FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

DANIELA TIAGO PEIXOTO

CROSS-SECTIONAL ANALYSIS OF THE AUTONOMIC NERVOUS SYSTEM: CORRELATIONS WITH PSYCHOLOGICAL DIMENSIONS AND PAIN SENSITIVITY IN WOMEN WITH FIBROMYALGIA, RHEUMATOID ARTHRITIS AND HEALTHY CONTROLS

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE REUMATOLOGIA

Trabalho realizado sob a orientação de:

PROF.DOUTOR JOSÉ ANTÓNIO PEREIRA DA SILVA

DRA. TÂNIA LOUZA SANTIAGO

MARÇO 2017

Cross-sectional analysis of the autonomic nervous system: correlations with psychological dimensions and pain sensitivity in women with fibromyalgia, rheumatoid arthritis and healthy controls

Daniela Tiago Peixoto[1], Tânia Santiago[1,2], José António Pereira da Silva[1,2]

[1]Faculdade de Medicina, Universidade de Coimbra, Portugal

[2] Serviço de Reumatologia, Centro Hospitalar e Universitário de Coimbra, Portugal.

Autora: Daniela Tiago Peixoto

E-mail: dtpeixoto@gmail.com

Março 2017

Acronyms

ANS: Autonomic Nervous System

BDI II: Beck Depression Inventory-II

CHUC: Hospital Center University of Coimbra

Ct: Controls

EPI: Eysenck Personality Inventory

EULAR: European League Against Rheumatism

FIQ-R: Revised Fibromyalgia Impact Questionnaire

FM: Fibromyalgia

FMUC: Faculty of Medicine University of Coimbra

HADS: Hospital Anxiety and Depression Scale

HF: High Frequency

HPA: Hypothalamic–pituitary–adrenal

HRV: Heart Rate Variability

IQR: Interquartil range

LF: Low Frequency

PPG: Photopletismography

PSAS: Pre-Sleep Arousal Scale

RA: Rheumatoid Arthritis

RMSSD: Root-mean square differences of successive R-R intervals

VLF: Very Low Frequency

SDNN: Standard deviation of the NN intervals.

Summary

RESUMO

Introdução: A disfunção do Sistema Nervoso Autónomo (SNA) tem sido descrita como tendo um papel importante na fisiopatologia de doenças reumáticas, nomeadamente na Fibromialgia (FM) e na Artrite Reumatóide (AR). A análise da variabilidade da frequência cardíaca (VFC) permite uma avaliação quantitativa da actividade do SNA. Alguns estudos sugerem uma associação entre a diminuição da VFC, o limiar da dor e as dimensões psicológicas, nomeadamente com um estado emocional negativo. Os autores sugerem existir uma associação entre doenças reumáticas e aumento da actividade simpática, mediada por um estado emocional negativo. O objectivo deste estudo é correlacionar os parâmetros da VFC com as dimensões psicológicas e com a dor, em doentes com FM, AR e controlos.

Métodos: Incluíram-se 60 mulheres (FM, n=20; AR, n=20 e controlos saudáveis, n=20). Foram preenchidos 5 questionários: inventário de personalidade de Eyesinck (EPI), escala de activação pré-sono (PSAS), inventário de depressão de Beck-II (BDI-II); questionário de impacto da fibromialgia (FIQ-R) e a escala hospitalar de ansiedade e depressão (HADS). O limiar e tolerância de dor foram determinados com um dolorímetro. A VFC foi analisada por fotopletismografia em posição sentada, durante 5 minutos, entre as 8h00 e as 10h00 da manhã e após um período de jejum.

A análise estatística considerou por um lado, os grupos de doença reumática (FM, AR e controlos saudáveis), e por outro os scores dos questionários (independentemente da doença reumática), divididos em tercis de alto e baixo score. No questionário BDI-II dividiu-se em 2 grupos, com score superior e inferior a 20, correspondentes a grupos com e sem depressão. Foram estudados os correlatos com os diferentes parâmetros de VFC, em ambas as situações.

Resultados: Na comparação de grupos de patologia, o grupo da FM apresentou scores mais altos de neuroticismo, ansiedade, depressão e distúrbios de sono, relativamente ao grupo controlo ($p<0,05$). Também se verificou um limiar e tolerância à dor inferiores no grupo com FM ($p<0,05$). No entanto, não se encontraram diferenças significativas nos parâmetros da VFC entre os grupos. Independentemente da patologia, o grupo com um score de BDI-II >20 (com depressão) apresentou valores de alta frequência (HF) inferiores (menor actividade parassimpática), e um rácio baixa/alta frequência (LF/HF) mais elevado (hiperactividade simpática), quando comparado com o grupo com score BDI-II<20 ($p<0,05$).

Discussão e conclusão: Este estudo confirma que a FM está associada a estados emocionais negativos, mas não encontrou diferenças significativas nos parâmetros da VFC entre os 3 grupos de doença. Os resultados confirmam que a depressão está associada à disfunção do SNA, especialmente à reduzida actividade parassimpática.

Este estudo sugere que as dimensões psicológicas, nomeadamente a depressão, devem ser consideradas quando se avalia o SNA e o seu impacto na patogénese da doença.

PALAVRAS CHAVE: Artrite reumatóide; Dimensões psicológicas; Dor; Fibromialgia; Sistema nervoso autónomo; Variabilidade da frequência cardíaca.

ABSTRACT

Introduction: Autonomic nervous system (ANS) dysfunction has been proposed to play a role in the pathophysiology and maintenance of rheumatic diseases, including fibromyalgia (FM) and rheumatoid arthritis (RA). Heart rate variability (HRV) analyses provide a quantitative marker of ANS activity. Some studies suggest an association between reduced HRV parameters, pain sensitivity and psychological dimensions, namely a negative emotional state. This led us to hypothesize an association between rheumatic diseases and higher sympathetic activity mediated by a negative emotional state. This study aims to establish correlates between HRV parameters with rheumatic disease groups, psychological dimensions and pain.

Methods: Sixty females (FM, n=20; Rheumatoid Arthritis (RA), n=20, and healthy controls (Ct), n=20) completed five questionnaires: Eysenck Personality Inventory (EPI), Pre-Sleep Arousal Scale (PSAS), Beck Depression Inventory-II (BDI II), Revised Fibromyalgia Impact Questionnaire (FIQ-R) and Hospital Anxiety and Depression Scale (HADS). Threshold and tolerance to pain was assessed with a dolorimeter. HRV analysis was performed by photopletismography between 8:00 and 10:00 am, after an overnight fast, in a sitting position, for 5-minutes.

Statistical analysis were performed considering: 1) the rheumatic disease groups (FM/RA/Ct) and 2) psychological scores, irrespective of disease group, divided in higher versus lower score tertiles. For the depression score (BDI-II), groups were divided in two groups (no depression and depression), regarding the cut-off of 20. Between-groups comparisons were performed with Kruskal-Wallis test and analysis of covariance (age was adjusted during analyses).

Results: When comparing groups, patients with FM had significantly higher scores of neuroticism, depression, anxiety and sleep disorders compared with RA and Ct ($p<0,05$). Lower threshold and tolerance to pain was also observed in FM patients ($p<0,05$). However, no statistically significant difference was observed in HRV parameters between disease groups.

