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Review Article

Is There a Role for Exercise in the Management of Bulbar Dysfunction in Amyotrophic Lateral Sclerosis?

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Purpose: The role of exercise in the management of people with amyotrophic lateral sclerosis (PALS) is controversial and currently unclear. The purpose of this review article is to review literature examining the impact of limb, respiratory, and oral motor exercise on function, disease progression, and survival in PALS and the transgenic ALS animal model.
Method: A literature review was conducted to examine relevant studies published in peer-reviewed journals between 1960 and 2014. All studies were appraised for quality of research and were assigned a level of evidence, and treatment outcomes were classified as either positive, negative, or neutral.
Results: A total of 18 exercise-based intervention studies on limb (13), respiratory (3), or speech (2) function were identified. Of the human clinical trials, 6 were experimental and 4 were exploratory. No experimental studies were identified examining the impact of targeted exercise on speech or swallowing function. Mild to moderate intensity limb or respiratory exercise, applied early in the disease, was noted to have a beneficial impact on motor function and survival.
Conclusion: Insufficient data exist to support or refute the role of exercise in the management of bulbar dysfunction in PALS. This represents a critical area of future investigation.

Amyotrophic lateral sclerosis (ALS) is a fatal neuromuscular disease causing rapid degeneration of motor neurons in the cerebral cortex, brainstem, spinal cord, and corticobulbar tracts. ALS is one of the most common disabling neuromuscular diseases among adults in the United States with 12,187 cases identified between 2010 and 2011 in a recent national ALS registry and a national prevalence estimate of 3.9 per 100,000 people (Mehta et al., 2014). Typical age of disease onset is 55 years, and average survival ranges between 2 and 5 years and is largely dependent on disease onset type (Kuhnlein et al., 2008). Clinical features of upper motor neuron (UMN) cell death include muscle stiffness or spasticity, slowness of movement, hypertonia, hyperreflexia, pseudobulbar signs, and pathologic reflexes. Degeneration of lower motor neurons (LMNs) in the brain stem or spinal cord causes atrophy, muscle weakness, hypotonia, fasciculations, and diminished reflexes. Varying combinations of these symptoms may appear at the initial presentation of ALS in either the limbs (70% of cases) or bulbar regions (30% of cases) and eventually spread to affect the lumbosacral, thoracic, cervical, and bulbar regions of the entire body (Wijesekera & Leigh, 2009).

The pathophysiologic mechanisms of ALS are complex and at present not completely understood. Current theories include roles for oxidative stress, protein misfolding and aggregation, skeletal muscle dysfunction, glutamate excitotoxicity, mitochondrial dysfunction, neuroinflammation, and apoptosis (Patel & Hamadeh, 2009). It is unfortunate that unlike other diseases, no major medical treatments have significantly advanced the care or survival rates in people with ALS (PALS). Riluzole, the only Food and Drug Administration–approved pharmacologic intervention for PALS, has only modest effects with a reported increase of 83 days of survival (Simmons, 2005). Therefore, new interventions that prolong or maintain function, quality of life, and survival are urgently needed in this challenging patient population (Miller et al., 2009b).

This review will first describe bulbar dysfunction and management of speech and swallowing dysfunction in ALS. The utility of exercise in health and disease is then introduced and its broad application in the field of speech-language pathology across other patient populations is discussed. A comprehensive review of literature examining

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the impact of exercise on motor function, disease progression, and survival in both PALS and the superoxide dismutase 1 (SOD1) transgenic ALS animal model will then be provided to critically examine the role of exercise in the management of ALS.

For this review, literature was electronically searched by one investigator for published reports in English between 1960 and 2014 by using MEDLINE-OVID, MEDLINE-ProQuest, MEDLINE-EIFL, EMBASE-OVID, The Cochrane Library Central Register of Controlled Trials (CENTRAL) CINAHL, EMBASE, and PubMed. In the first search, the key words "ALS," "motor neuron disease," "superoxide dismutase 1," or "SOD1" were included. Secondary key words included "treatment," "management," "rehabilitation," "exercise," "strengthening," and "aerobic." All published articles reporting the impact of an exercise intervention on any body system (limb, respiration, speech) were included. Each study was ascribed a Level of Evidence according to Sackett, Strauss, Richardson, Rosenberg, and Haynes (2000). Further, stage of research was noted as either "exploratory" or "experimental" following the broad framework of Clark, Lazarus, Arvedson, Schooling, and Frymark (2009). For the purpose of this particular review, *experimental* was defined as any prospective study utilizing an appropriate control (including a usual care group, sham group, or lead-in period to benchmark natural disease progression in the absence of any intervention). *Exploratory* was defined as any prospective study reporting the impact of an exercise intervention without an appropriate control, or a retrospective examination of PALS undergoing treatment who were compared with matched historical controls. A summary treatment impact classification (TIC) was ascribed to each study to denote if a positive, neutral, or negative overall outcome was observed after the specific exercise intervention studied in PALS or SOD1 animals.

Neurophysiologic Framework of Bulbar Dysfunction in ALS

UMNs are those motor neurons originating in the cortex that terminate in the brainstem or spinal cord, whereas LMNs originate in the brainstem (corticobulbar) or spinal cord (corticospinal) and terminate at the neuromuscular junction. In ALS, both UMN and LMN pathology give rise to spastic and atrophic bulbar pathophysiology that manifests into a spastic-flaccid dysarthria and dysphagia. Indeed, a reported 93% of PALS experience speech impairments, whereas 85% demonstrate swallowing dysfunction throughout the disease progression, with timing and presentation of bulbar symptoms largely dependent on disease onset type (Carpenter, McDonald, & Howard, 1978; Chen & Garrett, 2005). Supranuclear symptoms caused by UMN degeneration lead to spasticity of bulbar muscles that functionally relate to muscle stiffness and slowness of movement, hyperreflexia, hyperfunction, and decreased speed (Kuhnlein et al., 2008). Bulbar palsy, due to LMN degeneration of cranial brainstem nuclei, results in flaccid paresis, atrophy, fasciculations, and decreased strength and force generation of the tongue, soft palate, pharynx, larynx, jaw, and facial muscles (Kuhnlein et al., 2008). Degeneration of motor neurons in the spinal cord can also result in speech and swallowing dysfunction secondary to changes in the respiratory system that overlap with voice, cough, and swallow function (Kuhnlein et al., 2008; Rosenbek & Troche, 2013; Strand, Miller, Yorkston, & Hillel, 1996).

