L/min</td>
<td>204 ± 58</td>
<td>179 ± 73</td>
<td>158 ± 55</td>
</tr>
<tr>
<td>VC 6 mo postextubation, mL</td>
<td>1797 ± 683</td>
<td>896 ± 649</td>
<td>502 ± 353</td>
</tr>
<tr>
<td>Duration ventilator use, mo (range)</td>
<td>. . .</td>
<td>48 ± 55 (1-204)</td>
<td>71 ± 62 (1-228)</td>
</tr>
</tbody>
</table>

See Tables 1 and 3 for expansion of abbreviations.
for a comparable infant population, the success rate was significantly less (87% vs 100%) ($P < .05$) than for patients with assisted CPF $\geq 160$ L/m. Unmeasurable assisted CPFs indicate an inability to close the glottis and are associated with stridor, saliva aspiration, and less effective NIV and MAC.

An NIV/MAC protocol has been used to avoid over 100 hospitalizations for continuously ventilator-dependent (NIV) patients with NMD.\(^{20,35}\) Here we considered unweanable patients with NMD for whom intubation could not be avoided. Upon extubation, most patients with a VC of 200 mL or more eventually were weaned from continuous to part-time NIV by taking fewer and fewer mouthpiece IPPVs. Thus, the paradigm of weaning then extubation can be changed to extubation to permit self-weaning for patients with NMD. The notion that early tracheotomy after intubation somehow facilitates ventilator weaning\(^{46}\) should be reassessed for patients with NMD. NIV is also associated with over 75% fewer ventilator-associated pneumonias.\(^{6,44}\) Use of mouthpieces rather than "masks" interfaced in acute-care facilitated speech, oral intake, comfort, and glossopharyngeal breathing;\(^{45}\) eliminated the risk of skin pressure sores; and permitted air stacking to maintain pulmonary compliance,\(^{37,45}\) diminish atelectasis, and facilitate manually assisted coughing.

The purpose here was not to facilitate ventilator weaning or to consider long-term outcomes, but to extubate unweanable patients. Benefits included no mortality, fewer days intubated, no tracheostomies, and return home. Decannulation, too, can facilitate ventilator weaning.\(^{46}\) Avoidance of tracheostomy for continuous ventilator (NIV) users can also better maintain quality of life,\(^{47-49}\) significantly diminish long-term pneumonia and respiratory hospitalization rates,\(^{50}\) maximize ventilator-free breathing,\(^{48}\) and facilitate return home.\(^{49}\)

In conclusion, unweanable intubated patients with NMD who satisfy specific criteria can be successfully extubated to full NIV and MAC. Patients with measurable assisted cough flows should no longer be advised to refuse intubation for fear of extubation failure and tracheotomy. We no longer consider tracheotomy for any ventilator-dependent patients with NMD who satisfy Table 1 criteria, and now offer extubation to most with CPF $< 160$ L/m.

**Acknowledgments**

**Author contributions:** Dr Bach: wrote all drafts of the paper and, with Dr Handani, extubated all the patients in New Jersey. Mr Gonçalves: performed the extubations on all of the patients in Portugal, gathered data on the Portuguese patients, and added material to the text of the manuscript.

Dr Handani: performed the extubations on some of the patients in New Jersey, gathered data on the New Jersey patients, and added material to the text of the manuscript.

Dr Winck: oversaw the extubations on all of the Portuguese patients and added material to the introductory and "Discussion" sections of the manuscript.

**Financial/nonfinancial disclosures:** The authors have reported to CHEST the following conflicts of interest: Respironics, Inc, is the manufacturer of the CoughAssist, a device mentioned in this article. Dr Winck has been reimbursed by Respironics, Inc, for attending a sleep conference, received $4,500 for organizing two postgraduate courses on noninvasive ventilation for Respironics, Inc, and received $500 for lectures in a conference sponsored by Respironics, Inc. Mr Gonçalves received lecture honoraria of $4,000 from Respironics, Inc, for two postgraduate courses on noninvasive ventilation. Drs Bach and Handani have reported no conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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**References**

Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care


Extubation of Patients With Neuromuscular Weakness: A New Management Paradigm
John Robert Bach, Miguel R. Gonçalves, Irram Hamdani and Joao Carlos Winck

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Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves
Study 2

Noninvasive ventilation associated with mechanical assisted cough for extubation and decannulation in high spinal cord injury patients

Miguel R. Gonçalves, Tiago Pinto, Teresa Honrado, Teresa Oliveira, Celeste Dias, Ana Maria Mota and João Carlos Winck

(Critical Care Medicine, submitted)
Noninvasive ventilation associated with mechanical assisted cough for extubation and decannulation in high spinal cord injury patients

Concise title: *Extubation and decannulation in spinal cord injury*

Authors: Miguel R. Gonçalves, Tiago Pinto, Teresa Honrado, Teresa Oliveira, Celeste Dias, Ana Maria Mota and João Carlos Winck

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Abstract

**Purpose:** to compare extubation vs. decannulation outcomes of continuously ventilator dependent (CVD) high level spinal cord injured (SCI) patients.

**Methods:** 20 (3 females) CVD high level SCI patients with 44±16.3 years of age, were either extubated (n=13) or decannulated (n=7) to continuous noninvasive ventilation (NIV) and mechanically assisted coughing (MAC). Successful extubation/decannulation was defined by not requiring re-intubation/tracheotomy during hospitalization. Vital capacity (VC) and cough peak flows (CPF) were measured immediately (T1), at 48 hours (T2), and at 6 months (T3) after tube removal. Days using invasive ventilation, extubation/decannulation success rates, Intensive Care Unit (ICU) lengths of stay, days required for protocols and extent of ventilator dependence at discharge and after 6 months were analyzed. Readmissions and survival were evaluated at 1 year.

**Results:** All extubations and decannulations were successful. Extubation required significantly fewer ICU days than decannulation. The VC, unassisted and assisted CPF at T1, T2 and T3 improved significantly more for the extubation than for the decannulation. Patients had comparable ASIA levels and VCs at T1 but the extubation group had significantly higher VC at T2 and unassisted and assisted CPF at T2 and T3. All patients were discharged home using either NIV or breathing autonomously. During the year follow-up, 1 extubated patient was hospitalized due to a respiratory tract infection (RTI) and 1 died. Two decanulated patients were hospitalized for a RTI and a stroke. None required critical care.

**Conclusions:** Decannulation or avoidance of tracheostomy by extubation of CVD SCI patients can result in better respiratory outcomes.

**Key-words:** Noninvasive ventilation, Mechanical Insufflation-Exsufflation, Extubation, Decannulation, Spinal Cord Injury.
Introduction

Ventilatory insufficiency and impaired airway secretion clearance are common complications of high level spinal cord injury (SCI) and can lead to respiratory failure in both the acute and chronic stages. Standard invasive ventilatory management options include early intubation and tracheostomy for long term care [1].

High level SCI, ascending cord edema, spinal shock, and perhaps other factors can result in progressive ventilatory insufficiency usually shortly after hospital admission for SCI. Following intubation, failure to pass “spontaneous breathing trials (SBTs)” and ventilator weaning parameters [2] is common and often results in intubation and tracheostomy [1]. It is presumed that ventilator weaning is necessary before patients can be safely extubated/decanulated [3]. However, more recently, a successful extubation protocol was described for 157 continuously ventilator dependent (CVD) patients who could not pass SBTs before or after extubation [4]. Further, in 1990 Bach et al. reported the decannulation of “unweanable” CVD high level spinal cord injured (SCI) patients and their transition to non-invasive mechanical ventilation (NIV) and mechanically assisted coughing (MAC) [5].

Mechanical assisted cough is the use of mechanical insufflation-exsufflation (CoughAssist™, Phillips Respironics International Inc., Murrysville, Pa) via invasive tube or oronasal interface to fully expand and then fully empty the lungs, thereby expelling airway secretions. An abdominal thrust is applied simultaneously with exsufflation. By expelling secretions MAC can return SpO2 to normal, avoiding respiratory failure [6-7], and solving atelectasis [8-9].

Other than for occasional use of bi-level positive airway pressure at less than ventilatory support levels [10], there has been no further research in this domain. Despite the fact that cough impairment is one of the most common reasons for
extubation failure and respiratory complications long-term, there have been few studies that considered its evaluation[11-12] and the use of assisted coughing to facilitate extubation/decannulation of CVD SCI patients[4,13]

The role of NIV in the ICU continues to increase as evidence accumulates regarding the prevention of post-extubation respiratory failure [14-15]. However, few studies focus on the role of NIV in extubation and decannulation of high level SCI patients [16-17]. Since the patients in our study were CVD, total ventilatory support was necessary following tube removal. Our purpose is to report and compare extubation and decannulation success rates and outcomes of self-directed, CVD SCI patients using a management protocol that included continuous full setting NIV and MAC to maintain SpO2≥95% in ambient air [4,16].

Patients and Methods

This study received approval from the department and institutional review boards. Twenty (3 females) consecutively admitted, CVD high level SCI patients with 44±16.3 years of age, who failed multiple SBTs were studied between 2004 to 2009. There were 13 intubated patients (Group 1 –G1) and seven with tracheostomies (Group 2- G2). Besides CVD and failing multiple SBTs, inclusion criteria included the ability to cooperate, medical stability, and the resolution of surgical issues. Exclusion criteria were age less than 18 years, lung disease, lack of cooperation, traumatic head injury or otherwise impaired cognition, and chest trauma. Patients’ SCI levels were established according to American Spinal Injury Association (ASIA) criteria[18].

Vital capacity (VC) (Wright Mark 8 spirometer, Ferraris Ltd., London), unassisted and assisted CPF (Access Peak Flow Meter, Health Scan Products Inc., Cedar Grove, New Jersey) were measured immediately (T1), at 48 hours (T2), and 6
months after tube removal (T3) for both groups. Assisted CPF were measured by having
the patient air stack to the maximum lung volumes[19] that could be held by the glottis
then have an abdominal thrust applied as they cough into a peak flow meter[20].

Extubation and decannulation success was defined by not requiring re-intubation
or re-cannulation during the same hospitalisation. The days using invasive mechanical
ventilation (MV), VC and (unassisted and assisted) CPF at T1, T2, and T3, ICU lengths
of stay, days required for extubation/decannulation, and extent of ventilator dependence
at discharge and 6 months later were compared for the two groups. One year incidence
of readmissions and survival is reported.

**Extubation protocol:**

Criteria for extubation were: normal white blood cell count, chest radiograph
abnormalities cleared or clearing, oxyhemoglobin saturation greater than or equal to
95% in ambient air, and afebrile[4]. Once these criteria were met the nasogastric tube
was removed if present to facilitate immediate post-extubation nasal NIV, and
measurement of CPF and VC.

The extubation protocol included maintaining normal alveolar ventilation by full
ventilator support settings and using MAC (pressures 40 to 60 cm H$_2$O to -40 to -60 cm
H$_2$O with exsufflation-timed abdominal thrust) via the translaryngeal tube every 30 to
120 minutes as needed until SpO$_2$ remained $\geq 95\%$ in ambient air.

Patients were then extubated directly to mouth piece or nasal NIV with a
portable ventilator on pressure control with 18-20 cm H$_2$O or assist/control mode with
800 to 1500 ml delivered volumes and a back up rate of 10 to 12 per minute[21]. For
mouth piece NIV patients kept 15mm or 22mm angled mouth pieces accessible to their
mouths (Figure 1). Patients weaned themselves, when possible, by taking fewer and
fewer mouth piece intermittent positive pressure ventilations (IPPVs) as needed. For night-time ventilation patients used nasal, oral or oronasal interfaces. No supplemental oxygen was used.

Patients were taught how to maximally expand their lungs by “air stacking” (retaining consecutive) ventilator delivered volumes to the largest volume the glottis could hold[19]. Once the patient maximally air stacked, an abdominal thrust was timed to glottic opening to manually assist the cough[20,22]. The respiratory therapy and nursing staff were trained in and provided MAC via oro-nasal interfaces (Figure 2) post-extubation until airway secretion elimination was no longer a problem and the SpO2 no longer dipped below 95%. Generally, pressures of 40 to -40 cm H$_2$O were used with an exsufflation-timed abdominal thrust. All clinical staff used this strategy with oximetry as feedback to maintain SpO2 $\geq$ 95%. Re-intubation was indicated for acute distress and irreversible oxyhemoglobin desaturation.

**Decannulation protocol:**

Our protocol is similar to one previously described[16,23]. Besides having to satisfy the same criteria as for extubation, all patients from G2 had to be able to verbalize when the tube cuff was deflated, have effective swallow and be medically stable. Normal alveolar ventilation was maintained by adequate ventilator settings.

Supplemental oxygen therapy was discontinued and MAC used via tube (with cuff inflated) until SpO2 remained $\geq$95% in ambient. Through the tube MAC was used at gauge pressures of 50 to 60 cm H$_2$O to -50 to -60 cm H$_2$O. All of the patients were placed on portable volume-cycled ventilators or, when preferred by the patient, portable pressure-cycled ventilators. The cuffs were completely deflated for increasing periods, hourly, until cuff deflation could be tolerated both throughout daytime hours and
overnight. When necessary, the patient's tracheostomy tube diameter was changed to permit sufficient leakage for speech while maintaining adequate fit to permit effective assisted ventilation with delivered ventilator volumes generally of 1 to 2 liters to compensate leaks through the upper airway. Ventilator parameters were set on assist/control mode, rate 10 to 12, and were titrated to maintain paCO$_2$ levels between 35 to 40 mm Hg. Tracheal integrity, tracheostomy tube width, volitional glottic and vocal cord movements were evaluated through upper airway fiberoptic examination.

Patients were advanced to the use of 24 hour tracheostomy ventilation with a fenestrated tracheostomy tube with a deflated cuff, and after that period they were trained in the use of mouthpiece IPPV for daytime ventilatory support with the tracheostomy tube capped and ventilator settings adjusted. Each patient learned to close off the nasopharynx with the soft palate to prevent nasal leakage. Once daytime mouthpiece IPPV was mastered, effective NIV during sleep through a nasal or oronasal mask was also implemented. When the efficacy of continuous NIV had been observed and before definitive decannulation, the tracheostomy tube was replaced by a tracheostomy button that allowed more accurate measurement of VC and CPF.

After 48 hours, patients maintained NIV, the tracheostomy button was removed and a compressive silicon material was placed over an occlusive tracheostomy site dressing that was fit to avoid leaks. Although the tracheostomy site usually closed in 24 to 72 hours, if not closed after 2 weeks it was usually sutured closed.

**Statistical Analysis**

Results are expressed as mean and standard deviation. Statistical analysis was carried out using SPSS version 15.0 (SPSS, Inc, Chicago, IL). Differences between VC, unassisted and assisted CPF, as well as ICU length of stay, days on invasive MV, days
on protocol and ventilatory dependence at discharge were compared using the Wilcoxon rank test. A p value $\leq 0.05$ was considered significant.

**Results**

Demographic data are in Table 1. There were no significant differences on age and level of injury severity between groups and none of the patients had lung disease. All patients failed multiple SBTs before the application of the protocols. Other than for 3 local patients, the tracheostomy patients were transferred to our ICU for decannulation.

The patients required NIV for 43±8 and 45±7 of the first post-extubation/decannulation 48 hours, respectively. Outcomes data are noted in Table 2.

Vital capacity, unassisted and assisted CPF over time are shown in Figures 3 and 4 respectively. Both patient groups had significant improvements in VC and unassisted and assisted CPF from T1 to T2 and T2 to T3 ($p<0.05$). In addition, the extubated patients had significantly higher VC at T2 (1.5±0.50L or 40±15% of predicted normal vs. 0.9±0.4L or 24±8% of predicted normal, $p<0.05$), unassisted CPF (170±58L/min vs. 84±25L/min at T2, $p<0.05$; 247±60 L/min vs. 114±46 L/min at T3, $p<0.05$) and assisted CPF (263±78L/min vs. 198±41L/min at T2, $p<0.05$; and 359±98 L/min vs. 226±74 L/min at T3, $p<0.05$) than the decanulated patients.

All patients were successfully extubated/decanulated with no respiratory complications. Two decanulated patients’ stomas were sutured for final closure. All were discharged home with caregivers proficient in providing NIV, manually assisted cough and air-stacking. During the first post-discharge year, one extubated patient was hospitalized for a RTI and 2 decanulated patients (one on nocturnal-only NIV) were hospitalized, one for a RTI and the other for a stroke. None of the hospitalizations
resulted in intubation or critical care. One year post discharge, 1 extubated patient died from non-respiratory causes and 2 were lost to follow up. All others were alive and well.

Discussion

Seventy-four percent of ASIA A acute SCI patients above the C5 level have been reported to require intubation[24]and the overall incidence of tracheostomy in these cases was between 81 and 83%[3,25]. The number of respiratory complications in SCI including ventilator associated pneumonia (VAP) during the acute phase contributes significantly to both hospital length of stay and cost[26]. However, it is not ventilator use that causes VAP but the invasive interface [27]. After the conversion to NIV and MAC, none of the patients in this study developed pneumonia or other respiratory complications during the hospitalization.

Guidelines for respiratory management after SCI were published in 2005[28]. However, the guidelines assumed the need for tracheostomy for unweanable CMV patients. In 2006, Bach challenged the medical community to decanulate high level SCI patients to NIV to avoid the complications of tracheostomy, to facilitate training in glossopharyngeal breathing to increase autonomous breathing ability and security in the event of ventilator failure, and to return home [13]This work is the first to accept this challenge.

In this study, besides successful extubation and decannulation of CVD patients, after the protocol, only 9 (45%) of the total population used NIV at discharge and all others weaned to autonomous breathing. The use of high delivered NIV volumes has been reported to facilitate the weaning process and lessen risk of respiratory complications[29] as well as result in increased VC and CPF for patients who are
extubated[4] or decanulated[16,17,30] and our results are consistent with those studies. Moreover, it is not expected that continuous NIV can be a successful alternative to invasive ventilation, if patients use only mask ventilation[31]. Further, for both groups, mouthpiece ventilation normalized speech, provided normal daytime ventilation, permitted "air stacking" for lung expansion and assisted coughing, and weaning[4,21,30].

Aggressive use of MAC via translaryngeal and tracheostomy tubes was the main intervention that may have improved pulmonary function (VC and CPF) and normalized SpO2 in ambient air to satisfy the most important criterion for extubation/decannulation. Our findings are consistent with those of Bach et al.[16,32], however our patients were all successfully extubated despite some having assisted CPF below 160l/min at T1. This was possibly due to the more aggressive use of MAC up to every 15 min to maintain normal SpO2. Pillastrini et al.[33], too reported that mechanical in-exsufflation aided in clearance of bronchial secretions and increased forced VC, forced expiratory volume in 1 second, and peak expiratory flows for tracheostomized SCI subjects. Vital Capacity and CPF also improved in our patients because of lung expansion and secretions removal.

Transition from tracheostomy to continuous NIV was progressive and implied a specific protocol that included ventilation with a deflated cuff for increasing periods until it could be tolerated throughout daytime hours and overnight.

This “open system” ventilation[34] permitted the patients to improve their vocal cord function that was essential for successful NIV training with a capped cuffless fenestrated tube. In 2004 we reported that decannulation and conversion to NIV and MAC can facilitate ventilator weaning of CMV dependent patients[30]. It has also been reported that decanulated patients invariably prefer NIV over return to tracheostomy
ventilation for safety, convenience, appearance, comfort, facilitating effect on speech, sleep, and swallowing, and overall[35]. Despite this, until this study, no other has described the systematic extubation/decannulation of CVD SCI patients to noninvasive alternatives or the avoidance of tracheotomy for unweanable intubated patients.

In this study, both short–term and long term outcomes for the extubated patients were better than for the decanulated patients. Thus, it appears preferable, in this patient population, to prevent tracheotomy in the first place, whenever possible, rather than decanulate later on. Certainly, patients with severe bulbar-innervated muscle involvement, head injury, chest trauma, medical fragility, complicated courses including the need for surgical procedures over a greater than 3 or 4 week period are best managed by tracheotomy.

Our data show that the extubated SCI patients had significantly shorter ICU stays, were more quickly extubated than the decanulated patients decanulated, had higher VC at 48 hours after tube removal, higher unassisted and assisted CPF at 48 hours and at 6 months after tube removal than those decannulated. This can be due to the fact that extubated patients had significant less time on invasive ventilation with consequent less respiratory muscle deconditioning, were somehow less severely affected despite comparable VCs and ASIA levels at T1, or had less risk of upper airway instability and less secretion encumbrance or segmental atelectasis despite the same CPF and normal SpO2. Moreover, the decanulated patients needed MAC to clear airway secretions for longer periods of time as well as more time for NIV training and tracheostomy site closure.

The higher values of VC at 48 hours after extubation explains the greater number of extubated patients discharged to the community with no ventilatory support.
Although tracheostomy may have physiologic benefits over endotracheal tubes in terms of reduced work of breathing[36] and permitting more efficient suctioning, over 90% of the time suction catheters enter only the right mainstem bronchus resulting in 80% of pneumonias occurring on the left lungs of these patients[37] and work of breathing is readily compensated by providing pressure support during SBTs. There are no reports of better outcomes with tracheostomy ventilation when compared to the NIV/MAC protocols.

This study has the limitations by its retrospective nature and small number of participants suggesting caution when generalizing the importance of its outcomes.

Considering the incidence of mortality and respiratory morbidity in this population of SCI patients managed by standard ventilatory invasive techniques, the results of this study suggest that noninvasive methods of assisted ventilation and coughing can facilitate both extubation and decannulation with significant improvement on ventilatory dependence and pulmonary function and may facilitate return home rather than prolonged institutionalization for weaning attempts. Randomized controlled trials to evaluate these precepts may be unethical since noninvasive management is clearly effective.
Acknowledgments:

The authors wish to thank the medical, respiratory therapy and nursing staffs of both ICU and Pulmonology departments for their assistance and support in managing the patients.
Figure 1- Forty nine year old man with C4 ASIA A spinal cord injury extubated with no ventilator-free breathing ability, using volume cycled ventilation through a 15 mm angled mouth piece for ventilatory support.

Figure 2- Twenty- one year old man with a C3 ASIA A spinal cord injury, using post-extubation mechanically assisted coughing (MAC) with the CoughAssist™ (Philips Respironics International Inc.) via an oronasal interface at pressures of 40 to -40 cmH2O.
Figure 3 – Vital capacity at extubation (T1), after 48 hours (T2) and at 6 months follow up (T3)

Legend: VC – Vital Capacity (Liters).
# - p<0.05; & - p<0.05; ¶ - p < 0.05
Figure 4- Unassisted and Assisted CPF data at extubation (T1), after 48 hours (T2) and at 6months follow up (T3)

Legend: CPF – Unassisted cough peak flow (L/min); AsCPF – Assisted cough peak flow (L/min).
#1,#2,#3 – p <0,05; &1,&2,&3 – p <0,05
#2 and &2 – p <0,05; #3 and &3 – p <0,05
Table 1 – Demographic data

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42±19</td>
<td>48±11</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>male – 10 (77%)</td>
<td>male – 7 (100%)</td>
</tr>
<tr>
<td></td>
<td>female – 3 (23%)</td>
<td></td>
</tr>
<tr>
<td>**FVC, Liters (%) ***</td>
<td>0,5±0,6 (16±24)</td>
<td>0,2±0,3 (8±10)</td>
</tr>
<tr>
<td>**FEV1/FVC (%) ***</td>
<td>88±5</td>
<td>78±5</td>
</tr>
<tr>
<td>**CPF (L/min) ***</td>
<td>64±64</td>
<td>23±29</td>
</tr>
<tr>
<td><strong>Level SCI, n (%)</strong></td>
<td>C2-C3 – 4 (31%)</td>
<td>C2-C3 – 2 (29%)</td>
</tr>
<tr>
<td></td>
<td>C4-C5 –8 (62%)</td>
<td>C4-C5 –5 (71%)</td>
</tr>
<tr>
<td></td>
<td>C6 -1 (7%)</td>
<td></td>
</tr>
<tr>
<td><strong>ASIA scale, n (%)</strong></td>
<td>A – 11 (85%)</td>
<td>A- 6 (86%)</td>
</tr>
<tr>
<td></td>
<td>B – 2 (15%)</td>
<td>B- 1 (14%)</td>
</tr>
</tbody>
</table>

**Legend:** G1 – Extubated patients; G2 – Decannulated patients; N – number of patients; FVC – Forced Vital Capacity; FEV1 – Forced expiratory volume at 1st second; CPF- (Unassited) Cough Peak Flow; SCI – Spinal cord injury; ASIA – American Spinal Injury Association

* - measured at T1 (immediately after tube removal)

**Note** – p value is non-significant in all items between the 2 groups
Table 2 – ICU and discharge outcomes:

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on invasive mechanical Ventilation</td>
<td>15±12 &amp;</td>
<td>61±34 &amp;</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>22±16*</td>
<td>97±93*</td>
</tr>
<tr>
<td>Duration of protocol (days)</td>
<td>8±6 #</td>
<td>14±3 #</td>
</tr>
<tr>
<td>Ventilatory dependence at discharge, n (%)</td>
<td>SB – 8 (61%)</td>
<td>SB – 3 (43%)</td>
</tr>
<tr>
<td></td>
<td>nNIV - 5 (39%)</td>
<td>nNIV - 3 (43%)</td>
</tr>
<tr>
<td></td>
<td>cNIV – 1 (14%)</td>
<td></td>
</tr>
<tr>
<td>Ventilatory dependence at 6 months, n (%)</td>
<td>SB – 11 (85%)</td>
<td>SB – 4 (57%)</td>
</tr>
<tr>
<td></td>
<td>nNIV – 2 (15%)</td>
<td>nNIV – 2 (29%)</td>
</tr>
<tr>
<td></td>
<td>cNIV – 1 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation

Legend: : G1 – Extubated patients; G2 – Decannulated patients; ICU – Intensive Care Unit; Duration of protocol - days required to finish the protocol; SB – Spontaneous breathing; nNIV – nocturnal noninvasive ventilation; cNIV – continuous noninvasive ventilation

& - p<0.05
* - p < 0.05
# - p < 0.05
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Study 3

Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation:
A randomized controlled trial.

Miguel R. Gonçalves, Teresa Honrado, João Carlos Winck, José Artur Paiva

(Critical Care, submitted)
Effects of mechanical insufflation-exsufflation in preventing respiratory failure after extubation.
A randomized controlled trial.

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Abstract:
(Word count 341)

**Background:** Weaning protocols that include the use of noninvasive ventilation (NIV), decreases the incidence of re-intubation and ICU length of stay. However, the role of NIV in post-extubation failure is still not clear. Impaired airway clearance is associated with NIV failure. Mechanical Insufflation-Exsufflation (MI-E) is an assisted coughing technique that has been proven to be very effective in patients under NIV.

**Aims:** To assess the efficacy of MI-E as part of a protocol for patients that develop respiratory failure after extubation.

**Methods:** Patients under mechanical ventilation (MV) for more than 48 hours with specific inclusion criteria, who successfully tolerated an spontaneous breathing trial (SBT) were randomly allocated before extubation, either for (A) conventional extubation protocol (control group) or (B) MI-E extubation protocol (study group). Re-intubation rates, ICU length of stay and NIV failure rates were analyzed.

**Results:** Seventy five patients (26 females) with a mean age of 61.8±17.3 years old were randomized to control group (n=40, mean SAPS II) and to study group (n=35, mean SAPS II 45.0±15.0). MV time before enrollment for was 9.4 ±4.8 and 10.5±4.1days for control and study group respectively. In the 48 hours post extubation, 20 control patients (50%) and 14 study patients (40 %) used NIV. Study group patients had a significant lower re-intubation rate than controls; 6 patients (17%) vs 19 patients (48%), p<0.05 respectively and a significant lower time under MV; 17.8±6.4 vs 11.7±3.5 days, p<0.05, respectively. Considering only the sub-group of patients that used NIV, the re-intubation rates related to NIV failure were significantly lower in the study group when compared to controls; 2 patients (6%) vs 13(33%), p<0.05, respectively. Mean ICU length of stay pós - extubation was significantly lower in the study group when compared to controls (3.1± 2.5 vs 9.8± 6.7 days, p<0.05). There were no differences in the total ICU length of stay

**Conclusions:** Inclusion of MI-E in post-extubation failure may reduce re-intubation rates with consequent reduction in post-extubation ICU length of stay. This technique seems to be efficient in improving the efficacy of NIV in this patient population.
Introduction

The process of weaning from mechanical ventilation must balance the risk of complications due to unnecessary delays in extubation with the risk of complications due to early discontinuation and the need of reintubation[1]. Patients who require reintubation have been noted to have a significantly higher mortality rate than those who are successfully extubated on the first attempt[2].

Patients in the intensive care setting very often have impaired airway clearance. Endotracheal intubation prevents the patient from closing the glottis, which is necessary for effective coughing[3]. Care of the intubated patient includes direct suction applied through the endotracheal tube which clears a small portion of the airway, is ineffective for clearing secretions in the peripheral airways, and leaves the patient dependent upon mucociliary clearance rather than cough clearance[4]. Deep insufflation with a self-inflating ventilation bag can help, especially if accompanied by chest physiotherapy, but it does not recreate a cough[5].

Ventilator-associated pneumonia is an exceedingly common problem in intensive care units (ICUs), occurring in as many as 27% of patients [6]. The reasons for this are complex, but a significant role is played by the aspiration of upper-airway secretions and gastric contents[7]. In reality, “ventilator-associated” pneumonia is more “interface-associated” pneumonia as pathogenic mechanisms are related to the (invasive) interface used for mechanical ventilation rather than the ventilator itself [8]. Despite the many reports and reviews on ventilator-associated pneumonia, little emphasis is placed on airway clearance[9].

Predictors for successful weaning include respiratory rate less than 38 per minute and a rapid shallow breathing index below 100 breaths/min/L [10]. However,
even in patients who satisfy weaning criteria and pass ventilator weaning trials, there is an extubation failure rate of 10 to 20% [11].

Post-extubation respiratory failure is defined as the presence of signs and symptoms of respiratory distress in the first 48 hours after extubation. The reasons given for extubation failure include lack of improvement in work of breathing, hypoxemia, respiratory acidosis, retained secretions, and decreased consciousness [12]. However, if at extubation the lungs are healthy and ventilation can be fully maintained noninvasively[13], then the only remaining concern is the effective expulsion of airway secretions[14]. Despite the importance of this factor, no ventilator weaning parameter addresses the ability to cough.

Early extubation, coupled with the use of noninvasive ventilatory support has been used effectively to facilitate weaning[15-17], improve survival[18], decrease the incidence of ventilator-associated pneumonia[8, 19] and reduce ICU length of stay[18-19]. However there is a higher risk of NIV failure when applied in patients that develop ARF after extubation and the evidence that supports its application is controversial [20-22].

Despite a great interest in this field, the role of impaired airway secretion clearance on the outcome of post-extubation respiratory failure in critically ill ventilator dependent patient treated with non-invasive ventilation is still not clear. Airway clearance may be impaired in disorders associated with abnormal cough mechanics, altered mucus rheology, altered mucociliary clearance, or structural airway defects. A variety of interventions are used to enhance airway clearance with the goal of improving lung mechanics and gas exchange, and preventing atelectasis and infection [23].

Conventional techniques for augmenting the normal mucociliary clearance and cough efficacy have been used for many years to treat patients with respiratory
disorders from different etiologies. In recent years, new technologies and more advanced techniques have been developed to be more effective in acute respiratory failure. These techniques involve mechanical application of forces to the chest wall[24] or intermittent pressure changes to the airway to assist airway mucus clearance[25-26].

Mechanical insufflation-exsufflation (MI-E) applies positive pressure followed by negative pressure across the entire airway (both central and peripheral), in contrast to direct tracheal suction, which applies negative pressure to a small, localized area[27]. This therapy is perhaps the most physiologic recreation of a natural cough.

The purpose of this study is to assess the efficacy of MI-E as part of a weaning protocol for patients that develop acute respiratory failure after extubation.

**Methods:**

The data of this randomized control trial was gathered in a 12 bed general ICU between 2007 and 2009. The study was approved by the ethical institutional committee and review board.

**Patients:**

Patients older than 18 years and under mechanical ventilation, for more than 48 hours, for acute hypoxemic and/or hypercapnic respiratory failure from a specific etiology were considered potentially eligible for the study. Exclusion criteria included facial or cranial trauma, tracheostomy, active upper gastrointestinal bleeding, neurologic instability (inability to respond to direct simple orders), hemodynamic instability, lack of cooperation and confirmed diagnosis of neuromuscular disease.
All patients included were evaluated for discontinuation of mechanical ventilation through the application of a spontaneous breathing trial (SBT). The application of a SBT trial was considered appropriate when all of the following criteria were met: improvement of the condition that caused acute respiratory failure, respiratory rate less than 38 per minute, rapid shallow breathing index below 100 breaths/min/L [10] suspension of sedative medications, ability to stay alert and communicate, core temperature less than 38ºC throughout the last 24h, suspension of vasoactive drugs, with the exception of dopamine at doses lower than 5ug per kilogram of body weight per minute and partial pressure of oxygen greater than 60mmHg on an inspired fraction of oxygen(FiO2) of 0.40 (PaO2/FiO2 >200) or less, with a positive end-expiratory pressure (PEEP) of 5cmH2O

Discontinuation of mechanical ventilation was assessed by a trial of spontaneous breathing with a T tube on a FiO2 of 50% for up to 60 to 120 minutes. The SBT was considered successful when during the trial time none of the following symptoms were found: Respiratory Rate > 35bpm, SpO2 < 90 %, 20% variation of Heart rate or Blood pressure, respiratory distress, agitation and loss of conscience[28].

