UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

Amyotrophic Lateral Sclerosis: Exercise and Disease Progression

Anna Caroline Marques dos Anjos Braga

Orientadores: Prof. Doutora Anabela Cardoso Pinto Noronha Sanches

Prof. Doutor Mamede Alves de Carvalho

Tese especialmente elaborada para obtenção do grau de Doutor em Ciências Biomédicas (Neurociências)

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JURÍ:

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“O valor das coisas não está no tempo que elas duram, mas na intensidade com que acontecem. Por isso, existem momentos inesquecíveis, coisas inexplicáveis e pessoas incomparáveis.”

Fernando Pessoa

Acknowledgments:

First, I would like to be grateful to God for the gift of curiosity and stubbornness so present in myself since a very early age. The resilience came later... thank you God for more this gift...

I cannot fail to mention the unconditional support of my husband João Miguel and my daughters Ana Luísa and Joana. Forgive me for so many moments that abdicated of your presence to carry on this project.

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To all my colleagues, fellows of the Neurosciences Doctoral Program, employees of the Library of the Faculty of Medicine of Lisbon and to the unbeatable team of the Instituto de Formação Avançada in the FMUL; who did not allow me to give up and always gave me words of encouragement and encouragement ... To all of you thank you very much!

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And finally, I must express my deepest thanks to all people whom allowed me to do this work, and whom taught me more about Amyotrophic Lateral Sclerosis than any Congress, book or scientific article: the patients and their families that believed on this project also. True examples of courage...

Note to the readers

Several years ago, when I was in the Physiotherapy Faculty, I had learned that the neural cell was the only one not able to regenerates itself. Today, this affirmative seems totally non-sense... Over the years I have seen massive scientific advances in the Neurology area. I still remember about a fantastic short video of electronic microscopy about the first studies of neuroplasticity and axonal sprouting when I was working as Physiotherapist in Brazil in 1999. A New Millennium was beginning and the research on Neurology and Brain studies had been starting an astonishing epoch at the modern medicine. In Portugal, more specifically in the Hospital Santa Maria, I had my first clinical experience with ALS patients which was very frustrating. Because as a Physiotherapist, our role is strongly linked to recovery the function in our patients and the exercise is our master key. But this does not happen with ALS/MND disease. The possibility of submitting an ALS patient to performing exercise was and still is seen as senseless approach and potentially harmful. However, recent scientific works have been presenting the role of exercise as a potential contributor for neuroprotection.

In this Thesis, our main goals were to study the impact of an individualized exercise program on the functional decline and on the aerobic capacity in ALS; and assess the feasibility of a tele-monitoring for a home-exercise program that could help ALS patients to access a physiotherapy program to distance. As secondaries outcomes, we studied aspects related to management of the respiratory failure, the support for ALS caregivers, and disease progression in low resources settings.

This dissertation is structured in 8 chapters:

The first chapter of this thesis addressed a brief review about the clinical features of the disease and measurements of the functional decline. The Chapter 2 describe some aspects related to the prescription of exercise using Cardiopulmonary Exercise Testing (CPET).

The main contributions are addressed in the chapter 3 and 4 respectively - through 2 original articles, which describes the role of moderate aerobic exercise as determined by cardiopulmonary exercise testing (CPET) in ALS, and outcomes from a feasibility study about a tele-monitoring system to supervising home-based exercise in ALS.

Additional contributions are presented in the Chapter 5, 6 and 7, which are organized such as:

The Chapter 5 is divided in 3 sections where we presented:

- Section 5.1 - a brief review about Respiratory insufficiency in ALS,
- Section 5.2 - the diversity on the management of the respiratory insufficiency in ALS,
- Section 5.3 - the predictive value of the Non-Invasive ventilation settings and how this can influence the functionality and survival for ALS patients.

In the chapter 6 are described outcomes from a feasibility study about an innovative pilot project performed with ALS caregivers about home management for this disease.

The Chapter 7 present two originals research works about the disease progression in low resources settings, which are the first studies carried out with ALS patients in the African continent.

Finally, the eighth and last chapter describe a general discussion and conclusions about the results presented in the previous chapters of this thesis, and prospects for the future.

The research project aimed to study the role of exercise on the progression of amyotrophic lateral sclerosis and awarded a PhD Scholarship from the Foundation for Science and Technology (FCT - SFRH/BD/78413/2011). This work as well as all other studies included in this Thesis received approval of the Ethics Committee of the Faculty of Medicine of Lisbon.

Table of Contents:

Authorship

The papers below were presented in international conferences and further published in peer-reviewed journals:

- **Braga, Anna Caroline M**; Pinto, Anabela. *Healthcare Management in ALS patients. Its influence on Quality of Life.* Home HealthCare Management & Practice, Vol. 27(4)201-207; 2015. doi: 10.1177/1084822315588518. Impact Factor (SCI): 0.18 (Q4).

- **Braga, Anna Caroline M**; *A look at the diversity on management of respiratory failure in Amyotrophic Lateral Sclerosis*. Editorial in Respiratory Care Journal, Vol 60(4) 625-626; 2015 doi:10.4187/respcare.04014. Impact Factor (SCI): 1.8 (Q2).

- **Braga, Anna Caroline M**; Pinto, Susana; Pinto, Anabela. *Can Non-invasive Ventilation Settings Predict Functional and Survival Outcome in ALS Patients?* J Community Med Health Educ Vol 7 (2) 521;2017, doi:10.4172/2161-0711.1000521. Impact Factor (Copernicus Index):1.73(2017).

- **Braga, Anna Caroline M;** Pinto, Anabela; Pinto, Susana; de Carvalho, Mamede. *The Role of Moderate Aerobic Exercise as Determined by Cardiopulmonary Exercise Testing in ALS*, Neurology Research International, Vol Jan,2018. doi:10.1155/2018/8218697. Impact Factor(SCI): 1.49 (Q2).

- **Braga, Anna Caroline M;** Pinto, Anabela; Pinto, Susana; de Carvalho, Mamede. *Tele-monitoring of a home-based exercise program in ALS: a feasibility study*. Eur J Phys Rehabil Med. DOI: 10.23736/S1973-9087.18.05129-8. Epub 23 Jan 2018. Impact Factor (SCI): 1.70 (Q1).

- **Braga, Anna Caroline M;** Pinto, Anabela. *Home Caregivers Training program for Amyotrophic Lateral Sclerosis: insights from a pilot project*. Home HealthCare Management & Practice. Epub 18, 2018. doi.org/10.1177/1084822317753830. Impact Factor (SCI): 0.18 (Q4).

Presentations in Congresses with abstracts published in international journals:

- 28th INTERNATIONAL SYMPOSIUM ON ALS/MND. 7 – 9 Dec 2017, Boston, USA.
  - *Effects of social and cultural context on outcomes on the ALSFRS-R at South Africa*. **A C Braga**, F Henning. Poster presentation Published in: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal. Volume 18, 2017 - Issue sup2: Abstract Book. Impact Factor (SCI):3.054(Q1);
  - *Home telemonitoring for ALS early and late ventilated patients*. Pinto A, **Braga AC**, Guedes S et al. Poster presentation. Published in: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal. Volume 18, 2017 - Issue supplem: Abstracts Book. Impact Factor (SCI):3.054(Q1)

- 27th INTERNATIONAL SYMPOSIUM ON ALS/MND. 8 – 10 Dec 2016, Dublin, Ireland *Implementation of wireless device to monitor the cardiorespiratory response to aerobic exercise in ALS patients*. **Anna Caroline M.A. Braga**, Anabela Pinto, Mamede de Carvalho. Poster presentation. Published in: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal. Volume 17 - Issue supplem: Abstracts book. Impact Factor (SCI):3.054(Q1).

- 26th INTERNATIONAL SYMPOSIUM ON ALS/MND. 10 – 12 Dec 2015, Orlando, USA. *Teaching to take Care: Training course for home-based caregivers in amyotrophic lateral sclerosis: outcomes from a pilot project*. **Anna Caroline M.A. Braga**, Anabela Pinto. Poster presentation. Published in: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal. Volume 16 - Issue supplem: Abstracts book. Impact Factor (SCI):2.67(Q1).

- 2nd SYMPOSIUM OF PHYSIOTHERAPY - Higher School of Technologies – Cascais/Portugal, 14-15 February 2014. Speaker in Neurodegenerative Diseases Session. **Anna Caroline M.A. Braga;** Oral communication: *Amyotrophic Lateral Scleroses – Important aspect in the follow up – Prescription of exercise, Non-Invasive Ventilation and Weight Loss.*

- 24th INTERNATIONAL SYMPOSIUM ON ALS/MND. 5-8 December 2013 Milan, Italy. *Can NIV parameters settings and changes overtime predict functional and survival outcome in ALS patients?* **Anna Caroline M.A. Braga**, Anabela Pinto, Mamede de Carvalho.Platform Communication. Published in: Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal. Volume 6, 2013 - Issue supplem: Abstracts Book. Impact Factor (SCI):2.6 (Q1).

- 59th AMERICAN ASSOCIATION OF RESPIRATORY CARE CONGRESS, 16 – 19 Nov 2013, Anaheim, CA – USA. Speaker in Neuro Respiratory Disease Management Symposium. **Anna Caroline M.A. Braga;** Oral Communications:
  - *ALS Palliative Care: Burden of Caregivers Compared to Patient's Quality of Life*
  - *What Do We Need to Know to Follow up ALS Patients from Early to Terminal Disease?*

- 23rd EUROPEAN RESPIRATORY SOCIETY ANNUAL CONGRESS – Barcelona 7 -11 September 2013. Poster Session. *Can NIV parameters settings and changes overtime predict functional and survival outcome in ALS patients*? **Anna Caroline M.A. Braga**, Anabela Pinto, Mamede de Carvalho.

- 58th AMERICAN ASSOCIATION OF RESPIRATORY CARE CONGRESS, 10 – 13 Nov 2012, New Orleans, LA – USA. *Predictors of functional decline in ALS patients under NIV. Oral Presentation***. Anna Caroline M.A. Braga**, Anabela Pinto, Mamede de Carvalho. Published in: Respiratory Care abstract book. Volume 57,10. 2012 - Issue supplem: Impact factor (SCI):1.85(Q2).

- 13rd INTERNATIONAL CONFERENCE ON HOME MECHANICAL VENTILATION/ 4th EUROPEAN CARE RESPIRATORY ASSOCIATION CONGRESS, 15 – 17 March 2012-Barcelona/Spain. *Assessment of Caregivers Burden applying the Zarit Burden Interview (ZBI): correlation with functionality, QoL, mood disorders and technical aids*. **Anna Caroline M.A. Braga**, Anabela Pinto, Cátia de Jesus, Mamede de Carvalho. Poster presentation.

List of figures

List of Tables

List of Abbreviations

AAA - American Academy of Neurology

ALS – Amyotrophic Lateral Sclerosis

ALSFRS – Amyotrophic Lateral Sclerosis Functional Rating Scale

ALSFRS – R - Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised

ALS-FTD – Amyotrophic Lateral Sclerosis – Frontotemporal Dementia

APELA - ALS Portuguese Association

AT – Anaerobic Threshold

ATS - American Thoracic Society

BR back-up - Breath Rate back-up

BR mean - Breath Rate mean

BTPS - Body Temperature and Pressure Saturated

BWSS - Body Weight Supporting System

CNS – Central Nervous System

COPD - Chronic Obstructive Pulmonary Disease

CPET – Cardio Pulmonary Exercise Testing

ECG – Electrocardiogram

EFNS - European Federation of Neurology Societies

EPAP - Expiratory Positive Airways Pressure

ES - Expiratory Sensitivity

FVC - Functional Vital Capacity

%FVC predicted - Predicted value of Forced Vital Capacity

HR - Heart Rate

I: E - Inspiration: Expiration ratio

IPAP – Inspiratory Positive Airways Pressure

IS - Inspiratory sensitivity

LMN - Lower Motor Neuron

MEP – Maximum Expiratory Pressures

MET – Metabolic Equivalents

MIP - Maximal Inspiratory Pressure

MND - Motor Neuron Disease

NHU/d - Number of Hours of Use by day

NIV - Non-Invasive Ventilation

NPO - Nocturnal Pulse Oximetry

ODH - number of oxygen desaturations per hour

P.01 - Inspiratory pressure 100 milliseconds into an occluded inspiratory effort

$PaCO_2$ - Partial pressure of CO_2

PaO_2 - Partial pressure of Oxygen

PEEP - Positive End Expiratory Pressure

PEG - Percutaneous Endoscopic Gastrostomy

PFC - Peak Flow Cough

PFT - Pulmonary Function Test

PLS - Primary Lateral Sclerosis

PMA - Progressive Muscular Atrophy

RCP - Respiratory Compensation Point

REM - Rapid eye movement

RER - Respiratory Exchange Ratio

RI – respiratory insufficiency

ROM - Range of Motion

RT - Rise time

$SatO_2$<90 - percentage of time which SpO2 recording was below 90%

%Sat O_2 - % Oxygen saturation

% SpO_2 – mean percentage of oxygen saturation

%SC – percentage of Spontaneous Cycles

SNIP - Sniff Nasal Inspiratory Pressure

SVC – Supine Functional Vital Capacity

TDP-43 - Transactive response DNA binding protein 43 kDa

Time Sat <90% - percentage of recording time with oxygen saturation lower than 90%

UMN - Upper Motor Neuron

VCO_2 - Dioxide Carbon output

VE - Minute ventilation

VEGF - Vascular Endothelial Growth Factor

VO_2 – Oxygen uptake

List of Genes related to ALS (1993 – 2016)

SOD1 – Superoxide dismutase 1

NEFH – Neurofilament, heavy polypeptide

SETX - Senataxin

ALS2 – Amyotrophic Lateral Sclerosis 2 (juvenile)

DCTN1 – Dynactin 1

VAPB- Vesicle associated membrane protein (protein B and C)

ANG - Angiogenin

CHMP2B – Charged multivesicular body protein 2B

TARDBP – TAR DNA binding protein

FIG4 – Phosphoinositide 5

ELP3 – Elongator acetyltransferase complex subunit 3

FUS – Fused in sarcoma

SPG11 – Spastic paraplegia 11 (autossomal recessive)

ATXN2 – Ataxin 2

OPTN - Optineurin

VCP – Valosin contain protein

C9orf72 - chromosome 9 open reading frame 72

CHCHD10 - coiled-coil-helix-coiled-coil-helix domain containing 10

UBQLN2 – Ubiquilin 2

SQSTM1 – Sequestosome 1

PFN1 – Profilin 1

HNRNPA2B1 - heterogeneous nuclear ribonucleoprotein A2/B1

HNRNPA1 - heterogeneous nuclear ribonucleoprotein A1

TUBA4A – Tubulin Alpha 4a

MATR3 – Matrin 3

TBK1 - TANK-binding kinase 1

CCNF – Cyclin F

NEK1 - NIMA-related kinase 1

C21orf2 - chromosome 21 open reading frame 2

Note: names of genes searched in www.thebiogrid.org

Resumo

A Esclerose Lateral Amiotrófica (ELA) pertence a um grupo de doenças neurológicas conhecido como doenças do neurónio motor, as quais são caracterizadas por degeneração e morte progressiva dos neurónios motores. A doença manifesta-se por parésia progressiva e atrofia muscular, de início assimétrico, com envolvimento de sucessivas regiões anatómicas durante a progressão da doença. Em geral, a doença inicia-se de uma de duas formas fundamentais: com envolvimento dos músculos da região bulbar; ou com perda de força muscular dos membros superiores ou inferiores – forma dita medular. Embora outras formas raras de manisfestação também sejam citadas na literatura, tais como: respiratória (quando os músculos respiratórios são afectados inicialmente); axial (afecta inicialmente os músculos cervicais e paraespinhais) e a forma difusa (início generalizado da doença). Estas formas de apresentação determinam os sintomas iniciais. A progressão é variável. Algumas pessoas têm progressão lenta, enquanto outros têm uma rápida perda funcional. A perda de capacidade funcional condiciona dependência, com progressiva necessidade de um cuidador para realização de todas as suas actividades de vida diária.

A sobrevida média é de 3 - 5 anos desde os sintomas iniciais, e o evento fatal geralmente ocorre por insuficiência ou infeccção respiratória. Apesar de não haver tratamento capaz de suster a progressão, a gestão clínica desta doença evoluiu positivamente nos últimos anos. Devido aos avanços tecnológicos das intervenções médicas, como a assistência respiratória (ventiladores portáteis, sistemas de tosse assistida e monitorização), medidas alternativas para alimentação e o uso das tecnologias de apoio à comunicação. O uso de telemedicina em algumas valências têm vindo a demonstrar resultadores animadores.

Recentemente alguns estudos sugerem o exercício como potencial meio terapêutico, devido ao seu eventual efeito neuroprotector, descrito em alguns trabalhos. No entanto, o exercício aeróbico tem sido pouco estudado em doentes com ELA, devido ao receio de que o exercício possa ser prejudicial. Atendendo às recomendações da última revisão Cochrane sobre o exercício terapêutico na ELA, estudamos o impacto do exercício aeróbico na capacidade funcional e aeróbica dos doentes.

Os principais contributos desta tese foram: 1 - estudar a eficácia do exercício moderado e rigorosamente prescrito na evolução e sobrevida da ELA e, 2 - a avaliação da possibilidade de exercitar estes pacientes com o controlo a distância. O primeiro contributo está descrito no Capítulo 3, e estudou o impacto de um programa de exercícios baseado no teste de esforço cardiopulmonar sobre o declínio funcional e capacidade aeróbica dos doentes com ELA, num período de 6 meses. Foram incluídos 48 pacientes divididos em 2 grupos: G1 (n = 24), no qual os doentes realizaram exercício com intensidade determinada pelo teste de esforço cardiopulmonar(TECP); e G2 (n = 24) como grupo controlo. Medidas de funcionalidade (usando ALSFRS-R) e avaliação da função respiratória (capacidade vital forçada – CVF) foram realizados a cada 3 meses; o teste de esforço cardiopulmonar foi realizado na admissão ($T1$) e 6 meses depois ($T2$). Foram registados o consumo de oxigénio máximo atingido (VO_2pico), o dióxido de carbono exalado (VCO_2) e Ventilação Minuto (VE) no limiar anaeróbico e no pico do esforço. Os resultados mostraram que em $T1$ ambos os grupos eram idênticos, excepto pelo maior valor de CVF no G1 (p = 0,02). Em $T2$, o valor ALSFRS-R foi superior no G1 (p = 0,035). As variáveis cardiorespiratorias do TECP em $T2$ não sofreram alterações no G1, mas apresentaram diferenças significativas no G2 (p <0,05). Análises de regressão múltipla identificaram o exercício e o declínio funcional no *score* medular como predictores independentes da funcionalidade em *T2*. Com estes resultados, concluímos que um programa de exercícios aeróbicos baseado no teste de esforço cardiopulmonar é eficaz e pode trazer benefícios na ELA.

O segundo contributo principal desta Tese é apresentado no Capítulo 4 e analisou a viabilidade da tele-monitorização de um programa domiciliar de exercícios determinado pelo teste de esforço cardiopulmonar, que poderia ajudar os pacientes com ELA a aceder um programa de fisioterapia a distância; tal como permitir o controlo do esforço físico, a aderência e os possíveis eventos adversos, pela equipe médica. Monitorizamos 10 pacientes consecutivos com ELA durante 6 meses. Paciente e cuidadores consideraram o sistema de tele-monitorização de fácil utilização e a aderência foi excelente. A ausência de eventos adversos relevantes, e a monitorização contínua da frequência cardíaca e da saturação de oxigénio durante o exercício demonstraram que um programa domiciliar de exercício aeróbico moderado na ELA é clinicamente seguro.

Esta tese inclui também resultados de contributos secundários, os quais estão relacionados com relevantes questões problemáticas sempre presentes durante a progressão da doença tais como a gestão e abordagem da insuficiência respiratória (sub-capítulos 5.2 e 5.3), o suporte aos cuidadores (capitulo 6)e o potencial impacto de uma gestão clínica com escarsos recursos sobre a progressão da doença(Capitulo 7).

No sub-capítulo 5.2 apresentamos um trabalho sobre a falta de consenso acerca do momento ideal para início da VNI e sobre o uso de recursos alternativos no suporte respiratório. Realçamos o impacto da VNI e da traqueostomia nos cuidadores familiares e/ou informais, em especial como pode potencialmente afectar a qualidade de vida. Reforça-se a importância da avaliação da capacidade emocional, física, social e psicológica do cuidador de forma a poder lidar com as crescentes necessidades de cuidado destes doentes.

O sub-capítulo 5.3 apresenta resultados sobre a importância de uma gestão criteriosa no uso e configuração dos parâmetros da Ventilação Não-Invasiva (VNI), em particular o papel dos ajustes da ventilação e da aderência no declínio funcional e sobrevida dos doentes ventilados. Para tal foram analisados um vasto conjunto de dados registados a partir do *software* utilizado nos ventiladores, medidas de oximetria de pulso noturna e testes de função respiratória. Os nossos resultados sugerem que as variáveis que afetam o conforto respiratório do doente são relevantes para a aderência à VNI e afetam postivamente a sobrevida na ELA.

O Capítulo 6 apresenta resultados de um estudo sobre a viabilidade de um programa de treino para cuidadores. A progressão incerta da doença e os cuidados a longo prazo, assim como o número insuficiente de profissionais de saúde especializados determinam que a admissão desses doentes em hospitais ou em unidades de cuidados continuados seja uma opção complexa. Iniciativas que permitam uma melhor gestão da doença no domicílio podem ser uma solução alternativa. A incapacidade funcional dos doentes pode promover restrições financeiras significativas, e expõe as suas famílias a altos níveis de *stress*, os quais pode comprometer a prestação de cuidados de saúde adequados, levando à hospitalização destes pacientes. Neste projecto, identificamos um excelente nível de participação, bem como um bom resultado na avaliação da aprendizagem (acima

de 70%). O principal factor limitador à participação no programa de treino foi a ausência de um cuidador secundário.

O Capitulo 7 descreve resultados de 2 estudos realizados com doentes com ELA no continente Africano, os quais apresentam dados preliminares sobre a progressão da doença em um ambiente com recursos limitados para o sua gestão clínica.

O Capitulo 8 apresenta uma discussão geral e conclusões sobre os trabalhos incluídos nesta tese, bem como algumas propostas de investigação para o futuro.

Todos os trabalhos apresentados nesta tese pretenderam contribuir para uma visão mais alargada da gestão clínica da ELA, onde o papel do exercício associado a um suporte respiratório mais criterioso, e a presença de uma cuidador bem informado e treinado, possam em conjunto ser uma contribuição importante para a sobrevida e qualidade de vida do doente com ELA.

Palavras-chave: Esclerose Lateral Amiotrófica, Ventilação Não-Invasiva, Exercício, Telemedicina, Cuidadores.

Abstract

Amyotrophic Lateral Sclerosis (ALS) belongs to a group of neurological disorders known as motor neuron diseases, which are caused by gradual degeneration and consequent death of motor neurons. In general, the disease begins in one of two fundamental ways: with involvement of the muscles of the bulbar region; or with loss of muscle strength of the upper or lower limbs - spinal form. Although other rare forms of manifestation are also cited in the literature, such as: respiratory (when respiratory muscles are initially affected); axial (initially affecting the cervical and paraspinal muscles) and the diffuse form (generalized onset of the disease). These forms of presentation determine the initial symptoms. Patients may initially develop muscle weakness in the limbs resulting in various clinical conditions with paresis, speech problems with dysarthria, dysphagia, and respiratory symptoms with dyspnea, and evolve to complete loss of body movements control. The degree of functional disability and dependence resulting from ALS lead the patient to gradually needing a caregiver for all their activities of daily life.

The mean survival for ALS is around 3 - 5 years from first symptoms, and the fatal event usually occurs due to respiratory failure or infection. Although there is no effective treatment to halt disease progression, the clinical management has evolved positively in last years. The technological advance of medical interventions has contributed to a longer survival and higher quality of life. The monitoring of non-invasive ventilation has been very helpful for the clinical follow up and to decrease the anxiety experienced by caregivers. Unfortunately, the aerobic exercise is not a usual therapeutic option for ALS patients in the clinical management yet.

Physical exercise has been suggested to promote growth factor delivery in experimental animal models of ALS. However, the aerobic exercise is understudied in ALS patients due the suspicious that the exercise could be harmful for this population. Meeting the recommendations from the last Cochrane review about Therapeutic exercise in ALS, we have analyzed the impact of aerobic exercise in the ALS progression.

This thesis has 2 main contributions: 1 - To study the efficacy of moderated and accurate defined exercise program on the evolution and survival of ALS, and, 2 - to assess the feasibility to performing exercise monitored remotely from home in ALS patients.

In addition, this thesis includes results from additional contributions, which are related to relevant issues always present during disease progression such as management of the respiratory failure (sub-chapters 5.2 and 5.3), the support for ALS caregivers (Chapter 6), and the potential impact of clinical management on disease progression in an environment with lack of resources (Chapter 7).

In the sub-chapter 5.2 we present a work which describe the lack of consensus for the ideal timing to start NIV and about the use of alternative respiratory support. We address the impact of NIV and tracheostomy on family and / or informal caregivers, especially how it can affect quality of life. The importance of assessing the emotional, physical, social and psychological capacity of the caregiver is reinforced in order to cope with the increasing care needs of these patients.

The sub-chapter 5.3 presents results on the importance of a careful management in the use and configuration of Non-Invasive Ventilation (NIV) parameters, in particular the role of ventilation and adherence adjustments in functional decline and survival of ventilated patients. A wide range of data recorded from the software used in ventilators, nocturnal pulse oximetry measurements and respiratory function tests were analyzed. Our results suggest that the variables that affect the respiratory comfort of the patient are relevant for adherence to NIV and positively affect survival in ALS.

The Chapter 6 presents results of a feasibility study about a training program for caregivers. The uncertain progression of the disease and long-term care, as well as the insufficient number of skilled health professionals, determine that the admission of these patients to hospitals or to continuing care units is a complex option. Initiatives that allow better management of the disease at home can be an alternative solution. The functional disability of patients can promote significant financial constraints, and exposes their families to high levels of stress, which can compromise the provision of adequate health care, leading to the hospitalization of these patients. In this project, we identified an excellent level of participation as well as a good result in the evaluation of learning (above

70%). The main limiting factor for participation in the training program was the absence of a secondary caregiver.

The Chapter 7 describes results from2 studies conducted with ALS patients in the African continent, which present data on disease progression in an environment with limited resources for clinical management.

The Chapter 8 present a general discussion and conclusion of all works included in this Thesis.

All the papers presented in this thesis aim to contribute to a broader view of the clinical management of ALS, where the role of exercise associated with more careful respiratory support, and the presence of a well-informed and trained caregiver, can together be an important contribution for the survival and quality of life of the patient with ALS. We hope our work presented in this thesis may contribute to a wider understanding on the clinical management of ALS. In particular demonstrating that controlled exercise associated with careful respiratory support, and the presence of a well-informed and trained caregiver, may be an added value in the survival and quality of life for ALS patient.

Key words: Amyotrophic Lateral Sclerosis, Non-Invasive Ventilation, Exercise, Telemedicine, Caregivers.

Chapter 1:
Amyotrophic Lateral Sclerosis
A brief review

1. Amyotrophic Lateral Sclerosis - A brief review:

1.1 Introduction

Nowadays, the Amyotrophic Lateral Sclerosis (ALS) still is a condition extremely hard to define. It belongs to a cluster of clinical events that affects the motor neurons, known as Motor Neuron Diseases (MND). It is reasonable to say that ALS has the capacity to presents itself under different perspectives, dependent on who is analysing it. In a clinical perspective, ALS is seen as a progressive and pure motor syndrome combining upper and lower motor neuron involvement in multiple territories of the central nervous system (CNS), leading to death within a few years. A pathogenic vision describes ALS as a neurodegenerative disease, which the pathologic hallmark is the presence of ubiquitinated inclusions that stain with antibodies to the cellular protein TDP-43. The etiological point of view looks to ALS as a degenerative condition with a specific set of susceptible factors typically unmasked by ageing processes. From a biochemical perspective, ALS should be the consequence of one and/or all these events: excitotoxicity, oxidative stress, apoptosis, changes in axonal transport, calcium balance dysfunction, mitochondrial injury … etc. In the palliative care context, ALS is seen as a devastating terminal neurodegenerative disease with a highly unpredictable clinical course, hence palliative care follow-up should start soon after diagnosis (1). Scientifically, and due the significant advances that have been made about the understanding of MND pathogenesis, the researchers can describe ALS as a challenging complex disease involving an intricate combination of exogenous environmental factors and common and rare genetic variations (2), with a large phenotypic variability (3).

On the ALS patients and caregivers' point of view, the key words that would translate what ALS represent for them are: Loss and Adaptation. This disease affects not only the individual as well as it has catastrophic consequences on the family members.

The last decade has seen major improvements in the patient care. The impact of new technologies and approaches for communication, as social networks, have helped to reveal more information about this rare neurodegenerative condition to the public in general and increased the opportunities for funding for research.

ALS has a type of presentation extremely heterogeneous, with an average of one-year delay from first symptoms to diagnosis, and subsequent unpredictable rate of clinical progression. This progressive disability with preservation of consciousness leads to death usually due to respiratory problems. Up to this year (2018) the Riluzol® was the only drug able to modify the disease natural history but statistically it only prolongs life around 3-6 months (4,5). Recently, it was approved another drug called Edaravone® to be used with ALS patients in Japan, South Korea and United States. However, the benefits of this new drug still are unclear, since the primary outcome is not associated to a longer survival but with slight delay on the functional progression, without impact on respiratory function, which seems much less than the benefits from Riluzol®. Unluckily, drug administration and costs do not favor this new compound.

In ALS, the respiratory insufficiency (RI) can occur in different clinical stages, and there is good clinical evidence indicating that Non-Invasive Ventilation (NIV) intervention plays a critical role in prolonging life (6). However, the motor rehabilitation approach to ALS patients require more studies about the potential role of exercise in this population (7). Many patients with ALS specifically ask whether they can continue or start exercising regularly without risk of accelerating their disease (8). But some studies suggesting that low-grade exercise programs can have some benefit (9). However, there is no solid evidence that exercise exerts a harmful effect, although avoidance of very strenuous activity seems reasonable (10). The role of exercise as neuroprotective factor is controversial still, some authors conjecture that it has a neurotrophic action promoting neuronal plasticity. To support the beneficial role of the exercise there are a few animal and clinical studies.

In this dissertation, we studied the impact of a supervised aerobic exercise protocol on disease progression and the cardiorespiratory system of ALS patients, and evaluated the use of tele-monitoring system in ALS patients undergoing a home-based exercise program. Additionally, we presented results from other works related to: 1- management of respiratory insufficiency and its impact on the functional decline and survival in ALS patients, 2 – feasibility of training program for ALS caregivers, and 3 – Functional decline assessment and disease progression in low resources settings such as South Africa.

1.2 Clinical Characteristics:

ALS is included in the heterogeneous group of neurological disorders characterized by degeneration of motor neurons (2), MND. The other four conditions are: Primary Lateral sclerosis (PLS), Progressive Muscular Atrophy (PMA), Progressive Bulbar Palsy (PBP) and Pseudobulbar Palsy (11). Around the world, ALS has received several different names, such as Motor Neuron Disease in United Kingdom, Lou Gherig Disease in USA and Charcot Disease in France (11). Nowadays, the public in general recognize the disease due the exposition of people diagnosed with ALS linked to artistic, scientific or sporty areas. The work developed in this thesis studied patients with ALS.

Historically, there are two categories of presentation for ALS: sporadic and familial. However, the differences between familial and "apparently "sporadic ALS forms have not a defined and clear-cut boundary in the current genetic studies. The recent advent of high-throughput DNA sequencing instruments and exome wide gene capture tools has led to the identification of ALS linked variations in several additional genes (12). These advances have helped the understating on the polymorphous nature of the disease, and the ambiguity between sporadic and familial forms of ALS (13). The first known mutation linked to familial form was the SOD1 (Superoxide Dismutase 1) discovered in 1993(14).

The discovery of the gene C9orf72 in 2011 changed radically the understanding of ALS pathogenesis and reinforced the concept of ALS as a multisystem complex disease. The C9orf72 (Chromosome 9 open reading frame 72) gene provides instructions for making a protein that is abundant in the neurons in the cerebral cortex and in motor neurons. This protein seems to influence the production of RNA and proteins and the transport of RNA within the cell. Some studies suggest that a probable alteration on the C9orf72 function can be linked to pathogenesis of the ALS (15).