Speech Impairments in ALS

Table 1 provides a summary of perceptual ALS speech characteristics within a neuropathophysiologic framework of the governing UMN and LMN degeneration and associated bulbar pathophysiology. Speech in PALS is generally characterized by slow laborious speech, hypernasality with nasal air emission, defective articulation, imprecise consonants, low pitch and volume, altered prosody, and a strained and strangled voice quality (Darley, Aronson, & Brown, 1969a; Duffy, 2005; Kuhnlein et al., 2008; Tomik & Guiloff, 2010). The most deviant speech clusters identified in the seminal study of the dysarthrias by Darley et al. (1969b) included articulatory and resonatory incompetence, phonatory stenosis or incompetence, and prosodic changes. Although PALS will eventually demonstrate a mixed flaccid-spastic dysarthria, speech impairments correlate with the predominant neuropathology during the earlier stages of the disease. Therefore, individuals with predominant UMN pathology will demonstrate supranuclear symptoms that manifest clinically as a spastic dysarthria, whereas those with predominant LMN pathology and bulbar palsy will demonstrate a flaccid dysarthria (Duffy, 2005). Speech symptom onset is highly variable and dependent on disease onset type, ranging from 33 months prior to actual diagnosis (bulbar onset) to 60 months after diagnosis (limb onset; Yorkston, Strand, Miller, Hillel, & Smith, 1993). Turner et al. (2010) retrospectively reviewed medical records of 49 PALS with a bulbar onset and noted that the median time from disease onset to a complete loss of speech (anarthria) was 18 months. Although symptom progression rate is variable, speech decline follows a predictable sequence that has been described in a progression of 10 levels of speech function deterioration (Yorkston, Miller, & Strand, 2004). Eighty to ninety-five percent of PALS will be unable to meet their daily communication needs by using natural speech at some point during the disease progression (Beukelman, Fager, & Nordness, 2011).

Reduced speech intelligibility in PALS has been associated with decreased tongue force (Dworkin, 1980), smaller vowel space area and reduced second formant (F2) slope (Kent et al., 1992; Turner, Tjaden, & Weismer, 1995; Yunusova et al., 2012), longer phrase durations (Turner & Weismer, 1993), slow articulatory movement rates (DePaul & Brooks, 1993; Dworkin, Aronson, & Mulder, 1980; Kuruvilla, Green, Yunusova, & Hanford, 2012; Langmore & Lehman, 1994), reductions in repeated contraction rate during diadochokinetic tasks (Langmore & Lehman, 1994),

Table 1. Bulbar pathophysiology resulting from upper motor neuron (UMN) or lower motor neuron (LMN) degeneration and the corresponding perceptual speech signs in amyotrophic lateral sclerosis (ALS). ALS individuals' speech may include a combination of these speech signs and in the early stage will resemble the predominant governing pathophysiology (either spastic or flaccid dysarthria); it will eventually resemble a mixed flaccid-spastic dysarthria.

Site of damage	Bulbar pathophysiology	Speech signs
UMN (Degeneration of pyramidal neurons of layer five in the primary motor cortex, CST, and CBT)	Supranuclear symptoms: • Spasticity of bulbar musculature • Hyperadduction of vocal folds • Supraglottic hyperfunction • Decreased speed and rate of bulbar musculature • Hyperactive reflexes • Emotional labiality (pseudobulbar affect)	Spastic dysarthria: • Strained/strangled voice • Harsh voice • Slower speaking rate • Slow and imprecise articulation • Short phrases • Monopitch and monoloudness • Hypernasality
LMN (Degeneration of cranial nerve nuclei in the medulla oblongata and Pons)	Bulbar palsy: • Flaccid paresis of bulbar musculature • Bulbar muscle atrophy • Velopharyngeal incompetence • Decreased strength and force of bulbar musculature • Fasciculations • Decreased or absent gag • Vocal cord paresis • Incomplete vocal fold closure	Flaccid dysarthria: • Hypernasality • Nasal air emission during speech • Breathy voice • Hoarse voice • Low pitch • Decreased loudness • Monopitch and monoloudness • Slow and imprecise articulation • Shortened phrases

Note. CST = corticospinal tract; CBT = corticobulbar tract.

reduced peak change rate of the lower lip and tongue force (DePaul & Brooks, 1993), slower rates of syllable repetition (Dworkin et al., 1980), and reduced lingual speed (Kuruvilla et al., 2012). Reduced speech intelligibility in PALS is more closely related to the *slowing of articulatory movements* than *decreased strength of the articulators* (DePaul & Brooks, 1993; Kuruvilla et al., 2012; Langmore & Lehman, 1994) and likely reflects the fact that speech represents a submaximal task of the bulbar musculature. PALS rate loud environments and prolonged speaking conditions as the most difficult speaking environments (Ball, Beukelman, & Pattee, 2004) and the potential loss of speech function was rated as one of the worst symptoms of the disease (Hecht et al., 2002).

Swallowing Impairments

Dysphagia results from weakness (LMN) or spasticity (UMN) of muscles of deglutition innervated by trigeminal, facial, hypoglossal, glossopharyngeal, or vagal nerves including muscles of mastication, the tongue, lips, pharynx, and larynx (Kuhnlein et al., 2008). Typical dysphagic symptoms reported by PALS include the following: increased meal times and associated fatigue with eating, weight loss, choking, food sticking in the throat, difficulties swallowing saliva, and frequent respiratory infections. Although dysphagia is reported to occur in 85% of PALS (Carpenter et al., 1978; Chen & Garrett, 2005), it is eight times less likely to be the presenting symptom than dysarthria, and is more likely to be present at later stages of the disease (Sterling, Axline, & Ragland, 2013). Indeed, the incidence of dysphagia has been noted to rise by 9% for every one-point decrease in the ALS Functional Rating Scale (ALSFRS; Traynor et al., 2000), a validated index of global disease progression. Table 2 presents UMN and LMN bulbar pathology and the associated swallowing impairments typically noted across the four swallowing "stages." Decreased motility, strength, and coordination of orofacial and lingual musculature lead to difficulties in oral preparation, bolus containment, mastication, and oral transport during the oral preparatory and oral stages of swallowing (Kawai et al., 2003; Morimoto et al., 2013). This results in anterior spillage, inefficient anterior–posterior propulsion, residue of food and secretions in the oral cavity, and prolonged oral transit times (Kuhnlein et al., 2008; Tamburrini et al., 2010). Reduced tone and strength of pharyngeal, laryngeal, and submental musculature result in reduced hyolaryngeal excursion and reduced upper esophageal sphincter (UES) opening; decreased pharyngeal contraction; residue in the pyriform sinuses, valleculae and postcricoid region; impaired laryngeal vestibule closure; and subsequent penetration and aspiration during the pharyngeal stage of swallowing (Leder, Novella, & Patwa, 2004; Lo Re et al., 2007; Noh, Park, Park, Moon, & Jung, 2010). Increased oropharyngeal and hypopharyngeal transit times and reduced pharyngeal strength were recently identified as independent predictors of aspiration during swallowing in PALS (Plowman, Domer, Watts, Gaziano, & Tabor, 2014).