Patients who successfully tolerated the SBT were randomly allocated before extubation, using a computer-generated table either for (A) conventional extubation protocol (control group) or (B) MI-E extubation protocol (study group). During the first 48 hours after extubation, patients were observed for symptoms of acute respiratory distress/insufficiency as defined by dyspnea and the presence of at least two of the following: respiratory acidosis (pH < 7.35 with a PaCO2 >45mmHg), increased use of accessory respiratory muscles, increased respiratory rate (>35 bpm), and decreasing oxyhemoglobin saturation, i.e. Spo2 < 90% and PaO2 <80 mmHg with fiO2 > 50%.
Group A patients received (post-extubation) standard medical treatment (SMT), including NIV in case of specific indications, whereas Group B received the same post-extubation approach plus mechanical in-exsufflation (MI-E).

Patients with persistent weaning failure who failed 3 or more SBTs in one week were excluded.

**Standard medical therapy:**

All patients received post extubation standard medical therapy including supplemental oxygen as needed, respiratory chest physiotherapy, bronchodilators, antibiotics and any other therapies as directed by the attending physician.

Criteria for NIV were the same in the two groups. Patients were submitted to NIV, if they met at least one of the following criteria, as judged after they had undergone the assigned treatment: Respiratory Rate > 35bpm, SpO2 < 90 %, 20% variation of Heart rate or Blood pressure, dyspnoea with respiratory distress, PaO2< 60mmHg, PaCO2 > 45mmHg, pH < 7.35.

Noninvasive ventilation was provided via an ICU ventilator with noninvasive mode or via a portable pressure cycled ventilator through a oronasal mask as first choice. Other interfaces such as nasal, total face, helmet and mouthpieces were used in case of patient’s intolerance to the oronasal mask.

The fraction of inspired oxygen and the positive end-expiratory pressure were titrated to maintain the arterial oxygen saturation above 90 percent ( or PaO2 > 60mmHg). The ventilator settings were subsequently adjusted as needed for the patient’s comfort The facial skin was assessed every four hours to prevent damage from the tightly fitting mask.
The decision regarding when to discontinue noninvasive ventilation was left to the attending physician.

**Mechanical Insufflation-Exsufflation Protocol (study group):**

After passing the SBT and randomized to the study group, before extubation, all patients were submitted to a treatment of MI-E (3 sessions) with the Cough Assist™ (Philips Respironics, Inc) through the endotracheal tube with pressures set at 40 cm H2O for insufflation and -40 cm H2O for exsufflation pressure. An insufflation/exsufflation time ratio of 3 secs/2 secs and a pause of 3 sec between each cycle was used. Eight cycles were applied in every session with an abdominal thrust timed to the exsufflation cycle.

On top of the standard medical therapy, during the first 48 hours post extubation, each patient received 3 daily treatments by means of a light-weight, elastic oronasal mask. Treatments (3 sessions each) were divided between morning, afternoon and night, making a total of 9 daily sessions.

The daily treatment frequency and its outcomes were recorded in a diary by the nursing staff. All MI-E treatments were administered by a trained respiratory therapist, ICU physician or nurse.

**Criteria for reintubation:**

In both patient groups, the final decision to reintubate was left to and made by the attending physician, who recorded the single most relevant reason for reintubation. Reason to reintubate was the existence of at least one of the following, as judged after they had undergone the assigned treatment: (a) respiratory or cardiac arrest, (b) respiratory pauses with loss of consciousness, (c) respiratory distress despite 2 hour
treatment with SMT and NIV, (d) decreasing level of consciousness, (c) intolerance to NIV; (f) hypotension, with a systolic blood pressure below 90 mm Hg for more than 30 minutes despite adequate volume challenge, the use of vasopressors, or both and (g) copious secretions that could not be adequately cleared or that were associated with severe hypoxemia. The final decision to reintubate was made by the attending physician, who recorded the single most relevant reason for reintubation. Only reintubations required in the first 48 hours post-extubation was considered for this study.

Outcomes:

Reintubation rate was considered as primary endpoint. Total ICU length of stay, post-extubation ICU length of stay and reasons for reintubation and NIV failure were also analysed and compared between groups as secondary endpoints. A sub-group analysis, both for primary and secondary outcomes, was performed in patients that were submitted to post-extubation NIV

Statistical analysis:

Descriptive data are reported as mean± standard deviation (SD). Statistical analysis was performed by SPSS software (Release 15.0 SPSS, Chicago, II, USA).

Sample size calculation: The primary end-point variable was to decrease reintubation rates defined by the necessity of mechanical positive pressure ventilation through orotracheal intubation in the first 48 hours post-extubation in the treatment group.

Initial calculations revealed a required sample size of 33 subjects in each group with reintubation rates to be reduced by 30%. One interim analysis was performed after inclusion of 50% of the estimated patients using an α curtailment (p< 0.005) to correct the analysis.
Comparisons between groups: For all endpoints, differences between groups were analyzed by using a paired Student’s \( t \)-test for the parametric variables and unpaired Mann-Whitney for the non-parametric ones, respectively. P-values were considered significant if \(<0.05\).

Results:

A total of 92 patients were considered for the study period, 17 of which did not meet the inclusion criteria. Seventy five patients (26 females) with a mean age of 61.8±17.3 years old were randomized, 40 to control group and 35 to the study group. Baseline characteristics at baseline were similar in both groups, as well as the reasons for MV. Demographic data and patients characteristics at the entry of the study are listed in Table 1.

In the 48 hours post-extubation, 20 controls (50%) and 14 study patients (40%) used NIV. Considering this sub-group of patients, the re-intubation rates related to NIV failure were significantly lower in the study group when compared to controls; 2 patients (6%) vs 13(33%), \( p<0.05 \), respectively.

Outcomes of both patients groups in the first 48 hours post-extubation and ICU length of stay data are listed in Table 2. When compared to controls, both duration of invasive mechanical ventilation and post – extubation ICU length of stay were shorter by 6 days (\( p<0.05 \)), and reintubation rate was lower (17% vs 48%) in the study group.

There were no significant differences in total ICU length of stay.
Discussion:

The results found in this trial suggest that secretion management with MI-E may work as a useful complement technique to treat patients who develop ARF in the first 48 hours post-extubation. The use of MI-E had a stronger impact in preventing re-intubation in the group of patients that required NIV, as shown by the lower NIV failure rates in the patients that were submitted to MI-E.

Significant debate still exists concerning the precise indications and efficacy of NIV in this patient population[29] without any mention to the problem of impaired airway secretion.

The randomized controlled studies performed by Esteban et al [21]. and Keenan et al[20]. concluded that NIV is not efficient in reducing re-intubation rates, duration of invasive mechanical ventilation and ICU and hospital length of stay. None of these studies showed improvement in survival in patients that used NIV in addition to SMT. On the contrary, the trials conducted by Nava et al.[30] and Ferrer et al.[15] showed that NIV could prevent ARF after extubation. Several reasons may explain these differences. First, whereas the studies by Keenan et al[20] and Esteban et al[21] applied NIV after patients had developed symptoms of respiratory failure, the studies by Nava et al[30] and Ferrer et al[15] previously identified the high-risk patients and applied NIV immediately after extubation. As longer time from extubation to re-intubation is associated with worse outcome[31], delay in re-intubation correlates with worse survival rates in patients who received NIV for established post-extubation respiratory failure[20-21]. Thus, the early application of NIV seems crucial to avoid respiratory failure after extubation, and consequently re-intubation. Second, a significantly higher proportion of patients with chronic respiratory disorders were included in the studies.
that used early NIV in high risk patients, whereas the NIV post-extubation respiratory failure trials enrolled only 10–11% of patients with chronic pulmonary disease and used different definitions for post-extubation respiratory failure.

In our study, both study and control groups included 20% of patients with chronic respiratory disorders, and all patients were closely monitored during the first 48 hours for early detection of signs and symptoms that indicated post-extubation respiratory failure. Similarly Esteban et al.[21] and Keenan et al.[20] NIV was only applied after the development of those symptoms according to specific criteria. However, in our study NIV was applied in both study group patients and controls and only MI-E application was considered an independent variable.

Secretion encumbrance with impaired airway clearance has been considered an independent factor for extubation failure[32], and associated to NIV failure both in persistent weaning[19] and in post-extubation failure[21] patients. While it is relatively easy managing secretions through an endotracheal tube, it can be a serious problem after extubation and specially during NIV. Deep airway suction suctioning through the tube is a strategy most commonly used by nursing staff to manage secretions while patients are on invasive MV, however it can be traumatic, difficult to perform and often ineffective in the extubated patients since it must be performed blindly through the nose or the mouth.

This study randomly used MI-E (CoughAssist™, Phillips Respironics International Inc., Murrysville, Pa) pre- extubation via invasive tube and post-extubation through oronasal interface at sufficient inspiratory and expiratory pressures (minimum of 40 to -40 cm H2O) to fully expand and then fully empty the adult lungs in 6-8 seconds, thereby expelling airway secretions while avoiding both hyper and hypoventilation. The ability to use MI-E through the endotracheal tube immediately
before extubation was the main intervention that permitted the study group patients to
minimize the risk of post-extubation secretion encumbrance and, together with its 3
time daily noninvasively application, may have had influence on the reduction of re-
intubation and NIV failure rates.

Although MI-E has been described as a very efficient technique in the acute
setting for patients with neuromuscular disease (NMD), in the treatment of respiratory
failure due to upper respiratory tract infections[27], to avoid intubation[33] and to
facilitate extubation, decannulation and prevent post-extubation failure[34-36], the
evidence supporting the role of this technique in this other critical ill patient population
is lacking. Indeed, this study is the first randomized controlled trial focused on MI-E in
critical care.

The fact that there is strong evidence on the efficacy of MI-E in critically ill
patients with NMD, and the authors’ positive experience with this technique in this
patient population, was the ethical reasons to exclude them from the study. In fact, our
group recently reported a 97% extubation success to full-setting noninvasive ventilation
(NIV) and MI-E in 157 NMD patients who had previously failed extubations and/or
SBTs [37].

Potential limitations have to be taken into account when analyzing the
differences between the two groups. First, although there were no significant differences
in baseline characteristics at the entry of the study between the two groups hypoxemic
respiratory failure was slightly more frequent in group A and this may had impact on
the NIV failure rate in this patient group, since NIV is more likely to fail when severe
hypoxia is present[38]. Second, 6 controls and 4 study group patients were re-intubated
immediately with no indication for NIV. This fact was associated with causes that could
not be solved by MI-E, since cooperation with the technique is crucial in extubated patients.

Another potential limitation of this type of open clinical trials is the difficulty for a correct blinding of the investigators that might lead to possible bias. Despite the fact that we predefined the criteria for all relevant interventions and clinical decisions to be made by the attending physicians, as well as the outcome variables, this bias could not be entirely controlled.

Thus, our results recommend that MI-E for secretion clearance should be included in an extubation protocol in specific subgroups of patients that may require post-extubation NIV. However, because of the paucity of data, and the fact that this is a pilot study performed in a center highly experienced with MI-E, more studies are required to settle the issue.

Acknowledgments:

The authors wish to thank all medical and nursing staffs of the emergency department ICU of our institution, for their motivation, assistance and support in managing the patients according to the trial.
Table 1 – **Baseline characteristics of patients at entry into the study**  

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 40)</th>
<th>Group B (MI-E) (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62±19.2</td>
<td>61.4±15.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>21/19</td>
<td>28/7</td>
<td>NS</td>
</tr>
<tr>
<td>SAPS II</td>
<td>47.8±17.7</td>
<td>45±15</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of MV (days)</td>
<td>9.4±4.8</td>
<td>10.5±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with chronic pulmonary disorders (n,%)</td>
<td>9(23%)</td>
<td>7 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with hypoxemic respiratory failure (n,%)</td>
<td>24 (60%)</td>
<td>18(52%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Reasons of MV (n)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD exacerbations</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Community – acquired pneumonia</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hospital – acquired pneumonia</td>
<td>--</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Postoperative respiratory failure</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>--</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thoracic trauma</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>--</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Data is presented as mean ± standard deviation  
Legend- SAPS II - New Simplified Acute Physiology Score; MV – mechanical ventilation; COPD – chronic obstructive pulmonary disease; NS – Non significant
Table 2 – Post-extubation outcomes data

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 40)</th>
<th>Group B (MI-E) (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIV application, n (%)</td>
<td>20 (50%)</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>Reasons for NIV (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate &gt; 35bpm</td>
<td>5 (25%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>SpO2 &lt; 90%</td>
<td>4 (20%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>20% variation of HR or BP</td>
<td>1 (5%)</td>
<td>-----</td>
</tr>
<tr>
<td>PaO2&lt;60; PaCO2&gt;45</td>
<td>10(50%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Total period of MV (days)</td>
<td>17,8±6,4*</td>
<td>11,7±3,5*</td>
</tr>
<tr>
<td>Patients re-intubated (n,%)</td>
<td>19 (48%) *</td>
<td>6 (17%) *</td>
</tr>
<tr>
<td>Causes of re-intubation (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory pauses with loss of consciousness</td>
<td>---</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory distress after 2h NIV</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Decreasing level of consciousness</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>Intolerance to NIV</td>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>Hypotension (systolic BP&lt; 90 mm Hg for more than 30 minutes)</td>
<td>---</td>
<td>1</td>
</tr>
<tr>
<td>Secretion encumbrance associated with severe hypoxemia..</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>NIV failure rate, n (%)</td>
<td>13 (65%) *</td>
<td>2 (14%) *</td>
</tr>
<tr>
<td>Total ICU length of stay</td>
<td>19,3±8,1</td>
<td>16,9±11,1</td>
</tr>
<tr>
<td>Post-extubation ICU length of stay</td>
<td>9,8±6,7*</td>
<td>3,1±2,5*</td>
</tr>
</tbody>
</table>

Data is Data presented as mean ± standard deviation
Legend- NIV – Noninvasive ventilation; APS II - New Simplified Acute Physiology Score; MV – mechanical ventilation; COPD –chronic obstructive pulmonary disease; NS – Non significant
* - p<0,05
References:


Study 4

A Ventilator Requirement Index

John R. Bach, Miguel R. Gonçalves, Yuka Ishikawa, Michal Eisenberg, João Carlos Winck, Eric Altschuler
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
A Ventilator Requirement Index

ABSTRACT

Objective: To determine the efficacy of vital capacity (VC) and a proposed ventilator requirement index (VRI) for justifying ventilator prescription and use for patients with neuromuscular/chest wall diseases (NMD).

Design: Prospective observational study in which 319 patients with NMD, including 187 ventilator users, were separated into four groups: (1) asymptomatic, (2) abnormal specific screening factors and/or symptomatic, (3) ventilator use 8–20 hrs/day, and (4) >20 hrs/day of ventilator use. The VRI was defined as $60 \times \frac{Ti}{Ttot} \times (Vt/VC) \times RR$, where $Ti =$ inspiratory time of one breath (secs), $Ttot =$ total time of one breath (secs), $Vt =$ tidal volume (ml) at rest, $VC =$ vital capacity (ml), and $RR =$ respiratory rate.

Results: The overall analysis of variance $F$-tests and post hoc pairwise contrasts were significant ($P < 0.001$) for differences in the VC and VRI across groups. Thus, VC and VRI are independent predictors of group membership. Satisfying VC or VRI criteria signaled the highest number of patients benefiting from ventilator use.

Conclusions: The prescription of one or two ventilators can be justified by both VC and VRI, with the combination being most sensitive.

Key Words: Ventilator Requirement Index, Noninvasive Mechanical Ventilation, Respiratory Insufficiency, Home Mechanical Ventilation, Neuromuscular Disease

When a patient is not able to fully sustain the muscular work of breathing to maintain normal alveolar ventilation in the presence of increasing ventilatory load or decreasing work capacity, muscle fatigue can only be averted by symptomatic hypoventilation or by ventilatory assistance. Bellemare and Grassino examined the effects of the tension time index of the diaphragm (TTIdi) on inspiratory muscle endurance and fatigue. They define the point at which a target tension could no longer be sustained as the Tlim. In the case of the diaphragm, there are two main factors influencing Tlim or muscle fatigue. They
are the product of the TTIdi or the product of the fraction of time that the inspiratory muscles spend in contraction (Ti/Ttot) (the duty cycle of the inspiratory muscles), and the ratio of the tension generated at each contraction (Pdi) to the maximum Pdi that can be achieved during a near isometric contraction (PdiMax). Thus, TTIdi = (Ti/Ttot) × (Pdi/PdiMax). Tlim is the percentage of TTIdi such that effective diaphragm contraction is not sustainable. Because the diaphragm contracts mainly during inspiration, it should fatigue more rapidly at any given tension if Ti/Ttot is abnormally increased. It should also fatigue more rapidly at any given Ti/Ttot if the Pdi/PdiMax ratio increases with advancing inspiratory muscle weakness/dysfunction. Bellemare and Grassino\(^1\) report that the Tlim for patients with chronic obstructive pulmonary disease is (TTIdi equal to) 0.12. That is, with TTIdi greater than this, chronic obstructive pulmonary disease patients’ respiratory muscles fatigue. TTIdi = 0.15–0.2 was reported as “the critical zone for fatigue” in that fatigue could occur in less than 1 hr at this TTIdi level. Thus, diaphragm (inspiratory muscle) endurance could be predicted by the TTIdi. However, determining TTIdi requires placement of an esophageal balloon to measure Pdi and PdiMax. This makes it impractical for general use.

We have already demonstrated that tidal volume (Vt)/vital capacity (VC) can substitute for Pdi/ PdiMax, because the more Vt approaches VC, the less the inspiratory muscles have to sustain alveolar ventilation.\(^1\) Our previous data, on predominantly chronic obstructive pulmonary disease patients, suggest that a breathing intolerance index using Vt/VC can supplement VC criteria to help gauge the need for ventilator use by reflecting ventilatory reserve.\(^1\) Subsequently, we hypothesized that the index might better correlate with symptomatic inspiratory muscle dysfunction if it reflected ongoing inspiratory muscle action rather than effort over only one breath cycle. Thus, we multiplied the index (Ti/Ttot × Vt/VC) by respiratory rate, or 60 × Ti/Ttot\(^2\) × Vt/VC (an equivalent equation), to define a new ventilator requirement index (VRI). The purpose of this study was to determine whether this VRI could distinguish patients with neuromuscular diseases (NMD) with various levels of inspiratory muscle dysfunction and need for ventilator use, and whether such an index could add to the efficacy of simple VC measurement in indicating the extent of the need for ventilator use.

**MATERIALS AND METHODS**

This was a prospective analysis of data gathered on 332 consecutively referred patients with NMDs. It was approved by our institutional review boards. Three hundred nineteen of the 332 could achieve steady-state breathing sufficiently for six breaths to be averaged for data analysis, and 13 could not (were continuously ventilator dependent). Of the 319, there were 187 males and 132 females, 36.8 ± 19.1 yrs of age. They had the following diagnoses: Duchenne muscular dystrophy, 90 (mean age 22.7 range 9–45); non-Duchenne myopathy, 83 (mean age 28.8, range 13–78); amyotrophic lateral sclerosis, 64 (mean age 56.3, range 19–84); spinal muscular atrophy, 25 (mean age 25.3, range 16–53); poliomyelitis, 18 (mean age 60.9, range 44–77); myotonic dystrophy, 13 (mean age 38.3, range 29–48); spinal cord injury, 11 (mean age 28.8, range 18–52); myasthenia gravis, 6 (mean age 42.8, range 31–58); multiple sclerosis, 5 (mean age 48.1, range 34–59); Charcot–Marie–Tooth disease, 2 (ages 57 and 42); and miscellaneous, 15 (mean age 37, range 18–85).

All of the patients underwent evaluation for specific ventilator need–screening factors, which included symptoms of inspiratory muscle dysfunction (chronic alveolar hypoventilation) as previously published,\(^2\) recent or increasing fatigue, dyspnea at rest (especially on waking), morning headaches, nocturnal arousals associated with dyspnea/tachycardia or urination, difficulty arousing in the morning, difficulty in getting to sleep, personality changes or need for multiple naps, impairment of concentration, nightmares, signs of right-heart failure, anxiety, depression, and weight change. Dyspnea caused by walking or stair climbing was excluded because most patients were wheelchair dependent, because ambulation requires much greater minute ventilation than most activities from a wheelchair, and because nocturnal noninvasive mechanical ventilation (NIV) has not been reported to relieve exertional dyspnea.

Other abnormal screening factors were derived from spirometry (Wright spirometer, Mark 14, Ferraris Development and Engineering Co., Ltd, London), end-tidal CO\(_2\) levels (Microscan 8090 capnograph, Biochem International, Waukesha, WI), and pulse oximetry (SpO\(_2\)) (Ohmeda Model #3760 oximeter, Louisville, CO). They were VC measured in a sitting position less than 50% of predicted normal (Medicare standard), VC sitting/VC supine ratio greater than 1.2 (normal ratio <1.07), diurnal end-tidal carbon dioxide (CO\(_2\)) greater than 44 mm Hg, diurnal pulse oxymoglobin saturation (SpO\(_2\)) decreasing to less than 95%, and ventilator-free breathing ability <10 mins in any position. The VC was recorded as the maximum observed in five or more attempts. The American Academy of Respiratory Care Clinical Practice Guidelines were followed.\(^3\) The VC percentage of predicted normal was calculated as 100 times the VC (ml) divided by the predicted normal VC (ml), using the Baldwin formula: males’ predicted VC (liters) = \( \frac{[27.63 – 0.112 \times \text{age}]}{\text{height (cm)}} \times 1000\); females’ pre-
dicted VC (liters) = $[21.78 - 0.101 \times \text{age}] \times \text{height (cm)}/1000$. For patients with scoliosis, arm span was used rather than height. Some questionably symptomatic patients, especially those using accessory breathing muscles and not having clear symptoms or other abnormal screening factors, underwent polysomnography (13%) or nocturnal oximetry and end-tidal CO$_2$ monitoring (33%). Sleep end-tidal CO$_2$ maximum $>50$ mm Hg, nocturnal SpO$_2$ decreases $<95\%$ at least four times per hour or 10 mins or more total during the night, and apnea/hypopnea index $>10$/hr on polysomnography were considered abnormal screening factors.

The VRI was determined by Meteor digital spirometer with a liquid crystal diode monitor (Cardio-Pulmonary Technologies Inc.), using custom-prepared software to analyze flow and volume signals on a Windows-based personal computer (FMV-660MC/W, A Fujitsu Corp., Tokyo, Japan). The computer selected the six most consistent consecutive Vt waveforms with the patient sitting at rest, and it averaged them for the Ti, Ttot, and Vt data.

Group 1 patients were asymptomatic and had no abnormal specific screening factors. Group 2 patients had one or more abnormal screening factors. Forty-two of 97 patients were clearly and 55 were questionably symptomatic for hypoventilation. Group 3 patients depended on ventilator use 8–20 hrs/day for symptomatic relief (Fig. 1). Group 4 patients required ventilatory assistance around the clock (Fig. 2).

The four respiratory impairment categories were correlated with VRI and VC in the sitting position, using Spearman correlation coefficients. The VC was transformed into natural logarithm because the standard deviations seemed to correlate with means, and residuals from the analysis of variance model were obviously skewed. The Tukey–Kramer post hoc adjustment for multiple comparisons was used to protect $\alpha = 0.05$ for statistical significance. Data on 25 historical normals from a previous study, age $33.9 \pm 8.5$ yrs, were also multiplied by their respiratory rates and were considered for comparison.

RESULTS

The VRI and VC of 25 historical normals (group 0) and our group 1–4 subjects are shown in Table 1 and 2. The overall analysis of variance $F$-tests and post hoc pairwise contrasts were significant ($P < 0.001$) for all intergroup pairwise comparisons for both VC and VRI. Thus, VC and VRI were both independent, significant predictors of group membership ($P < 0.001$, $P = 0.0016$, respectively). On the basis of Spearman correlation coefficients, the four respiratory impairment categories correlated significantly with VRI ($r_S < 0.05$, $P < 0.001$) and VC ($r_S = -0.55$, $P < 0.001$) in the sitting position.

The Medicare ventilator prescription criterion of VC $<50\%$ captured 82 of 97 (85%) group 2 patients but also 12 of $35$ (35%) group 1 members. Having a VRI index $\geq 1.2$ captured 89 of 97 (92%) of group 2 and 16 of 35 (46%) group 1 members. At VRI $\geq 1.3$, these figures were 87/97 (90%) and 11/35 (31%), respectively; at VRI $\geq 1.1$, 91/97 (94%) and 17/35 (49%), respectively; and at 0.9, 93/97 (96%) and 23/35 (66%), respectively. Sensitivity is more important than specificity because ventilator prescription indication parameters need to support ventilator use for patients who can benefit from it, whereas patients who do not benefit sufficiently to offset the inconvenience and discomfort of ventilator use are unlikely to use ventilators, irrespective of parameter values. Thus, a VRI of 1–1.2 or greater may be useful to justify initial ventilator prescription, whether by volume-limited or pressure-limited ventilators such as bilevel positive airway pressure devices.
VRI = 1.2 or VC ≤50% of predicted normal captured 92 of 97 (95%) of group 2 members. This included 18 patients with initially questionable symptoms who, after a trial of NIV, appreciated sufficient benefit on fatigue and other mild symptoms to go on using it.

Of the group 3 ventilator users, 91 were using sleep-only NIV, and 54 were using NIV into daytime hours up to 20 hrs/day. Twenty-one patients had VC greater than 50% in the sitting position but still required nocturnal NIV. For all group 3 patients, except the 13 with myotonic dystrophy, symptoms were relieved, and normal daytime end-tidal CO₂ and SpO₂ were maintained early on with nocturnal ventilator use. The myotonic dystrophy patients tended to use nocturnal NIV sporadically and rarely throughout sleep. The NMD patients who eventually required more than nocturnal-only NIV often spontaneously used it into daytime hours, usually via 15-mm angled mouth pieces (Fig. 2), until they required it around the clock (group 4). They often used oximetry as feedback to use diurnal NIV sufficiently to maintain adequate alveolar ventilation to maintain SpO₂ ≥95%.

Whereas all of the group 4 patients were essentially continuous NIV users, they had sufficient breathing autonomy to establish six consistent Vt for a 2-min period of ventilator-free breathing. Considering Figure 3 for group 4, for whom it could be argued that a back-up (daytime use) ventilator is warranted, 37 of the 42 were captured by the criterion of VC ≥1100 ml (88%), with 109 of 277 also meeting this criterion in groups 1 through 3 (39%) (specificity 100 – 39, or 61%). At VC ≤1000, these figures were 34/42 and 99/277 (39%), respectively; at VC ≤800 ml, they were 33/42 and 76/277 (27%), respectively; and at 1200 ml, they were 38/42 and 120/277 (43%), respectively. Considering that sensitivity is more important than specificity when considering the safety afforded by having a back-up ventilator for around-the-clock users, and that less severely affected (with higher VC and lower VRI) continuous ventilator users can survive longer breathing autonomously or using a manual resuscitator or glossohyparyngeal breathing in the event of ventilator failure than the more severely affected (lower VC and higher VRI) patients, it seems that a VC of 1100 ml (capturing 88% of group 4 membership) as opposed to a VC of 1000 (capturing 81% with slightly higher specificity) might be the more appropriate threshold to support prescription of a second ventilator. Similarly, a VC of 700 ml (point at which the sensitivity and specificity lines cross on Fig. 3) strongly supports prescription of a second ventilator. Likewise, by similar analysis of Figure 4, a VRI of 2.4 captures 34 of 42 (81%) group 4 members and 125 of 277 (45%) group 1–3 patients. At a VRI of 2.2, sensitivity is unchanged (36/42) and specificity decreases, with 145/277 meeting the criterion (57%). At VRI = 3.3, the point at which sensitivity transects specificity in Figure 4, 31/42 (74%) group 4 and only 63/277 (23%) group 1–3 patients meet the criterion. This level might be considered to strongly support prescription of a second ventilator. Having a VRI ≥2.4 or VC ≤1100 captured 39 of the 42 (93%) group 4 patients.

In addition to the group 4 patients, 13 others required continuous ventilatory support but could not breathe long enough for the computer to establish a VRI by analyzing six consistent breaths. These patients either could not complete the study or, in three cases, had VRI <2.0 because Vt values were unsustainably low for steady-state analysis.

**DISCUSSION**

Third-party payors demand justification for the prescription of both initial and secondary ventilators. Decisions about ventilator use have been largely based on the results of polysomnograms, pulmonary function testing, and arterial blood gases. However, daytime arterial blood gases may be normal despite symptomatic nocturnal hypoventilation, and 30% of patients hyperventilate from the pain of arterial puncture, so normal PaCO₂ may need to be corrected for pH for evidence of hypercapnia. Further, conventional pulmonary function testing, including forced expiratory flows and volumes, is designed for patients with lung and airway diseases, rather than muscle weakness and hypoventilation. The VC measured

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### Table 1: Spirometric and ventilator use data

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age mean (SD)</th>
<th>Mean vital capacity, ml</th>
<th>Percent vital capacity</th>
<th>Hvuse per day, hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>25</td>
<td>33.9 ± 8.5</td>
<td>3680.4 ± 860.5</td>
<td>106.6 ± 13.7</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>37.7 ± 17.5</td>
<td>2735.7 ± 1174.5</td>
<td>79.3 ± 17.9</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>31.5 ± 20.0</td>
<td>1499.3 ± 697.2</td>
<td>43.2 ± 12.1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>145</td>
<td>40.6 ± 19.2</td>
<td>1184.1 ± 797.7</td>
<td>38.1 ± 13.0</td>
<td>9.65 ± 4.3</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>35.2 ± 15.1</td>
<td>550.3 ± 547.8</td>
<td>15.8 ± 9.1</td>
<td>23.3 ± 1.1</td>
</tr>
</tbody>
</table>

Hvuse, home ventilator use in hours per day. * Historical controls.
with the patient supine is not part of routine pulmonary function testing, but it reflects diaphragm weakness better than the VC measured in the sitting position. In a recent study, supine VC <75% of predicted normal was 100% sensitive and specific for predicting an abnormally low Pdi. Patients can have VC levels that approach normal when sitting but that are less than 50% of normal, and these patients might have no ability to breathe when supine. The inaccuracy of considering VC alone, especially in the sitting position, to indicate ventilator use has already been reported. Accessory muscle use and abdominal paradox were also both significantly negatively associated with Pdi, but these signs are not quantitative indications for ventilatory assistance. Numeric parameters such as respiratory rate, rapid shallow breathing index, maximal inspiratory pressure, and PaCO₂ have been offered as indicators for nocturnal NIV, but they have been unreliable. Current Medicare guidelines for ventilator use mandate a VC ≥50% of predicted normal, yet there are patients with NMDs who have 10% or less of predicted normal VC who are eucapnic and who breathe symptomatically unaided, and there are others with >70% of predicted normal VC who required continuous ventilatory support.

Although polysomnography has become popular in the assessment of NMD patients for sleep-disordered breathing, polysomnograms are programmed to interpret all hypopneas and apneas as central or obstructive in nature rather than from inspiratory muscle impairment. This often results in inappropriate treatment with continuous positive airway pressure or low-span bilevel positive airway pressure, methods that maintain airway patency but give little or no assistance to inspiratory muscles. Further, many asymptomatic NMD patients fail to appreciate benefit and do not tolerate NIV despite polysomnographic abnormalities. Polysomnography is also expensive and inconvenient.