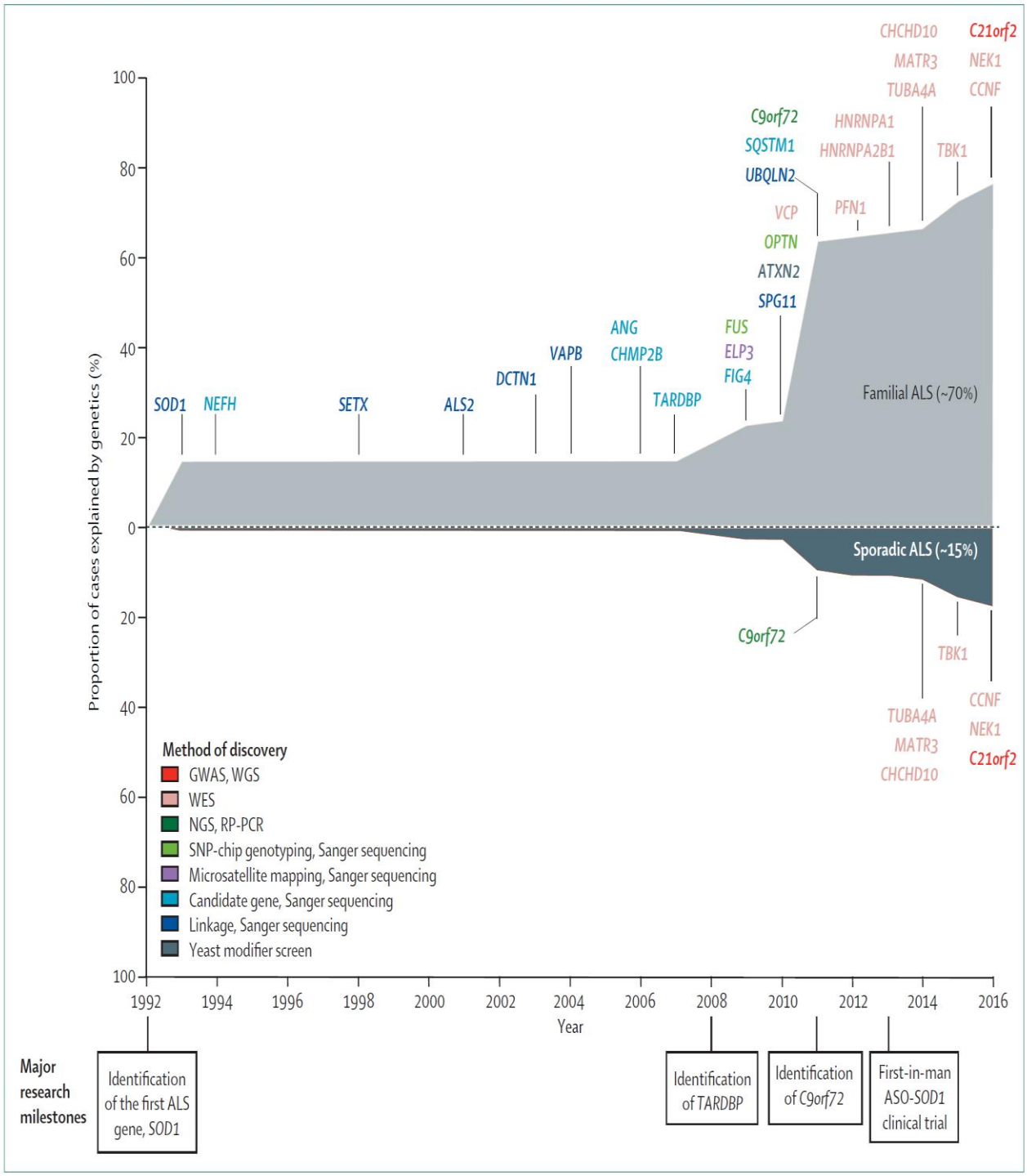
The diagnosis of C9orf72-related ALS/FTD is established by detection of a heterozygous pathogenic GGGGCC (G4C2) hexanucleotide repeat expansion in C9orf72 on molecular genetic testing (16). This hexanucleotide expansion is responsible for up to 10% of cases of apparently sporadic ALS in some populations (17), and for about 60% of cases of familial ALS (18).

C9orf72-related ALS/FTD is inherited in an autosomal dominant manner, with age-dependent penetrance. Although most affected individuals have an affected parent, the parents may be unaffected because of either incomplete or age-dependent penetrance in the parent or a *de novo* pathogenic variant in the proband. Each child of an individual with C9orf72-related ALS/FTD has a 50% chance of inheriting the pathogenic C9orf72 G4C2 hexanucleotide repeat expansion (16).

Others recent mutations include Angiogenin, FUS, UBQLN2, C9ORF72 (19), and more recently NEK1 (20), which interacts with other proteins involved in neuron degeneration.

Since early 2014, more than 20 genes had been identified as causative of, or highly associated with, ALS. Each of the seven novel genes (MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C21orf2, and CCNF since 2014) code for proteins associated with one or more molecular pathways known to be involved in ALS, which include dysfunction in global protein homoeostasis resulting from abnormal protein aggregation or a defect in the protein clearance pathway, mitochondrial dysfunction, altered RNA metabolism, impaired cytoskeletal integrity, altered axonal transport dynamics, and DNA damage accumulation due to defective DNA repair(18). The figure 1 shows an impressive scenery about the genetic discoveries with the more different types of research methodology.

Figure 1. Genetic Landscape of ALS between 1993 and 2016



Familial ALS cases constitute about 10% of all cases of ALS. Of this 10%, about 70% can be explained by genetics. Two substantial increases in genetic contribution to ALS were found in 2008 and 2011, corresponding to the identification of TARDBP (contributes to about 4% of familial and 1% of sporadic cases) and C9orf72 (contributing to about 40% of familial cases and 8% of sporadic cases). ALS – Amyotrophic Lateral Sclerosis. GWAS – genome-wide association study. WGS – whole-genome sequencing. WES – whole-exome sequencing. NGS – next-generation sequencing. RP-PCR – repeated-primed polymerase chain reaction. SNP – single nucleotide polymorphism. ASO – antisense oligonucleotide. Ref. (18)

Genes names – please, see list of genes in page 24.

The advances in the ALS genetic research have been enormous since the last decade, however a comprehensive review that may describe the most recent findings about this thematic is out of scope of this Thesis.

Although ALS usually starts in the fifth or sixth decade of life, an onset at almost any age has been described. Juvenile ALS is defined as ALS with age at onset before 25 years and the course of progression is generally slower than in other forms of ALS (21,22).

The estimated lifetime risk of developing ALS for individuals aged 18 or older is 1/350 for men and 1/420 for women. The male gender, increasing age and hereditary disposition are the main risk factors (4,23,24).

The ALS diagnosis is based on clinical history, examination, electromyography and exclusion of 'ALS-mimics' (*e.g.* cervical spondylotic myelopathies, multifocal motor neuropathy and Kennedy's disease) through appropriated investigations (25,26). The most relevant clinical characteristic is the combination of upper and lower motor neuron clinical signs.

At early stages, ALS presents a variety of signs and symptoms, making the diagnosis a hard task, which might take up to 12 months to be established (27). This disease affects, in a non-symmetric manner, muscles of the limbs, trunk and cranial nerves, with pyramidal signs, atrophy, fasciculation, fatigue and loss of strength. Usually, it progresses without alterations of other CNS pathways, namely the sensory tracts, cognition, coordination or sphincter function.

Nichols and colleagues (28) suggests that clinical presentation and disease progression can be dependent of the location of initial symptom onset. Their work refers, for example, that the bulbar-onset results from upper motor neuron degeneration and includes spasticity, hyperreflexia, difficulty of swallowing, speaking or breathing due, at least in part, to degeneration of the corticospinal tract (29).

The spinal-onset would produce characteristic signs of alpha motor neuron degeneration that include generalized muscle weakness, atrophy and fasciculation (29).

As aforementioned, ALS can present a phenotypic variability regarding the pattern of motor involvement. Swinnen and Robberecht (2014) published a very informative review that should help to clarify this question (3). Figure 2 from their article summarizes the

phenotypes that can be found in clinical practice. The authors highlighted that the method and timing of assessment of a patient account for a considerable proportion of the clinical variability. Recent findings call attention to the role that interneurons may play in ALS contributing to a loss of inhibitory function in cortical and spinal networks (27,28).

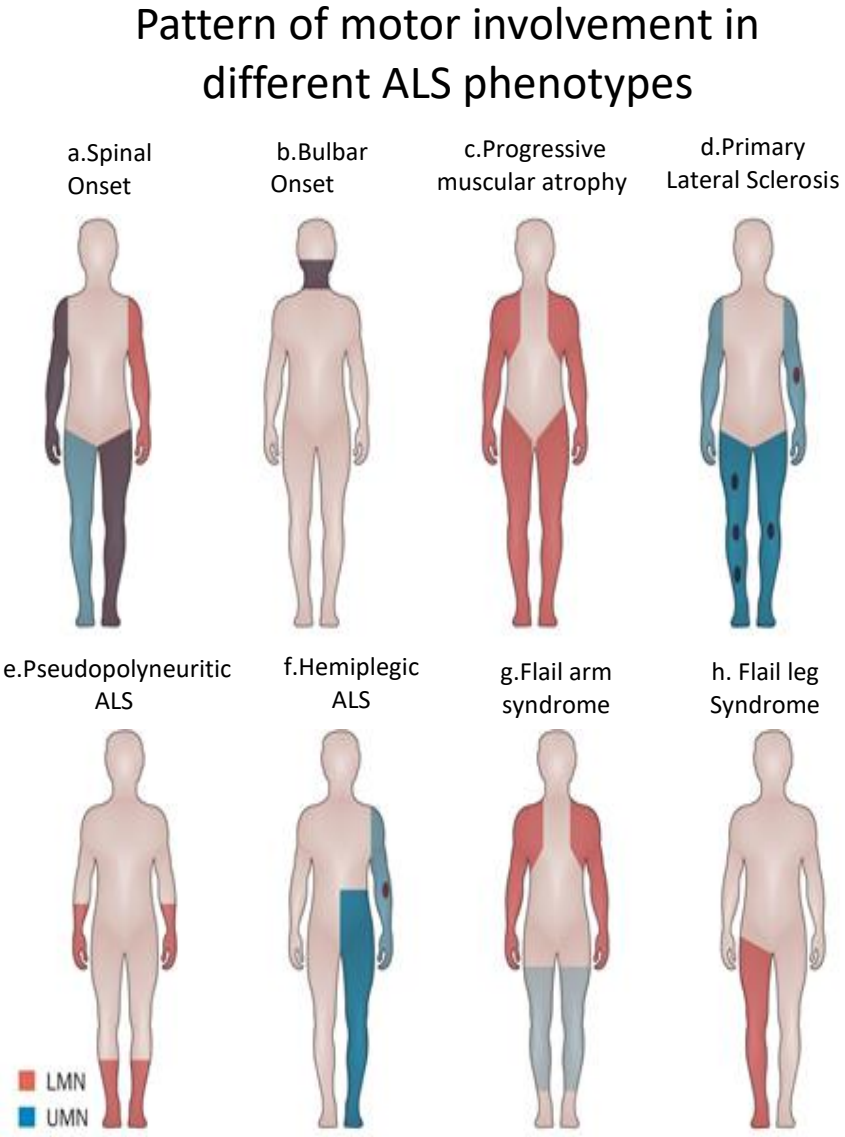


Figure 2. Pattern of motor involvement in different ALS phenotypes. Red indicates LMN involvement, blue indicates UMN involvement. Darker shading indicates more severe involvement. **a |** In spinal-onset ALS, patchy UMN and LMN involvement is observed in the all limbs. **b |** In bulbar-onset ALS, UMN and LMN involvement is observed in the bulbar muscles. **c** | In progressive muscular atrophy, LMNs in arms and legs are involved, often proximally. **d** | In primary lateral sclerosis, UMNs of arms and legs are primarily involved, but later in the disease, discrete LMN involvement can be detected. **e** | In pseudopolyneuritic ALS, only LMNs restricted to the distal limbs are involved. **f** | In hemiplegic ALS, unilateral UMN involvement with sparing of the face, and sometimes discrete LMN involvement, can be observed. **g** | In flail arm syndrome, LMN involvement is restricted to the upper limbs, but mild UMN signs can be detected in the legs. **h** | In flail leg syndrome, LMN involvement is restricted to the lower limbs, and is often asymmetric. Abbreviations: ALS, Amyotrophic Lateral Sclerosis; LMN, Lower Motor Neuron; UMN, Upper Motor Neuron. Adapted from [3].

Although commonly known as a disease affecting motor function, there are variants that presents cognitive deficits, such as Fronto-Temporal Dementia (ALS-FTD). This is largely acknowledged in the literature and numerous studies show that primary deficits in ALS-FTD occur in attention and concentration, cognitive flexibility, word generation, problem solving and planning, abstract reasoning, visual and perceptual skills, fluency and memory (30).

Controversially, there are few studies that report the presence of sensory (31) and autonomic dysfunction (32) during the progression of the disease.

Unfortunately, the survival is an unpredictable question. The fatal event usually occurs 3-5 years after the onset of symptoms, mostly linked to respiratory problems. A more detailed presentation about the Respiratory insufficiency in ALS is described in the Chapter 5, section 5.1 where we addressed aspects of the respiratory failure management.

In the last years, main areas, such as respiratory care, management of swallowing and/or dysphagia problems and augmentative communication, stimulated a large interest. The constant improvement in the care service delivery associated with the use of modern alternatives health care solutions seems to contribute to increased survival. Nevertheless, monitoring the consequences of the disease process still requires an enormous ongoing effort from patients, their families, caregivers and health professionals.

The next sub-chapter briefly describes the current tools used to measuring the disease progression and its functional impact.

1.3 Measurements of the disease progression and the functional impact: advantages and limitations

The unpredictability of progression rate in ALS require repeated patient assessment to weight the impairment of motor and/or respiratory function, and their consequences on activities of everyday life. There are a variety of scales that can be used, and the choice of which one depends on the clinical objective. The most known are: Norris scale, Appel ALS rating and the ALS Functional Rating Scale (ALSFRS). Most commonly used in ALS clinical trials include the Appel ALS rating and the ALSFRS (33). These scales are strongly correlated with patient survival (34).

The total Appel score consists of five sub-scores: bulbar, respiratory, muscle strength and lower and upper extremity function. Each one is composed of individual tests. A group score of six points is assigned if there is no dysfunction and group scores of 30-36 points are assigned for maximal dysfunction. The total Appel ALS score is 30 for healthy subjects and 164 for those with maximum impairment (34). The rate of change in the Appel ALS Rating Scale is a significant predictor of survival for subjects with ALS (35).

Another tool used is the Norris Scale that includes 28 clinical tests and six subjective evaluations (chewing, sphincter function and feeding) composing the evaluation of deficits and disabilities. Its main negative aspect is the weight given to upper limbs and under-evaluation of respiratory function that might compromise the assess of the prognosis of patients (36). Appel scale and Norris scale have been abandoned over time, due to their complexity and time necessary for application (33).

Currently, ALSFRS-R is mostly used scale. It was originally known as Amyotrophic Lateral Sclerosis Functional Rating Scale (34) and covers four domains (gross motor tasks, fine motor tasks, bulbar functions, and respiratory functions). More recently it was revised to comply with the importance of respiratory function (35,37). The revised-ALSFRS (ALSFRS-R) rates the ability to perform activities of daily living from 0 (total inability) to 4 points (no limitation) and incorporates respiratory items (dyspnea, orthopnea, respiratory insufficiency) (38). Although the ALSFRS-R seem to have a better balance between the domains, currently researchers are calling attention for some limitations of its use.

There are several publications that describes the efforts that have been done to improve the measurement of progression disease and highlight the need to develop a staging system that match with the observed progressive loss of independence or function. Rutkove (2015) refers that some of the disadvantages of this scale is the lack of sensitivity to progression in a short period of time and the effect of patient mood/effort on the scoring (39). Simon et al (2014) mentioned that one of the limitations of ALSFRS-R is the statistical manipulation required to handle data after death, and the clinical heterogeneity that distorts the link between total score and disease severity (40).

The platform "Patients like Me" is a patient network and real-time research platform that connects patients who have the same disease and track and share their own experiences. It has developed an extension to ALSFRS-R, which was named the ALSFRS-EX. The main reason for this initiative was the observed "floor effect" when using ALSFRS-R. The proposal introduced three new items related to the ability to use fingers to manipulate devices, ability to show facial emotional expression and ability to get around inside the home. A validation is still necessary to assess the utility of the ALFRS-EX (41). Another aspect which have exposed limitation on the use of the ALSFRS-R is the lack of "no use "for the NIV for those patients in low and middle-income countries, with respiratory impairment but no using NIV due to socioeconomics or cultural reasons (42). Preliminaries results from a pilot study done are included in this work also, and it was presented in the 28th ALS international symposium in Boston, USA (2017).

Despite these drawbacks, ALSFRS-R is the easiest and widely applied tool for research and routine clinical evaluation, able to measure the functional status in a single score.

The next chapter address the importance of using cardiopulmonary exercise testing for exercise prescription. As ALS is a type of disease that affects the respiratory function over the time, we must specify carefully the workload that ALS patients should exercising without compromising potentials neuroprotector and cardiorespiratory benefits.

Chapter 2:

The use of Cardiopulmonary Exercise Testing for Exercise prescription

2. The use of Cardiopulmonary Exercise Testing for Exercise prescription

This Chapter summarizes some important aspects about the use of Cardiopulmonary exercise testing for exercise prescription and recommendation for physical activity. The physical activity has a very well-defined role as contributor for a healthy lifestyle and the current literature is loaded with thousands of studies that reinforce the benefits on the mental health, cognitive performance, social behavior as well as on the functioning of the integrated different systems of our body.

The dose-response relations detected in observational studies indicate that the more physical activity, the greater the health benefit. Results from experimental studies indicate that even modest amounts of physical activity can have health benefits in high-risk youngsters (e.g., obese). To achieve substantive health benefits, the physical activity should be of at least a moderate intensity (43). But physical activity and exercise are terms that describe different concepts. Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities. However, Caspersen in 1985, defined exercise as *a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness.* Both terms often are confused with one another, and sometimes used interchangeably (44).

The neuroprotective effect from exercise has been supported by studies related to Angiogenesis and Neurogenesis. Both issues present a strong link to neurodegeneration process. Recent evidences suggest that physical activity may be a reasonable and beneficial method to improve functional recovery from both peripheral and central nerve injuries and to delay functional decay in neurodegenerative diseases (45). However, exercising impose risks that increase its intensity, age, and in the presence of cardiorespiratory diseases or other diseases (46).

In persons with neuromuscular disease that directly involves the cardiac and respiratory systems, deficits in performance may be primarily due to these limitations, along with loss of functional muscle tissue from the disease process. In the more slowly progressive

disorders, deconditioning may play an important role in limiting aerobic exercise performance (47).

The category of moderate-intensity exercise refers to exercising at sub-maximal workloads, during which energy is supplied by the aerobic energy system. Exercising within this zone results in a host of physiological responses to the increased metabolic demand for oxygen by the skeletal muscle, skin, and brain. Prolonged training at moderate aerobic intensities results in physiological adaptations, including increased blood volume, capillary density, mitochondrial size and density, improved fat mobilization, and thermoregulation. Collectively these adaptations represent improved cardio-respiratory fitness. This fitness can be quantified by measuring the maximum rate at which an individual can take up and utilize oxygen, known as the "$\dot{V}O_2$ max" (43,48).

A position statement published by Norton and colleagues (2010) (49) proposed the use of five categories (see table 1) to reflect groups of activities with similar relative physiological stress [within category] on the exercising individual.

Table 1. categories of exercise intensity with subjective and objective measures from Norton and Colleagues

Intensity category	Objective measures	Subjective measures	Descriptive measures
SEDENTARY	< 1.6 METs < 40% HR_{max} < 20% HRR < 20% VO_{2max}	RPE (C): < 8 RPE (C-R): < 1	• activities that usually involve sitting or lying and that have little additional movement and a low energy requirement
LIGHT	1.6 < 3 METs 40 < 55% HR_{max} 20 < 40% HRR 20 < 40% VO_{2max}	RPE (C): 8-10 RPE (C-R): 1-2	• an aerobic activity that does not cause a noticeable change in breathing rate • an intensity that can be sustained for at least 60 minutes
MODERATE	3 < 6 METs 55 < 70% HR_{max} 40 < 60% HRR 40 < 60% VO_{2max}	RPE (C): 11-13 RPE (C-R): 3-4	• an aerobic activity that is able to be conducted whilst maintaining a conversation uninterupted • an intensity that may last between 30 and 60 minutes
VIGOROUS	6 < 9 METs 70 < 90% HR_{max} 60 < 85% HRR 60 < 85% VO_{2max}	RPE (C): 14-16 RPE (C-R): 5-6	• an aerobic activity in which a conversation generally cannot be maintained uninterupted • an intensity that may last up to about 30 minutes
HIGH	≥ 9 METs ≥ 90% HR_{max} ≥ 85% HRR ≥ 85% VO_{2max}	RPE (C): ≥ 17 RPE (C-R): ≥ 7	• an intensity that generally cannot be sustained for longer than about 10 minutes

Categories of exercise intensity and the subjective and objective measures [both absolute and relative] accompanying each category. The relative intensity measures such as % HR_{max}, % HRR [Heart Rate Reserve = HR_{max} − resting HR] and % VO_2max [maximal oxygen uptake] will not always correspond to the same RPE (Rating Perceived Exertion) among individuals nor will the ability of clients to exercise for a specific duration at each intensity since this varies depending on training status and other personal characteristics. Subjective measures are from Borg's RPE scales where C= category scale [6–20] and C-R = category-ratio scale [0–10] [49].

Physical exercise requires the interaction of physiological control mechanisms to enable the cardiovascular and ventilatory systems to couple their behaviors to support their common function—that of meeting the increased respiratory demands (O_2 consumption [O_2] and CO_2 production [CO_2]) of the contracting muscles. Thus, both systems are stressed during exercise to meet the increased need for O_2 by the contracting muscles and the removal of metabolic CO_2. Therefore, by studying external respiration in response to exercise, it is possible to address the functional competence or "health" of the organ systems coupling external to cellular respiration (50).

To identify a safe and individualized level to prescribe an exercise program for patients or suggest a physical activity for healthy individuals, we may use a non-invasive measurement of the cardiovascular and respiratory system called Cardio Pulmonary exercise testing (CPET). It is a provocative test that combines standard methods of electrocardiogram (ECG) stress testing with indices of gas exchange, which allows the investigator to distinguish

between a normal and an abnormal response characteristic of disease, grading the adequacy of the coupling mechanisms, and assess the effect of therapy on a diseased organ system (50). The exercise tolerance is determined by three factors: pulmonary gas exchange; cardiovascular performance, including the peripheral vascular tree; and skeletal muscle metabolism (51). It can be quantified clinically by measurement of oxygen uptake (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE). These parameters are measured during exercise with rapidly responding gas analyzers capable of breath-by-breath determination of O_2 and CO_2 concentrations (52). The table 2 presents the most used variables to be integrated as part of a CPET assessment.

Table 2. Key Ventilatory variables to be integrated as part of a CPET assessment

$\dot{V}O_2$peak – Oxygen utilization ($mLO_2.Kg^{-1}.min^{-1}$): A measure of aerobic capacity.
VT: $\dot{V}O_2$ at the ventilatory threshold (mLO2.Kg-1.min-1): a measure of submaximal exercise tolerance.
RER: Respiratory Exchange Ratio: the ratio of exhaled CO_2 to inhaled O_2. Provide a means to quantify subject effort during the CPET. An RER ≥ 1.00 indicates good effort and RER ≥ 1.10 indicates excellent effort.
$\dot{V}O_2$/w (mL/min/w): Characterizes the ability of exercising muscle to extract oxygen. A low $\dot{V}O_2$/w relationship suggest cardiac or pulmonary impairment.
O_2 pulse (mL O_2/heart beat): approximates stroke volume.
$PetCo_2$: End-tidal CO_2 or the level of CO_2 in the air exhaled from the body (measured in mmHg). Reduced values indicate VQ mismatching and is consistent with worsening cardiac or pulmonary disease severity, and worse prognosis.
VE (L O_2/min): Minute Ventilation (based on tidal volume and respiratory rate) during the exercise. Peak VE can help to determine if the exercise tolerance or dyspnea relate to a pulmonary limitation.
VE/MVV: Assessment of the maximum minute ventilation during exercise relative to maximum voluntary ventilation which is determined during the Pulmonary Function Tests at rest. The VE/MVV ratio is normally ≤ 80% (and consistent with the premise that the pulmonary system is not limiting the exercise capacity); a ratio > 80% suggests pulmonary limitation.
VE/VCO_2 slope: Measurement of ventilatory efficiency (i.e. minute ventilation relative to CO2 exhalation). Whereas VE/VCO_2 slope is normally < 30, efficiency decreases with Heart Failure, intrinsic lung disease, and/or pulmonary hypertension.
Exercise oscillatory ventilation: Oscillation ventilatory pattern that indicates poor prognosis in patients with heart failure
Pulse Oximetry (% O_2 Saturation): Decline in hemoglobin excess oxygenation levels < 90% indicative of diminished ability to adequately increase alveolar-pulmonary capillary oxygen transfer during exercise.

Table 2. Adapted from reference (53)

The choice of parameters to be considered will depend on the indication to cardiopulmonary exercise testing in the individual subject or patient, namely, exercise tolerance assessment, prognostic stratification, training prescription, treatment efficacy evaluation, diagnosis of causes of unexplained exercise tolerance reduction, or exercise (patho)physiology evaluation for research purposes (54).

It follows a brief description about some of the most often parameters assessed in the CPET:

Oxygen Uptake ($\dot{V}O_2$):

It is the volume of O_2 extracted from the air inhaled during pulmonary ventilation in a period. It is usually expressed in $mL.min^{-1}$ or $L.min^{-1}$(Standard Temperature and Pressure Dry - STPD). Factors that can influence O_2 availability are oxygen-carrying capacity of the blood (available hemoglobin, arterial O_2 saturation, and dissociation curve shifts with temperature, CO_2, and pH), cardiac function (Heart Rate, stroke volume), redistribution of peripheral blood flow, and extraction by the tissues (capillarity density, mitochondrial density and function, adequacy of perfusion, and tissue diffusion) (55).

$\dot{V}O_2$peak and $\dot{V}O_2$max:

$\dot{V}O_2$max (Maximal oxygen uptake) was defined by Hill and Lupton in 1923 as the oxygen uptake attained during maximal exercise intensity that could not be increased despite further intensifications in exercise workload, thereby defining the limits of the cardiorespiratory system (56). In the practice, maximum VO_2 ($\dot{V}O_2$max) is defined as the highest value reached, despite progressive increase of the load applied, with the development of a plateau in the VO_2 curve during an incremental exercise test.

When no plateau can be identified, the highest value obtained at the end of an exhausting exercise is characterized as peak $\dot{V}O_2$, which, in practice, is used as $\dot{V}O_2$max (see example in the figure 3). The response is influenced by a central mechanism (cardiovascular and/or pulmonary) and peripheral function (skeletal muscle). The normal values depend on several factors, such as: age, gender, weight, height, physical activity level, genetic variability and ethnicity (57).

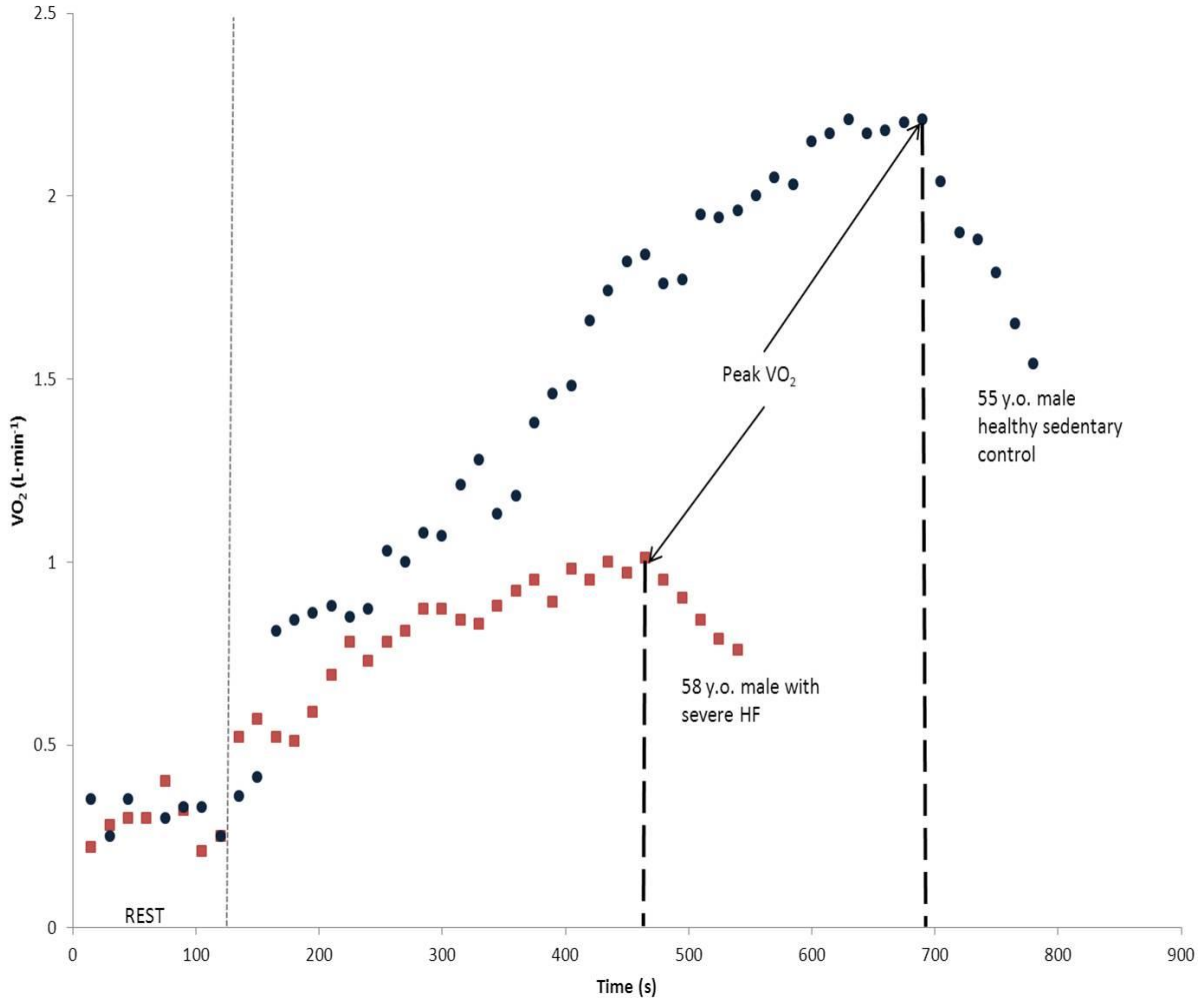


Figure 3. Example of a graph to identifying the VO_2 peak (58). Note: HF – Heart Failure

Carbon Dioxide Production ($\dot{V}CO_2$):

Refers to the amount of carbon dioxide exhaled from the body per unit time. It is expressed in ml/min and its value increases with progressive exercise. It continues to rise after the completion of exercise as the muscles continue to eliminate carbon dioxide before returning to baseline levels after several minutes. $\dot{V}CO_2$ during exercise is determined by similar factors to those that govern O_2 uptake: cardiac output, CO_2-carrying capacity of the blood, and tissue exchange (55).

Anaerobic Threshold (AT):

The ATS/ACCP statement (55) presents different nomenclature for the anaerobic threshold, such as: the lactate threshold, lactic acid threshold, gas exchange threshold, or ventilatory

threshold. The Anaerobic threshold – one of the most used term - is considered an estimator of the onset of metabolic acidosis caused predominantly by the increase rate of rise of arterial [lactate] during the exercise.

Alternatively, the term lactic acid threshold and Ventilatory threshold are used also, but the former should be applied only when Lactate is directly measured from blood samples. The latter one implies that a ventilatory response has occurred and that is due to metabolic acidosis, although the two may not be causally related (55). The AT is associated to changes in gas exchange in the lungs through the exercise.

During the initial (aerobic) phase of CPET, which lasts until 50–60% of $\dot{V}O_2$max is reached, expired ventilation (VE) increases linearly with $\dot{V}O_2$ and reflects aerobically the produced CO_2 in the muscles. Blood lactate levels do not change substantially during this phase, since muscle lactic acid production is minimal (51). The anaerobic threshold appears at about two-thirds of the way through a good maximal effort (See figure 4). In response to the progressive metabolic acidosis that develops during a normal maximal effort, we observe a compensatory increase in minute ventilation. Identifying whether this threshold is present is a critical part of test interpretation.

There are several ventilatory parameters which have been utilized in assessing ventilatory threshold, among which are oxygen consumption (VO_2), pulmonary ventilation (VE) respiratory exchange ratio (RER), excretion of CO_2 (VCO_2), and the ratio of ventilation to oxygen consumption (VE / VO_2). Due its easy application, one of most used method to identify the Ventilatory Anaerobic threshold is the V slope method (see figure 4).

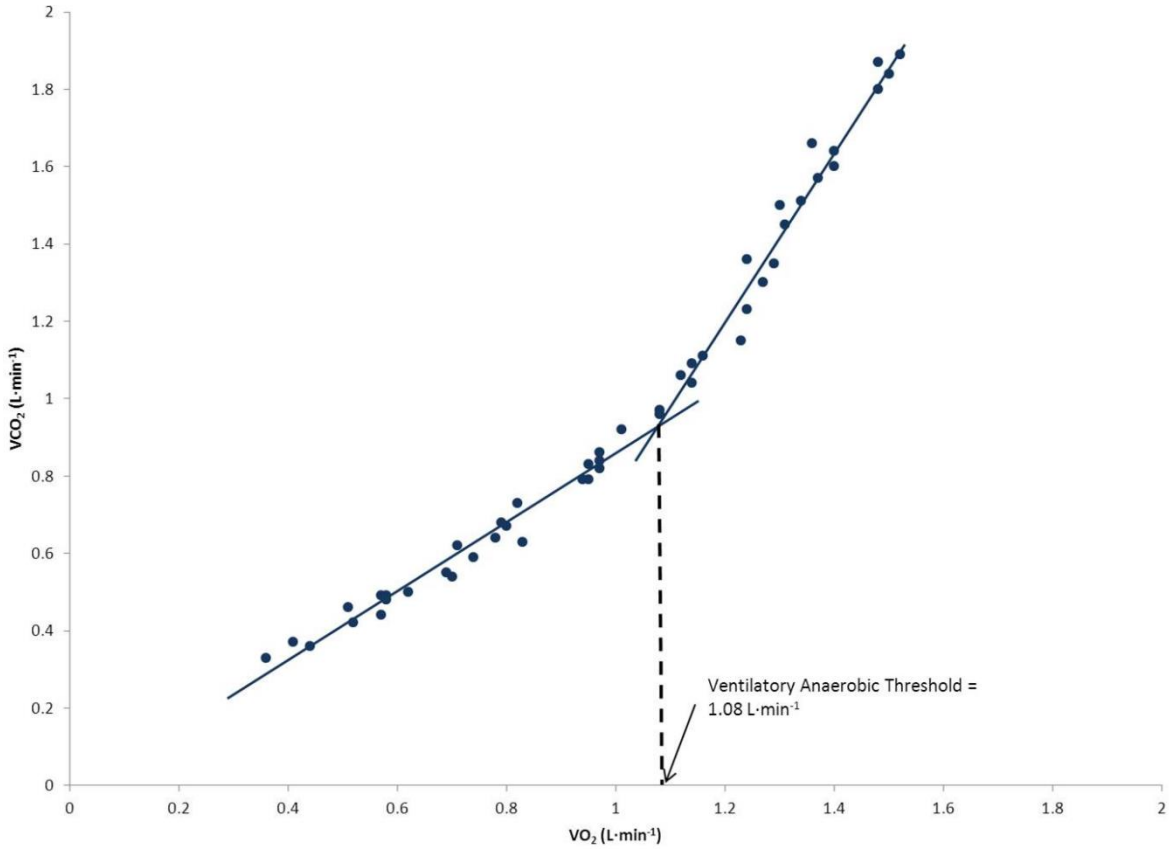


Figure 4. Identifying the Ventilatory Anaerobic Threshold (58). The anaerobic threshold is the point at which the slope of the relative rate of increase in VCO_2 relative to VO_2 changes.