UMN and LMN degeneration of respiratory musculature further contributes to impaired airway protection with the inability to generate adequate expiratory pressures to produce an effective cough (Park, Kang, Lee, Choi, & Kim, 2010; Ruoppolo et al., 2013). A recent study noted that in 24 PALS who demonstrated aspiration on videofluoroscopy, no patient was able to demonstrate an adequate and effective cough response to expel aspirant material (Gaziano, Tabor, Richter, & Plowman, 2015). Further,

Table 2. Bulbar pathophysiology resulting from upper motor neuron or lower motor neuron degeneration and the corresponding swallowing impairments in amyotrophic lateral sclerosis.

Bulbar pathophysiology	Swallow signs/impairments	Affected swallow stage
Labial paresis	• Poor oral containment of bolus	Oral preparatory
	• Anterior leakage	Oral
	• Drooling of saliva	
	• Thickening of saliva due to mouth breathing	
Paresis/spasticity of muscles of mastication	• Decrease strength, rate, and range of motion of mastication	Oral preparatory
	• Impaired bolus formation	Oral
	• Chewing fatigue	
Tongue atrophy and paresis	• Reduced base of tongue retraction	Oral preparatory
	• Decreased lingual pressure generation	Oral
	• Inefficient bolus transfer/propulsion	
	• Oral buccal residue	
	• Poor bolus control	
	• Premature spillage of bolus to valleculae	
	• Increased oropharyngeal transit time	
Velopharyngeal insufficiency	• Spillage of material into the nasopharynx	Oral
	• Nasopharyngeal regurgitation	
Paresis/spasticity of submental musculature	• Decreased hyolaryngeal excursion	Oral
	• Reduced UES opening	Pharyngeal
	• Residue in pyriforms, valleculae, and postcricoid region	
Paresis/spasticity of pharyngeal constrictors	• Decreased pharyngeal contraction	Pharyngeal
	• Decreased oropharyngeal pressure generation	
	• Poor bolus transit	
	• Retention in pyriforms and postcricoid region	
	• Increased hypopharyngeal transit time	
Vocal cord paresis	• Compromised airway protection	Oral
	• Aspiration from incomplete glottis closure	Pharyngeal
	• Poor respiratory/swallow coordination	Esophageal
	• Abnormal laryngeal adductor reflex—silent aspiration	
Hypertonic/hyperreflexive UES	• Reduced extent and duration of circopharyngeal opening	Esophageal
	• Residue in postcricoid region and increased risk of aspiration of residual material	
	• Bolus redirection	
Paretic/spastic muscles of inspiration and expiration	• Inability to generate adequate expiratory pressure to produce effective cough	Oral
	• Compromised airway protection	Pharyngeal
	• Poor respiratory/swallow coordination	Esophageal
	• Prolonged apnea duration during swallowing	

Note. UES = upper esophageal sphincter.

laryngopharyngeal sensory deficits have been reported in a high percentage of PALS (54%), which may further contribute to airway compromise during swallowing (Amin, Harris, Cassel, Grimes, & Heiman-Patterson, 2006).

Impact of Bulbar Impairment on Quality of Life and Survival

Clinical manifestations of bulbar symptoms are both functionally and psychologically devastating (Kraft et al., 2010; Paris et al., 2013). In patient surveys, PALS rated speech loss as one of the worst aspects of the disease (Hecht et al., 2002) and those with dysphagia reported social isolation, fear, and decreased mental health (Paris et al., 2013). In addition to impacting quality of life and mental well-being, tongue strength has been recently identified as an independent prognostic indicator of survival in ALS (Weikamp, Schelhaas, Hendriks, de Swart, & Geurts, 2012). Dysphagia and malnutrition increase the risk of death by almost eight times and contribute to 25.9% of ALS mortality (Chio et al., 2009; Yang et al., 2011). Therefore, bulbar dysfunction in PALS contributes to significant reductions in quality of life, may serve a prognostic role, and impacts survival.

Treatment Approaches for Bulbar Dysfunction in ALS

Current speech-language pathology treatment practices for PALS focus on promotion of compensatory and energy-conserving strategies, dietary modifications, nonoral tube feeding, and augmentative and alternative communication (AAC) devices to optimize safety, comfort, and quality of life (Beukelman et al., 2011; Hanson, Yorkston, & Britton, 2011; Kuhnlein et al., 2008; Miller & Britton, 2011). Primary goals of the speech-language pathologist are to (a) maintain the ability to eat and maximize speech intelligibility for as long as possible, (b) minimize the risk of aspiration, (c) manage sialorrhea and/or thick mucous, and (d) educate and counsel (Britton, Clearly, & Miller,

2013). Active interventions such as musculoskeletal and/or oral motor strengthening exercises have been discouraged by neurologists and health care professionals due to the fear that exercise may overburden the diseased muscle and hasten disease progression (Beukelman et al., 2011; Dal Bello-Haas & Florence, 2013; Mahoney, Rodriguez, Devries, Yasuda, & Tarnopolsky, 2004; Sinaki & Mulder, 1978).