Meeting VRI or VC criteria better indicates extent of ventilator need by comparison with VC or VRI alone or with other measures. This requires only simple spirometry with specific software. Anyone with neuromuscular weakness and symptoms of alveolar hypoventilation should be offered a trial of NIV. However, a VC <50% or a VRI >1.2 supports the justification of a ventilator for nocturnal use. Patients whose benefit from nocturnal NIV more than offsets the inconvenience of using it are likely to continue use, regardless of whether the ventilator is pressure cycled (bilevel positive airway pressure) or volume cycled. Nasal or oral interfaces can be used. Once a patient requires ventilator use >20 hrs/day, a second ven-

**TABLE 2 Ventilator requirement index and other pulmonary data**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MP, cm H2O (Mean ± SD)</th>
<th>MP, cm H2O (Median)</th>
<th>RR, bpm (Mean ± SD)</th>
<th>RR, bpm (Median)</th>
<th>SpO₂ % (Mean ± SD)</th>
<th>SpO₂ % (Median)</th>
<th>ECO₂ (Mean ± SD)</th>
<th>ECO₂ (Median)</th>
<th>Ti/Ttot (Mean ± SD)</th>
<th>Ti/Ttot (Median)</th>
<th>VT/VC (Mean ± SD)</th>
<th>VT/VC (Median)</th>
<th>Mean VRI (Mean ± SD)</th>
<th>Mean VRI (Median)</th>
<th>VRI, ventilator requirement index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>-69 ± 100</td>
<td>-34.9 ± 28.5</td>
<td>15.6 ± 1.5</td>
<td>15.1 ± 5</td>
<td>96.6 ± 2.3</td>
<td>95.7 ± 1.3</td>
<td>377 ± 4.4</td>
<td>40.1 ± 6.4</td>
<td>22.5 ± 6.9</td>
<td>22.3 ± 6.3</td>
<td>26.6 ± 5.4</td>
<td>25.1 ± 4.3</td>
<td>0.42 ± 0.10</td>
<td>0.41 ± 0.08</td>
<td>33.7 ± 5.8</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>-34.9 ± 28.5</td>
<td>-20.3 ± 21.8</td>
<td>21.5 ± 5.7</td>
<td>21.3 ± 4.5</td>
<td>95.7 ± 2.3</td>
<td>94.7 ± 3.0</td>
<td>40.1 ± 6.4</td>
<td>41.3 ± 7.3</td>
<td>22.5 ± 6.9</td>
<td>22.6 ± 5.4</td>
<td>36.9 ± 4.1</td>
<td>36.4 ± 3.9</td>
<td>0.43 ± 0.15</td>
<td>0.43 ± 0.07</td>
<td>37.0 ± 5.7</td>
</tr>
<tr>
<td>3</td>
<td>145</td>
<td>-20.3 ± 21.8</td>
<td>-7.4 ± 7.10</td>
<td>25.5 ± 6.9</td>
<td>22.6 ± 7.10</td>
<td>94.6 ± 2.6</td>
<td>94.6 ± 2.6</td>
<td>41.3 ± 7.3</td>
<td>43.1 ± 7.3</td>
<td>22.6 ± 5.4</td>
<td>22.3 ± 5.4</td>
<td>36.9 ± 4.1</td>
<td>36.9 ± 3.9</td>
<td>0.43 ± 0.07</td>
<td>0.43 ± 0.07</td>
<td>37.0 ± 5.7</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>-7.4 ± 7.10</td>
<td>-4.0 ± 6.3</td>
<td>7.10 ± 3.4</td>
<td>7.10 ± 3.4</td>
<td>94.6 ± 2.6</td>
<td>94.6 ± 2.6</td>
<td>41.3 ± 7.3</td>
<td>43.1 ± 7.3</td>
<td>22.3 ± 5.4</td>
<td>22.3 ± 5.4</td>
<td>36.9 ± 4.1</td>
<td>36.9 ± 3.9</td>
<td>0.43 ± 0.07</td>
<td>0.43 ± 0.07</td>
<td>37.0 ± 5.7</td>
</tr>
</tbody>
</table>

VC, vital capacity; MIP, maximum inspiratory pressure; RR, respiratory rate; SpO₂, percent oxyhemoglobin saturation; ECO₂, end-tidal CO₂ in mm Hg; Ti/Ttot, inspiratory time divided by total breath time; VT/VC, tidal volume divided by VC; VRI, ventilator requirement index.
The ventilator should be prescribed and might be justified by having a VC <1100 ml or VRI >2.5.

A limitation of interpreting these outcomes is the large number of diagnoses and age ranges studied. It has been noted that with age, larger absolute values and percentages of predicted normal VC are needed for one to maintain normal PaCO₂ levels. Thus, young patients with diagnoses like spinal muscular atrophy type 2 or Duchenne muscular dystrophy might be expected to maintain more normal alveolar ventilation at lower VC levels than older patients with amyotrophic lateral sclerosis or spinal cord injury, for example. Nevertheless, satisfying VC or VRI criteria may facilitate ventilator prescription justification to third-party payors.

**REFERENCES**


Study 5

Expiratory Flow Maneuvers of Patients with Neuromuscular Diseases

John R. Bach, Miguel R. Gonçalves, Sylvia Páez, João Carlos Winck, Sandra Leitão, Paulo Abreu
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
Expiratory Flow Maneuvers in Patients with Neuromuscular Diseases

ABSTRACT


Objectives: To compare cough peak flows (CPF), peak expiratory flows (PEF), and potentially confounding flows obtained by lip and tongue propulsion (dart flows, DF) for normal subjects and for patients with neuromuscular disease/restrictive pulmonary syndrome and to correlate them with vital capacity and maximum insufflation capacity.

Design: A cross-sectional analytic study of 125 stable patients and 52 normal subjects in which CPF, PEF, and DF were measured by peak flow meter and vital capacity and maximum insufflation capacity by spirometer.

Results: In normal subjects and in patients, the DF significantly exceeded PEF and CPF (P < 0.001). For normal subjects, PEF and CPF were not significantly different. For patients with neuromuscular disease/restrictive pulmonary syndrome, the CPF significantly exceeded PEF (P < 0.05). No normal subjects but 14 patients had DF lower than CPF. Thirteen of these 14 had the ability to air stack (maximum insufflation capacity greater than vital capacity), indicating greater compromise of mouth and lip than of glottic muscles. For 14 of 88 patients, maximum insufflation capacity values did not exceed vital capacity, mostly because of inability to close the glottis (inability to air stack). Nonetheless, for 11 of these 14 patients, the DF were within a standard deviation of the whole patient group; thus, bulbar-innervated muscle dysfunction was not uniform. CPF and PEF correlated with vital capacity (r = 0.85 and 0.86, respectively), and with maximum insufflation capacity (r = 0.76 and 0.72, respectively).

Conclusions: Measurements of CPF, PEF, and DF are useful for assessing bulbar-innervated, inspiratory, and expiratory muscle function. Care must be taken to not confuse them.

Key Words: Amyotrophic Lateral Sclerosis, Duchenne Muscular Dystrophy, Neuromuscular Disease, Cough Peak Flows, Peak Expiratory Flows, Dart Flows, Vital Capacity, Maximum Insufflation Capacity, Respiratory Muscles, Glottic Muscles
Both peak expiratory flows (PEF) and cough peak flows (CPF) have been described as useful clinical variables of respiratory muscle function.1 “Dart flows” (DF) are generated by creating pressure behind the lips and tongue with the mouth closed. As the lips open and tongue releases the air, in a maneuver like spitting or projecting a dart through a narrow tube, these flows can also be measured by peak flow meter. These flows can be confused with PEF and CPF and cause the latter to be overestimated. They are largely a function of the ability to seal the lips and control the tongue and buccal muscles.

The main cause of morbidity and mortality in patients with neuromuscular disease/restrictive pulmonary syndrome (NMD) is respiratory muscle dysfunction and, in particular, cough dysfunction.2–4 Inspiratory, expiratory, and bulbar-innervated muscle are required for effective coughing.5,6

Normal precough inspiration is to 85–90% of total lung capacity.7 Thus, cough flows are diminished for patients who have decreased ability to inflate the lungs, especially when vital capacity (VC) is <1500 ml.8 After a deep breath, the glottis is closed by intrinsic laryngeal (bulbar-innervated) muscles. The expiratory muscles (abdominal and intercostals) then contract, resulting in intrapleural pressures of 200 cm H₂O.9 On full glottic opening with hypopharyngeal patency maintained by other bulbar-innervated musculature, there is an explosive decompression that normally generates flows of 300–1200 liters/min to expulse airway secretions.

In patients with NMD, weak inspiratory muscles can be assisted by providing deep lung insufflations or by the stacking of consecutively delivered volumes of air held with a closed glottis to approach a maximum insufflation capacity (MIC).10–12 Expiratory muscles can be manually assisted by providing thoracoabdominal thrusts. The combination of applying an abdominal thrust to a maximally inflated lung is an assisted cough.1,10 Unassisted cough flows depend on inspiratory, expiratory, and bulbar-innervated musculature. However, air stacking ability and, therefore, assisted cough flows depend only on glottic control or on bulbar-innervated muscle function alone. Thus, the greater the difference between the MIC and the VC and between assisted and unassisted CPF, the greater is bulbar-innervated muscle function by comparison with inspiratory muscle function. Patients who cannot close the glottis cannot air stack. They may “huff” but cannot cough. CPF better reflect the capacity to expulse debris from the airways (cough efficacy) than do PEFs. CPF not exceeding 160 liters/min are associated with extubation failure.13

There are no standard normal values for CPF or DF, but PEF range from 500 to 700 liters/min for men and from 380 to 500 liters/min for women, and from 150 to 840 liters/min for children and adolescents, with variations due to age, race, sex, and height.14,15 For patients with asthma, their diminution generally indicates bronchospasm.16 The purpose of this study was to compare the CPF, PEF, and DF, to see if they correlate with VC or MIC, and to consider their use in the evaluation of the respiratory muscles.

METHODS

A cross-sectional study was conducted on all NMD patients entering an outpatient clinic between August 2003 and May 2004. The charts of the patients were reviewed for anthropometric data (age, sex) and for diagnosis. All cooperative NMD patients whose VCs were <80% of predicted normal were studied. No one meeting these criteria was excluded. Normal subjects were recruited, informed about the purpose of the study, and signed consent forms that were approved by the hospitals’ ethics committee. The patients and controls received a written description of the maneuvers and had a 3-min training period before the measurements were taken.

The following variables were measured: PEF according to the recommendations of the American Thoracic Society,17 CPF, and DF, all via an Access Peak Flow Meter (model 710, Health Scan Products, Cedar Grove, NJ), and VC (sitting and supine) and MIC via a spirometer (Mark 14, Ferraris Development and Engineering, London, UK). All of these measurements were done by a specifically trained respiratory therapist who was unaware of the study and recorded the highest value of four or more correctly performed efforts. The peak flow meter measured flows from 60 to 880 liters/min. Flows of <60 liters/min were recorded as 0 and flows of >880 liters/min were recorded as 881 liters/min. No patients had been hospitalized during the previous 30 days.

Statistical Analysis

Data for the categorical variables are expressed as number and percentage of patients. Data for the continuous variables are reported as median with dispersion of minimum, maximum, and interquartile range and range. The use of median values rather than mean values eliminated the effect of imprecisely measured ceiling and floor data.

Normally distributed continuous variables were compared using the unpaired and paired Student’s t test, as appropriate, and nonparametric continuous variables using Wilcoxon’s signed-
RESULTS

There were 125 patients with a mean age of 41 ± 21 (range, 7–82) yrs; 64% were men (n = 80) and 100 were >18 yrs old (80%). The patients’ diagnoses are listed in Table 1. The 52 normal subjects were 28.6 ± 9.8 (range, 19–58) yrs of age, 65.4 ± 11.4 (range, 49–100) kg, and 165.8 ± 8.4 (range, 152–183) cm tall. CPF, PEF, and DF data are presented in Table 2. Two patients were unable to attain any measurable flows, two had measurable CPF and PEF but not DF, nine had measurable CPF and DF but no measurable PEF, six had measurable DF but not CPF or PEF, and one patient had measurable PEF and DF but not CPF. The DF were significantly greater than CPF and PEF (P < 0.001) for both the normal subjects and the patient group. The CPF and PEF were not significantly different for the normal subjects. For the patient group, assuming unmeasurable flows to be 0 liters/min, the CPF were significantly greater than PEF (P < 0.01) (Table 2). The differences remained significant (P < 0.01) when considering adults only but not children only. The patients’ CPF remained significantly greater than PEF (P < 0.05) when the eight patients with unmeasurable CPF and PEF were eliminated and when PEF were estimated to be 59 liters/min for the nine patients with measurable CPF but not measurable PEF.

The flow data for the six patients (5.5%) with unmeasurable PEF and CPF but measurable DF are in Table 3. Thus, these patients had relatively well-preserved bulbar-innervated musculature, despite severe inspiratory and expiratory muscle weakness. This was consistent with their diagnoses of postpoliomyelitis and congenital muscular dystrophy, conditions that, relatively speaking, spare bulbar musculature.

There were two patients with unmeasurable DF who had severe bulbar amyotrophic lateral sclerosis yet had mean CPF of 205 liters/min. In fact, the CPF exceeded the DF for 12 patients: two children with non-Duchenne muscular dystrophy and ten adults, of whom seven had amyotrophic lateral sclerosis, two had fascioscapulohumeral dystrophy, and one had myotonic dystrophy. Only one was unable to air stack. These 12 patients had a greater capacity to air stack, as seen by a greater MIC–VC difference, than in the general group (Table 4), suggesting less compromise of glottic muscles than of the cheeks, lips, and tongue. The 16 patients whose PEF exceeded CPF and, thus, whose expiratory muscles were relatively preserved by comparison with bulbar-innervated muscles are considered in Table 5. The PEF of 11 normal subjects (21.1%) also exceeded their CPF.

The MIC was measured for 88 patients. For 14 of the 88, the MIC did not exceed the VC because of inability to firmly close the glottis or prevent air leakage out of the nose or mouth during the air-stacking process; their mean VC was 1518.6 ± 764.8 ml, significantly lower than the mean VC of the whole population (2000 ml, P < 0.03), suggesting more advanced disease. Eight of these 14 had CPF equal to or lower than PEF, confirming more severe compromise of facial and glottic musculature. In only three of these 14 cases were the DF lower than or equal to CPF, indicating that bulbar musculature was variably involved with relative sparing of the tongue and lips.

Good correlation was found between CPF and MIC (r = 0.76) (Fig. 1) and between PEF and MIC (r = 0.72) (Fig. 2). Correlation was also found between MIC and DF (r = 0.73). For the remaining 37 patients, MIC was not measured because the VC was too close to the normal range (3155 ± 1091.7 ml in 27 adults and 2861 ± 997.9 ml for the ten children) and bulbar musculature was clinically intact. There was also a direct correlation between CPF and PEF with VC (r = 0.85 and 0.86, respectively) and with MIC (r = 0.76 and 0.72, respec-

### TABLE 1 Diagnosis of neuromuscular patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>41</td>
<td>32.8</td>
</tr>
<tr>
<td>Duchenne–Becker muscular dystrophy</td>
<td>27</td>
<td>21.6</td>
</tr>
<tr>
<td>Other muscular dystrophies</td>
<td>18</td>
<td>14.4</td>
</tr>
<tr>
<td>Postpoliomyelitis</td>
<td>12</td>
<td>9.6</td>
</tr>
<tr>
<td>Myopathies (nonmuscular dystrophy)</td>
<td>8</td>
<td>6.4</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>6</td>
<td>4.8</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>Neuropathies</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Obesity hypoventilation syndrome</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>100</td>
</tr>
</tbody>
</table>

Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

February 2006

Expiratory Flow Maneuvers

Miguel Ramalho do Souto Gonçalves

183
tively) for the entire patient group (Fig. 3). This is not surprising because CPF and PEF are dependent on the ability to take a deep breath. DF also correlated with VC ($r_{p} = 0.79$), indicating relative preservation of tongue and lips in early disease.

**DISCUSSION**

Unlike in a previous report by Suarez et al.$^{18}$, although CPF were greater than PEF for normal subjects, we did not find the difference to be statistically significant. However, our patient population may have been too small to observe a significant difference.$^{18}$ As Suarez et al.$^{18}$ reported for patients with Duchenne muscular dystrophy, we did observe significantly greater CPF than PEF for patients with NMD.

The three flow maneuvers we studied are similar in that they are expiratory flows measured at the mouth using a peak flow meter. However, each method requires different respiratory muscle group combinations. With glottic closure, the greater transpulmonary pressures created by coughing rather than by PEF maneuvers resulted in greater flows measured at the mouth for 88.2% of patients and 78.9% of normal subjects. However, cough efficacy is dependent on the peak flow velocity, which is greater as airways narrow during

| TABLE 2 | Expiratory maneuvers for normal subjects and patients with neuromuscular diseases |
| --- | --- | --- | --- |
| Group | Statistics | CPF | PEF | DF |
| Normal patients | Median, liters/min | 455 | 445 | 881 |
| | Minimum, liters/min | 290 | 320 | 370 |
| | Maximum, liters/min | 880 | 720 | 881 |
| | Interquartile range, liters/min | 225 | 160 | 148 |
| | Range, liters/min | 590 | 400 | 510 |
| | Measurement above reference range of >880 liters/min, n (%)$^a$ | 0 | 0 | 34 (65.4) |
| | Measurement below reference range of <60 liters/min, n (%)$^b$ | 0 | 0 | 0 |
| Patients | Median, liters/min | 250 | 220 | 335 |
| | Minimum, liters/min | 0 | 0 | 0 |
| | Maximum, liters/min | 710 | 635 | 881 |
| | Interquartile range, liters/min | 210 | 188 | 270 |
| | Range, liters/min | 650 | 575 | 820 |
| | Measurement above reference range of >880 liters/min, n (%)$^a$ | 0 | 0 | 5 (4.0) |
| | Measurement below reference range of <60 liters/min, n (%)$^b$ | 9 (7.3) | 17 (13.5) | 5 (4.0) |
| | ≥18 yrs of age (n = 100), mean ± SD | 280.1 ± 167.6 | 225.6 ± 159.9 | 395 ± 260.3 |
| | <18 yrs of age (n = 25), mean ± SD | 248.4 ± 108 | 234.6 ± 98.5 | 332.8 ± 158.7 |

CPF, cough peak flows; PEF, peak expiratory flows; DF, dart flows.

$^a$ Flows of >880 liters/min were recorded as 881 liters/min.

$^b$ Flows of <60 liters/min were recorded as 0 liters/min.

| TABLE 3 | Patients with unmeasurable cough and expiratory flows vs. group as a whole |
| --- | --- | --- | --- |
| Patients with Unmeasurable CPF and PEF (n = 6) | All 125 Patients | P |
| Age, yrs | 29.5 ± 14.6 | 41 ± 21 | 0.06 |
| DF, liters/min | 128.3 ± 50.9 | 382.6 ± 244.1 | $<0.01$ |
| VC, ml | 358.3 ± 115.5 | 2000.0 ± 1245.6 | $<0.01$ |

CPF, cough peak flow; PEF, peak expiratory flow; DF, dart flows; VC, vital capacity. Data (except for significance) provided as mean ± standard deviation.
coughing, making coughing more effective at expulsing airway secretions than huffing, even though PEF and CPF may be comparable when measured at the mouth.\(^8\) The reduction of the cross-sectional area of the airways during coughing is due to smooth muscle constriction mediated by a vagal reflex (presumably preserved in these diseases) and due to dynamic compression of the airways generated by the expiratory (transpulmonary) pressure.\(^9,20\) The reduction in the cross-sectional area of the airways increases five-fold the velocity of gas and 25-fold the kinetic energy of the airstream. This explains why the subgroup of 16 patients (12.8%) with CPF lower than PEF nevertheless coughed rather than huffed to expel secretions. Effective CPF and PEF share the need for deep lung volumes, explaining their good correlation with VC and MIC.

The correlation of CPF with MIC or MIC–VC difference is explained by their dependence on bulbar-innervated muscle (glottic) function. CPF are also dependent on hypopharyngeal patency being maintained by bulbar-innervated hypopharyngeal musculature. DF, on the other hand, are independent of laryngeal and hypopharyngeal dysfunction and usually exceed CPF and PEF. However, DF do not emanate from the airways and require little or no inspiratory or expiratory muscle effort. We have several patients who operate sip-and-puff motorized wheelchairs and generate high DF, despite

### TABLE 4 Patients with cough peak flows (CPF) greater than dart flows (DF)

<table>
<thead>
<tr>
<th></th>
<th>CPF &gt; DF (n =12)</th>
<th>All Group (n = 125)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>1220.8 ± 611.9</td>
<td>2000.0 ± 1245.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MIC</td>
<td>1974.0 ± 643.3</td>
<td>2179.8 ± 1097.9</td>
<td>NS</td>
</tr>
<tr>
<td>MIC – VC</td>
<td>822.0 ± 580.3</td>
<td>632.1 ± 474.7</td>
<td>NS</td>
</tr>
<tr>
<td>CPF</td>
<td>179.2 ± 49</td>
<td>273.8 ± 157.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PEF</td>
<td>113.8 ± 55.8</td>
<td>227.4 ± 149.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DF</td>
<td>107.9 ± 75.1</td>
<td>382.6 ± 244.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

VC, vital capacity; MIC, maximum insufflation capacity; NS, not significant; PEF, peak expiratory flows. Data (except for significance) provided as mean ± standard deviation.

### TABLE 5 Patients with peak expiratory flows (PEF) greater than cough peak flows (CPF)

<table>
<thead>
<tr>
<th></th>
<th>PEF &gt; CPF (n =16)</th>
<th>Entire Group (n = 125)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>2042.3 ± 899.8</td>
<td>2000 ± 1245.6</td>
<td>NS</td>
</tr>
<tr>
<td>MIC</td>
<td>2324.2 ± 943.1</td>
<td>2179.8 ± 1097.9</td>
<td>NS</td>
</tr>
<tr>
<td>MIC – VC</td>
<td>588.5 ± 580.5</td>
<td>632.1 ± 474.7</td>
<td>NS</td>
</tr>
<tr>
<td>CPF</td>
<td>213.4 ± 103.2</td>
<td>273.8 ± 157.6</td>
<td>0.04</td>
</tr>
<tr>
<td>PEF</td>
<td>257.8 ± 92.0</td>
<td>227.4 ± 149.4</td>
<td>NS</td>
</tr>
<tr>
<td>DF</td>
<td>387.8 ± 168.4</td>
<td>382.6 ± 244.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

VC, vital capacity; NS, not significant; MIC, maximum insufflation capacity; DF, dart flow. Values (except for significance) provided as mean ± standard deviation.
having no measurable VC. DF, although also dependent on bulbar-innervated muscles but not glottic function, do not seem to reflect risk of respiratory complications. Inability to measure DF, however, is associated with ineffective saliva control and drooling. Thus, different patterns of bulbar-innervated muscle dysfunction occur. Figures 1 and 2 demonstrate that DF tend to correlate linearly with height and weight. In this way, DF are similar to PEF because these have also been reported to correlate with height and weight.\textsuperscript{21,22} Wohlgemuth et al.\textsuperscript{21} and Holcroft et al.\textsuperscript{22} also pointed out the need to caution their subjects from spitting during PEF measurements.

Although all of the flow maneuvers are dependent on effort and motivation, we do not think this was a confounding factor in our study because the three measures were obtained in the same visit, in varying order, by the same examiner, and only the maximum value of many attempts was recorded.

Measurement “ceiling” and “floor” artifacts are common in empirical studies. There are elaborate statistical procedures that can be employed to estimate the range of plausible effects of the measurement limitation on actual P values. However, in this study, simpler and more direct logic suffices. This is because DF values exceeded 880 liters/min for 65% of normal subjects but for only 4% of patients and because DF values were significantly greater for normal subjects than for patients even when analyzing the data using ceiling DF of 881 liters/min when the actual values had to be greater than this figure. Likewise, for both patients and normal subjects, DF were significantly greater than PEF and CPF even when a ceiling value of 881 liters/min was used. The P values, already <0.001, were even more significant when the analyses were repeated using greater values for DF. Thus, the restriction of measurement range produced a conservative bias in the test of significance of DF group differences.

In summary, assisted and unassisted CPF, PEF, and DF are useful measures of bulbar-innervated and respiratory muscle function for patients with NMD,\textsuperscript{4} permitting greater knowledge of the pattern of respiratory muscle compromise. DF, CPF, and MIC correlate with bulbar-innervated muscle function. It is important to pay special attention to the technique of each flow measurement because DF can be mistaken for CPF or PEF and respiratory risk can be underestimated. The techniques are simple, and the peak flow meter is inexpensive and widely available. Further study is warranted to determine standard values of PCF and DF by age, height, and weight. Peak flow meters with greater range need to be developed to more accurately measure high flows. Effective interventions to assist inspiratory and expiratory muscle function and the accurate characterization of risk of respiratory complications depend on accurate assessment of expiratory flow maneuvers.\textsuperscript{23–25}

**ACKNOWLEDGMENT**

We thank Dr. Luís Filipe Azevedo of the Department of Biostatistics and Medical Informatics, Oporto Medical School, University of Porto, for assistance in the data analyses.

**REFERENCES**

Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves
Study 6

*Lung Insufflation Capacity in Neuromuscular Diseases*

John R. Bach Kedar Mahajan Bethany Lipa, Lou Saporito, Miguel Goncalves, Eugene Komaroff,
Lung Insufflation Capacity in Neuromuscular Disease

ABSTRACT


Objective: To compare maximal passive lung insufflation capacity (LIC) with lung inflation by air stacking (to maximum insufflation capacity [MIC]) and with vital capacity (VC); to explore relationships between these variables that correlate with glottic function and cough peak flows (CPF); to demonstrate the effect of routine inflation therapy on LIC and MIC; and to determine the relative importance of lung inflation therapy as a function of disease severity.

Design: Case series of 282 consecutive neuromuscular disease (NMD) clinic patients 7 yrs and older with VC <70% of the predicted normal value. All cooperative patients meeting these criteria were prescribed thrice-daily air stacking and/or maximal passive lung insufflation to pressures of 40–80 cm H₂O, and they underwent measurements of VC, MIC, LIC, and unassisted and assisted CPF on every visit.

Results: Means ± standard deviations for VC, MIC, and LIC were 1131 ± 744, 1712 ± 926, and 2069 ± 867 ml, respectively, and, for unassisted and assisted CPF, they were 2.5 ± 2.0 and 4.3 ± 2.2 liters/sec, respectively, with all differences statistically significant (P < 0.001). MIC minus VC correlated inversely with LIC minus MIC (P = 0.01) and, therefore, with glottic function. Both MIC and LIC increased with practice (P < 0.001). Increases in LIC but not MIC over VC were greatest for patients with the lowest VC (P < 0.05). There were no complications of lung mobilization therapy.

Conclusions: Passive lung insufflation can distend the lungs of patients with NMD significantly greater than air stacking, particularly when glottic and bulb-innervated muscle dysfunction is severe. LIC, MIC, and VC measurements permit quantifiable assessment of glottic integrity and, therefore, bulb-innervated muscle function for patients with NMD. The patients who benefit the most from insufflation therapy are those who have the lowest VC.

Key Words: Neuromuscular Disease, Lung Insufflation Capacity, Pulmonary Compliance, Cough Flows, Air Stacking
Respiratory failure for patients with pediatric neuromuscular disease (NMD) is often caused by ineffective coughing during otherwise benign chest infections.\textsuperscript{1–3} Whereas a normal tidal volume can be 500 ml, a normal cough volume is 2.3 ± 0.5 liters.\textsuperscript{4} Indeed, the lower the VC, the poorer are cough peak flows (CPF) independently of expiratory (thoracoabdominal) muscle strength.\textsuperscript{5}

Lung expansion to optimize lung recoil pressure and increase CPF can be achieved by maximally “air stacking” consecutively delivered volumes of air held with a closed glottis. The maximum volume that can be held in this manner is defined as the maximum insufflation capacity (MIC).\textsuperscript{6} The MIC can exceed predicted inspiratory capacity (IC) in people with intact glottic function,\textsuperscript{7–9} but it only approaches predicted IC in patients with moderate to severe glottic dysfunction.\textsuperscript{6} With complete loss of glottic closure, MIC no longer exceeds VC; the NMD patient can no longer air stack or cough, and the glottis, and many, if not all, bulbar-innervated muscles, are extremely impaired. In this case, lung insufflation can only be provided by bypassing glottic function. This can be done by using a manual resuscitator with a closed expiratory port mimicking glottic closure, or by using a CoughAssist or volume-cycled ventilator at delivered volumes/pressures that approach predicted IC.\textsuperscript{6} The maximum passive lung insufflation volume achieved in this manner is defined as the lung insufflation capacity (LIC).

The goal of conventional prescriptions for “range-of-motion” mobilization of extremity articulations is to slow the development of musculoskeletal contractures for patients with limb muscle weakness. However, the prevention of chest wall contractures and lung restriction has only recently been addressed. In 2006, Lechtzin et al.\textsuperscript{10} reported the use of short-term noninvasive intermittent positive pressure ventilation (IPPV) to increase pulmonary compliance for patients with amyotrophic lateral sclerosis (ALS). In 2000, we demonstrated that lung volumes could be increased significantly over VC by air stacking to approach MIC for patients with NMD.\textsuperscript{6} This resulted in significantly increased (assisted) CPF that can decrease the risk of pneumonia.\textsuperscript{11,12} For patients such as those with advanced bulbar ALS whose MIC equals VC, assisted CPF cannot be increased by air stacking, and prognosis is poor.\textsuperscript{13}

The purpose of this work was to explore the following hypotheses: (1) lung volumes will be significantly greater by passive insufflation than by air stacking, especially in patients with severe bulbar-innervated muscle dysfunction, and both LIC and MIC will significantly exceed VC and increase CPF; (2) LIC-MIC will correlate inversely with MIC-VC and, therefore, correlate inversely with glottic integrity; (3) LIC and MIC can increase with practice; and (4) the greatest increases in MIC and LIC will be for the most severely affected patients, that is, with the lowest VC.

METHODS

The institutional review board approved this study. In 1979, we began to routinely prescribe air stacking and/or maximal (passive) lung insufflation at pressures of 40 cm H\textsubscript{2}O or more, three times daily, for all patients with VC less than 70–80% of normal. Beginning in 2005, we routinely measured VC, MIC, and LIC in all 290 consecutive patients 7 yrs and older whose VC were less than 70%. Exclusion criteria were inability to cooperate attributable to severe cognitive impairment, medical instability, and primarily lung/airways rather than ventilatory pump insufficiency. Two with DMD, one with congenital myotonic dystrophy, and two others with poorly characterized NMD could not cooperate. Three patients were acutely ill and hospitalized. No NMD patients had signs of lung/airways disease sufficient to warrant evaluation for concomitant chronic obstructive pulmonary disease or reversible bronchospasm. All lung volumes were measured by Wright spirometer model Mark 14 (Ferraris Ltd., London, England) and recorded as the greatest observed value in five or more attempts. The MIC was obtained by the patient air stacking volumes delivered via an oronasal interface from a manual resuscitator with a directed expiratory port and with either no pressure-limitation device or with the pressure release value deactivated, or obtained by air stacking via a volume-cycled mechanical ventilator for patients using daytime noninvasive ventilation. Once no more air could be held with a closed glottis, the patient exhaled into the spirometer to residual volume (MIC).\textsuperscript{7}

Cough peak flows, both unassisted and assisted, were measured by Access Peak Flow Meter (Health Scan Products Inc., Cedar Grove, NJ). The largest value of five or more attempts was recorded. Cough flows were assisted by air stacking to approach MIC and an expiratory-timed abdominal thrust.

The LIC was obtained by using the same manual resuscitator connected to a spirometer. The spirometer’s reset button was held and the expiratory port of the spirometer was occluded during insufflation. After insufflation to maximal observed lung (chest wall) expansion with maximum tolerable resistance to further insufflation, the spirometer’s reset button and the expiratory port of the spirometer were simultaneously released, and the patient exhaled to residual volume into the spirometer via a tightly held anesthesia (oronasal) inter-
The maximum insufflation pressure tolerated by the patient, and the corresponding resistance felt by the therapist, were then reproduced by insufflating the patient, using the CoughAssist. This was done to observe the pressures required for full insufflations to prescribe insufflation therapy three times daily at home. Thus, glottic closure was unnecessary for the measurement of LIC.

Correlation analysis was done between LIC-MIC and MIC-VC using Spearman correlation coefficients ($r_S$) with $P = 0.05$ as the level of statistical significance (alpha). The same Spearman correlation analyses were done for ALS and DMD patient subgroups. A categorical variable from VC was based on quartiles, and the correlations were run within each quartile. Wilcoxon signed ranks tests were used to determine possible significance in the differences between the means of the lung volume variables and also the CPF variables. The differences in the means of the lung volume variables (MIC – MIC, LIC – VC, and MIC – VC) by VC (sitting) levels were evaluated by analysis of variance.

**RESULTS**

The 290 patients had the following diagnoses: ALS/motor neuron disease 81, DMD 54, non-DMD muscular dystrophy 38, other myopathies 23, post-polio myelitis 26, spinal muscular atrophy 32, and other conditions 36. Two hundred eighty-two NMD patients met the criteria. Seventy-eight of these had multiple visits and had been prescribed maximal lung expansion therapy three times daily, with 10–15 cycles of air stacking/passive insufflations for a 6-mo to 24-yr period, before the most recent clinic visit, during which data points were taken for this study. Among the patients, 103, 116, and 69 were using continuous NIV, nocturnal-only NIV, or no aid, respectively.