Respiratory Exchange Ratio (RER):

Refers to the ratio of carbon dioxide production to oxygen consumption (VCO_2/VO_2). Under steady state conditions, the RER equals to respiratory quotient (RQ), whose value is determined by the fuels used for metabolic process. An RQ of 1.0 indicates metabolism of primarily carbohydrates, whereas an RQ of less than 1.0 indicates a mixture of carbohydrates with fat (RQ about 0.7) or protein (RQ about 0.8). At rest in normal individuals, the RER value will be around 0.8.

The term ”RQ” is often reserved for expressing events at the tissue level, which is difficult to measure and is not determined during the clinical exercise testing. The term ”RER” is usually measured by gas exchange at the mouth (55).

Ventilatory Efficiency (VE/ VCO_2):

Ventilatory efficiency describe the efficiency of pulmonary clearance of CO_2 during the exercise and reflects the match of the pulmonary ventilation to perfusion. The normal response of the VE/ VCO_2 slope or submaximal ratio expressions are both typically < 30. In the clinical practice, the VE/ VCO_2 is used as an index of disease severity in certain chronic populations (59). Figure 5 shows an example of assessment of VE/ VCO_2.

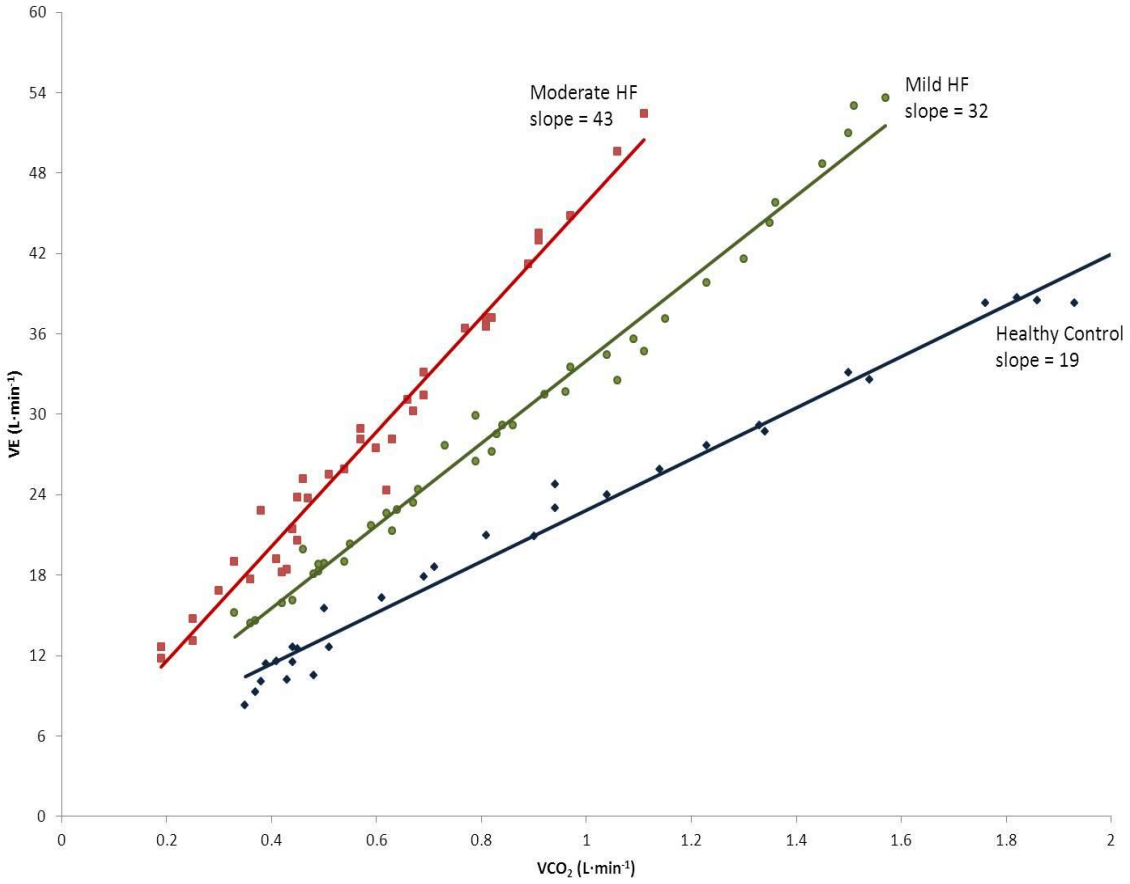


Figure 5. Assessment of VE/VCO2 slope in healthy control (athlete) compared to patients with mild and moderate Heart Failure (HF) (58)

Exercise Oscillatory Ventilation:

Exercise oscillatory ventilation (also sometimes referred to as exercise oscillatory breathing) is the exercise equivalent of Cheyne-Stokes respirations, in which there are significant oscillations in ventilation that persist through greater than 60% of the exercise test (Figure 6).

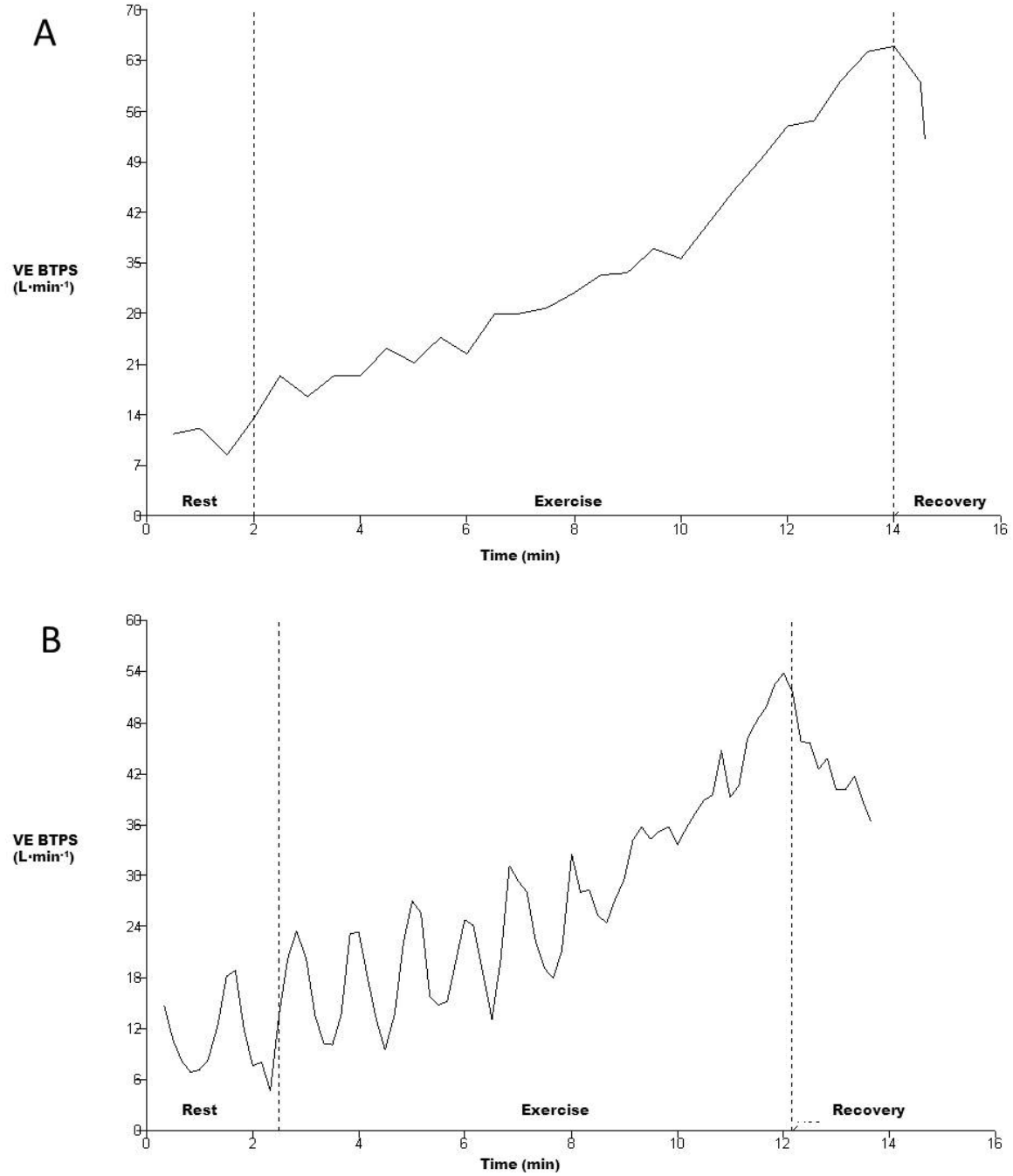


Figure 6. Assessment of Exercise Oscillatory Ventilation. A) Normal, linear, ventilatory response. B) Exercise oscillatory ventilation (58). Legend: BTPS, Body Temperature and Pressure Saturated.

Most CPET protocols generally fall into two broad categories: incremental tests up to maximal exercise; constant work rate test. The former is based on the progressive increase of the exercise intensity in a short time duration and can be performed on a cycle or a

treadmill. They are often used to quantify the changes in exercise tolerance after an intervention. The latter is based on externally imposed and constant cycling or walking cadence that the patient must maintain until exhaustion.

The primary endpoint of these protocols is thus the endurance time (or the distance which is a product of the speed and time). These tests are usually performed at a high fraction of peak exercise capacity typically representing 75–85% of peak cycling work rate or 80% of the estimated peak VO_2 during the incremental shuttle walking test. An implication (and a disadvantage of this) is that the constant work rate protocols have to be performed with the knowledge of the peak cycling or walking capacity (60). These approaches provide different information and have different clinical indications.

In the next chapters 3 and 4, we present our main contributions for this Thesis – the role of aerobic exercise determined by CPET on the ALS progression, and a feasibility study of a home-exercise program telemonitoring for ALS patients.

Chapter 3:
The Exercise and the Disease Progression

3. The Exercise and the Disease Progression:

This chapter presents the first main contribution of this thesis through an original article published in a peer review journal.

3.1 The role of moderate aerobic exercise as determined by cardiopulmonary exercise testing (CPET) in ALS:

3.1 Introduction:

Exercise is widely recommended to the general population due to its benefits to health and wellbeing. It improves the cardiovascular, respiratory, musculoskeletal, and endocrine functions and leads to psychological wellbeing. The role of exercise in the elderly, often with functional limitations and high risk of falls, is not yet completely clarified (61). In Amyotrophic Lateral Sclerosis (ALS), robust evidence about its risks and benefits is not established, and its putative neuroprotective role is still controversial (62,63).

Disease-specific guidelines are general exercise recommendations, which are part of standard of care for ALS, with instructions for stretching, range of motion exercises, balance, and physical activity, are based on preclinical data, small clinical studies, and research on exercise in other neuromuscular diseases. Recent and increasing evidence in animal models and clinical studies reinforces the concept of potential benefit of an exercise program, suggesting that moderated endurance exercise can delay disease onset and increase survival (61-66).

Aerobic exercise comprises a myriad of forms, and it is generally performed at a moderate level of intensity for longer duration than its counterpart: the anaerobic or strengthening exercise. The former refers to the use of oxygen to adequately meet energy demands during exercise via aerobic metabolism, which is critically related to the cardiorespiratory and vascular system's capacity to supply oxygen to the muscles, and the ability to clear carbon dioxide from the blood via the lungs (64). When the intensity of the exercise

exceeds the rate of oxygen supply to the muscles by the cardiovascular and respiratory systems, lactate builds up and quickly makes it impossible to continue the exercise.

The starting point of the exponential increase of lactate during a cardiopulmonary exercise testing (CPET) is the anaerobic threshold (AT). In ALS, AT may occur sooner than expected due to respiratory muscle weakness. However, no useful clinical symptom or sign is known as a marker of the AT and it can only be determined by direct measures of gas exchanges analysis through a cardiopulmonary exercise testing (CPET). On the other hand, the gap between AT and the respiratory compensation point (RCP), point of exercise intensity above which only anaerobiosis occurs, the training zone, may become narrowed or difficult to determine. In these circumstances, a safe limit is usually accepted by adding 10 to 20% of the work intensity at AT that must be uncovered. To overcome the difficulties and help the clinician to define the limits of the training zone and thus prescribe a moderate exercise program, the measurement of the aerobic capacity (VO_2) at anaerobic threshold (VO_{2AT}), at the Respiratory Compensation Point (RCP) or at peak of effort (VO_{2pk}), can be done using CPET with gas exchange analysis. The training zone can also be set from the lowest nadir of the curve VE/VO_2 to the lowest nadir of the curve VE/VCO_2 (65).

In addition, overtraining precautions are needed to avoid cramps, fasciculation, myalgia, prolonged post exercise fatigue, or soreness that are usually related to excessive neuronal hyperactivity and are clinical useful indicators of overwork. Post exercise fatigue should not interfere with daily life activities. If a patient has fatigue or pain that lasts longer than 30 minutes after exercise, the program needs to be reduced and modified (66,67). Moreover, as the etiology of nerve cell death in ALS is complex and multifactorial, with excitotoxic mechanisms playing a role together with reduced oxidative metabolism (68), it is relevant to evaluate the effects of the exercise on the functional status in ALS patients.

3.2 Objectives:

This work aimed to assess the effects of a 6-months moderate aerobic exercise program with intensity determined by the limits found during the CPET, as compared to standard care. The primary outcome was the functional status of ALS patients. Additionally, we evaluated the performance of CPET variables throughout the study.

3.3. Methods

Study Design:

We carried out a prospective, single blinded, quasi-randomized controlled trial (69), including 48 consecutive ALS patients referred to the Rehabilitation Department of Centro Hospitalar Lisboa Norte by neurologists who were blinded to the study. In our study, patients were allocated to two groups, based on geographical residence: Group 1 (G1, n = 24) included ALS patients with residence within the hospital outskirts; Group 2 (G2, n = 24) included patients with residence outside the limits of the hospital area. All patients in both groups were ambulatory and able to perform CPET before the admission (T1), but only 6 patients in G2 performed it mainly due to personal constraints. Table 15 describes the inclusion and exclusion criteria of the trial.

Table 3. Inclusion/Exclusion criteria

Inclusion Criteria
Age between 18-90 years
Diagnosis of definite, probable, or probable-laboratory supported ALS
Disease duration from first symptoms between 6-24 months
ALSFRS-R ≥ 30
FVC (%predicted) ≥ 70%
Exclusion criteria
Other diseases, like cardiac insufficiency and lung disorders, and physical limitation to exercise training
Heavy smoking habits, with laboratorial evidence of significant bronchial constriction
Signs of associated dementia or psychiatric disorders
Note: None of the patients were on tube feeding, invasive or non-invasive mechanical ventilation at admission (T1).

Exercise Training Protocol:

Patients in G1 and G2 performed a standard care exercise program, as determined by the American Academy of Neurology guidelines (4). It included daily exercises, such as Range of Motion (ROM) exercises, limbs relaxation, trunk balance, and gait training. While patients in G2 performed the program at home or at other rehabilitation units, G1 patients

were supervised in our Unit and, in addition to the standard care, they also performed an aerobic exercise protocol two times per week on a treadmill, with training zone determined by CPET.

The patient effort was set as of moderate intensity. When the training zone was not identified due to undetermined Respiratory Compensation Point (RCP), it was leveled-up 20% of the work rate at aerobic threshold achieved in the CPET. Noninvasive ventilation (NIV) was added as needed for both groups and adjustments to the aerobic exercise program were made in accordance with cardiorespiratory responses of each patient in G1 (23, 70-72). Body weight supporting system (BWSS) was used for patients with minimal lower limb weakness in G1. No BWSS was used during the training sessions in the G2.

Assessments:

All patients were assessed at first visit (diagnostic visit, T0), at study entry (T1), and 6 months after (T2) as follows.

Revised ALS Functional Rating Scale (ALSFRS-R).

All patients were evaluated with the revised ALS Functional Rating Scale (ALSFRS-R)each three months (38). This tool rates the functionality of the ALS patients in performing activities involving 4 different areas and sub scores, bulbar, upper limb, lower limb, and the respiratory function, each of its questions rated from 0 (total inability) to 4 points (no limitation). The last three questions address the respiratory function (dyspnea, orthopnea, and respiratory insufficiency) (38).

Respiratory Function Tests (RFT) and Nocturnal Pulse Oximetry (NPO).

Forced Vital Capacity (FVC) and NPO were performed as described elsewhere (73,74). The percentage of the predicted value of FVC was recorded for posterior analyses. RFT including maximal inspiratory and expiratory pressures, phrenic nerve conduction studies and oxygen saturation provided by NPO in terms of mean percentage of oxygen saturation (%SpO2), the percentage of recording time with oxygen saturation lower than 90% (Sat < 90%), and the number of oxygen desaturations per hour (ODI) were used to assess the need and appropriate time for nocturnal NIV adaptation in both groups (73).

Cardiopulmonary Exercise Testing (CPET).

Cardiopulmonary Exercise Testing (CPET) was performed at study entry (T1) and 6 months later (T2), using a treadmill (Woodway) coupled with a gas exchange analyzer (METALYZER 3B) with ergo-spirometry system using a breath-by-breath technology developed by CORTEX systems (see figure 7). Data were extracted and analyzed with application software Metasoft Studio.

The testing was customized and tailored to achieve symptom-limited exercise. A ramp modified protocol with increments of 5–15 Watts/minute, with a duration of 8 to 12 minutes, including 3-4 minutes for warmup and cooling down. Patients were continuously monitoring with pulsed oximetry and three ECG leads (50).

Figure 7. Patient performing CPET on the treadmill.

The peak effort and anaerobic threshold was attained in all included patients. We interrupted the test when the participants presented some of the following situations: reaching 75% of the predicted maximum heart rate (220-age), 55–65% of the predicted VO_2 maximum for age, gender, height and weight, and reaching fatigue evaluated by the Borg modified perceived scale or presented reduced neuromuscular performance. Other end-

testing flags were complaints of lower limbs' pain, dyspnea, presence of desaturation (SpO_2 ≤ 88%), or the achievement of Respiratory Compensation Point (RCP) (75).

The CPET variables analyzed were oxygen uptake expressed in L/min (VO_2), in percentage of predicted, or in metabolic equivalents (METs) at peak effort, anaerobic threshold (AT), and the respiratory compensation point (RCP) when achieved, Dioxide Carbon output in L/min (VCO_2), and minute ventilation in L/min (VE).

Data Analysis and Statistics.

Frequency distributions (median and interquartile) were calculated for age, disease duration, and categorical variables. Time measurements are expressed in months. The other continuous variables are presented with means ± standard deviation (m ± SD) and were expressed in absolutes values: time interval T0-T1, % FVC predicted, CPET variables (VO_2 peak, VO_2AT, MET's, and VE), ALSFRS-R score, its sub scores (bulbar, spinal, and respiratory), and respective slopes.

To assess the normality and variance, Kolmogorov Smirnov test was performed. Parametric tests were used to explore differences between groups and subgroups regarding total ALSFRS-R, its sub scores and slopes, % FVC, and CPET variables. Categorical variables (gender, region of onset, group, and use of NIV) were transformed from dummy to metric variables, to be submitted to stepwise multivariate linear regression analyses. We inputted the means for missing data points for both groups. Multiple regression model was applied to identify independent predictors of functional change at T2. All tests were 2-tailed, with significance set at 0.05 and power 0.7 (G∗. Power version 3.1.9.2). SPSS package software v. 22 was used.

Ethical Committee.

The present study was approved by the joint Ethics committee Centro Hospitalar Lisboa Norte - Faculdade de Medicina de Lisboa, based on the national legislation (Reg. Number 287/13 – 14 June 2013). All patients signed an informed consent.

3.4 Results:

We included 48 patients, 32 men. Disease duration from onset was similar between G1 (median = 9.50 months; IQR [25%–75%] 5.25–11.75) and G2 (median = 9.00 months; IQR [25%–75%] 5.25–12.00) (p = 0.7). The median age at study entry was 60.5 years for G1 (IQR [25%–75%] 54.25–76.25) and 63.0 years for G2 (IQR [25%–75%] 59.25–68.50) with nonsignificant difference (p = 0.4). Gender, region of onset, and ALSFRS-R and its sub scores were equivalent between groups. % FVC was significantly lower in G2 at entry (p=0.02). The study flow chart is shown in Figure 8. Clinical and demographic characteristics are summarized in Table 16. Twenty-four patients were randomized to G1, the active exercise group monitored in house and 24 to G2, the control group.

At *T*0 (diagnosis), G2 had a non-significantly higher percentage of older women with bulbar onset – 30% versus 12% in G1; ALSFRS-R total score and its sub scores were also similar between groups. At the start of study (*T*1) there was no difference between sub scores (Bulbar score: p = 0.14; Spinal score: p = 0.12; Respiratory score: p = 0.93). All patients were stable with oxygen saturation (SpO_2) ≥ 95%.

At end of study (*T*2), ALSFRS-R was significantly higher in G1 (p = 0.035). There was a nonsignificant trend for a reduced sub scores slopes in G1. To determine whether there was a difference on the decline of ALSFRS- R between groups, we calculated the slope of ALSFRS-R total between T0 and T1 (p = 0.19; CI 95% [−0.69–0.14]) and between T1 and T2 (p = 0.36; CI 95% [−0.86–0.32]), and the effect size (d) = −0.26 showed a small but positive effect favoring the exercise group G1 (see Figure 9).

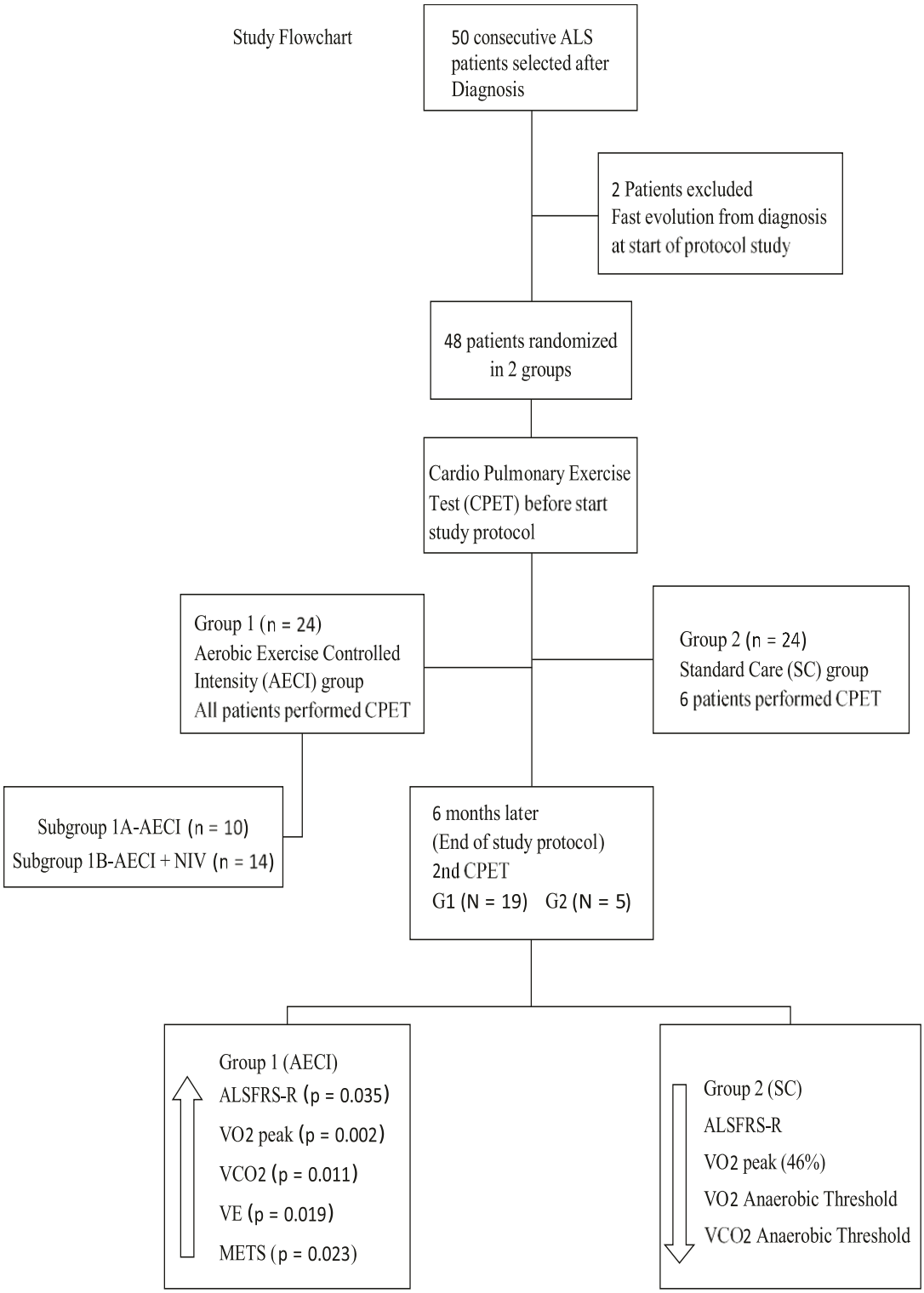


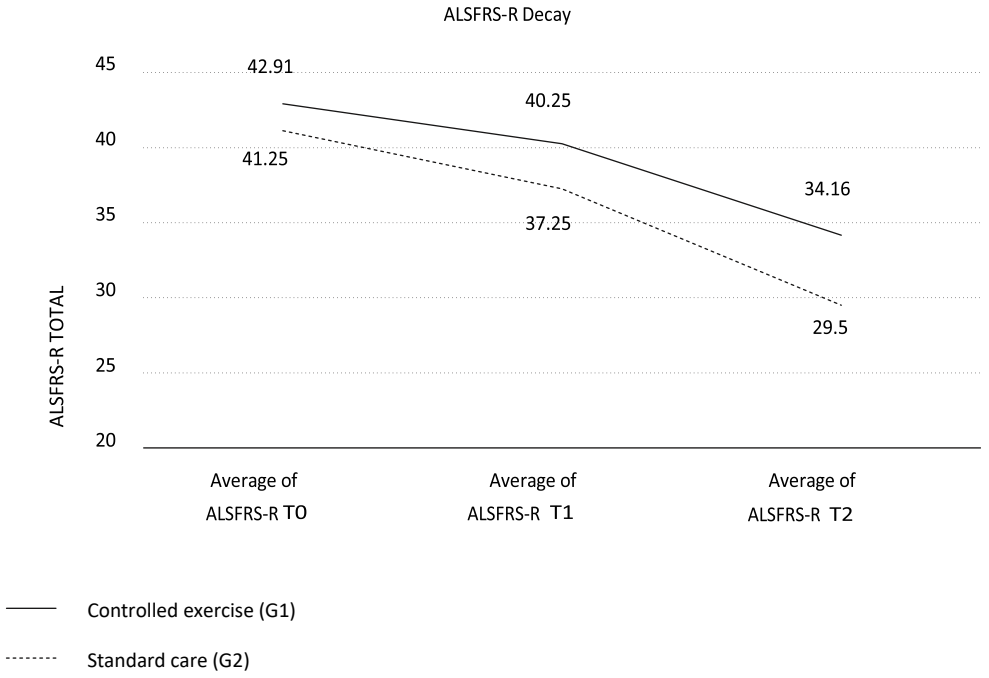
Figure 8. At the end of study, we can identify the main findings between groups. The arrows indicate the direction of the significant differences in G1 when compared with standard care group G2. The VO_2 peak in G2 reduced 46% since T1. AECI – Aerobic exercise with Controlled Intensity and NIV: Non-Invasive Ventilation.

Table 4. Clinical and demographic characteristics of the ALS patients at diagnosis (*T*0), admission to the study protocol (*T*1), and the end of study (*T*2). T-Test: mean and standard deviation values for both groups.

	Group 1 (n = 24)	Group 2 (n = 24)	p value
Male (%)	18 (75%)	14 (59%)	0.20
Spinal onset form (%)	21 (88%)	17 (70%)	0.12
Use of NIV *T*1-*T*2 (Yes – No)	14Y/10N	13Y/11N	0.75
Age at onset (years)	63.21 (±13.0)	62 (±12.06)	0.42
Time Interval (*T*0-*T*1) (months)	10.8 (±6.5)	10.79 (±7.7)	0.80
% FVC (*T*1)	99.64 (±21.8)	80.0 (±21.0)	**0.02**
ALSFRS-R total score (*T*0)	42.92 (±3.51)	41.13 (±4.83)	0.14
ALSFRS-R total score (*T*1)	40.25 (±5.00)	37.25 (±4.9)	0.042*
ALSFRS-R total score (*T*2)	34.1 (±7.1)	29.5 (±7.7)	**0.035**
ALSFRS-R Tot sc. slope (*T*1-*T*2)	1.01 (±0.92)	1.28 (±1.10)	0.36
ALSFRS-R bulbar slope (*T*1-*T*2)	0.15 (±0.24)	0.18 (±0.25)	0.62
ALSFRS-R spinal slope (*T*1-*T*2)	0.66 (±0.64)	0.75 (±0.97)	0.68
ALSFRS-R respiratory slope (*T*1-*T*2)	0.20 (±0.26)	0.30 (±0.32)	0.23

G1: controlled exercise Group, G2: standard care group, *T*0: at diagnosis; *T*1: at start of to study; *T*2: end of study; Sp: spinal onset, Bb: bulbar onset; use of NIV*T*1*T*2: use of noninvasive ventilation during period of study; % FVC predicted *T*1: % forced vital capacity predicted at start of study (*T*1); ALSFRS-T $_{\text{Total Diagnosis}}$: ALSFRS-R total at diagnosis moment; ALSFRS-$R_{total T2}$: ALSFRS-R total at end of study; slope ALSFRS-R $_{\text{Total } T1\text{-}T2}$: slope ALSFRS-R total between start and end of exercise protocol (*T*1-*T*2); significant results ($p \leq 0.05$) are represented in bold. **ALSFRS-R total score on T1 (Sub scores between G1 and G2 (NS): bulbar score: p = 0.14; spinal score: p = 0.12; Respiratory score: p = 0.93).*

Figure 9. Slope of ALSFRS-R total score between T0, T1, and T2 for both groups



Predictors of ALSFRS-R Total at End of Study: Multiple Linear Regressions Analyses.

We investigated the relationship between the functional score achieved at end of study and the following independent variables: age at study, gender, region of onset, use of NIV, group of intervention, and slopes of ALSFRS-R total. The stepwise multiple linear regression analysis adjusted to FVC at *T*1 showed that Bulbar Slope (B = −5.084; p = 0.12), Spinal Slope (B = −6.152; p < 0.001, and Group of intervention (B = 3.833; p = 0.021) were independent predictors. Together they explained 54.3% of the variance of the achieved ALSFRS-R score at end of study with adjusted $R^2 = 0.51$. The regression model was significant (p < 0.001), and analyses with Durbin Watson test showed that the data had no autocorrelation. We found an effect size $f^2 = 1.04$ favoring the intervention group.

Influence of Use of Non-invasive Ventilation on the ALSFRS-R at T2.

Subgroup 1A (n = 10) did exercise without NIV and Subgroup 1B (n = 14) used NIV during exercise sessions. G2 used NIV as needed. About 50% of patients in both groups used NIV (Table 16). However, a simple linear regression analysis did not confirm a significant influence of NIV on ALSFRS-R change at *T*2 (p = 0.7, $R^2 = 0.02$) (Figure 10).

