Relationship between sympathetic activity and pain intensity in fibromyalgia

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ABSTRACT

Objective. *Fibromyalgia (FM) is a syndrome characterised by chronic musculoskeletal pain, hyperalgesia on specific areas of tenderness (tender points) and by an autonomic nervous system dysfunction consistent with sympathetic overactivity. It is not known whether there is any relationship between the amount of cardiovascular sympathetic activity and the magnitude of pain. Our objective was to assess this potential relationship in patients with FM.*

Methods. *Electrocardiogram, finger blood pressure, respiration and postganglionic sympathetic discharge activity (muscle sympathetic nerve activity, MSNA) were continuously recorded at rest in 25 patients with primary FMS. The autonomic profile was assessed by MSNA and spectral indices of cardiac sympathetic (LF_{RR}) and vagal (HF_{RR}) modulation and of sympathetic vasomotor control (LF_{SAP}) computed by spectrum analysis of RR and systolic arterial pressure (SAP) variability. Cardiac baroreflex function was evaluated by the index α (α_{LF}). Baroreceptor modulation of the sympathetic vasomotor control (sBRS) was assessed by the MSNA/diastolic pressure relationship.*

Results. *Pain intensity was linearly correlated with LF_{RR}/HF_{RR} ($r^2=0.21$; $p=0.03$), LF_{SAP} ($r^2=0.26$; $p=0.02$) and MSNA (burst rate) ($r^2=0.45$; $p=0.003$). Pain intensity was inversely correlated with the α_{LF} index ($r^2=0.24$; $p=0.02$) and the sBRS ($r^2=0.28$; $p=0.03$). Thus, the higher the sympathetic drive to the heart and vessels, the higher the magnitude of chronic pain. Also, the gains of both the cardiac and MSNA baroreceptor control were inversely related to the pain intensity.*

Conclusion. *These findings raise the theoretical possibility that in FM patients the use of anti-adrenergic agents might lessen chronic pain intensity by reducing the underlying excessive sympathetic activity.*

Introduction

Fibromyalgia is a syndrome characterised by chronic widespread musculoskeletal pain and hyperalgesia on specific areas of tenderness called tender points (TP), besides many other non-rheumatologic features such as autonomic nervous system dysfunction, migraine, Raynaud's phenomenon, irritable bowel syndrome, sleep disorder (1).

Advances in the understanding of the mechanisms underlying pain in fibromyalgia syndrome (FMS) have been made (1-3), and some studies have hypothesised that neural sympathetic overactivity might play an important role in generating and sustaining chronic pain in this syndrome (4, 5). Indeed, cardiovascular autonomic abnormalities, consistent with sympathetic overactivity to the heart and vessels, have been shown by several studies (6, 7).

However, whether a direct relationship exists between the amount of cardiovascular sympathetic activity and the magnitude of pain it is still unknown. In addition, it is unclear whether the sympathetic overactivity is primarily central in origin or secondary to baroreceptor dysfunction. From the clinical standpoint addressing these aspects is crucial because the association of anti-adrenergic agents such as clonidine to the regular therapy might theoretically concur to ameliorate chronic pain in FM.

Thus, the aim of this study was to assess the potential direct relationship of cardiovascular sympathetic activity and pain in patients with FMS. In addition, baroreflex control of both heart rate and post-ganglionic sympathetic activity were evaluated.

Methods

Subjects

Twenty-five patients with primary FM (23 women, 2 men; age 45.6 ± 11.2 years), diagnosed according to the American College of Rheumatology classification criteria (8), took part in the study. The experimental protocol was approved by the Hospital Institutional Review Board and was conducted in accordance with the Declaration of the World Medical Association. All subjects provided written informed consent.

All subjects were non-smokers. Subjects presenting any disease known to affect the autonomic nervous system such as hypertension, diabetes, hyperthyroidism, hypothyroidism and other relevant medical conditions including inflammatory and autoimmune diseases were excluded on the basis of complete medical evaluation, electrocardiogram (ECG), and routine laboratory tests. Adrenal dysfunction was ruled out by appropriate laboratory tests. Patients' clinical features are reported in Table I. Drug treatment was discontinued at least 5 half-lives before testing.