Independently of the diagnosis, the values of HF - high frequency (parasympathetic activity) were lower in the depression group (BDI II score > 20), compared to the no depression group ($p<0.05$). The ratio of low/high frequency (LF/HF) was also higher among the depression group than the control group ($p<0.05$).

Discussion and Conclusion: This study confirms that FM is related to negative emotional states, but did not find significant differences in the HRV between the three rheumatic disease groups. The results confirm that depression is accompanied by dysfunction of the ANS, specifically lower parasympathetic activity. These results suggest that psychological dimensions, namely depression, must be taken into account when evaluating the ANS and its impact in disease pathogenesis.

KEY WORDS**:** Autonomic nervous system; Fibromyalgia; Heart rate variability; Pain; Psychological dimensions; Rheumatoid arthritis.

INTRODUCTION

Autonomic nervous system (ANS) with both sympathetic and parasympathetic systems together with HPA axis is the principal regulatory system of the body through neurotransmitters (cathecolamines for the sympathetic system), and the balance between the sympathetic and parasympathetic activity is essential to preserve homeostasis.[1] Among the techniques used in ANS evaluation, the heart rate variability (HRV) has arising as a simple, fast and non-invasive measure of the autonomic impulses, representing one of the most promising quantitative markers of the autonomic balance.[2,3] The HRV describes the oscillations in the interval between consecutive heart beats (RR interval), as well as the oscillations between consecutive instantaneous heart rates. It is a measure that can be used to assess the ANS modulation under physiological conditions, such as wakefulness and sleep conditions, different body positions, physical training and also pathological conditions.[2,3] Changes in HRV patterns provide a sensible and advanced indicator of health involvements. Higher HRV is a signal of good adaptation and characterizes a health person with efficient autonomic mechanisms, while lower HRV is frequently an indicator of abnormal and insufficient adaptation of the autonomic nervous system.[3–5]

The ANS dysfunction has been proposed to play a role in the pathophysiology and maintenance of rheumatic diseases, including fibromyalgia (FM) and rheumatoid arthritis (RA).[2,6–9] FM is one of the most frequent diagnosis in the rheumatologic practice[10] with a prevalence in the Portuguese population about 3,6%[11]. It´s a disease characterized by chronic widespread complaints with generalized musculoskeletal pain, fatigue, reduced muscle strenghth, mood disturbances, sleep disruption, decreased quality of life and functional limitation.[6,12,13] The etiology and pathogenesis are still not

fully understood.[10,12,14] A consistent line of research has shown that FM patients have signs of autonomic dysfunction, specifically signs of increased sympathetic activity [2,8,15–17] The dysautonomia of FM is characterized by persistent ANS hyperactivity at rest and hyporeactivity during stress. ANS hyporeactivity appears to be correlated with persistent fatigue and other clinical symptoms associated with FM, including low blood pressure, dizziness and faintness. Sympathetic hypereactivity is related to pain and is responsible for other systemic features of FM, including the Raynaud´s phenomenon, the irritable bowel syndrome and paresthesias.[2,7,18]. Therefore it has been proposed that such autonomic dysfunction is the cause of the multiplicity of FM symptoms and that FM is a sympathetically-maintained neuropathic pain syndrome. A systematic review of 2013, reported that the majority of the researchers observed lower HRV in FM patients compared to healthy control persons, as well as increased sympathetic activity.[19] Although, direct comparisons between HRV parameters in FM are lacking and some confounders weren´t take into account.

Psycological dimensions seem also to contribute considerably to the development of fibromyalgia. The prevalence of psychiatric conditions among patients affected by fibromyalgia is higher than among subjects complaining of other rheumatic diseases. The most common disorders associated are anxiety, somatization, dysthymia, panic disorders, posttraumatic stress, and overall depression. Depression worsens fibromyalgic symptoms and vice versa, and antidepressants represent a cornerstone of fibromyalgia therapy.[12,20–24]

Most studies looking for autonomic performance in FM have used HRV analysis as a probing instrument[2,4,25,26] and have correlated it with the symptoms, namely with pain severity and sleep disorders.[2,5,8,25,26]. These studies which evidence a predominant sympathetic activity in FM patients have proposed the HRV has a biomarker of this

syndrome[2,4,26] However, this pattern of sympathetic activity is not specific of FM neither RA and may be a key mechanism shared with other functional disorders, such as irritable bowel syndrome and interstitial cystitis[25,27], frequently associated with FM.

In addition, the literature supports that the prevalence of ANS dysfunction in Rheumatoid Arthritis (RA), is about 60%.[9] The profile of ANS dysfunction found in RA patients includes low HRV, reduced parasympathetic activity and elevated sympathetic activity. [9,28] Interestingly, neuroticism has been also associated with the regulation of the ANS and pain responses[20,29]

The above observations raise the hypothesis that the association between rheumatic diaseases and higher sympathetic tone may be mediated by psychological dimensions. This led us to hypothesize an association between rheumatic diseases and higher sympathetic activity mediated by a negative emotional state. This study aims to establish correlates between HRV parameters with rheumatic disease groups, psychological dimensions and pain in FM, RA and control groups.

MATERIALS AND METHODS

Participants

All the participants were women, aged 26-75 years old. One part of the participants was recruited from a larger study about FM, in FMUC (Faculty of Medicine University of Coimbra), the Cognifibro study. The other part was recruited from the Rheumatology Department of CHUC. Twenty healthy females recruited from the hospital staff composed the healthy control group. Selected patients were contacted by phone and invited to participate.

Three groups of patients, FM patients (n=20), RA patients (n=20), and healthy controls (Ct, n=20) have been set up in this cross-sectional study. FM patients were classified according to the American College of Rheumatology classification criteria[30] and RA patients classified according to the 2010 ACR (American College of Rheumatology) and EULAR (European League Against Rheumatism) classification criteria[31].

Exclusion criteria were: patients with FM in association with RA, diagnosed with psychosis, dementia or neurologic disorders.

The ethical committee of the FMUC approved the protocol and the participants signed an informed consent form.

Data collection and questionnaires

All proceedings were performed in the morning between 8:00 and 10:00 am, and the participants were fasting for at least 8 hours. After receiving an explanation of the study procedures and having an opportunity to present any questions and discuss all issues, they have completed a standardized questionnaire about demographic and basic disease data, and five self-report validated questionnaires in Portuguese:

a) Eyesinck Personality Inventory (EPI) – 12 item version[32] with 6 items to measure neuroticism and the other 6 items to measure extroversion. Score 6-24 in each personality trait.[33]

b) Pre-sleep arousal scale (PSAS), to describe how intensely patients experience somatic and cognitive symptoms (each subscale with 8 items, scored 8-40) when they fall asleep and distinguish normal sleepers from those with sleep disorders and insomnia.[34]

b) Beck Depression inventory-II (BDI-II)[35], one of the most used psichometric test with 21 itens for measuring the severity of depression, scored 0-63: no depression (<20), moderate depression (21-30), severe depression (31-40) or extremely depression (>40).

c) Revised Fibromyalgia Impact Questionnaire (FIQ-R)[36], with 3 domains (function, overall impact and function), to detect the spectrum of problems and the severity of symptoms related to FM , scored 0-100.

d) Hospital Anxiety and Depression Scale (HADS)[37], to determine the levels of anxiety and depression: each personality trait evaluated by 7 itens, each one scored 0 to 3.

