

Respiratory management of ALS: past and present

Amyotrophic lateral sclerosis (ALS) represents the most common type of motor neuron disease (MND) with an annual incidence of 1-2.6 cases per 100 000 persons and an average age of onset of 55-60 years. Most cases represent a sporadic form of the disease, while 5-10% are familial (Rafiq, Proctor, McDermott and Shaw, 2012).

ALS is characterized by preferential degeneration of both upper and lower motor neurons, resulting in progressive weakness and amyotrophy of skeletal and bulbar muscles. The clinical presentation of ALS is quite heterogeneous, determined by its region of onset, relative mixture of upper and lower motor neuron signs, and rate of progression (Ravits and La Spada, 2009). Nevertheless, the disease is incurable and invariably fatal, and taking into account the aforementioned factors, the median life expectancy from onset of symptoms to death ranges from 20 to 48 months (Chiò et al., 2009). Death typically occurs as a result of respiratory complications, with respiratory failure and bronchopneumonia/pneumonia being the most frequent causes. While the latter results from the inability to cough and thus expel secretions (and aspirate inhaled due to oropharyngeal dysphagia) from the airways, both are direct sequelae of weakened respiratory muscles and their decreased capacity to overcome the respiratory load.

It is therefore not surprising that respiratory function is an important predictor of survival, with a decreased forced vital capacity (FVC) at diagnosis being the most relevant factor for patients' prognosis (Chiò et al., 2009). While the onset of respiratory muscle weakness tends to develop gradually later in the course of the disease, it can be the presenting feature for around 3% of patients subsequently diagnosed with respiratory-onset ALS (Gautier et al., 2009).

Respiratory impairment often begins with sleep-disordered breathing (SDB) resulting from hypoventilation during REM sleep, prompting the patient to wake frequently to maintain sufficient ventilation. This leads to early morning headaches, unrefreshing sleep, daytime somnolence, poor concentration, confusion or anxiety (Rafiq, Proctor, McDermott and Shaw, 2012). It follows that respiratory function in ALS patients therefore significantly predicts their quality of life, and its support and maintenance represent an important aspect in caring for them (Rafiq, Proctor, McDermott and Shaw, 2012), as well as an area of active research.

Advances in respiratory management over the last decades have resulted in improving patients' quality of life and increasing survival, with emerging evidence that these interventions might be more effective in prolonging survival than riluzole (Pinto and Carvalho, 2014). However, not all the approaches were successful, as will be discussed later.

Historically, ventilatory support as a therapeutic option for ALS patients is relatively recent, considering that negative and later positive pressure ventilators became widespread during the poliomyelitis epidemics in the middle of the twentieth century (Pinto and Carvalho, 2014).

Traditionally, assisted ventilatory support in ALS has been achieved with invasive mechanical ventilation via tracheostomy (TIVM) (Kim, Bireley, Hayat and Kafaie, 2020), allowing also direct airway suctioning to remove secretions. TIVM extends survival for an average of 5 years, with age >60 years at disease onset being a negative prognostic factor (Pinto and Carvalho, 2014). TIVM is typically initiated with uncuffed tubes, allowing the patients to eat and talk, until the replacement by cuffed tubes becomes inevitable, potentially leading to various complications such as accumulation of secretions, local infections, tracheoesophageal fistula, pneumothorax or tracheal stenosis (Pinto and Carvalho, 2014). Cuffed tubes also prevent production of effective speech and while speaking valves and fenestrated tubes assisting phonation have been developed, they are not without risks (Pandian, Boisen, Mathews and Cole, 2019). However, speech is an important factor for patients' quality of life and therefore this aspect deserves due consideration.

Despite development of new equipment with improved gas exchange and ventilator pressure, quality of life was not shown to be clearly improved (Andersen et al., 2011) but was nonetheless still perceived as positive by more than 80% of patients after TIVM (Gruis and Lechtzin, 2012).

TIVM comes with long-term morbidity, significant family and caregiver burdens and substantial healthcare costs. Therefore, TIVM should only be initiated after an informed discussion because its potential discontinuation (e.g., when performed as an emergency procedure) might not be legally and ethically possible (Pinto and Carvalho, 2014).