Procedure

All subjects were studied after a light breakfast not containing alcohol or caffeine beverages, in a quiet room with a dim light and comfortable temperature. In every subject, we recorded the ECG, noninvasive blood pressure (Finapres; Ohmeda 2300, Atlanta, GA, USA), and respiratory activity by a thoracic bellows connected to a pressure transducer. Direct recording of the post-ganglionic muscle sympathetic neural activity (MSNA) was obtained from the right peroneal nerve by microneurography technique (9). Briefly, a unipolar tungsten electrode with uninsulated tip was placed in the right peroneal nerve near the fibular head for multiunit postganglionic sympathetic nerve recording. The raw neural signal was amplified (1000-fold amplification), fed to a band pass filter (bandwidth between 700 and 2000 Hz), rectified and integrated (time constant 0.1 s) by a nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City, IA, USA).

Integrated MSNA, ECG, arterial pressure, and respiratory activity signals were digitised at 300 samples/s by an analogical to digital board, and recorded on a pc for off-line analysis.

Plasma epinephrine and norepinephrine were measured on venous blood samples.

A 100-mm visual analogue scale (VAS) was applied to evaluate the current level of overall body pain at rest (0 = no pain, 100 = worst pain ever felt). The number of tender points were assessed by palpation with the pulp of the thumb, at a pressure of about 4kg and counted according to the methodology proposed by Wolfe *et al.* (8). Also, a disability index was obtained by means of the Healthy Assessment Questionnaire (HAQ) (10).

Every subject underwent instrumentation as described. Thirty minutes after instrumentation, baseline data acquisition was initiated in the supine position and a blood sample was withdrawn for catecholamine evaluation.

Data analysis

Microneurography was considered to reflect MSNA according to established criteria (11). The methods used for signal processing, autoregressive spectrum and cross-spectrum analysis of RR interval and systolic arterial pressure variability, and respiration, have been described in detail elsewhere (12, 13). There are 2 main oscillatory components, the amplitude of which is modulated by changes in cardiovascular neural control (12, 14, 15). One is the high frequency (HF, ≈ 0.25 Hz). If obtained from RR variability, HF_{RR} provides an index of the vagal modulation of the sinoatrial node discharge (14). The second oscillatory component is indicated as low frequency (LF, 0.1 Hz). In the case of systolic arterial pressure (SAP) variability, LF_{SAP} is a marker of the sympathetic vasomotor control (12, 14-16). The LF component of RR variability (LF_{RR}) when expressed in normalised units (n.u.) may reflect the sympathetic efferent modulation to the sinoatrial node and its changes (12, 14, 15). Normalisation is achieved by dividing the absolute power of each component by total variance (minus the power of the very low frequency component) and multiplying by 100 (12). The LF_{RR}/HF_{RR} ratio furnishes a further index to evaluate the sympathovagal interaction to the sinoatrial node activity (12, 15). Arterial baroreflex control of heart rate was assessed by bivariate spectrum

Table I. Clinical features of patients with FMS.

Characteristic	FMS (n = 25)
Gender (M/F)	23/2
Age (years)	43.7 ± 12.3
Disease duration (years)	5.7 ± 4.9
No. of tender points (0–18)	14.1 ± 2.0
Pain visual analogue scale (0–100 mm)	66.1 ± 14.7
Fatigue (0–100 mm)	58.7 ± 20.3
Health Assessment Questionnaire (0–3)	0.74 ± 0.57

Table II. Patients' haemodynamic and respiratory variables. Data are mean ± SE.