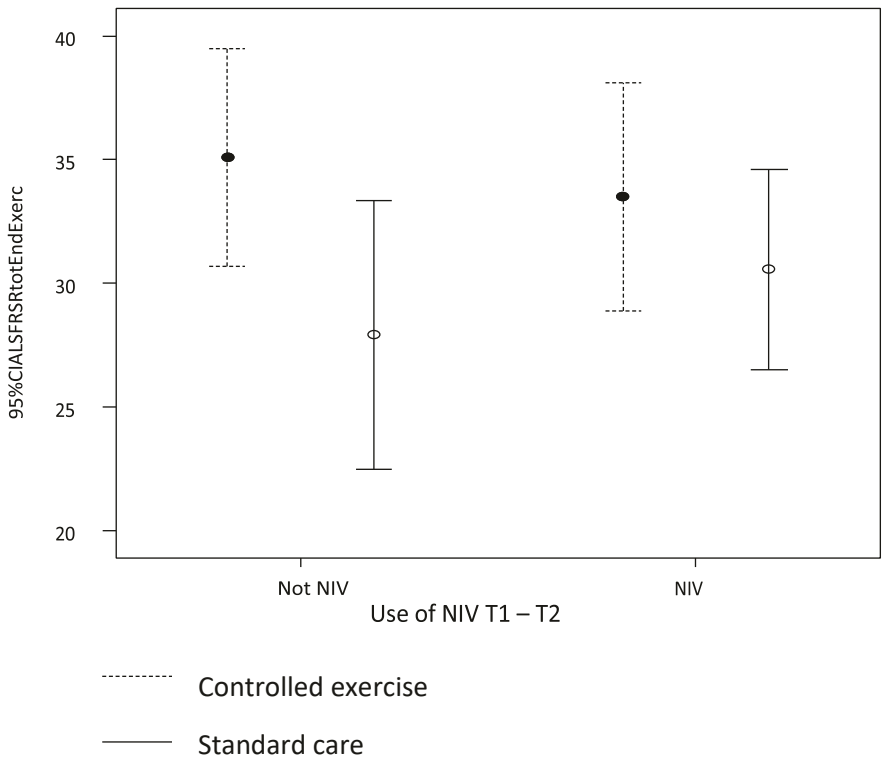


Figure 10. Influence of Use of NIV on ALSFRS-R at end of study, Confidence Interval 95% (−3.08–6.04; p= 0.7).

Performance of Cardiopulmonary Exercise Testing (CPET) Variables during the Study.

In G1 all patients completed the exercise program, but only 19 (79%) were gait-independent on at the second CPET evaluation. In G2, 6 patients performed a first CPET and only one patient of those did not perform the second CPET. Out of the remaining patients (18 patients), only six of them had had gait-independence at T2 (29%).

CPET Variables at Peak Effort.

We found no differences between groups regarding CPET variables (VO_2, VCO_2, VE, METs, and RCP) both at AT and peak effort at T1. The average peak VO_2 in % of predicted for G1 was 60.8% (±21.2) and G2 was 44.16% (±12.45) (p = 0.07). As all the patients presented to CPET in T1 and T2 indicated equal variances on the homogeneity test, which allowed us to assume the implications to the differences between groups with different sample sizes. At T2 there were significant differences between groups related

to VO_2peak (p = 0.002), METs (p = 0.023), VCO2 (p = 0.011), and VE (p = 0.019) (see Table 5). The confidence intervals with significant differences at end of study for VO_2 peak are presented in Figure 11.

Table 5. Cardiopulmonary exercise testing measurements on the peak of effort. T-test.

CPET variables (L/min)	Group 1 exercise (n = 24) Mean (±S. D)	Group 2 standard care (n = 6) Mean (±S. D)	P value (between groups G1-G2)
VO2Predicted	2.06 (±0.58)	1.87 (±0.54)	0.47
% VO2Predicted	60.8 (±21.2)	44.16 (±12.45)	0.07
VO2peak *T*1	1.17 (±0.50)	0.83 (±0.32)	0.13
VO2peak *T*2	1.05 (±0.36)	0.45 (±0.24)	**0.002***
METS *T*1	6.38 (±8.40)	3.74 (±1.10)	0.45
METS *T*2	4.93 (±1.97)	2.64 (±1.28)	**0.023***
RCP *T*1	0.88 (±0.15)	0.83 (±0.08)	0.45
RCP *T*2	0.86 (±0.13)	1.22 (±0.90)	0.42
VCO2 *T*1	1.01 (±0.41)	0.69 (±0.27)	0.086
VCO2 *T*2	0.95 (±0.40)	0.42 (±0.19)	**0.011***
VE *T*1	32.8 (±11.4)	24.06 (±7.3)	0.088
VE *T*2	31.4 (±11.27)	17.8 (±5.21)	**0.019***
HRmax1	87.8 (±27.08)	95.2 (±17.1)	0.5
HRmax2	96.06 (±20.8)	102.0 (±14.8)	0.49

*T*1: start of study, *T*2: end of study. VO_2 predicted *T*1, VO_2 predicted at start of study; % VO_2 predicted *T*1, % VO_2 predicted at start of study; VO_2 peak (oxygen uptake at peak effort peak), VCO_2 (carbon dioxide output), METS (metabolic equivalent), RCP (respiratory compensation point), VE (minute ventilation) expressed in L/min, and HR max (heart rate maximum) expressed in beats/minute. *__Significant results ($p \leq 0.05$) are represented in bold.__

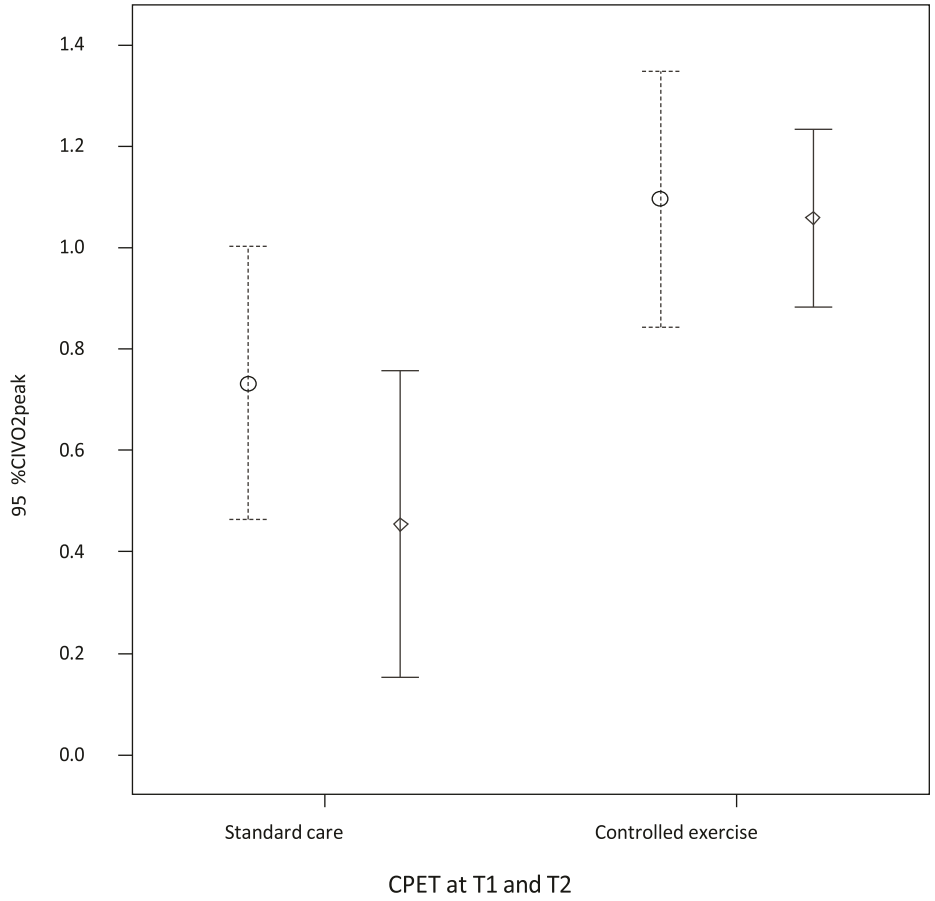


Figure 11: VO_2 Peak at T1 (p = 0.13, [CI: −0.78–0.11]) and at T2 (p = 0.002, [CI: −0.96–−0.25]).

CPET Variables at Anaerobic Threshold.

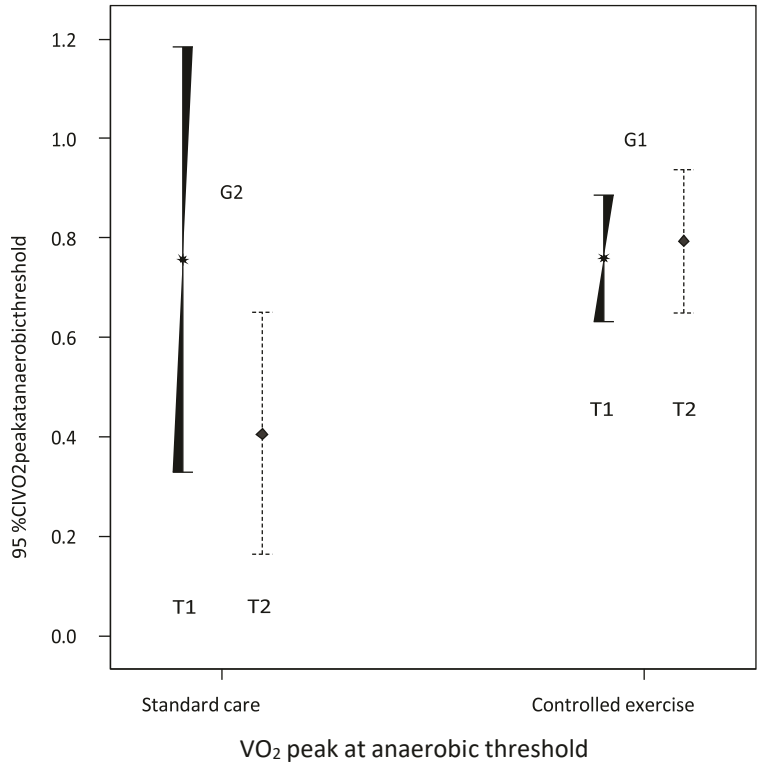
Regarding the work capacity in the anaerobic threshold, there were no significant differences at entry, but significant differences ($p < 0.05$) at *T*2 for VO_2 and VCO_2. These variables were significantly higher in G1 than in G2 (Table 6). The confidence interval with significant differences at end of study for VO_2AT is presented in Figure 12.

Table 6. Cardiopulmonary exercise testing measurements at the anaerobic threshold (AT). T-test.

CPET variables (L/min)	Group 1 (n = 24) (mean ± sd)	Group 2 (n = 6) (mean ± sd)	p value t-test (G1-G2)
VO_2AT *T*1	0.80 (0.25)	0.83 (±0.28)	0.8
VO_2AT *T*2	0.79 (±0.29)	0.40 (±0.15)	**0.02***
METS *T*1	3.62 (±1.7)	3.77 (±0.95)	0.8
METS *T*2	3.54 (±1.38)	2.15 (±0.97)	0.07
VCO_2 *T*1	0.70 (±0.27)	0.71 (±0.29)	0.9
VCO_2 *T*2	0.68 (±0.35)	0.30 (±0.14)	**0.03***
VE *T*1	22.6 (±6.40)	23.3 (±8.17)	0.8
VE *T*2	25.2 (±12.2)	14.62 (±2.85)	0.10

*T*1: admission, *T*2: end of study. VO_2 AT (oxygen uptake peak at anaerobic threshold), VCO2 (carbon dioxide output), METs (metabolic equivalent), and VE (minute ventilation) are expressed in L/min.
*__*Significant results* (p ≤ 0.05) *are represented in bold*__.

Figure 12.VO_2 at the Anaerobic Threshold, T1 (p = 0.8, [CI 95%: −0.23–0.29]) and T2 (p = 0.02, [CI 95%: −0.70–−0.06]).



Aerobic Capacity and ALSFRS-R at End of Study.

While patients in the G1 presented a stable condition regarding aerobic capacity, anaerobic threshold, and ventilatory capacity, the patients in the G2 showed significant decrease for the same aspects between $T1$ and $T2$ (Tables 5 and 6). Peak VO_2 decreased 10.25% in G1 and 46% in G2. There were significant differences on the oxygen uptake, CO_2 output, and ventilatory capacity with a very high effect size (d = 1.99) analyzed by Cohen's d on peak VO_2 between groups. In addition, we found a significant and positive correlation between ALSFRS-R total score at end of study and peak VO_2, METS, VCO_2, and VE (see Table 7) but no correlation of ALSFRS-R at T1 with the same variables.

Table 7. Correlations between ALSFRS-R total score and CPET variables on the peak of effort at *T2*.

CPET variables (L/min)	ALSFRS- R total score Pearson correlation (R)	*P*-value Sig. (2-tailed)
METS	**0.491**	**0.017***
RCP	0.256	0.239
VCO_2	**0.580**	**0.004***
VE	**0.585**	**0.003***
VO_2Peak	**0.544**	**0.007***

ALSFRS-R (ALS functional scale revised), METs (metabolic equivalent), VCO_2 (carbon dioxide output), RCP (respiratory compensation point), VO_2 peak (oxygen uptake peak), and VE (minute ventilation) expressed in L/min. ***Significant results* (*p* ≤ 0.05) *are represented in bold.***

3.5 Discussion:

Nowadays, there is no strong evidence showing a potential harmful effect of exercise in ALS. The unpredictable progression of the disease, the different phenotypes, the frequent methodological shortcomings, and ethical issues affect most of the studies.

A weak muscle can be damaged if overworked, which can easily happen in ALS as it is already functioning close to its maximal limits (76). This is the reason why some experts have discouraged exercise programs in ALS. These all make daily activities harder to do (77). Moderate exercise may have a beneficial effect on free-radical balance and improve muscle fiber oxidative metabolism, with potential impact against excitotoxicity (78). The role to

protect against oxidative stress has special significance as in ALS the motor neurons are particularly susceptible to oxidative damage (79).

On top of this, if defective mitochondrial energy metabolism plays a role in cell death in neurodegenerative disorders and exercise may trigger added neuron excitability, we considered it of utmost relevancy to evaluate the effect of a moderate exercise program with work intensity close to the AT precisely determined by CPET.

To the best of our knowledge, only three studies have been published on aerobic exercise capacity in ALS, with exercise intensity established by determination of CPET (80-82). All of them showed a reduced peripheral O_2 utilization suggested to be consistent with physical deconditioning as the main cause of impaired exercise capacity in ALS, possibly related to impaired oxidative metabolism, early AT, and low peak oxygen uptake. The latter was not found in the other neuromuscular disorders. However, none of those studies evaluated the effect of a moderate exercise program on oxygen uptake around AT throughout disease progression.

Our study is relevant due to the probable implications regarding the potential benefit of the rigorous exercise intensity prescription determined in the CPET and the risk of unsupervised exercise above the anaerobic threshold (83). Indeed, there are no clinical determinants of AT such as the time limit to fatigue, work intensity to fatigue, or ventilatory responses; in addition, peak oxygen uptake (peak VO_2) cannot be used to estimate anaerobic capacity due to the large contribution of intraindividual variability (84) .

This is the first exercise trial applying a moderate exercise protocol with intensity rates precisely defined through gas exchanges measures. Despite the limitations of a small sample, even over the apparent heterogeneity at the beginning of the protocol, but not at diagnosis, we counter these differences by recognizing that patients in G2 had a larger percentage of older women with bulbar onset who were expected to have a poorer prognosis regarding bulbar slopes and scores in G2. And patients in G1 had a larger proportion of spinal onset, who were expected to present a more progressive rate of decline of ALSFRS-R spinal scores or slopes. However, neither of these assumptions was observed, most likely because of the effect of exercise program that the two groups were instructed to follow during this period, showing no differences in the spinal, bulbar, or

respiratory slopes at T2 (Table 4). Using a multiple linear regression model, we found the group of intervention as a significant independent predictor (B = 3.833; p = 0.021).

These observations taken together with the significant difference in ALSFRS-R spinal sub score favoring G1 patients at T2 ($f2$) = 1.04 and the mean difference of functional decline expressed on the ALSFRS-Total score between groups after 6 months, also showing a small but positive effect favoring the exercise group (d) = 0.26 (Figure 9), strengthen our interpretation of a positive effect of exercise in this study.

Our results concur with the recent study by Lunetta and colleagues (85) that also showed that a strictly monitored moderate exercise program may significantly reduce motor deterioration in ALS patients. Interestingly they were not able to improve survival, an essential point to demonstrate a neuroprotection effect, and the authors were not clear regarding the definition of moderate exercise.

Actually, the possibility of a muscle fiber to increase its size and becoming stronger while maintaining endurance capacity depends primarily on a set of different factors, such as the application of appropriate stimuli (i.e., sustained contractile activity combined with short, powerful mechanical loading), availability of the essential substrates, the capacity to increase oxygen transport (e.g., by improving heart and lung function or angiogenesis, hematocrit and myoglobin), and prevention of tissue hypoxia with chronically reduced cellular energy status.

Moreover, the cellular oxygen supply can be improved by increasing the capillarization, the hematocrit, or myoglobin concentration (86), in which the regulation involves the hypoxia inducible factor-1 (HIF-1α). The HIF-1α mediates the expression of erythropoietin and angiogenic growth factors, such as vascular endothelial growth factor (VEGF), known to be implicated in ALS pathogenesis (87). VEGF can be increased in serum concentrations in ALS patients both by moderate exercise and noninvasive ventilation as previously shown by our team (88,89). Thus, we took it into consideration and applied a moderate exercise program and NIV as needed in order to enhance a hypothetical neuroprotective effect, such as suggested by Dal Bello-Haas and Florence, 2013 (7).

Unexpectedly, NIV did not exert any influence on ALSFRS-R at T2 (p = 0.46, R^2 = 0.02) (Figure 10). Given the well-known effects of NIV on survival, quality of life, exercise tolerance, and

sleep quality, the most likely explanation is related not only to the very similar approach of initiation of NIV in both groups but also to the short timeframe of observation.

No doubt these factors will also have to be considered in further studies, when addressing the major issue of neuroprotection and survival benefit. However, whether these results corresponded just to an expected initial distal plasticity as shown by Blizzard and colleagues, 2015 (90), or a positive effect on neuroprotection, as suggested in a previous study of our team (89), remains to be explained and will be the focus of a future longitudinal study that due to the extensive and expensive nature of the needed evaluations will justify a multicenter trial.

Regarding the performance of CPET variables during the study, the anaerobic threshold (AT), also called the ventilatory threshold (VT), is an index used to estimate exercise capacity. It constitutes a reliable and reproducible index of submaximal exercise intensity that is defined as the highest VO_2 that can be sustained without developing a lactic acidosis, a response that is generally observed at 40 to 60% of peak VO_2 independently of patient-motivation.

A key utility of AT is that it provides information at a submaximal level of exercise intensity (i.e., it does not require a physiologically maximal exercise effort) and is also considered more consistent with a patient's ability to perform daily activities, especially because exercising beyond the AT for sustained periods eventually results in fatigue.

In addition, we used the most common method that entails the graphing values of VCO_2 versus VO_2 to identify the AT as the point where there is a shift in slope along a line of identity between these gas measurements (modified V-slope method) (65). Mean values of oxygen uptake at AT expressed in % of achieved peak VO_2 at T1 was 69%, which allowed us to cast some doubts over the deconditioning clinical situation of our patients in both groups at entry in the study. At T2, patients in G2 showed significant differences with a very rapid decrease of VO_2(AT), though it happened in an even higher percentage (88%) of VO_2 peak probably due to a primarily neurogenic impairment. On the other hand, these results also show that deconditioning was not the main reason of poor performance, usually identified with low VO_2 and early AT, though it still is a common point of view.

Together with a respiratory compensation point (RCP) > 0.80 (see Table 5) in both evaluations and groups, it shows not only the existence of peripheral muscle underutilization of oxygen as described by other authors, but specifically a primarily impairment of muscle performance probably due to atrophy and loss of muscle bulk with a late increase in lactate and low VO_2, exactly the opposite results for a mitochondrial myopathy with an early increase in lactate, combined with a very low VO_2 peak, as shown by Takken and colleagues, 2010 (91). Likewise, we recognized a primarily neurogenic impairment instead of deconditioning.

Our study does not address the important issue of muscle oxygen extraction impairment, a dysfunction recently described in ALS (92). In future studies this evaluation should be added to investigate the impact of exercise in ALS.

Peak VO_2 is an important metric because it defines the limits of the cardiopulmonary system. Although commonly expressed in L/min, this value naturally increases as body mass increases. To better facilitate inter-subject comparisons, peak VO_2 is usually normalized and expressed in ml/Kg/min. However, the relationship of peak VO_2 and weight is not linear with inherent imprecision associated with weight normalized values; thus, we recorded VO_2 either in L/min or in percentage of predicted values or in METs.

Remarkably, our results showed a significant more stable course of peak VO_2 in patients of G1 suggesting that exercise prescribed and performed according to the CPET evaluation has a positive impact on functional decline. However, we cannot discard the effect of a supervised exercise program with expert physiotherapists also able to modify the work intensity according to individual physiologic responses at each session.

Moreover, it is not possible to exclude a bias effect due to a better respiratory function in G1 (%FVC), though its measurement is sometimes problematic in patients with bulbar weakness (88). Indeed, the lower FVC in G2 patients was likely due to an insufficient tight seal with pursed lips for accurate measurement. Nevertheless, we adjusted our results to the FVC by a stepwise multiple linear regression analysis and found an effect size $f2 = 1.04$ favoring the intervention group strengthening our principal conclusion. These findings support our hypothesis that aerobic exercise with control of intensity leveled by CPET can be safe and beneficial for ALS patients prolonging ambulatory skills.

Indeed, exercise, when prescribed and supervised appropriately, may be physically and psychologically important for people with ALS, especially in the earlier stages of the disease and before significant muscular atrophy occurs. Although it may not improve the strength of muscles already weakened by ALS, strengthening exercises with low to moderate weights and aerobic exercises such as swimming, walking, and bicycling, at submaximal levels may be important components of an overall management plan (7). An exercise prescription in a rehabilitation program for ALS patients should follow an assessment by CPET with aerobic capacity measurements and be performed under strict and competent supervision.

3.6 Conclusions:

Moderate exercise protocol with CPET evaluations can be safe and beneficial and should be considered in the multidisciplinary approach to ALS patients.

The next chapter address the second main contribution of this Thesis.

Based on the paper published:

- Anna Caroline Marques Braga, Anabela Pinto, Susana Pinto, and Mamede de Carvalho, “The Role of Moderate Aerobic Exercise as Determined by Cardiopulmonary Exercise Testing in ALS,” Neurology Research International, vol. 2018, Article ID 8218697, 10 pages, 2018. doi:10.1155/2018/8218697

Chapter 4:
Tele-monitoring of a home-based exercise program in ALS:
A feasibility study

4. Tele-monitoring of a home-based exercise program in ALS: A feasibility study

4.1 Introduction:

Amyotrophic Lateral Sclerosis (ALS) is associated with progressive functional limitation and impairment in accessing interdisciplinary care centers (93), causing dropouts in hospital-based rehabilitation programs. In addition, potential exercise benefit in ALS, still is a controversial issue. Recent evidence favors exercise in early stages (85) and highlights the need of further research, namely on aerobic exercise (7). Currently, exercise recommendation is mainly supported by exploratory clinical studies in ALS and results observed in other neuromuscular diseases as described in the previous chapter.

4.2 Objective:

We have been concerned on using cardiopulmonary exercise test (CPET) to quantify exercise intensity, to avoid overtraining in patients undergoing rehabilitation.

Considering the common problem of limited access to interdisciplinary care in ALS, we have conducted a feasibility study using a Tele-Monitoring System (TMS) to record physical effort, compliance and adverse events from patients performing home-based exercise program for 6 months follow up.

4.3 Methods:

We prospectively included 10 patients willing to participate (written informed consent) followed in our unit. We selected a homogenous ALS population respecting the following inclusion criteria: disease duration between 6-24 months; ALS revised-functional rating scale (ALSFRS-R) ≥30 and forced vital capacity (FVC) >70% of the predicted value. Smokers, as well as patients with significant bronchial constriction on spirometry, with other medical conditions or clinical signs of dementia, were excluded.

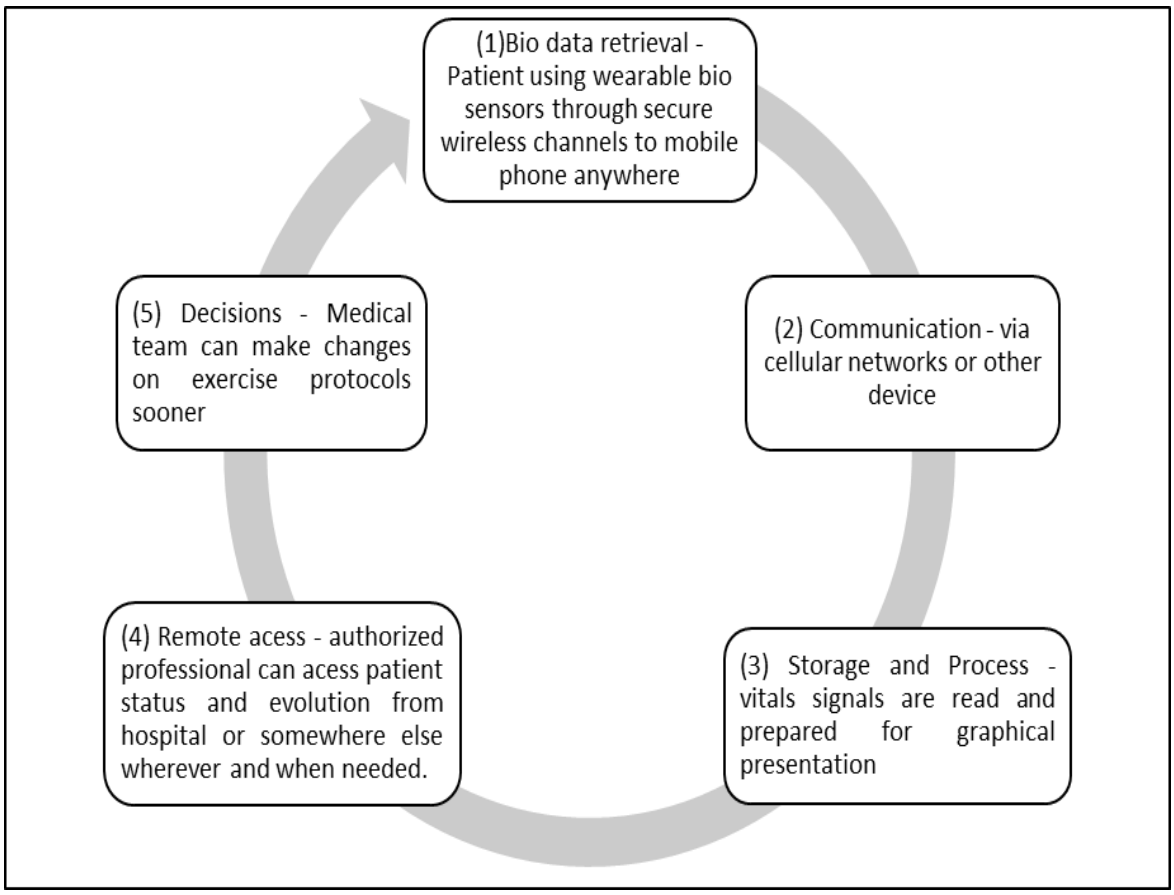
All patients were taking Riluzole©, but none was using tube-feeding or non-invasive ventilation (NIV) at entry. Patients underwent a symptom-limited treadmill-ramp protocol, with the training zone detected between the first and second ventilators thresholds (VT1 and VT2) by CPET using a gas exchanges analyzer (CORTEX 3B®). Peak oxygen uptake and carbon dioxide output were analyzed and metabolic equivalents (METs) were derived. Patients were committed to perform at least one exercise session/week using the Tele-monitoring system and advised to exercising above the VT1, not surpass 75% of the predicted maximum heart rate (HR) [220-age]) and to keep percutaneous oxygen saturation (SpO2) ≥ 93%.

Each session consisted of walking on a treadmill or walk outdoor (approximately 15 minutes with 5 minutes for warming up phase before and 5 minutes later for cooling up phase) for 6 months. Compliance was assessed by the number of exercise sessions completed by the patient as recorded in the Tele-monitoring system and a minimum of 24 session was defined as supporting protocol feasibility.

4.3.1 Remote Mobile Monitoring System

This digital platform allows regularly monitor the readings of a selected set of vital signals through non-intrusive wireless bio-sensors biosensor with a secure Bluetooth connection to a mobile phone, including Heart Rate and SpO_2 (finger oximeter). See figure 13. The vital signals can be defined by the healthcare team and requested for the monitoring provider previously. The data can be available within seconds after the readings. This allow us to verify the exercise performance remotely in a real time, and if the patient's effort is suitable or not (Figure 14). This approach allows the healthcare team make changes in theirs exercise protocol without delays and no patient´s dislocations to hospital frequently.

Figure 13. Functioning of Remote mobile monitoring system – Vital Mobile Cycle, with permission of Vital Mobile Health™ (94)



Data were available for analyses within seconds after the recordings. Subjects (patients and caregivers) received instructions about how to use the devices. Investigators were available on phone or email to solve any question.

The following adverse events were systemically evaluated: fatigue, dyspnoea, SpO_2 ≤88%, Hear rate and pain that could impair exercise. Differences between ALSFRS-R and METs at entry and at 6-months were tested with non-parametric statistics ($p<0.05$ was set as significant).

Figure 14. Graphic representation of the Telemonitoring System measures in the digital platform.

4.3.2 Ethical Committee:

The study was approved by the Ethics Committee of Hospital Santa Maria-CHLN, and patients signed an informed consent.

4.4 Results:

Clinical features and cardiorespiratory response to exercise are summarized in table8. No patient dropout and no significant adverse event impairing exercise was disclosed. In 6 patients, the maximum HR was transitorily above the maximum predicted value, which was promptly correct by the monitoring protocol. Regarding compliance, the average number of sessions was 29. In the end of this study, 70% of patients presented a level of physical activity (adjusted to gender and age) of 4.6±0.85 METs, which is considered a moderate level (95). In the six months period, both ALSFRS-R and METs declined significantly (p=0.008 and p=0.015, respectively) as expected; however, both FVC and SpO2 on exercise did not change significantly (table 8). The ALSFRS-R slope was like described in the literature.

Table 8. Results (10 ALS patients), mean (± S.D) *			
Male/female ratio	7/3		
Age at Study	57 (±9.1)		
Region of Onset (Spinal/Bulbar)	9/1		
Disease Duration (Diagnosis – T1) months	7.6 (±4.12)		
ALSFRS-R total slopeT1-T2 mean (± S.D)	- 0.81 [0 – (-) 2.16]		
	At entry	At 6 months	p-value
%FVC	101.8 (±20.3)	95.4 (±13.4)	0.066
ALSFRS-R total score	43.0 (±2.1)	36.4 (±6.9)	**0.008**
METS mean	5.6 (±1.7)	3.8 (±1.4)	**0.015**
SpO_2 mean	95.25 (±1.2)	94.73 (±1.7)	0.944

Sp – Spinal; Bb – Bulbar; PMHR – Predicted Heart Rate Maximum, %FVC – Forced Vital Capacity predicted, ALSFRS-R – Amyotrophic Lateral Sclerosis Functional Rating – Revised, METs– metabolic equivalent mean reached on CPET, HR– Heart Rate mean; SpO_2 mean - Percentage of Saturation of oxygen. ***Significant differences are in bold*** (Wilcoxon signed-rank test). *S. D - Standard deviation

4.5 Discussion:

The use of tele-rehabilitation in the healthcare delivery model has been successfully trialled in patients with various diseases. When patients are unable to access the specialized centres, tele-monitoring can allow the healthcare team to interact with patients and their families in the home environment. Moreover, it has the potential to engage local and community-based services with the specialized centres in the decision-making process. The benefits of tele-health for ALS patients on NIV have been reported before (96).

In this study, patient and caregivers considered the tele-monitoring system user-friendly and the compliance was excellent. The continuous monitoring O_2 saturation and Heart Rate during exercise demonstrated that a home-based exercise program is clinically safe when designed around the anaerobic threshold (VT1) thus limiting overtraining with possible

fatigue or dyspnoea. Patients with overtraining signals were timely contacted and advised to keep their physical effort as predefined, which would be impossible without this facility.

Although, we are positive about the advantages of tele-monitoring exercise in ALS, a few constraints should be mentioned before larger implementation, such as underestimation of the perceived fatigue, data-protection, data accessibility, financial investment and the large physician time consuming. Nonetheless, we believe that further technological advances will certainly incorporate algorithms and alerts to advising patients or caregivers whenever the performing exercise are out of the limits pre-established by the clinical team.

4.6 Conclusions:

Despite of the small sample of patients and the exploratory profile of this study, we suggest that tele-monitoring use for exercise control is feasible and safe in ALS patients. Future studies should include cost-benefit evaluation and impact on the quality of life of patient and caregivers.

The next chapters present the additional contributions of this Thesis.

Based on the paper published:

Braga AC, Pinto A, Pinto S, de Carvalho M. Tele-monitoring of a home-based exercise program in ALS: a feasibility study. Eur J Phys Rehabil Med 2018;54. DOI: 10.23736/S1973-9087.18.05129-8

Chapter 5:
Management of Respiratory Failure with Non-Invasive Ventilation

5.1 Respiratory Insufficiency in ALS – a brief review:

The respiratory muscle dysfunction present in ALS has a strong impact on survival and quality of life of these patients. The consequent respiratory failure, usually associated to pneumonia and ineffective cough, is the most frequent cause of death. Attempts to compensate the respiratory failure is an important piece of ALS management. Besides the respiratory muscles, we must pay attention to neural control of breathing (97). Although still disputable, ALS is probably associated with alterations on the central respiratory network including possible changes of rhythm generation with impact on respiratory muscles (28). The so-called respiratory muscles are those that provide the motive power for the act of breathing. Thus, although many of these muscles are involved in a variety of activities, such as speech production, cough, vomiting and trunk motion, their primary task is to displace the chest wall rhythmically to pump gas in and out of the lungs (98).

The muscles responsible for the proper functioning of our breathing are divided into four functional groups: inspiratory muscles, expiratory muscles, accessory muscles of the breath and the muscles of the upper airways.

