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Reduction of parasympathetic influence in fibromyalgia and its relationship with psychiatry in a specialized center of national reference

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Original article

ABSTRACT

Background

Fibromyalgia (FM) is characterized by chronic widespread pain, fatigue, sleep disturbances, depression, anxiety and dysautonomia (sympathetic hyperactivity).

Objective

To compare the heart rate variability (HRV) in women: 20 patients with FM *vs.* 20 controls by Holter 24 hrs.

Method

The measurement consisted of segments of five minutes. The frequency domain is determined by the natural logarithm of the LF/HF (Low/High Frecuencies) reason. Simple ANOVA was used for two groups of dimensional variables.

Results

The age range was 30-60 years. Nine presented psychiatric comorbidity: depression (77.7%) and anxiety (22.3%). There were differences ($F = 24.45$, $p < 0.0001$) in LF/HF between groups in the nocturnal phase of registration (22 pm to 2 am) showing increased sympathetic activation in patients. In the SDNN index (standard deviation of intervals between heartbeats) there were significant differences on December 9 periods of record. In pNN50 index (percentage of intervals which differ by more than 50 milliseconds), the control group showed higher values of 6 to 12 hrs. Nocturnal variation was observed in 22 hrs ($F = 22.37$, $p = 0.0001$) until 6am ($F = 30.27$, $p = 0.0001$). The rMSSD indicator (square root of the mean of the differences in heart rate) showed higher values for the control group from 22 hrs ($F = 67.71$, $p = 0.0001$) until 6am ($F = 80.35$, $p = 0.0001$).

Discussion and conclusion

The results reflect the decreased parasympathetic influence in patients with FM.

This confirms the participation of parasympathetic nervous system in the pathophysiology of FM.

Key words: Fibromyalgia, chronic pain, disautonomy, heart rate variability, depression, anxiety.

RESUMEN

Antecedentes

La fibromialgia (FM) se caracteriza por dolor crónico generalizado, fatiga, alteraciones del sueño, depresión, ansiedad y disautonomía (hiperactividad simpática).

Objetivo

Comparar la variabilidad de la frecuencia cardiaca (VFC) en mujeres: 20 pacientes con FM vs. 20 controles, mediante Holter de 24 hrs.

Método

La medición consistió en segmentos de cinco minutos. El dominio de la frecuencia se determinó por logaritmo natural de la razón LF/HF (Low/High Frecuencies). Se utilizó ANOVA simple para dos grupos de variables dimensionales.

Resultados

El rango de edad fue de 30 a 60 años. Nueve mujeres presentaron comorbilidad psiquiátrica: depresión (77.7%) y ansiedad (22.3%). Hubo diferencias ($F=24.45$, $p<0.0001$) en LF/HF entre los grupos en la fase nocturna del registro (22 hrs a 2 am), mostrándose mayor activación simpática en las pacientes. En el índice SDNN (desviación estándar de intervalos entre latidos) existieron diferencias significativas en 9 de 12 periodos del registro. En el índice pNN50 (porcentaje de intervalos que difieren en más de 50 milisegundos), el grupo control mostró valores más altos de 6 a 12 hrs. La variación nocturna se observó de 22 hrs. ($F=22.37$, $p=0.0001$) hasta las 6 am ($F=30.27$, $p=0.0001$). El indicador rMSSD (raíz cuadrada de la media de las diferencias de la frecuencia cardiaca) mostró valores más altos para el grupo control desde las 22 hrs. ($F=67.71$, $p=0.0001$) hasta las 6am ($F=80.35$, $p=0.0001$).

Discusión y conclusión

Los resultados reflejan la disminución del influjo parasimpático en las pacientes con FM.

Esto confirma la participación del sistema nervioso parasimpático en la fisiopatología de la FM.

Palabras clave: Fibromialgia, dolor crónico, disautonomía, variabilidad de la frecuencia cardiaca, depresión y ansiedad.