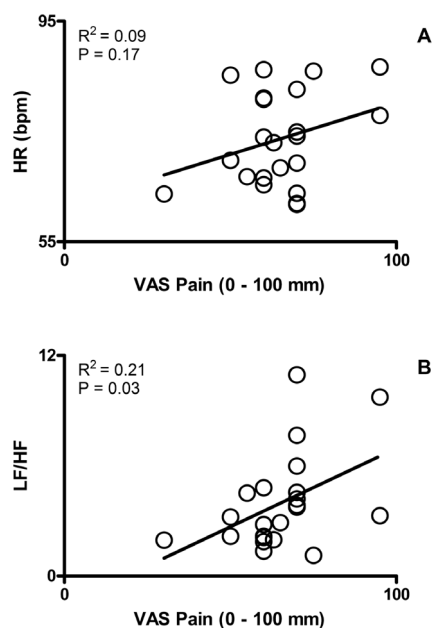|	FMS (n=25)
HR (bpm)	74 ± 2
RR (ms)	826 ± 19
SAP (mmHg)	128 ± 4
DAP (mmHg)	82 ± 13
Resp (cycles/min)	17 ± 1

HR: heart rate (beats/min); SAP: systolic arterial pressure; DAP: diastolic arterial pressure; Resp: respiratory frequency.

**Table III.** Indices of autonomic activity at rest in FMS patients. Data are mean ± SE.

	FMS (n=22)
MSNA (bursts/min) (N=17)	21.4 ± 0.8
MSNA (bursts/100 beats) (N=17)	31.5 ± 2.6
NE (pg/ml) (N=17)	240.1 ± 21.6
E (pg/ml) (N=17)	27.0 ± 4.8
RR σ^2 (ms^2)	1608.2 ± 387.7
LF_{RR} (ms^2)	632.4 ± 141.0
LF_{RR} (nu)	67.3 ± 3.5
HF_{RR} (ms^2)	213.5 ± 91.0
HF_{RR} (nu)	21.8 ± 2.1
LF_{RR}/HF_{RR}	3.9 ± 0.5
SAP σ^2 (mmHg^2)	18.2 ± 3.4
LF_{SAP} (mmHg^2)	7.3 ± 1.5
α_{LF} (ms/mmHg)	12.9 ± 2.1
sBRS (%/mmHg)	-2.3 ± 0.9

MSNA: muscle sympathetic nerve activity; NE: norepinephrine; E: epinephrine; σ^2: variance; LF_{RR}: low frequency component of RR variability; HF_{RR}: high frequency component of RR variability; nu: normalised units; LF_{SAP}: low frequency component of systolic arterial pressure variability; sBRS: sympathetic baroreflex sensitivity.
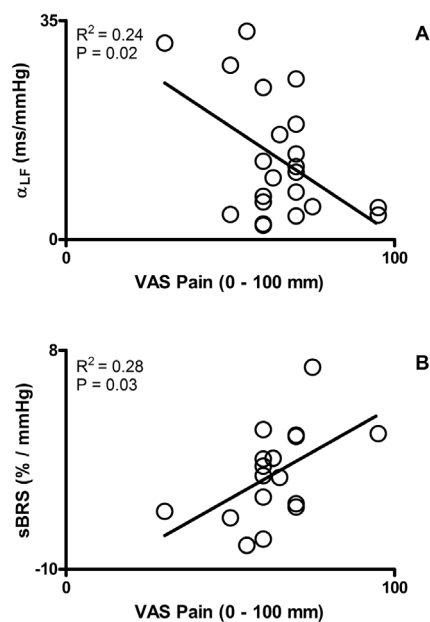
Fig. 1. Relationship of the pain assessed by a 100-mm visual analogue scale (VAS) with heart rate (**A**) and low frequency (LF)/high frequency (HF) ratio (**B**).
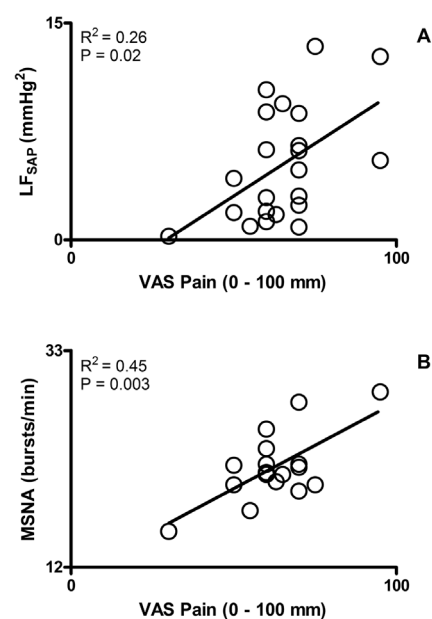
Fig. 2. Relationship of the pain assessed by a 100-mm visual analogue scale (VAS) with low frequency (LF) of systolic arterial pressure (SAP) (**A**) and muscle sympathetic nerve activity (MSNA) (**B**).