Pain sensitivity assessment

All participants were submitted to an assessment of pressure pain sensitivity through the application of increasing pressure on the ungueal bed of the non-dominant hand thumb, using a validated dolorimeter under a structured procedure[23]. The lowest pressure at which the participant describes pain was taken as a measure of pain sensitivity. The highest pressure tolerated by the participant was designated as pain tolerance. Each patient was represented by the mean of three measurements.

Analysis of Heart Rate Variability Parameters

The HRV evaluation was performed using a Photopletismography (PPG) Stress Flow device (Biotekna srl. Venice, Italy). To control diurnal variation, HRV was measured between 8 a.m. and 10 a.m. in a quiet environment at room temperature and the participants were fasting for at least 8 hours. The recordings were made over a period of 5 min. Each participant was seated in a chair, and the sensors were placed on the second

finger of each hand. Before the measurement, participants rested for at least 10 minutes, and after that they were instructed to breathe spontaneously without talking during the procedure.

Through an algorithm the heart rate and respiratory cycles were analysed and the HRV parameters were calculated. HRV evaluation was performed using time and frequency domain analysis. In the time domain analysis, the mean HR (Heart Rate), SDNN (Standard deviation of the NN intervals) and RMSSD (root-mean square differences of successive R-R intervals) describes the oscillations in the interval between consecutive heart beats and reflects the sympathetic and parasympathetic activity. In addition, frequency domain analysis was performed to obtain the total power spectrum and its components: high frequency power (HF), reflecting vagal-parasympathetic activity, low frequency power (LF), reflecting combined sympathetic and parasympathetic activity and very low frequency (VLF) components. We also calculated the ratio of the low-to-high frequency of spectra power (LF/HF) that is an index of the the sympathetic to parasympathetic balance of heart rate fluctuation[38]

All investigations took approximately 30 minutes for each subject, excluding a resting period.

Statistical analysis

Data were analysed using SPSS 19.0 version. Statistical analyses were performed considering on the rheumatic disease groups (FM/RA/Ct) and the psychological scores, irrespective of disease group.

Non parametric tests were conducted to determine between-group differences. Comparisons between the personality traits and pain sensitivity/tolerance of the three

groups were performed using the Kruskal–Wallis test. As the majority of the variables was not approximately normally distribuction, data were presented as median and interquartile range (IQR). P-values lower than 0.05 were considered statistically significant. Analysis of covariance (age was adjusted during analyses) were conducted to determine between-group differences in HRV parameters.

Irrespective of disease group, the ANS parameters and the personality traits were also analysed. Univariate analysis of variance were conducted to compare the ANS parameters in two tertils of patients (n=20), each of them with lower and higher scores of neuroticism, extroversion, depression, ansiety, sleep disorders, pain sensitivity and pain tolerance. Regarding the BDI-II, we analysed two different groups of patients, one with score below 20 (no depression, n=49) and another one with score equal or above 20 (depression, n=11).

RESULTS

Demographics characteristics

Demographic characteristics of the participants are summarized in Table 1. The distribution of age is difference between the RA group and healthy controls (p=0,013) and between FM and RA groups (p=0,008)

Table 1 – Demographic characteristics of the participants**.**

	FM (n=20)	**RA (n=20)**	**HC (n=20)**
Age (years)	49,50 (43,25-55,0)	61,00 (54,50-65)	49,50(36,50-61,25)
Formal education (years)	11,50 (8,0-12,0)	11,00 (4,50-16,0)	15,00 (12-17,75)
Disease duration (years)	10,00 (8,0-17,75)	17,50 (9,5-22,75)	-
Marital status			
Single	2(10%)	1(5%)	4(20%)
Married	15 (75%)	15 (75%)	14 (70%)
Divorced	2 (10%)	2 (10%)	1 (5%)
Widow	1 (5%)	2 (10%)	1 (5%)
Medication, n (%)	18 (90%)	16 (80%)	10 (50%)
Analgesics	10 (50%)	4 (20%)	0 (0%)
NSAIDs	4 (20%)	11 (55%)	0 (0%)
Antidepressant	11 (55%)	5 (25%)	1 (5%)
Anxiolytic	7 (35%)	5 (25%)	2 (10%)
Muscle Relaxant	9 (45%)	2 (10%)	9 (0%)
Anticonvulsivants	6 (30%)	2 (10%)	0 (0%)
Beta blockers	1 (5%)	2 (10%)	1 (5%)
Antihipertensive	6 (30%)	9 (45%)	1 (5%)
Others	17 (85%)	18 (90%)	8 (40%)

Data are presented as median (interquartil range) or number (percentage).

Personality traits, sleep disorders, pain sensitivity/tolerance and HRV parameters. Comparision between the three diagnostic groups.

Significative differences were found in the personality traits (neuroticism, depression and anxiety) and sleep disorders across the three groups (FM, RA and Ct). FM patients presented higher levels of neuroticism, depression, ansiety and disturbed sleep than RA patients and Ct. Also, the pain sensitivity and pain tolerance were significantly different across the three groups, with the FM group presenting lower pain sensitivity and tolerance. The results are summarized in table 2.

Table 2 – Results for Personality traits, sleep disorders, pain sensitivity and pain tolerance, in the three diagnosis groups (n=20). The results were obtained with Kruskal-Wallis test.

		Score	**p value**
Neuroticism	**FM**	15,50 (13,25-17,00)	**0,000***
	RA	11,00 (10,00-14,00)	
	Ct	12,00 (10,00-14,75)	
Extroversion	**FM**	14,50 (12,00-17,00)	0,391
	RA	15,50 (13,00-18,00)	
	Ct	16,00 (15,00-17,00)	
PSAS Cognitive	**FM**	27,00 (22,25-29,00)	**0,000***
	RA	17,00 (12,50-19,00)	
	Ct	19,00 (15,00-21,00)	
PSAS Somatic	**FM**	27,50 (21,75-29,75)	**0,000***
	RA	13,00 (10,25-22,75)	
	Ct	11,50 (8,25-15,00)	

BDI II	**FM**	19,00 (13,25-23,75)	**0,000***
	RA	10,50 (4,50-16.75)	
	Ct	7,00 (2,00-12,00)	
FIQ-R	**FM**	61,92 (48,04-71,83)	**0,000***
	RA	28,70 (13,88-51,92)	
	Ct	5,33 (1,50-9,71)	
Anxiety (HADS)	**FM**	10,50 (8,25-14,00)	**0,001****
	RA	8,50 (7,00-11,75)	
	Ct	8,00 (5,00-9,00)	
Depression (HADS)	**FM**	8,00(6,25-10,00)	**0,000*****
	RA	5,50 (2,50-9,75)	
	Ct	2,00 (1,00-4,00)	
Pain Sensivity (Kgf)	**FM**	3,62 (2,37-4,25)	**0,012***
	RA	5,35 (3,14-6,28)	
	Ct	5,50 (2,20-7,00)	
Pain Tolerance (Kgf)	**FM**	6,11 (3,98-8,59)	**0,002****
	RA	8,36 (5,92-11,55)	
	Ct	10,78 (7,05-12,21)	

Data are presented as median (interquartil range) or number (percentage).