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BACKGROUND

Fibromyalgia is a chronic syndrome mainly characterized by the presence of generalized, diffuse, and chronic pain, with no apparent anomalies, and accompanied by other symptoms such as fatigue, sleep disturbances, paresthesia, problems with concentration, anxiety, and depression.[1,2] This generates important changes in the physical, psychological, and social function of those who have the condition. Various studies show that the percentage of the population affected ranges from 2%-5%.[3] It is more frequent in women, with an average onset age that varies between 30 and 60 years.[4] Although there is still no clear etiology, current research indicates a neuro-endocrine-immunological dysfunction,[5] problems with central sensitization,[6] and an alteration to the Autonomic Nervous System (ANS). The latter is highly adaptable and allows the organism to maintain its equilibrium when experiencing stress. The lack of flexibility and a rigid system can lead to somatic and psychological pathologies.[7] One of the ways this response is measured is by means of heart rate variability (HRV); this can be studied in the *time domain* (milliseconds), either by standard deviation (SDNN) of all the populations of intervals between beats or by means of the percentage of adjacent pairs of these intervals which differ by more than 50 milliseconds between one and the next (pNN50) during a certain period of time. A greater rate of variability in the time domain means a greater parasympathetic influence. Another index to assess heart rate variability is the root mean square of successive differences of cardiac frequency (rMSSD). Its measurement in terms of the *frequency domain* is done through a spectral analysis and it provides information on the variance (power) in the heart rhythm explained through periodic oscillations in cardiac frequency (CF) in different bands of frequency.[8,9] The high frequency band (HF) represents the action of the Parasympathetic Nervous System (PNS), while the low frequency band (LF) reflects a greater predominance of sympathetic action.[8,10] One study[11] revealed that compared with controls, before an orthostatic stressor, patients with FM could not increase the LF band in response to standing up. Another study[12] assessed the circadian behavior of the ANS through a 24 hour Holter test while subjects went about their daily activities, and the analysis in both the time and frequency dimensions demonstrated that patients with FM had alterations compatible with incessant sympathetic hyperactivity during the day, but particularly during the night. Various other studies report that FM patients have dysautonomia consistent with hyperactivity of the Sympathetic Nervous System (SNS) which becomes hyporeactive to stress.[13-15] However, alterations in the HRV have also been found in mental health conditions. In comparison with healthy controls and non-psychiatric controls, a greater LF/HF index has been found in patients with major depressive disorder (MDD) and anxiety disorders[16,17] which would indicate a reduction in vagal tone, reflecting a deficit in the flexibility of physiological mechanisms.[7] Some studies[18] indicate the association between depression, reduced HRV, and the use of antidepressants,[19] emphasizing the relationship between major depression and cardiovascular disorders, which is measured in part by the reduction in HRV.[20] The high prevalence reported between FM and MDD[21-26] together with the findings of reduced HRV in patients with a chronic pain condition,[27] necessitates treatment such as cognitive behavioral therapy (CBT), transcranial magnetic stimulation (TMS), and biological feedback (BF) being taken into account to increase the HRV[28] and help to control depressive symptoms.[29,30] An important starting point is that of this study, to identify the differences in HRV in controls and in FM patients who also have psychiatric disorders.

METHOD

Design

This was a comparative and cross-sectional study with two independent samples.

Participants

The sample was obtained of patients at the National Institute of Psychiatry Ramón de la Fuente Muñiz who attended cognitive behavioral group therapy for patients with fibromyalgia. The inclusion criteria were the following: women, aged between 30 and 60, with a diagnosis of FM. The exclusion criteria were: comorbidity with a rheumatologic or cardiovascular condition, psychotic states, or pregnancy. The sample was therefore formed of 40 women in two groups: 20 patients with FM and 20 controls paired by age (±2 years).

The controls were healthcare professionals (psychologists, doctors, social workers, nutritionists, and nurses), and administrative staff at the Institute. It should be noted that none of these staff, primarily nurses, worked the night shift. During the study, patients and controls avoided consuming cola drinks, tobacco, and caffeine. All participants provided their informed consent.

Procedure

Participants were assessed with the M.I.N.I. International Neuropsychiatric Interview[31] –based on the Spanish, computerized version of the DSM-IV and the ICD-10–. These were applied by a psychiatrist in order to determine if any psychiatric diagnosis was present. In consultation with the Department of Clinical Services, each of the participants were seen twice. The first was to explain the procedure, sign the informed consent, and fit a Holter recorder (a portable monitor for 24 hour electrocardiographic recording, model

Table 1. Demographic data of patients with fibromyalgia and controls

	Fibromyalgia		Control	
	Median	S.D.	Median	S.D.
Age [years]	49.80	5.90	47.50	8.10
Education [years]	14.30	4.10	15.90	3.20
	N	%	N	%
Marital status				
No partner	7	35	9	45
Partner	13	65	11	55
Occupation				
Paid work	12	60	19	95
Unpaid work	8	40	1	5

DMS 300-7). The second was to retrieve the recorder and migrate the data to a piece of software for later review and analysis. The recording began between 08:00 and 08:30 hrs.