analysis of RR interval and SAP variability. The index α, computed as the square root of the ratio between the powers of the spectral components of RR interval and SAP variability in the low frequency band (17), provides the gain of arterial baroreceptor sensitivity. The gain of the baroreflex modulation

Fig. 3. Relationship of the pain assessed by a 100-mm visual analogue scale (VAS) with cardiac baroreflex gain (α_{LF} index) (**A**) and sympathetic baroreceptor control (sBRS) (**B**).

of the sympathetic activity to the vessels (sympathetic baroreceptor control, sBRS) was obtained by assessing the inverse relationship between DAP values and the occurrence of a MSNA burst, having taken into account the baroreflex latency (18). According with the methodology described by Hart and colleagues (18), DAP values were grouped into bins of 1 mmHg, the average of different diastolic values within a bin was computed together with the percentage of MSNA detection associated to the considered values of DAP. Finally a linear regression analysis was computed relating each diastolic value with the corresponding percentage of sympathetic burst occurrence. The slope of the regression line was taken as an estimate of sBRS when the regression coefficient was significant ($p<0.05$).

Statistical analysis
Data are expressed as mean ± SE. Linear regression was performed to determine the relationship between the cardiovascular autonomic indices and the pain scores assessed by a 100-mm VAS. Significance level was set at 5%.

Results
Table I summarises the clinical features of the FMS patients we studied.

Notice the large female prevalence, as expected, and the relevant number of the tender points.

The haemodynamic and respiratory variables characterising the studied population are summarised in Table II. MSNA indices, catecholamine measures, spectral markers of autonomic profile obtained by HR and BP variability and baroreceptor function indices are condensed in Table III.

There was no significant correlation between pain and HR ($R^2=0.09$; $p=0.17$, Fig. 1A). A direct correlation between pain and the spectral index of cardiac sympathovagal balance, LF_{RR}/HF_{RR}, was found ($R^2=0.21$; $p=0.03$, Fig. 1B) such that the greater the pain intensity the higher were the LH/HF values, that is the higher the cardiac sympathetic modulation.

Similarly, LF_{SAP}, the spectral index of the sympathetic vasomotor control, was linearly correlated with pain intensity ($R^2=0.26$; $p=0.02$, Fig. 2A). Finally, there was a linear correlation between the sympathetic efferent discharge activity (MSNA burst rate) and the pain intensity ($R^2=0.45$; $p=0.003$, Fig. 2B) indicating that the highest level of pain were associated with greater sympathetic discharge activity.

As to the baroreflex control of heart rate, there was a linear inverse relationship between the baroreceptor gain (α_{LF} index) and pain intensity ($R^2=0.24$; $p=0.02$, Fig. 3A). Pain magnitude was also inversely correlated with the gain of the sympathetic baroreceptor control (sBRS, $R^2=0.28$; $p=0.03$, Fig. 3B).

Discussion
The results of the present study suggest that chronic pain intensity in fibromyalgia patients is related to the overall cardiovascular sympathetic activity. Thus, the higher the sympathetic drive to the heart and to the vessels, the higher the magnitude of the chronic pain.