Specific speech treatment recommendations have included teaching PALS to (a) conserve energy for speaking tasks with frequent rest to reduce fatigue (Beukelman et al., 2011), (b) exaggerate articulation (Yorkston et al., 2004), (c) incorporate rate-reducing strategies and improve respiratory efficiency through phrasing (Francis, Bach, & DeLisa, 1999; Tomik & Guiloff, 2010), (d) minimize background noise (Tomik & Guiloff, 2010), and (e) seek timely evaluation and implementation of AAC devices to support communication (when speaking rate is between 100 and 125 words per minute on the Speech Intelligibility Test; Beukelman, Ball, & Fager, 2008). In addition, prosthetic devices to manage velopharyngeal impairment and hypernasality have been recommended (Enderby, Hathorn, & Servant, 1984; Esposito, Mitsumoto, & Shanks, 2000; Gonzalez & Aronson, 1970; Ono, Hamamura, Honda, & Nokubi, 2005; Suwaki, Nanba, Ito, Kumakura, & Minagi, 2008).

Current swallowing management recommendations include (a) dietary modifications, (b) postural changes, and (c) percutaneous endoscopic gastrostomy (PEG) placement. Solazzo et al. (2011) observed that swallowing maneuvers (throat clear, chin tuck, head turn, and head tilt) were effective at reducing penetration and/or aspiration in 79% of PALS. Timely placement of PEG tubes ensures adequate nutritional intake, hydration, weight stabilization, and access for medications (Mazzini et al., 1995) and has been noted to extend survival by 6 months in PALS (Spataro, Ficano, Piccoli, & La Bella, 2011). PALS are highly susceptible to malnutrition because they function at a higher resting metabolic rate (Bouteloup et al., 2009; Weiner, Magadle, Beckerman, Weiner, & Berar-Yanay, 2003a), whereas at the same time they typically consume less calories due to dysphagia, fatigue with eating and drinking, limb weakness that impairs the ability to self-feed, reduced appetite, or avoidance behaviors associated with meal times (Kuhnlein et al., 2008; Limousin et al., 2010; Ngo, Steyn, & McCombe, 2014). This creates the perfect storm for the development of malnutrition and further muscle wasting that go beyond the catabolic effects of the disease itself (Plowman, 2014). Because malnutrition increases the risk of death by 7.7 times in this patient population (Chio et al., 2009), early PEG placement is crucial, and the speech-language pathologist needs to be an educator and advocate for its timely implementation (Plowman, 2014). Current American Academy of Neurology guidelines state that PEG placement should occur prior to forced vital capacity falling below 50% because surgical placement below this threshold may be inappropriate and even unsafe (Miller et al., 2009a). Other surgical interventions to treat swallowing dysfunction in PALS include total laryngectomy to prevent risk of aspiration (Garvey, Boylan, Salassa, & Kennelly, 2009), botulinum toxin injection to the cricopharyngeus muscle (Restivo et al., 2013), or cricopharyngeal myotomy (Janzen, Rae, & Hudson, 1988) to treat UES hyperactivity. Therefore, the speech-language pathologist's role in the treatment of dysphagia has historically been as an educator of safe swallowing strategies, compensatory strategies, dietary modifications, and feeding tube placement to maximize safe swallowing and to optimize adequate nutritional intake.

Could Exercise Play a Role in Management of ALS Individuals?

The role of exercise in the treatment of ALS remains a controversial issue. Historical treatment recommendations have been based upon the premise that exercise should be avoided due to the potential for overuse injury, resulting in subsequent worsening of function (Bello-Haas et al., 2007; Sinaki & Mulder, 1978; Tomik & Guiloff, 2010). This notion, however, has not been empirically tested and available data are insufficient to conclude that overuse weakness or functional decline actually occurs following exercise in PALS (de Almeida, Silvestre, Pinto, & de Carvalho, 2012; Pinto, Swash, & de Carvalho, 2012). Although a denervated muscle may be more susceptible to overuse damage, evidence suggests that physical inactivity and disuse atrophy may further debilitate individuals with ALS (Dalbello-Haas, Florence, & Krivickas, 2008; de Almeida et al., 2012). Further, recent data indicate that exercise induces cellular and morphological adaptions in motor neuron function and may serve to maintain and prolong motor function in both health and disease. In healthy and diseased animals, exercise has been documented to induce cortical and spinal synaptogenesis and angiogenesis, proliferate astrocytes, increase antioxidant capacities, increase growth factor signaling, increase protein synthesis, increase axonal transport, induce dendritic restructuring, decrease oxidative stress, and decrease muscular hypertrophy/atrophy (Adkins, Boychuk, Remple, & Kleim, 2006; McCrate & Kaspar, 2008; Patel & Hamadeh, 2009). As previously noted, ALS is thought to be due to a number of interrelated and complex molecular events that include: oxidative stress, glutamatergic excitotoxicity, defective axonal transport, insufficient growth factor signaling, mitochondrial dysfunction, and protein misfolding (Patel & Hamadeh, 2009). In theory, exercise applied at the appropriate dose, intensity, and time in PALS might have the potential to ameliorate these aberrant processes, as well as prevent disuse atrophy known to be present in PALS.

The utilization of exercise as a treatment modality in the field of speech-language pathology has received growing attention in recent years. Progressive lingual resistance training has been studied in animal models, healthy adults, and across a number of disordered patient populations. Animal models afford the ability to investigate central and peripheral neuromuscular changes associated with interventions not afforded in human clinical trials. Using a healthy rodent model, targeted tongue resistance exercise has been noted to increase protrusive tongue forces that

were associated with changes in muscle fiber size and variability (Connor et al., 2009), remodeling of serotonergic inputs into the hypoglossal nucleus (Behan et al., 2012), and increased levels of brain-derived neurotrophin factor in hypoglossal nuclei (Schaser, Stang, Connor, & Behan, 2012). In an animal model of Parkinsonism (6-hydroxydopamine), targeted tongue resistance training improved tongue force and timing deficits (Ciucci et al., 2013) and led to a reduction in motor stimulation thresholds for evoking tongue cortical motor maps via intracortical microstimulation (Plowman, Maling, Thomas, Fowler, & Kleim, 2014). These basic science studies demonstrate that a behaviorally driven targeted input (progressive lingual resistance training) was capable of driving changes in the peripheral and central nervous system in both healthy and diseased animals.

In healthy individuals, participation in a progressive lingual resistance training program yielded increases in maximal isometric tongue forces in both young and older adults (Clark, 2012; Clark, O'Brien, Calleja, & Corrie, 2009; Lazarus, Logemann, Huang, & Rademaker, 2003; Robbins et al., 2005). To date, only one group has examined the impact of lingual training on central changes in the nervous system. Using transcranial magnetic stimulation, Svensson, Romaniello, Wang, Arendt-Nielsen, and Sessle (2006) measured changes in tongue corticomotor projections following a 1-hr targeted tongue protrusion task in 11 healthy adult volunteers. In this study, 1 hr of targeted training was sufficient to induce neuroplastic changes with a noted reduction in motor thresholds, increased motor evoked potential amplitudes, and an expansion of tongue topographic cortical maps 30 min after targeted tongue training (Svensson et al., 2006).

