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Review Article

Current Topics on Respiratory Physiopathology in Neuromuscular Diseases

Odair Henrique Gaverio Diniz*

Ms, Programa de Pós-graduação em Ciências da Cirurgia, FCM, UNICAMP, Campinas, São Paulo, Brazil

***Corresponding Author:** Odair Henrique Gaverio Diniz, Ms, Programa de Pós-graduação em Ciências da Cirurgia, FCM, UNICAMP, Campinas, São Paulo, Brazil.

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Abstract

Background: Respiratory failure remains the leading cause of morbidity and mortality across a spectrum of neuromuscular disorders (NMDs), ranging from central nervous system pathologies to primary muscle degenerations. Recent advancements in disease-modifying therapies (DMTs) and molecular interventions have fundamentally altered the natural history of these conditions.

Objective: This review aims to synthesize the respiratory pathophysiological mechanisms of Parkinson's Disease (PD), Multiple Sclerosis (MS), Myasthenia Gravis (MG), Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA), and Duchenne Muscular Dystrophy (DMD), emphasizing the transition from palliative management to active functional preservation.

Methods: A comprehensive literature review was conducted, focusing on diagnostic gold standards (e.g., McDonald Criteria for MS, genetic testing for SMA), pulmonary function testing (PFT) nuances, and the impact of novel pharmacological agents such as antisense oligonucleotides, gene therapies, and immunomodulators.

Results: The pathophysiology of NMDs is characterized by a complex interplay between muscle weakness, bulbar dysfunction, and autonomic dysregulation. In PD and ALS, respiratory impairment often precedes overt clinical symptoms. In SMA and DMD, novel therapies (e.g., Risdiplam, Eteplirsen) demonstrate a "dissociation effect," where muscle strength is stabilized despite a continued decline in lung volume due to skeletal complications. Furthermore, immunomodulatory insights in GBS and ALS provide new targets for reducing mechanical ventilation dependence.

Conclusion: Modern respiratory management of NMDs requires an integrative approach that combines proactive ventilatory support with early molecular intervention. Understanding the specific respiratory trajectories of each phenotype is crucial for optimizing clinical outcomes and patient autonomy in the era of precision medicine.

Keywords: Neuromuscular Diseases; Respiratory Insufficiency; Disease-Modifying Therapies; Amyotrophic Lateral Sclerosis; Spinal Muscular Atrophy; Pulmonary Function Tests; Gene Therapy; Non-invasive Ventilation

Introduction

Each neuromuscular disease exhibits a distinct natural history and specific sequelae within the respiratory system [1]. Frequently observed clinical features include the deterioration of respiratory muscle strength, leading to reduced vital capacity and impaired cough efficacy [2,3]. Furthermore, additional manifestations encompass bulbar dysfunction, oropharyngeal dysphagia [2,4], diminished sleep quality [5,6], and dysregulation of ventilatory control [1].

Diagnostic frameworks leveraging gene discovery technologies have become indispensable for precision identification, facilitating the elucidation of pathophysiological mechanisms and the advancement of targeted therapies [7]. Concurrently, molecular strategies have yielded substantial progress in developing potential therapeutic interventions [8]. This narrative review synthesizes current pulmonary management strategies across a spectrum of neuromuscular disorders, integrating foundational knowledge with seminal literature findings from the past decade.

Central nervous system diseases

Parkinson's disease

Respiratory pathophysiology

Extrapyramidal akinetic syndromes frequently induce increased tone in both extensor and flexor muscles, resulting in the "lead-pipe" rigidity characteristic of Parkinson's disease (PD) and related parkinsonian syndromes, such as striatonigral degeneration [9-11]. This extrapyramidal dysfunction significantly impairs voluntary respiration, often rendering patients unable to intentionally modulate their breathing patterns [12,13].

The respiratory involvement in PD extends beyond simple muscle weakness; it encompasses dysregulation of autonomic ventilatory control and impaired cough coordination, both of which predispose patients to microaspiration and infectious complications [16]. Furthermore, PD is characterized by altered responses to hypercapnia and hypoxia, alongside discoordination of the respiratory musculature [12]. These dysfunctions are often compounded by reduced thoracic mobility and a flexed trunk posture, which significantly diminish lung volumes and exacerbate restrictive ventilatory defects [19]. Rigidity and bradykinesia further compromise chest wall expansion and diaphragmatic efficiency, ultimately reducing lung compliance [17].

