Amyotrophic Lateral Sclerosis and Cardiac Function: How can we do with Hummingbird’s Racing Hearts?

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Received Date: June 19, 2021
Published Date: July 09, 2021

Abstract

Amyotrophic lateral sclerosis (ALS) is a degenerative disease that classically affects the motor neuron, causing paralysis, flaccidity and death. However, although its etiopathogenesis is not fully elucidated, it is known that its involvement is not only motor, but also has a strong interaction with the autonomic nervous system, with cardiovascular, gastrointestinal and sleep effects, for example. The disease, which leads to death mainly from respiratory complications, also has underestimated cardiovascular effects, like increased heart rate variability, malignant arrhythmias and sudden death. These aspects raise several questions, such as whether there is a direct correlation between autonomic effects and the underlying disease, whether the onset of autonomic symptoms occurs at an early or late stage of the disease and whether there is an effective therapy to modulate these alterations. A valid question is whether the use of beta-blockers would be effective in modulating symptoms related to increased heart rate and in preventing sudden death and malignant arrhythmias found in some of these patients. It is also important to highlight the role of motor and respiratory physiotherapy in controlling complications of the respiratory system and in improving the quality of sleep of patients with ALS. With this, it is important that we see that amyotrophic lateral sclerosis is not an exclusive motor neuron disease, but has other mechanisms that have not yet been fully clarified, including autonomic changes. Thus, we must direct therapies and studies to these changes, which have a direct impact on the patient’s morbidity, mortality and quality of life.

Keywords: Amyotrophic lateral sclerosis; Autonomic nervous system; Autonomic modulation
Views and Reviews

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of both lower and upper motor neurons, which leads to muscle weakness, paralysis, and death. Currently, there is no effective therapy. The majority of ALS cases are sporadic, with no known family history; unfortunately, the etiology remains largely unknown. In most individuals, the mechanisms underlying the disease’s development are poorly understood, although some patients have the familial disease and harbormutations in genes that have various roles in neuronal function. Very recent studies have identified that the degeneration of motor neurons in ALS is apoptotic cell death that may occur by an abnormal programmed cell death (PCD) mechanism [1,2]. The deaths directly caused by ALS result from respiratory complications. This occurs primarily from the patient’s inability to ventilate as respiratory muscle weakness progresses. In patients with bulbar weakness, aspiration of secretions or food may occur and precipitate pneumonia, resulting in further respiratory compromise; therefore, aggressive respiratory management is necessary in the comprehensive care of patients with ALS. Another common cause of death in ALS is sudden cardiac death [3-6].

Changes in the Autonomic Nervous System in ALS

In recent years, several studies have shown that ALS is more than a pure motor neuron disease. The autonomic nervous system is also involved in ALS, since increased heart rate variability [4,6] and increased QTc intervals in electrocardiography (EGC) have been reported [7]. Decreased heart rate variability and a loss of correlation between blood pressure and heart rate also have been described [8,9]. Cardiac involvement has been reported in ALS by ECG, echocardiography [10], and postmortem examination. The involvement of the autonomic nervous system could increase the risk of heart rhythm disturbances or sudden cardiac death [11,12]. Subclinical cardiac involvement has been reported [13,14], including non-specific ECG and echocardiographic abnormalities.

ALS patients with respiratory-dependent ALS die of sudden cardiac arrest or anoxic encephalopathy following circulatory (collapse) problems, which may be associated with sympathetic hyperactivity. Ample evidence exists for subclinical dysfunction of cardiovascular, sudomotor, gastrointestinal, salivary, and lacrimal regulation, even in early ALS cases. Autonomic disturbances may lead to circulatory collapse or sudden death in respiratory dependent patients. Several studies suggest the existence of sympathetic hyperactivity in ALS [15].

These aspects raise several questions: Are the autonomic changes directly linked to the underlying disease? Cardiological changes are early or appear late during the course of the disease, especially when patients are in need of ventilatory support; can respiratory rehabilitation processes contribute to the worsening of cardiac dysautonomy? Is there any prophylactic for dysautonomic treatment?

Tanaka et al. [16] investigated cardiac sympathetic modulation in 63 patients and 10 healthy volunteers using cardiac [(123)I] metaiodobenzylguanidine (MIBG) scintigraphy in the early phase and washout ratio (WR) at the time of diagnosis. The WR of cardiac [(123)I] MIBG scintigraphy, which indicates cardiac sympathetic activity, was significantly increased in these patients compared with a control. Patients with an increased WR exhibited a higher progression rate compared with those with normal WR. Moreover, the survival of ALS patients with increased WR was significantly decreased compared with those with normal WR. The cardiovascular consequences related to ALS are relatively underappreciated. The disease invokes a systematic degeneration of autonomic neurons leading to autonomic dysfunction. Patients with advanced amyotrophic lateral sclerosis experience loss of heart rate variability and enhanced vasomotor responses [17,18].