The patient population had mean ± standard deviation values of 1131 ± 744 ml for VC, 1712 ± 926 ml for MIC (significantly greater than VC, $P = 0.001$), and 2069 ± 867 ml for (passive) LIC (significantly greater than MIC and VC at $P < 0.001$) at the most recent evaluation. For 46 of the 78 patients with two or more measurements who were prescribed daily air stacking/lung insufflation, the MIC and LIC increased 462 ± 260 and 365 ± 289 ml, respectively, despite a decrease in VC of 209 ± 97 ml. The increase in lung volumes by air stacking to approach MIC combined with abdominal thrust resulted in CPF of $4.3 \pm 1.7$ liters/sec by comparison with unassisted CPF of $2.5 \pm 2.0$ liters/sec ($P < 0.001$). Patients’ diagnoses, VC, MIC, LIC, CPF, and extent of ventilator use are noted in Table 1. Although they could not be measured, “cough” flows

---

**FIGURE 1** Air is delivered via the manual resuscitator (bottom) to full lung expansion, with the exhalation port of the spirometer manually covered so that the insufflated air does not exit the patient (or enter the spirometer) until its exhalation port is uncovered at maximally tolerated lung inflation (top).
### Table 1 Patient diagnoses

<table>
<thead>
<tr>
<th>Major Diagnoses</th>
<th>No. of Patients</th>
<th>Mean Age</th>
<th>Mean VCsit</th>
<th>Mean MIC</th>
<th>Mean LIC</th>
<th>Mean CPF</th>
<th>Mean ACPF</th>
<th>&gt;8 hrs</th>
<th>8 hrs</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMD</td>
<td>53</td>
<td>26 (14-44)</td>
<td>622 (1-2710)</td>
<td>595</td>
<td>1252 (220-3280)</td>
<td>670</td>
<td>1696 (840-3400)</td>
<td>548</td>
<td>1.58 (0.1-5.7)</td>
<td>1.7</td>
</tr>
<tr>
<td>Myotonic</td>
<td>6</td>
<td>47 (36-53)</td>
<td>2038 (1190-3580)</td>
<td>864</td>
<td>2280 (1190-3720)</td>
<td>874</td>
<td>2447 (1380-3850)</td>
<td>851</td>
<td>4.03 (2.7-4.7)</td>
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</tr>
<tr>
<td>Other myopathies</td>
<td>55</td>
<td>39 (11-85)</td>
<td>1195 (270-2770)</td>
<td>642</td>
<td>1741 (420-3360)</td>
<td>825</td>
<td>2026 (500-3600)</td>
<td>791</td>
<td>3.11 (0.1-7.5)</td>
<td>1.8</td>
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<tr>
<td>SMA</td>
<td>31</td>
<td>19 (7-56)</td>
<td>86 (30-2160)</td>
<td>554</td>
<td>1254 (30-2780)</td>
<td>748</td>
<td>1544 (320-3100)</td>
<td>670</td>
<td>1.76 (0.1-4.6)</td>
<td>1.5</td>
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<tr>
<td>ALS</td>
<td>76</td>
<td>57 (27-82)</td>
<td>1351 (20-3480)</td>
<td>789</td>
<td>1939 (150-5100)</td>
<td>1080</td>
<td>2409 (780-5400)</td>
<td>898</td>
<td>2.55 (0.1-7.5)</td>
<td>2.1</td>
</tr>
<tr>
<td>Post-polio</td>
<td>25</td>
<td>64 (49-85)</td>
<td>1026 (0-2400)</td>
<td>574</td>
<td>1877 (900-2950)</td>
<td>603</td>
<td>2168 (1220-3200)</td>
<td>596</td>
<td>3.00 (0.1-8.2)</td>
<td>2.2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>36</td>
<td>44 (16-58)</td>
<td>1354 (250-1760)</td>
<td>700</td>
<td>1984 (380-3800)</td>
<td>984</td>
<td>2229 (450-3850)</td>
<td>985</td>
<td>3.05 (0.1-7.5)</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>282</td>
<td>42 (7-85)</td>
<td>1131 (0-3580)</td>
<td>744</td>
<td>1712 (30-5100)</td>
<td>926</td>
<td>2069 (320-5400)</td>
<td>867</td>
<td>2.52 (0.1-9.7)</td>
<td>2.0</td>
</tr>
</tbody>
</table>

VC, vital capacity; MIC, maximum insufflation capacity; LIC, lung insufflation capacity; CPF, cough peak flows; ACPF, assisted CPF; ALS, amyotrophic lateral sclerosis.

### DISCUSSION

This work describes a simple technique for providing deep inspirations or resistive exercise whenever lung volumes or achieved with any insufflation. For the 282 patients, the Spearman correlation coefficient revealed a strong negative association between VC (sitting) and the LIC obtained for the 15 patients, with the LIC not exceeding the VC in any patient. The LIC did not significantly trend in any patient with VC (sitting), with marginal statistical significance (r = 0.048). For the 282 patients, the Spearman correlation coefficient revealed a strong negative association between VC (sitting) and the LIC obtained for the 15 patients, with the LIC not exceeding the VC in any patient. The LIC did not significantly trend in any patient with VC (sitting), with marginal statistical significance (r = 0.048).
Inability to air stack no longer means that patients cannot simply and inexpensively expand their lungs beyond IC.

This study demonstrates that like MIC minus VC and assisted minus unassisted CPF, LIC too, is an objective, quantifiable, reproducible measure that (inversely) correlates with glottic integrity. Glottic function is the most important aspect of bulbar-innervated muscle function for NMD patients because it is most important for airway protection and cough effectiveness and, therefore, permits the use of NIV to avoid otherwise inevitable respiratory failure leading to death or tracheostomy with decreased quality of life. In fact, in a recent study, all decanulated/extubated patients with sufficient glottic function for (assisted) CPF greater than or equal to 160 liters/min were successfully extubated, whereas those with less than 160 liters/min failed extubation within 48 hrs. Previously reported correlates of bulbar-innervated muscle function have been based on subjective-only assessments of speech and swallowing.

Some patients were hypercapnic on presentation and had lungs stiff to the extent that using a manual resuscitator to increase tidal volumes to normalize CO₂ failed to do so and resulted in high airway pressures and chest discomfort. With regular lung mobilization therapy and nocturnal NIV, however, five such patients became able to renormalize CO₂ when breathing autonomously without chest discomfort. This is consistent with previous studies in which passive lung insufflation volumes were greatly diminished for patients who were ventilated at constant pressures/volumes without regular deep insufflations. Patients supported by NIV at large delivered volumes (1100–1500 ml) physiologically vary tidal volumes, can air stack to deep lung volumes as a function of their bulbar-innervated muscle integrity, and can better retain lung distensibility. Thus, if pressure-cycled ventilators such as “BiPAP” units (with which air stacking is impossible) are used for nocturnal NIV, patients with diminished VC should be equipped for air stacking/maximal insufflations. One DMD patient who had been using continuous tracheostomy ventilation at 250 ml delivered volumes for 9 yrs, had PaCO₂ 76 cm H₂O, and could not tolerate a 100-ml volume increase without chest pain. By contrast, our 53 DMD patients who practice daily insufflation, mean age 26 ± 7 yrs, tolerated delivered volumes that exceeded VC by 1074 ± 406 ml. Eight of these patients with VC less than 200 ml (mean 101 ml) have LIC values of 874 ± 548 ml and LIC values of 1414 ± 764 ml.

In conclusion, regular lung insufflation, either by air stacking (to approach MIC) or by passive lung insufflation (to approach LIC), is indicated for all NMD patients with diminishing VC. Because the goal is to approach the predicted IC, passive insufflation is used when the patient obtains a deeper volume in this manner than by air stacking (i.e., when bulbar musculature is very weak). It is often beneficial to prescribe both methods.

REFERENCES
Study 7

Indications and Compliance of Home Mechanical Insufflation-Exsufflation in Patients with Neuromuscular Diseases

João Bento, Miguel Gonçalves, Nuno Silva, Tiago Pinto Anabela Marinho João Carlos Winck
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves
Indications and Compliance of Home Mechanical Insufflation-Exsufflation in Patients with Neuromuscular Diseases

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ABSTRACT

Introduction: Neuromuscular disease (NMD) patients frequently have impaired cough. Mechanical insufflation-exsufflation (MI-E) has proven efficacy in improving airway clearance, however data related to its long-term home use is lacking. The purpose of this study was to describe indications, safety and compliance of home MI-E in NMD patients.

Methods: Four years observational analysis of 21 NMD patients on home MI-E. Diagnosis included bulbar and non-bulbar Amyotrophic Lateral Sclerosis (ALS) and other NMD. Median age was 58 years. Only cooperative patients with unassisted baseline Peak Cough Flow (PCF) < 270 L/min were included. All patients were under continuous mechanical ventilation (6 by tracheostomy). Pulmonary function before initiation of MI-E (median): FVC = 0.81 L, MIP = 28 cmH₂O, MEP = 22 cmH₂O and PCF = 60 L/min. MI-E was performed by previously trained non-professional caregivers, with an on-call support of a trained health care professional. Patients had pulse oximetry monitoring and applied MI-E whenever SpO₂ < 95%.

Results: Ten patients (9 ALS) used MI-E daily. Eleven patients used MI-E intermittently, during exacerbations, and in 8 patients early application of MI-E (guided by oximetry feed-back) avoided hospitalization. All tracheostomized patients used MI-E daily and more times a day than patients under NIV. Four patients (3 bulbar ALS), were hospitalized due to secretion encumbrance. MI-E was well-tolerated and there were no complications. In general, caregivers considered MI-E effective. During this period, 4 patients died, related to disease progression.

Conclusions: Home MI-E is well tolerated, effective and safe if used by well trained caregivers. MI-E should be considered as a complement to mechanical ventilation.

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Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves

Introduction

Patients with neuromuscular diseases (NMD) frequently have weak respiratory muscles and a deteriorated cough mechanism. Effective coughing depends on the capacity of the inspiratory muscles to achieve an inspiration of about 80% of total pulmonary capacity, followed by closure of the glottis and a pause with an increase in pulmonary volume. After the contraction of the expiratory muscles, intrathoracic pressure increases and, when the glottis opens, air is expelled and secretions are propelled to the central airways. Therefore, deterioration of the cough reflex in patients with NMD is related to weakness of the respiratory muscles, bulbar dysfunction that causes disability to control the glottis or even a deformity of the chest wall due to scoliosis. Deterioration of the cough reflex causes insufficient airway clearance, pneumonia, atelectasis, and respiratory failure related to the accumulation of secretions. Based on basal function, a peak cough flow (PCF) < 160 l/min has been proposed as an indication of an ineffectual cough. However, even a basal PCF < 270 l/min has been associated with pulmonary complications, since, during acute disease, there are additional reductions of the force of the respiratory muscles with an even greater reduction of PCF. As a result, management of airway secretions, especially during intercurrent airway infections, is a significant problem in patients with NMD and is the main cause of morbidity, prolonged hospitalisation, intensive care admissions and mortality. The techniques to improve airway clearance can reduce complications related to the accumulation of secretions and hospitalisation rates to a minimum. However, in patients with chest wall deformity, physiotherapy and manually assisted expectoration techniques can be ineffectual. These techniques are also time-consuming and require an appropriately trained carer.

Mechanical Insufflation-exsufflation (MIE) is a mechanically assisted cough technique. It gradually applies positive pressure to the airways, followed by a rapid change due to negative pressure. It can be applied using a face mask or a tracheotomy tube. In 1953, the first device for mechanical assistance of coughing was marketed. Since then, various studies have confirmed its efficacy. MIE is considered more effective than other reference techniques to increase the coughing mechanism. In spite of ever greater experience and knowledge, mechanical ventilation (MV) (especially during acute disease) is the mainstay of treatment are the responsibility of the Hospital. All the strategies related to clinical assessment of patients, adaptation of devices and programs for carer training are carried out by professionals from the Pneumology Service of the NMD ambulatory clinic.

All the patients prescribed home MIE were included in this study. An observational analysis was carried out with a 4 year follow-up. The patients were recruited in the Pneumology Service from those on the multidisciplinary NMD clinic. The protocol was approved by the Investigation Committee of the Hospital and the study was carried out according to the ethical directives for investigation in humans and the principles of the Helsinki Declaration.

Patients

Patients were studied from February 2005 to February 2009. Home MIE was prescribed for 21 NMD patients (15 men) of a median age of 58 years (27-72 years). The diagnosis included bulbar and non-bulbar amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD) and other NMD. The demographic data of the population studied are described at table 1. Inclusion criteria were as follows: diagnosis of NMD, basal assisted < 270 l/min and continuous dependence on mechanical ventilation (24 hours a day). For the prescription of home MIE the decision criteria was insufficient assisted PCF, after a technique of air entrapment (in patients with non-bulbar ALS) in combination with abdominal thrust. All patients with NMD receiving mechanical ventilation through a tracheotomy were also included.

Patients who could not cooperate or did not receive dedicated care were excluded. All patients depended on continuous home
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

J. Bento et al / Arch Bronconeumol. 2010;46(8):420-425

Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Amyotrophic lateral sclerosis</th>
<th>Duchenne muscular dystrophy</th>
<th>Other neuromuscular diseases</th>
<th>Multiple sclerosis</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, number</td>
<td>15</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Age (onset of respiratory deterioration)</td>
<td>62 (46-72)</td>
<td>32 (30-34)</td>
<td>35 (27-36)</td>
<td>68</td>
<td>58 (27-72)</td>
</tr>
<tr>
<td>Duration of symptoms, months</td>
<td>26 (9-90)</td>
<td>83 (27-139)</td>
<td>38 (8-271)</td>
<td>7</td>
<td>29 (7-271)</td>
</tr>
<tr>
<td>FVC (l and predictable%)</td>
<td>0.99 (0.4-193)</td>
<td>0.4 (0.26-0.54)</td>
<td>0.6 (0.26-0.84)</td>
<td>0.7</td>
<td>0.8 (0.26-193)</td>
</tr>
<tr>
<td>FEV₁ (l and predictable%)</td>
<td>32.5% (15-48%)</td>
<td>9.5% (7-12%)</td>
<td>14% (7-20%)</td>
<td>29%</td>
<td>27.5% (7-48%)</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>0.95 (0.3-1.76)</td>
<td>0.37 (0.24-0.48)</td>
<td>0.57 (0.24-0.84)</td>
<td>0.67</td>
<td>0.72 (0.24-1.76)</td>
</tr>
<tr>
<td>MEP (cmH₂O)</td>
<td>34% (7-56%)</td>
<td>10.5% (7-13%)</td>
<td>16.5% (7-23%)</td>
<td>33%</td>
<td>28.5% (7-56%)</td>
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<tr>
<td>MEP (cmH₂O)</td>
<td>31 (0-45)</td>
<td>14 (0-28)</td>
<td>16 (0-28)</td>
<td>ND</td>
<td>28 (0-45)</td>
</tr>
<tr>
<td>MIP (cmH₂O)</td>
<td>27 (0-56)</td>
<td>15 (3-27)</td>
<td>21 (3-27)</td>
<td>ND</td>
<td>22 (0-56)</td>
</tr>
<tr>
<td>Spontaneous PCF (l/min)</td>
<td>60 (0-250)</td>
<td>90 (80-100)</td>
<td>115 (80-150)</td>
<td>40</td>
<td>60 (0-250)</td>
</tr>
<tr>
<td>Assisted PCF (l/min)</td>
<td>160 (0-260)</td>
<td>170 (160-180)</td>
<td>192.5 (130-250)</td>
<td>80</td>
<td>160 (0-260)</td>
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<tr>
<td>NIV, No. of patients</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Tracheotomy, No. of patients</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Time undergoing continuous ventilation support, months.</td>
<td>24.5 (9-51)</td>
<td>81.5 (24-139)</td>
<td>37 (7-271)</td>
<td>6</td>
<td>29 (7-271)</td>
</tr>
</tbody>
</table>

FEV₁ indicates forced expiratory volume in first second; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; NIV, non-invasive ventilation; PCF, peak cough flow.

Mechanical ventilation through a volume limited time-cycled ventilator (mean current volume 1,000 ml). At the beginning of the study, 6 patients had tracheotomy tubes and 15 patients used continues NIV combining ventilation through a mouthpiece during the day and ventilation with a face-mask during the night.

Before entering the ambulatory MIE protocol, 20 patients had come to the emergency service due to respiratory complications related to the accumulation of secretions (median 3 hospitalisations per patient) and 12 patients had required hospitalisation due to respiratory infections (median 2 hospitalisations per patient).

Determinations

All patients underwent pulmonary function, respiratory muscle force and PCF screening. Pulmonary function was determined by spirometry (Vmax 229, Autobox, Sensormedics), registering the maximum expiratory volume during the first second of forced expiration (FEV₁), and forced vital capacity (FVC). All lung function tests were carried out in a sitting position according to reference procedures defined by the ATS-ERS 2005 work group. 19

Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were determined with a portable pressure manometer (Micro RPM, Micromedical Limited) during maximum inspiratory and expiratory manoeuvres through the mouthpiece, starting with the residual volume (MIP) and from total lung capacity (MEP). These determinations were performed according to reference procedures defined by the ATS-ERS 2002 work group. 19 The manoeuvres were repeated until three determinations with a variability < 5% were obtained.

The PCF was only determined in non-tracheotomised patients by requesting the patient in a sitting position to carry out a cough manoeuvre beginning by total lung capacity (TLC) by means of a standard (Assess Healthscan products, Inc.) flow-meter connected to a face-mask.

Maximum insufflation capacity (MIC) was assessed by spirometry requesting the patient to retain 2 consecutive air volumes supplied by a manual resuscitator bag (air entrainment technique). 20 Bulbar deterioration and glottic dysfunction were evaluated in non-tracheotomised patients by assessing the MIC/FVC ratio. It was considered that patients with a ratio # < 1 presented bulbar dysfunction. For patients with appropriate bulbar function assisted PCF is determined after the air entrainment test with synchronised manual abdominal compression synchronised with the cough effort.

Since the patients with bulbar dysfunction could not carry out the air entrainment test, assisted PCF was only determined by application of manual abdominal compression.

Protocol for Home MIE

Home MIE was carried out using the Cough-Assist® (Philips, Respironics, Inc) device using an oronasal mask or a non-fenestrated tracheotomy tube with an inflated cuff. Both patients and carers were trained in the use of a portable pulse-oximeter ( Nomin 9500 oximeter Minneapolis Plymouth USA) and given information on the use of MIE in their homes, in which a MIE session was applied in each episode of SpO₂ < 95%, until a value > 95% was obtained. 23 For better tolerance periods of rest with ventilation between sessions were applied. Before the prescription of home MIE, all the patients and carers in our service were convened to receive specific training on the technique with a specialized respiratory physiotherapist. Training included device management (adjustments and circuit connections) and a practical seminar with clinical simulations, and also detection of clinical signs necessary to determine efficacy. Each session consisted of 6-8 cycles of insufflation-exsufflation with mean pressures of 40 to 40 cmH₂O. The duration of each cycle was 3 seconds for insufflation, 2 seconds for exsufflation and 4 seconds for the post-exsufflation pause. During the exsufflation phase, patients were trained to cough, at the same time a carer applied abdominal compression. The adaptation of the technique was gradual, pressure was increased progressively to obtain an adequate chest expansion at a comfortable level to eliminate secretions.

Home MIE was always administered by non-professional trained carers (family members or private assistants) with the support of a health care professional with experience from a home care private company (nurse or respiratory physiotherapist). In case of doubt, the carer called the health professional to resolve the problem or to help carry out the technique in difficult situations. Both patients and carers were trained to detect early signs of respiratory failure or respiratory infections and were instructed to contact service staff (pneumologist or respiratory physiotherapist) on appearance of the first sign. Whenever dyspnoea increased, secretions accumulated or a value of SpO₂ < 95% persisted, in spite of continuous use of the ventilator and an aggressive home technique (with the support of expert health carers), the patients were instructed to come in to the emergency service (ES) of the local hospital. The aim of the treatment
was defined as satisfactory control of acute dyspnoea or secretion accumulation, confirmed by pulse-oximetry data ($\text{SpO}_2 > 95\%$).

### Variables Analysed

A descriptive statistical analysis was performed using the SPSS 14.0 database for Windows. Data presented are function on diagnosis, symptom duration, time on mechanical ventilation, spirometry, force of respiratory muscles and assisted and non-assisted PCF. Compliance, tolerance and efficacy were assessed based on daily frequency of MIE use, number of complications, number of visits to the ES due to episodes of secretion accumulation and number of hospitalisations related to airway infections. Clinical files were analysed to assess the number of visits to the ES and the number of hospitalisations prior to the MIE protocol.

Intolerance and adverse effects of the technique were also examined.

### Results

A total of 21 patients with NMD undergoing continuous mechanical ventilation (6 with tracheotomies) and home MIE treatment were studied. The diagnoses were the following: Amyotrophic lateral sclerosis (ALS) ($n = 5$), Duchenne muscular dystrophy (DMD) ($n = 2$), other NMDs ($n = 3$) and multiple sclerosis (EM) ($n = 1$) (table 1). Other NMDs included a heterogeneous group of diseases: Myopathy due to cytoplasmic inclusion bodies, type 2 spinal muscular atrophy and non-classified myopathies. Lung function prior to MIE can be seen at table 1.

Median time of onset of respiratory deterioration of the patients were 29 months (7-271 months) and had been using home ventilation support treatment for a median of 29 months (7-271 months) before their inclusion in the protocol (table 1). As to the ALS patients, at the beginning of the program, there were 6 patients with severe bulbar dysfunction. During follow-up, there was disease progression, so that, at the end of treatment, 10 patients presented severe bulbar dysfunction, 5 of them had undergone tracheotomy (5 rejected it). There was also a patient with non-classified myopathy, ventilated through a tracheotomy, without bulbar dysfunction, that rejected decannulation to VNI.

Compliance with MIE is shown in table 2. This technique was used daily by 10 patients (7 with bulbar ALS and 1 with non-classified myopathy) (table 2). The 6 patients with tracheotomy (5 with bulbar ALS and 1 with non-classified myopathy) and 4 patients undergoing VNI (2 with bulbar ALS that rejected tracheotomy and 2 with non-bulbar ALS) used the technique daily. The data related to daily frequency of sessions in the groups of daily users are shown in table 3. In this group, the patients with tracheotomies used MIE more times a day than those with VNI (table 3).

The technique was used intermittently by 11 patients (table 2). The patients described in this study suffered from severe ventilation failure and continuously depended on mechanical ventilation (24 hours a day). They had all used volume limited time-cycled ventilation for many years before inclusion in the study.

### Discussion

The efficacy of MIE to increase PCF and improve the efficacy of cough manoeuvre has already been demonstrated.\cite{1,4,7,13,14,21} Chatwin et al compared different interventions (cough assisted by physiotherapy, cough assisted by VNI, cough assisted by exsufflation and MIE) with non-assisted cough and showed that MIE was the technique associated with the greatest increase in PCF.\cite{4} Oximetry data has shown the usefulness of this technique since it makes it possible to detect a sudden decrease of oxygen saturation as a consequence of a mucous plug.\cite{2,5,21} The patients described in this study suffered from severe ventilation failure and continuously depended on mechanical ventilation (24 hours a day). They had all used volume limited time-cycled ventilation for many years before inclusion in the study.

This study was based on the protocol proposed by Bach et al, that consists in home treatment with a VNI support, oximetry monitoring during 24 hours and the use of MIE guided by the data from this ($\text{SpO}_2 < 95\%$).\cite{3,5,21,23,24} In this study home MIE was carried out by non-professional carers of the patients with the support of health professionals trained in home care.

Few studies have described home respiratory treatment with MIE in patients with NMD, although many studies describe the efficacy of the combination of cough assistance techniques, manual and mechanical, in acute in-hospital situations.\cite{8,9,21} Although MIE carried out by non-professional carers has been considered effective and well tolerated, it causes certain controversy and we still require more data on its home use in the long term.\cite{9,21,23,24}

In our strategy, the main condition for effective home care after hospital discharge was the presence of appropriately trained and
motivated carers. This study supports the importance of an appropriate early training phase, administered to both patients and carers in the hospital, as has also been proposed by Tzeng et al. Furthermore, this study confirmed that carers with appropriate training and motivation can detect respiratory worsening and effectively use a home MIE protocol. Patients with neuromuscular diseases, especially ALS, can suffer progressive disease with early decrease of respiratory muscle force and cough deterioration, both associated with premature death. The natural course of NMD does not make it possible to clarify the influence of home MIE on visits to the ES/hospitals. The number of episodes before and after the home MIE protocol is not comparable. Indeed, before beginning home treatment, the patients’ cough reflex was more powerful and therefore, they suffered fewer episodes of secretion accumulation. In contrast to other NMD, ALS also includes glottic muscle control. In general, in patients with non-bulbar NMD non-invasive support treatment may be used and they have a higher survival rate. However, the almost inevitable progression to bulbar dysfunction is one of the more negative characteristics of this disease and the main reason due to which, in contrast to other NMD, tracheotomy becomes necessary to prolong survival. The MIC/FVC ratio has been widely used to assess bulbar function, due to the fact that appropriate glottic function is necessary to accumulate consecutive volumes of air to achieve MIC. Furthermore, a severe bulbar dysfunction is also responsible for dysfunction of the higher respiratory airway muscles in this group of patients. Sancho et al have identified two types of bulbar ALS patients: those that only suffer from failure of glottis closure that cannot entrap air but in which MIE can be effective and those that present a dynamic collapse of the upper respiratory airways in which MIE is not effective and can even cause risk. In this study, ALS, the most usual diagnosis, is seen in a heterogeneous group: from a non-bulbar disease with inadequate PCF to a severe bulbar disease that requires tracheotomy. This in itself represents an additional problem concerning patient acceptance or associated problems (local inflammation, increase of secretions and infections), Indeed, although it was offered to all patients with severe bulbar dysfunction, some continued to reject it and preferred to continue with VNI and the MIE protocol. Bach et al have also described the fact that patients with severe bulbar ALS can receive support treatment with the combined use of VNI and MIE, which delays tracheotomy, as long as they can maintain an oxygen saturation > 95% with ambient air. However, these patients required careful regular supervision to anticipate the failure of a non-invasive strategy, so that therapeutic options can be examined and analysed with patients and their families, so that decisions can be made beforehand and not at the time of a respiratory crisis. Farrero et al have suggested that a follow-up every 3 months or on patient demand makes it possible to opportunely recognise disease progression.

In this study, each MIE session consisted of 6–8 cycles of insufflations-exsufflations with mean pressures of 40 to –40 cm H₂O, titrated according to patient tolerance. Chatwin and Sivasothy have considered that lower pressures are more comfortable and involve fewer risks. However, the adjustments used in this study are widely preferred due to their effects on patient welfare and their efficacy and are also suggested by the manufacturers. In general, they are well tolerated and have been considered the most effective means of obtaining higher values of PCF with practically no complications. In spite of this, we paid special attention to careful individual titration of the MIE pressure, to obtain maximum chest expansion, respecting welfare, which can justify the tolerance and absence of complications seen in this study. The application of MIE was adjusted to the needs of each patient in as far as frequency of use, considering daily and intermittent users. With intermittent users it was not possible to register the number of MIE sessions per month or week because compliance was not regular and depended on the number and severity of respiratory exacerbations. In contrast, daily users reported that they used the device every day, independently of exacerbations, both for secretion control and for lung insufflation and to revert episodes of SpO₂ < 95%. This study also shows that patients that had undergone tracheotomy used MIE daily and more times a day than patients with VNI. This fact may be due to local inflammation and the increase of secretions related to tracheotomy. We also found that some patients with bulbar ALS, incapable of air entrapment, did not only use MIE as a technique for cough assistance, but also for lung insufflation.

According to this study, both patients and carers described greater efficacy in clearance of airway secretions with this home protocol. Its early application, guided by oximetry data with normalisation of oxygen saturation with ambient air, prevented visits to the Emergency Service due to secretion accumulation. Patients stated that, during these episodes, without MIE, they would have had to go to hospital due to their acute respiratory problems. Furthermore, there were very few episodes in which home MIE was not sufficient to resolve the problem of secretion accumulation and made it unnecessary to visit the ES or to require hospitalisation. None of these patients required intubation. Indeed, it would seem that the protocol reduces the risk of airway infection and prevents both visits to the ES and hospitalisations. Bach et al have reported that patients with NMD dependent on VNI that used MIE guided by oximetry data can be treated at home without risk or need of hospitalisation.

This study did not show any complications related to use of the device. Potential complications are very infrequent and include abdominal distension, increase of gastroesophageal reflux, haemoptysis, chest and abdominal discomfort, acute cardiovascular events, barotraumas and pneumothorax. Bach et al have not described any complications in more than 500 batches of MIE. Some simple but prudent measures to prevent complications are: brief
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care

Miguel Ramalho do Souto Gonçalves

pauses between applications (to avoid hyperventilation), avoiding applications after meals, appropriate treatment of gastroesophageal reflex and reduction of insufflation pressure according to tolerance. During the study period, 4 patients with bulbar ALS died. The main cause of death was rapid progressive disease with severe bulbar dysfunction. These 4 patients had constantly rejected tracheotomy. The limitations of this study are the fact that it is observational, the reduced number of patients including the absence of a control group. However, shortly after beginning this protocol, the benefits of the treatment as far as efficacy in management of accumulated secretions, preventing visits to the Emergency Service and improvement of quality of life in these patients became evident. As a result, we consider that it would not be ethical to deprive the patients of a treatment that has been shown to be effective.

Conclusion

The most important conclusion of this study is that it is possible to treat patients with severe NMD with sufficient clearance of the secretions of their respiratory airways with home MIE based on careful training of non-professional carers. This is valid for patients with VNI and those with tracheotomies. According to the patients, greater use of MIE during respiratory infections can prevent visiting the emergency service.

This technique can be considered a useful complement to ventilation support in these patients.

References

Study 8

At Home and on Demand Mechanical Cough Assistance Program for Patients With Amyotrophic Lateral Sclerosis

Michele Vitacca, Mara Paneroni, Debora Trainini, Luca Bianchi, Giuliano Assoni ND, Manuela Saleri RTD, Sonia Gilè PHD, João C. Winck and Miguel R. Gonçalves
At Home and on Demand Mechanical Cough Assistance Program for Patients With Amyotrophic Lateral Sclerosis

ABSTRACT


Objective: To establish a cost-effective telephone-accessed consultation and mechanical in-exsufflation (MI-E) and manually assisted coughing, oximetry feedback program for 39 patients with amyotrophic lateral sclerosis.

Design: Rapid access to healthcare consultation and to MI-E was provided to treat episodes of distress as a result of secretion encumbrance not reversed by suctioning and associated with a decrease in oxyhemoglobin saturation (SpO₂) baseline. Avoided hospitalizations, defined by relief of respiratory distress and return of SpO₂ baseline to ≥95% by continuous ventilator use and assisted coughing, were recorded. Patient satisfaction was queried at 6 mos, and a cost analysis was performed of continuous vs. on demand MI-E use.

Results: Thirty-nine patients made a total of 1661 calls in 7.46 ± 5.8 mos of follow-up. Twenty-seven patients had 66 home care visits by a respiratory therapist for a total time commitment of 89.7 ± 99.3 min/patient/mo. Twelve patients, all ventilator users, were also brought mechanical in-exsufflators for mechanically assisted coughing for 47 respiratory episodes. Thirty hospitalizations were avoided. Seventy-five percent of the patients were extremely satisfied. Mean monthly cost per patient for on-demand telephone consultation, professional home healthcare visits, and MI-E as deemed necessary was €403 ± €420 or 59% less than for continuous MI-E rental. Hospitalization costs were also spared.

Conclusions: An on-demand consult and MI-E access program can avoid hospitalizations for patients with amyotrophic lateral sclerosis with significant cost savings.

Key Words: Amyotrophic Lateral Sclerosis, Home Care, Acute Respiratory Failure, Mechanically Assisted Coughing
For patients with neuromuscular diseases, including amyotrophic lateral sclerosis (ALS), continuous dependence on noninvasive intermittent positive pressure ventilation (NIV) can markedly prolong survival,\textsuperscript{1} maintain optimal quality-of-life,\textsuperscript{2} and along with mechanically assisted coughing (MAC)\textsuperscript{3–5} can be used in the home to avoid hospitalizations, acute respiratory failure with endotracheal intubation, and tracheotomy.\textsuperscript{4,6,7} MAC is the use of mechanical in-exsufflation (MI-E)\textsuperscript{8} with an exsufflation-timed abdominal thrust. Although effective when continuously available, expense can be mitigated by on-demand rather than continuous access if on-demand use can be demonstrated to be effective.

Severe bulbar-innervated muscle dysfunction with inability to protect the airways can render MI-E ineffective, and even when effective, patients can require considerable assistance and training.\textsuperscript{1,7,9} In Europe, home respiratory care is often inadequate because home care companies provide only equipment, not assistance, instruction, or expertise for which the patient must depend on emergency services,\textsuperscript{10} and there is great burden on caregivers.\textsuperscript{11} Thus, hospitalization rates and lengths of stay are high, especially when acute respiratory failure and intubation result in tracheotomy. Even in the United States, it has been reported that the mean hospitalization duration for patients with neuromuscular disease undergoing tracheotomy is 72 days, most of which is spent in intensive care\textsuperscript{12,13} at great expense, and long and expensive ventilator weaning unit stays often follow this.

