Autonomic Nervous System Derangement in Fibromyalgia Syndrome and Related Disorders

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Abstract

Fibromyalgia syndrome is a chronic, painful musculoskeletal disorder of unknown etiology and/or pathophysiology. During the last decade many studies have suggested autonomic nervous system involvement in this syndrome, although contradictory results have been reported. This review focuses on studies of the autonomic nervous system in fibromyalgia syndrome and related disorders, such as chronic fatigue syndrome and irritable bowel syndrome on the one hand and anxiety disorder on the other, and highlights techniques of dynamic assessment of heart rate variability. It raises the potentially important prognostic implications of protracted autonomic dysfunction in patient populations with fibromyalgia and related disorders, especially for cardiovascular morbidity and mortality.

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Fibromyalgia syndrome is an idiopathic chronic pain syndrome characterized by generalized pain and specific tender points [1]. The condition affects women more frequently than men, with a prevalence of about 1% in women aged 19–29 years and approximately 7% in those aged 70–79 [1]. The pathophysiology of fibromyalgia is not clear, and neurochemical or central pain and soft tissue or peripheral mechanisms have been variously suggested [2–4].

Much interest has recently been expressed in the possible role of the autonomic nervous system in the pathogenesis of this disorder. The aim of this review is to report on the evidence for autonomic system derangement in fibromyalgia and related disorders.

Methods of assessing autonomic functions

There is no single test for assessing autonomic function. Investigators have used a variety of techniques to examine the function of the autonomic nervous system in this syndrome. These techniques include muscle sympathetic nerve activity; microcirculation with or without provocative stress; biochemical markers such as catecholamine concentration, norepinephrine levels, and plasma levels of neuropeptide Y; and physiologic tests such as orthostatic test, Valsalva test, and heart rate variability analysis.

During the last decade much progress was made in understanding autonomic hemodynamic regulation through power spectral analysis of heart rate variability. Spectral analysis of heart rate variability provides important information on sympathovagal interactions and has been applied to the evaluation of autonomic function in tilt tests.

Heart rate variability

Heart rate is not constant, but oscillates around a mean value. These oscillations are due to modulations of autonomic nervous system activity, which control heart rate through the sympathetic and parasympathetic systems. The cyclic changes in sinus rate over time are termed heart rate variability [5]. Power spectral density analysis provides the basic information of how power (variance) distributes as a function of frequency. It has been shown that harmonic oscillations in heart rate are concentrated into at least three distinct bands: high frequency bands (0.15–0.5 Hz), low frequency bands (0.04–0.15 Hz) and very low frequency (0.01–0.04 Hz) components of the total variance ("power") of heart rate.

Numerous studies have suggested that HF is a marker of vagal activity [6]. The LF power is proposed by some researchers [6] to be a marker of both sympathetic and parasympathetic activity, and may be associated with baroreceptor activity. There is, however, no consensus on the association between LF and sympathetic nervous system activity. The Task Force of the European society of Cardiology and the North American Society of Pacing and Electrophysiology [6] and others, regard LF as reflecting sympathetic activity directly. Factors known to enhance sympathetic activity increase the LF component, e.g., postural changes such as tilt test and standing up, mental/emotional and physical stress, sympathomimetic pharmacologic agents, baroreceptor unloading by nitroglycerin infusion, and coronary occlusion [6]. Conversely, bilateral stellectomy and β-adrenergic blockade are associated with a reduction in peak LF power [6]. Because LF may also be influenced by parasympathetic activity, the LF/HF ratio provides a measure of the sympathovagal balance – where an increase in the LF/HF ratio reflects a predominance of sympathetic over parasympathetic activity – and may estimate sympathetic tone more

HF = high frequency
LF = low frequency

accurately than LF alone. The VLF component has not yet been given a precise physiological meaning and is subject to considerable debate, having been attributed variously to thermoregulatory processes, peripheral vasomotor activity, and the renin-angiotensin system.

Power analysis of heart rate variability, which is reliable and non-invasive, can utilize the assessment of cardiovascular autonomic regulatory responses to provide a general indication of peripheral sympathetic and parasympathetic tone and can thus be used to explore the nature of sympathetic-parasympathetic interactions.

Heart rate variability involves a complex interaction between several mechanisms working to maintain heart rate and blood pressure within normal limits. In normal subjects this can include the reaction to activity or postural changes, physical exercise and mental/emotional stress. Heart rate variability has proven useful in the study of various diseases such as hypertension, diabetic neuropathy, heart failure, myocardial ischemia and acute myocardial infarction [6].