Druschky et al. [19] evaluated 40 individuals with ALS and the autonomic cardiac nervous system’s involvement in the early stages. Both sympathetic and parasympathetic dysfunction was observed in 40% out of all patients. The results indicate that ALS patients with mild to moderate impairment may have evidence of cardiovagal denervation or postganglionic sympathetic adrenergic cardiac. The original concept of ALS as an isolated degeneration of motor neurons seems, according to these findings, to extend to a more widespread understanding of the disease which multisystemic involvement.

A new problem is the incidence of pTDP-43 aggregates in the skeletal and cardiac muscles of patients with ALS and those with neuromuscular diseases (NMDs) and non-NMDs. Two types of pTDP-43 aggregates were distinguishable morphologically: dense and short linear filamentous. In ALS, pTDP-43 aggregates were most frequent in the diaphragm muscle. The mean density of pTDP-43 aggregates in ALS was significantly higher than that in NMDs and non-NMDs. Findings indicate that pTDP-43 aggregates in skeletal and cardiac muscle are a myogenic pathological marker in multiple diseases including ALS and undoubtedly further enhance muscle and myocardial denervation [19]. Another point worth mentioning is the sleep pattern in patients with ALS. This group showed significant sleep alteration: decreased total sleep time and sleep efficiency, increased nocturnal awakenings, reduced REM sleep, and reduced CAP rate. Moreover, a significant reduction in HRV parameters was observed during all sleep stages, indicative of impaired autonomic oscillations. It seems crucial to us to create a treatment strategy for autonomous modulation in this population. ALS-associated respiratory insufficiency differs in mechanism from the more common causes of dyspnea, such as diseases of pulmonary or cardiac origin [20].

The first question raised and answered based on the relevant literature would be: Could the use of beta-blockers promote relief of symptoms related to increased heart rate, and, we ask, could they play a role in encouraging catabolism? Another interrogation
that lead us to the second question would be: Does the autonomic alteration distort a strategy to avoid future cardio-pulmonary problems? In view of this, could we design drug and rehabilitation strategies to offer comfort, reducing the symptoms associated with increased heart rate? It seems clear, from what has already been explained above, that catabolic function in patients with ALS is already present at the beginning of the clinical picture, mainly in the bulbar form. The observed autonomic dysfunction initially leads to tachycardia episodes, late associated with symptomatic supraventricular hypertension in some cases. However, observations suggest that the problem may be greater [21-25].

In the evaluation of patients who had sudden cardiac death, paroxysmal sympathetic hyperactivity was observed as a risk factor [26]. Empirically, some therapeutic measures for sympathetic hyperactivity have been suggested, with the use of non-selective beta-blockers, such as propranolol and labetalol, being apparently effective in preventing episodes. Selective beta-blockers do not appear to be effective [27]. Another study identified significant prolongation of the QTc interval in patients with advanced disease, associated with sympathetic hyperactivity, as a possible cause of sudden death in this population [28,29]. This would benefit from the use of beta-blockers in these patients, not only for symptom control, but eventually reducing the risk of sudden death. However, targeted studies still need to be carried out to confirm that hypothesis. The prolongation of the QTc interval in patients with ALS must be observed carefully during the outbreak of COVID-19, since many patients have been using hydroxychloroquine, which is a treatment that has no proven effectiveness in COVID-19 but has been misused by many patients on their own or wrongly prescribed by their physicians. It is worth noting that hydroxychloroquine can prolong the QTc interval [30,31], which is highly relevant in the case of ALS patients, who may already have this electrocardiographic alteration. Thus, quaternary prevention should be performed to encourage the abandonment of the use of hydroxychloroquine as a treatment for covid-19, especially in patients with ALS.

When analyzing the cardiovascular autonomic pattern at rest, two distinct groups can be observed, those with increased cardiac sympathetic activity and those with decreased activity. However, in both groups it is altered to the postural challenge. Thus, a head-up tilt table test, associated with heart rate variability by Holter and variation in systolic blood pressure over 24 hours could identify prognostic factors and help to improve the clinical management of these patients [30].