The inspiratory muscles are the external intercostal and the diaphragm. The *serratus posterior* and *anterior* may help inspiration. The expiratory muscles are the internal *intercostal and abdominal muscles*. The accessory muscles are the *sternocleidomastoid, scalenus anterior, medius* and *posterior, pectoralis major* and *minor* and *latissimus dorsi*. Some of these muscles are illustrated in the figures 15, 16 and 17.

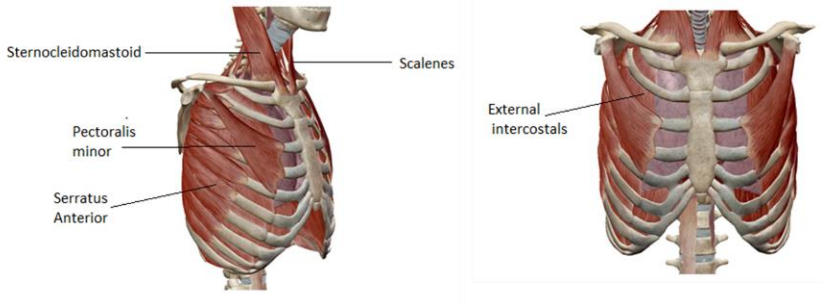


Figure 15. Inspiratory and accessory muscles *(Anatomy & Physiology – Visible Body® app 2015)*

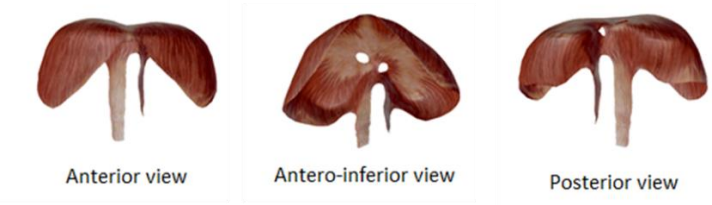


Figure 16. Diaphragm muscle, *(Anatomy & Physiology – Visible Body® app 2015)*

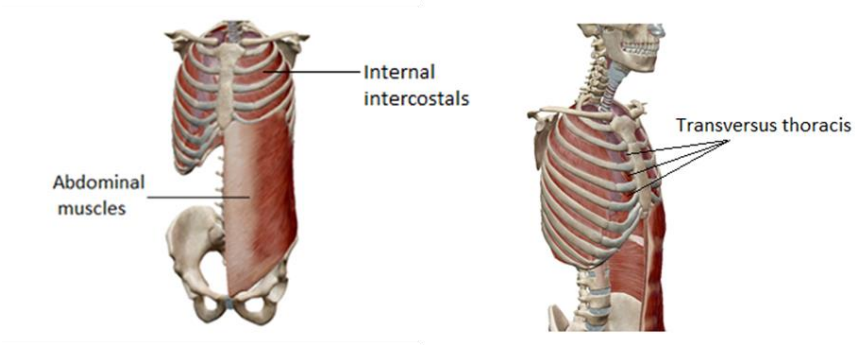


Figure 17. Expiratory muscles, (*Anatomy & Physiology – Visible Body® app 2015*)

The muscles of the upper airways involved in the breathing process are the *genioglossus muscle* (tongue), the *hyoid muscles and the Laryngeal muscles* (not present in the figures). The laryngeal muscles are divided in: intrinsic and extrinsic laryngeal muscles. The intrinsic muscles group is compounded by: adductor muscles (lateral cricoarytenoid muscle, thyroarytenoid muscle and the interarytenoid muscle; the abductor muscle, posterior cricoarytenoid muscle; and the tensor muscle, cricothyroid muscle. The extrinsic muscles group is formed by the infrahyoid strap muscles (sternothyroid, sternohyoid, and thyrohyoid muscles), the mylohyoid, digastric, geniohyoid, and the stylopharyngeus muscles, all acting in concert to provide laryngeal stabilization, and indirectly affecting the vocal fold position (99).

The laryngeal muscles must control the vocal folds for multiple functions, opening for inspiration, closing for airway protection during swallow, and rapid opening and closing to build up pressure for airway clearance during cough (100). Respiration and swallowing have opposing biomechanical effects on upper airway musculature; dilation for inspiration to allow unobstructed air intake into the lungs, which contrasts with oropharyngeal

compression for squeezing the bolus through the pharynx and the upper esophageal sphincter. The control of these two systems is coordinated in neurons involved in these two integrative systems in the brain stem (101).

In many neuromuscular disorders, muscle weakness involves the respiratory muscles to an equal or even greater extent than other skeletal muscles. The degree of limb muscle weakness cannot be used as a reliable guide to the presence of respiratory muscle impairment, since the correlation between the two may be quite poor (98,102,103).

Respiratory muscle involvement may also be masked because patients with weak limb muscles spontaneously decrease their overall activity level, thereby reducing the daily physiologic effort made by the respiratory system. In addition, early symptoms of diaphragmatic muscle weakness may be subtle (104). For all these reasons, it is not unusual for respiratory muscle weakness to go undetected until a clear respiratory failure be precipitated by an acute episode of pulmonary aspiration or infection.

The supine position, sometimes adopted during sleep, comes up a mechanical disadvantage to a weakened diaphragm. Afterwards, the first signs of respiratory discomfort affecting the quality of sleep arise. With the ongoing progression of the disease, problems like hypoventilation develops. The main symptoms of hypoventilation include non-restorative sleep, fatigue, daytime drowsiness and morning headaches (73).

Paralysis of the diaphragm is the most often cause attributed to the origin of respiratory disorders during sleep. This muscle represents 60% to 70% of inspiratory muscle strength and has been the subject of numerous studies, which show its involvement in the respiratory insufficiency in ALS. Diaphragm failure leads to symptoms of dyspnea, and dyspnea at rest is a symptom meaning severe paresis of the diaphragm (105).

Patient must undergo regular respiratory function assessment to identify early signs of impairment. The importance of early detection of respiratory insufficiency is also related to the use of NIV that prolong survival and improve patients' quality of life (106).

The current clinical guidelines (23,73) and last Cochrane systematic review (6) refers that NIV is the treatment of choice in the management of Respiratory Insufficiency in ALS.

In our unit at Centro Hospitalar Lisboa Norte, the respiratory function assessment is performed each three months, except for slow progressions. It includes percentage of the predicted value of Functional Vital Capacity (FVC) and Slow Vital Capacity (VC), and Sniff Nasal Inspiratory Pressure (SNIP) - in particular for patients with poor cooperation when performing spirometry; maximal inspiratory (MIP) and expiratory (MEP) pressures, inspiratory pressure in the first 100 milliseconds time frame during MIP effort (P0.1), phrenic nerve motor response and overnight oxygen saturation provided by Nocturnal Pulse Oximetry (NPO).

NPO calculates the mean percentage of oxygen saturation (% SpO2), the percentage of recording time with oxygen saturation lower than 90% (Sat <90) and the number of oxygen desaturations per hour. All these complementary investigations are used to define the proper time for NIV adaptation, in addition to clinical assessment (73).

FVC is predictive of hypercapnia (107) and it is generally used to monitor respiratory function in ALS patients (108-111). Measurement of FVC (or slow vital capacity) in the supine position may be a better indicator of diaphragm weakness. In normal individuals, there is a small decrease in FVC (or slow vital capacity) in the supine position compared to FVC (or slow vital capacity) in the sitting position. The decrease in FVC in the supine position (or slow vital capacity) is greater in patients with diaphragmatic weakness. The more recent study published by Pinto (109) describe that FVC and slow vital capacity are very highly correlated, and both are strongly correlated with MIP and MEP, still they are moderately correlated with respiratory sub-score of ALSFRS-R in spinal-onset patients, but correlation with respiratory sub-score of ALSFRS-R in bulbar-onset patients is poor. As the diaphragm is the only active inspiratory muscle during the phase REM sleep (Rapid Eyes-Movement sleep), patients with diaphragm weakness likely experience nocturnal hypoventilation, oxygen desaturation and sleep-disordered breathing. On polysomnography ALS patients shown reduced total sleep time, with frequent arousals, central hypopnea, increased sleep in the phase 1 and decreased REM sleep duration (112). Home NPO is a simple and helpful procedure that is valid as a criterion for initiating and monitoring NIV effectiveness. Generally, it is used as an instrument for modifying NIV settings. The guidelines of the American Academy of Neurology (AAA) and European Federation of Neurology Societies recommend the initiation of NIV when symptoms of respiratory impairment are associated

with abnormal findings on measuring respiratory function. The table below shows the current criteria (73) used to assess the need of NIV.

Table 9. Signs and symptoms, and Respiratory function tests related to respiratory muscle weakness in ALS:

Respiratory Signs and Symptoms:
Dyspnea
Tachypnea
Orthopnea
Disturbed sleep due to nocturnal desaturation/arousals
Morning headache
Use of auxiliary respiratory muscles at rest
Paradoxical respiration
Daytime fatigue
Excessive daytime sleepiness (ESS > 9)
Respiratory Function tests:
Forced vital capacity <80% of predicted value
Sniff nasal pressure <40 cmH2O
MIP <60 cmH2O
Significant nocturnal desaturation on overnight oximetry
Morning blood gas pCO2 > 45 mmHg

Table ESS, Epworth Sleepiness Score; NIPPV, non-invasive positive pressure ventilation (73)

In addition to NPO, currently, there are studies that support the use of Non-Invasive transcutaneous measure of CO_2 ($TcCO_2$) to directly assess nocturnal hypercapnia and to detect residual hypoventilation with higher sensitivity (113). Additional monitoring of CO_2 can help to differentiate between hypoxemia related to ventilation/perfusion mismatch and hypoventilation, and also is useful in determining the degree of compliance to NIV. (114,115).

Nowadays, the existing management options are focused on the control of symptoms and aims to alleviate the effects of disease progression on respiratory function, they are: NIV, assisted-coughing device, respiratory physiotherapy to help in the clearance of secretions and prophylactic vaccination.

The next two sub-chapters presents outcomes from works related to the management of respiratory insufficiency in ALS.

Sub-Chapter 5.2 - A look at the diversity on management of respiratory failure in Amyotrophic Lateral Sclerosis;

Sub-Chapter 5.3 - Can NIV parameters settings and changes overtime predict functional and survival outcome in ALS patients?

5.2 A look at the diversity on management of respiratory failure in Amyotrophic Lateral Sclerosis:

This work presents a discussion about the still present lack of consensus on the management of respiratory failure in ALS patients. It is based on an editorial published in Respiratory Care. 2015 April; 60(4):625-6.

In 2015, Sancho et al (116) performed prospective study about medically stable ALS patients, to determine possible clinical or functional predictors of need of Non-Invasive Ventilation (NIV) during an acute episode of lower respiratory tract infection.

The authors used the criteria of the American College of Chest Physicians (117) to initiate NIV at home. Currently, the decision to initiate NIV presents some variability, as previously acknowledged in the literature (118). If we analyze Sancho's study regarding the current NIV guidelines, most of those patients should have started NIV, as they presented a percentage of predicted Functional Vital capacity (%FVC) < 75% and Maximum Inspiratory Pressure (MIP) lower than - 60 cm H_2O. In addition to those criteria, currently most ALS centers consider also the presence of respiratory signals/symptoms.

Sancho et al (2015) reported a population of 33 patients, 23 subjects with spinal-onset and 10 bulbar-onset. From the whole sample, 18 patients did not require NIV during an acute event of respiratory infection. In this group (*n*=18), 15 patients had spinal-onset and 3 bulbar-onset. In a multivariate logistic regression analysis, the only variables that predicted the need for NIV (*n*=15) were %FVC (Odds Ratio 1.06, CI 95% 1.01-1.11) and Peak Flow Cough (Odds Ratio 2.57, 95% Confident Interval 1.18-5.59). However, most of them were spinal patients, who present a better prognosis compared to bulbar patients. Certainly, the region of onset should be considered when analyzing predictors for NIV. As ALS population was small, further research is necessary to validate those findings.

Another interesting aspect in this study was the use of mechanically assisted coughing, which was recommended when Peak Cough Flow was lower than 4.25 L/s. But it was not specified how many spinal and bulbar patients used cough-assist device.

Andersen and colleagues (119) performed a study on the effects of the cough-assist device. The authors stressed the importance of laryngeal dysfunction, which can compromise the benefit of cough-assist in bulbar patients, particularly in those with hypotonic bulbar

paresis. Laryngeal adduction severely reduces the size of the laryngeal inlet, with negative implication in airflow and cough-assist. In these cases, we must consider whether invasive mechanical ventilation should be a better option to manage respiratory support and airways clearance.

The guidelines advising about the decision to initiate NIV have been updated. The main criteria, beyond of %FVC, include: sniff nasal inspiratory pressure (SNIP), maximal inspiratory pressure (MIP), symptoms related with respiratory muscle weakness, nocturnal and diurnal desaturation and hypercapnia, and – more recently – phrenic nerve response. But cultural and economic aspects still influence on the NIV usage (23,72,73,120).

It should be remembered that, following initiation of respiratory support at home, caregivers have a very important role in the ventilatory support. This is particularly true for patients with bulbar ALS who decide to receive invasive-mechanical ventilation after failure of NIV. Besides the use of a ventilator, there are other respiratory support aids that caregivers need be able to use. Vianello and colleagues (121) suggest that administration of the cough-assist is effective and safe even if provided by trained non-professional caregivers and should be part of disease management at home. It could be used in combination with NIV to decrease the need for hospitalization and increase patient quality of life.

However, the revised report of European Task force on ALS clinical management (73) refers that mechanical ventilation causes strain on caregivers, reducing their quality of life by increasing their responsibilities related to the management of the ventilator, and increasing the caring costs. Thus, we must be careful regarding the evaluation of the emotional, physical, social and psychological capacity of caregiver to deal with increasing needs of care of a family member with ALS.

The caregiver quality of life and their support should be considered as a independent variable with relevant weight when evaluating possible predictors of success or failure of NIV in patients with ALS.

In Europe, some countries are using tele-monitoring system to follow-up patients with ALS using NIV. The association of home-monitoring with more efficient portable ventilators might implicate higher costs to the Health Service, but recent studies have demonstrated cost-effectiveness by the use of the NIV home-monitoring in European countries (96,122). Pinto and colleagues referred that the investment for implementing this system is not

significant, in particular considering long-term cost estimation, since it would reduce unnecessary hospital visits (96).

Health care models that combine technology with patient-centered care may imply directly on non-medical costs, such as days of wages lost due to absenteeism of caregivers. Future studies must include the impact of tele-monitoring on costs of the health services, including hospital readmissions, and the effects on the caregivers' quality of life.

Based on Editorial published in:

Braga, AC M A; A look at the diversity on management of respiratory failure in Amyotrophic Lateral Sclerosis. Editorial in Respiratory Care Journal (USA), April 2015 60:4 625-626; doi:10.4187/respcare.04014

5.3 – Can Non-Invasive Ventilation settings predict functional and survival outcome in ALS patients?

This study analyzed the predictors of functional decline (ALSFRS-R) and survival related to NIV settings, NIV compliance data, Nocturnal Pulse Oximetry (NPO) and Pulmonary Function Tests (PFT). It has received an award as the best original research abstract (*Respironics Fellowship in Mechanical Ventilation*) in the 58th *American Association of Respiratory Care* (New Orleans, 2012) and published in the *Journal of Community Medicine and Health Education* (7:521, 2017).

5.3.1 Introduction:

The lack of low-cost specific tools, which could be associated with ALSFRS-R to define prognosis, is a constraint factor in the follow-up of ventilated patients. Abundant evidence shows the NIV critical role in prolonging life in compliant patients (4,70). Compliancy to NIV is frequently defined by the number of hours of use during the day (nhu/d) and is generally accepted as a predictor of survival (123). However, proper management implies not only the need to obtain full adherence, but also synchrony and comfort to achieve NIV effectiveness (124). As such, other variables beyond number of hours/day, namely the ventilation settings of NIV equipment need to be evaluated regarding their potential role as markers of functional and survival outcome. As the causes of death in ALS are diverse (125-129), it is important to clarify whether respiratory discomfort on NIV is present from NIV start to near the time of death, and if they could be amenable by intervention.

5.3.2 Objectives:

This study aimed to investigate the prognostic factors of functional decline and survival in ALS ventilated patients, among compliant ventilated ALS patients, considering all variables recorded by the equipment software (96), from the initial adaptation until death or end of study. We hypothesized that different clinical decisions regarding parameters settings will affect both survival and compliancy and that our results would contribute and reinforce the need of close surveillance of ALS ventilated patients as shown by Claude Rabec and colleagues in 2011 (120).

5.3.3 Methods:

Our study followed an exploratory, observational and prospective design. We included 60 ALS ventilated stable subjects followed in our ALS clinic from 2007-2012, with regular use of NIV (> 4h/day), Compliancy was evaluated and considered effective as described elsewhere, more than 4h of use per day (nhu/d) after one month of NIV initiation associated with improvements on NPO - SpO_2mean > 93%, resting heart rate between 60-90 bpm and eupnea with lower breath rate on NIV (BR< 16 bpm).

Included patients were classified with definitive, probable or probable-laboratory supported disease, on the revised El Escorial criteria, aged between 18 to 75 years. Subjects with gastrostomy, cognitive impairment or other medical condition, as heart or lung disorders, oncological diseases or previous history of stroke were excluded. Patients were prospectively evaluated at entry, over disease progression and in the end of 5 years-period. Patients were split in two groups: G1 (n=29) - subjects who died over the follow-up-period of 5 years; and G2 (n=31) - subjects who were alive in the end of the study time (2007-2012). All data were registered and compared between groups, including: timing to NIV adaptation expressed as a percentage of time of the total disease duration; NIV device settings; compliancy data; functional decline (ALSFRS-R); duration of NIV use (days); and total survival from disease onset.

Functional Assessment and NIV initiation:

All patients were clinically evaluated every 3 months, functional evaluation was quantified by ALSFRS-R (38). Indication for NIV initiation was supported by the presence of respiratory symptoms (respiratory sub-score of the ALSFRS-R < 12) or signs of respiratory insufficiency, associated with abnormal NPO findings (SpO2mean < 95% for patients without previous respiratory condition) (73,74) , or reduced FVC (< 80%), or decreased MIP (< 60 cmH_20), or hypercapnia, in accordance to the NICE in 2010 (23).

NPO was measured continuously during sleep, by fingertip infra-red pulse oximeter (Wristox2®, Model 3150-Nonin). Mean oxygen saturation (SpO2mean), percentage of time with O_2 saturation below 90% (Sat< 90) and the number of dips/hour associated with ≥ 4% lowering of SpO2 were measured. A minimum of 6 hours of recording was necessary for analysis. PFTs were performed using standard equipment according to the American

Thoracic Society (ATS) recommendations (130). Predicted values of conventional pulmonary function parameters were calculated by normalizing to the reference values proposed by the European Community for Steel and Coal (131). We used predicted FVC value and predicted MIP and MEP values. All these investigations are part of our usual routine care. Evaluations were performed with a periodicity of 3 months. Functional scores and PFTs were evaluated by physicians blinded to the study.

Upon recommendation, all patients were ventilated with a Bipap Goodknight 425-ST bi-level device (Tyco™ Healthcare Group LP, California, USA), in our unit. Initial, after achieving full compliance (≥4 hours of use/ day), and last parameters settings, were registered as well as compliancy data on the same occasions (132) .

Our Ethical Committee approved this study and participants signed informed consent.

Data and Statistical Analysis:

Kolmogorov-Smirnov test analyzed the normality of the sample. We compared the differences between the two groups using a chi-square test, t-test or a Mann-Whitney non-parametric test as appropriate. Survival curve from symptoms onset was plotted using Kaplan-Meier estimates. Correlation analyses among variables were tested. Categorical variables (gender, onset-region, and group) were transformed from dummy variables to metric variables to be integrated into the Cox-regression models.

In addition, continuous variables with non-uniform distribution were dichotomized and tested with chi-square test and if significant differences were found, they were dichotomized and binned by its median value for further consideration in a subgroup analysis. We used multiple Cox regression models to identify predictors of functional decay and survival. The independent variables were:

NIV settings – Inspiratory Positive Airways Pressure (IPAP), Expiratory Positive Airways Pressure (EPAP), Inspiratory sensitivity (IS), Expiratory Sensitivity (ES), Rise time (rT), Breath Rate $_{back\text{-}up}$ ($BR_{back\text{-}up}$);

NIV compliancy data – the percentage of Spontaneous Cycles (%SC), the mean Breath Rate observed (BR_{mean}), the Inspiration: Expiration ratio (I: E), the Number of hours usage/day (nhus/day);

NPO measurements - Heart Rate (HR), Mean oxygen saturation (SpO_2mean), percentage of time which SpO_2 recording was below 90% (Sat< 90);

RFTs – Forced Vital Capacity (FVC), Maximum Inspiratory Pressure (MIP), Maximum Expiratory Pressure (MEP), Inspiratory pressure 100 milliseconds into an occluded inspiratory effort (P.01), Partial pressure of CO_2 ($PaCO_2$) and Partial pressure of O_2 (PaO_2).

The sample size was calculated with G*Power, Version 3.1.9. (Effect size d = 0.8). The statistical significance level was $p \leq 0.05$.

5.3.4 Results:

Group Comparisons:

Sixty subjects were included in this study (43 males and 17 females divided in two groups: G1 (n=29; dead); and G2 (n=31; alive) at 5-years of follow up. Men were predominant in both groups. NIV was initiated at 50% time of the total disease duration in both groups (p=0.12). At admission, no significant differences were found between groups regarding clinical and demographic characteristics (see table 10).

Table 10.: Demographic and clinical characteristics of groups at NIV adaptation*			
	G1 (N=29)	G2(N=31)	p-value
Male/female ratio	24/5	19/12	0.39
Age of Onset	63.4(±13.2)	67.2(±10.7)	0.23
Type of Onset(S/B) ratio	22/7	23/8	0.29
Limbs (Upper/Lower) ratio	15/14	16/15	0.62
Disease Duration up to NIV (days)	764.5(±599.6)	564.7(±316.0)	0.12
ALSFRS-R (mean ±S. D)			
ALSFRS-R Total	31.86(±6,09)	33.52(±3.69)	0.20
Spinal $_{\text{sub-score}}$	18.74(±5.7)	20.16(±3.56)	0.16
Bulbar $_{\text{sub-score}}$	10.45(±2.01)	10.84(±1.84)	0.43
Respiratory $_{\text{sub-score}}$	10.72(±1.75)	10.71(±1.73)	0.97
Respiratory Function Test (mean ±S. D)			
Forced vital Capacity (FVC), %predicted	82.7(±19.58)	92.7(±19.8)	0.74
Maximum Inspiratory Pressure	55.3 (±24.0)	53.15(±23.4)	0.53
Maximum Expiratory Pressure	68.8(±26.2)	72.8(±19.93)	0.42
Mouth Occlusion Pressure	91.9(±31.3)	89.0(±32.8)	0.74
Nocturnal Pulse Oximetry (mean ±S. D)			
SpO2mean	93.64(±2.7)	93.75(±1.24)	0.10
Sat<90	5.86(±15.03)	3.15(±3.53)	0.60
Heart rate	73.34(±14.08)	68.10(±11.05)	0.12

*Non-significant difference between groups at admission. G1 – dead; G2 – alive. Legends – see Data and statistical analysis section

In the end of the 5-years' time, significant differences were found between groups regarding the functional score and NPO data: heart rate and Sat < 90 are summarized in table 11.

G2 showed a higher functional score on the ALSFRS-R [p=0.001], as well as on the spinal and bulbar sub-scores (p=0.006 and p=0.01, respectively).

The respiratory sub-score (p=0.76) and functional slopes (ALSFRS-R total [p= 0.21], spinal [p=0.35] and respiratory [p=0.40] slopes) showed no significant difference. The bulbar slope revealed significant differences, with a slower decline in G2 (p=0.025). Sat < 90 (p=0.034) and mean heart rate (p= 0.005) in NPO were more favorable in G2 at the end of the observation period.

In general, NIV setting were similar between groups, but breath rate back-up was lower in G2 (11.98±1.40; p<0.028). Regarding compliancy data, BR mean showed a lower value in G2 (12.88±1.42; p<0.011).

Table 11. Clinical characteristics at end of study (t-test)			
Mean ± S. D	**G1**	**G2**	***P* value**
Functional Scores and Slope			
Bulbar $_{\text{sub-score}}$	6.04 (±4.44)	9.00 (±4.13)	**0.016***
Spinal $_{\text{sub-score}}$	7.13 (±5.86)	13.92 (±8.15)	**0. 006***
Respiratory $_{\text{sub-score}}$	7.12 (±2.81)	7.32 (±1.86)	0.76
ALSFRS-R $_{\text{Total}}$	18.08 (±8.67)	28.51 (±11.49)	**0.001***
Bulbar slope$_{/\text{month}}$	0.24 (±0.28)	0.08 (±0.9)	**0.025***
Spinal slope$_{/\text{month}}$	0.70 (±0.93)	0.48 (±0.75)	0.350
Respiratory slope$_{/\text{month}}$	0.17 (±0.17)	0.22 (±0.23)	0.401
ALSFRS-R Total slope$_{/\text{month}}$	1.10 (±1.39)	0.72 (±0.61)	0.213
Nocturnal Pulse Oximetry			
SpO_2mean	92.51 (±3.29)	93.90 (±1.61)	0.064
Sat < 90	10.30 (±20.75)	1.20 (±1.96)	**0.039***
Heart Rate	77.53 (±16.39)	66.39 (±9.21)	**0.005***
Bipap Ventilation Settings			
Breath Rate Back up	12.76 (±1.39)	11.92 (±1.40)	**0.028***
IPAP	18.46 (±2.59)	17.76 (±3.42)	0.40
EPAP	4.7 (±0.48)	4.4 (±0.68)	0.07
IS	1.3 (±0.8)	1.3 ±0.8)	0.73
ES	2.0 (±1.7)	1.7(±1.4)	0.76
Compliancy Data			
BR mean	13.97 (±1.66)	12.88 (±1.42)	**0.011***
%Spontaneous Cycles	30.0 (±23.2)	28.6 (±20.1)	0.9
I: E ratio	0.4 (±0.08)	0.05 (±0.05)	0.7
Rise Time	1.4 (±0.7)	1.3 (±0.7)	0.5
Clinical Characteristics			
Time to NIV (days)	764.5 (±600.6)	564.7 (±316.8)	0.12
Disease Duration from Onset(days)	1482.7 (±895.1)	1340.3 (±518.6)	0.46
Total Use NIV (days)	769.9 (±554.9)	698.3 (±501.0)	0.60

*Statistical significance p≤ 0.05 in bold. G1 – dead; G2 – alive. Legends – see Data and Statistical analysis section

Finally, Kolmogorov-Smirnov test analyzed the distribution of continuous variables. As the variable IPAP at the end of observation showed a non-uniform distribution between groups, it was dichotomized and binned by its median value (IPAP=18 cmH_2O). As we identified significant differences (p=0.05) between groups related to level of IPAP (See table 12), we also considered this IPAP level as new dependent variable (IPAP < or > 18cmH_2O) and performed a subgroup analysis to evaluate its effect on functional decline and survival.

Table 12. Kolmogorov-Smirnov Test

	Gender	Type of onset	Limbs	Level of IPAP*	NIV start (%dis. duration)	NIV use (days)	N hours of use/day
Mann-Whitney U	353.00	430.50	449.00	279.50	356.00	413.00	308.00
Wilcoxon W	788.00	836.50	884.00	714.50	762.00	878.00	773.00
Z	-1.83	-0.07	-0.01	-1.97	-0.92	-0.39	-1.56
Asymp. Sig (2-tailed)	0.07	0.94	0.99	0.05	0.36	0.70	0.12

Legend: * Group 1 - IPAP <18 cmH2O; Group 2 - IPAP >18 cmH2O

Correlations Analyses:

Statistical significant correlations (Pearson two-tail sig.) were searched between the dependent variables Disease Duration from symptoms onset and Total Use of NIV (days) with Functional scores and slopes, ventilation settings, NIV compliancy, NPO and PFT as independent variables. We found significant correlations among the following variables Functional slopes, IPAP, EPAP and BR backup, BR mean, SpO_2mean, and MIP. (see table 13).

Table 13. Partial correlation analyses among Functional Slope per month, NIV settings, PFT, NPO, Disease duration and Total use of NIV			
Variables		**Disease Duration**	**Total Use of NIV**
Functional Slope per month			
ALSFRS-R total slope	R	-0.408	- 0.362
	p	**0.006***	**0.016***
Bulbar slope	R	-0.296	-0.269
	p	0.051	0.07
Spinal Slope	R	-0.386	-0.341
	p	**0.010***	**0.024***
Respiratory Slope	R	-0.375	-0.432
	p	**0.012***	**0.003***
NIV settings			
IPAP	R	0.293	0.540
	p	**0.041***	**<0.001****
EPAP	R	0.236	0.328
	p	0.10	**0.021***
BR_{mean}	R	0.447	0.269
	p	**0.001****	0.62
$BRb_{ack\ up}$	R	0.297	0.341
	p	**0.038***	**0.016***
Pulmonary Function Test			
MIP	R	0.371	0.231
	p	**0.020***	0.15
Nocturnal Pulse Oximetry			
$SpO2_{mean}$	R	0.326	0.250
	p	**0.017***	0.089

R – Pearson Correlation, *p* – p-value. *Correlation is significant at the 0.05 level (2 tailed); ** Correlation is significant at the 0.01 level (2 tailed). Legends – see Data and statistical analysis section

Multiple Cox Regression Analyses.

We carried out a Multiple Cox regression analyses stratified to type of disease onset to identify predictors for ALSFRS-R $_{Total}$ slope from onset to death or end of study, for Disease Duration from onset, and for the Total NIV use.

Table 14. Predictors of ALSFRS-R Slope among NIV settings, NPO, PFT, and clinical characteristics. Multiple Cox regression model

Variables	B	SE	Wald	p-value
NIV settings/Compliacy				
% Spontaneous Cycles	0.457	0.165	7.633	**0.006**
I : E ratio	21.360	9.383	5.182	**0.02**
NºHoursUse/day	0.319	0.222	2.073	0.15
BR mean	-2.177	1.357	2.572	0.10
IPAP	-1.153	0.604	3.649	**0.05**
EPAP	-1.147	1.532	0.560	0.45
IS	-4.624	1.475	9.826	**0.002**
ES	1.369	0.582	5.536	**0.01**
rT	8.580	3.949	4.720	**0.03**
BR_{backup}	2.819	1.669	2.852	0.09
Nocturnal Pulse Oximetry (NPO)				
SpO_{2mean}	1.313	0.873	2.264	0.13
Sat<90	-0.046	0.167	0.078	0.78
HR	0.047	0.079	0.352	0.55
Pulmonary Function Test (PFT)				
% FVC	-0.120	0.089	1.829	0.17
MIP	-0.195	0.117	2.795	0.09
MEP	0.331	0.163	4.116	**0.04**
P01	-0.189	0.075	6.377	**0.01**
PaO2	0.075	0.103	0.536	0.46
PaCO2	-0.239	0.208	1.328	0.24
SatO2	3178	1.391	5.222	**0.02**
Clinical Charactheristics				
Gender	-15.901	7.000	5.160	**0.02**
Evolution until NIV	-0.015	0.005	8.042	**0.005**
Age at onset	-0.116	0.133	0.762	0.38
Disease duration	0.012	0.004	9.011	**0.003**

Legends – ***NIV settings/Compliancy*** – percentage of Spontaneous Cycles **(%SC)**, Inspiration: Expiration ratio **(I: E)**, Number of hours usage/day **(nhus/day)**, mean Breath Rate observed **(BR_{mean})**, Inspiratory Positive Airways Pressure **(IPAP)**, Expiratory Positive Airways Pressure **(EPAP)**, Inspiratory sensitivity **(IS)**, Expiratory Sensitivity **(ES)**, Rise time **(rT)**, Breath Rate back-up **($BR_{back-up}$)**; ***NPO measurements*** - Mean oxygen saturation **(SpO_2mean)**, percentage of time which SpO_2 recording was below 90% **(Sat< 90),** Heart Rate **(HR)**; **PFTs** – Forced Vital Capacity percentage of the predicted value **(% FVC)**, Maximum Inspiratory Pressure **(MIP)**, Maximun Expiratory Pressure **(MEP)**, Inspiratory pressure 100 milliseconds into an occluded inspiratory effort **(P.01)**, Partial pressure of O_2 **(PaO_2),** Partial pressure of CO_2 **($PaCO_2$)** and Oxygen Saturation **($SatO_2$). -2 Log Likelihood: 57.507; X^2: 60.921; p<0. 001.***Statistical significance p≤ 0.05 in bold.

The variables with relevant explanatory power on ALSFRS-R $_{Total}$ slope among the NIV parameters data were (table 14): percentage of spontaneous cycles (%SC) (B=0.45; p= 0.006) inspiratory/expiratory ratio[I:E] (B= 21.3; p=0.02), rise time (RT) (B=8.58; p= 0.03), inspiratory sensitivity (IS) (B= - 4.62; p= 0.002), expiratory sensitivity (ES) (B=1.36; p= 0.01) and IPAP (B= -1.15; p= 0.05), with a significant model : -2-Log LL = 57.5; Chi-sq = 60.92; p< 0.0001; and effect size f2: 0.56.

Regarding the predictors for the disease duration from onset, we identified in a significant Cox regression model (-2-Log LL = 61.381; Chi-sq = 36.22; p< 0.0001) similar variables related to NIV settings and compliancy, which were found as predictors for the functional slope per month (table 15). However, a Cox regression model did not identify any significant predictor for the Total NIV use among the NIV settings, NIV Compliancy, RFT or NOP.