Statistical analysis

The categorical variables are presented in frequency and percentages, and the dimensionals with medians and standard deviations. The unit of analysis recorded was segments of five minutes. For analysis of the frequency domain, the natural logarithm of the LF/HF ratio was determined. The roundness of the data found was analyzed, finding that the covariance matrix differed from the identity matrix, because of which the data was considered independent over time. A simple ANOVA was used for both groups and for the dimensional variables in the study. Version 18 of the SPSS statistics software package was used.

RESULTS

The average age for the group with FM was 49.8, and for the control group it was 47.5. In terms of education, patients had an average of 14.3 years of study, while the control group had 15.9 years. Of the patients, 13 had a partner and seven did not, while in the control group, 11 had a partner and nine did not. The control group was basically formed by people in employment (19), but only 12 of these had remunerated work (table 1).

The patients were diagnosed according to the criteria from the American College of Rheumatology[32] with severity from moderate to severe and an average development of seven years. Nine patients had a psychiatric diagnosis. The most common diagnosis was major depressive disorder, in 77.7%, followed by generalized anxiety disorder (GAD) in 22.3%. Eight of the nine patients had more than one psychiatric diagnosis. The greatest comorbidity was with anxiety disorder (44.3%) and dysthymia with GAD (22.3% (table 2).

Table 2. Diagnoses of patients with fibromyalgia

	First Dx		Second Dx	
Psychiatric diagnosis	N	%	N	%
Dysthymia	0	0	1	11.1
Generalized anxiety disorder	2	22.3	2	22.3
Anxiety disorder	0	0	3	44.3
Major depressive disorder	7	77.7	2	22.3

Table 3. Treatment and psychiatric comorbidity in patients with fibromyalgia

Psychiatric treatment	N	%
Dual antidepressants	2	20
SSRI antidepressants	5	50
Tricyclic antidepressants	2	20
Pain moderators	3	30
Benzodiazepine	1	10

The psychiatric treatment used was selective serotonin reuptake inhibitors (SSRIs) in 50%, with tricyclic antidepressants in 20% and dual antidepressants in another 20%. Some 30% of the patients took pain regulators and only one patient used benzodiazepines (table 3).

In terms of the LF/HF index, a highly significant difference was found between both groups [F=24.45, p<0.001] for the period between 22:00 hrs through 00:00 hrs, with the highest median for the group of patients which reflects greater sympathetic activation. A significant difference between the groups [F=5.01, p<0.05] was also found from 00:00 hrs through 02:00 hrs, with greater activation for the patients. Between 04:00 hrs and 06:00 hrs, a tendency to significance was observed [F=3.17, p=0.0754], which indicated greater sympathetic activity in the patients. In the period between 08:00 hrs and 10:00 hrs, there was a tendency to significance [F=3.36, p=0.0670] which would indicate a mildly greater activation for the control group (figure 1).

In the SDNN index, significant differences were found between the groups for basically the majority of the periods (nine out of 12), which comprised 24 hours of measurement. There was a difference between the groups for the period 08:00 hrs through 10:00 hrs as well as for the period 20:00 hrs through 22:00 hrs (figure 2).

In the pNN50 index, it was found that the groups differed in various measurement periods, with the morning hours of 06:00 through 08:00 [F=52.44, p=0.001], 08:00 hrs through 10:00 hrs, [F=15.89, p=0.001] and 10:00 hrs through 12:00 hrs [F=10.64, p=0.001] being particularly notable. A statistically significant difference was found between the hours of 12:00 and 14:00 [F=5.60, p=0.0183]. No differences were observed between the groups during the hours of 14:00 though 16:00. In the afternoon, from 16:00 through 18:00 hrs, there was a significant difference [F=31.6, p=0.001], and nocturnal variation was observed from 22:00 hrs [F=22.37, p=0.001], which was also the case between 00:00 hrs and 02:00 hrs [F=40.91, p=0.001]. Statistically significant differ-