**Rehabilitation in ALS and Cardiovascular Modulation Autonomic**

About rehabilitation, especially cardiovascular responses, which could impact autonomic modulation, great attention should be paid to the prescription of physical exercise. Since already committed neuromuscular units will be recruited, this fact can cause the metaboreflex [21] related to peripheral musculature to be triggered early, due to aspects such as deconditioning and frank catabolism, in addition to altering the process of vagal reentry, due to the metabolic expense assumed during exercise, this hypothesis could be explained by the excess post-exercise oxygen consumption (EPOC) [22]. Despite presenting a high cost, but the ideal would be that the prescription was performed based on peak oxygen consumption [23], however many times this type of assessment of functional capacity is not required for patients with ALS, being often restricted prescribing the use of HR, which is a variable affected by dysautonomia. Therefore, physical exercise, an essential tool for controlling autonomic modulation in patients with ALS, needs to have its intensity very well defined, and an excellent cost-benefit ratio.

**Respiratory Physiotherapy in ALS And Cardiovascular Modulation Autonomic**

Another strategy with regard to rehabilitation is the Respiratory Physiotherapy being started as soon as possible since once we can promote better gas exchange, and that there are few areas of atelectasis, the respiratory effort will tend to be less, requiring less work on the respiratory muscles, especially the diaphragm and intercostal. This goal can be achieved with the use of non-invasive positive pressure ventilation at two pressure levels (BiPAP) [24].

The specific training of the respiratory muscles also deserves attention since it presents evidence that it can promote improvement in the strength and resistance of the muscles responsible for breathing [25] and could assist in the regulation of autonomic modulation due to being a breath controlled and with resistance evoking phenomena of respiratory sinus arrhythmia, which would end up not only promoting an increase in inspiratory muscle strength but also a possible re-reduction of vagal control, however despite the physiological plausibility, this strategy still lacks evidence. The point of intersection between Respiratory Physiotherapy and Motor Physiotherapy would be to make the patient with ALS able to perform the exercises using BiPAP; such a strategy is used to increase exercise tolerance, especially aerobic.

**Conclusion**

In conclusion, with this, it is important that we see that amyotrophic lateral sclerosis is not an exclusive motor neuron disease but has other mechanisms that have not yet been fully clarified, including autonomic changes. Thus, we must direct therapies and studies to these changes, which have a direct impact on the patient’s morbidity, mortality and quality of life.

**Author’s contribution**

Orsini M; Oliveira ASB; Freitas MRG; Sant Anna Jr M.- Writing, Data curation, literature rewire conceptualization, design the study, rewired of the literature, project administration, conceptualization, visualization. Castro R; Nasimento JF; Brito RS - Literature rewire, conceptualization, rewired of the literature, visualization
Acknowledgement

None.

Conflict of Interest

No conflict of interest.