Pairwise comparasions using Kruskal Wallis test:

*There are differences between FM group and both AR and CS groups.

**There are differences between FM and HC groups

***There are differences between FM and HC groups and also between RA and HC groups, but the distribution between FM and RA groups is similar.

In what concern to ANS evaluation, univariate analysis was conducted to determine between-group differences in HRV parameters (age was adjusted during analysis).

No significant difference was found in HRV parameters across the FM, RA and Ct groups. The results are summarized in table 3.

Table 3 – Results for time and frequency domains of HRV measures in patients with FM, RA and in healthy controls.

Time Domain	**FM (n=20) median (IQR)**	**RA (n=20) median (IQR)**	**Ct (N=20) median (IQR)**	**p value**
Mean HR (bpm)	76,60 (62,60-91,15)	70,10 (60,38-74,58)	72,60 (64,48-80,33)	0,087
SDNN (ms)	34,50 (27,5-45,5)	31,50 (22,50-72,75)	44,00 (30,00-72,75)	0,147
RMSSD (ms)	24,00 (17,25-40,25)	23,50 (17,50-83,00)	31,00 (18,00-65,75)	0,19
Frequency domain				
Total power	7,01 (6,58-7,68)	6,83 (6,19-8,39)	7,58(6,79-8,54)	0,132
VLF power	6,50 (5,57-7,27)	6,23 (5,55-7,17)	6,48 (6,15-7,27)	0,222
LF power	5,70 (5,05-6,33)	5,70 (4,63-7,32)	6,20 (5,30-6,89)	0,116
HF power	5,62 (4,64-6,21)	5,39 (4,83-7,53)	6,00 (4,85-7,22)	0,106
LH/HF ratio	0,80 (0,60-2,3)	0,75 (0,60-1,38)	1,20 (0,75-1,75)	0,334

Mean HR: mean heart rate; **SDNN**: standard deviation of the NN intervals; **RMSSD:** the square root of the mean squared differences of successive NN intervals; **VLF**: very low frequency; **LF**: low frequency; nu: normalized units; **HF**: high frequency; **ms**: milliseconds.

Personality traits and HRV parameters, irrespective the diagnosis. Comparision between first and third tertile groups, by analysis of covariance.

For the analysis of variance, age was adjusted during analyses, because age is known to affect HRV.[39,40] No statistically significant difference was observed in HRV parameters between 1st and 3rd tertile groups for psychological dimensions, except for BDI-II score, for depression. The values of HF power (parasympathetic activity) were lower in the depression group (BDI score >20) compared to the no depression group ($p<0.05$). The ratio of LF/HF was also higher among the depression group than the control group ($p<0.05$).

No statistaclly difference was observed in the higher and lower pain sensitivity and tolerance tertils regarding HRV parameters. The results are summarized in the appendix 1.

DISCUSSION AND LIMITATIONS

When comparing diagnosis groups, FM patients show significantly higher scores of neuroticism, anxiety, and depression as well as more changes in the sleep pattern in our study – table 2. Also, significantly lower scores of pain sensitivity and tolerance to pain were found among our FM patients - table 2.

However, significant difference was not found in the distribution of HRV parameters across the three groups (FM, RA and Ct) - table 3. FM patients presented a suggestive

trend for lower values of SDNN e RMSSD, as described in some studies[6,15,26] but we haven´t found a higher sympathetic activation neither a higher ratio LH/HF as reported previously in other studies[2,6,16]. The lower values of SDNN and RMSSD means that patients have a lower HRV that is an indicator of abnormal and insufficient adaptation of the autonomic nervous system, provoking poor patient's physiological function [3].

In addition and irrespective of diagnosis, no statistically significant difference was observed in HRV parameters between lower and higher scored tertile groups for psychological dimensions, except for depression – appendix 1. The value of HF power (parasympathetic activity) was lower in the depression scored group (BDI II>20) compared to the no depression group of patients with BDI-II scored under 20 ($p<0,05$). The ratio of LF/HF was higher among the depression group ($p<0,05$). This confirms that depression is associated to ANS dysfunction. This results also emphazise that the presence of psychiatric symptoms may have a profound impact on the severity and the course of fibromyalgia. High levels of depression are associated with more physical symptoms and poorer functioning. In fact, the presence of psychological symptoms in these patients is a predictor of persistent pain[21,24,41].

This study has to be interpreted in light of several limitations. First, the reduced sample size is certainly relevant. However, because all subjects were evaluated within a relatively short period of 3 months between October and December and in fasting was intended to minimize bias from seasonal or daily fluctuations.

Second, we performed a 5-minute assessment of HRV analysis. The majority of the studies used different outcome measures to analyse HRV. For example, 30 minutes Holter monitor recording including periods of supine and orthostatic position[5], Muscle Sympathetic Nerve Activity (MSNA) by microneurography[7], 10 or 15 minutes

continuous ECG in supine position[6,42], 20 minutes electrocardiogram[8] or 24h holter[26]. This certainly compromised comparisons between different studies.

No consensus regarding the relative accuracy of HRV has yet been reached. While HRV is less invasive, time-efficient, simple, and more sensitive than the classic autonomic test[2], it requires considerable initial investment and is more sensitive to confounders such as medication, patient age, or the vulnerability to motion artifacts than ECG[43] For example, advancing age (as seen in the RA group) seems to result in a decline of HRV, most likely due to a decrease in efferent parasympathetic tone and reduced β-adrenergic responsiveness.[2]

In a comparison study between photoplethysmography and ECG five minute recording was found that photoplethysmography provided accurate interpulse intervals to measure HRV, suggesting that this technique may prove a practical alternative to ECG for HRV analysis[43].

In a systematic review about autonomic function and RA, an association between increased inflammation and ANS dysfunction (increased sympathetic activity, reduced cardiovagal baroreflex sensitivity and reduced HRV) was found. The majority of the studies reported at least one abnormality in RA patients and they concluded that the prevalence of ANS dysfunction is about 60%.[9] This fact might have contributed to the similar distribution of ANS parameters between RA and FM groups.

Finally, at the time of the study, FM and RA patients were taking various medications that are known to interfere with the ANS (table 1). This fact may have contributed to alter the results. In a meta-analysis, there was a trend of higher LF values in subjects taking anticonvulsants[44]. In addition, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants were associated with lower SDNN, LF and HF, but selective serotonin reuptake inhibitors were not significantly associated with HRV[45] Another

study raised the theoretical possibility that in FM patients the use of anti-adrenergic agents (eg clonidine) might lessen chronic pain intensity by reducing the underlying excessive sympathetic activity[7]. Taken in account these reports, the medication certainly may have influenced the HRV parameters.

CONCLUSION

Our results confirm that depression is accompanied by ANS dysfunction, especially lower parasympathetic activity, suggesting that psychological dimensions may influence the ANS function. Thus, depression must be taken into account when evaluating the ANS and its impact in disease pathogenesis.