In diseased states, progressive lingual resistance programs have resulted in improvements in lingual strength and performance (Malandraki et al., 2012; Robbins et al., 2007; Steele et al., 2013; Yeates, Molfenter, & Steele, 2008). Individuals with acquired traumatic brain injury who underwent a 3-month lingual resistance program showed increases in maximum isometric tongue pressure generation that were functionally accompanied by increased lingual pressure generation during saliva swallowing and improved swallowing airway safety (Steele et al., 2013). Increases in isometric lingual pressures have also been noted in stroke patients who completed targeted tongue strengthening protocols (Robbins et al., 2007; Yeates et al., 2008), and these improvements were associated with increased swallowing pressures and reduced oropharyngeal residue (Robbins et al., 2007). In a patient with neurodegenerative disease (inclusion body myositis and Sjogren's syndrome), lingual resistance training led to the stabilization of posterior isometric tongue pressure generation and preserved swallowing abilities during the intervention and maintenance periods (Malandraki et al., 2012).

Another exercise intervention that has been studied as a treatment modality for bulbar dysfunction in the field of speech-language pathology is expiratory muscle strength training (EMST). EMST represents an active rehabilitative strength training protocol through daily expiratory resistance threshold training by blowing or expiring into a hand-held calibrated, one-way, spring-loaded valve to mechanically drive and engage the expiratory and submental musculature (Wheeler, Chiara, & Sapienza, 2007; Wheeler-Hegland, Rosenbek, & Sapienza, 2008). EMST has been noted to increase maximum expiratory pressure generation capacities in young healthy adults (Baker, Davenport, & Sapienza, 2005), instrumentalists (Sapienza et al., 2002), professional vocalists (Wingate, Brown, Shrivastav, Davenport, & Sapienza, 2007), the sedentary elderly (Kim et al., 2009), individuals with Parkinson's disease (PD; Pitts et al., 2009; Saleem, Sapienza, & Okun, 2005; Silverman et al., 2006; Troche et al., 2010), multiple sclerosis (Chiara, Martin, Davenport, & Bolser, 2006), and chronic obstructive pulmonary disease (Weiner et al., 2003a, 2003b). Improvements in subglottic air pressure generation capacities after EMST have been noted to improve voluntary cough production (reduced compression phase duration, reduced expiratory rise time, and increased cough volume acceleration) in the sedentary elderly (Kim et al., 2009) and in individuals with PD (Pitts et al., 2009). Improved voluntary cough production after EMST in PD was associated with improved airway protection during swallowing (Pitts et al., 2009). The documented impact of EMST on cough function and airway protection is highly relevant for individuals with reduced airway protection or excessive mucous build-up in the lower airways (Laciuga, Rosenbek, Davenport, & Sapienza, 2014). A Class 1B randomized sham controlled clinical trial examined the impact of EMST on swallowing in individuals with PD and found increases in maximum expiratory pressures, hyolaryngeal excursion, UES opening, and improved airway protection (Troche et al., 2010).

Both EMST and progressive lingual resistance training harness several key principles of plasticity, namely: *load, intensity, repetition,* and the *"use it or lose it"* phenomenon (Burkhead, Sapienza, & Rosenbek, 2007; Clark, 2003; Kleim & Jones, 2008). Targeted tongue training, if completed with functional swallowing tasks or maneuvers, uses the *task specificity* principle. EMST, on the other hand, likely improves functional swallowing outcomes via the *transference* principle of plasticity by increasing subglottic pressure generation capacities that have a cross-system effect on the coordination, velocity, and strength of cough and thereby the ability to expel aspirant materials during swallowing (Pitts et al., 2009). Indeed, a relationship between cough volume acceleration of voluntary cough and airway safety (Penetration-Aspiration Scale scores; Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996) has been reported in stroke (Smith Hammond et al., 2009), PD (Pitts et al., 2010), and ALS (Plowman et al., 2013), further highlighting the potential role this treatment option could have for improving functional swallowing outcomes and airway safety. In theory, EMST or lingual training might represent useful management strategies in PALS who are documented to have impaired, weak, and ineffective cough function to aspirant materials and reduced lingual pressure generation resulting in residue and subsequent aspiration

(Gaziano et al., 2015). Figure 1 depicts a physiological framework of ALS dysfunction and a theoretical framework for the implementation of such intervention strategies to maximize functional reserve capacities and promote the maintenance of swallowing, breathing, and airway protection in ALS.

Recent Evidence Suggests Exercise May Be Beneficial in ALS

In this review article, eight basic science and 10 human clinical published studies were identified that report the impact of exercise in transgenic ALS animals or PALS. Tables 3 and 4 include each of these published works and provide a summary of the aim, study type, level of evidence, specific exercise protocol used, pertinent findings, and assignment of a TIC.

Transgenic SOD1 Animal Studies

Emerging basic science data in the SOD1 transgenic mouse model of ALS suggest that mild–moderate aerobic exercise may be beneficial in delaying disease onset, increasing life span, improving motor neuron function, and improving motor performance. As can be seen in Table 3, a total of eight studies have been published over the past decade. Six of these document positive outcomes after exercise interventions that include: (a) slower disease onset and progression (Carreras et al., 2010; Deforges et al., 2009; Kirkinezos, Hernandez, Bradley, & Moraes, 2003; Veldink et al., 2003); (b) increased survival/lifespan (Carreras et al., 2010; Deforges et al., 2009; Gerber, Sabourin, Hugnot, & Perrin, 2012; Kaspar, Frost, Christian, Umapathi, & Gage, 2005; Kirkinezos et al., 2003; Liebetanz, Hagemann, von Lewinski, Kahler, & Paulus, 2004; Veldink et al., 2003); (c) promotion of motor neuron survival and protection against cell death (Carreras et al., 2010; Deforges et al., 2009; Gerber et al., 2012; Kaspar et al., 2005); (d) reduction in muscle hypoplasia and atrophy (Deforges et al., 2009); and (e) reduction in astrogliosis and maintenance of oligodendrocytes (Carreras et al., 2010; Deforges et al., 2009; Gerber et al., 2012) when low to moderate intensity aerobic exercise programs were utilized. High intensity exercise, however, was noted to hasten disease onset (Carreras et al., 2010) and decrease motor performance and life expectancy (Mahoney et al., 2004) in two studies.