Table 15. Predictors of Disease Duration among NIV settings and compliancy. Multiple Cox regression model

Variables	B	SE	Wald	p-value
NIV settings				
% Spontaneous Cycles	0.091	0.044	4.335	**0.037**
I:E ratio	-2.136	4.643	0.212	0.645
IPAP	-0.343	0.162	4.470	**0.034**
EPAP	-1.361	0.765	3.162	0.075
IS	1.689	0.719	5.515	**0.019**
ES	-0.473	0.205	5.320	**0.021**
RT	-1.058	1.014	1.089	0.297
BR_{backup}	0.780	0.594	1.724	0.189
NIV Compliacy				
NºHoursUse/day	0.173	0.089	3.798	0.051
BR $_{mean}$	-1.814	0.784	5.357	**0.021**

Legend - see Data and Statistical Analysis section. ***Statistical significance p≤ 0.05 in bold***

Survival estimates with Kaplan-Meier curves in the G2:

Survival function with Kaplan-Meier curves were analyzed with and without censoring as all patients in G2 were alive, and no significant differences were found regarding the disease duration from onset as well as to total NIV use (days).

As all patients in G2 were alive at the end of the study we only considered the Kaplan-Meyer estimates curve regarding functional decline. In addition, we evaluated the KM estimates for disease duration from onset and Total NIV use facing the new group identified by the average of IPAP (GIPAP 1: IPAP <18cmH20; GIPAP 2: > 18 cmH20) used by all participants. We performed a Kaplan-Meier statistic stratifying groups by IPAP level, we observed that the total time of NIV use was significantly longer in patients using higher levels of IPAP in the end of the observation period (L-R: Chi–sq = 6.251; p= 0.012) - see figure 18. In addition, the slope of the respiratory sub-score also showed to be significantly influenced by IPAP level, with faster slopes in the group with lower IPAP level (L-R: 124.03, Chi-sq:25.98, p<0.001, see Fig. 19)

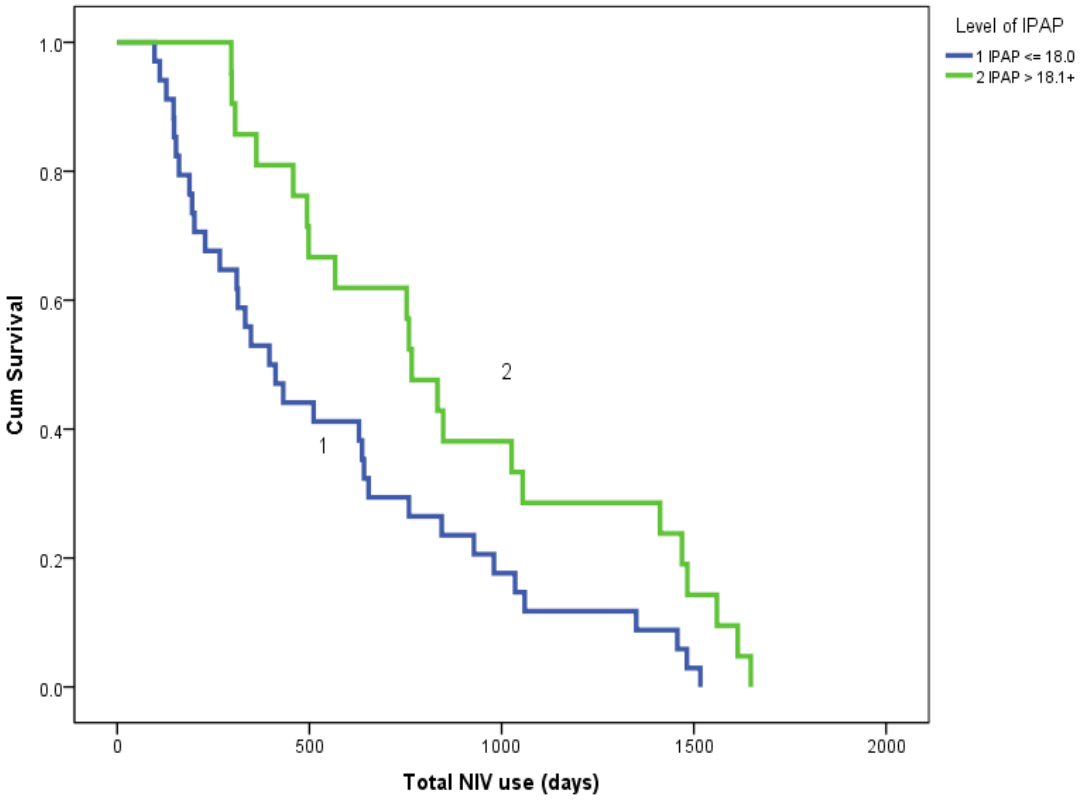


Figure 18. Kaplan Meier curve estimate for NIV use (days) stratified by IPAP level

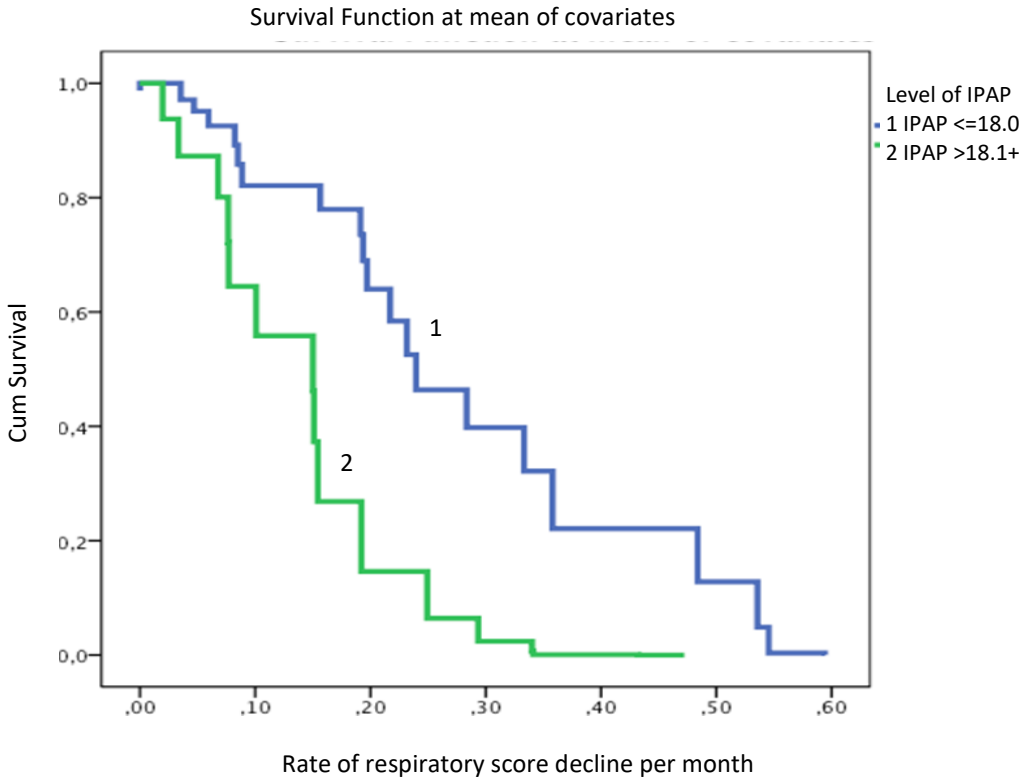


Figure 19. Kaplan Meyer curve estimate for rate of respiratory sub-score slope per month stratified by the IPAP level. Legend: 1 IPAP: <=18.0 cmH_20; 2 IPAP: > 18.1+ cmH_20

5.3.5 Discussion:

Non-Invasive Ventilation (NIV) allows a wide range of ventilation parameters and settings, thus it is mandatory to have accurate information about these issues to better understand the interplay between patient and ventilator (120). Currently, the usual criteria to follow-up ALS ventilated patients has only considered compliant those patients under NIV that have used the equipment more than 4 hours/ day. In the present study we also considered whether it was effective.

We endeavor to follow-up home NIV only in stable ALS patients to obviate the need of a closer surveillance and, at the same time, to accommodate the frequently different degrees of compliancy in each patient. However, to validate compliance, symptoms of discomfort related to masks use (leaks, face/nose pain, nasal congestion, etc) that could influence adherence (133) were solved by high quality technicians who visited patients regularly to solve those issues (134).

Despite some limitations detailed later, this study showed for the first time the importance of analyzing the compliancy data and ventilation settings as independent predictors of functional decline evaluated by its slope/month (see table 14), the NIV use in days (Fig.18) and of the total disease duration from symptoms onset (Fig. 19).

Our results strongly suggest that the variables affecting the respiratory comfort of patient (IPAP, IS, rT, and BR back-up), are indeed a prerequisite to a better NIV compliance (% of spontaneous cycling, I/E ratio, nº of hours of use/day and the BR mean) and can influence the functional decline.

Moreover, the higher the IPAP pressure and the higher inspiratory sensitivity, the lower total ALSFRS-R decline/month, the lower ALSFRS-R respiratory sub-score decline/month as well as the longer NIV use (L-R: $\chi 2=6.251$; $p=0.012$), all of these results, together with higher ALSFRS-R slope associated to higher rT and higher BR back-up are in line with Dreher and colleagues work in 2010 (135). This latter work and the Kim and colleagues contribution (2011) (136) also recognized the value of high intensity non-invasive ventilation in stable hypercapnic COPD patients in a randomized crossover trial.

Overall, these results showed that the functional decline was significantly affected by parameter settings. Indeed, the faster slopes were related to higher percentage of spontaneous cycling, lower inspiratory and expiratory ratio; lower inspiratory sensitivity and lower IPAP, thus suggesting the need of a close surveillance and above all, the need to keep patients' respiratory mechanics and central drive well captured by the ventilator during sleep.

The limited available literature about the Patient-Ventilator Asynchrony in neuromuscular patients suggests that severe asynchrony may be associated with increased work of breathing and sleep disruption (137,138). Patient-ventilator interaction is complex and multifactorial, and it is dependent on respiratory system conditions, various disease states, neural function and clinical response. When optimized, the patient-ventilator interaction can provide to patient more comfort during positive-pressure breaths, and improvements on the sleep quality results in a better quality of life (139-142).

Although influenced by a number of factors, the mechanical augmentation of tidal volume during higher IPAP pressure decreases the intensity and duration of inspiratory muscle contraction, reducing patient work of breath (143) . The percentage of spontaneous cycles activated by patient also influenced the functional decline showing that the higher % of spontaneous cycling was associated with higher ALSFRS-R slope/month (B= 0.457; p= 0.006)and a lower disease duration (B=0,091, p=0,037). This is probably explained by the increase of unnecessary inspiratory effort.

A study carried out by Vitacca and colleagues (144) reported discrepancies between Bilevel mechanical ventilator settings to optimize work of breath and settings chosen by COPD patients to maximize comfort.

In general, longer inspiratory time improve oxygenation by increasing the mean airway pressure (longer period of high pressure increases mean airway pressure over the entire respiratory cycle), allowing gas re-distribution from more to less compliant alveoli. It can also decrease the peak pressure by decreasing inspiratory flow.

Regarding the role of the Rise time as functional slope predictor, it is well known that it determines the speed of rise of the flow or pressure. A very short rise times may be more uncomfortable for the patient and longer rise times may result in a lower tidal volume or higher pressure being required due to decrease of inspiratory flow.

The inspiratory sensitivity determines how easy it is for the patient to trigger the ventilator to deliver a breath. In general, increased sensitivity is preferable to improve patient-ventilator synchrony, but excessively high sensitivity may result in false or auto-triggering. In this study, the IS also showed a beneficial effect in the ALSFRS-R decline (B= -4.624; p=0.002) and this result is just in line with a study performed by Gonzales (145) that described the adjustment of cycling criteria and rise time that could potentially impact breathing frequency, work of breathing, trigger timing and patient-ventilator synchrony, with potential consequences for the respiratory comfort and compliance of patient.

ALS patients with respiratory symptoms have hypoxic events, hence a full adherence to NIV with higher IPAP and inspiratory sensitivity and low breath rates can help to minimize this problem, modulating the neural drive as shown by the statistically significant difference of lower BR mean and BR back-up in G2 patients (see table 11).

5.3.6 Conclusions:

As ALS natural history is closely related to hypoxia, and motor neurons are particularly vulnerable to hypoxic conditions because of their high oxygen consumption and poor antioxidant enzymatic defenses (87), the ventilation settings and its changes help to provide improvements on respiratory symptoms as well as on daytime arterial blood gas levels and nocturnal oximetry measurements. Thus, it is important to carefully titrate parameters settings until full compliance is achieved and have a close follow-up up to the final disease stages.

Currently, the use of capnography measurements showed to be an efficient tool both for assessing nocturnal hypoventilation and compliance to NIV treatment of ALS patients (136) and should be more available. Although important, in this present study we did not evaluated this method.

The main findings in this study were related to predictor role of NIV settings and nocturnal pulse oximetry data. Indeed, minor changes on the nocturnal pulse oximetry data (Sat< 90; Heart Rate and SpO_2 mean), became significantly different close to end of clinical evolution or end of study, and they were related to disease duration from the onset. This suggests that a status of eupnea, which provides a heart rate and breath rate closer to resting pattern during the night, must be achieved as soon and longer as possible. In addition, oximetry studies during follow-up can help to identify and the correct changes on abnormal pattern of sleep.

We recognize the limitations impacted by the type of study and emphasized that these results may have been influenced by sample size and ALS center biased. Therefore, more studies should be conducted on a fully randomized trial to validate these findings.

In the future, the need for an individualized approach based on closer clinical management should be part of treatment attitude for ALS ventilated patients. Problems that can affect compliance deserve closer attention and should be addressed timely throughout the disease process as at the end of the disease small but significant parameters settings change do impact on functional decline.

Compliance plays a very important role in clinical decision-making. It can make the difference on the survival in these patients and suggests that NIV can have a modifier role play on follow up when a more rigorous management is achieved.

Based on paper:

Braga ACM, Pinto S, Pinto A (2017). Can Non-invasive Ventilation Settings Predicts Functional and Survival Outcome in ALS Patients? J Community Med Health Educ 7:521. doi:10.4172/2161-0711.1000521

Chapter 6:
The Support for the Caregivers During the Disease Progression

6. Home Caregivers Training Program for Amyotrophic Lateral Sclerosis: Insights from a Pilot Project:

This work reports a feasibility study on a training program for ALS caregivers considering the learning level achieved at the end of Training program. This training program was developed together with Portuguese ALS association and funded by National Rehabilitation Institute. It was presented on 25th International ALS/MND Symposium in Orlando, USA 2015.

6.1 Introduction:

ALS generates a total dependency for all activities of daily life, and the subsequent respiratory muscles weakness leads to the need of respiratory support. The health care management of patients with ALS focuses on the symptomatic control (146) to maximize the quality of life and decrease the burden of the disease for patients and caregivers (147).

Previous studies have reported that patients under ALS specialized and multidisciplinary care have greater benefits (147) . Currently, the specialized and multidisciplinary health care management is part of the American Academy of Neurology–endorsed ALS quality measures (24).

ALS is a disease with long-term health care needs, and ideally, community health services linked to specialized clinical services must perform its clinical management. ALS progression exposes caregivers to a high level of physical and psychological demand. The constant physical effort of caring patients with mobility impairment and the management of interventions such as mechanical ventilation and use of feeding devices at home can contribute for a high level of distress (146) . The lack of specialized centers, or the distance between patient home and the health centers that could provide support for patients with ALS during clinical intercurrences, may potentially contribute to the rate of readmissions of ALS patients in acute hospital services. Providing specific and basic training for ALS caregivers can help to address this situation.

6.2 Objective:

We evaluated the level of learning achieved at the end of Training Program and whether this type of intervention should be recommended for efficacy testing. This study did not test the effectiveness. The Training Program was based on the most recent ALS clinical management guidelines and aimed to provide skills which could allow the ALS patients' caregivers caring of their family member at home safely.

6.3 Methods:

We carried out an exploratory and observational feasibility study with ALS patients 'caregivers, after the completion of the Training Program for ALS caregivers created by the Portuguese ALS association. ALS patients were followed up in the ALS/Motor Neuron Disease clinic of two academic hospitals: in Lisbon and Oporto city. The criteria to participate in the Training Program were: be a family member or formal caregiver or known person of an ALS patient, literacy, age above 18 years, and availability to be present during the period of the TP. The exclusion criteria were: be a caregiver of other neuromuscular clinical conditions than ALS (e.g., Duchenne dystrophy, Guillain-Barre syndrome, etc.), illiteracy and lack of availability to full time presence during the Training Program. Caregivers were informed about the Training Program during the Neurology consultations.

In addition, informative material, such as flyers and posters, were displayed on in the Neurology and Rehabilitation services in both hospitals, and in the website of the ALS Portuguese association. The participants did not receive any financial compensation. The participation was free of costs but limited to 15 participants for each Training Program, to better accommodate the participants for hands-on sessions and providing enough time for discussion. Trainers contacted the participants via telephone to identify reasons for absences after the Training Program has started.

Feasibility Criteria

The compliance was assessed through a diary register of the list of participants. All participants had to be present at least 75% of the Training Program to receive a certificate

of completion. Each Training Program should have at least 10 participants to be considered feasible.

Learning Assessment

Participants undertaken a written examination with multiple-choice questions. The number of questions allocated to each module was weighted based on complexity and relevance of each module (see Table 16). The trainers considered the mark ≥50% as a successful completion on the written exam due to the extensive and massive amount of information that had been provided to nonprofessional caregivers. The trainers considered that 50% of learning retention after the whole Training Program would be a reasonable start point for future editions.

The Training Program

It was developed by the team of health care professional volunteers of the Portuguese ALS Association which included a registered nurse, a physiotherapist and a social worker, all of them with clinical and academic expertise in neuromuscular disease. A biomedical engineer helped the ALS Association team with the augmentative and alternative communication module. The main goal of the Training Program (TP) was to help patients and caregivers to cope with the main challenges usually reported during the consultations in the local ALS/MND clinic over the years.

The total duration for each Training Program were 2 full days + 1 half day in the weekends (32 hours total duration). It was divided into 10 modules with theoretical and hands-on practice approaches which included the following topics:

- Module 1: General concepts about ALS: a brief and didactic clinical review about the disease;
- Module 2: Rights and duties: A social worker presented to the caregivers the current legislation and social support provided by the National Health Service and the Social Security Department;
- Module 3: Communication skills: A registered nurse demonstrated strategies to reach a better communication between ALS patients, caregivers and health care team;

- Module 4: Basic daily care and nutrition: A registered nurse demonstrated practical guidance to performing activities of daily life, such as hygiene care and feeding - since oral intake to the management of percutaneous endoscopic gastrostomy (PEG);

- Module 5: Therapeutic management: Because ALS is a nonexclusive disease, a registered nurse provided orientation to the caregivers about polypharmacy and comorbidities;

- Module 6: Augmentative and Alternative communication devices: A biomedical engineer demonstrated how the technology could help patients and families to maintain a communication pathway;

- Module 7: Mobility, transfer, and positioning: A physiotherapist demonstrated basic techniques to help the caregivers to maintain the patient's mobility, how to transfer patients from the bed to chair/wheelchair as well as provided strategies for a better positioning of the patient in a safe way. It was also demonstrated how to avoid pressure wounds in ALS patients and back injuries for the caregivers;

- Module 8: Respiratory support: A physiotherapist explained the main reasons for using a respiratory support in ALS patients and what kind of devices might be used;

- Module 9: Emergency situations: A registered nurse discussed about the most usual clinical situations and how to manage them, such as choking, falls, and some of consequences of the immobility which need special attention of the caregivers, such as deep venous thrombosis;

- Module 10: Caregiver self-care: A physiotherapist and a registered nurse discussed with the caregivers about the impact of burnout on their mental and physical health and presented strategies to coping with the stress.

Table 16. Questions of the Written Exam.

Module	Questions allotted
1. General concept about ALS	3
2. Rights and obligations for patients and caregivers	2
3. How to communicate better with ALS family members and health care team	1
4. Basic daily care and nutrition	2
5. Respiratory support: noninvasive ventilation, oximetry assessment, and use of Cough Assist®	2
6. Polypharmacy, comorbidities, and follow-up	1
7. Augmentative and Alternative communication	3
8. Mobility, transfer, and positioning (pressure wound prevention and use of technical aid for mobility and transfers)	3
9. Emergency situations	x
10. Caregiver self-care	5

Note. ALS = amyotrophic lateral sclerosis; X= none question was allotted to this module

The theoreticals approaches included slide presentations and round tables that discussed the main concerns of the caregivers related to the theme in each module. The practical sessions were performed using hands-on approaches, and the caregivers had the opportunity to handle the most used equipment and devices in ALS patients such as: wheelchairs, transfer board, splints, portable ventilators (BIPAPs), oximeter, Cough Assist® machine, nebulizers, PEG and technical aids for feeding and for helping patients to change clothes.

The characteristics of the Training Program regarding the resources used and the time allotted in each module are described in Table 17.

Funding and Project Management

The project "Training Program for ALS Caregivers" was submitted on behalf of Portuguese ALS association for funding through the national program of the National Institute for Rehabilitation. It has been approved and funded 2 years consecutively.

Financial support under this national program aims to promote the exercise of the rights of people with disabilities through the development of annual projects for nongovernmental organizations (NGOs) that integrate the principles of United Nations Convention on the Rights of Persons With Disabilities (148).

The funding allowed performing 5 Training Programs during 2 years in two big cities of Portugal: Lisbon (Southern region—3 TP) and Oporto (Northern region—2 TP). It helped on the acquisition of technical aids used during the hands-on sessions, stationery items and travel expenses of the trainers' team as well as acquisition and dislocations of equipment from Lisbon to Oporto city (a distance around 450 km between both). The Training Program in Lisbon was held in the installations of Portuguese ALS association and, in Oporto, in the São João do Porto Academic Hospital.

At the end of each Training Program, participants received a questionnaire to score the level of satisfaction with their participation using a Likert scale rating from 1 to 5 (1 = very unsatisfied, 2 = unsatisfied, 3 = slight satisfied, 4 = satisfied, and 5 = very satisfied). This questionnaire reported details about the structure of the program (level of knowledge of the instructor, methodology used [theoretical/hands-on], relevance of contents, audiovisual equipment, objectivity and duration of the Training Program). It was a compulsory request from the funder. The Training Program project was approved by the Ethical Committee of the National Institute of Rehabilitation, Govern of Portugal. The study was approved by the Institutional Review Board of the ALS Portuguese Association.

Statistical Analyses

We used descriptive statistical analyses—frequency distribution for categorical variables and mean ± standard deviation for continuous variables. We used SPSS package version 19.

Table 17. Description of the Training Program.

Modules	Theme	Professional involved	Hours allotted	Equipment used (hands-on sessions)	Theoretical (T)/hands on (Ho)
1st day					
1. General concepts about ALS	Brief clinical review about ALS	PT	2	—	T
2. Rights and obligations for patients and caregivers	Social support and legislation of the National Health System for ALS patients	SW	2	—	T
2nd day					
3. How to communicate better with ALS patients and health care team	Communication skills	Nurse	4	—	T
4. Basic daily care and nutrition	Hygiene care, feeding (oral intake and PEG)	Nurse	4	Aids to daily living[a]—PEG syringe for demonstration	T/Ho
3rd day					
5. Respiratory support	Respiratory management: noninvasive ventilation, oximetry assessment, and use of Cough Assist®.	PT	4	BiPAP machine, portable oximeter, Ambu bag, and ex-insufflator (Cough Assist®)	T/Ho
6. Polypharmacy, comorbidities, and follow-up	Therapeutic management	Nurse	2	—	T
7. Technical aids for communication	Augmentative and alternative communication devices	BE	1	Tablets and portable computer	T/Ho
4th day					
8. Mobility, transfer, and positioning (pressure scar prevention and use of technical aids for mobility and transfers)	Mobility	PT	6	Recliner, wheelchair, transfer boards, walking frames, and rollators	T/Ho
9. Emergency situations: choking, deep venous thrombosis, sudden death falls—What to do?	Emergency situations	Nurse	1	—	T
5th day					
10. Caregiver self-care	Burnout prevention	PT/nurse	4	—	T
Written examination and satisfaction questionnaire completion, and closure of the Training Program	Assessment		2	—	T
Total			32 hours		

Note. ALS = amyotrophic lateral sclerosis; PEG = percutaneous endoscopic gastrostomy. [a]Aids to daily living—dressing, bathing, and dinning (cups and drinking aids and kitchen supplies). PT – Physiotherapist; SW – Social Worker; BE – Biomedical Engineer.

6.4 Results:

A study flowchart (Figure 20) summarizes the sociodemographic characteristics, final marks in the written exam, scores in the questionnaire of satisfaction and the relationship between the caregiver and the ALS patients. The participation on the Training Program was excellent. The total number of registrations requested for all the Training Programs was 84. However, the number of participants was lower than the inscriptions requested.

We had 77 participants for all five Training Programs. Each one had an average of 15 participants. The main reason to declining participation was the lack of secondary caregiver during the weekends. The percentage of successful completion in the written exam (average) was 70% (73. 32% in Lisbon, and 78. 47% in Porto). Table 18 presents the percentage of the participants with correct answers for each module. The level of satisfaction with the participation in the Training Program was 80.5% very satisfied, 13% satisfied and 6.5% for abstentions.

Thirty percent of participants were not present full time during the Training Program and the main causes were absence of a secondary caregiver and/or a clinical intercurrence with the ALS patients. All participants reported that the participation in the Training Program was a very pleasant experience with great interaction and sharing of knowledge that helped them to coping better with the consequences of the disease.

Figure 20. Study flow chart

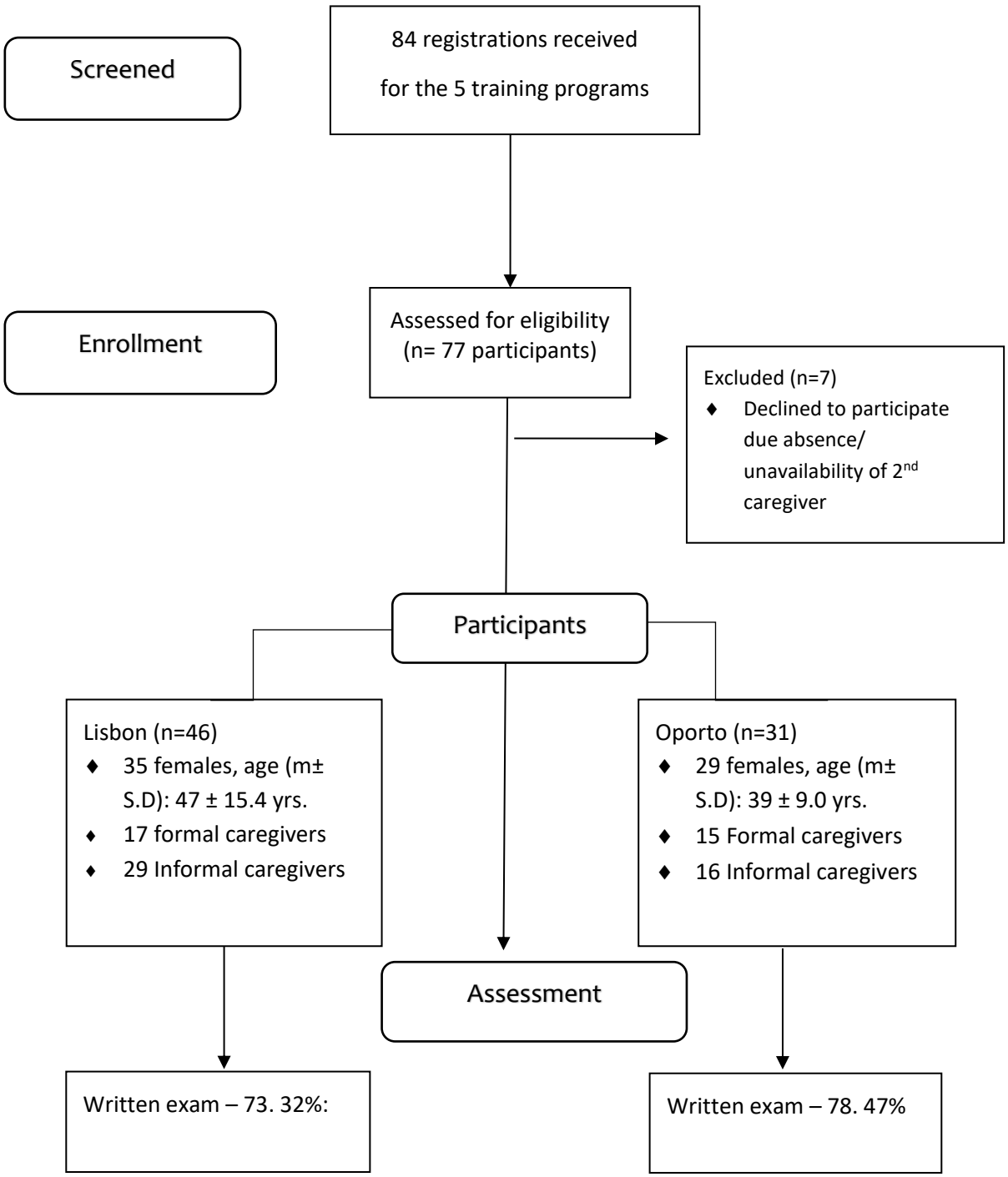


Table 18. Percentage of the participants with correct answers for each module (N = 77).

Modules	
1. General concept about ALS	84%
2. Rights and obligations for patients and caregivers	95.4%
3. How to communicate better with ALS family member and with health care team	81.8%
4. Basic daily care and nutrition	90.9%
5. Respiratory support: noninvasive ventilation, oximetry assessment, and use of Cough Assist	45.4%
6. Polypharmacy, comorbidities, and follow-up	90.9%
7. Augmentative and alternative communication	45.4%
8. Mobility, transfer, and positioning (pressure scar prevention and use of technical aids for mobility /transfers)	72.7%
9. Emergency situations	X
10. Caregiver self-care	69%
Note. ALS = amyotrophic lateral sclerosis; X= none question was allotted to this module	

6.5 Discussion:

The uncertain timeframe progression and long-term care required for the ALS management make that the admission of these patients in acute hospitals a non-sustainable option. Moreover, most of the nursing home facilities in our country have no specialized health staff to supply all the ALS patient needs. Initiatives that improve the care management at home can be an alternative solution.

An important part of the clinical management is identifying and following-up the caregiver capacity to perform self-care and care to the patient (149). This follow-up may include home evaluations and provide information about the disease progression, drug interactions, and identification of a contact person in the community health center, to quickly manage complications/exacerbation of the clinical status or emergencies, including back-up plan for caregiver incapacity.

Education and training of the caregiver facilitate the adherence to the proposed health-care plan favoring greater clinical benefits (150). The involvement of a specialized palliative care staff can improve the family satisfaction, symptom management, and decreases costs (151).

In this study, we identified familiar caregivers with active productive life and/or with family responsibilities such as children care. For those who are retired and/or older caregivers, the physical impairments make these tasks harder. The written test showed us that there are areas where caregivers still need more support even after the Training Program, namely, respiratory support and augmentative and alternative communication. These findings are aligned with previous studies about stressors in caregivers of terminal diseases (152). The total functional disability in ALS has the potential to produce significant financial constraints, because the family members responsible for the patients care needs to leave their jobs or invest personal financial resources. These families may develop high levels of stress, which can compromise the delivery of a proper health-care leading to hospitalization of ALS patients.

Our study focused on assessing the practical aspects for implementing Training Program for ALS caregivers, such as predicted cost, main barriers for participation and learning of target skills from an appropriate intensity and duration of the Training Program through theoretical and hand-on approaches. We identified an excellent level of participation by the ALS caregivers as well as a very good outcome in the assessment of learning.

The main challenge identified on the first Training Program was related to the rate of participation per day, which was slightly unstable. A further addendum to the project allowed more flexibility to caregivers to participate more effectively, and participants received a certificate of completion for an attendance of 75%.

The limitations to our pilot study are related to the lack of internal or external validity as well as absence of size effect analyses. However, we believe, to the best of our knowledge, that this is the first feasibility study which describes Training Program for ALS caregivers. It can be worth for the readers and may help them to identify starting points for future similar initiatives.

6.6 Conclusions:

A simple delivery of technical aids to address the functional disability of the patient does not has by itself the capacity to reduce the stress of all social and emotional losses added to functional impairments throughout the disease progression. The training of caregivers of patients with chronic progressive and disabling disease must be part of the clinical management. This type of initiative has the potential to be replicated or adapted in other countries. Further studies must validate the effectiveness of the Training Program and should assess its impact on the proper utilization of health care services and hospital admissions, as well as on the quality of life of patients and caregivers.

Based on paper published in:

Braga, A; Pinto, A. Training program for Amyotrophic Lateral Sclerosis home caregivers: insights from a pilot project. *Home and Healthcare Management & Practice*. *Accepted on 18 Dec 2017. Epub on 18 Jan 2018.*

Chapter 7:
Disease Progression in Low resources settings:
Preliminaries results from studies with South African ALS patients

This chapter presents results of 2 works performed in South Africa which appointed a potential impact of the low resource settings on the disease progression. The first work demonstrated the inconsistencies identified in the ALSFRS-R score during performance of a longitudinal study about the clinical course of MND/ALS in the Western Cape Province – South Africa. The second work presents preliminaries outcomes from a data comparison between ALS patients in Portugal and South Africa related to sociodemographic and clinical management.

7. Disease Progression in Low resources settings - Preliminaries results from studies with South African ALS patients

7.1. Effects of socio-economic and cultural factors on the ALSFRS-R in South African ALS patients: A pilot study

7.1.1 Introduction:

The gold standard tool currently used worldwide for measurement of ALS functionality and disease progression is the ALSFRS-R. The respiratory sub-scores on the ALSFRS-R assess the respiratory functionality through questions 10 (dyspnea), 11 (orthopnea) and 12 (respiratory insufficiency). The Item 12 of ALSFRS-R assesses the respiratory insufficiency based on actual non-invasive ventilation (NIV) usage by the patient. In low and middle-income countries, such as South Africa, NIV usage is influenced by availability of equipment, cultural considerations, and access to healthcare, which is dependent on socioeconomic circumstance. This may lead that the item 12 scores reflect more these external factors rather than the respiratory insufficiency, and therefore, can mask the decline of the ALSFRS-R in a setting where the Non-Invasive Ventilation is not used often.