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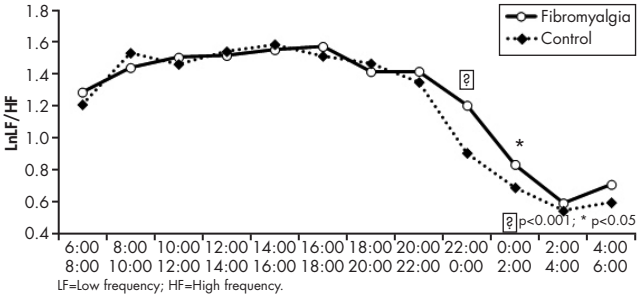

Figure 1. Differences in the LF/HF index between patients with fibromyalgia and controls.

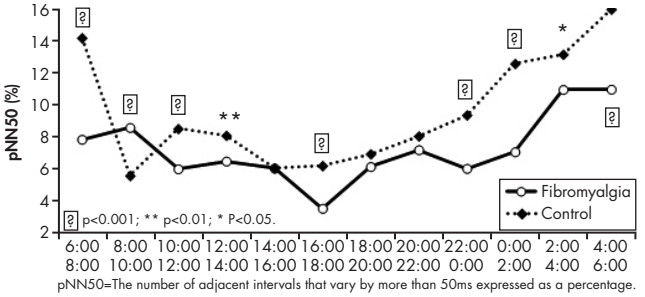

Figura 3. The pNN50 index in patients with fibromyalgia and controls.

ences were found between 02:00 hrs and 04:00 hrs, [F=5.24, p=0.0224] as well as in the period from 04:00 hrs through 06:00 hrs [F=30.27, p=0.001] (figure 3).

Finally, for the rMSSD indicator, in almost all of the periods, values above average were obtained for the control group, especially during the night: there were significant differences between 20:00 hrs and 22:00 hrs [F=11.72, p=0.006]; from 22:00 hrs through 00:00 hrs [F=67.71, p=0.001]; from 00:00 hrs through 02:00 hrs [F=87.16, p=0.001]; from 02:00 hrs through 04:00 hrs [F=38.35,p=0.001]; and from 04:00 hrs through 06:00 hrs [F=80.35, p=0.001]. No differences were found in the period between 18:00 hrs and 20:00 hrs (figure 4).

It is confirmed that the pNN50 index is highly correlated with the rMSSD, r=0.974 for FM and r=0.986 for the control group.

DISCUSSION AND CONCLUSION

The results of this study confirm the phenomenon of dysautonomia in patients with fibromyalgia. Clear differences were observed in the LF/HF index between patients and the control group in the nocturnal recording phase, specifically between the hours of 22:00 and 02:00. As there is an increase in the influx of the sympathetic system during sleeping hours, it is understandable that one of the most frequent complaints reported by these patients is poor quality sleep; this is a phenomenon that has also been confirmed in other studies on FM and in the male and female population.[12,15,33,34]

In the measurement of both the SDNN and the rMSSD indexes, significant differences are found in the period between 22:00 hrs and 08:00 hrs. This result confirms what various authors report as hyperactivity,[35] a hyperactivity that is highly dysfunctional because upon altering the sleep cycle, it facilitates the presence of greater pain or tiredness, and with it, a reduction in activity during the day. A night of non-restorative sleep in people with FM is then followed by high instances of pain and alterations in attention the following day.[36]

The differences found between the groups in the pNN50 index in the measurement periods from 06:00 hrs through 12:00 hrs, where the control group has higher values, reflect the other characteristic of dysautonomia;[12,13] that is, the reduction in the sympathetic influx in patients at time when they need to be ready for action. This has been reported by the majority of patients attending treatment at the National Institute of Psychiatry Ramón de la Fuente Muñiz, when describing their difficulty in starting activities before noon.