Figure 1. Neuroanatomical framework for bulbar dysfunction in amyotrophic lateral sclerosis (ALS). Spasticity and atrophy from upper motor neuron (UMN) and lower motor neuron (LMN) degeneration, respectively, leads to a reduction in muscular strength and a resultant increase in effort. Reduced strength and increased effort equates to a reduction in functional physiologic reserve for people with ALS (PALS). Taking into account the noted physiologic impact expiratory muscle strength training and lingual resistance training has had in other neurologic patient populations and recent findings in both animal and human clinical research of the limb motor system, an intervention schema is introduced to be applied during the early stages of the disease and at mild to moderate intensity that theoretically might improve functional reserve capacities and maintain breathing, swallowing, and airway protection in individuals with ALS. References that support statements in this figure are as follows: (A) Baker et al., 2005; Chiara et al., 2006; Saleem et al., 2005; Sapienza et al., 2002; Troche et al., 2010; Weiner et al., 2003b; (B) Pitts et al., 2009; (C) Kim et al., 2009; Pitts et al., 2009; Troche et al., 2010; (D) Clark, O'Brien, et al., 2009; Clark, 2012; Lazarus et al., 2003; Malandraki et al., 2012; Robbins et al., 2005; Robbins et al., 2007; Steele et al., 2013; Yeates et al., 2008; (E) Robbins et al., 2007; Steele et al., 2013; (F) Robbins et al., 2007; Steele et al., 2013; (G) Steele et al., 2013.

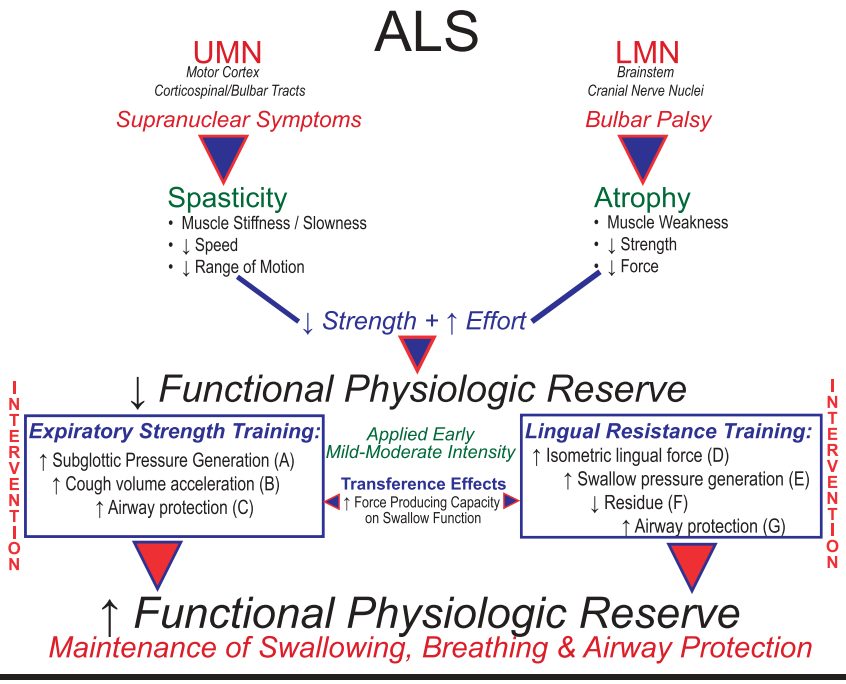

Table 3. Literature review table of exercise studies in the superoxide dismutase 1 transgenic animal model of amyotrophic lateral sclerosis summarizing (a) exercise type (endurance vs. strength), dose, and intensity; (b) specific outcomes; and (c) overall treatment impact classification (TIC; positive [+], neutral [o], or negative [–]).

Author	Exercise type	Findings	TIC
Kirkinezos et al. (2003)	Endurance: treadmill running MEX versus controls 30 min/×5 days	• Significant increase in lifespan in male MEX-trained animals (+10 days) • Slowed disease progression in male MEX-trained animals • Nonsignificant increase in female MEX-trained animals (+5 days)	+
Veldink et al. (2003)	Endurance: treadmill running MEX versus sedentary versus controls 45 min/×5 days	• Delayed disease onset in female MEX animals • Increased lifespan in female MEX animals (+4 days) • No differences in muscle morphometry and motor neuron count	+
Liebetanz et al. (2004)	Endurance: wheel running HEX versus sedentary 400 min/×5 days	• No significant differences in disease onset in sedentary versus HEX animals • Nonsignificant trend for increased survival in HEX animals	o
Mahoney et al. (2004)	Endurance: treadmill running HEX versus sedentary 45 min/× 5 days	• HEX did not impact disease onset • HEX decreased motor performance and hastened death (male animals)	–
Kaspar et al. (2005)	Endurance: running wheel MEX versus MEX + IGF versus sedentary Ad libitum exposure	• MEX (+21 days) and IGF (+29 days) treatment extended lifespan • MEX and IGF treatment preserved motor neurons • Synergistic maximal effect on survival with IGF + MEX treatment (+83 days)	+
Deforges et al. (2009)	Endurance: swim, treadmill run Swimming versus running versus sedentary HEX versus LEX versus sedentary 30 min/× 5 days	• Delayed disease onset in swimmers (+16) and runners (+4) • Increased survival time by 20% in swimmers, no effect in runners • Preserved motorneurons (swimmers by 21%, runners by 4%) • Decreased muscle atrophy/hypoplasia, nestin-positive cells in both EX groups • Decreased apoptosis, astrocytes, and maintained oligodendrocytes in swimmers	+
Carreras et al. (2010)	Endurance: treadmill running HEX versus MEX versus sedentary 60 min/×5 days versus 30 min/×3 days versus none	• MEX: Delayed disease onset, increased spinal cord motor neuron count, increased lifespan • HEX: Hastened disease onset	MEX: + HEX: –
Gerber et al. (2012)	Endurance: treadmill running LEX versus MEX versus HEX versus sedentary treadmill versus sedentary 15 min/× 5 days	• Increased lifespan in all EX groups and sedentary treadmill versus sedentary group (from +3.5 to +17.5 days) • Preservation of motor neurons in MEX and HEX versus sedentary treadmill group • Decrease in microglia and astrocytes in LEX animals	+

Note. MEX = moderate intensity exercise; HEX = high intensity exercise; IGF = insulin-life growth factor; LEX = low intensity exercise; EX = exercise.