To our knowledge, this is the first study which addressed the relationship between the direct recording of the sympathetic nerve activity and the intensity of pain in fibromyalgia patients. Notably, the causality of such a relationship could not be assessed by the present analyses, and whether a progressive increase in

chronic pain intensity might result in an increased sympathetic activity or a leading exceeding sympathetic firing might induce or facilitate chronic pain, still remain to be clarified. Martinez-Lavin and colleagues (19) showed that patients with fibromyalgia were characterised by norepinephrine-evoked pain, thus suggesting that fibromyalgia may be a sympathetically maintained pain syndrome, similarly to the Complex Regional Pain Syndrome Types I and II. In these disorders, because of the presence of sympathetic overactivity, body nociceptors may develop catecholamine sensitivity, enabling the norepinephrine released by the sympathetic nerve fibres to activate or iper-sensitise the afferent neurons, eventually resulting in increased nociceptive firing (20, 21). In keeping with these concepts, we and others have previously shown that fibromyalgia patients were characterised by an increased cardiac and vascular sympathetic activity in recumbent position compared with age and gender matched healthy controls (6, 7), thus hypothesising that the overall increased sympathetic activity might take part in the central nervous system sensitisation process (22) and play a crucial role in generating and sustaining chronic pain (23). On the other hand, Fazalbhoy *et al*. (24) studied the changes in MSNA, blood pressure and HR after a long-lasting pain was induced. The authors concluded that chronic pain may have long-lasting effects on the sympathetic control of blood pressure, causing a sustained increase in MSNA, blood pressure and HR in some subjects. Differences in the study protocols and in the studied populations might account for the diverging findings and conclusions. An important result of the present study is the finding that chronic pain intensity was inversely related to the gain of the arterial baroreflex control of heart rate.

Studies have shown an inverse relationship between lower cardiac baroreflex functioning and higher levels of clinical pain (2, 3), similarly to our results. Based on the observation that experimental activation of the carotid baroreceptors may trigger marked anti-nociceptive effects (25) it has been hypothesised that a deficient arterial baroreceptor functioning might contribute to the increased pain sensitivity characterising fibromyalgia.

A possible explanation for this association relies on the interaction between the autonomic and sensory systems occurring in the nucleus tractus solitarii (NTS), which receives baroreceptor input from the glossopharyngeal and vagus nerves and neurones projection from spinal laminae involved in nociceptive processing. Also, several structures known to be involved in pain pathways modulation, such as the periaqueductal gray, the nucleus raphe magnus and rostral ventrolateral medulla, proved to receive direct or indirect inputs from the NTS (21). Therefore, baroreceptor afferents may alter nociceptive processing and subjective pain experience through modulation of the activity of above structures (21, 26).

In the present study, the indices of baroreceptor modulation of heart rate and sympathetic nerve activity (α_{LF} and sBRS, respectively) were both correlated to the pain intensity showing a similar pattern. Indeed, there was an inverse relationship between α_{LF} and pain intensity, as discussed above, and similarly the gain of the sympathetic baroreceptor modulation (sBRS) linearly decreased according to the progressive enhancement of pain magnitude. Because in the present study the magnitude of the efferent sympathetic activity (MSNA) was directly related to the intensity of pain (see fig 2B), MSNA and sBRS behaved in the opposite manner in relation to chronic pain. This is not a surprising finding given the inverse functional relationship between sympathetic burst activity (MSNA) and the restraining modulation exerted by baroreceptor control (sBRS) on MSNA (18). Previous studies have hypothesised that the sympathetic over-activity in fibromyalgia might be due to a primary central nervous system sympathetic drive (6, 7). The functionally inverse relationship between sympathetic efferent activity and sympathetic baroreceptor restraining modulation seems to be still maintained in these patients, as far as the relationship with chronic pain is concerned.

Conclusions and future perspectives

In patients with fibromyalgia, pain intensity was directly related with the cardiovascular sympathetic overactivity. In addition, the gains of both the arterial baroreflex control of heart rate and of the sympathetic baroreceptor modulation were related to the pain magnitude, although in a different fashion. These findings potentially bear important clinical implications since the reduction of an exceeding sympathetic activity by the use of anti-adrenergic agents such as the clonidine, might result in a decrease in chronic pain intensity.

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