Autonomic nervous system derangement in fibromyalgia

Many studies suggest autonomic nervous system involvement in this syndrome, although contradictory results have been reported. Backman and colleagues [7] were the first to observe striated muscle sympathetic hyperactivity in fibromyalgia syndrome, by measuring maximum voluntary handgrip strength as well as various contraction characteristics in the adductor pollicis muscle after electrical stimulation of the ulnar nerve with and without sympathetic blockade (guanethidine). They found a lower basal muscle relaxation rate in fibromyalgia patients, whichi increased during sympathetic blockade. The authors suggested that increased muscle sympathetic nerve activity is a possible mechanism [7].

In contrast to these findings, by using a microcirculatory response to a cold pressor stress, Vaeroy and colleagues [8] reported that auditory stimulation and cold pressor tests elicited diminished vasoconstrictor response in fibromyalgia patients as compared to controls. These authors proposed the hypothesis of an attenuated sympathetic activity and/or concomitant exaggerated cholinergic response.

Contradictory findings were reported by both Russell [3] and Yunus et al. [2] who used the release of catecholamines as an alternative measure of sympathetic activity, showing similar baseline levels of plasma and urinary catecholamines in fibromyalgia patients and controls. This was in part replicated by Elam et al. [9] who recorded muscle sympathetic activity with microneurography (direct measurement of the sympathetic activity from the peroneal nerve) and found no difference in baseline sympathetic activity between fibromyalgia patients and controls. Furthermore, patients did not show exaggerated sympathetic nerve responses to static handgrip or jaw muscle contractions, post-contraction ischemia or mental stress. Thus the authors concluded that muscle sympathetic nerve overactivity does not indicate fibromyalgia. Qiao and coworkers [10] measured electrodermal and microcirculatory parameters at baseline and after acoustic stimulation or cold pressor tests, confirming the observation of a decreased sympathetic response to diverse stimuli. In contrast, Bennett et al. [11] reported opposite results using the Nielsen test (cold-induced vasospasm). They demonstrated that fibromyalgia patients had a higher than expected rate of a positive Nielsen test (cold-induced increase in finger systolic blood pressure) and an increase in the number of alpha 2-adrenergic receptors on thrombocytes (upregulation). In agreement with Bennett's findings, Lapossy et al. [12], using capillary videomicroscopy of the nail folds in a cold provocation test, showed that 38% of the fibromyalgia patients responded to the cold provocation to induce vasospasm compared with only 8% of controls.

Mengshoel et al. [13] measured catecholamines during rest and in response to prolonged exercise, and observed normal physiological muscle fatigue responses (maximal voluntary contraction, electromyographic amplitude, heart rate and VO_2), except for the lack of increase in plasma catecholamine concentrations during exercise. Kosek et al. [14] evaluated the influence of submaximal isometric contraction on pressure pain thresholds in fibromyalgia patients and in healthy volunteers, before and after skin hypoesthesia. PPTs were determined with pressure algometry over the quadriceps femoris muscle before, during and following an isometric contraction. They found that fibromyalgia patients responded with a paradoxical lowering of pain threshold as compared to normal controls. The authors suggested that the decrease of PPTs during isometric contraction in fibromyalgia patients could be due to sensitization of mechano-nociceptors caused by muscle ischemia and/or dysfunction in pain modulation during muscle contraction. In other words, the findings could be due to an aberrant response of the sympathetic nervous system to isometric contraction and possibly descending adrenergic anti-nociceptive pathways.

Martinez-Lavin and coworkers [15] assessed the sympathetic-parasympathetic balance in female fibromyalgia patients and its response to orthostatic stress, by short-term measurement of heart rate variability. They found that patients with fibromyalgia demonstrate a deranged sympathetic response to an active orthostatic stress (standing up) as compared to normal control subjects. These researchers also noted that the sympathetic component is markedly increased in supine patients, as compared to normal control subjects in the same posture. Following an active orthostatic stress this component is decreased in fibromyalgia patients while the heart rate itself is increased. In a comment to this report, Keleman et al. [16] described a similar study with comparable results. Bou-Holaigah and colleagues [17] demonstrated an abnormal response to 45 minutes of 70 degree tilt in 60% of patients but in none of the controls. After administration of isoproterenol infusion, this rate increased to 95% in fibromyalgia

VLF = very low frequency

PPTs = pressure pain thresholds

patients and to 40% in the control group. They also found that many fibromyalgia patients have orthostatic intolerance.