It is important to note that in this animal model of ALS, exercise is typically applied prior to the onset of symptoms. Although this has the advantage of studying the impact of exercise on disease onset and progression rates, it does not translate well to the human clinical condition. At present, there are no studies examining the impact of oral motor exercise on swallowing and survival in the transgenic ALS model. More work is clearly needed to further understand the impact exercise has in the transgenic ALS model on disease progression and survival with studies targeting oral motor structures. Table 3 details each of these animal studies and provides a summary TIC as either a positive, neutral, or negative impact on the specific outcomes studied.

Human Clinical Studies

Ten clinical studies have reported the impact of exercise in PALS that range from weaker Class 4 (individual case study) to stronger Class 1b (randomized control trial) levels of evidence (Sackett et al., 2000). As can be seen in the summary table of these data (see Table 4), six studies have reported significant clinical gains after exercise interventions in PALS. Specific exercise interventions studied in

Table 4. Literature review table of published human clinical studies investigating the impact of exercise in individuals with amyotrophic lateral sclerosis (ALS) summarizing aims, study design, level of evidence (Sackett et al., 2000), specific exercise protocol, research findings, and treatment impact classification (TIC; positive [+], neutral [o], or negative [–]).

Author	Aim	Study type evidence level	Exercise protocol	Findings	TIC
Dworkin & Hartman (1979)	Impact of oral motor interventions in a 49-YOF patient with bulbar onset ALS	Case report (N = 1) Level 4 Exploratory	Resistance tongue exercises "Regular articulation and swallowing training" Isometric exercises of extremities	• Significant reduction in lateral tongue strength and alternate lingual motion rate over the 6-month period • Dysarthria and dysphagia worsened over 6 months • Concluded that the efficacy of treatment could not be tested due to rapid bulbar onset disease progression	–
Bohannon (1983)	Impact of limb resistance training in a 56-YOF patient with spinal onset ALS	Case report (N = 1) Level 4 Exploratory	Upper extremity proprioceptive neuromuscular facilitation therapy (20 repetitions, ×4 days/week, ×2 months)	• Improved static strength in 14 UE muscle groups • Decreased strength in four UE muscles	+
Watts & Vanryckeghem (2001)	Impact of bulbar exercise programs in a 72-year-old patient with bulbar onset ALS	Case report (N = 1) Level 4 Exploratory	LSVT (×4/week: ×2 weeks) Traditional voice articulation Isometric oral motor strengthening (weekly 1.5-hr session)	• LSVT resulted in reduction in voice quality • Voice and articulation therapy deemed ineffective • Speech and swallowing deteriorated over 4.5 months • Concluded that no treatment generalizations could be made due to rapidly progressing ALS.	–
Drory et al. (2001)	Effect of limb resistance exercise on motor deficit, disability, fatigue, pain, and QOL	RCT (N = 25) Level 2b Experimental	Limb resistance versus usual care Moderate load (15 min ×2 daily, for up to 6 months)	• Three months post: less deterioration on ALSFRS, fatigue severity scale, pain, and SF-36 for exercise group • Six months post: no significant differences between groups	+ o
Pinto et al. (1999)	Impact of exercising patients with ALS to anaerobic threshold on motor decline	RCT (N = 20) Level 2b Experimental	Anaerobic treadmill + BIPAP versus BIPAP Individualized program: until anaerobic threshold was met (10–15 min per day)	• Significant reduction in rate of forced vital capacity decline and slower clinical course (Spinal Norris Scale) in exercise group • Significant difference in Functional Independence Measure scores but not Barthel scores	+
Bello-Haas et al. (2007)	Effects of resistance exercise on function, fatigue, and QOL in patients with mild ALS	RCT (N = 27) Level 2b Experimental	Limb resistance + stretching versus stretching (moderate load) ×3 days/week, ×6 months	• No adverse effects of limb resistance training • Lead to significantly better/less decline in global function (ALSFRS) and QOL (SF-36) at 6 months	+

(*table continues*)

Table 4 *(Continued).*

Author	Aim	Study type evidence level	Exercise protocol	Findings	TIC
Cheah et al. (2009)	Determine safety and efficacy of IMT for improving respiratory function	RCT (*N* = 29) Level 1b Experimental	IMT Moderate load, progressive resistance (15%, 30%, 45%, 60% of maximal SNIP) 10 min ×3 days, ×7 days/week, ×3 months	• IMT improved maximum inspiratory pressure by 6.1% • IMT improved inspiratory respiratory muscles and delayed disease progression (ALSFRS) • Detraining occurred 2 months post IMT cessation	+ +
Sanjak et al. (2010)	Determine feasibility, safety, and tolerability of treadmill training	Cohort (*N* = 9) Level 4 Exploratory	Aerobic supported treadmill training 30 min/day, ×3 days/week, ×2 months	• Significant improvements in rate of perceived exertion, ALSFRS, gait speed, distance, stride length • Maintained for 8 weeks	+
Pinto et al. (2012)	Impact of IMT in early-affected patients with ALS	Parallel sham group randomized delayed start (*N* = 26) Level 1b Experimental	IMT (30–40% MIP) versus Sham (9 cm H_2O) 10 min ×2 daily, ×7 days/week 8 months (early intervention group) or 4 months (late intervention group)	• Transient improvement in ALSFRS respiratory score, PEF, SNIFF, and maximum voluntary ventilation • No significant group difference in total ALSFRS scores • Minor positive transient effect but no clear +/– effect	o
Pinto & de Carvalho (2013)	Determine the long-term impact of IMT on survival in ALS	Case control Level 3b Experimental	IMT (30–40% MIP) ×7 days/week 18 patients from Pinto et al., 2012 versus age/gender matched historical controls	• IMT patients had significantly longer survival (+14 months) • IMT = significant prognostic indicator for survival	+

Note. YOF = year-old female; UE = upper extremity; LSVT = Lee Silverman Voice Treatment; QOL = quality of life; RCT = randomized controlled trial; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale, SF-36 = Short-Form 36; BIPAP = bilevel positive airway pressure; IMT = inspiratory muscle training; SNIFF = sniff nasal inspiratory pressure; MIP = maximum inspiratory pressure; PEF = peak expiratory flow.