To help reduce costs, avoid hospitalizations, and establish an optimal MI-E provision regimen at home, we studied a telephone-accessed integrated care\textsuperscript{14} program with oximetry feedback that provided equipment and professional home care services on an “as needed basis” to treat clinical exacerbations and related respiratory problems.

\section*{METHODS}

All 47 patients with a diagnosis of ALS according to El Escorial criteria\textsuperscript{15} referred to our rehabilitation department for adaptation and training in some combination of cough assistance, mechanical ventilation, and tracheostomy management were analyzed. Our center has 145 beds for multidisciplinary intermediate care. Reimbursement depended on diagnosis and comorbidities. Exclusion criteria were death before enrollment, location >80 km from the center, and inadequate care providers or cooperation. The protocol was approved by the ethics committee, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1975, revised in 1983, clinical trials identifier #NCT00613899). All patients gave informed consent.

\section*{Hospital Phase: Training}

All patients were offered the telephone-accessed integrated care program that included telephone access to a triage nurse who directed the calls to a pulmonologist, neurologist, psychologist, or physio-respiratory therapist (RT) for consultation\textsuperscript{14} and possibly home visit. The patients were educated and trained in oximetry feedback (9500 by Nonin, Minneapolis Plymouth) to maintain or return SpO\textsubscript{2} to ≥95% by manually assisted coughing or MAC or both as needed\textsuperscript{4,16,17} and in mechanical ventilation, including interface use, cleaning, humidification, safety, and tracheostomy care, as appropriate. Manually assisted coughing involved the application of deep lung insufflation followed by abdominal thrust. For MAC, the maximum tolerated MI-E pressures (range, 35–60 cmH\textsubscript{2}O) were used. The tube cuff was inflated for MI-E use via tracheostomy tubes.\textsuperscript{18}

The patients were told to contact the call center for: dyspnea, 3% reduction in baseline SpO\textsubscript{2}, 20% increase in need for deep airway suctioning,\textsuperscript{18} increased airway mucus congestion or changes in secretion properties,\textsuperscript{19} fever, headache, asthenia, sleepiness, or confusion, and consideration for antibiotic therapy.\textsuperscript{16}

Before discharge, the patients underwent pulmonary function testing, including spirometry (VMAX 20, Sensor Medicis, Yorba Linda, CA) and peak cough flow measurement via a standard peak flow meter (MiniRight Peak Flow Meter, Clement Clarke International, England, UK) connected to a facial interface.\textsuperscript{20}

\section*{Home Phase}

An RT called each patient every 7 days. The calls and home visits reinforced the oximetry/assisted coughing protocol. MI-E was brought to patients for whom, despite NIV or tracheostomy intermittent positive pressure ventilation (ITV) and manually assisted coughing, the SpO\textsubscript{2} would not remain >94%.\textsuperscript{3,4,16} All patients were instructed to call the emergency service for hospitalization if the SpO\textsubscript{2} remained <95% despite continuous ventilatory support and assisted coughing, including MAC.

\section*{Outcome Measurements}

Mortality and the number of telephone calls for assistance, respiratory exacerbations with SpO\textsubscript{2} baseline <95%, RT home visits, home MAC rentals, days of home MAC requirement, the percentage of SpO\textsubscript{2} improvement with intervention, side effects of MAC, avoided hospitalizations defined by relief of dyspnea and return of SpO\textsubscript{2} baseline to
≥95% by assisted coughing and continuous ventilatory support without hospitalization, and hospitalizations were recorded. At 6 mos, patients were also telephoned to question their satisfaction and estimate the efficacy of the program.

**Costs**

On-call telephone access costs have been already reported by our group. The RT home visits and rental costs for suction machine, manual resuscitator, and ventilator were additional. Per diem MI-E rental costs were compared with continuous rental costs in Italy and in the United States. The latter information was provided by an accredited respiratory home care company (Millennium Respiratory Services, Whippany, NJ) at Medicare reimbursement rates. Inpatient respiratory rehabilitation admission costs were €289 per day, and critical care costs were €1600 per day. When applicable, costs were converted from dollars to euros.

**Statistical Analysis**

Descriptive data are reported as mean ± SD. Statistical analysis was performed by using SPSS software (Release 12.0 SPSS, Chicago, IL). For all parameters, the differences between treatment times were analyzed using a paired Student’s t test for the parametric variables and an unpaired Wilcoxon-test for the nonparametric ones. P values <0.05 were considered significant.

**RESULTS**

Between October 2006 and September 2008, 47 consecutive patients with ALS were screened. Eight were excluded: three died before enrollment, two refused to participate, one lived >80 km from the referring center, one showed poor compliance, and one had no caregiver. The remaining 39 received riluzole and were followed up for 7.46 ± 5.8 mos. Twenty-seven of the 39 were ventilator users. Their baseline anthropometric, clinical, and functional characteristics are shown in Table 1. All tracheotomized patients (n = 12) required continuous TIV, whereas the NIV patients (n = 15) used NIV 8–16 hr/d.

**Telephone-Accessed Integrated Care Program**

The total nurse/RT time commitment was 1.49 ± 1.65 hr/patient/mo or the equivalent of a 0.4 full-time RT. During the 7.46 ± 5.8-mo follow-up, there were 1661 calls with a high interindividual variability (6.65 ± 6.45, range 1–138). All except one call to a physician was triaged to an RT. Seven and one-half percent of the calls triggered a home RT visit. Sixty-seven home visits were required and 38 had MI-E delivered.

Outcomes and hospitalization data are listed in Table 2. Overall, 10 NIV users (26%) died: two suddenly and eight from respiratory causes and refusing intubation. Only 1 of the 10 called the center. No TIV user died.

All MAC deliveries were for TIV and NIV users who were also followed up for a longer than average period of time. Table 3 shows outcomes of MAC intervention performed during a 12.6 ± 3.3-mo period. The latency period for initiating home MAC use was 3 ± 3 mos for the tracheotomy patients and 10 ± 3 mos for the NIV users. The TIV users required MI-E twice as many days per month as the NIV users.

**TABLE 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD (range)</td>
<td>62 ± 11 (39–83)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>21/18</td>
</tr>
<tr>
<td>Years of disease*</td>
<td>3.47 ± 3.21</td>
</tr>
<tr>
<td>Distance from the referring center, Km (range)</td>
<td>34 ± 18 (1–80)</td>
</tr>
<tr>
<td>Bulbar/nonbulbar involvementb</td>
<td>23/16</td>
</tr>
<tr>
<td>No ventilator use (n)</td>
<td>12</td>
</tr>
<tr>
<td>NIV users (n)</td>
<td>15</td>
</tr>
<tr>
<td>TIV users (n)</td>
<td>12</td>
</tr>
<tr>
<td>VC, % predicted (n)</td>
<td></td>
</tr>
<tr>
<td>PCF, cmH₂O (n = 27) no-T patients</td>
<td>186 ± 113</td>
</tr>
<tr>
<td>PEF, cmH₂O (n = 12)</td>
<td>88 ± 51</td>
</tr>
</tbody>
</table>

aFrom diagnosis.  
bFrom time of respiratory therapist evaluation.  
TIV, tracheostomy mechanical ventilation; NIV, noninvasive mechanical ventilation; VC, vital capacity; PCF, peak cough flow; PEF, peak expiratory flow.
Table 4 shows costs. One NIV and two nonventilator users underwent tracheotomy during the study. Comparing the costs of "on-demand" MI-E with standard continuous use for the 6660 days of ventilator use for the 27 patients, the cost savings was €108,758.

The daily rental of MI-E in the United States is $10 per day for a monthly rental and Medicare reimbursement of $424 (€301). Rental for mechanical ventilation, MI-E, and supplies and on-call RT services is about $1000 per month or about 30% greater than the cost of this rental program. The avoidance of 34 hospitalizations added to the cost savings.

All 39 patients were satisfied with the project, and 86% of the MAC users considered it effective, whereas 14% considered it somewhat effective. There were no significant side effects of assisted coughing, including MAC.

**DISCUSSION**

For patients with ALS, a program of telephone access and as needed home intervention, including manually assisted coughing and MAC, was shown to be feasible, well tolerated, and cost effective. A previous ALS study used continuous videoconferencing and telephone consultation for four patients with ALS, although it was limited by the small number of subjects and by their

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### TABLE 2 Outcomes of home care visits

<table>
<thead>
<tr>
<th>Total Patients Having Home Visits (n = 27)</th>
<th>Patients With Home Visits Only (n = 15)</th>
<th>Patients With Home Visits Plus MI-E(^a) (n = 12)</th>
<th>TIV Users Having Home Visits and Provision of MI-E (n = 9)</th>
<th>NIV Users Having Home Visits and Provision of MI-E (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total respiratory exacerbations, n</td>
<td>67</td>
<td>20</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>Home visits without MI-E delivery, n</td>
<td>13</td>
<td>4</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Home visits plus provision of MI-E, n</td>
<td>21</td>
<td>0</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Patients hospitalized, n</td>
<td>18</td>
<td>8</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Total hospitalizations, n</td>
<td>33</td>
<td>16</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Avoided hospitalizations, n</td>
<td>34/67 (51%)</td>
<td>4/20 (22%)</td>
<td>30/47 (64%)</td>
<td>27/40 (67%)</td>
</tr>
</tbody>
</table>

\(^a\)Home respiratory therapist (RT) visit for reinforcement of instruction in manually assisted coughing and provision of a mechanical insufflator-exsufflator for mechanically assisted coughing (MAC). TIV, tracheostomy intermittent positive pressure ventilation; NIV, noninvasive intermittent positive pressure ventilation; MI-E, mechanical insufflation-exsufflation.

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### TABLE 3 Outcomes of the 12 users of mechanically assisted coughing

<table>
<thead>
<tr>
<th>Patients Having RT Visits and Provision of MI-E (n = 12)</th>
<th>TIV Users Having RT Visits and Provision of MI-E (n = 9)</th>
<th>NIV Users Having RT Visits and Provision of MI-E (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total home MI-E rentals, n</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Mean change in (\text{SpO}_2) (%) with intervention, all baselines were corrected</td>
<td>+3.2 ± 0.8</td>
<td>3.5 ± 0.9</td>
</tr>
<tr>
<td>Total MI-E rental days, n</td>
<td>46.7 ± 27.4</td>
<td>56.7 ± 24</td>
</tr>
<tr>
<td>Time to normalization of baseline (\text{SpO}_2) &lt;20 days</td>
<td>33%</td>
<td>0</td>
</tr>
<tr>
<td>20 and 40 days</td>
<td>17%</td>
<td>34%</td>
</tr>
<tr>
<td>&gt;40 days</td>
<td>50%</td>
<td>66%</td>
</tr>
<tr>
<td>Days of home MI-E rental, n</td>
<td>54.2 ± 30.0</td>
<td>50 ± 28.2</td>
</tr>
</tbody>
</table>

\(^a\)Home respiratory therapist (RT) visit for reinforcement of instruction in manually assisted coughing and provision of a mechanical insufflator-exsufflator for mechanically assisted coughing (MAC). TIV, tracheostomy intermittent positive pressure ventilation; NIV, noninvasive intermittent positive pressure ventilation; MI-E, mechanical insufflation-exsufflation; \(\text{SpO}_2\), pulse oxyhemoglobin saturation.
inability to master the use of the Internet and Webcams.\textsuperscript{21}

Patients with severe bulbar-innervated muscle dysfunction and those with only moderate dysfunction but without tracheostomy tubes are considered to have a poor prognosis.\textsuperscript{9} However, our results indicate that the severity of clinical exacerbations as a result of airway secretion encumbrance in such patients can be monitored and secretion expulsion guided by oximetry. Normalization of $\text{SpO}_2$ baseline by aggressive assisted coughing and MAC can avert hospitalization despite continuous ventilatory support. This can only be effective with trained care provider assistance.\textsuperscript{16}

This is consistent with the findings of Bach et al.\textsuperscript{12,22,23} who in one study demonstrated that an uncorrected decrease in baseline $\text{SpO}_2 < 95\%$ resulted in 33 of 35 patients with ALS dying or requiring tracheotomy within 2 mos, but that about one-half of such patients' baseline $\text{SpO}_2$s can be temporarily normalized by MAC for about 11 mos.\textsuperscript{4} Thus, a motivated caregiver can often use NIV and cough assistance to prevent acute respiratory failure for ALS as has also been described for patients with Duchenne muscular dystrophy\textsuperscript{3,24} and other patient populations.\textsuperscript{16}

Oximetry monitoring with on-demand medical attention and MAC is a cost-saving alternative to institutionalization and to continuous access to MI-E. In one study in which the indication for continuous home MI-E prescription was assisted, peak cough flow $< 300$ L/m as opposed to the mean of 186 L/m (unassisted) peak cough flow in our patients, the average period of time before MI-E was needed to avert a hospitalization with continuous rental was 11 mos.\textsuperscript{3} In our study, 56\% of the patients did not obtain MI-E at all, and those who used it, did so for $< 20\%$ of the total follow-up period.

In conclusion, the telephone access and on-demand MAC program increased both the patients’ and clinicians’ feelings of security for home management and was effective in averting hospitalizations for patients with ALS. Limitations of the study are (1) lack of controls; (2) lack of quality-of-life assessment; and (3) lack of outcomes comparisons with programs in which MI-E access is continuous.

**ACKNOWLEDGMENTS**

We thank Mario Melazzini, who is a doctor, patient, and profound human being, for his joy of being alive. We also thank Millennium Respiratory Services, Whippany, NJ, for their support in providing data.
REFERENCES


Study 9

*Home mechanical cough assistance for acute exacerbations in neuromuscular disease*

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(Respiratory Medicine, submitted)
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
Home mechanical cough assistance for acute exacerbations in neuromuscular diseases.


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Abstract

**Background:** Mechanically assisted coughing (MAC) has been used successfully in hospital for patients with neuromuscular disease (NMD), however, limited data exist on long-term home use.

**Objective:** To determine outcomes of home MAC for NMD patients using tracheostomy mechanical ventilation (TMV) or noninvasive ventilation (NIV) during acute episodes.

**Material and methods:** The study was performed in two centers with NMD clinics. Forty six NMD patients (14 females) continuously ventilator dependent (28 using NIV and 18 TMV) with a mean age 51.3±22.3 years, were analyzed. Pulmonary function and cough efficacy were assessed during routine evaluations. Hospitalization rates, avoided hospitalizations defined by normalization of SpO2 within 24 hours by continuous ventilatory support and MAC, and resort to deep airway suctioning were recorded. Treatment tolerance and side effects were also assessed.

**Results:** During 42±57 months of follow up, for 180 acute episodes, 146 hospitalizations were avoided. Hospitalization rates for NIV users were significantly lower than for TMV users. Home MAC during acute episodes normalized baseline SpO2 and decreased resort to deep airway suctioning via tracheostomy tube per day. In all MAC sessions there were no complications.

**Conclusion:** Home MAC with oximetry feedback is effective and can avoid hospitalizations for both NIV and TMV users.

**Key words:** Home mechanical ventilation, Mechanical assisted cough, Neuromuscular disorders,
Introduction

Mechanical assisted cough (MAC) is the use of mechanical insufflation-exsufflation (MI-E) (1) with an exsufflation-timed abdominal thrust. It can be applied via oral, oronasal interfaces or via invasive airway tubes preferably with inflated cuffs (2). The physiological effects and efficacy of MAC have been described for adults (1, 3-6) and children (7-8).

Patients with neuromuscular diseases (NMD) have respiratory muscle weakness and impaired cough (9-10). For these patients, up to continuous use of noninvasive ventilation (NIV) can maintain quality of life,(11) and markedly prolong survival (12) that is, nevertheless, punctuated by respiratory tract infections (RTIs). Intercurrent RTIs are the main cause of morbidity, prolonged hospitalizations, acute respiratory failure (ARF), intensive care admissions, and mortality (13-16). The use of mechanically assisted coughing (MAC) has been reported to be effective in preventing ARF and for avoiding hospitalizations in patients with Duchenne Muscular Dystrophy (DMD) (16).

In hospital application, MAC has been described as a first-line intervention for NMD patients with ARF (2, 7, 17-20), however, its efficacy and optimal application in the home has not been widely explored. The purpose of this study was to describe the outcomes of home MAC for avoiding hospitalizations in NMD patients.

Material and Methods

The data were retrospectively gathered in two centers with NMD clinics and extending home care organizations that include the provision of MAC. The study was approved by the institutions’ review boards.
Patients

A 4 year follow up observational analysis was performed for 46 totally ventilator dependent patients (14 females) that included 33 with ALS and 13 with other NMDs (5 Duchenne muscular dystrophy (DMD), 3 spinal muscular atrophy (SMA) type 1, 3 SMA type 2, 1 multiple sclerosis and 1 congenital muscular dystrophy) with mean age 51.3±22.3 years. Inclusion criteria were: NMD diagnosis, baseline assisted cough peak flow (CPF) <270 L/min and continuous ventilator dependence (> 20h per day) and decrease in SpO2 baseline below 95% during intercurrent episodes of respiratory distress. Patients with lung disease, inability to cooperate and without dedicated caregivers were excluded.

Measurements

Unassisted and assisted CPF were noted for NIV users and peak expiratory flow (PEF) noted for TMV users. Spirometric (Vmax 229, Autobox, Sensormedics) recording of forced expiratory volume in one second (FEV1) and forced VC (FVC) was noted. In TMV users, tracheotomy pulmonary function tests were performed through the non-fenestrated tracheotomy tube with an inflated cuff. All pulmonary function testing was done in sitting position according to standard procedures(21).

Unassisted CPF was measured by having the patient cough forcefully through a standard peak flow meter (miniRight, standard range Peak Flow Meter Clement Clarke International England) connected to a facial mask. Assisted CPF involved the patient “air stacking” to approach maximum insufflation capacity (22) using their volume-cycling ventilator or a manual resuscitator and coughing into the peak flow meter as the abdominal thrust was applied at glottic opening (3). Bulbar impairment and glottic dysfunction correlated with unassisted/assisted CPF ratio for NIV users. Patients with a ratio =1 could not close the glottis and were considered to have severe “bulbar” impairment (10, 13, 23).
Home oximetry feedback/MAC protocol

All patients and their caregivers attended a hospital-based educational program on lung expansion techniques (air stacking), manual assisted coughing, and MAC with oximetry feedback. MAC training included adjustment of settings on the Cough-Assist® (Philips, Respironics, Inc, Murrysville, PA) and use during practical clinical simulations, as well as training in awareness of symptoms and signs of airway congestion that indicate need for MAC via oronasal mask or via tracheostomy tube that had to be with an inflated cuff (2). The Cough-Assist® and an oximeter (Nonin 9500 oximeter Minneapolis Plymouth USA) was then provided for home use.

Secretion encumbrance that caused SpO2 to decrease to less than 95% despite continuous full-setting ventilatory support in ambient air with dyspnea, that did not revert after manually assisted coughing techniques, or, for patients with tracheotomy tubes, after several secretion mobilization and suctioning sessions, indicated an acute episode and resort to MAC with settings suggested by medical literature.(1, 3, 24) A effective MAC application by trained non-professional caregivers (family members, private attendant) was the expulsion of airway secretions by MAC that resulted in return of SpO2 to≥95%. A trained health care professional (respiratory therapist or nurse) was always available 24h/day on free on-call to answer questions as well as to go to the home to supervise MAC in difficult situations (25). Patients and caregivers were also instructed to detect early signs of respiratory tract infections and instructed to contact our staff for medical therapy.

Hospitalization avoidance was defined as MAC-engendered expulsion of mucus with resulting normalization of SpO2 to values equal to baseline within 24 hours. Whenever dyspnea and secretion encumbrance or SpO2 <95% persisted despite continuous ventilator use and aggressive MAC (more than 4 sessions per hour), patients were instructed to go to Emergency Departments of local hospitals. In addition, the TMV users were instructed to seek attention if requiring an increase in the need for airway suctioning. These were the criteria established for hospital admission.
Outcome Monitors

Numbers of: acute episodes of secretion encumbrance with desaturation indicating need for MAC, hospitalizations, and avoided hospitalizations were analyzed and compared between NIV and TMV patient groups. SpO2 baseline values during acute episodes were compared with pre-morbid baseline values and values at recovery (after a 24h MAC application). For TMV patients, the number of deep airway suctionings were also recorded both during the acute episode and at recovery. Tolerance and side effects were monitored.

Statistical Analysis

Statistical analysis was performed by SPSS 15.0 software (SPSS, Chicago, IL, USA). Descriptive data are reported as mean±SD. Comparisons between groups were done using the Mann-Whitney U-test and differences between baseline, acute episode and recovery were compared using the Wilcoxon rank test. A p value ≤ 0.05 was considered significant.

Results

During a follow up of 42±57 months, 46 subjects, that included, 28 (61%) NIV users and 18 (39%) TMV users, were studied. All had CPFs that satisfied the inclusion criteria. Demographic data and clinical and functional characteristics are listed in table 1.

The home oximetry feedback/MAC protocol was used for a total of 180 (mean 3.9±2.9 per patient) acute episodes of respiratory insufficiency due to secretion encumbrance during the follow up of the study. During these episodes SpO2 significantly decreased in all patients in comparison with baseline and significantly reverted in 24 hours after MAC (Figure 1). In TMV patients, during the acute episodes, the number of deep airway suctionings significantly increased in comparison with baseline and after MAC significantly decreased again in 24 hours to values similar to baseline (Figure 2). Hospitalization data and outcomes are listed in table 2.
During the follow up period 10 patients died (8 NMV and 2 TMV users), 4 suddenly and presumably from cardiac arrhythmia (3 ALS and 1 SMA type 1), 3 with ALS from pneumonia, and 2 ALS patients from stroke. All MAC sessions were well-tolerated and there were no complications related to the treatment.

Discussion

The organization of home MAC access and patient compliance with it has already been reported by our group for ALS patients (25). We have now reported data that focused on the clinical effects of home MAC during acute episodes of secretion encumbrance in ALS and other NMD patients. The results confirm that hospitalizations for ARF can be avoided for NMD patients by a protocol of oximetry feedback for using ventilatory support and MAC in the home (12, 15-16, 26). Moreover our findings support the clinical justification for availability and prescription of cough assist devices and portable oximeters at home for this patient population, specially during intercurrent RTI’s.

Provided that supplemental oxygen therapy be avoided, oximetry was critical since, once artefact is ruled out, all desaturations indicated less than full ventilatory support (airflow leak or inadequate ventilator settings), airway secretion congestion, and if the latter was not resolved by MAC, persistent SpO2 decrease was caused by pneumonia or other persistent complications of congestion(5, 15, 17, 27) Since all patients were continuously ventilator dependent during the episodes, had the oxyhemoglobin desaturations and dyspnea not been reversed by MAC, they would have had to have been hospitalized for problems related to upper respiratory tract infections and inability to clear secretions. However, in our study, as a result of the protocol, 81% of the acute episodes resolved without hospitalization.

These results are consistent with those reported by Gomes-Merino et al (16) that, with a similar approach, described hospitalization avoidance and survival increase in a population with Duchenne muscular dystrophy under NIV. Our study focused on other NMD diagnoses including having 71% ALS patients.
Moreover, we found that, while the incidence of acute episodes was the same, the TMV users had significantly more hospitalizations per desaturation episode than NIV users. This may be due specifically to complications caused by the invasive tubes (28-30) and unrelated to MAC or by poorer bulbar-innervated muscle function and airway protection mechanisms in the ALS population despite TMV with cuff inflation (31-32).

Indeed, it is well known that the severely impaired bulbar-innervated muscle function in ALS can render MAC ineffective (5, 12) via the upper airway and necessitate tracheostomy to be effective (13, 32). Bach et al. described that persistent SpO2 < 95% in room air despite optimal use of NIV and MAC, indicates need for tracheostomy in ALS patients (26) and presumably in patients with other NMDs as well. In our study, MAC not only significantly improved SpO2 in all patients, it also significantly decreased the number of airway suctionings in TMV patients. All TMV patients in this study had bulbar muscle impairment and the fact that only 3 NIV users had bulbar impairment, may justify the good results of MAC on reversion of desaturations at home.

The main requisite for home MAC prescription was the presence of adequate and motivated patients and caregivers to learn the protocol from trained health care professionals. Our results imply that the training and equipping be done early, before ARF occurs, and in the outpatient setting as reported by Tzeng et al (15). Our results confirm that the caregiver can successfully use MAC at home cough with oximetry feedback and can early detect possible acute episodes of secretion encumbrance. However, according to our experience, to guarantee an optimal continuous support to the caregiver, an easy access by phone to a health care professional 2nd opinion, 24 h/day is strongly advised.

Limitations of the study include its retrospective nature with no control group, the small number of patients and multiple diagnoses. Thus, we advise caution in the generalization of the results.

In conclusion, it is possible and effective to manage episodes of acute respiratory decompensation, related to secretion encumbrance, in continuously ventilator dependent NMD patients in the home with patient and care provider training and equipping in a protocol of MAC with oximetry feedback. This is true for patients dependent on either NIV or TMV.
Table 1: Patient baseline characteristics

<table>
<thead>
<tr>
<th>Patients, (n)</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD (range)</td>
<td>51±22 (1-83)</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>32/14</td>
</tr>
<tr>
<td>Years of Onset*</td>
<td>5.7±5.6</td>
</tr>
<tr>
<td>Follow up after mechanical ventilation, months ± SD (range)</td>
<td>42±57 (6-300)</td>
</tr>
<tr>
<td>Bulbar/Non bulbar Involvement**</td>
<td>21/25</td>
</tr>
<tr>
<td>NIV users (n, %)</td>
<td>28 (61%)</td>
</tr>
<tr>
<td>TMV users (n, %)</td>
<td>18 (39%)</td>
</tr>
<tr>
<td>VC, Liters (%)</td>
<td>Tot – 1.0 ±0.5 (31±13%)</td>
</tr>
<tr>
<td></td>
<td>TMV users – 1.1 ±0.51 (34±10%)</td>
</tr>
<tr>
<td></td>
<td>NIV users – 0.97 ±0.52 (30±14%)</td>
</tr>
<tr>
<td>FVC/FEV1 (%)</td>
<td>Tot - 88±12</td>
</tr>
<tr>
<td></td>
<td>TMV users - 86±12</td>
</tr>
<tr>
<td></td>
<td>NIV users - 88±13</td>
</tr>
<tr>
<td>Unassisted PCF, L/min (NIV users)</td>
<td>92±86</td>
</tr>
<tr>
<td>Assisted PCF, L/min (NIV users)</td>
<td>198±65</td>
</tr>
<tr>
<td>PEF, cmH20 (TMV users)</td>
<td>40±28</td>
</tr>
</tbody>
</table>

Legend: TMV – tracheostomy mechanical ventilation; NIV- noninvasive mechanical ventilation; Tot- Total population; VC - vital capacity; PCF – Peak Cough Flow; PEF . Peak Expiratory Flow; *from diagnosis; **from time of entry in the study
Table 2 – Outcomes of Home MAC and hospitalization data

<table>
<thead>
<tr>
<th></th>
<th>Patients under tracheostomy mechanical ventilation (n=18)</th>
<th>Patients under noninvasive mechanical ventilation (n = 28)</th>
<th>Total patients (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total home acute episodes of secretion encumbrance with MAC activation, nr</td>
<td>78</td>
<td>102</td>
<td>180</td>
</tr>
<tr>
<td>Home acute episodes of secretion encumbrance with MAC activation (per patient), mean±SD</td>
<td>4.3±3.7</td>
<td>3.6±2.3</td>
<td>3.9±2.9</td>
</tr>
<tr>
<td>Total Hospitalizations, nr</td>
<td>21</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Hospitalizations (per patient), mean±SD</td>
<td>1.2±1.3 *</td>
<td>0.5±0.7 *</td>
<td>0.7±1.0</td>
</tr>
<tr>
<td>Avoided Hospitalizations, nr</td>
<td>57/78 (73%)</td>
<td>89/102 (87%)</td>
<td>146/180 (81%)</td>
</tr>
</tbody>
</table>

Legend: MAC – mechanical assisted cough; nr - number
* p < 0.05
Figure 1 – Oxygen saturation (SpO2) monitoring during baseline, acute episode and at recovery (after MAC)

Legend: MAC – mechanical assisted cough

* p < 0.05 - when comparing baseline to acute episode and acute episode to after MAC
Figure 2 – Number of deep airway suctionings in TMV patients during baseline, acute episode and at recovery (after MAC)

Legend: MAC – mechanical assisted cough

* p < 0.05 - when comparing baseline to acute episode and acute episode to after MAC
References


Study 10

*Evolution of Noninvasive Management of End-Stage Respiratory Muscle Failure in Neuromuscular Disease*

Miguel R. Gonçalves, John R. Bach, Yuka Ishikawa, Eduardo Luis DeVito, Francisco Prado, Pamela Salinas, Marie Eugenia Domínguez, Emilia Luna Padrone, Mauro Vidigal-Lopes, Rita Guedes, Douglas McKim, Marcello Villanova, Seong-Woong Kang, Emilio Servera, Jesús Sancho, Michel Toussaint, Philippe Soudon, Michelle Chatwin, Anita K. Simonds, Martin Bachmann, Michael Baumberger, Tsz-Kin Kwok, Konrad Bloch, David Birnkrant, Juan Isquierdo, Ditza Gross, Louis Saporito, Brian Weaver, Alice Hon, Bilal Saulat and João Carlos Winck,

*(CHEST, in preparation for submission November 2010)*
Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
Evolution of Noninvasive Management of End-Stage Respiratory Muscle Failure in Neuromuscular Disease

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20- Ditza Gross, Telavive University Hospital, Israel
Abstract

From 20 centers in 18 countries, data are presented on 1623 nocturnal only ventilated neuromuscular disease patients (NMD) that include amyotrophic lateral sclerosis, Duchenne muscular dystrophy and spinal muscular atrophy type 1, in which 760 (47%) progressed to continuous full-setting noninvasive ventilation (NIV) over a follow up of 15 years. A protocol of oximetry feedback using mechanically assisted coughing and full-setting NIV permitted safe 229 safe extubations and 35 decanulations of patients who could not pass spontaneous breathing trials (SBTs) before or after extubation/decanulation. After the follow up period, 522 (69%) patients are still alive on continuous full-setting NIV and tracheostomy was placed in a total of 140 (9%). An expert panel reviewed recommendations of previous consensus and reviews on NIV use, respiratory evaluations and assisted coughing in NMD to consider changes and updated recommendations based on the evolution in practice patterns.

Introduction and Historical Perspective

Before 1953 noninvasive ventilation referred to the use of body ventilators like the iron lung\(^1\). Despite their success for continuous ventilatory support, tracheostomy positive pressure ventilation (TMV) became the standard for ventilatory support after a 1952 Danish polio epidemic for which there were few iron lungs\(^2\). Since TMV facilitated mobilizing patients from iron lungs because positive pressure ventilators could be rolled behind wheelchairs this invasive approach spread to the United States.
Then in 1953 Dr. John Affeldt wrote, “...some of our physical therapists, in struggling with (iron lung) patients, noticed that they could simply take the positive pressure attachment, apply a small plastic mouthpiece..., and allow that to hang in the patient's mouth....We even had one patient who has no breathing ability who has fallen asleep and been adequately ventilated by this procedure, so that it appears to work very well, and I think does away with a lot of complications of difficulty of using (invasive) positive pressure. You just hang it by the patients and they grip it with their lips, when they want it, and when they don't want it, they let go of it. It is just too simple.”

Patients who were using body ventilators around the clock began using mouth piece noninvasive intermittent positive pressure ventilation (NIV) during daytime hours. Many then refused to go back to body ventilator use and used mouth piece NIV around-the-clock. Losing the mouth piece during sleep could have meant death but there is no indication that that ever happened.

In 1956 Harris Thompson released a portable 28 lb. Bantam ventilator. The next year it was noted, “If a patient is going to be left a respirator cripple with a very low VC, a tracheotomy may be a great disadvantage. It is very difficult to get rid of a tracheotomy tube when the VC is only 500 or 600 cc and there is no power of coughing, whereas, as we all know, a patient who has been treated in a respirator (body ventilator) from the first can survive and get out of all mechanical devices with a VC of that figure.” Thus, it was recognized that TMV could result in greater ventilator dependence because of deconditioning, tube induced secretions, hyperventilation, bypassing upper airway afferents, and possibly other factors.
In 1968 the *lipseal* interface came onto the market. Lipseals prevented loss of the mouth piece during sleep and diminished air leakage, normalizing alveolar ventilation during sleep even for patients with little or no measurable vital capacity (VC). Mouth piece/lipseals were used up to continuously for long-term ventilatory support for 257 patients managed by Goldwater Memorial Hospital and by others scattered around the country from 1968 through the advent of nasal NIV in 1987 when it was first recognized that nasal NIV could provide full ventilatory support for a multiple sclerosis patient with 100 ml of VC. Despite this no other centers reported using mouthpiece NIV for diurnal ventilatory support in NMD until Servera et al. did so to avert intubations in 2005 and Toussaint et al. for continuous support in 2006.