References

1. Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logrosino G, et al. (2017) Amyotrophic lateral sclerosis. Nat Rev Dis Primers 3: 17071. Erratum in: Nat Rev Dis Primers 3: 17085.
2. Martin LJ, Price AC, Kaiser A, Shaikh AY, Liu Z (2000) Mechanisms for neuronal degeneration in amyotrophic lateral sclerosis and in models of motor neuron death (Review). Int J Mol Med 5(1): 3-13.
3. Gil J, Funalet B, Verschueren A, Daniel-Brunaud V, Canu W, et al. (2008) Causes of death amongst French patients with amyotrophic lateral sclerosis: a prospective study. European Journal of Neurology 15: 1245-1251.
4. Saptaro R, Lo Re M, Piccoli T, Piccoli F, La Bella V (2010) Causes and place of death in Italian patients with amyotrophic lateral sclerosis. ActaNeurol Scand 122: 217–23.
5. Garcia P, Pradat P, Salachas F, BrunetEA G, le Forestier N, Selhein D, et al. (2008) Causes of death in a post-mortem series of ALS patients. Amyotroph Lateral Scler 9: 59-62.
6. Merico A, Cavinato M (2011) Autonomic dysfunction in the early stage of ALS with bulb involvement. Amyotroph Lateral Scler 12: 363-367.
7. Asai H, Hirono M, Udaka F, Shimada K, Oda M, Kubori T, et al. (2007) Sym pathetic disturbances increase risk of sudden cardiac arrest in spinal ALS. J Neurol Sci 254: 78-83.
8. Pavlovic S, Stevic Z, Milovanovic B, Milicic B, Rakovcevic-Stojanovic V, et al. (2010) Impairment of cardiac autonomic control in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 11: 272-6.
9. Murata Y, Harada T, Ishizaki F, Izumi Y, Nakamura S (1996) An abnormal relationship between blood pressure and pulse rate in amyotrophic lateral sclerosis. ActaNeurol Scand 96: 118-122.
10. Gydivy HJ, Kurf A, Endruhn S, Ludolph AC, Sperfeld AD (2006) Cardiomyopathy in motor neuron diseases. J NeurolNeurosurg Psychiatry 77: 671-3.
11. Tanaka Y, Yamada M, Kourmura A, Sakurai T, Hayashi Y, et al. (2013) Cardiac sympathetic function in the patients with amyotrophic lateral sclerosis: analysis using cardiac [123I] MIBG scintigraphy. J Neurol Neurosurg Psychiatry 84: 2380-6.
12. Pinto S, Pinto A, De Carvalho M (2012) Decreased heart rate variability predicts death in amyotrophic lateral sclerosis. Muscle Nerve 46: 341-345.
13. SanchoJ, Servera E, Diaz JL, Bafuris P, Marín J (2011) Home tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis. Thorax 66: 948-952.
14. Shimizu T, Hayashi H, Kato S, Hayashi M, Tanabe H, et al. (1994) Circulatory collapse and sudden death in respiratory-dependent amyotrophic lateral sclerosis. J Neurol Sci 124: 45-55.
15. Bakadzhieva R, Gurevich T, Korczyn AD (2005) Autonomic impairment in amyotrophic lateral sclerosis. CurrOxin Neurol 18(5): 487-93.
16. Tanaka Y, Yamada M, Kourmura A, Sakurai T, Hayashi Y, et al. (2013) Cardiac sympathetic function in the patients with amyotrophic lateral sclerosis: analysis using cardiac [123I] MIBG scintigraphy. J Neurol Neurosurg Psychiatry 84: 2380-6.
17. Shemisa K, Kaelber D, Parikh SA, Mackall JA (2014) Autonomic etiology of heart block in amyotrophic lateral sclerosis: a case report. J Med Case Rep 8: 224.
18. Pavlovic S, Stevic Z, Milovanovic B, Milicic B, Rakovcevic-Stojanovic V, et al. (2010) Impairment of cardiac autonomic control in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 11(3): 272-6.
19. Druschky A, Spitzer A, Platsch G, Claus D, Feistel H, et al. (1999) Cardiac sympathetic derangement in early stages of amyotrophic lateral sclerosis demonstrated by 123I-MIBG-SPECT. ActaNeurol Scand 99(S): 308-14.
20. Pivarla N, Korpela J, Vuori A, Saerensranta T, Ollikka KT, et al. (2015) Amyotrofinenlateraalskleneros ja hengitysvaajuus [Amyotrophic lateral sclerosis and respiratory insufficiency]. Duodecim 131(12): 127-35.
21. Romer LM, Lovering AT, Havercamp KC, Pegelow DF, Dempsey JA (2006) Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans. J Physiol 571(Pt 2): 425-439.
22. Matsuo T, Ohkawara K, Seino S, Shimojo N, Yamada S, et al. (2012) Cardiorespiratory fitness level correlates inversely with excess post-exercise oxygen consumption after aerobic-type interval training. BMC Res Notes 5: 646.
23. Braga ACM, Pinto A, Pinto S, Carvalho M (2018) The Role of Moderate Aerobic Exercise as Determined by Cardiopulmonary Exercise Testing in ALS. Neurosurg Res Int 2018: 9218697.
24. Dorst J, Ludolph AC (2019) Non-invasive ventilation in amyotrophic lateral sclerosis. Ther Adv Neurol Disord 12: 1756286419857040.
25. Ferreira GD, Costa AC, Plentz RD, Coriolle CC, Sbruzzo G (2016) Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis. Physiotherapy 102(3): 221-228.
26. Shimizu T, Hayashi H, Kato S, Hayashi M, Tanabe H, et al. (1994) Circulatory collapse and sudden death in respiratory-dependent amyotrophic lateral sclerosis] J Neurol Sci 124(1): 45-55.
27. Rabinstein AA, Benarroch EE (2008) Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol 10(2): 151-157.
28. Asai, Hirohide, Makito Hirano, Fukashia Uda, Keiji Shima, Masaya Oda, et al. (2007) Sym pathetic disturbances increase risk of sudden cardiac arrest in sporadic ALS. Journal of the neurological sciences 254(1-2): 78-83.
29. Finsterer J, Stöllberger C, Maetz C (2016) Sudden cardiac death in neuromuscular disorders. Int J Cardiol 203: 508-15.
30. Dalla Vecchia L, Di Maria B, Marinou K, Sideri R, Lucini A, et al. (2015) Cardiovacular neural regulation is impaired in amyotrophic lateral sclerosis patients. A study by spectral and complexity analysis of cardiovascular oscillations. Physiol Meas 36: 659-670.
31. Simão MCSA, Godoy TJ, Oliveira AM, Borja BM, Almeira FS, et al. (2020) Chloroquine and hydroxychloroquine: the risk of QT interval prolongation when using the recommended dose for the treatment of COVID-19. Embronic Journal Collection Health 12: 1-7.