Consequently, progressive deterioration of pulmonary function often culminates in chronic respiratory failure. Alveolar hypoventilation, a common feature emerging from respiratory muscle weakness, may evolve into acute respiratory failure if not identified early, particularly during intercurrent respiratory infections [15]. Despite their clinical significance, these respiratory alterations are frequently underestimated by both clinicians and patients, even in the early stages of the disease [17,18].

Etiology and diagnostic framework

While the exact etiology of PD remains elusive, it is widely accepted that the disease arises from a synergistic combination of environmental factors and genetic susceptibility [20-25]. Pathologically, PD is defined by the selective loss of dopaminergic neurons and the systemic accumulation of Lewy bodies, which are comprised of alpha-synuclein aggregates [26,27].

The diagnostic gold standard remains clinical, based on the identification of cardinal motor features, sustained response to dopaminergic agents, and the subsequent emergence of motor fluctuations [28,29].

These criteria, formalized by the UK Parkinson's Disease Society Brain Bank, achieve a diagnostic accuracy exceeding 90% [30,31]. Such precision is vital for differentiating PD from atypical parkinsonian syndromes, including multiple system atrophy and progressive supranuclear palsy [32]. Beyond clinical evaluation, Magnetic Resonance Imaging (MRI) serves as a critical tool to exclude alternative neurodegenerative pathologies [34]. Additionally, the assessment of respiratory function—specifically inspiratory and expiratory muscle strength—is fundamental for early management, as deficits are detectable even in asymptomatic patients when compared to age- and sex-matched healthy controls [14].

Therapeutic interventions

The management of PD focuses on addressing both motor and non-motor manifestations through pharmacological and surgical strategies. Primary symptomatic treatment targets dopaminergic

pathways using non-ergot dopamine agonists, such as ropinirole, pramipexole, and rotigotine [35].

For patients in advanced stages, Deep Brain Stimulation (DBS) has demonstrated high efficacy in modulating motor signs [36]. Botulinum toxin may also be employed for the targeted treatment of focal dystonias and specific motor symptoms, providing significant symptomatic relief [33]. Given the high morbidity associated with pulmonary decline, targeted respiratory interventions and regular pulmonary function monitoring are essential components of a comprehensive therapeutic plan [14,15].

Multiple sclerosis

Pathophysiology and respiratory impact

Multiple Sclerosis (MS) is a chronic, immune-mediated primary disorder of the central nervous system. While its pathogenic mechanisms remain only partially elucidated, the disease is characterized by two distinct patterns of chronic progression: primary progressive and secondary progressive MS. In their early stages, these forms involve focal inflammatory lesions marked by perivenular accumulation of T and B lymphocytes, disruption of the blood-brain barrier, demyelination, and acute axonal transection [37,38].

The accumulation and progression of these focal lesions frequently result in significant respiratory impairment. This encompasses a spectrum of dysfunctions, including respiratory muscle weakness, bulbar dysfunction, and dysregulation of central respiratory control. Furthermore, MS patients are highly predisposed to sleep-disordered breathing, particularly obstructive sleep apnea and nocturnal ventilatory dysfunction, which contribute to a continuous spectrum of respiratory symptoms. Consequently, polysomnography has become an increasingly essential diagnostic tool to investigate the high prevalence of sleep-related respiratory disorders in this population [1,39].

Diagnostic framework

The diagnostic workflow for MS has been significantly refined by the 2017 McDonald Criteria, which facilitated earlier and more accurate identification of the disease. Diagnosis typically begins with a clinical presentation suggestive of inflammatory demyelinating lesions within the central nervous system.

Neuroimaging via Magnetic Resonance Imaging (MRI) remains the cornerstone of diagnosis, enabling the detection of cortical and white matter lesions, regardless of whether they are symptomatic. A critical advancement in the 2017 criteria was the reintegration of cerebrospinal fluid (CSF) analysis. The identification of oligoclonal bands in the CSF serves as a vital biomarker for dissemination in space, particularly in cases where MRI fails to demonstrate dissemination in time through post-gadolinium T1-weighted imaging in asymptomatic patients [40,41].

Therapeutic management

Given its chronic and multifaceted nature, MS necessitates a comprehensive treatment approach aimed at mitigating pathological progression and preserving functional autonomy.

Disease-Modifying Therapies (DMTs): These pharmacological interventions are designed to attenuate neuroinflammation and limit further demyelination. A notable high-efficacy monotherapy is natalizumab; however, its clinical use requires rigorous monitoring due to the associated risk of progressive multifocal leukoencephalopathy (PML) [44,45].