In a previous study applying PSA of heart rate variability to female fibromyalgia subjects, we demonstrated a significant reduction in heart rate variability and vagal tone, and augmented sympathetic activity at rest, compared to normal age-matched controls [18]. The above reflects a basal autonomic state of hyperactivation characterized by increased sympathetic and decreased parasympathetic tone. Quality of life, physical function, anxiety, depression and perceived stress were moderately to highly correlated with vagal tone and sympathetic activity and the sympathovagal ratio. Our findings support those of other groups showing that fibromyalgia patients suffer from a basal hyperactivity of the sympathetic nervous system.

Subsequently, Martinez-Lavin et al. [19] reported that patients with fibromyalgia have diminished 24 hour heart rate variability due to an increased nocturnal predominance of the LF band oscillations, consistent with an exaggerated sympathetic modulation of the sinus node. In another study the same authors [20] also demonstrated that fibromyalgia patients have an aberrant circadian rhythm of autonomic nervous tone with persistent nocturnal sympathetic hyperactivity. This abnormality is associated with increased awakenings. The authors suggested that nocturnal sympathetic hyperactivity may be the cause of sleep disorders in fibromyalgia. These studies support the proposition that such patients have a decreased sympathetic response to stress.

Since there may be differences in the clinical manifestation between male and female patients with fibromyalgia, especially in autonomic dysfunction, we assessed the interaction between the sympathetic and parasympathetic systems in postural change in male patients with fibromyalgia, using PSA of heart rate variability [21]. This revealed that in male fibromyalgia patients at rest sympathetic hyperactivity occurs concomitantly with reduced parasympathetic activity. During postural changes, male fibromyalgia patients demonstrated an abnormal sympathovagal response. These results provided the physiological basis for the orthostatic intolerance in male fibromyalgia patients. Since numerous examples of different rates of certain illnesses between males and females (presumably based on biologic differences) usually reflect important aspects of the underlying pathophysiology, we addressed the question whether the autonomic dysfunction in males is similar to that of females. Comparing previous data on a group of male fibromyalgia patients [21] with data on a female fibromyalgia sample [18] showed that women with fibromyalgia exhibit more augmented sympathetic activity and reduced vagal tone than males with fibromyalgia. The above reflects a more severe autonomic dysfunction in females with fibromyalgia than in males with fibromyalgia. We conclude that gender differences must be considered in studies of cardiac autonomic modulation and heart rate variability.

PSA = power spectral analysis

All of these later studies strongly support the notion that autonomic dysregulation is frequent in fibromyalgia. Such dysautonomia is characterized by unrelenting basal sympathetic hyperactivity, associated with deranged sympathetic response to different stressors. This paradoxical behavior of the autonomic nervous system (sympathetic hyperactivity with hyporeactivity) nevertheless agrees with the basic physiological principle that chronic hyperstimulation of the beta-adrenergic receptors leads to receptor desensitization and downregulation.

The role of the autonomic nervous system in fibromyalgia is an important area of investigation. The question regarding the primary or secondary role of enhanced sympathetic activity in fibromyalgia might be answered by longitudinal studies of subjects who are initially ill. Does the syndrome result from augmented sympathetic activity with altered responsiveness of neural regulatory mechanisms?

Pathophysiology of dysautonomia

One may speculate that the pathophysiologic mechanisms in fibromyalgia patients include a reduction in plasma volume, secondary to a compensatory natriuresis and diuresis in response to the redistribution of blood from the periphery to the central intravascular compartment that occurs during recumbency and other deconditioning states [22].

It is postulated that the abnormal overactivity of the sympathetic autonomic system at rest could be related, in part, to symptoms such as fatigue, sleep disturbances, paresthesias and irritable bowel syndrome. The abnormal autonomic response to sympathetic challenges could explain findings such as low muscle tissue oxygen, abnormal muscle phosphate metabolism [23], decreased threshold for pain, and increased fatigue in patients with fibromyalgia.

The abnormal sympathovagal response to postural change in fibromyalgia patients seems to indicate that the activation of one or more groups of arterial or cardiopulmonary baroreceptors may be impaired and thus contribute to the inadequate response. In light of the evidence that fibromyalgia patients have an abnormal drop in blood pressure in stage 1 of upright tilt [17], we suggest that other factors may be involved in the abnormal sympathovagal response to postural change, and that decreased responsiveness of the baroreflex to fluctuations in blood pressure [24] and increased venous pooling that are due to disuse atrophy of the leg muscles, increased leg compliance and loss of venomotor tone, result in decreased cardiac preload. Alternatively, the diminished or absent sympathetic response to posture changing in patients with fibromyalgia results from a state of chronic autonomic overstimulation at rest, preventing further response.