7.1.2 Objective:

We aimed to investigate the presence of a potential bias – “a false higher total score” - due to lack of provision in ALSFRS-R related to “no use of NIV”.

7.1.3 Methods:

We carried out a pilot study with 103 ALS patients whom are part of a longitudinal study in the Western Cape Province, South Africa. Inclusion and exclusion criteria are summarized in the table 19. We analyzed a sub-group of patients (n=37) who presented with the following criteria: (1) % FVC < 80% of predicted with or without respiratory symptoms or (2) % FVC > 80% of predicted but with respiratory symptoms as assessed by Q10 and Q11 on the ALSFRS-R. We compared both of those criteria to Non-Invasive Ventilation usage measured by Q12 since the first visit (T0) up to 12 months (T2) with 6 months interval.

Table 19. Inclusion and Exclusion criteria

Inclusion Criteria
Age between 18 or older
Diagnosis of possible, probable or definitive according the revised El Escorial criteria for ALS (with Awaji electrodiagnostic criteria)
Diagnosis of PLS, PMA or Progressive Bulbar Palsy
Exclusion criteria
Residing beyond the borders of the Western Cape Province of South Africa (i.e. patients referred for consultation from neighboring provinces or countries
Presence of a different underlying neurological disorder complicating the assessment and diagnosis
Inability to attend follow-up visits at the Division of Neurology, Tygerberg Hospital

7.1.4 Results:

Our sample (n=37) had 26 males, 31 spinal-onset, with mean age at diagnosis of 56.6 years (±10.6), and mean disease duration at inclusion of study: 16.5± 12.7 months. The mean ALSFRS-R (±SD) was 35.7 ± 7.45 at T0, 29.4± 9.35 at T1 (up 6 months), and 27.4± 9.78 at T2 (up 12 months). Clinical and demographics features are summarized in Table 20. The percentage of patients with FVC < 80% was 83.8% at T0, 86.7% at T1, and 94.1% at T2. Dyspnea (Q10 – score < 4) was present in 56.8% of patients at T0, 75.7% at T1 and 81.0% at T2, while orthopnea (Q11 score < 4) was present in 18.9% at T0, 48.6% at T1, and 61.9% at T2. Twenty-two patients (59.45%) had FVC < 80% and respiratory symptoms in Q10 and Q11 at T0, and maintained this situation at T1, but did not start NIV (Q12 score = 4) at T1. Only 5 patients (13.5%) were using NIV (Q12 score < 4) at T1. At T2, 21 patients were alive, 4 patients did not need NIV, and 6 (28.6%) patients were using NIV (Q12 score < 4). Eleven patients met criteria for starting NIV but did not do so (Figure 21).

Figure 21. Flow chart study

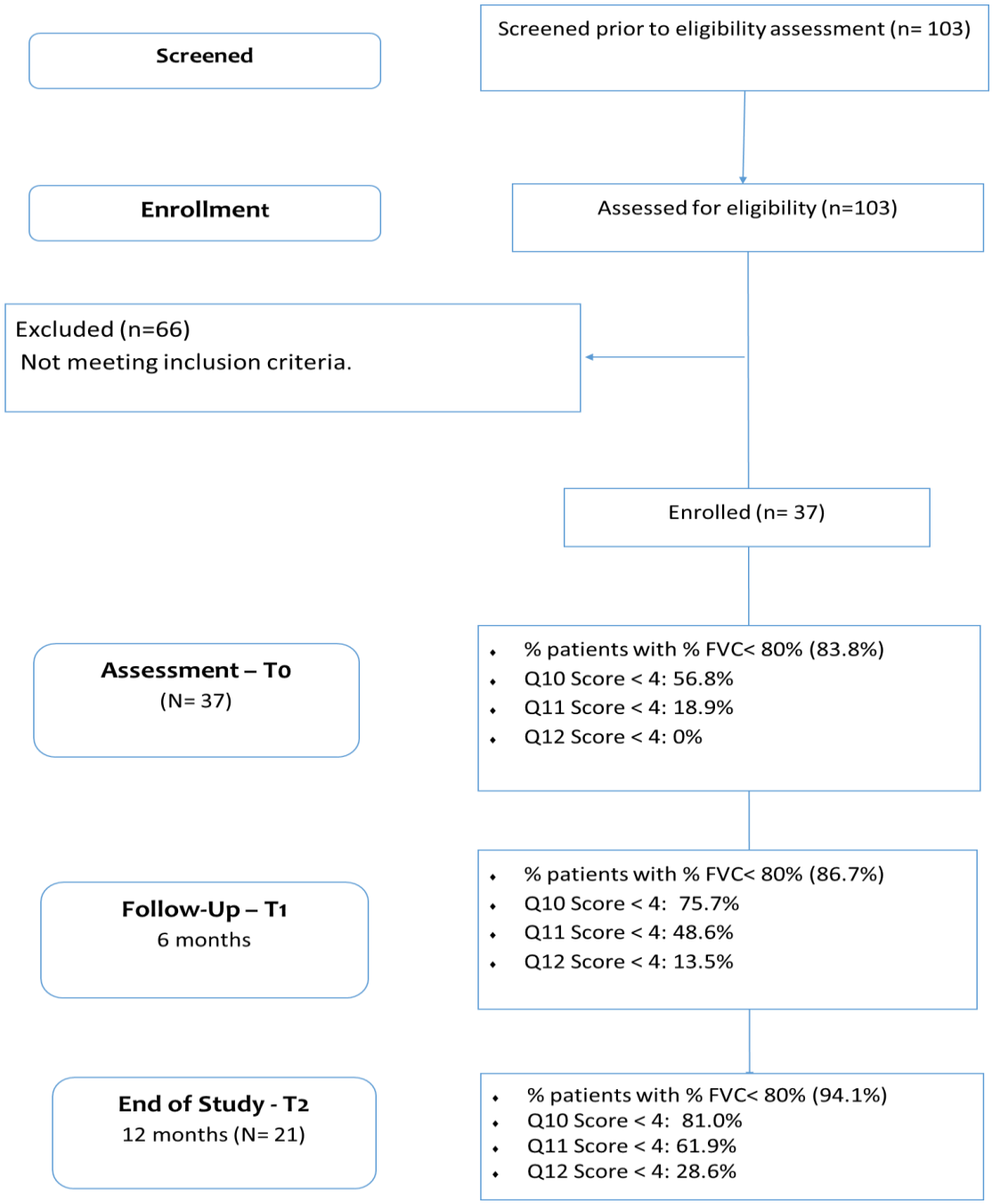


Table 20. Results

Results (37 ALS patients), mean (± S.D)			
Male/female ratio	26/9		
Age at Study	56.6 years (±10.6)		
Disease Duration $_{\text{at study inclusion}}$	16.5± 12.7 months		
Region of Onset(Spinal/Bulbar)	31/6		
	At entry (T0)	At 6 months(T2)	At 12 months (T2)
ALSFRS-R $_{\text{total score}}$	35.7 ± 7.45	29.4± 9.35	27.4± 9.78

7.1.5 Discussion:

As ALSFRS-R does not make provision for "non-use of NIV" in patients with respiratory impairment, a score of 4 on the Q12 is assigned despite the presence of clear respiratory impairment. This may lead to a discrepancy between Q12 and the other items assessing respiratory function on the ALSFRS-R, and subsequent false high scores on the respiratory sub-scale of the ALSFRS-R. Ultimately, this may lead to plateauing of the total ALSFRS-R score, which could potentially introduce bias on the total score in cohort studies or clinical trials in lower and middle-income countries.

7.1.6 Conclusions:

Researchers should be aware of the shortcomings of the ALSFRS-R with respect to the evaluation of respiratory function. Our findings suggest that ALSFRS-R should be restructured or adapted for use in situations where cultural or socioeconomic factors influence the management of respiratory failure in ALS patients.

Based on the Poster presentation:

Braga, AC: Henning, F. Effects of socio-economic and cultural factors on the ALSFRS-R in South African ALS patients: A pilot study. In 28th ALS international symposium in Boston, USA (2017). *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration Journal*. Volume 18, 2017 - Issue sup2: Abstracts from the 28th International Symposium on ALS/MND(A. Braga & Hennig, 2017)

7.2 Comparative study between Portuguese and South African ALS populations: Preliminaries results

7.2.1 Introduction:

Nowadays, we can identify epidemiologic data of ALS from Europe, North America (i.e. United States and Canada), Asia and the Pacific region. There is no published information about ALS from the African Continent.

This brief report presents preliminary data from ALS patient in South Africa unknown up to now. Those South African data were compared with a Portuguese population data regarding the socio-demographic characteristics and clinical follow up. It is expected that this report comes up a small and original contribute about the presence of ALS in African Continent.

7.2.2 Objective:

The objective in this study was not compare different outcomes but verify similarities and differences between a very well defined European ALS population and a never studied African ALS population. It is expectable that we identify discrepancies between these two populations.

7.2.3 Material and methods:

This is a prospective descriptive exploratory study aiming to compare data between Portuguese and South African ALS populations. Data from South African sample were part of a longitudinal study about the incidence and clinic course of MND/ALS in Western Cape Province, which still is ongoing in the Division of Neurology of the Tygerberg Academic Hospital (TBH) and Faculty of Medicine and Health Sciences (FMHS) in Stellenbosch University. This study has been conducted by Dr. Franclo Henning. The deadline for completion of this study is 2020. Data from Portuguese sample came from a study performed to evaluate the role of exercise on disease progression held at Neuromuscular Unit – Neurology Service – Centro Hospitalar Lisboa Norte, which was presented in chapter 4 of this Thesis.

The data analysed in both countries were related to: age of symptom onset and/or ALS diagnosis, ALSFRS-R score at diagnosis, survival up to NIV and PEG, gender distributions, type of onset, survival on the first 12 months from diagnosis. In addition, it is included data of risk factors and cause of deaths for ALS from South Africa.

The Portuguese sample included medical records review of 48 ALS patients registered in the Neuromuscular Unit – Neurology Service – Centro Hospitalar Lisboa Norte – in Lisbon. This Portuguese neuromuscular unit was a specialized ALS Center, which included a Senior Neurologist, a Rehabilitation Physician, a Physiotherapist, a Social Worker, Speech and Language Therapist, and an Occupational Therapist. The follow up of ALS patient is done each three months and there is a regular dedicated ALS Neurology consultation twice per week.

The regular examinations include: functional assessment each 3 months with the revised ALS Functional Rating Scale (ALSFRS-R), the need for Non-Invasive Ventilation (NIV) support which is assessed based on the results of percutaneous nocturnal pulsed oximetry, respiratory function test and abnormal phrenic nerve response as well as the presence of respiratory symptoms (in according with respiratory sub-score of the Amyotrophic Lateral Sclerosis Functional Scale-Revised [R of ALSFRS-R] < 12), and sometimes daytime blood gases and SNIP. Nocturnal pulse oximetry (NPO) is measured continuously during sleep, by fingertip infra-red pulse oximeter. Mean oxygen saturation (SpO^2mean) overnight and Time of $SatO_2$<90 (percentage of time which SpO^2 recording was below 90%) data are collected. Regarding the Respiratory function tests (RFT) it is used %FVC and slow vital capacity, MIP, MEP, and P0.1. All these examinations are part of the usual routine care at the Portuguese unit. The clinical follow up with Allied health professionals is done in according with medical referral.

Data from South African sample were collected at the Neuromuscular Unit in Division of Neurology – Tygerberg Academic Hospital at Cape Town; Western Cape Province. It was included a cohort of 67 ALS/MND patients with follow up until 12 months. Study data were collected and managed using REDCap electronic data capture tools hosted at Stellenbosch University (153). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export

procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Clinical records collected during the consultations are inserted in this database and only authorized personal can access the data. The period of data collection in this study in South Africa was 18 months.

The South African neuromuscular unit is compounded of an MND/ALS specialized Senior Neurologist, who is the responsible for a dedicated MND/ALS clinic. This clinic also provide consultation with Allied health professionals (Occupational Therapist, Speech and Language Therapist, Physiotherapist and Dietitian). The follow up of MND/ALS patient is done each three months and a dedicated Neurology consultation occurs once per week. The regular examinations include: assessment with the revised ALS Functional Rating Scale (ALSFRS-R), and the need for Non-Invasive Ventilation (NIV) is assessed based on the results in Respiratory function tests: Functional Vital Capacity (FVC) – % predicted, Maximum Inspiratory pressure (MIP), Maximum Expiratory Pressure (MEP), and Sniff nasal as well as the presence of respiratory symptoms reported during clinical assessment.

Statistical Analysis:

It was performed the Kolmogorov-Smirnov test to analyze the normality of the sample. Differences between two groups were compared using t-test or a Mann-Whitney test as appropriate for the continuous variables (age at onset, disease duration from onset, evolution up to NIV and up to PEG since the diagnosis, and functionality by ALSFRS-R) and categorical variables (gender, site of onset, NIV use, PEG use and survival up to 12 months from the diagnosis). Significance was set at $p \leq 0.05$. Statistical analysis was carried out in IBM SPSS Statistics 22 (Chicago, IL).

7.2.4 Results:

It was analysed data from 115 patients in total, *n*= 48 in Portugal and *n*=67 in South Africa. The gender distribution and region of onset were very similar between countries. Most patients were male, with the spinal onset. The demographic and clinical characteristics are summarized in Table 21. The survival within the first 12 months after diagnosis was significantly different between ALS patient's populations (p=0.005) (see table 22) as expected. A Spearman's correlation analyses identified that survival in the 12 months from

diagnosis in Portugal was correlated to NIV use (Rho= - 0.32, p=0.024), gender (Rho=0.30, p=0.042) and type of onset (Rho= 0.38, p=0.007), but South African survival in the same time frame did not show any significant relationship with same variables. The cause of death on the first 12 months are detailed in the table 23.

Table 21: Demographic and clinical characteristics of groups

	PT (N=48)	Range	SA(N=67)	Range	p-value
Male¥	32 (66.7%)	-	45 (67.2%)	-	1.0
Age of Onset*	62.02 (±12.44)	34 - 86	58.9(±12.08)	34 - 81	0.18
Type of Onset ratio¥ (Sp/Bb/Resp)	77.1% Sp (37) 22.9% Bb (11)	-	79.1% Sp (53), 19.4% Bb (13) 1.5% (1) Respir.	-	1.0
Disease duration from onset(months)*	11.5 (±7.9)	0.40 – 33.6	13.57(± 9.0)	3 - 47	0.20
Evolution up to NIV (months)	7.30(±8.04)	0.13– 31.13	8.1(±6.3)	2.27-21.33	0.78
Evolution up to PEG (months)*	25.0 (±13.4)	5.67-55.30	3.14 (±2.7)	0.23 – 6.30	**<0.001**
ALSFRS – R Diagnosis (mean ±S. D)					
ALSFRS-R*$_{\text{Total score}}$	42.02(±4.27)	30 - 47	37.15(±7.13)	15 - 47	**<0.001**
Respiratory Function Test (mean ±S. D)					
Forced vital Capacity (FVC)% predic*	89.4(±23.6)	32 - 166	72.6(±23.5)	23 - 123	**0.001**
NIV patients up to 12 months from diagnosis					
Ratio Yes/No NIV use¥	70.8% Yes 29.2% No	-	21.4% Yes 78.6% No		**<0.001**
PEG patients up to 12 months from diagnosis					
Ratio Yes/No PEG use¥	29.2% Yes 70.8% No		9.5% Yes 90.5% No		0.09

Legends: Sp – Spinal, Bb – Bulbar, Resp.- Respiratory, NIV – Non-Invasive Ventilation, PEG – Percutaneous Endoscopic Gastrostomy, % predic - % predicted. Significant differences in bold. **(T-Test*, ¥ Mann-Whitney test)**

Table 22: Survival up to 12 months PT vs SA (Mann-Whitney Test) * p=0.005

	PT (N=48)	SA(N=67)
Dead between diagnosis and 12 months	2 (4.2%)	18(26.9%)
Alive up to 12 months after diagnosis	46 (95.8%)	24 (35.8%)
Loss of follow up after diagnosis	---	17 (25.4%)
Loss of follow up after 2nd visit from diagnosis (6 months)	---	8 (11.9%)

*The test was performed just for the survival on the first 12 months(N=90). The variables loss of follow up are expressed just for descriptive proposal.

Table 23. Cause of Death up to 12 months from diagnosis in SA (N=18)	
Unknown	16.7%
Respiratory failure	61.1%
Sudden death	5.6 %
Aspiration/Pneumonia	11.1%
Sepsis	5.6%

Regarding the follow up of ALS patients by Allied Health Professionals, the Portuguese sample had a full follow up by Physiotherapist (PT), Occupational Therapist (OT) and Speech and Language Therapist (SLT) in a Rehabilitation and/or Neurology service in the Centro Hospitalar Lisboa Norte, at Lisbon. Whenever necessary, ALS patients were referred for others Rehabilitation services in their residence area. In this study it was not identified data about Allied Health Professional (AHP)'s follow-up for ALS patients at Tygerberg Hospital, except for eventual attending on the MND clinic which happened each three months. This clinic started to work at 2015, and ALS patients receive orientations from Allied Health Professionals to manage the consequences of disease progression and follow up from a Senior Neurologist. There are no AHP treatment sessions during this clinical follow up.

During the disease progression ALS patients cope with additional problems beyond the mobility, such as: respiratory failure and loss of weight/swallowing problems, and a few cases with behaviour changes also. The clinical management for feeding problems were significantly different between countries regarding the timing to introduce the PEG use, but regarding the respiratory management there was no difference at the timing to start NIV usage. (See table 21). The difference found was related to the number of patients who had started NIV usage.

We found that 70.8% Portuguese patients were using NIV up to 12 months from diagnosis, while only 21.4% of South African patients started NIV in the same period. Regarding the PEG placement, we found that 29, 2% of Portuguese were submitted to PEG procedure, while only 9.5 % of South African patients performed this procedure in the period of 12 months from diagnosis. All these differences will be commented in the Discussion section.

7.2.5 Discussion:

In African continent we have scarce information about MND/ALS patients, exception made for those countries that present organized health systems as South Africa. Data about the course of motor neuron disorders hails mainly from North America and Europe - regions with predominantly Caucasian populations. None studies have been reported about MND in population groups of African or mixed origin the sub-Saharan region and South Africa until now.

A recent systematic review (154) about the global epidemiology of ALS published on 2013 whose the number of studies by region included: 25 in Europe (11 in Italy), 5 in North America, 6 in Asia and the Pacific, and 1 in Uruguay (South America). In all that studies, most of them referred that the mean ± standard deviation (SD) age for ALS disease onset was 61.8 ± 3.8 years (range 54–67); mean ± SD age for ALS diagnosis was 64.4 ± 2.9 years (range 58–68), and the mean ± SD diagnostic delay was 12.6 ± 2.6 months (range 8.6–16.8).

In this comparative study, the mean age for ALS onset identified in our findings in the Portuguese sample was like the systematic review, but different for South African population, which presented a younger affected population. Additionally, in both countries, it was found a range of age disease onset wider (30' - 80' years old), which is different of the findings in the aforementioned Systematic review. Our finding is closer to the Chinese ALS population, which are younger also (55.07 ±10.74;33-80) (155). A wider range of age of ALS onset (30's – 80's) is an interesting finding whether we consider the life expectancy for both populations. In South Africa the life expectancy at birth for 2017 was estimated in 61.2 years for males and 66.7 years for females. Although in South Africa the life expectancy was around 60's years, we identified patients with age onset around the 80's. However, it might be affected by the sample size also. This study analysed an ALS/MND population in Western Cape Province – South Africa that contains only 11.5 % of South Africa population (156) , and a higher development level with a health system with more available resources. Those can be considered confounding factors.

Comparatively with South Africa, the life expectancy at birth in Portugal is higher: 76.2 for males, and 82.9 for females in according with latest data published by Index Mundi in 2017

(157). The population distribution estimates by ethnic group and age in South Africa is demonstrated in the table 24.

Table 24. Mid-year population estimates for whole South Africa by population group and gender, 2017

Population group	Male		Female			Total
Number	**% distribution of males**	**Number**	**% distribution of females**	**Number**		**% distribution of total**
African	22 311 400	80.8	23 345 000	80.8	45 656 400	80.8
Coloured	2 403 400	8.7	2 559 500	8.9	4 962 900	8.8
Indian/Asian	719 300	2.6	689 800	2.4	1 409 100	2.5
White	2 186 500	7.9	2 307 100	8.0	4 493 500	8.0
Total	**27 620 600**	**100,0**	**28 901 400**	**100,0**	**56 521 900**	**100,0**

The functionality (ALSFRS-R) and the Forced vital capacity (%FVC predicted) at the diagnosis moment were significant different between countries(p=0.001), although the range of age of onset were similar. In South Africa the patients presented a lower level of functionality and %FVC predicted compared to Portugal, suggesting a more aggressive disease progression.

We identified a higher number of patients submitted to PEG up to 12 months from diagnosis in Portugal than SA, but the evolution up to use of PEG was shorter in SA than Portugal. This finding suggests that in SA the patients were in a more advanced stage of the disease than Portugal at the diagnosis moment and can be confirmed by the lower ALSFRS-R and FVC. Regarding the Non-invasive ventilation patients, it was identified a higher number in Portugal than SA (see table 21). However, this can be potentially related to healthcare access and/or lack of official policies for respiratory care in SA. The Survival in SA was shorter than in Portugal up to first 12 months in male patients with spinal onset without NIV use. In Portugal we found a shorter survival only in 2 patients under NIV, who were female and bulbar patients, whom in according with the current literature, present a worse prognosis. As describe previously, most of cause of death in SA cohort were related to respiratory problems.

All these factors suggest that in the SA cohort the disease presented a disease evolution more aggressive than Portugal. However, it is not possible affirm with certainty whether this faster progression in SA was related or not to other confounding factors like other co-morbidities, social conditions and health care access, whom could have affected the diagnosis timing and the NIV access. Further studies need be addressed to clarify this point of view.

In Portugal, the healthcare policy for patients that need respiratory support at home are very well defined in documents issued by the National Health System, which are based on the national consensus from experts in the field with scientific support of international guidelines (158). Patients have access to respiratory support at home based on a clinical report from a specialist consultant from the National Health System.

Regarding the clinical management in South African sample, it was identified no guidelines or official documents from National Department of Health related to prescription of respiratory support at home.

The data (empirics) that describing the main obstacles to start the NIV usage were identified from healthcare professionals in the clinical practice and from personal reports of patients. That can be described as: "*…patients and families often are not aware of benefits of NIV usage…", "…most patients are dependent on MND/ALS association and others charity associations to obtain portable ventilators…", "… NIV often is introduced at late stage due to lack of specialized ALS care out of limits of big cities that would ensure early identification of the respiratory failure…"*.

Social factors like power supply for patients in poor communities and /or cultural factors exclude those patients from the NIV use, and the financial costs often limits the access to basic systems which do not include humidification and different interfaces that would improve the NIV compliancy. All these factors contrast with the reality described in the trials performed in more developed countries and must be object of further analyses.

A study published by Braga (150) in 2015 refers that 90% of ALS patients in the Portuguese Neuromuscular unit in Lisbon were referred for Medicine and Rehabilitation Service and received technical aids and respiratory support. However, this study analysed regionals differences between ALS follow up in Portugal and cannot be considered representative of

all ALS Portuguese population. Regarding the role of exercise in the rehabilitation context, there is not data about the clinical approach of Physiotherapist in ALS/MND patients published in the African continent.

7.2.6 Conclusions:

A recent systematic review published in 2014 (159) about the Epidemiology of neurodegenerative diseases in sub-Saharan Africa(SSA) concluded that the body of literature on neurodegenerative disorders in SSA is large about dementia and HIV-related neurocognitive disorders but limited for other neurodegenerative disorders. Shortcomings are related to few population-based studies, heterogeneous diagnostic criteria and uneven representation of countries on the continent. There are important knowledge gaps that need urgent action, to prepare the sub-continent for the anticipated local surge in neurodegenerative diseases. The work from Quansah and colleagues (160) in Sub-Saharan Africa shows that the published literature about MNDs is based in populations 'studies, and describes only disease prevalence, genetic factors, and other risk factors. Its findings are indicators that the amount of research evidence on MNDs in this region of Africa is scanty; and suggested that molecular and genetics-based studies are particularly lacking.

Neurodegenerative disorders research is leaded by South Africa with a network involving the USA, the UK, as well as African countries such Zambia. The chief field that emerged was on patient and hereditary as well as treatment. Public health policies were lacking fields in research whereas prevalence is estimated to be important in every country (161).We hope this report with preliminaries outcomes can contribute to launch some starting points for futures studies on the ALS/MND in South Africa.

Chapter 8:

General Discussion and Conclusions

8. General Discussion and Conclusions:

8.1 Introduction:

Amyotrophic Lateral Sclerosis (ALS) belongs to a wider group of disorders known as motor neuron diseases, which are caused by gradual degeneration and death of motor neurons. These motor neurons initiate and provide vital communication links between the brain and the voluntary muscles. The disease starts in an unsymmetrical mode and regardless of where the symptoms first appear, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Individuals may develop problems with moving, swallowing (dysphagia), speaking or forming words (dysarthria), and breathing (dyspnea), until the individual lose the total control of the body movements. Despite no effective treatment, the clinical management of the disease evolved drastically in the last years. Supportive care is best provided by multidisciplinary teams of health care professionals, and Physiotherapy can enhance an individual's independence and safety throughout the course of ALS using special equipment and recommendations of exercises programs without overworking muscles, which beyond improvement on the cardiovascular system may also help to fight fatigue and depression.

The cardiovascular benefits from an aerobic exercise program was one of the main findings from this study. In addition, we tested positively the feasibility to perform a controlled home-exercise protocol in ALS patients by using modern monitoring facilities. A number of further results were considered relevant for our work, in particular the importance of NIV device settings adaptation over disease progression, teaching home management of ALS patients for nonprofessional caregivers, disease-care in non-developed countries and its impact on respiratory care as compared to our ALS center in Lisbon.

8.2. The contribution of this thesis for the role of exercise on the disease progression:

The controversy about exercise in ALS is a long-standing issue, not solved by the few studies available. While exercise is seen as a powerful therapy, it can also bring risks related to progressive neuronal degeneration, ageing, and the possible presence of other co-morbidities. In ALS patients, weakness due to neuronal loss and physical deconditioning (loss of muscle performance) from inactivity are associated. Immobility can cause several muscle-skeletal complications, as joint tightness and contractures progressing to pain.

Physical exercise has been suggested to promote growth factor delivery in experimental animal models of ALS. However, the aerobic exercise is understudied in ALS patients due the suspicious that the exercise could be harmful for this population. Meeting the recommendations from the last Cochrane review about therapeutic exercise in ALS, we decided to study the impact of aerobic exercise in ALS progression.

We hypothesized that aerobic exercise could contribute for a potential delay in the disease progression. Additionally, we decided it would be important to analyze the aerobic capacity performance before and after the protocol.

In our study, we identified a delay of 5.7% on the functional decline favoring the intervention group (effect size d= -0.26). In the intervention group VO_2 peak remained stable as compared with 46% decrease in the control group. These results reinforce the positive outcome described in previous (162) and more recent publications (85), which supports the concept that physical activity is not a risk factor for ALS progression, and may slow functional decline.

The preservation of the VO_{2peak} throughout study time period is a relevant finding that is coherent with Mezzani and colleagues results (82), who showed that the reduced peripheral O_2 utilization is consistent with deconditioning as the main cause of impaired exercise capacity in this population.

Lanfranconi et al (92) study evaluated the muscle oxidative function during the exercise using near infrared spectroscopy (NIRS) and CPET. They suggested that "*the clinical evaluation alone can hardly discriminate the real exercise tolerance otherwise measurable*

by CPET: some ALS patients considered "inefficient" at the ALSFRS-R showed a still residual capacity from the VO_{2peak} point of view". Our results agree with the authors.

The sustained aerobic capacity in the controlled exercise group compared to standard care group allow us to affirm that the aerobic exercise is safe and provide benefits for ALS patients whether a controlled intensity and closer specialized supervision are present. Our explorative trial showed a very high statistical power and can be considered conclusive. Regarding a possible effect from aerobic exercise on the neuroprotection effect, as suggested in the previous study of our team (89), remain unexplained and must be focus of a future longitudinal study.

The main limitations and concerns that can arise during this type of work are related to dropouts or decreased motivation of some patients to cooperate due to fast progression. The unpredictability of the disease and the extensive and expensive nature of the costs to evaluate biomarkers linked to functional outcomes, sometimes, also can compromise outcome analysis. Because this, the use of multicentric trials can be a more suitable choice to overcome these limitations.

We believe that our findings can support future therapeutic approaches and help to demystify the belief that the exercise can be harmful for ALS patients.

8.3 The contribution of this Thesis for the use of telemedicine to monitoring rehabilitation programs for ALS patients.

There is a growing interest on the use of telemedicine for supporting patients, including those requiring rehabilitative services which can help to manage their condition (163).

As we describe previously in the Chapter 4, the level of suitable physical effort that ALS patients may perform, without a specialized supervision, is a hard task. Nevertheless, the difficult to access an interdisciplinary care in community-based settings is a reality for ALS patients in several countries. Some of the barriers to access ALS centers are related to long commute to central hospitals and the probable need of a caregiver to help them during dislocations. Eventually, patients often choose to abandon the physiotherapy follow up. All these concerns lead us to assess the feasibility to delivery an individualized aerobic exercise program monitored through wireless device which could address this issue.

The early detection of overtraining as well as the prevention of shortfalls on care should be part of the clinical management. A physician-centered clinical management model is not sustainable for critical patient as in Amyotrophic lateral sclerosis (ALS). The Tele-rehabilitation already has been proposed (163-165) as a health service option that may improve exercise-related outcomes, ensuring patient safety during exercise and facilitate the access to rehabilitation interventions in other clinical conditions.

Moreover, it has the potential to engaging local and community-based services with the specialized centers letting the clinical decision-making process faster and closer. It should be explored in a context of collaborative self-management (166) and perceived as a complementary means to maintain individuals in their own community, or as an alternative to conventional hospital outpatient and physicians visits (167) .

Although some controversies issues arise, like storage and protection of data, accessibility, financial investment, health staff training and a potential lack of humanization on the patient-healthcare professional relationship, we can suggest that our findings may provide substantial improvements to accessibility of rehabilitations programs.

The main limitations in our study are related to potential selection bias, small sample and an exploratory nature of study meaning that a further validation is necessary on a larger

trial before being generalized. Despite of these limitations, the feasibility outcome for the use of tele-monitoring system for exercise program in ALS patients was established.

8.4: The contribution of this Thesis for the Management of Respiratory Failure with Non-Invasive Ventilation:

Evidence from several retrospective and some prospective studies indicated that NIV may be associated with improvement in survival (6), and the use of NIV in ALS has greatly increased. Unfortunately, the interaction between patient and ventilator is frequently suboptimal and that patient-ventilator asynchrony is common. Our findings indicated the need of a closer collaboration between the patient and clinician regarding to set up for respiratory parameters of NIV to reach all the benefits on the symptomatic management for the respiratory failure in ALS patients.

In our study presented in sub-chapter 5.3, we hypothesized whether the ventilation settings and compliancy data joined to respiratory function measurements would have influence on the functional decline as well as on the survival in ventilated ALS patients. We analyzed a set of data recorded from the software used in the Non-invasive ventilators, measurements from Nocturnal pulse oximetry and respiratory function tests in a prognostic model to identifying predictors of functional decline and survival in a cohort of ventilated patients.

We identified parameters of Non-invasive ventilation (IPAP, IS, rT, and BR back-up), compliancy data (%of spontaneous cycling, I/E ratio, nº of hours of use/day and the mean BR) and Nocturnal pulse oximetry data (SpO_2mean) as predictors of functional decline, and it suggests that the variables affecting the respiratory comfort of patient are indeed a prerequisite to a better NIV compliance and affects the ALS survival. This was the first study which analyzed the ventilators settings as survival predictive factor.

The modern technology has provided portable mechanical ventilators with very sensitive algorithms, which allow detecting a large range of respiratory symptoms-related variables. However, as cited by Kallet and colleagues, 2011 (143) "…*while the act of breathing is mechanical and quantifiable, it is also a sensory experience upon dependent on the individual*."

The human being has the capacity to identify unique breath-related sensations that sometimes cannot be detected by the equipment, and in this point, a trustable relationship

between the clinician and patient, respecting and validating theirs limits and complaints may have a potential impact on the NIV compliancy and on the survival of an ALS patient.

Compliance plays a relevant role on the respiratory support. An optimized approach which avoid a NIV failure and compliance concerns, are the added value of a closer follow up on the respiratory insufficiency. Non-Invasive Ventilation can have a modifier role play on disease progression whether a rigorous management is achieved and can make the difference on the survival in these patients.

8.5 The contribution of this Thesis for the understanding on the role of caregivers in the management of disease:

Nowadays, the current guidelines about ALS clinical management highlights the role of the caregiver and the *side effects* related to their role during the disease progression.

In 2005, Vianello and colleagues (121) reported in their study that the use of mechanical Insufflation-Exsufflator (MI-E) for clearance of secretions was effective and safely carried out by trained nonprofessional caregivers (i.e., patient's home care attendant and/or family members), and emphasizes that the combined use of NIV and MI-E into home management of respiratory problems can potentially reduce the need for hospitalization and maintains higher quality of life. In 2010, Paganini and colleagues (168) studied the burden of care in ALS caregivers and suggest that the patient's loss of physical functions was positively related with caregiver burden, anxiety, and somatic expression of depression.