Respiratory and Rehabilitation Strategies: Beyond immunosuppression, rehabilitation focused on maintaining pulmonary function and enhancing respiratory muscle strength is crucial for managing long-term sequelae [42,43].

This integrated strategy—combining targeted DMTs with proactive respiratory care—is essential for improving the quality of life and outcomes for patients living with MS.

Diseases of the neuromuscular junction

Myasthenia gravis

Myasthenia gravis (MG) is a chronic autoimmune disease that targets the neuromuscular junction, specifically affecting the motor endplate by attacking acetylcholine receptor (AChR) antigenic sites. Anti-AChR antibodies lead to a reduction in ACh availability at the muscle endplate. Weakness across various muscle groups, including respiratory muscles, is frequently associated with bulbar involvement. Elderly patients with comorbidities may present with nonspecific exertional dyspnea following deconditioning or weight gain. In the event of an acute crisis, respiratory failure may ensue. Diaphragmatic weakness should be suspected in patients reporting

dyspnea when leaning forward, as orthopnea is a hallmark diagnostic indicator of diaphragmatic impairment. Furthermore, MG can manifest as a paraneoplastic syndrome, often associated with small-cell lung cancer. Therapeutic management may include thymectomy in selected cases, frequently resulting in symptomatic improvement [46,47].

Lambert-eaton myasthenic syndrome (LEMS)

Both Lambert-Eaton Myasthenic Syndrome (LEMS) and MG present with symptoms related to muscle weakness, although LEMS has a lower prevalence than MG. Similar to MG, LEMS is associated with small-cell lung cancer and can affect the respiratory muscles. The antigenic target in LEMS is the presynaptic P/Q-type voltage-gated calcium channel (VGCC). The reduction of calcium influx at the terminal plate leads to diminished ACh release into the synaptic cleft of the neuromuscular junction, potentially resulting in transmission failure. While respiratory involvement and overt respiratory failure are generally late-stage findings, they are typically observed in individuals with nonspecific neuromuscular weakness [48,49].

Diagnosis and classification

Both MG and LEMS are diagnosed through the identification of specific antibodies, enabling individualized and targeted treatments. Therapeutic interventions may involve immunomodulators or immunosuppressive agents, depending on clinical circumstances [50]. MG is classified into several types, including congenital myasthenic syndrome, neonatal myasthenia gravis, juvenile myasthenia, and early-onset or late-onset myasthenia gravis [51]. The diagnostic gold standard for MG relies on clinical neurological examination supplemented by serological and electrophysiological testing [52].

Therapeutic management

Pharmacological treatment for MG often involves pyridostigmine, combined with low-dose prednisone on alternate days. This dosage may be increased in cases of respiratory weakness with bulbar involvement. During myasthenic crises or severe exacerbations, plasmapheresis and immunomodulatory treatment with intravenous immunoglobulin (IVIg) are indicated. Symptomatic treatment for LEMS is primarily conducted with 3,4-diaminopyridine (3,4-DAP). Additionally, immunosuppressive drugs similar to those used in MG may be utilized for LEMS management [53,54].

Acute polyneuropathies: Guillain-Barré syndrome (GBS)

Therapies and prognosis

Although the primary focus remains on the acute phase, novel approaches aim to reduce the duration of mechanical ventilation dependence.

- **Complement Inhibitors:** In clinical trials, the monoclonal antibody ANX005 (a C1q inhibitor) has been shown to reduce the duration of artificial ventilation by a median of 28 days and accelerate the recovery of muscle strength [55-57].
- **Prognostic Scoring (EGRIS-Kids):** For pediatric respiratory management, the new EGRIS-Kids score—based on age, bulbar palsy, and weakness at admission—enables the prediction of respiratory failure risk (ranging from 4% to 50%). This facilitates early decision-making regarding interventions or intensive care unit (ICU) transfer [55-57].

Motor neuron disease (MND)

Amyotrophic Lateral Sclerosis (ALS) is a progressive and relatively rare neurodegenerative disease that affects both upper and lower motor neurons. It is characterized primarily by progressive weakness leading to muscle atrophy and spasticity [58]. Compared to other neurodegenerative disorders, ALS progression is exceptionally rapid, evolving toward paralysis with a survival range of 1 to 5 years following initial symptoms. Patients and caregivers frequently report a progressive loss of activities of daily living (ADL), with only 5% of patients surviving beyond a decade. While the exact etiology remains unknown, several mechanisms are discussed, including hereditary factors, glutamate excitotoxicity, and viral infections. Common causes of death in ALS include aspiration pneumonia and paradoxical abdominal movements [1].