This study also emphasizes the specificity and the important role of psycological dimensions in fibromyalgia pathophysiology. Despite FM patients have had higher scores of neuroticism, depression and ansiety, the association between these psychological dimensions and ANS dysfunction remains uncertain.

Further studies with a higher number of patients are warranted to clarify the association between the ANS dysfunction, the psycological dimensions and the FM symptoms. Further elucidation and research could have important implications in the understanding of the pathophysiology and different dimensions of rheumatic diseases and in the modulation of pain by the ANS. It´s also important to explore the HRV parameters as potential and useful biomarkers that may became part of pathophysiology study of the rheumatic diseases.

ACKNOWLEDGEMENTS

For all the support, I would like to sincerely thank to:

- Prof. Dr. José António Pereira da Silva, Dra Tânia Santiago, Dra Cátia Duarte, Dr. Carlos Costa, Prof. Francisco Caramelo, Enfº Ricardo Ferreira and Enfª Andrea Marques
- All the women who participated in this study.
- Fernando, my husband and Fernando, my son.
- My parents and all the rest of my family
- My friends, especially Cristiana.

REFERENCES

1. Di Franco M, Iannuccelli C, Valesini G. Neuroendocrine immunology of fibromyalgia. Ann N Y Acad Sci. 2010;1193:84–90.

2. Staud R. Heart rate variability as a biomarker of fibromyalgia syndrome. Fut Rheumatol. 2008;3(5):475–83.

3. Vanderlei LCM, Pastre CM, Hoshi RA, Carvalho TD de, Godoy MF de. Noções básicas de variabilidade da frequência cardíaca e sua aplicabilidade clínica. Rev Bras Cir Cardiovasc. 2009;24(2):205–17.

4. Evans S, Seidman LC, Tsao JC, Lung KC, Zeltzer LK, Naliboff BD. Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. J Pain Res. 2013 Jun;6:449–57.

5. Dziuba A, Lockhart NA, Schubiner H, Clauw DJ, Williams DA, Lumley MA. Cross-Sectional Analysis of Heart Rate Variability in Patients with Fibromyalgia (FM): Correlations with Baseline Clinical Measures. Arthritis Rheumatol. 2015;67:82.

6. Kang JH, Kim JK, Hong SH, Lee CH, Choi BY. Heart rate variability for quantification of autonomic dysfunction in fibromyalgia. Ann Rehabil Med. 2016;40(2):301–9.

7. Zamunér AR, Barbic F, Dipaola F, Bulgheroni M, Diana A, Atzeni F, et al. Relationship between sympathetic activity and pain intensity in fibromyalgia. Clin Exp Rheumatol. 2015;33:S53–7.

8. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. 2000 Feb;29(4):217–27.

9. Adlan AM, Lip GYH, Paton JFR, Kitas GD, Fisher JP. Autonomic function and rheumatoid arthritis-A systematic review. Semin Arthritis Rheum. 2014;44(3):283–304.

10. Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M, et al. Prevalence of fibromyalgia: a survey in five European countries. Semin Arthritis Rheum. 2010 Jun;39(6):448–53.

11. Fietta P. Fibromyalgia: state of the art. Minerva Med. 2004 Feb;95(1):35–47, 47–52.

12. Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE, et al. Fibromyalgia syndrome: Etiology, pathogenesis, diagnosis, and treatment. Pain Res Treat. 2012;2012(June).

13. George HM. Abordagem Diagnóstica da Fibromialgia. Direção Geral da Saúde. 2016;17:1–4.

14. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995 Jan;38(1):19–28.

15. Di Franco M, Iannuccelli C, Alessandri C, Paradiso M, Riccieri V, Libri F, et al. Autonomic dysfunction and neuropeptide Y in fibromyalgia. Clin Exp Rheumatol. 2009;27(5 SUPPL. 56).

16. Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. Semin Arthritis Rheum. 2013 Oct;43(2):279–87.

17. Martínez-Lavín M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. Semin Arthritis Rheum. 2000 Feb;29(4):197–9.

18. Branco JC. State of the art on Fibromyalgia mechanism - Review. Acta Reumatol Port. 2010;35:10–5.

19. Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. Semin Arthritis Rheum. 2013 Oct;43(2):279–87.

20. Čukić I, Bates TC. The Association between Neuroticism and Heart Rate Variability Is Not Fully Explained by Cardiovascular Disease and Depression. Cheng XW, editor. PLoS One. 2015 May 7;10(5):e0125882.

21. Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. Pain. 1989 Feb;36(2):209–18.

22. Charles ST, Gatz M, Kato K, Pedersen NL. Physical health 25 years later: the predictive ability of neuroticism. Health Psychol. 2008 May;27(3):369–78.

23. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic

pain cohort. Arthritis Rheum. 2005 May;52(5):1577–84.

24. Malin K. Personality and Fibromyalgia Syndrome. Open Rheumatol J. 2012;6:273–85.

25. Martínez-Martínez L-A, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol. 2014 Apr;20(3):146–50.

26. Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. Arthritis Res Ther. 2011;13(6):R185.

27. Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. Curr Rheumatol Rep. 2000 Apr;2(2):116–23.

28. Koopman FA, Tang MW, Vermeij J, de Hair MJ, Choi IY, Vervoordeldonk MJ, et al. Autonomic Dysfunction Precedes Development of Rheumatoid Arthritis: A Prospective Cohort Study. EBioMedicine. 2016 Apr;6:231–7.

29. Paine P, Worthen s. f., Gregory l. j., Thompson d. g., Aziz Q. Personality differences affect brainstem autonomic responses to visceral pain. Neurogastroenterol Motil. 2009 Nov;21(11):1155-e98.

30. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The american college of rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum. 1990 Feb;33(2):160–72.

31. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010

Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569–81.

32. Totterdell BSE. The Standard Shiftwork Index: a battery of questionnaires for assessing shiftwork-related problems. Work and Stress; 1995. 4-30 p.

33. Silva, C. F., Azevedo, M. H. P. e Dias MRVC. Estudo padronizado do trabalho por turnos-versão portuguesa do SSI. Psychologica. 1995;13:27–36.

34. Azevedo MH, Bos SC, Soares MJ, Marques M, Pereira AT, Maia B, et al. Longitudinal study on perfectionism and sleep disturbance. World J Biol Psychiatry. 2010 Mar 10;11(2 Pt 2):476–85.

35. Beck,A.T.;Steer,R.A,Brown G. Beck Depression Inventory-Second Edition (BDI-II) | National Child Traumatic Stress Network - Child Trauma Home. Manual of Beck Depression Inventory-II . San Antonio , TX: Psychological Corporation; 1996.

36. Costa C, Pinto AM, Pereira AT, Marques M, Macedo A, Pereira da Silva JA. Psychometric properties of the Revised Fibromyalgia Impact Questionnaire (FIQR) - A contribution to the Portuguese validation of the scale. Acta Reumatol Port. 2016;2016(3):240–50.

37. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007 Mar;12(2):225–37.

38. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North

American Society of Pacing and Electrophysiology. Circulation. 1996 Mar 1;93(5):1043–65.

39. Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-term heart rate variability--influence of gender and age in healthy subjects. Hernandez A V, editor. PLoS One. 2015 Mar 30;10(3):e0118308.

40. Stein PK, Kleiger RE, Rottman JN. Differing effects of age on heart rate variability in men and women. Am J Cardiol. 1997 Aug 1;80(3):302–5.

41. Ramírez-Maestre C, López Martínez AE, Zarazaga RE. Personality characteristics as differential variables of the pain experience. J Behav Med. 2004 Apr;27(2):147–65.

42. Lee K, Choi S, Kang J, Yim Y, Kim J, Lee J, et al. Comparison of heart rate variability and classic autonomic testing for detection of cardiac autonomic dysfunction in patients with fibromyalgia. 2016;

43. Lu G, Yang F, Taylor JA, Stein JF. A comparison of photoplethysmography and ECG recording to analyse heart rate variability in healthy subjects. J Med Eng Technol. 2009 Nov 15;33(8):634–41.

44. Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia. 2012 Feb;53(2):272–82.

45. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol Psychiatry. 2010 Jun 1;67(11):1067–74.

APPENDIX

Appendix 1

Univariate analysis of variance between the lower (1^{st}) and higher (3^{rd}) score tertils (n=20) of depression, ansiety, extroversion, sleep disorders, pain sensivity and pain tolerance and the ANS parameters. The two groups of BDI-II are relative to a score<20 (no depression, n=49) and a score >20 (depression, n=11)).

		FC	p	SDDN	p	RMSSD	p	Total Power	p	VLF	p	LF	p	HF	p	LF/HF	P
Neuroticism	1^{st}	68,4 (53,6-87,2)	0,353	32,0 (15,0-210)	0,553	22,5 (14-270)	0,589	6,89 (5,2-10,5)	0,322	6,23 (4,0-8,6)	0,616	5,6 (3,4-9,4)	0,247	5,1 (4,1-9,8)	0,346	1,2 (0,3-3,7)	0,629
	3^{rd}	73 (50,6-)		34,5 (20-158)		24 (11-228)		7,1 (6,0-9,4)		6,5 (4,7-9,0)		5,9 (4,4-8,3)		5,6 (4,4-8,8)		1,0 (0,3-6,1)	
Extroversion	1^{sr}	73,4 (50,6-107,7)	0,200	32,5 (17,0-80,0)	0,419	24,0 (11,0-93,0)	0,349	6,9 (5,5-8,7)	0,710	6,2 (4,7-7,4)	0,459	5,6 (3,4-7,5)	0,991	5,4 (4,2-7,9)	0,741	1,3 (0,4-3,7)	0,366
	3^{rd}	69,0 (58,3-98,3)		33,5 (15,0-158,0)		23,5 (14,0-228,0)		7,0 (5,2-9,9)		0,3 (4,0-7,7)		5,7 (3,5-9,0)		5,6 (4,2-9,2)		0,9 (0,3-3,5)	
Depression HADS	1^{st}	68,3 (53,6-87,2)	0,116	33,5 (24,0-132,0)	0,507	23,5 (14,0-127,0)	0,634	7,0 (6,3-9,8)	0,805	6,26 (5,7-8,2)	0,700	6,0 (4,6-8,4)	0,713	5,3 (4,1-9,1)	0,582	1,25 (0,5-3,7)	0,888
	3^{rd}	73,0 (50,6-107,7)		33,5 (17,0-100,0)		24,0 (11,0-93,0)		7,0 (5,5-9,2)		6,5 (4,7-9,0)		5,7 (3,4-7,9)		5,4 (3,7-7,9)		0,9 (0,3-6,1)	
Ansiety HADS	1^{st}	70,2 (53,6-87,2)	0,268	39,0 (15,0-210,0)	0,808	24,5 (15,0-270,0)	0,901	7,3 (5,2-10,45)	0,648	6,4 (4,0-8,6)	0,546	6,0 (3,5-9,4)	0,669	5,4 (4,2-9,8)	0,698	0,95 (0,3-3,5)	0,579
	3^{rd}	75,0 (50,6-107,7)		33,0 (12,0-158,0)		19,5 (10-228)		7,0 (4,9-9,4)		6,6 (4,3-7,8)		5,7 (3,6-8,3)		5,1 (3,2-8,8)		0,8 (0,3-6,1)	
Depression BDI-II	No dep <20	70,5 (46,7-103,6)	0,251	40,0 (12,0-210,0)	0,123	28,0 (10,0-270,0)	0,102	7,24 (4,87-10,4)	0,114	6,5 (4,0-9,0)	0,274	6,0 (3,4-9,4)	0,197	5,7 (3,2-9,8)	**0,045**	0,9 (0,3-3,7)	**0,019**
	Dep >20	81,1 (50,6-107,7)		32,0 (17,0-79,0)		18,0 (11,0-81,0)		6,9 (5,6-8,8)		6,6 (4,9-7,8)		5,6 (4,4-7,9)		4,8 (3,7-7,5)		1,8 (0,4-6,1)	
PSAS total	1^{st}	72,0 (53,6-87,2)	0,246	38,0 (17,0-270,0)	0,594	28,0 (17,0-270,0)	0,546	7,2 (5,2-10,4)	0,677	6,3 (4,0-8,6)	0,960	6,1 (3,5-9,4)	0,581	5,7 (4,4-9,8)	0,285	0,9 (0,3-3,5)	0,200
	3^{rd}	71,2 (50,6-107,7)		33,5 (17,0-158,0)		22,5 (11,0-228,0)		7,0 (5,7-9,4)		6,5 (4,7-7,8)		5,6 (4,48,3)		5,3 (3,7-8,8)		1,3 (0,3-6,1)	
Pain sensitivy	1^{st}	71,3 (46,7-107,7)	0,765	44,5 (17,0-210,0)	0,512	31,0 (11,0-270,0)	0,761	7,6 (5,6-10,5)	0,578	6,6 (5,1-8,6)	0,340	6,0 (4,4-9,4)	0,952	5,9 (3,7-9,8)	0,714	0,8 (0,4-3,1)	0,315
	3^{rd}	69,3 (53,6-83,4)		32,0 (12,0-143,0)		23,0 (10,0-218,0)		6,9 (4,9-9,9)		6,2 (4,3-7,8)		5,7 (3,6-9,0)		5,1 (3,2-9,2)		1,1 (0,3-6,1)	
Pain tolerance	1^{st}	72,0 (46,7-107,7)	0,597	39,0 (15,0-210,0)	0,426	27,0 (11,0-270,0)	0,306	7,3 (5,2-10,4)	0,895	6,5 (4,0-8,6)	0,730	5,7 (3,5-9,4)	0,905	5,7 (3,7-9,8)	0,406	0,7 (0,3-3,1)	0,106
	3^{rd}	69,3 (53,6-95,2)		32,0 (19,0-143,0)		22,0 (14,0-178,0)		6,9 (5,7-9,9)		6,2 (4,9-9,0)		5,8 (4,4-9,0)		5,1 (4,1-9,2)		1,3 (0,3-6,1)	

Appendix 2

EPI – INVENTÁRIO DE PERSONALIDADE DE EYESINCK:

A seguir estão algumas frases que dizem respeito ao modo como reage, sente e atua. Para cada uma das questões procure indicar qual das respostas representa a sua maneira habitual de agir ou sentir, colocando um círculo no algarismo que melhor descreve o seu caso. Não há respostas certas ou erradas: o que nos interessa é a sua reação imediata a cada uma das perguntas.