With the advances in ventilator technology, availability of home ventilators and sophisticated communication devices, patients seem to be more likely to opt for TIVM (Spittel et al., 2020). However, the rates and practice vary greatly among countries and in some cases even among individual regions. In general, the TIVM rate is the highest in Japan and other Asian countries with 27%-45% of ALS patients (Rimmer et al., 2019), 2-6% in the USA and 1.5% in Canada. Interestingly, northern Italy has a higher rate than northern Europe, 10.6% vs 5.25%, respectively (Pinto and Carvalho, 2014). This is not just because of variations in healthcare systems and medical insurance, but also due to different cultural and social aspects and attitude of physicians with regards to life-prolonging measures. However, it should be noted that affordability might not be the ultimate factor – for example, both Germany and Finland have healthcare systems that cover all TIVM related costs, and yet the TIVM rate has increased in Germany (Spittel et al., 2020) but decreased in Finland (Kotanen et al., 2020).

Up until the mid-1990's there was no alternative available to patients who declined TIVM to prolong their life (Pinto and Carvalho, 2014). Non-invasive ventilatory support (NIV), utilizing a mechanical ventilator to provide positive pressure through a nasal or face mask, had been known, but the first report evaluating its use in ALS patients appeared only in 1993. The author reported that continuous use of NIV in ALS patients can delay or eliminate the need for tracheostomy in some, and while survival did not seem affected, quality of life improved (Bach, 1993). Several subsequent studies reported similar findings, with the only randomized controlled trial of ALS patients on NIV demonstrating that survival and quality of life improved in the subgroups without severe bulbar involvement (Bourke et al., 2006). Further research mostly provided evidence that while NIV has a positive impact on quality of life, survival negatively correlated with the degree of bulbar involvement and represents a significant prognostic factor (Kim, Bireley, Hayat and Kafaie, 2020). Recent findings suggest that this phenomenon might be explained by upper airway obstruction with decreased central drive, resulting from bulbar hyperreflexia and degeneration of the corticobulbar pathway (Sancho et al., 2019).

Despite the documented benefits of NIV on both survival and quality of life, their exact mechanisms remain uncertain. It is possible that NIV positively impacts survival by improved oxygenation and cellular metabolism, lung compliance and central respiratory drive (Rafiq, Proctor, McDermott and Shaw, 2012). With regards to quality of life, the improvements most commonly concern daytime sleepiness, dyspnoea, quality of sleep, fatigue and depression, likely resulting from alleviation of nocturnal hypoventilation (Pinto and Carvalho, 2014).

Compared to TIVM, the complications involved with NIV are less severe and include uncomfortable mask interface, skin irritation, dry mouth or persistent cough. However, as many as 30% of ALS patients do not tolerate NIV, and more so those with severe bulbar impairment, in whom proper saliva control needs to be in place to reduce the risk of aspiration (Rafiq, Proctor, McDermott and Shaw, 2012).

While the use of NIV is recommended by international guidelines on ALS care, there are no definite criteria for its initiation, appropriate settings and efficiency measurements, which contributes to variances in study results and their possible misinterpretations (Kim, Bireley, Hayat and Kafaie, 2020). A major factor is the heterogeneity of ALS with variable patterns of pulmonary function decline, which makes it difficult to establish a threshold for initiation of NIV (Kim, Bireley, Hayat and Kafaie, 2020).

Nowadays, some departments routinely utilize home telemonitoring of their patients with NIV, which allows physicians to remotely (over the internet) review patient's data and adjust NIV settings accordingly, thus reducing healthcare costs and improving both patient's and caregiver's quality of life (Pinto and Carvalho, 2014). With the advance of complex telehealth solutions, this might be an important part to be integrated for complex care for ALS patients.

With regards to availability and the use of NIV, it seems to be less influenced by the negative attitude of physicians towards life prolonging measures than in the case of TiVM, but understandably still related to the health insurance coverage in individual countries. Demographically, NIV is most frequently chosen by young males and those who are married, who also have – probably due to family support – longer survival (Fiorentino et al., 2018).

However, NIV is still an intervention, and it would be desirable to delay its initiation by slowing the rate of diaphragmatic involvement. It is therefore not surprising that research turned to diaphragm pacing (DP), a technique for respiratory assistance that had been around for several decades. To support respiratory function and possibly also delay atrophy of respiratory muscles, DP utilizes phrenic electrodes that generate electrical impulses to stimulate the diaphragm (Woo et al., 2020). The need for a thoracotomy, a significant issue with regards to its potential complications, was eliminated by introduction of devices that can be implanted laparoscopically (McDermott et al., 2016).