Respiratory pathophysiology in ALS

Spontaneous respiration in ALS is compromised by the loss of motor neurons in the anterior horn of the spinal cord. The diaphragm and intercostal muscles are innervated by the phrenic nerve (C3-C5) and thoracic spinal nerves, respectively. Complications arise as motor neurons across the thoracic segments lose innervation [59]. Due to high mortality rates, regular pulmonary function tests (PFTs) are conducted to estimate survival and guide therapeutic decisions. Patients with early-onset bulbar weakness tend to exhibit respiratory symptoms sooner and experience faster disease progression [56,59].

Respiratory support and monitoring

Mechanical ventilation is indicated when Forced Vital Capacity (FVC) < 50% or Maximal Inspiratory Pressure (MIP) < 60 cmH_2O. Standard initial settings involve an inspiratory pressure of approximately 12 cmH_2O and an expiratory pressure of 4 cmH_2O. Non-invasive ventilation (NIV) significantly enhances life expectancy and quality of life, particularly in patients with moderate or no bulbar impairment.

Slow Vital Capacity (SVC) is often a more accurate reflection of diaphragmatic function in prolonged cases. FVC may not be the ideal parameter for assessing true respiratory muscle strength in ALS due to alterations in the pressure-volume curves. Consequently, Maximal Inspiratory Pressure and Maximal Expiratory Pressure (MEP) are the preferred tests. Nocturnal desaturation ($SpO_2 \leq 90\%$ for a cumulative minute) serves as an early indicator of respiratory insufficiency. While carbon dioxide levels can be monitored via venous blood or portable devices for home use, arterial blood gas (ABG) analysis in the morning remains the gold standard for diagnosing respiratory failure [56,60].

Diagnosis and new perspectives: immunomodulation

The diagnosis of ALS relies on clinical and neurological examinations identifying progressive upper and lower motor neuron signs. Complementary assessments include blood tests, neuroimaging, nerve conduction studies, muscle biopsy, and cerebrospinal fluid analysis [61].

- **Immunotherapy (NP001):** Recent evidence positions ALS as an immuno-neurological disease where inflammatory regulation directly impacts respiratory function. The use of NP001 (a macrophage regulator) demonstrated specific efficacy in patients with a BMI ≥ 25 and age ≤ 65 (indicators of systemic inflammation). In this subgroup, treatment slowed the decline of vital capacity by approximately 31% and extended overall survival, confirming that preserving respiratory function through immune modulation is a viable therapeutic target.
- **Respiratory Mediation:** Statistical models indicate that respiratory function acts as a mediator between Autonomic Nervous System (ANS) activity and global functionality. Increased sympathetic nervous system (SNS) activity correlates with better respiratory function, which in turn enhances cognition and antioxidant capacity [62]. This suggests that interventions optimizing respiration could positively impact multiple domains of the disease [59].

Spinal muscular atrophy (SMA)

Spinal Muscular Atrophy (SMA) Type I, or Werdnig-Hoffmann disease, is linked to the *5q11.2-13.3* chromosomal locus. It is an autosomal recessive disorder in its most acute form. Common manifestations include diminished fetal movements and congenital skeletal deformities, particularly of the thorax, hips, and feet, alongside respiratory difficulties. This neurodegenerative disease is caused by mutations in the *SMN1* gene, resulting in a deficiency of the SMN protein, which is essential for motor neuron survival [63].

In respiratory muscle weakness, the inability of the muscles to generate force prevents normal pressure and flow levels during inspiration and expiration. Thoracic anatomy may be compromised, and the weakness of respiratory muscles, particularly the diaphragm, is often heightened. Evidence suggests that early respiratory management—including cough assist devices, invasive or non-invasive mechanical ventilation, and adequate nutritional care—promotes improved quality of life and extended survival [64,65].

In the natural history of SMA Type I without respiratory support, pulmonary complications typically emerge by the second or third month of age. Patients present with acute respiratory failure, often triggered by respiratory tract infections and thoracic infections characterized by tracheobronchial secretion retention. To assess respiratory function in children, non-invasive techniques are preferred, including spirometric parameters, Peak Cough Flow (PCF), ventilatory patterns, and thoraco-abdominal contribution during Quiet Breathing (QB) [66,67].