Once articles on nasal NIV proved its efficacy in long term ventilated patients nasal and oro-nasal NIV were used in critical care. Interfaces designed for treatment with CPAP were modified for use with ventilator circuits. Nevertheless, most long-term use of these interfaces was for “sleep disordered breathing” whereas inspiratory muscle failure was not specifically addressed. This was in part due to the fact that PaCO2 monitoring and assessment of inspiratory muscle failure were not included in polysomnography that is programmed to interpret paradoxical chest wall motions as obstructive and/or central apneas rather than from respiratory muscle dysfunction. This may justify that neuromuscular disease (NMD) patients have been treated by nocturnal continuous positive airway pressure (PAP) or low span (spans less than 10 cm H2O) bi-level PAP, often referred to as “noninvasive ventilation” rather than by up to continuous full setting NIV as they would eventually require with end-stage respiratory muscle failure.
The use of CPAP and bi-level PAP has been reported in over 100 NMD papers including in the 50 reviewed in this work, and in many it resulted in statistical prolongation of life before continuous support became necessary and patients either developed ARF and underwent tracheotomy or died\textsuperscript{16-17}. Bi-level PAP at low spans were considered inadequate for patients with little or no VC\textsuperscript{18-19}. Bi-level PAP devices also do not permit air stacking\textsuperscript{6}, have low autonomy internal batteries\textsuperscript{20}, and not always make possible for infants to trigger\textsuperscript{21}. Meanwhile, portable ventilators, rather than bi-level devices, have been used by continuously NIV dependent patients for up to 56 years.

Airway secretion congestion, especially during intercurrent respiratory tract infections (RTIs) can result in acute respiratory failure (ARF)\textsuperscript{22} and intubation, and with failure to pass spontaneous breathing trials (SBTs), tracheotomy or death\textsuperscript{23}. The ability to increase cough flows by mechanically assisted coughing (MAC), available since 1993 facilitated long-term use of NIV by permitting patients to avert pneumonia and ARF\textsuperscript{22, 24-25} as well as for “unweanable” patients to be extubated without resort to tracheotomy\textsuperscript{26-27}.

**Methodology**

At the 69\textsuperscript{th} Congress of the Mexican Society of Pulmonologists and Thoracic Surgeons in April 2010, clinicians from centers who use NIV for full, long-term ventilatory support submit their data for three diagnoses: Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy type 1 (SMA 1). Other centers were invited to send their data soon after. An expert panel considered the evolution NIV reviews and consensus statements since 1993 and the importance of complimentary interventions that permit long-term NIV as an alternative to TIV.
**Results**

The data from 20 NMD centers in 18 countries on prolongation of life for NMD patients as defined by continuous NIV dependence with little or no autonomous breathing ability are in Tables 1-3. Data is presented as mean±SD for each center and the total data display (all centers together) was performed using a mean correction factor for all the items analyzed.

The centers with experience in extubation/decannulation of unweanable NMD patients to NIV/MAC despite failing all SBTs, reported 229 safe extubations in DMD, ALS and SMA1 patients and had 5 of 222 DMD, 52 of 139 ALS and 7 of 33 SMA1 continuous NIV users undergo tracheotomy. Centers reported that 47% of ALS, 54% of DMD and 39% of SMA 1 patients progressed to become continuously ventilator dependent without being hospitalized or developing ARF.

**Review of Evolution of NIV Reviews/Consensuses and Recommendations**

Three members of the panel (MRG, JRB, AH) reviewed 50 consensuses and Medline reviews from 1993-2010 with keywords for: NMD, DMD, ALS, SMA type 1, NIV, respiratory management, respiratory care, long term ventilation, and ARF. The 50 NMD NIV references included 34 on various NMDs, 5 only on DMD, 5 on SMA 1, and 6 on ALS.

The literature was analyzed for the use over time of the following: oxygen therapy, peak cough flow evaluation and augmentation, air stacking, low pressure (≤30
cmH2O) and high pressure (≥ 40 cm H2O) MAC, bi-level PAP used at both low and high spans, NIV that includes nasal and mouthpiece NIV, part-time (<23 hours/day) and full-time (>23 hours/day), oximetry feedback for NIV and MAC, elective tracheotomy without meeting reported criteria for tracheotomy\textsuperscript{28}, and extubation/decanulation of unweanable patients to NIV. The importance of each was considered by the panel. Table 4 lists the reference papers and the evolution of intervention utilization over time.

**Oxygen therapy**

Avoidance of supplemental oxygen was recommended by 24 of the 50 papers and its use ignored by the rest. Home oxygen therapy was strongly discouraged by consensuses of 2004\textsuperscript{29} and 2010\textsuperscript{30}. This panel concurred, recommending that supplemental oxygen be used only for hospitalized patients when full-setting NIV and MAC can not normalize (≥95%) oxyhemoglobin saturation (SpO2) and then only when the patient can be readily intubated. Low flow oxygen has been reported to exacerbate hypercapnia in NMD\textsuperscript{31}. Most such patients who become CO2 narcotic do so receiving oxygen rather than assisted ventilation. Besides decreasing ventilatory drive it appears to exacerbate mouth leak of nasal NIV during sleep thereby exacerbating nocturnal hypercapnia and renders oximetry less useful as a gauge of hypoventilation, airway mucus congestion, atelectasis and pneumonia\textsuperscript{6,22,32}. Oxygen supplementation, instead of no treatment or assisted ventilation was reported to result in significantly more pneumonias, hospitalizations, and hospitalization days\textsuperscript{31}. Supplemental oxygen and morphine are indicated for euthanasia such as in advanced bulbar-ALS patients who satisfy criteria for but refuse tracheotomy\textsuperscript{33}. 

240 Miguel Ramalho do Souto Gonçalves
Lung insufflation techniques: “air stacking”

Air stacking was cited in 21 of the 50 consensuses, in only 2 papers before 2002 but in 6 of 12 since 2009. Deep passive or active (air stacking) lung insufflation is required to prevent chest wall contractures and lung restriction, to maximize cough peak flows (CPF)\textsuperscript{54} and voice volume, promote lung growth, and prevent chest deformity in children with NMD\textsuperscript{6}. Air stacking involves the glottis holding consecutively delivered air volumes (from a volume-cycled ventilator or a manual resuscitator) until maximum possible lung inflation, the “maximum insufflation capacity” (MIC)\textsuperscript{35}. The panel unanimously recommended that NMD patients with VCs less than 80\% of normal practice daily air stacking and, if unable, passive maximal lung expansion. The MIC-VC is also recommended as an objective, reproducible, quantitative measure of glottic integrity\textsuperscript{36}. For small children with paradoxical breathing who can not air stack, nocturnal NIV can prevent pectus excavatum and promote lung growth and chest wall development\textsuperscript{37,38}

Evaluation and augmentation of cough peak flows (CPF)

Evaluation of CPF was cited in 25 of 50 papers, only one before 2000 but all but 5 since 2009. Measurement of unassisted and assisted CPF is useful to indicate introduction of manually assisted coughing and MAC\textsuperscript{39}. Manually assisted coughing consists of maximal air stacking followed by a cough-timed abdominal thrust. These “assisted CPF” are measured by peak flow meter and, when less than 270 to 300 L/m, indicate need for access to MAC especially during intercurrent respiratory tract infections (RTI)\textsuperscript{40}. The
Panel unanimously recommended routine measurement of CPF and augmenting them when they are less than 270 L/m.

**Noninvasive Ventilation (NIV)**

Three reviews and consensuses of respiratory management of NMD did not mention NIV. Of the remaining 47, 11 recommended high span (IPAP, EPAP spans>10 cm H2O) bi-level PAP and 29 only low span PAP. Ten of 50 papers recognized the use of NIV for full ventilatory support but none noted that tracheostomy could be avoided by this when the patients are critically ill. In 1993 indication for tracheotomy was described as need for NIV over 15 hours a day. In that report, there was only one dissenting voice who argued for continuous NIV use both in acute and chronic settings (the second author).

The use of some daytime mouth piece NIV was recommended in 16 of 47 papers but despite this, its use has been reported in only four centers. This panel unanimously felt that low bi-level spans suboptimally rest inspiratory muscles and insufficiently support patients with little or no VC. Further, since most of currently available pressure-cycled units are limited to less than 40 cm H2O, they can be inadequate for patients with poor pulmonary compliance. However, the panel unanimously recommended that bi-level PAP be introduced to all patients symptomatic for hypoventilation who can not air stack because of bulbar-innervated muscle impairment of glottic closure as in bulbar ALS. The panel also unanimously recommended that volume cycling be used for all patients capable of air stacking unless it caused excessive abdominal distension. Nocturnal NIV can then be easily extended through daytime hours as needed by switching from nocturnal nasal to diurnal mouth
piece NIV. When less than full support settings is used, tracheostomy or death becomes inevitable.

**Mechanically Assisted Cough**

Mechanically assisted coughing (MAC) is defined as mechanical insufflation-exsufflation (Cough Assist™, Phillips Respironics, Inc.) (MI-E) with an exsufflation-timed abdominal thrust. The MI-E delivers positive then negative pressures via an oro-nasal interface or invasive airway tube to full clinical expansion then emptying of the lungs. Only 12 papers mentioned MI-E at what this panel considers effective absolute pressures of >35 cm H2O, 19 recommended low pressures, 3 noted no MI-E settings, and 15 did not even mention MI-E. Only 3 papers cited the importance of MAC, that is, MI-E with an abdominal thrust. None cited the use of MAC via invasive airway tubes, found to be so critical for extubation/decanulation of patients failing SBTs. MAC can also significantly decrease hospitalization rates. The panel unanimously recommended that MAC be used, whether noninvasively or via invasive airway tube, for all NMD patients with airway secretion congestion to prevent pneumonia and to facilitate extubation/decanulation.

**Extubation and Decannulation**

Despite NIV and MAC, aspiration and intercurrent RTIs can result in pneumonia and ARF and early tracheotomy has been proposed to “minimize respiratory complications”. Before 2010, no papers described the extubation or decanulation of continuously ventilator dependent patients who could not pass SBTs before or after
extubation/decanulation. The conventional approach presupposes that ventilator weaning is necessary for safe extubation. A 2010 publication reported successful extubation of 155 of 157 unweanable NMD patients in 2 centers using a protocol including extubation to full setting NIV with the patients subsequently “weaning” themselves by taking fewer and fewer mouth piece NIVs as needed, and using MAC to clear secretions. Protocols for decanulation of unweanable patients to NIV/MAC have also been described, with advantages noted by patients for safety, convenience, appearance, comfort, speech, sleep, swallowing, and general acceptability. The panel unanimously recommended that all NMD patients with some bulbar-innervated muscle function be extubated or offered decanulation to full setting NIV and MAC with oximetry feedback. It appears that the great majority of NMD patients for whom post-extubation assisted CPF attain 160 L/m can be successfully extubated to full-setting NIV and MAC.

Tracheostomy

Tracheostomy for end-stage respiratory management was cited in 46 of 50 of the papers. Conventional strategies recommend tracheotomy when continuous NIV is required, when intubated patients are unable to pass SBTs, and electively, for example, for impending surgery. Even without ventilator use tracheostomies are often retained because of lack of familiarity with MAC for clearing airway secretions. This is true despite long-term complications of tracheostomy mechanical ventilation (TMV). In addition, patients using TMV tend to become and remain continuously ventilator dependent whereas when extubated/decanulated to continuous NIV and having VCs of 250 ml or more, wean to nocturnal only NIV; tracheostomy renders cough impossible.
because glottic closure does not maintain thoraco-abdominal pressure and it results in air leaks around the walls of the tube\textsuperscript{63}. This panel unanimously recommended that tracheotomy be indicated for all patients who aspirate so much saliva that SpO2 baseline decreases and remains below 95\% despite optimal NIV and MAC and that can not be reversed by translaryngeal intubation over a 1 month period as has only been reported for patients with ALS\textsuperscript{28}.

**Oximetry Feed-back Protocol**

An oximetry, NIV/MAC protocol consists of using an oximeter for feedback to maintain SpO\textsubscript{2}≥95\% by full-setting NIV and aggressive MAC as needed\textsuperscript{22}. The protocol was recommended in 8 of 50 papers and in only 1 before 2003. Since supplemental oxygen is avoided, patients and care providers are instructed that, once artifact is ruled out, SpO\textsubscript{2} below 95\% is due to: hypoventilation with hypercapnia, airway secretion congestion, and if not expeditiously managed, gross atelectasis or pneumonia\textsuperscript{28, 64}. The protocol is most important during RTIs and for extubation/decanulation\textsuperscript{27}. If the baseline SpO\textsubscript{2} during RTIs decreases below 95\% despite the protocol, the patient presents for a formal evaluation. The panel unanimously agreed that, since it is impossible to develop ARF with SpO2≥95\% in ambient air, patients should be taught the protocol once CPF can not exceed 270 to 300 L/m to prevent pneumonia and ARF, particularly during intercurrent RTIs that can be managed at home\textsuperscript{24-25}.
Discussion

Mechanisms by which nasal or mouthpiece/lipseal NIV can improve the clinical picture include: resting respiratory muscles and decreasing metabolic demand, increasing tidal volumes and relieving hypercapnia, resetting chemoreceptors, opening atelectatic areas, maintaining airway patency, improving ventilation/perfusion matching, maintaining lung and chest wall range-of-motion and possibly compliance, improving mucociliary clearance, and most importantly, by assisting, supporting, and substituting for inspiratory muscle function\textsuperscript{6,32}.

This work keyed on three NMD diagnoses, however, continuous full-setting NIV via mouth pieces had already been reported for 257 mainly post-polio survivors in 1993\textsuperscript{7}, 59 high level traumatic tetraplegics decanulated to full-setting NIV\textsuperscript{65-67} and patients with non-Duchenne muscular dystrophies and other myopathies\textsuperscript{18,68}. All of the centers reporting data in this study had long-term full-time NIV users with other diagnoses but it was felt that limiting the data to these common and severe conditions would be more practical and establish the point.

Nocturnal- only nasal NIV or bi-level PAP can at best marginally prolong life and delay ARF. It can possibly do so by providing moderately deeper lung volumes to assist in coughing. With advancing weakness, full-setting NIV can eventually be needed continuously without requiring intubation and hospitalization, thereby avoiding ARF and ultimately pressure by physicians to recommend tracheotomy.

Most conventionally managed patients develop ARF and die or undergo intubation and tracheotomy due to airway congestion during RTIs\textsuperscript{22}, the cause of 90\% of episodes of ARF for DMD patients without access to NIV and MAC\textsuperscript{24,69}. Suctioning...
patients' airways via the nose or mouth is rarely effective and impairs breathing. Whereas with “invasive suctioning” there is little chance of a suction catheter entering the left mainstem bronchus, “noninvasive suctioning” using MI-E would not favor right over left airway clearance.  

Since MAC can only replace inspiratory and expiratory muscle function, it can not be used to avert tracheotomy indefinitely if glottic dysfunction prevents air stacking and airway protection to maintain baseline SpO2 (≥95%) as eventually occurs in advanced bulbar ALS. The patients who benefit most from MAC are those whose bulbar muscle function is impaired but can maintain adequate airway patency but is insufficient to permit optimal air stacking for assisted CPF over 250 to 300 L/m. The data presented suggest that reported “NIV failure” can result from inadequate NIV interfaces, from inadequate ventilator settings, when MAC is not used, and when mouth piece NIV is not used for air stacking or daytime support.

Whereas some recent consensuses recommend most of the interventions that this panel considers important, all gave sufficient rationales to resort to tracheotomy for advanced patients, largely because none reported extubating or decanulating unweanable patients. Indeed, the 2010 DMD consensus was the first to make all of the recommendations that this panel considered important, however, they concluded that tracheostomy was appropriate when: preferred by the patient and clinician; NIV could not successfully be used by the patient; when there was inability of “the local medical infrastructure to support NIV”; for three extubation failures despite optimal use of NIV and MAC; for aspiration of airway secretion to the extent that SpO2 remains below 95% despite optimal use of NIV and MAC. However, this panel of 11 experts had only 4 with
any experience in continuous NIV including via mouthpiece and only one from a center where NMD patients who failed SBTs are extubated without tracheotomy.

This is markedly different from this panel in which every member has continuous long-term NIV users and at least 5 are from centers that routinely extubate and decanulate “unweanable” NMD patients including 155 consecutive successful extubations of unweanable NMD and SCI patients\(^{27}\). In addition, no one on this panel has ever noted any patient who: “preferred” to undergo tracheotomy when they could be managed by NIV and MAC. We suggest that only the patients not offered expert NIV/MAC “prefer” tracheostomy. Other than for severely mentally retarded patients no one on this panel has encountered a DMD patient who could “not successfully use NIV.” We are also unaware of “inability of local medical infrastructure to support NIV” except in countries where ventilator use is not funded. The centers that extubate unweanable DMD patients have not yet had a DMD patient fail 3 extubations and, thereby, require tracheotomy. None on this panel has witnessed a DMD patient aspirate so much saliva that the SpO2 remained below 95% (or normal SpO2 for altitude) and thereby require a tracheostomy as per tracheotomy indications for ALS\(^{28}\). Thus, while the 2010 panel’s NIV use recommendations are comprehensive up to the point of requiring intubation\(^{30}\), this panel suggests that with the ability to consistently extubate continuously ventilator dependent DMD patients and others, resort to tracheotomy should be much less common. A basic problem with the tracheotomy recommendations of the 2010 consensus is that they can be interpreted by any clinician to justify tracheostomy rather than organizing a support system of comprehensive instruction and training in NIV and MAC. Such a premise perpetuates invasive care whereas noninvasive management is less costly, requires less
technology and skilled nursing, facilitates community care and quality of life, and is invariably preferred by patients$^{51}$.

For SMA 1 it is as yet unclear whether all will some day require tracheostomy tubes for survival. Thus far, survival has been extended to up to age 17 using full-time NIV for 16 years or more for children continuously NIV dependent since as young as 4 months of age$^{72-73}$. There are now 5 such severely affected SMA 1 patients over age 15, all with VCs less than 20 ml, and none with baseline SpO2 less than 95% because of saliva aspiration. Thus, it is likely that at least some of these typically severe SMA1 patients will survive into adulthood without tracheostomy tubes despite continuous ventilatory support since infancy. Despite these outcomes, consensuses of experts as recently as 2009 report that 95% of SMA 1 children die before 18 months of age with a mean age of death at 25 weeks$^{74-75}$. Although acknowledging that NIV treated SMA 1 children can live much longer, in disbelief and without justification they dismissed this as reflecting “less severely affected children”.

**End of life and palliative care issues**

Over a 6-year period, many journals published numerous papers on the futility of managing ALS with palliative care without once referring to prolonging life by NIV/MAC$^{33,76-80}$. The data from our 1623 NIV supported patients (that include 822 ALS) suggest the inappropriateness of using palliative care precepts for properly equipped and trained patients with adequate personal care support. A number of our DMD patients, for example, are over age 40 and/or have depended on continuous NIV for over 20 years. Unlike patients deciding about tracheotomy, few patients refuse NIV or MAC when
dyspneic from inspiratory or expiratory muscle insufficiency. Our panel unanimously agreed that no properly trained and equipped patients that do not meet our criteria for tracheotomy have ever chosen elective tracheotomy or to cease NIV/MAC and die. Thus, it was unanimously felt that the use of the term “palliative respiratory care” for NMD patients perpetrates the misconception that “NIV” is only for symptom relief rather than to prolong life.

**Conclusion**

In conclusion, up to total failure of inspiratory and expiratory musculature without severe bulbar-innervated muscle dysfunction is not indication for tracheotomy. Tracheostomy ventilation has neither been demonstrated to be associated with better survival nor better quality of life than full-setting NIV, and all patients having used both TMV and NIV and who are decanulated prefer NIV overall as well as for speech, swallowing, sleep, appearance, and security.\(^{303}\) The panel recommends against elective tracheotomy for any NMD patient not meeting our criteria.\(^{116}\)
Table 1 – Data on Amyotrophic Lateral Sclerosis

<table>
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<tr>
<th>Center</th>
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<th>Duration ptNIV</th>
<th>Number FtNIV</th>
<th>Age FtNIV</th>
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<td>2</td>
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Legend – N ptNIV – number of patients beginning nocturnal noninvasive ventilation (NIV); Age ptNIV- age when beginning part-time (nocturnal) NIV; Duration ptNIV-time of use of NIV<20 hours per day; N ftNIV - number of patients progressing to >20 hr/d ventilator dependence; Duration ftNIV-duration of continuous NIV support; Current Age - age currently or at time of death; Still Alive-number of continuously NIV dependent patients still using continuous NIV; Ext-Number of extubations of “unweanable” patients to full-setting NIV support; Decan-Number of continuously ventilator dependent patients decanulated to NIV; Deaths- respiratory/total; TMV – number of patients under tracheostomy ventilation; NK – not known

Total ptNIV – 822 patients  Total ftNIV – 335 patients  Total Extubations – 26  Total Decanulations – 10
Total Deaths – 216 patients  Total Tracheostomy – 96  Median Age ptNIV – 58.1±12.6 years
Median Duration ptNIV -1.0±0.8 years  Median Age ftNIV - 56.2±4.9 years  NumberFtNIVnoHosp - 85
Median Duration ftNIV - 3.4±1.3 years  Current Age – 59.3±7.6 years  Still Alive – 186 ftNIV patients
### Table 2 – Data on Duchenne Muscular Dystrophy

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Legend – N ptNIV – number of patients beginning nocturnal noninvasive ventilation (NIV); Age ptNIV - age when beginning part-time (nocturnal) NIV; Duration ptNIV-time of use of NIV<20 hours per day; N ftNIV - number of patients progressing to >20 hr/d ventilator dependence; Duration ftNIV-duration of continuous NIV support; Current Age - age currently or at time of death; Still Alive-number of continuously NIV dependent patients still using continuous NIV; Ext-Number of extubations of "unweanable" patients to full-setting NIV support; Decan-Number of continuously ventilator dependent patients decanulated to NIV; Deaths- respiratory/total; TMV – number of patients under tracheostomy ventilation; NK – not knowned.

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### Table 3 – Data on Spinal Muscular Atrophy type 1

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Legend – N ptNIV – number of patients beginning nocturnal noninvasive ventilation (NIV); Age ptNIV – age when beginning part-time (nocturnal) NIV; Duration ptNIV-time of use of NIV<20 hours per day; N ftNIV – number of patients progressing to >20 hr/d ventilator dependence; Duration ftNIV-duration of continuous NIV support; Current Age – age currently or at time of death; Still Alive-number of continuously NIV dependent patients still using continuous NIV; Ext-Number of extubations of “unweanable” patients to full-setting NIV support; Decan-Number of continuously ventilator dependent patients decanulated to NIV; Deaths-respiratory/total; TMV – number of patients under tracheostomy ventilation; NK – not knowned

Total ptNIV – 101 patients  
Total ftNIV – 40 patients  
Total Extubations – 142  
Total Decanulations – 0

Total Deaths - 18  
Total Tracheostomy – 15  
Mean Age ptNIV – 0.43±0.2 years

Mean Duration ptNIV - 0.56±0.5 years  
Mean Age ftNIV – 0.68±0.3 years  
Number FtNIV noHosp - 14

Mean Duration ftNIV – 6.0±3.8 years  
Current Age – 7.6±2.4 years  
Still Alive – 28 ftNIV patients

Noninvasive ventilation and mechanical assisted cough: efficacy from acute to chronic care
TABLE 4 - The Evolution of Consensus and Review Articles on Noninvasive Ventilation and Neuromuscular Disease.

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Legend: Year - year of publication, O2 - oxygen avoidance, CPF - cough peak flow; AS- air stacking; MAC – mechanical assisted cough; lpMAC - mechanically assisted coughing with low pressure (<35); hPMAC – mechanical assisted coughing, high pressure (>35); lsp- low span BiPAP; hsp - high span BiPAP; MP – mouthpiece NIV, ptNIV - part-time NIV (up to 16 hours/day); fNIV - full-time NIV (>20 hours/day); TMV – tracheostomy mechanical ventilation; SpO2 feedback – protocol with oximetry feedback.
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256

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GENERAL DISCUSSION

All 10 studies that were part of this thesis were clinical and had direct positive impact on the patients studied in which NIV was insufficient due to secretion encumbrance. The addition of new measurements (VRI, MI-LIC, DF, PCF-PEF) in the chronic setting permitted the correct indication for lung expansion and air stacking techniques. MAC was able to achieve adequate CPF to clear secretions and was crucial to invert the ARF episode and avoid hospitalizations. Failure to provide adequate settings for effective nocturnal ventilatory support, mouthpiece IPPV, and manually and mechanical assisted coughing continue to make respiratory failure inevitable for the great majority this patient population.

Acute Respiratory Failure

During acute critical care, in most patients, mechanical ventilation is a short-term treatment used for up to 7 days to support or replace spontaneous breathing until the cause of respiratory failure resolves or results in death. Patients who receive mechanical ventilation for more than 7 days, when remain unweanable after 4 weeks of resolution of the acute respiratory failure (ARF) episode, have been classified as chronic ventilator-dependent patients(19). Intubated ventilator supported patients can develop hypo- or hypercapnia, decreases in pulmonary function because of airway mucus, and inspiratory muscle deconditioning.

When there is no need for an artificial airway, conventional extubation attempts follow successful “spontaneous breathing trials (SBTs) and the passing of ventilator weaning parameters(411). This may either cause anxiety because the patient is not ready to
breathe autonomously, or the schedule is too conservative, delaying respiratory muscle reconditioning. Further, the use of pulse oximetry, which can signal the presence of airway mucus encumbrment as well as their elimination with treatment, is lost with oxygen administration that is typically arbitrarily used in this setting. Some patients with muscle weakness are unable to sustain spontaneous breathing effort and are dependent on mechanical ventilation for life support. Some of them may be successfully treated with partial time NIV (nocturnal and for daytime periods), but patients who require continuous mechanical ventilation usually require more attention and support that is most cases end in tracheostomy ventilation(415).

Until our study nr 1, there have been no studies that focused on extubation of adult complete ventilator dependent NMD patients. (155, 190). A recent controlled post-extubation respiratory failure study of 106 patients included 2 with pure restrictive syndromes but none with NMD and all had passed SBTs despite hypercapnia. They were extubated to either supplemental O2 alone or in conjunction with bi-level PAP at spans of up to 14 cm H2O, pressures inadequate to sustain our patients(497). A meta-analysis of 12 extubation studies to bi-level PAP demonstrated decreased mortality, ventilator associated pneumonia, length of stay, and resort to tracheotomy, however unweanable NMD patients were uniformly excluded in all papers(20). Eligibility for extubation was based on “readiness for weaning” and failure of SBTs in 30 minutes or more. The outcomes of these studies were important to justify extubation to NIV for primarily lung/airways diseases patients with some autonomous breathing ability. For such patients SpO2>90% is usually acceptable with or without supplemental oxygen. Unlike all previous studies, patients included in study nr 1 had no ability to autonomously sustain breathing before or after extubation with VCs as low as 0 ml, so no control group extubation to O2 would be possible, ethical, or permissible by any
review board. For our patients long-term inability to maintain SpO2≥95% despite continuous NIV and MAC in ambient air is the indication for tracheotomy(481).

The success of our protocol was not only from providing continuous full-setting NIV via a variety of interfaces, but from frequent and aggressive MAC (up to every 30 min) both pre- and post-extubation to expel secretions and maintain or return SpO2 over 95%. Such a regimen simulates the normal need to cough during episodes of bronchitis/pneumonia. The aggressive use of MAC via the endotracheal tube was the main intervention that resulted in normalization of SpO2 in ambient air, the most important criterion for extubation.

In an earlier study of extubation to NIV, of possible independent variables including extent of need for ventilatory support, age, VC, and maximum CPF measured at extubation, only maximum CPF predicted extubation success or failure for 62 consecutive extubation/decannulation attempts on 49 consecutive self-directed NMD patients (358). Thirty-four of the patients were continuously ventilator dependent both pre- and post-extubation/decannulation. In that study none of the 15 extubation/decannulation attempts on those with maximum CPF below 160 L/m succeeded as opposed to an 89% success rate in this study. The most likely reasons for the difference between then and now are: baseline SpO2 criterion for extubation 92% vs. 95% and thus the earlier patients had more residual airway secretions or lung disease at extubation; 5% vs. 39% of patients with pre-extubation experience with NIV and MAC; less hospital staff experience with NIV and MAC; 50 of 62 were decanulated (not extubated); the patients were in various hospital locations; and MAC was used less often and without family involvement (9, 462).
The 87% first attempt extubation success rate on patients with maximum CPF<160 L/m study nr 1 is greater than the 82.4% (61 of 74) success rate reported for extubating ventilator dependent infants with SMA type 1 according to an almost identical protocol(498). The difference is most likely due to the ability of these patients, as opposed to babies, to fully cooperate with NIV and MAC. The SMA 1 patients may have also had more severe bulbar-innervated muscle dysfunction. Thus, while the extubation success rates for our patients with CPF<160 L/m were higher than those for a comparable infant population they were significantly less (89% vs. 100%) (p<0.05) than for patients with assisted CPF≥160 L/m. Unmeasurable assisted CPF indicate inability to close the glottis and are often associated with airway collapse (stridor) and saliva aspiration that render MAC less effective.

An NIV/MAC protocol has already been demonstrated to have avoided over 100 hospitalizations for continuously NIV dependent NMD patients (63, 127, 481). Study nr 1 considered unweanable NMD patients for whom an acute hospitalization and intubation could not be or were not avoided.

In this study, patients were extubated when the following criteria were satisfied: no supplemental oxygen requirement to maintain SpO2 greater than 94%, chest radiograph abnormalities cleared or clearing, respiratory depressants discontinued, airway secretions less than on admission, and any nasal congestion cleared. Thus, once the patient is afebrile with a normal white blood cell count and the SpO2 is normal on room air, the nasogastric tube is first removed to facilitate immediate post-extubation nasal IPPV. MAC is then provided via the upper airway via an oral-nasal interface and the oximetry feedback protocol is followed.
The general notion that early tracheotomy after intubation somehow facilitates ventilator weaning (436) should be reassessed for patients with NMD. In most instances, upon extubation, patients with VC of 250 ml or more eventually weaned from continuous to nocturnal-only aid by taking fewer and fewer mouth piece IPPVs. Thus, the paradigm of weaning then extubation can be changed to extubation then weaning.

Employing noninvasive rather than invasive mechanical ventilation has also been reported to decrease risk of ventilator associated pneumonia by 75% or greater(103, 499) and other subsequent complications associated with invasive airway tubes. Use of mouth pieces rather than other interfaces for daytime ventilatory support also facilitated speech, oral intake, comfort, and air stacking to deep lung insufflations to maintain pulmonary compliance, (127, 362, 500) diminished atelectasis, and augmented CPF(362). Nasal interface skin pressure was also avoided with mouthpiece use.

The main purpose of study nr 1 was not to facilitate ventilator weaning or to consider long-term outcomes but simply to extubate unweanable NMD patients without tracheotomy. It has already been suggested that extubation and decannulation can facilitate ventilator weaning and quality of life(438). Likewise, over 10,000 patient-years of continuous noninvasive ventilatory support has already been reported(9) and no one has demonstrated greater outcomes or survival by invasive rather than by noninvasive means for this patient population.

In study nr 2 we report 13 intubated and 7 tracheostomized SCI patients (above C5-C6, ASIA A and B) completely ventilatory dependent that were all successfully extubated and decanulated with specific protocols. It is has been described that 74% of ASIA A SCI patients above the level of C5 required intubation(441) and the overall incidence of tracheostomy in these cases was between 81 and 83%(442-443). The number of
respiratory complications during this phase contributes significantly to both hospital length of stay and costs(444).

Guidelines for respiratory management after SCI were published in 2005 (501), however these recommendations relied on evidence that did not pertain to the acute ventilatory impairment of the SCI population. In 2006, Bach challenged the medical community to decanulate high level SCI patients to NIV to avoid the complications of tracheostomy, to facilitate training in glosso-pharyngeal breathing to increase autonomous breathing ability and security in the event of ventilator failure, and to return home (502) **Study nr 2** is the first to accept this challenge.

In this study, besides successful extubation and decannulation of totally ventilator dependent patients, after the protocol, only 9 (45%) of the total population used NIV at discharge and all others weaned to autonomous breathing. The use of high delivered NIV volumes has been reported to facilitate the weaning process and lessen risk of respiratory complications(503) as well as result in increased VC and CPF for patients who are extubated(487) or decanulated(358, 438, 504) and our results are consistent with those studies. Moreover, it is not expected that continuous NIV can be a successful alternative to invasive ventilation, if patients use only mask ventilation(492). Further, for both groups, mouthpiece ventilation normalized speech, provided normal daytime ventilation, permitted "air stacking" for lung expansion and assisted coughing, and weaning(87, 438, 487).