	Quase nunca	Poucas vezes	Muitas vezes	Quase sempre
1.Gosto de muita excitação e alarido à minha volta.	1	2	3	4
2.O meu humor tem altos e baixos.	1	2	3	4
3.Sou uma pessoa cheia de vida.	1	2	3	4
4.Sinto-me infeliz sem ter motivos para isso.	1	2	3	4
5.Gosto de me misturar com as pessoas.	1	2	3	4
6.Quando me aborreço preciso de alguém amigo para conversar.	1	2	3	4
7.Considero-me uma pessoa que confia na sorte.	1	2	3	4
8.Sou perturbada por sentimentos de culpa.	1	2	3	4
9.Vou e divirto-me muito numa festa animada.	1	2	3	4
10.Considero-me uma pessoa tensa, muito nervosa.	1	2	3	4
11.Gosto de pregar partidas.	1	2	3	4
12.Sofro de insónias.	1	2	3	4

Appendix 3

PSAS – PRE-SLEEP AROUSAL SCALE

Pretendemos investigar o que sente na mente e no corpo antes de começar a dormir. Por favor descreva a intensidade com que sente cada um dos sintomas abaixo indicados, quando está a tentar pegar no sono. Por favor faça um círculo no número que considera mais adequado.

1. De maneira nenhuma 2. Um pouco 3. Moderadamente 4. Muito 5. Muitíssimo

Quando estou a tentar adormecer:

1. Preocupo-me em adormecer.	1	2	3	4	5
2. Revejo ou medito sobre os acontecimentos do dia.	1	2	3	4	5
3. Tenho pensamentos tristes, depressivos ou ansiosos.	1	2	3	4	5
4. Preocupo-me com outros problemas, sem ser com o dormir.	1	2	3	4	5
5. Sinto-me mentalmente desperta, ativa.	1	2	3	4	5
6. Não sou capaz de deixar de pensar, "desligar".	1	2	3	4	5
7. Os pensamentos continuam a correr na minha cabeça.	1	2	3	4	5
8. Sou distraída pelos sons, ruídos no ambiente.	1	2	3	4	5
9. Sinto o coração acelerado, batimentos fortes ou irregulares.	1	2	3	4	5
10. Tenho uma sensação de agitação, nervoso no corpo.	1	2	3	4	5
11. Sinto falta de ar ou respiração difícil.	1	2	3	4	5
12. Tenho uma sensação de aperto, tensão nos músculos.	1	2	3	4	5
13. Sinto frio nas mãos, pés ou no corpo em geral.	1	2	3	4	5
14. Tenho problemas no estômago (sensação de um nó, nervos, náuseas, azia,	1	2	3	4	5
15. Sinto suor na palma das mãos, pés ou outras partes do corpo.	1	2	3	4	5
16. Tenho a sensação de boca ou garganta seca.	1	2	3	4	5

Appendix 4

BDI-II - BECK DEPRESSION INVENTORY II

O questionário seguinte é constituído por vários grupos de afirmações. Em cada grupo escolha uma única afirmação, a que melhor descreve a forma como se tem sentido nas duas últimas semanas.

1. Tristeza
□ Não me sinto triste
□ Ando triste muitas vezes
□ Sinto-me sempre triste
□ Estou tão triste ou infeliz que já não o suporto

2. Pessimismo
□ Não me sinto desencorajada em relação ao futuro
□ Sinto-me mais desencorajada em relação ao futuro do que costumava
□ Já não espero que os meus problemas se resolvam
□ Não tenho qualquer esperança no futuro e acho que tudo só pode piorar

3. Fracassos Passados
□ Não me considero uma falhada
□ Fracassei mais vezes do que deveria
□ Quando considero o meu passado, o que noto é uma quantidade de fracassos
□ Sinto-me completamente falhada como pessoa

4. Perda de Prazer
□ Tenho tanto prazer como costumava ter com as coisas que eu gosto
□ Eu não gosto tanto das coisas como costumava
□ Tenho pouco prazer com as coisas que eu costumava gostar
□ Não obtenho qualquer prazer das coisas que eu costumava gostar

5. Sentimentos de Culpa
□ Não me sinto particularmente culpada
□ Sinto-me culpada por muitas coisas que fiz ou deveria ter feito
□ Sinto-me bastante culpada a maioria das vezes
□ Sinto-me culpada durante o tempo todo

6. Sentimentos de Punição
□ Não sinto que estou a ser castigada
□ Sinto que posso ser castigada

□ Espero vir a ser castigada
□ Sinto que estou a ser castigada

7. Auto-depreciação
□ Aquilo que acho de mim é o que sempre achei
□ Perdi a confiança em mim própria
□ Estou desapontada comigo mesma
□ Não gosto de mim

8. Auto-criticismo
□ Não me culpo ou critico mais do que costumava
□ Critico-me mais do que costumava
□ Critico-me por todas as minhas falhas
□ Culpo-me por tudo o que de mal me acontece

9. Pensamentos ou Desejos Suicidas
□ Não tenho qualquer ideia de me matar
□ Tenho ideias de me matar mas não as levarei a cabo
□ Gostaria de me matar
□ Matar-me-ia se tivesse oportunidade

10. Choro
□ Não choro mais do que costumava
□ Choro mais do que costumava
□ Choro por tudo e por nada
□ Apetece-me chorar, mas já não consigo

11. Agitação
□ Não me sinto mais inquieta que o normal
□ Sinto-me mais inquieta que o habitual
□ Estou tão inquieta ou agitada que é difícil parar quieta
□ Estou tão inquieta ou agitada que tenho que me manter em movimento ou a fazer alguma coisa

12. Perda de interesse
□ Não perdi o interesse nas outras pessoas ou nas minhas actividades
□ Estou menos interessado pelas coisas e pelas outras pessoas do que antes
□ Perdi a maioria do meu interesse nas coisas e nas outras pessoas
□ É difícil interessar-me por qualquer coisa que seja

13. Indecisão
□ Tomo decisões como sempre fiz
□ Acho mais difícil tomar decisões do que o habitual
□ Tenho muitas mais dificuldades em tomar decisões do que antigamente
□ Sinto-me incapaz de tomar qualquer decisão

14. Sentimentos de inutilidade
□ Não me considero uma incapaz/inútil
□ Não me considero tão válida e útil como costumava
□ Sinto-me mais inútil, em relação às outras pessoas
□ Sinto-me completamente inútil

15. Perda de energia
□ Tenho a mesma energia de sempre
□ Sinto-me com menos energia do que o habitual
□ Não me sinto com energia para muitas coisas
□ Não me sinto com energia para nada