Therapeutic update: Stabilization and dissociation of strength and volume

Disease-modifying therapies (Nusinersen, Risdiplam, and Onasemnogene Abeparvovec) have transformed the natural history of SMA from rapid decline to stabilization or slow progression.

- **Risdiplam:** In adults with SMA Types 2 and 3, 24-month treatment resulted in the stabilization of FVC, preventing the expected annual decline. Additionally, a significant

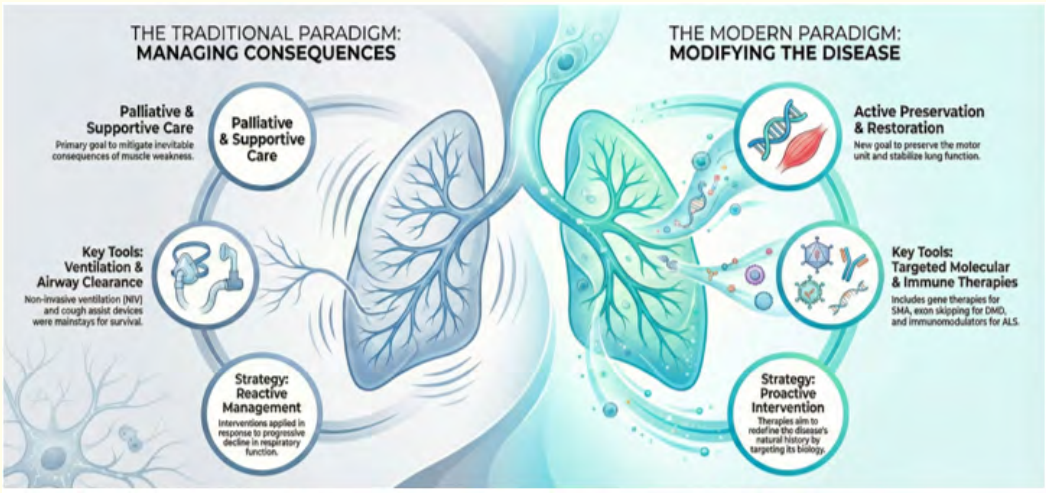

Figure 1: Traditional versus Modern care for pulmonary care on neuromuscular diseases.

improvement in Peak Expiratory Flow (PEF) was observed, suggesting benefits in cough strength and airway clearance.

- **Nusinersen:** Data in children reveal a notable dissociation. After three years of treatment, respiratory muscle strength (measured by MIP and MEP) was preserved or improved. However, percent predicted FVC (ppFVC) continued to decline (approximately 13.5% by the third year), likely due to scoliosis progression and disproportionate body growth relative to lung volume. Nevertheless, treatment delayed the need for non-invasive ventilation (NIV) and reduced hospitalizations.
- **Onasemnogene Abeparvovec:** Real-world cohorts show that patients transitioning from Nusinersen to gene therapy maintained respiratory stability without requiring tracheostomy or increased daily ventilatory support [75].

Evaluation Parameter	Natural History (Untreated)	Post-Molecular Therapy	Dissociation
Muscle Strength (MIP, MEP, PCF, PEF)	Constant decline	Stabilization or Improvement	Biological Success: Protection of the motor unit and neuromuscular junction.
Lung Volume (FVC/ ppFVC)	Constant decline	Persistent Decline	Mechanical Failure: Impact of scoliosis, thoracic rigidity, and body growth.

Table 1: The Respiratory Dissociation Effect (SMA and DMD).

Duchenne muscular dystrophy (DMD)

Attenuation of respiratory decline

In dystrophinopathies, molecular therapies do not reverse the disease but attenuate the rate of restrictive respiratory deterioration through mechanisms such as Exon Skipping:

- **Eteplirsen (Exon 51):** Long-term treatment reduced the annual decline of ppFVC to approximately 2.3%–3.3%, compared to 6.0% in historical controls.
- **Golodirsen (Exon 53):** Three-year data show an 8.4% decline in FVC, indicating relative preservation of pulmonary function.
- **Ataluren (Nonsense mutations):** In non-ambulatory patients, ataluren was associated with a statistically significant delay (approx. 3 years) in the decline of ppFVC below the 60% threshold.

Dystrophic isoforms and the brain-muscle connection

The neuropathology of DMD and BMD has evolved from a purely muscular view to a systemic understanding where specific isoforms dictate both motor severity and the central competence to execute motor tasks [76].