Patients with high SCI are expected to be ventilator weaned with supplemental oxygen, despite some combination of hypercapnia and airway mucus encumbrance. This effectively is the main reason for patients to require reintubation(445) and tracheostomy(442) that did not occur in any patient extubated in **study nr 2**. As in **study nr 1**, aggressive
use of MAC via translaryngeal and tracheostomy tubes was the main intervention that may have improved pulmonary function (VC and CPF) and normalized SpO2 in ambient air to satisfy the most important criterion for extubation/decannulation. Our findings are consistent with those of Bach et al.(358, 505), however our patients were all successfully extubated despite some having assisted CPF below 160l/min (at extubation). This was possibly due to the more aggressive use of MAC up to every 15 min to maintain normal SpO2. Pillastrini et al.(506), too reported that mechanical in- exsufflation aided in clearance of bronchial secretions and increased forced VC, forced expiratory volume in 1 second, and peak expiratory flows for tracheostomized SCI subjects. Vital Capacity and CPF also improved in our patients because of lung expansion and secretions removal.

Decannulation protocols in long term mechanical ventilated patients have been described in other studies (507-508), however these reports only consider decannulation when ventilatory weaning was achieved and considered as failures the patients who could not be weaned from the ventilator, without considering the use of NIV. Therefore patients from study nr 2 would have been considered “unweanable” under current recommendations (415, 431).Transition from tracheostomy to continuous NIV was progressive and implied a specific protocol that included ventilation with a deflated cuff for increasing periods until it could be tolerated throughout daytime hours and overnight.

This “open system” ventilation(509) permitted the patients to improve their vocal cord function that was essential for successful NIV training with a capped cuffless fenestrated tube. In 2004 we reported that decannulation and conversion to NIV and MAC can facilitate ventilator weaning of CMV dependent patients(438). It has also
been reported that decanulated patients invariably prefer NIV over return to tracheostomy ventilation for safety, convenience, appearance, comfort, facilitating effect on speech, sleep, and swallowing, and overall (439). Although there are studies that report successful extubation and decannulation rates with the use of NIV and MAC in high SCI patients (97, 358), study nr 2 is the first to compare the extubation with the decannulation outcomes using the same protocol in this patient population.

In this study, both short–term and long term outcomes for the extubated patients were better than for the decanulated patients. Thus, it appears preferable, in this patient population, to prevent tracheotomy in the first place, whenever possible, rather than decanulate later on. Certainly, patients with severe bulbar-innervated muscle involvement, head injury, chest trauma, medical fragility, complicated courses including the need for surgical procedures over a greater than 3 or 4 week period are best managed by tracheotomy.

Data from study nr 2 also show that the extubated SCI patients had significantly shorter ICU stays, were more quickly extubated than the decanulated patients decanulated, had higher VC at 48 hours after tube removal, higher unassisted and assisted CPF at 48 hours and at 6 months after tube removal than those decannulated. This can be due to the fact that extubated patients had significant less time on invasive ventilation with consequent less respiratory muscle deconditioning, were somehow less severely affected despite comparable VCs and ASIA levels at extubation, or had less risk of upper airway instability and less secretion encumbrance or segmental atelectasis despite the same CPF and normal SpO2. Moreover, the decanulated patients needed MAC to clear airway secretions for longer periods of time as well as more time for NIV training and tracheostomy site closure. The higher values of VC at 48 hours after extubation
explains the greater number of extubated patients discharged to the community with no ventilatory support.

Although tracheostomy may have physiologic benefits over endotracheal tubes in terms of reduced work of breathing and permitting more efficient suctioning, over 90% of the time suction catheters enter only the right mainstem bronchus resulting in 80% of pneumonias occurring on the left lungs of these patients and work of breathing is readily compensated by providing pressure support during SBTs. There are no reports of better outcomes with tracheostomy ventilation when compared to the NIV/MAC protocols.

Improvement in VC, CPF and SpO2 following MAC has been reported (54, 60, 62, 84). Studies 1 and 2 are consistent with those reports in acute setting with direct impact on extubation and decannulation outcomes. A controlled study with a crossover design controlled study would be needed to compare the effectiveness of noninvasive secretion management (MAC) to invasive airway suctioning, however, due to the significant efficacy of MAC in severe totally ventilator dependent patients with muscle weakness, it would not be ethical to include this patient population in such trials.

In critical care, patients’ mucociliary elevators are impaired by intubation. Thus, mucus accumulation can greatly hamper ventilator weaning and the ability to remain extubated and is one of the main reasons for patients to require reintubation. These effects are exacerbated by the tendency of intubated patients to develop malnutrition often in part due to the presence of the tube. Thus, it is not surprising that conventional extubation is very significantly less often successful by comparison to extubation using respiratory muscle aids. Early extubation, coupled with the use of noninvasive ventilatory support has been used effectively in several critical ill populations to facilitate weaning (20, 114,
155), improve survival(161), decrease the incidence of ventilator-associated pneumonia(103, 153) and reduce ICU length of stay(153, 161). However there is a higher risk of NIV failure when applied in patients that develop ARF after extubation and the evidence that supports its application is conflicting (159-160, 446).

The results found in the trial included in study nr 3 suggest that secretion management with MI-E may work as an useful complement technique to treat patients who develop ARF in the first 48 hours post-extubation. The efficacy of MI-E had a stronger impact in preventing re-intubation in the group of patients that required NIV, justified by the lower NIV failure rates in the patients that were submitted to MI-E. By contrast, significant debate still exists concerning the precise indications and efficacy of NIV in this patient population(512) without any mention to the problem of impaired airway secretion.

The randomized controlled studies performed by Esteban et al (159). and Keenan et al(160). concluded that NIV is not efficient in reducing re-intubation rates, duration of invasive mechanical ventilation and ICU and hospital length of stay. None of these studies showed improvement in survival in patients that used NIV other than SMT. In contrary, the trials conducted by Nava et al.(190) and Ferrer et al.(155) found positive outcomes with NIV in preventing ARF after extubation. Several reasons may explain these differences. First, whereas the studies by Keenan et al(160) and Esteban et al(159) applied NIV after patients had developed symptoms of respiratory failure, the studies by Nava et al(190) and Ferrer et al(155) previously identified the high-risk patients and applied NIV immediately after extubation. Because longer time from extubation to re-intubation is associated with worse outcome(32), the delay in re-intubation correlates with worse survival rates in patients who received NIV for established post-extubation respiratory failure(159-160). Thus, the early application of NIV seems crucial to avoid
respiratory failure after extubation, and consequently re-intubation. Second, a significantly higher proportion of patients with chronic respiratory disorders were included in the studies that used early NIV in high risk patients, whereas the NIV post-extubation respiratory failure trials enrolled only 10–11% of patients with chronic pulmonary disease and used different definitions for post-extubation respiratory failure.

In our study, both experimental and control groups included 20% of patients with chronic respiratory disorders, and all patients were closely monitored during the first 48 hours for early detection of signs and symptoms that indicated post-extubation respiratory failure. As in the trials by Esteban et al.(159) and Keenan et al.(160) NIV was only applied after the development of those symptoms according to specific criteria. However, in our study NIV was applied in both study group patients and controls and only MI-E application was considered an independent variable.

Secretion encumbrance and impaired airway clearance have been considered an independent factor for extubation failure(513), and associated to NIV failure both in persistent weaning(153) and in post-extubation failure(159) patients. While it is relatively easy managing secretions through an endotracheal tube, it can be a serious problem after extubation and specially during NIV. Deep airway suction suctioning through the tube is a strategy most commonly used by nursing staff to manage secretions while patients are on invasive MV, however it can more traumatic, difficult to perform and often ineffective in extubated patients since it must be performed blindly through the nose or the mouth.

It has been reported that conventional chest physical therapy for secretion management does not increase the chances of weaning and extubation success (357). However,
critically ill patients may have normal mucociliary clearance but ineffective CPF which itself has been associated with extubation failure (37, 358).

**Study nr 3** randomly used MI-E (CoughAssist™, Phillips Respironics International Inc., Murrysville, Pa) pre-extubation via invasive tube and post-extubation through oronasal interface at sufficient inspiratory and expiratory pressures (minimum of 40 to -40 cm H2O) to fully expand and then fully empty the adult lungs in 6-8 seconds, thereby expelling airway secretions while avoiding both hyper and hypoventilation. The ability to use MI-E through the endotracheal tube immediately before extubation was the main intervention that permitted the patients from the study group to minimize the risk of post-extubation secretion encumbrance and, together with its 3 time daily noninvasively application, may have had influence on the reduction of re-intubation and NIV failure rates.

Although MI-E has been described as a very efficient technique in the acute setting for patients with neuromuscular disease (NMD), in the treatment of respiratory failure due to upper respiratory tract infections (246), to avoid intubation (27) and to facilitate extubation, decannulation and prevent post-extubation failure (358, 438, 505), the evidence supporting the role of this technique in this other critical ill patient population is lacking. Indeed, **study nr 3** is the first randomized controlled trial focused on MI-E in critical care.

The fact that there is strong evidence on the efficacy of MI-E in critical ill patients with NMD, and the authors’ positive experience with this technique in this patient population (**study nr 3**), was the ethical reasons to exclude them from the **study nr 3**.

Potential limitations have to be taken into account when analyzing the differences between the two groups. First, although there were no significant differences in baseline
characteristics at the entry of the study between the 2 groups patients from the conventional extubation group had slightly more hypoxemic respiratory failure which may have had impact on the NIV failure rate in this patient group, since NIV is more likely to fail when severe hypoxia is present(156). Second, 6 controls and 4 study group patients were re-intubated immediately with no indication for NIV. This fact was associated with causes that could not be solved by MI-E, since cooperation with the technique is crucial in extubated patients, fact that justified the best outcomes in patients that required NIV.

**Chronic Respiratory Failure**

Numerical parameters such as respiratory rate (RR), Rapid Shallow Breathing Index, maximal inspiratory pressure, and PaCO2 have been offered as indicators for nocturnal NIV but have been unreliable(514). Although numerous unsubstantiated opinions have also been given on indications for initiating nocturnal NIV, and current Medicare guidelines for ventilator use mandate VC less than 50% of predicted normal, no universally accepted objective parameters have yet been defined(18, 101, 515). Decisions about ventilator use are largely based on the results of polysomnograms, pulmonary function testing, and arterial blood gas samples. However, daytime arterial blood gases may be normal despite symptomatic nocturnal hypoventilation. Indeed, 30% of patients hyperventilate from the pain of arterial puncture(516). Polysomnograms do not distinguish apneas/hypopneas due to central and obstructive events from those due to inspiratory muscle weakness(517). Further, conventional pulmonary function testing is designed for patients with lung and airways diseases rather than muscle weakness.
Forced VC, flow and diffusion studies evaluated with the patient in the sitting position reflect lung/airways disease. The VC measured with the patient supine is not part of routine pulmonary function testing but better reflects diaphragm weakness. In a recent study, supine VC less than 75% of predicted normal was 100% sensitive and specific for predicting an abnormally low transdiaphragmatic pressure (Pdi)(518). Indeed, patients can have VCs approaching normal when sitting but be less than 50% of normal and have no ability to breathe when supine. The inaccuracy of considering VC alone, especially in the sitting position, to indicate ventilator use has also been reported by others(519).

Most often, asymptomatic patients with NMD are offered nocturnal continuous PAP or low-span bi-level PAP on the basis of routine polysomnograms. This approach is valid for treating central or obstructive apneas but not severe inspiratory muscle weakness and hypoventilation for which high ventilator volumes and pressures are needed for ventilatory support and muscle rest(10). The failure of skeletal muscle to continue to generate a given tension is defined as muscle fatigue. When a patient is not able to sustain the muscular work of breathing in the presence of increasing ventilatory load or decreasing work capacity, muscle fatigue can occur and ventilatory assistance become necessary. Bellemare and Grassino quantitated inspiratory muscle fatigue by measuring the time elapsed between the onset of diaphragm contraction and the point at which a target tension can no longer be sustained (Tlim)(456). In the case of the diaphragm, there are two main factors influencing muscle fatigue or Tlim. The first is the Ti/Ttot or duty cycle of the diaphragm. Since the diaphragm contracts mainly during inspiration, it should fatigue more rapidly at any given tension if Ti/Ttot is abnormally increased. The second is Pdi/PdiMax or the mean trans-diaphragmatic pressure swing developed with each inspiration. The diaphragm should fatigue more rapidly at any given Ti/Ttot,
if the Pdi/PdiMax is greater than normal. They reported the relationship between Tlim and TTIdi, that is, (Ti/Ttot) x (Pdi/PdiMax), and determined that Tlim = 0.1(TTIdi). Thus, diaphragm endurance time could be predicted by the TTIdi. Determining TTIdi requires placement of an esophageal balloon to measure Pdi and PdiMax. This makes it impractical for general use. It has already demonstrated that Vt/VC can substitute for Pdi/PdiMax because the more Vt approaches VC, the less the ability of inspiratory muscles to sustain alveolar ventilation(520). Our data suggest that the VRI using Vt/VC can supplement VC to help gauge the need for ventilator use by reflecting ventilatory reserve.

In a previous study, Koga et al. described a breathing intolerance index (Ti/Ttot x Vt/VC) in patients with lung/chest wall disease including 11 who were nocturnal-only ventilator users, and in healthy subjects, and observed that it could be useful for justifying ventilator use (520). In study nr 4 we proposed a Ventilator Requirement Index (VRI) were we multiplied the Ti/Ttot x Vt/VC x respiratory rate (RR), to determine whether this index could distinguish patients with NMDs with various levels of inspiratory muscle dysfunction and need for ventilator use.

An accurate index of extent of ventilator need can be important to justify the prescription of one, two, or no ventilators. Patients with symptomatic hypoventilation on the basis of inspiratory muscle dysfunction benefit from ventilator use at least during sleep(89). These patients can use either pressure-cycled (BiPAP™) or volume-cycled machines. Likewise, two ventilators are required when a patient is continuously ventilator dependent. Considering our data, anyone with NMD who appears to be symptomatic for alveolar hypoventilation or who has a VC less than 50% or VRI greater than 1.2 should have a trial of nocturnal NIV for symptomatic relief. Even 8 of 18 patients without obvious symptoms but with VC less than 50% or VRI greater than
1.2 felt sufficient benefit to go on using nocturnal NIV once introduced to it. Thus, documentation of a VRI greater than 1.2 or a VC less than 50% is justification for the prescription of a trial of part-time ventilator use. Once a patient requires ventilator use greater than 20 hours day, a second ventilator should be prescribed provided that the VC is less than 1000 ml or the VRI is greater than 2.5.

Maximum inspiratory pressures and maximum expiratory pressures are direct measures of inspiratory and expiratory muscle strength. For patients with primarily ventilatory impairment expiratory muscles are usually weaker than inspiratory muscles(521). Expiratory muscle weakness not only decreases peak expiratory flows but it decreases CPF(461). Routine pulmonary function testing includes the measurement of maximum expiratory pressures and peak expiratory flow rates but not CPF(495, 522).

Cough peak flows are generally between 40 and 50% greater than peak expiratory flows in normals as well as in patients with DMD(464). In severe bulbar ALS patients, however, they may not be measurable because of inability to close the glottis(461). Despite their importance, CPF have not yet been standardized.

Besides inspiratory and expiratory muscle weakness, CPF are also decreased by bulbar muscle dysfunction that impairs glottic retention of an optimal breath, that impairs glottic patency, vocal cord movement, and pharyngeal dilator function, and that leads to aspiration of food or saliva. CPF are the best indication of the functional integrity of bulbar musculature. They are also decreased by upper or lower airway obstruction, anatomical or functional.

In study nr 5 we found that “dart flows” (DF) are significantly greater than CPF which are, in turn, significantly greater than PEF for normals as well as for this group of
patients with NMD. The fact that CPF are normally greater than PEF in healthy people as well as for patients with Duchenne muscular dystrophy has already been reported(464). These three flow maneuvers are similar in that they are expiratory flows measured at the mouth using a peak flow meter. However, each method of flow generation requires different respiratory muscle groups.

With glottic closure, the greater transpulmonary pressures created by coughing rather than by PEF maneuvers resulted in flows measured at the mouth being greater for the former except for 12.8% of patients. However, cough efficacy is dependent on the peak flow velocity which is greater as airways narrow during coughing, making coughing more effective at expulsing airway secretions than huffing even though PEF and CPF may be comparable when measured at the mouth(54). The reduction of the cross sectional area of the airways during coughing is due to smooth muscle constriction mediated by a vagal reflex (presumably preserved in these diseases), and due to dynamic compression of the airways generated by the expiratory (transpulmonary) pressure(523). The reduction in the cross sectional area of the airways increases fivefold the velocity of gas and 25 fold the kinetic energy of the airstream. This explains why the subgroup of 16 patients (12.8%) with CPF lower than PEF coughed rather than huffed to expel secretions. Effective CPF and PEF share the need for deep lung volumes, explaining their good correlation with VC and MIC.

The correlation of CPF with MIC or MIC, VC difference is explained by their dependence on bulbar-innervated muscle (glottic) function. Whereas diminished CPF and MIC-VC difference can be due to laryngeal dysfunction and are associated with elevated risk of respiratory complications, DF usually exceed CPF and PEF. However, DF are measured at the mouth but do not emanate from the airways and require little or no inspiratory or expiratory muscle effort. DF, while also dependent on bulbar-
innervated muscles but not glottic function, do not appear to reflect risk of respiratory complications. Inability to create measurable DF, however, is associated with ineffective saliva control and drooling. These flows can also be confused with CPF if the clinician is not careful to listen for glottic closure during CPF measurements. For nine patients, seven with motor neuron disease, maximum DF were less than CPF. Thus, different patterns of bulbar-innervated muscle dysfunction occur. In this way, DF are similar to PEF since Wohlgemuth et al. (524) and Holcroft et al. (525) have pointed out the need to caution their subjects from spitting during the measurement of PEF.

Although all of the flow maneuvers are dependent on effort and motivation, we don’t think this was a confounding factor in our study since the three measures were obtained in the same visit, in varying order, by the same examiner, and only the maximum value of many attempts was recorded.

The techniques are simple and the peak flow meter required for measuring CPF and PEF is very inexpensive and more widely available than spirometers required for measuring VC and MIC. Assessment of both assisted and unassisted CPF is a convenient method to objectify bulbar-innervated muscle function and respiratory risk (364). A larger study is warranted to determine standard values of CPF and DF by age, height, and weight. Peak flow meters with greater range should be developed to more accurately measure the high range flows (526).

Like limb articulations and other soft tissues, the lungs and chest wall, too, require regular motion to prevent chest wall contractures and lung restriction. As has been recognized since at least 1952, this can only be achieved by air stacking, by providing deep insufflations (via the upper airway or by "sighs" for patients using invasive
mechanical ventilation), or by nocturnal noninvasive ventilation for patients who cannot cooperate with air stacking or insufflation therapy (83).

Kang and Bach also proved that the CPF value could be even higher if it is performed through the Maximum Insufflation Capacity (MIC). The MIC is related to the pulmonary compliance and with the pharyngeal and oropharingeal muscles function (362). For most patients with NMD, while the VC decreases with time the MIC increases for years before, however in ALS patients with bulbar impairment the decrease of VC is proportional to the decrease of MIC (527).

The goal of conventional prescriptions for “range-of-motion” mobilization of extremity articulations is to slow the development of musculoskeletal contractures for patients with limb muscle weakness. However, the prevention of chest wall contractures and lung restriction has only recently been addressed. In 2006, Lechtzin et al. (528) reported the use of short-term noninvasive intermittent positive pressure ventilation (IPPV) to increase pulmonary compliance for patients with amyotrophic lateral sclerosis (ALS). Kang et al. demonstrated that lung volumes could be increased significantly over VC by air stacking to approach MIC for patients with NMD. This resulted in significantly increased (assisted) CPF that can decrease the risk of pneumonia. For patients such as those with advanced bulbar ALS whose MIC equals VC, assisted CPF cannot be increased by air stacking, and prognosis is poor (10).

**Study nr 6** describes a simple technique that bypasses glottic function for providing deep lung insufflations and for quantitating them as Lung Insufflation Capacity (LIC).

Patients with NMD often lose VC to the extent that they can expand their lungs to only a small fraction of predicted volumes. For example, DMD patients’ VC decrease to approximately 10% of predicted normal by age 20 (529) and typical SMA type 1
patients’ VC have been reported to never exceed 250 ml(530), which, by age 10, amounts to less than 10% of the predicted normal value(531). Incentive spirometry is, therefore, useless because such patients’ tidal volumes approach their deepest breaths, and these cannot exceed a small percentage of their insufflation capacity (IC). Likewise, in reviews of studies in which inspiratory resistive exercise was performed by NMD patients, no effect on VC, lung volumes, or maximum inspiratory or expiratory pressures was reported(532). On the other hand, expanding the lungs well beyond IC by air stacking or by single, deep insufflations permits greater lung distension, voice volume, and CPF and can decrease atelectasis and loss of pulmonary compliance(364). Our results show that the benefits can be greatest for the most advanced patients with the lowest VC. The fact that lung expansion to LIC -VC trends inversely with VC, whereas MIC -VC does not, indicates that, for the most advanced patients, it is increasingly important to expand the lungs by passive insufflation rather than by air stacking. In addition, MIC and LIC can increase with practice.

Inability to air stack no longer means that patients cannot simply and inexpensively expand their lungs beyond IC. Study nr 6 demonstrates that like LIC-MIC, too, is an objective, quantifiable, reproducible measure that (inversely) correlates with glottic integrity. Glottic function is the most important aspect of bulbar-innervated muscle function for NMD patients (364, 461)because it is most important for airway protection and cough effectiveness and, therefore, permits the use of NIV to avoid otherwise inevitable respiratory failure leading to death or tracheostomy with decreased quality of life(63).

In this study, some patients were hypercapnic on presentation and had lungs stiff to the extent that using a manual resuscitator to increase tidal volumes to normalize CO2 failed to do so and resulted in high airway pressures and chest discomfort. With regular
lung mobilization therapy and nocturnal NIV, however, five such patients became able to renormalize CO2 when breathing autonomously without chest discomfort. This is consistent with previous studies in which passive lung insufflation volumes were greatly diminished for patients who were ventilated at constant pressures/volumes without regular deep insufflations (468, 528). Patients supported by NIV at large delivered volumes (1100–1500 ml) physiologically vary tidal volumes, can air stack to deep lung volumes as a function of their bulbar innervated muscle integrity, and can better retain lung distensibility(9). Thus, if pressure-cycled ventilators such as bi-level units (with which air stacking is impossible) are used for nocturnal NIV, patients with diminished VC should be equipped with a manual resuscitator or a volume cycled ventilator for air stacking/maximal insufflations.

**Home mechanical ventilation**

Although only about 31% of ventilator users in acute hospitals have neuromuscular ventilatory failure by comparison to 60% with cardiopulmonary disorders, because neuromuscular ventilator users have a better prognosis and tend to use ventilators much longer, they constitute over 50% of home mechanical ventilator users in the United States(474)The population of home mechanical ventilator users has, in fact, more than doubled since 1987(248) in Europe.

The vital use of manually assisted coughing was reported in only 18%, and MI-E in only 5% of the clinics that prescribe respiratory care for patients with NMD(377). Thus, failure to provide effective nocturnal ventilatory support, mouthpiece IPPV, and
assisted coughing continue to make respiratory failure inevitable for the great majority of people with NMD.

Approaches to preventing peripheral airway secretion retention at home for patients with NMD include the use of medications to reduce mucus hypersecretion or to liquefy secretions, and facilitation of mucus mobilization. The latter can include manual or mechanical chest percussion or vibration, direct oscillation of the air column, and postural drainage. The goal is to transport mucus from the peripheral to the central airways from where it can more easily be eliminated by manual assisted coughing and mechanical assisted cough (MAC).

Home ventilated patients with NMD, however, do not have adequate inspiratory and expiratory strength for sufficient cough flows. Thus, instead of overemphasizing the effort-intensive use of secretion drainage techniques, these patients mostly need to learn how to normalize their cough flows by using inspiratory and expiratory muscle aids. Moreover, chest clapping also causes hypoxia so at times supplemental oxygen needs to be administered(533).

Study nr 7 describes the indications of home MAC and its safety and compliance in NMD patients. Oximetry feedback has proven usefulness by allowing to detect a sudden decrease in SpO2 resulting from mucus plug (127, 481) Patients referred in this study presented severe ventilatory failure and were on continuous mechanical ventilation through noninvasive interfaces or tracheostomy.

The main condition for an efficacious home care after hospital discharge was the presence of an adequate and motivated caregiver. In this study home basis MI-E was centred in non-professional caregivers, with the support of a trained health care professional in a home on-call regime. Moreover, it describes the importance of an
educational phase, introduced early to both patients and caregivers in the hospital, as also proposed by Tzeng et al(127). Therefore, study nr 7 confirms that the caregiver, when trained and motivated, can successfully use MI-E at home, and detect early signs and symptoms of possible clinical respiratory worsening.

According to the methods applied in studies 5 and 6 of this thesis, bulbar muscle function was evaluated, because severe bulbar dysfunction is responsible for malfunction of the upper airway muscles, creating a dynamic collapse during the exsufflation phase of MI-E, making this technique ineffective in this group of patients(10, 60, 396). In this study ALS, which is the most common diagnosis, represents a heterogeneous group: from non-bulbar with inadequate CPF to severe bulbar requiring tracheostomy. The need of tracheostomy represents itself an extra problem either concerning to its acceptance by the patients or associated to tracheostomy related problems (local inflammation, increased secretions and infections)(534-537).

Moreover, even though tracheostomy was proposed to all our severe bulbar patients, some still rejected tracheostomy and preferred to continue with NIV and MAC protocol at home. Bach et al have also reported that even severe bulbar ALS patients, can be supported by combined used of VNI and MAC, delaying tracheostomy as long as the SpO2 can be maintained above 95% in room air(481). However, these patients require a close periodic monitoring in order to anticipate failure of non-invasive approach, so that therapeutic options can be explored and discussed with patients and family, with the intention that decisions can be made in advance rather than at the time of a respiratory crisis(538).
In this study nr 7 each home MAC session consisted of 6 to 8 MI-E cycles at mean pressures of 40 to -40 cmH₂O, titrated according to patients’ tolerance. Chatwin et al.(56) and Sivasothy et al.(539) have considered lower pressures to be more comfortable and safe. However our settings are widely preferred for both comfort and effectiveness and were also similar to those suggested by physiological studies.(57, 62, 365). Moreover, we had special attention on a careful individualized MI-E pressure titration, trying to achieve maximal chest expansion, respecting comfort, which may justify the tolerance and absence of complications.

According to patients and their caregivers there were few episodes in which home MAC was not sufficient to deal with secretions encumbrance and emergency department visits or hospitalizations were necessary. Other studies have already reported that NMD patients dependent on NIV and using MAC guided by oximetry feedback may be safely managed at home without hospitalizations (10, 63, 127, 470).

We observed in study nr 7 that patients use home MAC according to their needs and following oximetry feedback that consisted on using an oximeter for to maintain SpO2 greater than 94% by maintaining effective alveolar ventilation and airway secretion elimination. Some patients used it daily and others intermittently during RTIs. This study also showed that all patients with tracheostomy used MAC daily and more times a day than patients under NIV, which used it more intermittently during RTIs. This fact may be justified to local inflammation and increased secretions related to tracheostomy.

Study nr 7 showed that compliance of home MAC is different among NMD patients and the organization of home care MAC programs in this population with severe ventilatory impairment requires more study. Study nr 8 questioned that, although MAC can be effective when continuously available at home (63, 127), expense can be
mitigated by on-demand rather than continuous access if on-demand MAC use can be demonstrated to be effective. This study demonstrated that, for patients with ALS, a program of telephone access, educational intervention, and on-demand home assisted coughing interventions was shown to be feasible, very well accepted and resulted in significant cost savings.

Although there are a number of studies that describe the efficacy of manual and mechanical cough assistance techniques in hospital acute situations, until now there have been no studies that focus directly on the feasibility and management of cough assistance techniques at home for ALS patients. Only one previous ALS study used continuous videoconferencing and telephone consultation for only four ALS patients. It was also limited by the patients’ inability to master the use of the Internet and Webcams(540).

Severe bulbar patients and moderate bulbar patients without tracheotomy had a poor prognosis and high risk of death as previously noted(396). As in study nr 7, these results also confirm that clinical worsening related to secretion encumbrance can be detected by oximetry and SpO2 baseline normalized by MAC in the home setting for ALS patients(481).

Study nr 8 also confirmed that respiratory care of advanced ALS is only effective if families and care providers assist with oximetry and assisted coughing. Thus, a motivated caregiver can successfully use at home cough assistance to prevent lung pathology and hospitalizations. The higher number of avoided hospitalizations in the patients with clinical worsening, that activated home MAC may suggest that this approach can reduce and/or prevent respiratory infections with consequent reduction in number of hospitalizations in ALS patients.
When home visits are performed by a health care professional, the “on request” use and rental of MI-E devices prescribed by a multidisciplinary team of experts, can offer a clinical service together with a significant financial saving compared with continuous care strategy prescription (to all ALS patients for all the days) of home cough assist devices. This choice, up to now, is particularly costly and has not been demonstrated to be the best approach to achieve a good cost/benefit. Oximetry monitoring with on-demand professional attention and MAC is a cost-saving alternative that is not only relevant for the European health care system but also for the American system where the continuous prescription of MI-E is widely used even though most patients do not need assisted coughing every day. Indeed, study nr 8 showed that 56% of the patients did not need to use MAC and those who used it, did so for <20% of the total follow-up period. Moreover we also confirmed in study nr 8, that ALS patients under tracheostomy have more necessity to use MAC, justified by the higher number of episodes of clinical worsening compared to the patients under NIV. We found also in study nr 8, that this on-demand program adds considerably to the patients’ and clinicians’ feelings of security in managing such patients at home with concomitant positive outcomes and reduced costs.

After confirming in studies 7 and 8, the feasibility, patients’ compliance and better organization of efficient home MAC access, in study nr 9, we reported data that focused on the clinical effects of home MAC during acute episodes of secretion encumbrance in ALS and other NMD patients, all totally ventilator dependent either through NIV or by tracheostomy.

The results of study nr 8 confirm that hospitalizations for ARF can be avoided for NMD patients by a protocol of oximetry feedback for using ventilatory support and MAC in the home (10, 63, 127, 481). Moreover these findings support again the clinical
justification for availability and prescription of cough assist devices and portable oximeters at home for this patient population, especially during intercurrent RTI’s. Since all patients were continuously ventilator dependent during the episodes, had the oxyhemoglobin desaturations and dyspnea not been reversed by MAC, they would have had to have been hospitalized for problems related to upper respiratory tract infections and inability to clear secretions. However, in study nr 9, as a result of the protocol, 81% of the acute episodes resolved without hospitalization.

These results are consistent with those reported by Gomes-Merino et al (63) that, with a similar approach, described hospitalization avoidance and survival increase in a population with Duchenne muscular dystrophy under NIV. Study nr 9 focused on other NMD diagnoses including having 71% ALS patients. Moreover, we found that, while the incidence of acute episodes was the same, the tracheostomy users had significantly more hospitalizations per desaturation episode than NIV users. This may be due specifically to complications caused by the invasive tubes (534, 537, 541) and unrelated to MAC or by poorer bulbar-innervated muscle function and airway protection mechanisms in the ALS population despite tracheostomy with cuff inflation(396, 542)

In our study, MAC not only significantly improved SpO2 in all patients, it also significantly decreased the number of airway suctionings in the tracheostomy patients. All tracheostomy patients in this study had severe bulbar muscle impairment and the fact that only 3 NIV users had bulbar impairment, may justify the good results of MAC on reversion of desaturations at home.

Our results in study nr 9 implied that the patient and caregiver training and home equipping be done early, before acute respiratory failure (ARF) occurs, and in the outpatient setting as reported by Tzeng et al (127). Our results confirm that the
caregiver can successfully use MAC at home cough with oximetry feedback and can
early detect possible acute episodes of secretion encumbrance.

According to the results of studies 7, 8 and 9, nasotracheal deep airway suctioning
should be the last resort considered for both NIV and tracheostomized NMD patients
with upper or lower airway secretion encumbrance. Even though indications for airway
suctioning have not been determined, patients with tracheostomy tubes are routinely
suctioned on average of 8 times a day and 30 or more times per day when they have
chest infections(47). At best, suctioning can clear only superficial airway secretions.
Suctioning misses mucus adherent between the tube and the tracheal wall and the left
main stem bronchus 54 to 92% of the time that can lead to a high incidence of left lung
pneumonias, potentially fatal mucus plugging, and perceived need for
bronchoscopies(511). Results from a survey indicate that 42% of institutions prescribed
cough assistance devices for outpatient use(543) in tracheostomized patients. Moreover
Garstang et al(399) reported that patients have a significant preference of mechanical
insufflation-exsufflation (MI-E) through the tube over deep suctioning as a mean of
removing secretions.

As a conclusion, to support the evidence of this line of research in the clinical practice,
study nr 10 analysed the historical evolution of practice regarding the use of
noninvasive mechanical ventilation (NIV) and complementary interventions for long-
term full-time noninvasive ventilatory support of patients with NMD and reported data
from different international centers that provide continuous NIV for this patient
population as an alternative to tracheostomy.