In the US, a pilot trial showed encouraging results and The Food and Drug Administration (FDA) approved DP for ALS patients in 2011 (Onders et al., 2014). However, a few years later, two randomized controlled trials of DP in ALS patients (DiPALS writing Committee, 2015; Gonzalez-Bermejo et al., 2016) disappointingly reported not only mortality and severe procedure-related complications in the DP groups, but surprisingly also a shortened survival compared to the controls. Similar findings were reported by one cohort study and two case reports (Woo et al., 2020).

A possible reason for finding no survival benefit in these two trials might be due to enrolling patients with possibly too advanced denervation who would not have been considered suitable candidates in the original US study, where a different method was used to assess the function of the phrenic nerve. In addition, concerns were expressed about the fact that the original study that led FDA to approve DP was not published in any peer-reviewed journals (Mitsumoto, 2015).

However, this would only explain why survival was not improved but not why it was actually shortened in the DP group. While there is some evidence that surgery accelerates progression of ALS (Pinto, Swash and de Carvalho, 2013), the procedure was performed in all participants, thus suggesting that pacing itself is actively harmful (DiPALS writing Committee, 2015). However, the exact mechanism is yet to be elucidated.

In light of the results, DP is currently not recommended in patients with ALS, even though it could be – as suggested by sparse reports – beneficial in a very specific and highly selected subgroup of patients (DiPALS writing Committee, 2015).

Apart from the means of respiratory support described in the previous paragraphs, research has been also focused on exercise of ventilatory muscles. Inspiratory muscle training (IMT) already demonstrated positive results in patients with chronic obstructive pulmonary disease, myasthenia gravis or spinal muscular atrophy type 3 (Pinto and Carvalho, 2014). Only a few studies were performed to evaluate IMT in ALS patients, and while the results demonstrated its safety along with improvement of muscular strength and endurance, there was generally no evidence of efficacy in terms of alteration of the natural course of the disease (Pinto and Carvalho, 2014). However, this could be due to inconsistencies in methodology with regards to exact description of the exercise, its duration, load and frequency, which was demonstrated to be a common issue (Pinto and Carvalho, 2014). Therefore, given the safety of IMT, more research should be done to investigate its potential positive effect on survival, as hinted by a single randomized, control-group study from 2012 (Pinto, Swash and de Carvalho, 2012).

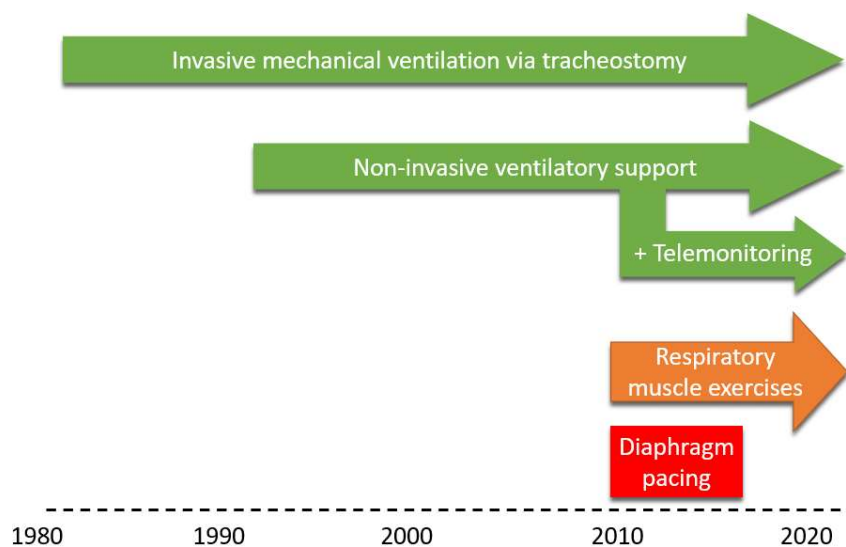


Figure 1. An overview of the individual approaches to respiratory support and the approximate time frame of their use in the care of ALS patients. The colours indicate general benefit (in terms of survival) of each approach, with green representing positive, orange - neutral/unknown, and red - negative.

In conclusion, research especially in the last three decades led to significant advances in the respiratory management of ALS patients. This includes not only improvement of both survival and quality of life with NIV or seemingly less significant improvements such as better vocalization for patients with TIVM, but also the realization that approaches working for other conditions might actually harm people with ALS, as demonstrated in the case of DP. And while further research is underway, it is important to note that it is limited by the heterogeneity of ALS as well as its relative rarity, making it difficult to study sample sizes that are large enough to provide meaningful results. Perhaps that makes the advances achieved so far even more valuable.

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