16. Alterações no Padrão de Sono nas duas últimas semanas
□ Não notei qualquer mudança no meu sono
□ Durmo um pouco mais do que o habitual
□ Durmo um pouco menos do que o habitual
□ Durmo muito mais do que o habitual
□ Durmo muito menos do que o habitual
□ Durmo a maioria do tempo durante o dia
□ Acordo cerca de 1-2 horas mais cedo que é costume e não consigo voltar a dormir

17. Irritabilidade
□ Não estou mais irritável que o normal
□ Estou mais irritável que o habitual
□ Estou mais irritável que o normal
□ Estou irritável o tempo todo

18. Alterações no Apetite
□ Não notei qualquer alteração no meu apetite
□ Tenho um pouco menos de apetite do que o habitual
□ Tenho um pouco mais de apetite do que o habitual
□ O meu apetite é muito menor que o normal
□ O meu apetite é muito maior que o normal
□ Perdi por completo o apetite
□ Anseio por comida o tempo todo

19. Dificuldades de Concentração
□ Concentro-me tão bem como antes
□ Não me consigo concentrar tão bem como antes
□ É difícil manter as minhas ideias em qualquer coisa por muito tempo
□ Acho que não consigo concentrar-me em nada

20. Cansaço ou Fadiga
□ Não me sinto mais cansada/fatigada que o habitual
□ Canso-me mais facilmente que o costume

□ Estou demasiado cansada ou fatigada para fazer uma série de coisas que costumava fazer
□ Estou demasiado cansada ou fatigada para fazer a maioria das coisas que costumava fazer

21. Perda de Interesse Sexual
□ Não notei qualquer mudança recente no meu interesse pela vida sexual
□ Encontro-me menos interessado pela vida sexual do que costumava estar
□ Atualmente sinto-me menos interessado pela vida sexual
□ Perdi completamente o interesse que tinha pela vida sexual

Appendix 5

F I Q-R – Versão Portuguesa Experimental

INSTRUÇÕES:

Para cada uma das seguintes nove questões, assinale com uma cruz (X) a caixa que melhor indica em que grau a fibromialgia dificultou cada uma das seguintes tarefas **na última semana**. Se não desempenhou alguma das atividades neste período, indique a dificuldade com que desempenhou pela última vez essa atividade. Se não pode desempenhar uma atividade, assinale a última caixa à direita.

Escovar ou pentear o seu cabelo	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Caminhar continuamente durante 20 minutos	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Preparar uma refeição	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Aspirar, esfregar ou varrer o chão	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Levantar e carregar um saco cheio de mercearias	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Subir um lanço de escadas	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Mudar os lençóis da cama	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Estar sentado numa cadeira durante 45 minutos	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade
Fazer compras de supermercado	Sem dificuldade ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Com muita dificuldade

INSTRUÇÕES:

Para cada uma das seguintes duas questões, assinale com uma cruz (X) a caixa que melhor indica o impacto global da sua fibromialgia, **ao longo da última semana**.

A fibromialgia impediu-me de cumprir os objectivos da semana	Nunca☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Sempre
Estive completamente perturbada pelos meus sintomas de Fibromialgia	Nunca☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Sempre

INSTRUÇÕES:

Para cada uma das seguintes dez questões assinale com uma cruz (X) a caixa que melhor indica a intensidade destes sintomas comuns de fibromialgia, **ao longo da últimasemana**.

Por favor assinale o seu nível de dor

Sem dor☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Dor insuportável

Por favor assinale o seu nível de energia

Muita energia☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Sem energia

Por favor assinale o seu nível de rigidez

Sem rigidez☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Muita rigidez

Por favor assinale a qualidadedo seu sono

Acorda descansada☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Acorda muito cansada

Por favor assinale o seu nível de depressão

Sem depressão☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Muito deprimida

Por favor assinale o seu nível de problemas de memória

Boa memória☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Memória muito fraca

Por favor assinale o seu nível de ansiedade

Sem ansiedade☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Muita ansiedade

Por favor assinale o seu nível de dor quando lhe tocam ou apertam

Sem dor☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Muita dor

Por favor assinale o seu nível de problemas de equilíbrio

Sem desequilíbrio☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Grave desequilíbrio

Por favor assinale o seu nível de sensibilidade a ruídos fortes, luzes brilhantes, cheiros e frio

Sem sensibilidade☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐Extrema sensibilidade

Appendix 6

HADS - ESCALA DE ANSIEDADE E DEPRESSÃO HOSPITALAR

Este questionário foi construído para ajudar a saber como se sente. Pedimos-lhe que leia cada uma das perguntas e faça uma cruz (X) no espaço anterior à resposta que melhor descreve a forma como se tem sentido na última semana.

Não demore muito tempo a pensar nas respostas. A sua reacção imediata a cada questão sera provavelmente mais correcta do que uma resposta muito ponderada.

Por favor, faça apenas uma cruz em cada pergunta.

1. Sinto-me tenso/a ou nervoso/a:

( ) Quase sempre

( ) Muitas vezes

( ) Por vezes

( ) Nunca

2. Ainda sinto prazer nas coisas de que costumava gostar:

( ) Tanto como antes

( ) Não tanto agora

( ) Só um pouco

( ) Quase nada

3. Tenho uma sensação de medo, como se algo terrível estivesse para acontecer:

( ) Sim e muito forte

( ) Sim, mas não muito forte

( ) Um pouco, mas não me aflige

( ) De modo algum

4. Sou capaz de rir e ver o lado divertido das coisas:

( ) Tanto como antes

( ) Não tanto como antes

( ) Muito menos agora

( ) Nunca

5. Tenho a cabeça cheia de preocupações:

( ) A maior parte do tempo

( ) Muitas vezes

( ) Por vezes

( ) Quase nunca

6. Sinto-me animado/a:

( ) Nunca

( ) Poucas vezes

( ) De vez em quando

( ) Quase sempre

7. Sou capaz de estar descontraidamente sentado/a e sentir-me relaxado/a:

( ) Quase sempre

( ) Muitas vezes

( ) Por vezes

( ) Nunca

8. Sinto-me mais lento/a, como se fizesse as coisas mais devagar:

( ) Quase sempre

( ) Muitas vezes

( ) Por vezes

( ) Nunca

9. Fico de tal forma apreensivo/a (com medo), que até sinto um aperto no estômago:

( ) Nunca

( ) Por vezes

( ) Muitas vezes

( ) Quase sempre

10. Perdi o interesse em cuidar do meu aspecto físico:

( ) Completamente

( ) Não dou a atenção que devia

( ) Talvez cuide menos que antes

( ) Tenho o mesmo interesse de sempre

11. Sinto-me de tal forma inquieto/a que não consigo estar parado/a:

( ) Muito

( ) Bastante

( )Não muito

( ) Nada

12. Penso com prazer nas coisas que podem acontecer no futuro:

( ) Tanto como antes

( ) Não tanto como antes

( ) Bastante menos agora

( ) Quase nunca

13. De repente, tenho sensações de pânico:

( ) Muitas vezes

( ) Bastantes vezes

( ) Por vezes

( ) Nunca

14. Sou capaz de apreciar um bom livro ou um programa de rádio ou televisão:

( ) Muitas vezes

( ) De vez em quando

( ) Poucas vezes

( ) Quase nunca