- **DMD and the Dp140 Isoform:** The absence of the Dp140 isoform is associated with significantly worse respiratory trajectories (ppFVC 4.3 points lower) and reduced upper limb strength. Current hypotheses suggest that Dp140 deficiency causes deficits in executive functions and cerebral processing, impairing the patient's ability to plan and execute complex motor tasks, such as spirometry [77,78].
- **Becker (BMD) and Protein Structure**: Severity in BMD depends on how mutations alter the residual dystrophin. The del45–49 deletion results in a severe phenotype due to the loss of flexibility in the protein's rod domain. Conversely, deletions like del45–55 preserve function longer, provided that nNOS (neuronal Nitric Oxide Synthase) remains localized at the sarcolemma [79].

Disease	Primary Respiratory Mechanism	Key Diagnostic Tool
Parkinson's	Extrapyramidal rigidity and Autonomic dysfunction	Clinical exam/Spirometry
Myasthenia Gravis	Post-synaptic NMJ failure (AChR)	AChR Antibodies/Electrophysiology
SMA Type I	Motor neuron loss and Diaphragm reliance	Genetic testing (SMN1)/QB measures
ALS	Upper/Lower motor neuron degeneration	EMG/ SVC and MIP/MEP

Table 2: Respiratory Correlation.

Condition Type	Target Diseases	Recommended Tests and Metrics	Monitoring Frequency
Acute	GBS/MG	SBC (Single Breath Count), Neck Flexion Strength (MRC), VC, MIP, MEP, Bulbar/ Facial weakness assessment, and Paradoxical breathing.	Every 4–6 hours during the acute progressive phase to establish trajectory.
Chronic (Adult)	ALS	FVC (Sitting/Supine), SVC, ALSFRS-R (Total and Respiratory sub-scores), and Oxygen Saturation.	Every 6 months after diagnosis.
Pediatric	SMA/DMD	PFTs (ppFVC, FEV_1/FVC), PCF (Peak Cough Flow), MIP, MEP, and Polysomnography (AHI, nocturnal CO_2).	Annual routine evaluation or according to motor milestones.
Neuromodulation	SCI	MIP, FEV_1, FVC, and autonomic markers (BP, Heart Rate Variability – HRV).	During mapping sessions and periodically during rehabilitation interventions.
Adult Stability	SMA (Treated)	FVC, PEF (Peak Expiratory Flow), MFM-32, RULM, and PROMs (SF-36, Fatigue Severity Scale).	Every 12 to 24 months to assess treatment efficacy.

Table 3: Respiratory Monitoring Recommendations.

Conclusion

The understanding of respiratory pathophysiology in neuromuscular diseases and spinal cord injury has undergone a fundamental paradigm shift. Historically, clinical management was limited to ventilatory support and airway clearance to mitigate the inevitable consequences of muscle weakness. Today, the field has transitioned from a purely palliative strategy to an active approach of motor unit preservation and functional restoration.

While precise diagnosis and NIV remain essential pillars, disease-modifying therapies have redefined the natural history of these conditions. In SMA and DMD, the focus has shifted from managing decline to stabilizing lung function and addressing the dissociation between muscle strength and thoracic volume. Parallelly, in ALS and GBS, the recognition of immuno-inflammatory mechanisms and autonomic mediation has opened new therapeutic windows to protect respiratory function before irreversible degeneration occurs.

In summary, modern respiratory management requires an integrative perspective: it is no longer merely about ventilating the lungs, but about modulating the biology of the neuromuscular system to preserve vital capacity and patient autonomy for as long as possible.

Author Contributions

- **Conceptualization:** Odair Henrique Gaverio Diniz
- **Data curation:** Odair Henrique Gaverio Diniz
- **Formal analysis:** Odair Henrique Gaverio Diniz
- **Investigation:** Odair Henrique Gaverio Diniz
- **Methodology:** Odair Henrique Gaverio Diniz
- **Supervision:** Odair Henrique Gaverio Diniz
- **Validation:** Odair Henrique Gaverio Diniz
- **Visualization:** Odair Henrique Gaverio Diniz
- **Writing – original draft:** Odair Henrique Gaverio Diniz
- **Writing – review and editing:** Odair Henrique Gaverio Diniz

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No author declared competing interests.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Generative AI And AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT and Gemini in order to rephrase some sentences avoiding unnecessary repetitions. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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