Dysautonomia in disorders related to fibromyalgia

Autonomic dysfunction has been documented in conditions closely allied to fibromyalgia syndrome, such as irritable bowel syndrome [25–27], chronic fatigue syndrome [28,29], and migraine headaches [30]. A growing number of reports have

demonstrated disordered autonomic function in patients with irritable bowel syndrome. Although a number of different methods were used to assess autonomic function, the reports point to a generally decreased vagal (parasympathetic) outflow or increased sympathetic activity in conditions usually associated with slow or decreased gastrointestinal motility, while other studies found either an increased cholinergic activity or a decreased sympathetic activity in patients with symptoms compatible with an increased motor activity.

Karling et al. [27] found that patients with irritable bowel syndrome have significantly increased sympathetic activity, whereas parasympathetic activity does not differ from that of controls. Heitkemper and colleagues [26] conducted a circadian study of heart rate variability and found that patients with irritable bowel syndrome have nocturnal sympathetic hyperactivity. Finally, Adeyemi et al. [25] reported that patients with irritable bowel syndrome have deranged sympathetic response to orthostatic stress.

Stewart [28] reported that patients with chronic fatigue syndrome demonstrated a dysautonomia with orthostatic intolerance. De Becker et al. [29] also observed changes indicating sympathetic hyperactivity in chronic fatigue syndrome patients exposed to stress. These findings thus suggest that similar autonomic dysfunction is found in patients with fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome.

Abnormalities in autonomic function have also been described in migraine disorders, with some suggestions of basal sympathetic hypoactivation [30] as well as instability of the sympathetic tone. Autonomic dysregulation has also been found in heart rate variability studies of patients with panic disorder [31], generalized anxiety disorder, depression and post-traumatic stress disorder [32,33]. It is thus possible that these findings are characteristic of anxiety disorders and/or depression in general and are not specific. It is also possible that the various clinical syndromes have common underlying pathophysiologic disturbances.

In order to explore the specificity of the findings in fibromyalgia patients, we compared the data of a group of male fibromyalgia patients with previous data of a group of panic disorder [31] and PTSD patients [Table 1] matched for age and smoking. Panic disorder and PTSD patients were selected because of the involvement of depression and anxiety in these disorders, alarming somatic symptoms in general, and cardiovascular symptoms in particular, and because the autonomic nervous system seems to be intimately involved in the initiation and manifestation of panic attacks and PTSD. Our results demonstrated similarities in the autonomic parameters in male fibromyalgia patients and PTSD patients. There are some important phenomenological similarities between fibromyalgia and PTSD. Firstly, there is a high degree of comorbidity with depression and anxiety in both fibromyalgia and PTSD. Depression as a cause of fibromyalgia is a much-debated issue [34]. Symptoms of depression and anxiety are often found in fibromyalgia patients, whose estimated lifetime prevalence of depression ranges from 20% to 83% in clinical studies [35]. Secondly, fibromyalgia and PTSD are disorders associated with increased stress and stressor perception [36]. This explanation is supported by findings of a blunted "stress response" in fibromyalgia and in PTSD, including decreased production of cortisol in response to corticotropin-releasing hormone or adrenocorticotropic hormone and low 24 hour urine free cortisol [37]. Thirdly, anti-depressants, especially the newer generation of drugs such as selective serotin re-uptake inhibitors, have proven to be clinically beneficial in fibromyalgia and are in common use in all depression and anxiety-related disorders, including PTSD [38]. Tricyclic anti-depressants, especially amitriptyline hydrochloride, imipramine hydrochloride and doxepin hydrochloride, have been found useful and effective in the treatment of fibromyalgia, both with and without depression; however, none has yet been formally approved for

PTSD = post-traumatic stress disorder

Table 1. Power spectral analysis in male fibromyalgia patients vs. male PTSD patients, male panic disorder patients and normal male controls

Frequency domain	I – Fibromyalgia (n=19)	II – Post-traumatic stress disorder* (n=14)	III – Panic disorder** (n=15)	IV – Controls (n=19)	Post hoc test
Power in normalized units					
LF %	91.8±3.6	90.4±4.1	84.0±6.1	77.3±12.5	I≠III, IV ; II≠IV
HF %	8.2±3.6	9.6±4.1	16.0±6.1	22.6±12.5	I≠III, IV ; II≠IV
LF/HF	13.6±6.3	11.9±7.4	6.0±2.6	4.8±3.1	I, II≠III, IV
(The mean of individual ratios)					
Heart rate [4] (beat/min)	82.75±8.6	83.1±9.6	74.0±4.8	64.7±7.9	I, II≠III, IV III≠IV
R-R interval [5] (msec)	0.73±0.085	0.85±0.07	0.814±0.05	0.943±0.14	I≠II, IV II, III≠IV