PALS have included: (a) aerobic treadmill training (Pinto et al., 1999; Sanjak, Bravver, Bockenek, Norton, & Brooks, 2010), (b) limb resistance training (Bello-Haas et al., 2007; Bohannon, 1983; Drory, Goltsman, Reznik, Mosek, & Korczyn, 2001), (c) inspiratory muscle strength training (Cheah et al., 2009; Pinto & de Carvalho, 2013; Pinto et al., 2012), and (d) oral motor strengthening exercises (Dworkin & Hartman, 1979; Watts & Vanryckeghem, 2001). Aerobic treadmill training in people with mild to moderate ALS has lead to significant improvements in forced vital capacity and functional independence measure scores (Pinto et al., 1999), improved gait speed and stride length (Sanjak et al., 2010), and positively impacted global disease progression (Sanjak et al., 2010). Limb resistance training interventions have been associated with improvements in static strength (Bohannon, 1983); less deterioration in global function, fatigue, pain, and Short-Form 36 scores (Drory et al., 2001); and improved global function and patient-reported quality of life (Bello-Haas et al., 2007). Inspiratory muscle strength training interventions have lead to nonsignificant and transient improvements in maximum inspiratory pressures (Cheah et al., 2009; Pinto et al., 2012) and transient improvements in the ALSFRS respiratory subscale score, peak expiratory flows, sniff nasal inspiratory pressures, and maximum voluntary airflows (Pinto et al., 2012). Both of the inspiratory muscle strength trials concluded that treatment effects were unclear and further investigation was needed. Pinto and colleagues followed 18 of the patients from their inspiratory muscle strength randomized clinical trial (Pinto et al., 2012) and reported that participation in this strength program increased survival by 14 months when they compared these patients to age, gender, and disease severity matched historical controls (Pinto & de Carvalho, 2013). Further, inspiratory muscle strength training was identified as an independent prognostic indicator for survival (Pinto & de Carvalho, 2013).

To date, only two case studies (representing a Class IV level of evidence) have been performed to examine the effect of active interventions on speech function (Dworkin & Hartman, 1979; Watts & Vanryckeghem, 2001). Dworkin and Hartman (1979) first presented a case report of a 49-year-old man with ALS and moderately impaired speech and swallowing function who was 11 months postsymptom onset at the time of their evaluation. The patient underwent resistance tongue exercises with "regular articulation and swallowing training," a palatal lift to reduce hypernasality and nasal regurgitation, and isometric exercises of the extremities. Subjective performance measures were taken over a 6-month period, and a significant reduction in both lateral tongue strength and lingual alternate motion rate were noted. Dysarthria and dysphagia worsened from being "moderately impaired" to "severely impaired" over this time period. It is unfortunate to note that no information was provided on the specific exercise protocol conducted, the number of treatment sessions completed, and treatment duration in this report, making it difficult to deduce exactly what type of treatment protocol was initiated. Dworkin and Hartman (1979) concluded that the efficacy of their interventions could not be tested due to the rapid progression of the ALS disease.

Two decades later, Watts and Vanryckeghem (2001) reported the impact of a series of active treatments on a 72-year-old female with bulbar onset ALS who was initially misdiagnosed with a Parkinsonism-related syndrome, multiple system atrophy. The patient underwent 2 weeks of Lee Silverman Voice Treatment (LSVT), four times a week, which was then followed by a weekly 1.5-hr therapy session of traditional voice, articulation, and isometric oral motor strengthening exercises. Given the report that this individual had a "hoarse, strained, and pressed" (p. 3) perceptual voice quality, it is unclear why the LSVT was chosen for this individual. The LSVT program resulted in a worsening in voice quality and increased the number of voice breaks due to ventricular compression. Further, voice and articulation therapy were deemed ineffective, and voice and swallowing functions deteriorated over this time period. The authors concluded that no generalizations could be made from this single case study for the treatment of dysphonia, dysarthria, and dysphagia in PALS because it lacked the needed controls. However, it was an example of how rapidly progressive forms of ALS are challenging to manage. Given that ALS is a rapidly degenerating disease, the need for a control group or "lead-in" period to benchmark bulbar disease progression is critical in any intervention study in order to draw valid conclusions.

Similar to speech treatment data, however, no controlled studies exist examining the effectiveness of interventions for swallowing dysfunction in PALS (Britton et al., 2013; Miller et al., 2009a, 2009b; Miller & Britton, 2011; Rosenbek & Troche, 2013; Watts & Vanryckeghem, 2001). In the absence of any randomized control trials investigating therapeutic interventions for bulbar dysfunction in PALS, there exists insufficient data to support or refute interventions for dysarthria and dysphagia in ALS and this represents a much-needed area for further study (Hanson et al., 2011; Miller et al., 2009a, 2009b; Miller & Britton, 2011; Tomik & Guiloff, 2010).

Conclusions

A total of 18 basic and clinical published studies were identified that examined the role of exercise on limb, respiratory, and oral motor function in ALS. Fourteen experimental basic and human clinical studies suggest that limb and respiratory exercise, applied early and at mild to moderate intensities, may have a positive impact for maintaining motor neuron integrity, motor function, and survival in ALS. Although no controlled studies currently exist regarding the relative role of exercise for the management of dysarthria and dysphagia in PALS, these recent data suggest that we need to consider the possible complementary role of mild forms of exercise to maintain airway protection, swallowing safety, swallow transit, and speech intelligibility in this challenging patient population. Because dystussia is prevalent in PALS, mild to moderate intensity EMST might represent a useful program to maintain subglottic

pressure generation abilities, cough, and airway protection in patients with early stage disease. Figure 1 presents a theoretical rationale and schema for such a therapeutic approach in PALS. Likewise, reduced lingual strength might be targeted with the use of a mild–moderate intensity regime of lingual resistance training early in the disease to improve or maintain tongue strength, bolus propulsion, and minimize oral and pharyngeal residue and subsequent aspiration in this patient population. In theory, participation in such protocols might build a good foundation for improving or maintaining force-producing capacities, increasing functional reserve, and thereby maintaining swallowing, respiration, and airway protection in PALS. These represent areas for future research and investigation.

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