Based on these premises, it was performed a pilot project, in parallel with this thesis, to develop and implementing a home caregivers training program to provide essential care skills to manage the disease progression and helping the caregivers to cope with the physical and emotional challenges. We aimed to fill the gap and meet the recommendations for ALS caregivers and burden of care suggested in the guidelines for clinical management in ALS published by European Federation of Neurology Societies (EFNS) in 2012.

The training program was carried out in 2013 and 2014 and reached a total of 77 caregivers in Lisbon and Porto. As Oliver and colleagues (149) have suggested "*an important part of the clinical management is identifying and following up the caregiver capacity to perform self-care and ability to provide safe care to the patient*".

In this project, we identified an excellent level of participation as well as a very good outcome in the assessment of learning (above 70% successful approval), and the aim of provide care skills for ALS caregivers based on scientific evidence was achieved. On the other hand, the main limitation factor to participation in the project was the absence of a secondary caregiver. Unfortunately, the lack of specialized healthcare professional in health community centers still is a potential challenge in the improvement on the quality

of life and personal life autonomy for the ALS caregivers in Portugal. Further studies must analyze the impact of these initiatives on the quality of life for caregivers and patients, and the cost effectiveness for the healthcare system.

Currently, this training program still is performed by the APELA, and others public health services adopted the idea and started adapted training programs for ALS caregivers in cities at the countryside of Portugal.

8.6 The contribution of this Thesis for the understanding on the disease progression in Limited resources setting:

In the South African context, the clinical management of ALS suffers from a lack of specialized healthcare professionals. The respiratory support to manage respiratory failure in ALS faces hard challenges regarding NIV use. This is largely related to unavailability, which is dependent on socioeconomic and/or cultural circumstances. We performed two exploratory studies aiming to understand the effects of cultural and social environment on disease management and progression. The first study investigated the presence of potential bias in the respiratory sub-score due to NIV unavailability, which can lead to flattening of the ALSFRS-R decline, and thereby resulting in inaccurate assessment of disease progression. The second study explored similarities and differences with the management of ALS in Lisbon.

Despite the social and economic development in Europe and USA, ALS patients in South Africa potentially share the same personal, social, and healthcare burden. The health systems in developed countries potentially might relief the impact of these stressors in the ALS patients and their families, but in lower and middle-income countries these stressors are a very relevant concern. The lack of a specialized support, underprivileged access to healthcare and absence of alternative solutions, which allows a better clinical management of the disease, constitutes a worrying reality for the ALS patients and their families in South Africa. More funding is necessary for research, to clarify the policymakers about the devastating emotional, social and economic effects that this disease can cause in the families. These preliminary results hope inspire other researchers to give more attention to the different economic and social contexts in the development of clinical guidelines. We suggest studies about alternative solutions that can be applied in low resource settings.

The main limitations of these studies are their exploratory nature and small samples sizes. Future investigations must be performed to confirm these findings.

8.7 Prospects for the future:

The research on the potential role of exercise on the ALS has relatively increased last years. Previous studies from colleagues in our unit have demonstrated relevant contributions of the exercise in ALS. A study from Pinto and colleagues (63) suggests that the respiratory muscle training in early stages of the disease may provide a transitory mild benefit as measured on the clinical evaluation and respiratory fatigue tests, and a longer survival compared to the control group.

In this thesis, it was possible to identify a sustained aerobic capacity in the exercise-controlled group compared to control group, suggesting a clear benefit of the use of CPET to tailoring an exercise program for ALS patients. It would be interesting to analyze if the aerobic capacity could be related with changes on the Vascular Endothelial Grow Factor as suggested previous study in 2014 (89).

VEGF is one of the critical factors released in the tissues surrounding the small vessels during the process of angiogenesis (169). Studies from others neuromuscular diseases using low-to moderated-intensity strength and aerobic exercise programs have shown beneficial effects like increase of both angiogenesis and neurogenesis processes in regions of the brain (170) .

Previous studies showed that locomotion on a treadmill can increase the density of blood vessel and cortical and striatal angiogenesis in the brain (45).

Recently the use of modern techniques as Near InfraRed Spectroscopy (NIRS) was applied to detecting early stages of oxidative deficiency in ALS, disclosing individual impairments in the O_2 transport and utilization chain during an exercise protocol. NIRS is a non-invasive method that allows the monitoring of tissue oxygenation using the principle that near-infrared light absorption characteristics of hemoglobin (Hb) and myoglobin depend on their O_2 saturation at different wavelengths (780 and 850 nm, respectively) (171,172).

Considering the growing interest about the exercise impact as non-pharmacologic therapy in ALS in the last years, the understanding of how tailored exercise programs can influencing neuroprotection through modulation of neurotrophic factors still need more research. Open questions are the impact of exercise on the progressive loss of motor

neurons and the impact of exercise on the levels of neuroprotective factors like as VEGF. Perhaps, a future study should consider a tailored exercise program VEGF level variation and neurophysiologic studies to quantify lower motor neuron pool. Further studies are needed to answer these questions.

References:

References:

1. Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: "prepare for the worst and hope for the best". Jama. 2007;298(2):207-16.

2. Riva N, Agosta F, Lunetta C, Filippi M, Quattrini A. Recent advances in amyotrophic lateral sclerosis. J Neurol. 2016;263(6):1241-54.

3. Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. Nat Rev Neurol. 2014;10(11):661-70.

4. Miller RG, Jackson CE, Kasarskis EJ ea. Practice parameters update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Neurology. 2009;73.

5. Orsini M, Oliveira AB, Nascimento OJM, Reis CHM, Leite MAA, de Souza JA, et al. Amyotrophic Lateral Sclerosis: New Perspectives and Update. Neurology International. 2015;7(2):5885.

6. Radunovic A, Annane D, Rafiq MK, Brassington R, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;10: Cd004427.

7. Dal Bello-Haas V, Florence JM. Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database Syst Rev. 2013(5): Cd005229.

8. Kiernan MC. Amyotrophic lateral sclerosis and the neuroprotective potential of exercise. J Physiol. 2009;587(Pt 15):3759-60.

9. de Almeida JPL, Silvestre R, Pinto AC, et al. Exercise and Amyotrophic Lateral Sclerosis. Neurological Sciences. 2012;33(9).

10. Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, et al. Controversies and priorities in amyotrophic lateral sclerosis. Lancet Neurol. 2013;12(3):310-22.

11. Talbot K. Motor neuron disease. Postgraduate Medical Journal. 2002;78 (923):513-9

12. Therrien M, Dion PA, Rouleau GA. ALS: Recent Developments from Genetics Studies. Curr Neurol Neurosci Rep. 2016;16(6):59.

13. Pochet R. Genetics and ALS: Cause for Optimism. Cerebrum. 2017. 121.

14. Siddique T, Ajroud-Driss S. Familial amyotrophic lateral sclerosis, a historical perspective. Acta Myol. 2011;30(2):117-20.

15. Sellier C, Campanari ML, Julie Corbier C, Gaucherot A, Kolb-Cheynel I, Oulad-Abdelghani M, et al. Loss of C9ORF72 impairs autophagy and synergizes with polyQ Ataxin-2 to induce motor neuron dysfunction and cell death. Embo j. 2016;35(12):1276-97.

16. Cruts M, Engelborghs S, van der Zee J, al. e. C9orf72-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.Posted on 2015 Jan 8.

17. Al-Chalabi A, van den Berg LH, Veldink J. Gene discovery in amyotrophic lateral sclerosis: implications for clinical management. Nature Reviews Neurology. 2016; 13:96.

18. Chia R, Chiò A, Traynor BJ. Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. Lancet Neurol. 2018;17 (1):94-102.

19. Li H-F, Wu ZY. Genotype-phenotype correlations of amyotrophic lateral sclerosis. Transl Neurodegener. 2016;5(3):3.

20. Kenna KP, van Doormaal PTC, Dekker AM, Ticozzi N, Kenna BJ, Diekstra FP, et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. Nat Genet. 2016;48(9):1037-42.

21. Pupillo E, Messina P, Logroscino G, Beghi E. Long-term survival in amyotrophic lateral sclerosis: a population-based study. Ann Neurol. 2014;75 (2):287-97.

22. van Rheenen W, Shatunov A, Dekker AM, McLaughlin RL, Diekstra FP, Pulit SL, et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. Nat Genet. 2016.

23. Excellence NIfHaC. The use of non-invasive ventilation in the management of motor neurone disease. NICE Clinical Guideline 105. London, UK2010

24. Miller RG, Brooks BR, Swain-Eng RJ, Basner RC, Carter GT, Casey P, et al. Quality improvement in neurology: Amyotrophic lateral sclerosis quality measures: Report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. Neurology. 2013;81(24):2136-40.

25. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. Orphanet Journal of Rare Diseases. 2009; 4:3-.

26. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, et al. A comprehensive review of amyotrophic lateral sclerosis. Surgical Neurology International. 2015; 6:171.

27. Turner MR, Kiernan MC. Does interneuronal dysfunction contribute to neurodegeneration in amyotrophic lateral sclerosis? Amyotroph Lateral Scler. 2012;13(3):245-50.

28. Nichols NL, Van Dyke J, Nashold L, Satriotomo I, Suzuki M, Mitchell GS. Ventilatory control in ALS. Respir Physiol Neurobiol. 2013;189(2):429-37.

29. Cleveland DW, Rothstein JD. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. Nat Rev Neurosci. 2001;2(11):806-19.

30. Woolley SC, Jonathan SK. Cognitive and behavioral impairment in amyotrophic lateral sclerosis. Phys Med Rehabil Clin N Am. 2008;19(3):60717, xi.

31. Pugdahl K, Fuglsang-Frederiksen A, de Carvalho M, Johnsen B, Fawcett PR, Labarre-Vila A, et al. Generalised sensory system abnormalities in amyotrophic lateral sclerosis: a European multicentre study. J Neurol Neurosurg Psychiatry. 2007;78(7):746-9.

32. Pinto S, Pinto A, M D. Decreased heart rate variability predicts death in amyotrophic lateral sclerosis. Muscle & nerve. 2012; September:341-5.

33. Cudkowicz M, Qureshi M, & Shefner J. Measures and Markers in Amyotrophic Lateral Sclerosis. 2004;1(2):273–83.

34. Couratier P. Functional rating scales for Amyotrophic Lateral Scleroses. Rev Neurol (Paris). 2006; Apr (4):502-7.

35. Haverkamp LJ, Appel V, Appel SH. Natural history of ALS in a database population. Validation of a scoring system and a model for survival prediction. Brain. 1995; Jun (118 (Pt3)):707-19.

36. Orsini M, Freitas MR, Mello MP, Botelho J, Cardoso F, Nascimento O, et al. Evaluation Measures in Amyotrophic Lateral Sclerosis. Rev Neurocienc. 2008;16/2:144-51.

37. Montes J, Levy G, Albert S, Kaufmann P, Buchsbaum R, Gordon PH, Mitsumoto H.Development and evaluation of a self-administered version of the ALSFRS-R. Neurology. 2006; Oct (67 (7)):1294-6.

38. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169:13-21.

39. Rutkove S. Clinical measures of disease progression in ALS. Neurotherapeutics. 2015; 12:384-93.

40. Simon NG, Turner MR, Vucic S, et al. Quantifying Disease Progression in Amyotrophic Lateral Sclerosis. Annals of Neurology. 2014;76(5):643-657. doi:10.1002/ana.24273.

41. Wicks P, Massagli MP, Wolf C, Heywood J. Measuring function in advanced ALS: validation of ALSFRS-EX extension items. Eur J Neurol. 2009;16(3):353-9.

42. Braga A, Henning F. Effects of socio-economics and cultural factors on the ALSFRS-R in South African ALS patients: a pilot study.; Boston, USA: Taylor & Francis; 2017.

43. Thomas AG, Dennis A, Bandettini PA, Johansen-Berg H. The Effects of Aerobic Activity on Brain Structure. Frontiers in Psychology. 2012; 3:86.

44. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports. 1985;100(2):126-31.

45. Cobianchi S, Arbat-Plana A, López-Álvarez VM, Navarro X. Neuroprotective Effects of Exercise Treatments After Injury: The Dual Role of Neurotrophic Factors. Current Neuropharmacology. 2017;15(4):495-518.

46. Pinto AC. Exercise role in neuromuscular disorders: A brief review and future directions. Revista Portuguesa de Pneumologia. 2006;12(1, Supplement 1): S21-S5.

47. Kilmer DD. Response to Aerobic Exercise Training in Humans with Neuromuscular Disease. American Journal of Physical Medicine & Rehabilitation. 2002;81(11).

48. Åstrand P-O, Rodahl K, Dahl HA, and, Stromme SB. Text- book of Work Physiology - 4th: Phys iological Bases of Exercise: Champaign.

49. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. Journal of Science and Medicine in Sport. 2010;13(5):496-502.

50. Wasserman K. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications: Wolters Kluwer Health /Lippincott Williams &Wilkins; 2012.

51. Albouaini K, Egred M, Alahmar A. Cardiopulmonary exercise testing and its application. Postgraduate Medical Journal. 2007;83(985):675-82.

52. Datta D, Normandin E, ZuWallack R. Cardiopulmonary exercise testing in the assessment of exertional dyspnea. Annals of Thoracic Medicine. 2015;10 (2):77-86.

53. Forman DE, Myers J, Lavie CJ, Guazzi M, Celli B, Arena R. Cardiopulmonary Exercise Testing: Relevant but underused. Postgraduate Medicine. 2010;122(6, November).

54. Mezzani A. Cardiopulmonary Exercise Testing: Basics of Methodology and Measurements. Ann Am Thoracic Soc. 2017;14(Supplement_1): S3-s11.

55. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-77.

56. Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD. Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. Med Sci Sports Exerc. 2007;39(1):103-7.

57. Herdy AH, Ritt LEF, Stein R, de Araújo CGS, Milani M, Meneghelo RS, et al. Cardiopulmonary Exercise testing: Background, Applicability and Interpretation. Arquivos Brasileiros de cardiologia.2016; 107(5):467-81.

58. Forman DE, Bensimhon D,Chase P. Cardiopulmonary exercise testing. In https://www.thecardiologyadvisor.com/cardiology/cardiopulmonary-exercisetesting/article/584128/. Decision Support Medicine, LLC; 2017.

59. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. Circulation. 2011;123 (6):668-80.

60. Borel B, Provencher S, Saey D, Maltais F. Responsiveness of Various Exercise-Testing Protocols to Therapeutic Interventions in COPD. Pulm Med. 2013.

61. WHO. World Health Organization - Physical activity Fact Sheet nº385. 2015.

62. Mahoney DJ, Rodriguez C, Devries M, Yasuda N, Tarnopolsky MA. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve. 2004;29(5):656-62.

63. Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2012;13(1):33-43.

64. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122 (2):191-225.

65. Binder RK, Wonisch M, Corra U, Cohen-Solal A, Vanhees L, Saner H, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. Eur J Cardiovasc Prev Rehabil. 2008;15(6):726-34.

66. Majmudar S, Wu J, Paganoni S. Rehabilitation in amyotrophic lateral sclerosis: why it matters. Muscle Nerve. 2014;50(1):4-13.

67. Cup et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil. 88 (11), 1452 – 1464. Doi: 10.1016/j.ampr.2007.07.24

68. Beal MF. Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illnesses? Ann Neurol. 1992;31(2):11930.

69. Collaboration Cochrane. Supplementary Guidance for authors undertaking reviews with the Cochrane Consumers and communication review Group England - UK2009 [Available from: http://cccrg.cochrane.org/author-resources.

70. Pinto AC, Evangelista T, Carvalho M, Alves MA, Sales Luis ML. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. J Neurol Sci. 1995;129 Suppl:19-26.

71. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. Lancet Neurol. 2006;5(2):140-7.

72. Chetta A, Aiello M, Tzani P, Olivieri D. Assessment and monitoring of ventilator function and cough efficacy in patients with amyotrophic lateral sclerosis. Monaldi Arch Chest Dis. 2007;67(1):43-52.

73. Andersen PM et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. European Journal of Neurology. 2012;19::360–75.

74. Pinto A, de Carvalho M, Evangelista T, Lopes A, L S-L. Nocturnal pulse oximetry: a new approach to establish the appropriate time for non-invasive ventilation in ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003; Apr. (4(1)):31-5.

75. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624.

76. Vucic S, Krishnan AV, Kiernan MC. Fatigue and activity dependent changes in axonal excitability in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2007;78(11):1202-8.

77. Dal-Bello Haas, Florence JM, Krivickas LS. Therapeutic Exercise for people with Amyotrophic Lateral Sclerosis or Moor Neuron Disease. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD005229. doi: 10.1002/14651858.

78. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Hypotheses to explain the association between vigorous physical activity and amyotrophic lateral sclerosis. Med Hypotheses. 1991;34(2):144-8.

79. Anand A, Thakur K, Gupta PK. ALS and oxidative stress: the neurovascular scenario. Oxid Med Cell Longev. 2013; 2013:635831.

80. Siciliano G, D'Avino C, Del Corona A, Barsacchi R, Kusmic C, Rocchi A, et al. Impaired oxidative metabolism and lipid peroxidation in exercising muscle from ALS patients. Amyotroph Lateral Scler Other Motor Neuron Disord. 2002;3(2):57-62.

81. Sanjak M, Paulson D, Sufit R, Reddan W, Beaulieu D, Erickson L, et al. Physiologic and metabolic response to progressive and prolonged exercise in amyotrophic lateral sclerosis. Neurology. 1987;37(7):1217-20.

82. Mezzani A, Pisano F, Cavalli A, Tommasi MA, Corra U, Colombo S, et al. Reduced exercise capacity in early-stage amyotrophic lateral sclerosis: Role of skeletal muscle. Amyotrophic Lateral Sclerosis. 2012;13(1):87-94.

83. Battista RA, Foster C, Andrew J, Wright G, Lucia A, Porcari JP. Physiologic responses during indoor cycling. J Strength Cond Res. 2008;22(4):1236-41.

84. Hill DW, Rowell AL. Significance of time to exhaustion during exercise at the velocity associated with VO2max. Eur J Appl Physiol Occup Physiol. 1996;72(4):383-6.

85. Lunetta C, Lizio A, Sansone VA, Cellotto NM, Maestri E, Bettinelli M, et al. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. J Neurol. 2016;263(1):5260.

86. van Wessel T, de Haan A, van der Laarse WJ, Jaspers RT. The muscle fiber type-fiber size paradox: hypertrophy or oxidative metabolism? Eur J Appl Physiol. 2010;110(4):665-94.

87. Moreau C, Gosset P, Kluza J, Brunaud-Danel V, Lassalle P, Marchetti P, et al. Deregulation of the hypoxia inducible factor-1α pathway in monocytes from sporadic amyotrophic lateral sclerosis patients. Neuroscience 2011 Jan 13; 172:110-7. 2011; Jan 13(172):110-7.

88. Paganoni S, Cudkowicz M, Berry JD. Outcome measures in amyotrophic lateral sclerosis clinical trials. Clin Investig (Lond). 2014;4(7):605-18.

89. Carilho R, de Carvalho M, Swash M, Pinto S, Pinto A, Costa J. Vascular endothelial growth factor and amyotrophic lateral sclerosis: the interplay with exercise and noninvasive ventilation. Muscle Nerve. 2014;49(4):545-50.

90. Blizzard CA, Southam KA, Dawkins E, Lewis KE, King AE, Clark JA, et al. Identifying the primary site of pathogenesis in amyotrophic lateral sclerosis - vulnerability of lower motor neurons to proximal excitotoxicity. Dis Model Mech. 2015;8(3):215-24.

91. Takken T, Groen WG, Hulzebos EH, Ernsting CG, van Hasselt PM, Prinsen BH, et al. Exercise stress testing in children with metabolic or neuromuscular disorders. Int J Pediatr. 2010;2010.

92. Lanfranconi F, Ferri A, Corna G, Bonazzi R, Lunetta C, Silani V, et al. Inefficient skeletal muscle oxidative function flanks impaired motor neuron recruitment in Amyotrophic Lateral Sclerosis during exercise. Scientific Reports. 2017; 7:2951.

93. Hobson EV, Baird WO, Cooper CL, Mawson S, Shaw PJ, McDermott CJ. Using technology to improve access to specialist care in amyotrophic lateral sclerosis: A systematic review. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17(5-6):313-24.

94. Health V. Remote Mobile Monitoring Services 2014 [Available from: http://www.vitalmobile.eu

95. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007;39(8):1423-34.

96. Pinto A, Almeida JP, Pinto S, Pereira J, Oliveira AG, de Carvalho, M. Home telemonitoring of non-invasive ventilation decreases healthcare utilization in a prospective controlled trial of patients with amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2010; 81:1238-42.

97. Gregory SA. Evaluation and management of respiratory muscle dysfunction in ALS. NeuroRehabilitation. 2007;22(6):435-43.

98. Matecki S, Basil JP. Section iv - respiratory muscles and control of breathing. Respiratory consequences of neuromuscular disease. In: Inc BD, editor. Physiologic Basis of Respiratory Disease. United Sates of America: BC Decker Inc; 2005. p. 319.

99. Rosen CA, Simpson B. Anatomy and Physiology of the Larynx. In: Springer, editor. Operative Techniques in Laryngology. 1 ed: Springer-Verlag Berlin Heidelberg; 2008. p. 3 - 8.

100. Fregosi RF, Ludlow CL. Activation of upper airway muscles during breathing and swallowing. Journal of Applied Physiology. 2014;116(3):291.

101. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev. 2001;81(2):929-69.

102. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99(5):696-702.

103. Vincken W, Elleker MG, Cosio MG. Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders. Am J Med. 1987;82 (1):53-8.

104. Lechtzin N. Respiratory effects of amyotrophic lateral sclerosis: problems and solutions. Respir Care. 2006;51(8):871-81; discussion 81-4.

105. Pinto A. O papel da Reabilitação na Insuficiência Respiratória da Esclerose Lateral Amiotrófica. Portugal: University of Lisbon; 2004.

106. Piepers S, Van den Berg JP, Kalmijn S, Van der Pol WL, Wokke JH, Lindeman E, et al. Effect of non-invasive ventilation on survival, quality of life, respiratory function and cognition: a review of the literature. Amyotroph Lateral Scler. 2006; 7:195-200.

107. Pinto S, Turkman A, Pinto A, Swash M, de Carvalho M. Predicting respiratory insufficiency in amyotrophic lateral sclerosis: the role of phrenic nerve studies. Clin Neurophysiol. 2009;120(5):941-6.

108. Fallat RJ, Jewitt B, Bass M, Kamm B, Norris FH, Jr. Spirometry in amyotrophic lateral sclerosis. Arch Neurol. 1979;36(2):74-80.

109. Pinto S, de Carvalho M. Correlation between Forced Vital Capacity and Slow Vital Capacity for the assessment of respiratory involvement in Amyotrophic Lateral Sclerosis: a prospective study. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(1-2):86-91.

110. Ringel SP, Murphy JR, Alderson MK, Bryan W, England JD, Miller RG, et al. The natural history of amyotrophic lateral sclerosis. Neurology. 1993;43 (7):1316-22.

111. Schiffman PL, Belsh JM. Pulmonary function at diagnosis of amyotrophic lateral sclerosis. Rate of deterioration. Chest. 1993;103(2):508-13.

112. Ferguson KA, Strong MJ, Ahmad D, George CF. Sleep-disordered breathing in amyotrophic lateral sclerosis. Chest. 1996;110(3):664-9.

113. Ogna A, Nardi J, Prigent H, Quera Salva M-A, Chaffaut C, Lamothe L, Chevret S, Annane D, Orlikowski D, Lofaso F: Prognostic Value of Initial Assessment of Residual Hypoventilation Using

Nocturnal Capnography in Mechanically Ventilated Neuromuscular Patients: A 5-Year Follow-up Study. Frontiers in Medicine 2016, 3:40.

114. Esquinas AM: Non-invasive ventilation in amyotrophic lateral sclerosis. Hypoventilation and oxygen desaturation: two faces of the same coin? Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2014, 15(1-2):154-154.

115. Nardi J, Prigent H, Adala A, Bohic M, Lebargy F, Quera-Salva MA, Orlikowski D, Lofaso F: Nocturnal oximetry and transcutaneous carbon dioxide in home-ventilated neuromuscular patients. Respir Care 2012, 57(9):1425-1430.

116. Sancho J, Servera E, Banuls P, Marin J. Predictors of need for noninvasive ventilation during respiratory tract infections in medically stable, nonventilated subjects with amyotrophic lateral sclerosis. Respir Care. 2015;60 (4):492-7.

117. Physicians ACoC. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD and nocturnal hypoventilation: A Consensus Conference Report. Chest. 1999;116(2):521-34.

118. Radunovic A, Mitsumoto H, Leigh PN. Clinical care of patients with amyotrophic lateral sclerosis. Lancet Neurol. 2007;6(10):913-25.

119. Andersen Tea. Laryngeal Response Patterns to Mechanical Insufflation-Exsufflation in Healthy Subjects. Am J Phys Med Rehabil & Vol 92, No 10, October. 2013.

120. Rabec C, Rodenstein D, Leger P, Rouault S, Perrin C, J. G-B. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. Thorax. 2011;66.

121. Vianello A et al. Mechanical Insufflation–Exsufflation Improves Outcomes for Neuromuscular Disease Patients with Respiratory Tract Infections. Am J Phys Med Rehabil. 2005; Vol. 84, (No. 2).

122. Lopes de Almeida JP, Pinto A, Pinto S, Ohana B, de Carvalho M. Economic cost of home-telemonitoring care for BiPAP-assisted ALS individuals. Amyotroph Lateral Scler. 2012;13(6).

123. Lechtzin N, Scott Y, Busse AM, Clawson LL, Kimball R, Wiener CM. Early use of non-invasive ventilation prolongs survival in subjects with ALS. Amyotroph Lateral Scler. 2007;8(3):185-8.

124. Stieglitz S. Technological Aspects and Safe Use of Noninvasive Mechanical Ventilation Devices: Key Technical and Practical Recommendations. In: Esquinas AM, editor. Noninvasive Mechanical Ventilation: Theory, Equipment, and Clinical Applications. Cham: Springer International Publishing; 2016. p. 123-9.

125. Spataro R, Lo Re M, Piccoli T, Piccoli F, V. LB. Causes and place of death in Italian patients with amyotrophic lateral sclerosis. Acta Neurol Scand. 2010;122.

126. Sancho J, Servera E, Dıaz JL, Bañuls P, Marín J. Home tracheotomy mechanical ventilation in patients with amyotrophic lateral sclerosis: causes, complications and 1-year survival. Thorax. 2011; 66.

127. Kurian KM, Forbes RB, S C, Swingler RJ. Cause of death and clinical grading criteria in a cohort of amyotrophic lateral sclerosis cases undergoing autopsy from the Scottish Motor Neurone Disease Register. J Neurol Neurosurg Psychiatry 2009;80.

128. Corcia P, Pradat P, Salachas F, Bruneteau G, Forestier N, Seilhean D, et al. Causes of death in a post-mortem series of ALS patients. Amyotrophic Lateral Sclerosis. 2008;9.

129. Asai H, et al. Sympathetic disturbances increase risk of sudden cardiac arrest in sporadic ALS. Journal of the Neurological Sciences. 2007;254.

130. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36

131. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993; 16:5-40.

132. de Almeida J P, Pinto AC, Pereira J, Pinto S, M. d. Implementation of a wireless device for real-time telemedical assistance of home-ventilated amyotrophic lateral sclerosis patients: a feasibility study. Telemed J E Health. 2010;16.

133. Berry RB, Chediak A, Brown LK, Finder J, Gozal D, Iber C, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6.

134. Teschler H,Stampa J, Ragette R, Konietzko N, Berthon-Jones M. Effect of mouth leak on effectiveness of nasal bilevel ventilatory assistance and sleep architecture. European Respiratory Journal.1999;14(6):1251.

135. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus lowintensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010;65(4):303-8.

136. Kim SM, Park KS, Nam H, Ahn SW, Kim S, Sung JJ, et al. Capnography for assessing nocturnal hypoventilation and predicting compliance with subsequent noninvasive ventilation in patients with ALS. PLoS One. 2011;6.

137. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care. 2011;56(1):25-38.

138. Jolliet P TD, Vignaux L. Patient-ventilator interaction during non-invasive ventilation. In: Yearbook of intensive care and emergency medicine Berlin, Heidelberg, New York: Springer Verlag; 2009.

139. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med. 2007;3(5):519-28.

140. Crescimanno G, Canino M, Marrone O. Asynchronies and sleep disruption in neuromuscular patients under home noninvasive ventilation. Respir Med. 2012;106(10):1478-85.

141. Gentile MA. Cycling of the mechanical ventilator breath. Respir Care. 2011;56(1):52-60.

142. Scharf SM, Maimon N, Simon-Tuval T, Bernhard-Scharf BJ, Reuveni H, Tarasiuk A. Sleep quality predicts quality of life in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2010; 6:1-12.

143. Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. Respir Care. 2009;54(1):102-15.

144. Vitacca M, Nava S, Confalonieri M, Bianchi L, Porta R, Clini E, et al. The appropriate setting of noninvasive pressure support ventilation in stable COPD patients. Chest. 2000;118(5):1286-93.

145. Gonzales JF, Russian CJ, Gregg Marshall S, Collins KP. Comparing the effects of rise time and inspiratory cycling criteria on 6 different mechanical ventilators. Respir Care. 2013;58(3):465-73.

146. Blackhall LJ. Amyotrophic lateral sclerosis and palliative care: where we are, and the road ahead. Muscle Nerve. 2012;45(3):311-8.

147. Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurol. 2015;14(4):435-42.

148. Instituto Nacional de Reabilitação I, Portugal Gd. Programas de financiamento 2013 [Available from: http://www.inr.pt/content/1/3415/programa-de-financiamento-projectos-peloinr-ip.

149. Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, et al. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol. 2016;23(1):30-8.

150. Braga AC, Pinto A. Health Care Management in ALS patients: Its influence on Quality of Life. Home Health Care Management and Practice. 2015:1 - 7.

151. Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. Jama. 2008;299(14):1698-709.

152. Oliver DJ, Turner MR. Some difficult decisions in ALS/MND. Amyotrophic lateral sclerosis: official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2010;11(4):339-43.

153. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

154. Chiò A, Logroscino G, Traynor B, Collins J, Simeone J, Goldstein L, et al. Global Epidemiology of Amyotrophic Lateral Sclerosis: A Systematic Review of the Published Literature. Neuroepidemiology. 2013;41(2):118-30.

155. Ye S, Ji Y, Li C, He J, Liu X, Fan D. The Edinburgh Cognitive and Behavioural ALS Screen in a Chinese Amyotrophic Lateral Sclerosis Population. PLOS ONE. 2016;11(5): e0155496.

156. Africa SS. Mid-year population estimates report. South Africa2017.

157. Mundi I. Portugal Demographics Profile 2018 Internet2018 [21.02.2018]. Available from: https://www.indexmundi.com/portugal/demographics_profile.html.

158. Saúde Md. Cuidados Respiratórios Domiciliários. In: Saúde DGd, editor. atualizada a 05/03/ 2013 ed. Portugal: Ministerio da Saúde; 2013.

159. Lekoubou A, Echouffo-Tcheugui JB, Kengne AP. Epidemiology of neurodegenerative diseases in sub-Saharan Africa: a systematic review. BMC Public Health. 2014; 14:653.

160. Quansah E, Karikari TK. Motor Neuron Diseases in Sub-Saharan Africa: The Need for More Population-Based Studies. Biomed Res Int. 2015; 2015:298409.

161. Poureau B. Progressive and self-limiting neurodegenerative disorders in Africa: a new prominent field of research led by South Africa but without strong health policy. Pan Afr Med J. 2016 Apr 22; 23:220. eCollection 2016

162. Pinto AC, Evangelista T, de Carvalho M, Paiva T, de Lurdes Sales-Luis M. Respiratory disorders in ALS: sleep and exercise studies. J Neurol Sci. 1999;169(1-2):61-8.

163. Wellbeloved-Stone CA, Weppner JL, Valdez RS. A Systematic Review of Telerehabilitation and mHealth Interventions for Spinal Cord Injury. Current Physical Medicine and Rehabilitation Reports. 2016;4(4):295-311.

164. Brooks D. Telehealth technology: an emerging method of delivering pulmonary rehabilitation to patients with chronic obstructive pulmonary disease. Can Respir J. 2011;18(4):196.

165. Chan C, Yamabayashi C, Syed N, Kirkham A, Camp PG. Exercise Telemonitoring and Tele rehabilitation Compared with Traditional Cardiac and Pulmonary Rehabilitation: A Systematic Review and Meta-Analysis. Physiother Can. 2016;68(3):242-51.

166. Cooper CB. Respiratory applications of telemedicine. Thorax. 64. England2009. p. 189-91.

167. Pare G, Jaana M, Sicotte C. Systematic review of home telemonitoring for chronic diseases: the evidence base. J Am Med Inform Assoc. 2007;14 (3):269-77.

168. Pagnini F, Rossi G, Lunetta C, Banfi P, Castelnuovo G, Corbo M, et al. Burden, depression, and anxiety in caregivers of people with amyotrophic lateral sclerosis. Psychol Health Med. 2010;15(6):685-93.

169. Bloor CM. Angiogenesis during exercise and training. Angiogenesis. 2005;8 (3):263-71.

170. Tang K, Xia FC, Wagner PD, Breen EC. Exercise-induced VEGF transcriptional activation in brain, lung and skeletal muscle. Respir Physiol Neurobiol. 2010;170(1):16-22.

171. Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. Can J Appl Physiol. 2004;29(4):463-87.

172. Grassi B, Quaresima V. Near-infrared spectroscopy and skeletal muscle oxidative function in vivo in health and disease: a review from an exercise physiology perspective. J Biomed Opt. 2016;21(9):091313.