Results are expressed in normalized units, as mean SD.
* Published data (from Cohen et al., 1997, 1998).
** Published data (from Cohen et al., 2000).
[4] F= 11.3, P = 0.0000 ; [2] F= 11.3, P = 0.0000 ; [3] F= 10.3, P = 0.0000 ; [4] F= 18.04, P = 0.0000 ;
[5] F= 13.1, P = 0.0000.

these indications in the absence of associated depression. The fact that SSRIs are effective in both fibromyalgia and PTSD may indicate that pathophysiological disturbances are related to serotonin metabolism.

Amir et al. [39] investigated the prevalence of fibromyalgia syndrome, quality of life, and functional impairment among PTSD patients as compared with control subjects. The prevalence of fibromyalgia in the PTSD group was 21% vs. 0% in the control group. PTSD subjects suffering from fibromyalgia were more tender, reported more pain, lower quality of life and higher functional impairment, and suffered more psychological distress than the PTSD patients without fibromyalgia. A study of the prevalence of PTSD in fibromyalgia patients is in progress.

Power spectrum analysis and cardiovascular morbidity

Experimental and clinical studies demonstrate that cardiovascular autonomic regulation plays an important role in cardiac morbidity and mortality. Previous studies indicate that decreased vagal activity, defined in terms of low heart rate variability and low HF, is associated with a variety of disease states and increased risk of mortality including sudden cardiac death. Apart from possible contributions to our understanding of altered autonomic nervous system functioning in fibromyalgia, PSA of heart rate variability may yield important insights into cardiovascular morbidity in this condition. Various cardiovascular diseases and mental disorders have been shown to be associated with alterations in autonomic nervous system function. Subjects with dual diagnoses may be at increased risk owing to increased autonomic nervous system involvement.

Wolfe and researchers [40] studied the mortality rates among 1,747 consecutive fibromyalgia patients without concomitant inflammatory illnesses, and showed that mortality is increased in fibromyalgia patients. The predictive variables for mortality from infection and pneumonia are the same as those in rheumatoid arthritis and osteoarthritis, and may reflect other physical illnesses present concomitantly in fibromyalgia. In light of the evidence that mortality is increased in fibromyalgia patients, and since changes in heart rate variability are also predictive risk factors for cardiovascular morbidity and mortality, follow-up studies are necessary to determine the course and effect of autonomic dysregulation in patients with fibromyalgia.

Conclusions

Studies investigating the involvement of the autonomic nervous system in the pathogenesis of fibromyalgia have reported conflicting results – some authors suggest that these patients have normal resting autonomic tone while others maintain that resting vagal tone is increased or decreased. Still, in the last few years, research has presented mounting evidence that dysautonomia is prevalent in fibromyalgia patients. However, many of these studies involved only small numbers of patients, were inadequately controlled, and examined the immediate response to tilt in patients susceptible to vasovagal response. This again adds confusion to the issue.

Since changes in heart rate variability are also predictive risk factors for cardiovascular morbidity, follow-up studies are necessary to determine the course and effect of autonomic dysregulation in patients with fibromyalgia. The cause and pathophysiologic basis of these changes in autonomic function remain unexplained.

Overall, it must be stated that changes in autonomic nervous system function are known to accompany various diseases. The task of understanding these changes and characterizing them can be substantially facilitated by the application of spectral analysis of heart rate variability, a simple, non-invasive, reliable tool that supplies real-time clinical data reflecting physiological parameters. The degree of specificity of this physiologic parameter is equivocal since we do not yet know whether specific disorders are accompanied by specific characteristic autonomic phenomena or whether these phenomena represent non-specific markers reflecting a hyper-aroused state, possibly even stemming from the stress of suffering from a disease, per se. Were it feasible to mount an extensive clinical trial, this tool could serve to describe and define the autonomic changes characterizing specific disorders. There is no evidence at present to indicate that such specificity might exist, making such a study unlikely to come about. Even so, the very simplicity and non-invasive nature of assessing heart rate variability by spectral analysis renders it useful in clinical studies on the effects of various medications on the hyperactive stress states that accompany so many disorders and affect the physical and mental deterioration of the patient.

SSRIs = selective serotonin re-uptake inhibitors

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