It has already been described that 55 to 90% of conventionally managed DMD patients
die from pulmonary cardio-complications between 16.2 and 19 years of age and
uncommonly after age 25(544). Studies have reported outcomes of tracheostomy IPPV for patients who undergo prophylactic tracheostomy or who survive an initial episode of respiratory failure and who subsequently undergo tracheostomy. Baydur et al.(545) reported 7 DMD patients who received full-time tracheostomy, from the mean age of 22.3 to 28.5 years. Two of the 7 died from pneumonia and 5 of the 7 patients were reported as having had pneumonia or recurrent pneumonias. Soudon et al.(546) reported a 3.6 year mean survival for 23 tracheostomy IPPV users, most of whom had DMD. Eagle et al. reported survival of 200 DMD patients as 19.5 years for those untreated and 24.8 years for those receiving tracheostomy IPPV(544).

In 80% of the NMD clinics in the U.S, patients are being offered nocturnal-only “low span” NIV on the basis of polysomnograms(377). Many of these patients are found to have nocturnal desaturations and frequent hypopneas. The hypopneas tend to be associated with reduced chest wall movement or with chest wall paradox suggesting non-central origin, that is, inspiratory muscle weakness(547-548). In DMD patients, the use of “low span” NIV has been shown to prolong tracheostomy-free survival by a matter of months-only with respiratory failure ultimately inevitable(549-551). Simonds et al.(17) began it for 23 DMD patients with a one year survival of 85%, 2 year survival of 73%; and a 5 year survival was less than 40% with at least 5 deaths due to respiratory failure. As the VC decreases below 800 ml DMD patients often begin to rock back and forth in their wheelchair to compress their abdomens during exhalation to increase their tidal volumes. They also tend to develop hypercapnia during sleep at this point. They eventually begin to use accessory breathing muscles and usually remain grossly asymptomatic, though, until their VCs decrease below 450 ml and hypercapnia extends into daytime hours. (552). This first occurs during sleep and eventually with the patient awake. It is usually around this time that nocturnal NIV is indicated (553).
SMA type I is typically characterized by profound global weakness were early respiratory failure is the major cause of morbidity and mortality and most children do not survive beyond 2 years of age without specialised treatment(530). Oskoui et al.(554) showed that survival of children with SMA type I from the international SMA register born in 1995–2006 has increased compared with those born in 1980 –1994. They concluded that this was due to more patients receiving ventilation (82% vs. 31%), MI-E (63% vs. 8%) and supplementary feeding (78% vs. 40%).

There has been consensus and international statement on the standards of care in SMA with specific reference to the management of infants in the with SMA type I(555-556). These documents do not address care of infants with non severe SMA type 1. These statements tend to ignore that clearly, as for patients with other NMDs, the survival of many SMA type 1 patients with or without severe bulbar muscle involvement can be prolonged by ventilatory support both by NIV or via indwelling tracheostomy tubes, as long as respiratory muscle aids are provided.

Pulmonary complications and respiratory failure account for at least 84% of ALS mortality(557). and death can occasionally occur in as little as 2 months from onset of symptoms and can occur at the time of initial presentation to a physician(396).

In the U.S. less than 10% of ALS patients undergo tracheotomy(558). However, 80 to 97% of ALS tracheostomy continuous ventilator users are glad to have chosen mechanical ventilation, are satisfied with their lives, and would use mechanical ventilation over again if they had to(10, 559). Thus, tracheostomy can at times prolong survival by 10 years or more. However, deterioration in physical functioning and in the ability to communicate, limited family resources, and most importantly, lack of a national personal attendant care policy, often make it difficult for ALS patients to be
managed in the community(538). In addition, as well as from airway mucus plugging, much of the sudden death post-tracheotomy may be due to autonomic dysfunction(560).

From 20 centers in 17 countries, study nr 10 keyed on analyzing 1623 nocturnal only ventilated NMD patients in which 760 (48%) progressed to continuous full-setting NIV over a follow up of 15 years. A protocol of oximetry feedback using mechanically assisted coughing (MAC) and full-setting NIV permitted 228 safe extubations and 35 decannulations of patients who could not pass spontaneous breathing trials (SBTs) before or after extubation/decannulation. After the follow up period, 522 (69%) patients are still alive on continuous full-setting NIV and tracheostomy was placed in a total of 140 (8%). This study focused only in patients with DMD, ALS and SMA type 1, however, all of the centers reporting data in this study had long-term full-time NIV users with other diagnoses but it was felt that limiting the data to these common and severe conditions would be more practical and establish the point.

Mechanisms by which nasal or mouthpiece IPPV can improve the clinical picture include: resting respiratory muscles and decreasing metabolic demand, increasing tidal volumes and relieving hypercapnia, resetting chemoreceptors, opening atelectatic areas, maintaining airway patency, improving ventilation/perfusion matching, maintaining lung and chest wall range-of-motion and possibly compliance, improving mucociliary clearance, and most importantly, by assisting, supporting, and substituting for inspiratory muscle function. Although mouthpiece IPPV is being used for ventilatory support since 1953 (42) very few studies reported its use for long-term management(1, 87, 90, 491-492).

Nocturnal-only nasal NIV or bi-level PAP can at best marginally prolong life and delay ARF. It can possibly do so by providing moderately deeper lung volumes to assist in
coughing. With advancing weakness, full-setting NIV can eventually be needed continuously without requiring intubation and hospitalization, thereby avoiding ARF and ultimately pressure by physicians to recommend tracheotomy.

The data presented suggest that reported “NIV failure”(15, 561-562) in cooperative NMD patients can result from inadequate NIV interfaces, from inadequate ventilator settings, when MAC is not used, and when mouth piece IPPV is not used for air stacking or daytime support.

Patients usually require daytime mouthpiece IPPV with the ventilator on the back of the wheelchair and the mouth piece adjacent to the mouth once the VC is less than 350 ml(491). About 15% of patients eventually lose the ability to use mouthpiece IPPV because of oro-motor weakness(44, 87). These patients typically prefer to use nasal IPPV around-the-clock rather than undergo tracheotomy(563).

Other than for severely mentally retarded patients no center included in study nr has encountered a DMD patient who could “not successfully use NIV.” Thus, while the NIV recommendations from a recent consensus panel(529) are comprehensive up to the point of requiring intubation, we suggest that with the ability to consistently extubate continuously ventilator dependent DMD patients and others, resort to tracheotomy should be much less common.

For SMA 1 it is as yet unclear whether all will some day require tracheostomy tubes for survival. Thus far, survival has been extended to up to age 17 using full-time NIV for 16 years or more for children continuously NIV dependent since as young as 4 months of age. According to study nr 10, one center reported 5 of such severely affected SMA 1 patients over age 15, all with VCs less than 20 ml, and none with baseline SpO2 less than 95% because of saliva aspiration. Thus, it is likely that at least some of these
typically severe SMA1 patients will survive into adulthood without tracheostomy tubes despite continuous ventilatory support since infancy.

Over a 6-year period, numerous papers published on the futility of managing ALS and other NMD patients with palliative care without once referring to prolonging life by NIV/MAC(166, 564-570). Palliative care can be defined as interventions for easing pain, dyspnea, and other symptoms that accompany the dying process of patients with terminal illnesses. However, publications fail to distinguish between “palliative care” for terminal cancer and organ supporting interventions for neuromuscular diseases, many of which cause end-organ failure of only one system, the neuromuscular system and in particular, end-stage respiratory muscle failure(571).

The data from this thesis suggest the inappropriateness of using palliative care precepts for properly equipped and trained patients with adequate personal care support. Some of our NMD patients, for example, are over age 40 and/or have depended on continuous NIV for over 20 years and numerous patients becoming continuously ventilator dependent without hospitalization or intubation, demonstrates that death from end-organ respiratory muscle failure is often avoidable without resort to invasive measures.

The pervading NMD respiratory paradigm is that diminishing VC bodes poorly for prognosis. The use of NIV and MAC as described in this thesis, to prolong life by continuous ventilatory support is contrary to current emphasis on invasive interventions and high technology. Thus it is considered that tracheotomy is the only option for prolonging survival and a crisis decision must eventually be made to "go on a respirator (undergo tracheostomy) for the rest of your life" or die(572). This often leaves patients and families feeling hopeless and depressed. Thus, conventional management strategies are invasive and reactive rather than noninvasive and proactive, ignoring the problem
until ARF results in intubation or death. Since NMDs are considered to be terminal, clinicians tend to do not prevent ARF or need for invasive airway tubes(166)

It was unanimously agreed upon by the centers involved in study nr 10 that no properly equipped and trained NIV patients that do not meet our reported criteria for tracheotomy has ever chosen to electively undergo tracheotomy or stop NIV/MAC and die. Thus, it was unanimously felt that the use of the term “palliative respiratory care” for NMD patients perpetrates the misconception that “noninvasive ventilation” is only useful for symptom relief rather than to prolong life by continuous ventilatory support.
CONCLUSIONS

- Intubated patients with NMD unable to pass spontaneous breathing trials achieve successful extubation by using full NIV and MAC. Our extubation success rates for these patients, suggest the avoidance of tracheotomy for ventilator dependent NMD disease patients who have some residual bulbar-innervated muscle function and who satisfy our extubation criteria. This can now be offered even to those with CPF less than 160 L/m.

- Considering the incidence of mortality and respiratory morbidity in the population of high SCI patients managed by standard ventilatory invasive techniques, we suggest that noninvasive methods of assisted ventilation and coughing may facilitate both extubation and decannulation with significant improvement on ventilatory dependence and pulmonary function and may facilitate return home rather than prolonged institutionalization for weaning attempts. Although some authors suggest a benefit on performing early tracheostomy, we would like to suggest that for cooperative high level SCI patients, an extubation protocol including full time NIV and MAC, can produce better outcomes and avoid the necessity of tracheostomy.

- Our results recommend that MI-E devices for secretion clearance should be included in an extubation protocol in specific subgroups of patients that may require post-extubation NIV.

- The VRI as a simple, noninvasive index can be used as a complement and/or alternative to VC in the evaluation of ventilatory impairment requiring ventilatory assistance in NMD patients. Further validation of this index in other populations and in the acute care setting as a weaning parameter is warranted.

- Cough Peak flows, PEF, and DF are useful measures of bulbar-innervated and respiratory muscle function for patients with NMD, permitting greater knowledge of the pattern of respiratory muscle compromise. It is important to pay special attention to the technique of each flow measurement since DF can be
mistaken for CPF or PEF and respiratory risk can be underestimated. Effective interventions to assist inspiratory and expiratory muscle function and the accurate characterization of risk of respiratory complications depend on accurate assessment of expiratory flow maneuvers.

- Regular lung insufflation, either by air stacking (to approach MIC) or by passive lung insufflation (to approach LIC), is indicated for all NMD patients with diminishing VC. Because the goal is to approach the predicted IC, passive insufflation is used when the patient obtains a deeper volume in this manner than by air stacking (i.e. when bulbar musculature is very weak).

- It is possible to manage severe NMD patients with inadequate airway clearance on a home-based MAC regimen centred on trained non-professional caregivers. This is valid for patients under NIV and for those requiring tracheostomy. MAC should be considered as a useful complement to ventilatory support in these patients at home.

- A telephone access and on-demand MAC program offers a technologic update to increase both the patients’ and clinicians’ feelings of security for home management and was effective in averting hospitalizations for patients with ALS, with concomitant positive results in reducing home care costs.

- Home MAC use with oximetry feedback during respiratory infections can avoid hospitalizations and effectively manage episodes of acute respiratory decompensation, related to secretion encumbrance, in continuously ventilator dependent NMD patients dependent on either NIV or tracheostomy.

- Since neither DMD, SMA, nor essentially any other NMD full time NIV users appear to meet the same criteria established to indicate tracheotomy for patients with advanced bulbar-ALS, these patients can be safely maintained using up to continuous NIV with good survival outcomes. Assisted lung ventilation and normal SpO2 can be maintained indefinitely during sleep as well as during daytime hours for patients with little or no VC by using NIV at full ventilatory support.
RESUMO

Introdução

Um dos desenvolvimentos mais importantes na área da ventilação mecânica ao longo dos últimos 15 anos foi o surgimento da ventilação não-invasiva (VNI) como uma técnica crescente do arsenal terapêutico em cuidados intensivos. Além disso, tem sido utilizada como terapêutica domiciliária em pacientes com insuficiência respiratória crónica, de diferentes etiologias. De facto, a população sob ventilação mais do que duplicou desde 1987.

Os argumentos para o uso da VNI dizem respeito principalmente às suas vantagens sobre a ventilação mecânica invasiva, com redução significativa das complicações relacionadas com cuidados intensivos, tais como trauma da via aérea superior, pneumonia associada a ventilação mecânica e elevado nível de sedação. Para os pacientes sob ventilação mecânica domiciliária a VNI tem vantagens sobre a ventilação por traqueostomia, nomeadamente uma maior facilidade de adaptação do paciente e cuidadores maior conforto menor com redução de custos.

Para pacientes totalmente dependentes do ventilador, com fraqueza muscular, a eficácia da tosse está normalmente comprometida e a acumulação de secreções é frequente. O manejo adequado de secreções com técnicas manuais ou mecânicas de tosse assistida deve ser considerado antes do falhaso da VNI ser declarado.

São necessárias mais linhas de investigação com foco numa estratégia continuada de cuidados respiratórios que incluem VNI optimizada e continua associada a tosse assistida mecanicamente (TAM) em pacientes com fraqueza muscular e grave limitação ventilatória, para justificar a aplicação de protocolos específicos que poderão melhorar a sobrevida desta população.
Objectivos

✓ Descrever as taxas de sucesso/falhanço na extubação de pacientes colaborantes com fraqueza muscular, totalmente dependentes do ventilador, incapazes de tolerar uma prova de ventilação espontânea, com um protocolo que inclui VNI optimizada e continua e TAM numa unidade de cuidados intensivos (UCI)

✓ Descrever e comparar as taxas de sucesso na extubação e descanulação e seus resultados em pacientes com lesão vértebro medular alta, orientados e totalmente dependentes do ventilador com um protocolo que inclui VNI optimizada e continua e TAM para manter SpO2 > 95% em ar ambiente

✓ Avaliar a eficácia da TAM como parte integrante de um protocolo de desmame em pacientes que toleram a prova de ventilação espontânea, mas desenvolvem falência respiratória pós extubação

✓ Determinar se um novo índice de requerimento ventilatório (IRV) poderá contribuir para a distinção de pacientes com doença neuromuscular (DNM) com vários níveis de disfunção dos músculos inspiratórios e dependência ventilatória e verificar se este índice poderá acrescentar algo à eficácia da medida da capacidade vital (CV) para indicar o suporte ventilatório

✓ Comparar os valores de pico fluxo da tosse (PFT), pico de fluxo expiratório (PFE) e de um fluxo potencialmente simulador obtido através de uma propulsão da língua e lábios (“dart flow”, DF) em indivíduos saudáveis e em pacientes com DNM/patologia restritiva e correlacionar estes valores com a CV e a máxima capacidade de insuflação (CMI)

✓ Comparar a capacidade máxima de insuflação passiva (LIC) com a capacidade de insuflação por “armazenamento de ar” (CMI) e com a CV, no sentido de explorar relações entre estes valores e correlacioná-los com a função glótica e PFT. Demonstrar os efeitos de insuflações diárias na LIC em MIC, bem como a sua importância na caracterização da severidade da doença.

✓ Descrever as indicações de TAM domiciliária e explorar a segurança, frequência e eficácia em pacientes com DNM, totalmente ventilados por VNI ou por traqueostomia
✓ Optimizar o protocolo de TAM domiciliário com monitorização de oximetria, com a inclusão de uma consulta telefónica, no sentido de reduzir os custos e evitar internamentos hospitalares em pacientes com DNM, totalmente ventilados por VNI ou por traqueostomia.

✓ Reportar dados de vários centros acerca da eficácia e resultados de uso contínuo de VNI em pacientes com distrofia muscular de Duchenne, esclerose lateral amiotrófica e atrofia muscular tipo 1 ventilados cronicamente no seu domicílio e avaliar a evolução das recomendações sobre esta matéria publicados nas recentemente publicadas revisões e conferências de consenso.

**Resultados**

Taxa de sucesso na extubação à primeira tentativa com VNI e TAM foi de 95% (149 pacientes). Todas as tentativas de extubação em 98 pacientes com PFT assistidos ≥ 160 L/min foram bem sucedidas. A dependência de VNI contínua e autonomia ventilatória prévia à intubação correlaciona-se com o sucesso da extubação (p <0,005). Seis dos oito pacientes que inicialmente falharam a extubação foram bem sucedidos na tentativa subsequente. Apenas dois pacientes com PFT assistidos imensuráveis foram submetidos a traqueotomia.

Quando comparados com os pacientes com lesão vértebro-medular alta que foram decanulados, os pacientes extubados apresentaram menor tempo de internamento em UCI com menor tempo de duração do protocolo de VNI e TAM. Após o protocolo, CV, PFT voluntário e assistido melhorou significativamente em todos os pacientes. Os pacientes extubados apresentaram melhores valores de CV e PFT às 48h pós-extubação e melhores valores de PFT aos 6 meses de follow up.

Setenta e cinco pacientes críticos (26 mulheres) com idades e índices de gravidade similares, que toleraram com sucesso o desmame foram randomizados pré-extubação para receber tratamento convencional (grupo controlo) e para receber o mesmo tratamento com a inclusão de TAM (grupo estudo) Nas 48 horas pós-extubação, 20 pacientes do grupo controle (50%) e 14 pacientes do estudo (40%) utilizaram VNI.
Pacientes do grupo de estudo tiveram uma significativa taxa mais baixa de re-intubação em relação ao grupo de controlo, 6 (17%) vs 19 (48%), pacientes respectivamente. Considerando apenas o subgrupo de pacientes que usaram VNI, as taxas de re-intubação relacionados ao falhanço da VNI foram significativamente menores no grupo de estudo, quando comparado ao grupo controle, 2 (6%) vs (33%) pacientes, respectivamente. O tempo de internamento em UCI pós – extubação foi significativamente menor no grupo de estudo (3,1 ± 2,5 vs 9,8 ± 6,7 dias).

O IRV superior a 1,2 foi atingido por 82 dos 91 pacientes que beneficiaram de assistência ventilatória parcial. A CV inferior a 50% do normal previsto foi atingido por 82 dos 91 pacientes que beneficiaram de assistência ventilatória parcial. Tendo em conjunto, um IRV superior a 1,2, e um VC inferior a 50% do normal previsto foi atingido por 87 dos 91 pacientes. Da mesma forma, o IRV superior a 2,5 foi atingido por 35 dos 42 pacientes que necessitaram de assistência ventilatória superior a 20 horas/dia em que se exigia um ventilador suplente. Uma CV inferior a 1000 ml foi atingida por 36 de 42 pacientes. Tendo em conjunto um índice superior a 2,5 ou inferior a 1000 VC ml foi atingido por 38 dos 42 pacientes que necessitaram de assistência ventilatória superior a 20 horas/dia em que se exigia um ventilador suplente.

Para os pacientes com DNM, o DF foi significativamente maior do que PFT (p <0,01) que, por sua vez, excedeu significativamente o PEF (p <0,05). 14 pacientes tiveram DF inferior PFT. Treze desses 14 tinham a capacidade de armazenamento de ar (CMI> CV), indicando maior comprometimento da boca e dos lábios do que dos músculos da glote. Para 14 dos 88 pacientes com DNM, os valores de CMI não excederam a CV, principalmente devido à incapacidade de encerrar a glote. PFT e PEF correlacionam-se com a CV (r = 0,85 e 0,86, respectivamente), e com a CMI (r = 0,76 e 0,72, respectivamente).

Em pacientes com DNM, os valores de CV, CMI e LIC foram de 1131 ± 744, 1712 ± 926 e 2069 ± 867 ml, respectivamente, e os valor por PFT voluntário e assistido foram de 2,5 ± 2,0 e 4,3 ± 2,2 litros / seg, respectivamente, com todas as diferenças
estatisticamente significativas (P <0,001). CMI menos a CV correlacionou inversamente com a LIC menos CMI (p <0,01) e, portanto, com a função glótica. Ambos os valores de CMI e LIC aumentaram com a prática (p <0,001). Aumentos na LIC, foram maiores para os pacientes com menor CV (p <0,05).

Pacientes com DNM usam TAM em casa diariamente ou de forma intermitente durante as exacerbações agudas. Todos os pacientes traqueostomizados usaram TAM diariamente e mais vezes por dia do que pacientes sob VNI. Os cuidadores foram considerados competentes e eficazes na aplicação de TAM em casa, com boa tolerância e sem complicações.

Durante 42 ± 57 meses de seguimento, por 180 episódios agudos, 146 internamentos foram evitados. As taxas de hospitalização para os pacientes sob VNI foram significativamente inferiores do que para os traqueostomizados. TAM domiciliário, durante os episódios agudos normalizou a SpO2 e diminuiu o nº diário de aspirações profundas através do tubo de traqueostomia. O custo médio mensal por paciente para a TAM domiciliário por demanda com consulta telefónica profissional, foi de € 403, que representaram 420 € ou 59% menos do que o preço de uma prescrição contínua TAM domiciliário.

Vinte centros de 17 países apresentaram 1492 pacientes com DNM ventilados parcialmente durante a noite em que 713 (48%) evoluíram para suporte ventilatório não invasivo contínuo durante um seguimento de 15 anos. Um protocolo de monitorização por oximetria para a aplicação de TAM e VNI continua em ar ambiente permitiu 228 extubações bem sucedidas e 35 descanulações seguras de pacientes incapazes de passar por provas de respiração espontânea. Após o período de seguimento, 493 (69%) pacientes estão ainda vivos e em pleno uso contínuo de VNI. A traqueostomia foi colocada em um total de 125 (8%) pacientes.
Conclusões

✔ Um protocolo que inclui VNI continua e optimizada com TAM permite a extubação segura de pacientes com fraqueza muscular devido a DNM e com lesão vértebro-medular alta, que são incapazes de tolerar provas de ventilação espontânea. Embora alguns autores sugerem benefícios na realização da traqueostomia precoce, resultados sugerem que, para pacientes com lesão vértebro-medular com bom nível de cooperação, a extubação com a aplicação de um protocolo que inclui VNI e MAC, pode produzir melhores resultados e evitar a necessidade de traqueostomia.

✔ A aplicação de TAM para manejo de secreções aplicado em subgrupos específicos de pacientes pode produzir melhores resultados da VNI para o tratamento da insuficiência respiratória, pós-extubação.

✔ A IRV pode ser usado como um complemento e / ou alternativas para a CV na avaliação do comprometimento ventilatório e necessidade de assistência ventilatória em pacientes com DNM.

✔ Picos de fluxo da tosse, PFE e DF são medidas úteis para avaliar a função da musculatura bulbar em pacientes com DNM, permitindo um maior conhecimento do padrão de comprometimento dos músculos respiratórios.

✔ Insuflação pulmonar regular seja por armazenamento de ar seja por insuflações passivas são indicadas para todos os pacientes com DNM e CV significativamente reduzido. Insuflação passiva é utilizada quando o paciente apresenta comprometimento grave da musculatura bulbar.

✔ É possível manejar no domicílio a acumulação de secreções e exacerbações agudas relacionadas, em pacientes com DNM, com um regime á demanda de TAM centrado na formação e treino de cuidadores não- profissionais e com acesso a consulta telefónica profissional. Este protocolo foi eficaz na prevenção de hospitalizações em pacientes com esclerose lateral amiotrófica e outras DNM totalmente ventilados seja por VNI contínua ou traqueostomia.
A ventilação pulmonar assistida e SpO2 normal pode ser mantida durante o sono, bem como durante o dia em pacientes com DNM com pouca ou nenhuma CV usando VNI em suporte ventilatório contínuo. A eficácia da VNI continua. Resultados depende mais da função da musculatura bulbar do que a capacidade vital.
SUMMARY (Abstract)

Introduction

One of the most important developments in the field of mechanical ventilation over the past 15 years has been the emergence of noninvasive positive pressure ventilation (NPPV) as an increasing part of the critical care armamentarium. Moreover, it has been effectively used for long term management in patients with chronic respiratory failure, from different etiologies. Indeed, the population of home mechanical ventilator users has, in fact, more than doubled since 1987.

The attraction for NPPV relates primarily to its advantages over invasive mechanical ventilation with significant reduction of related critical care complications such as upper airway trauma, ventilator associated pneumonia and high level of sedation. For patients with long-term home mechanical ventilation, NPPV has advantages over tracheostomy mechanical ventilation, including greater ease of administration, reduced need for skilled caregivers, enhanced patient comfort, and lower costs.

For totally ventilator dependent patients with muscle weakness, cough is normally impaired and secretion accumulation is frequent. Adequate secretion management with manual or mechanical cough augmentation techniques might be advisable before NPPV is declared failed or contraindicated in this population, both in acute and chronic settings.

Research on a continuum strategy of care, from acute to chronic settings that include NPPV coupled with mechanical assisted cough (MAC) in severely ventilatory impaired patients with muscle weakness is warranted to support the application of specific protocols that may improve survival in this patient population.
Purpose

✔ Report extubation success/failure rates in cooperative, totally ventilator dependent muscle weakness patients, unable to pass weaning trials, using a protocol that include full, continuous NPPV and MAC in the intensive care unit.

✔ Report and compare extubation and decannulation success rates and outcomes of self-directed, totally ventilator dependent patients with high spinal cord injury using a management protocol that include full, continuous NPPV and MAC to maintain SpO2≥95% in ambient air.

✔ Assess the efficacy of MAC as part of a weaning protocol for patients that pass specific weaning trials but develop acute respiratory failure after extubation.

✔ Determine whether a new designed ventilator requirement index (VRI) could distinguish patients with neuromuscular disease (NMD) with various levels of inspiratory muscle dysfunction and ventilator dependence and if such an index could add to the diagnostic efficiency of simple vital capacity (VC) measurement in determining need for ventilator use.

✔ Compare cough peak flows (CPF), peak expiratory flows (PEF), and potentially confounding flows obtained by lip and tongue propulsion (‘‘dart flows’’, DF) for normals and for patients with neuromuscular disease/restrictive pulmonary syndrome (NMD) and correlate them with vital capacity (VC) and maximum insufflation capacity (MIC).

✔ Compare maximal passive lung insufflation capacity (LIC) with lung inflation by air stacking MIC and with vital capacity (VC); to explore relationships between these variables that correlate with glottic function and cough peak flows (CPF); to demonstrate the effect of routine inflation therapy on LIC and MIC; and to determine the relative importance of lung inflation therapy as a function of disease severity.
Describe the indications of MAC treatment at home as well as, determine its safety, compliance and efficacy within NMD patients under continuous NPPV and tracheostomy.

Establish an optimal MAC with oximetry feedback provision regimen at home, with a telephone consultation to help reduce costs and avoid hospitalizations in NMD patients under continuous NPPV and tracheostomy.

Report multicentric data and outcomes of the use of NPPV for full, long-term ventilatory support in Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy type 1 (SMA 1) and consider the evolution of practice recommendations reported in reviews and consensus statements.

Results

First attempt extubation success rate with NPPV and MAC in was 95% (149 patients). All 98 extubation attempts on patients with assisted cough CPF ≥ 160 L/m were successful. Dependence on continuous NPPV and duration of dependence prior to intubation correlated with extubation success (p<0.005). Six of 8 patients who initially failed extubation succeeded on subsequent attempts and only two patients with no measurable assisted CPF underwent tracheotomy.

When compared to high SCI patients that were decannulated, extubated patients had a lower ICU length of stay with less time on NPPV and MAC protocol. After the protocol, VC, unassisted and assisted CPF significantly improved in all patients. Extubated patients had higher values of VC and CPF at 48h post-extubation and higher values of CPF at a 6 month follow up.

Seventy five critical ill patients (26 females) with similar age and gravity successfully weaned were randomized pre extubation to receive conventional post-extubation
treatment (control group) and to the same treatment with MAC (study group) In the 48 hours post extubation, 20 control patients (50%) and 14 study patients (40%) used NPPV. Study group patients had a significant lower re-intubation rate than controls; 6 (17%) vs 19 (48%), patients respectively. Considering only the sub-group of patients that used NIV, the re-intubation rates related to NIV failure were significantly lower in the study group when compared to controls; 2(6%) vs (33%) patients respectively. Post – extubation ICU length of stay was significantly lower in the study group (3.1± 2.5 vs 9.8± 6.7 days).

A VRI greater than 1.2 captured 82 of 91 patients who benefited from part-time ventilatory assistance. A VC less than 50% of predicted normal captured 82 of 91 patients who benefited from part-time NPPV. Having an index greater than 1.2 or a VC less than 50% of predicted normal captured 87 of 91 such patients. Likewise, a VRI greater than 2.5 captured 35 of 42 patients who required ventilatory support greater than 20 hours per day and required a back-up ventilator. Having a VC less than 1000 ml captured 36 of 42 such patients. Having an index greater than 2.5 or a VC less than 1000 ml captured 38 of 42 patients who required a back-up ventilator for full-time ventilatory support.

For NMD patients, the DF were significantly greater than CPF (p<0.01) which, in turn, significantly exceeded PEF (p<0.05). 14 patients had DF lower than CPF. Thirteen of these 14 had the ability to air stack (MIC>VC) indicating greater compromise of mouth and lip than of glottic muscles. For 14 of 88 NMD patients MIC values did not exceed VC, mostly because of inability to close the glottis (inability to air stack). Nonetheless, in 11 of these 14 patients the DF were within the standard deviation of the whole group, thus, bulbar-innervated muscle dysfunction was not uniform. CPF and PEF correlated with VC (r= 0.85 and 0.86, respectively), and with MIC (r=0.76 and 0.72, respectively).
In NMD patients, VC, MIC, and LIC were 1131 ±744, 1712±926, and 2069± 867 ml, respectively, and, for unassisted and assisted CPF, they were 2.5±2.0 and 4.3±2.2 liters/sec, respectively, with all differences statistically significant (P<0.001). MIC minus VC correlated inversely with LIC minus MIC (P <0.01) and, therefore, with glottic function. Both MIC and LIC increased with practice (P <0.001). Increases in LIC but not MIC over VC were greatest for patients with the lowest VC (P <0.05).

Patients with NMD used MAC at home either daily or intermittently during acute exacerbations. All tracheostomized patients used MI-E daily and more times a day than patients under NPPV. Caregivers were competent and considered MAC effective at home with good tolerance and no complications.

During 42±57 months of follow up, for 180 acute episodes, 146 hospitalizations were avoided. Hospitalization rates for NPPV users were significantly lower than for tracheostomy users. Home MAC during acute episodes normalized baseline SpO2 and decreased resort to deep airway suctioning via tracheostomy tube per day. Mean monthly cost per patient for on-demand home MAC with professional telephone consultation, was €403, that represented 420€ or 59% less than the rental for continuous home MAC prescription.

Twenty centers from 17 countries presented 1492 nocturnal only ventilated neuromuscular disease (NMD) patients in which 713 (48%) progressed to continuous full-setting noninvasive ventilation (NIV) over a follow up of 15 years. A protocol of oximetry feedback using mechanically assisted coughing (MAC) and full-setting NIV permitted safe 228 safe extubations and 35 decannulations of patients who could not pass spontaneous breathing trials (SBTs) before or after extubation/decannulation. After the follow up period, 493 (69%) patients are still alive on continuous full-setting NIV and tracheostomy was placed in a total of 125 (8%).
Conclusions

✓ Continuous full setting NPPV and MAC permits safe extubation of NMD and high SCI patients that are unable to pass spontaneous breathing trials. Although some authors suggest a benefit on performing early tracheostomy, we would like to suggest that for cooperative high level SCI patients, an extubation protocol including NPPV and MAC, can produce better outcomes and avoid the necessity of tracheostomy.

✓ Secretion clearance with MI-E, applied in specific subgroups of patients may produce better outcomes of NPPV to treat post-extubation respiratory failure.

✓ The VRI can be used as a complement and/or alternative to VC in the evaluation of ventilatory impairment requiring ventilatory assistance in NMD patients.

✓ Cough Peak flows, PEF, and DF are useful measures of bulbar-innervated and respiratory muscle function for patients with NMD, permitting greater knowledge of the pattern of respiratory muscle compromise.

✓ Regular lung insufflation, either by air stacking (to approach MIC) or by passive lung insufflation (to approach LIC), is indicated for all NMD patients with diminishing VC. Passive insufflation is used when the patient has severe impairment of the bulbar musculature.

✓ It is possible to manage secretion encumbrance and acute exacerbations at home in NMD patients, with an on demand MAC regimen centred on trained non-professional caregivers and telephone consultation. This was effective in averting hospitalizations for patients with ALS and other NMD patients either on continuous NPPV or tracheostomy.

✓ Assisted lung ventilation and normal SpO₂ can be maintained during sleep as well as during daytime hours for patients with little or no VC by using NPPV at full ventilatory support. Successful outcomes of continuous NPPV in NMD patients depends more on the bulbar muscle function than on the vital capacity.
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