In our sample of patients with FM, almost half had depression, which confirms the high prevalence reported in this condition.[21-26] This is one of the reasons why within this psychiatric institution, there has been a designated space since 2007 for the multi-disciplinary treatment of patients with fibromyalgia.[37]

Given that FM and the use of antidepressants alter

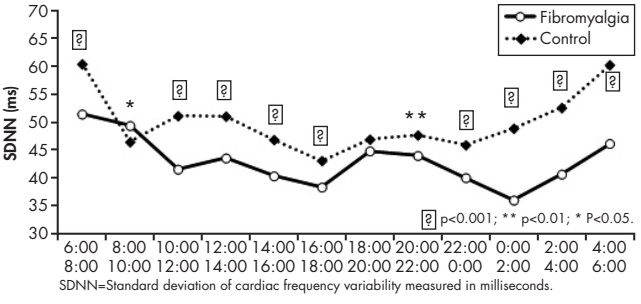

Figure 2. Differences in the SDNN index between patients with fibromyalgia and controls.

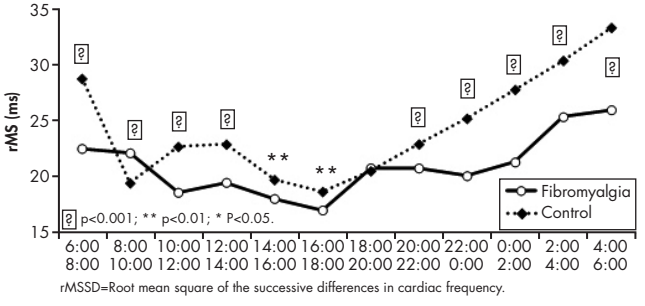

Figure 4. Differences in the rMSSD indicator between patients with fibromyalgia and controls.

HRV,[19,20] we think that the patients who also had a psychiatric disorder could have had even more potential for a reduced HRV in comparison with healthy patients and patients with FM only. However, in our study, there were no significant differences in any of the variables between those who had a psychiatric diagnosis and those who only had FM. Even so, it is difficult to determine to what point low HRV depends on one condition or another. Although more controlled studies with greater independent samples are required, the association found between dysautonomia and depression necessitates that this relationship be taken into account in pharmacological and non-pharmacological treatments currently considered to be the pillars of managing the condition, such as antidepressants and cognitive behavioral therapy. This is because even if medications have demonstrated a reduction in some symptoms of depression, they do not impact on the flexibility of HRV. Furthermore, it is important to consider that patients with FM frequently have more than one psychiatric diagnosis.

As well as the effectiveness that CBT has shown in improving the symptomatology of these patients,[38] there is evidence that TMS and BF can increase HRV after controlling depressive symptoms[28,30] which makes them a non-invasive technique that are coadjuvant in the wellbeing of the patient through direct involvement in a change in the HRV, thereby avoiding polypharmacy, a condition that is also very frequent in these patients due to the great number of symptoms they report.[39]

As suggested by some studies[35,40] the measurement of HRV can be a biomarker for FM, however it also seems to be useful in depression and other chronic pain conditions,[27] given that as some authors have stated,[41,42] FM could be part of the disorders from the affective spectrum that together with depression and other medical and anxiety conditions, share common pathophysiological elements. It is important that healthcare professionals take this response into account in the assessment and treatment currently offered for these conditions, making use of complementary strategies to potentialize their effects.

It is necessary to reiterate the impact of good heart function on general health, given that as referred to in the neurocardiological findings, the heart seems to be intimately involved in psychophysiological coherence.[43] It communicates with the brain, influencing the processing of information, perceptions, emotions, and health,[44] and sending significant messages to the brain that are understood and obeyed.[45] As such, only a holistic model which allows for better comprehension and management of the mind-heart interaction, together with knowledge and utilization of non-invasive techniques for the analysis and therapeutic management of patients with complex illnesses such as FM, will make treatments more effective, reduce the risk of comorbidity, and improve quality of life for these patients.

Limitations and suggestions

It is important for future studies to consider the comparison of HRV in patients with depression *vs.* patients with FM only, *vs.* patients with both, applying clinimetrics that include the level of severity of both the psychiatric disorders and the FM. It is recommended to increase the sample size and control the type of antidepressants and dosage to have greater precision in the results obtained. Furthermore, it is recommended to have data that takes account of the way in which the patients experience symptoms to confirm and/or clarify the data obtained with the instruments used. For example, have a record which considers variables such as bedtime, waking time, physical activity, diet during the study, as well as the presence of stressful events and the way they are dealt with.

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Conflict of interest

The authors do not declare any conflicts of interest.

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