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Heart rate variability as a biomarker of fibromyalgia syndrome

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Abstract

Fibromyalgia (FM) is a chronic pain syndrome characterized by widespread mechanical tenderness, fatigue, nonrefreshing sleep and depressed mood. Several biological abnormalities have been described in FM patients, including elevated substance P in the cerebrospinal fluid, increased CNS sensitivity to painful and nonpainful stimuli and pervasive dysfunction of the autonomic nervous system (ANS). Such ANS abnormalities include, but are not limited to: tachycardia, postural intolerance, Raynaud's phenomenon, and diarrhea or constipation. Heart rate variability (HRV) analysis of FM patients can be used to assess ANS dysfunction, specifically related to sympathovagal balance, which has provided evidence for nonabating sympathetic hyperactivity in this chronic pain population. Although not specific for FM, ANS dysfunction can be readily determined by HRV analysis requiring only computer analysis of electrocardiogram recordings by commercially available software. HRV has been shown to correlate with FM pain and is sensitive to change; in particular, pain related to physical and mental stressors. Thus, ANS dysfunction as assessed by HRV analysis may serve as a useful biomarker, and may become part of future FM diagnostic criteria and serve as a surrogate end point in clinical trials.

Keywords

autonomic nervous system; heart rate variability; mechanisms; pain

In 2001, the NIH defined biomarkers as: "characteristics that can be objectively measured and evaluated as an indication of normal or pathogenic processes or pharmacological responses to a therapeutic intervention" [1]. Perfect biomarkers (i.e., surrogate end points) completely mediate the effects of the exposure on the outcome of interest. However, for most biomarkers, there are unmeasured factors that mediate the effects of the exposure on the outcome and, almost always, measurement of the biological mediators imperfectly represents the true bioactivity of the mediators. Thus, single biomarkers in complex illnesses such as fibromyalgia (FM) are only likely to approximate relevant end points for measurement. Nevertheless, mounting evidence is pointing to an increasing number of possible biomarkers for FM, including:

- Measures of central sensitization [2]

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- Abnormal pain inhibition/increased pain facilitation [3]
- Neuro-endocrine, as well as autonomic dysfunction [4]

This article will focus on heart rate variability (HRV) as a readily available measure of abnormal autonomic nervous system (ANS) function, and its possible role as a biomarker for FM.

Autonomic nervous system & physiological rhythms

Many physiological processes display cyclic changes, such as circadian, hormonal, respiratory, cardiac, vascular, autonomic and cellular rhythms [5]. Furthermore, these cycles are linked and give rise to physiologically relevant communication. In the case of the ANS, heart rate rhythms and cardiovascular–respiratory coordination are tightly linked to autonomic responsiveness and functionality, and can be readily assessed by power spectral analysis, autonomic information flow and phase synchronization statistics, including mathematical modeling. For example, the complexity of autonomic rhythms and their interplay characterizes cardiovascular status in health and disease for cardiac and many other diseases [6]. There are interactions between circadian rhythms and cell/tissue proliferation, and links between the ANS and circadian systems. Adaptive responses of these systems to stressors are key features of good health and it is unclear which mediators are responsible for complex autonomic and/or circadian dysfunctions in many chronically ill patients, including those with FM.

Biological rhythms – ranging from seconds to days – involve multiple physiological variables including heart rate, respirations, blood pressure and hormonal fluctuations. One of the most important ways to regulate these rhythms involves the ANS and the circadian system [7]. In humans, circadian rhythms are driven by a pacemaker located in the suprachiasmatic nucleus of the hypothalamus [8]. The suprachiasmatic nucleus is a self-sustaining oscillator that maintains its daily activities for weeks, even when totally isolated. Although many biological rhythms influence each other, the interaction between heart rate and respirations, that is, respiratory sinus arrhythmia, is one of the best-studied examples in physiology [9].

Heart rate variability

Heart rate variability is a term used to describe the fluctuations of heart rate, as well as the oscillation in the interval between consecutive heartbeats (RR intervals) [10,11]. Other terms that have been used for HRV include cycle length variability, heart period variability, RR variability and RR interval tachogram. Although all these terms appropriately focus on the interval between consecutive beats and not the heart rate, they have not gained as wide acceptance as HRV. Under resting conditions, the electrocardiogram (ECG) of healthy individuals shows periodic variation in RR intervals. One of the causes for this rhythmic phenomenon is termed respiratory sinus arrhythmia, which is mostly the result of parasympathetic influences on the sinus node occurring primarily with expiration, and is absent or attenuated during inspiration. Other factors affecting RR intervals are related to centrally generated brainstem rhythms and baroreceptor feedback influences, as well as both sympathetic and parasympathetic input [12–14]. High-frequency cyclic fluctuations like respiratory sinus arrhythmia are mediated entirely by parasympathetic outflow [15], whereas slower fluctuations seem to occur due to baroreflex activity or thermoregulation [16]. The greatest variation in HRV occurs in circadian patterns, mediated by complex and poorly understood neuro-humoral mechanisms [17]. In addition, exercise and emotions also show effects on HRV [18]. Importantly, fluctuations in HRV reflect autonomic modulation and have prognostic significance in health and disease. As HRV is a cardiac measure derived from the ECG, it is not able to distinguish central autonomic activity (in the autonomic centers of the brain) from peripheral activity (the contribution of the sinus node).

In 1963, it was first described that fetal distress was preceded by alterations in HRV before any appreciable changes were noted in heart rate itself [19]. Subsequently, investigators identified several physiological rhythms integrated in the beat-to-beat intervals [20,21]. In 1978, using power spectral analysis to quantitatively evaluate heart rate fluctuations [22], the association of increased mortality with reduced HRV was first reported in patients after myocardial infarction [23]. Subsequent investigations supported the important role of HRV as a strong and independent predictor of mortality after acute myocardial infarction [24,25]. With the availability of digital multichannel ECG recorders, HRV has become more widely used to obtain valuable information about many other chronic conditions, including FM.

HRV as a biomarker of ANS function

Although our understanding of HRV is incomplete, it appears to be a reliable biomarker of adapative responsiveness to stress, including both dynamic and cumulative load [26]. Acute stressors (i.e., public speaking tasks) as well as chronic stressors (i.e., chronic illness) have been shown to lower HRV [27]. In addition, advancing age seems to result in a decline of HRV, most likely due to a decrease in efferent parasympathetic tone and reduced β-adrenergic responsiveness [28]. In contrast, regular physical activity has been found to raise HRV, presumably by increasing parasympathetic tone [29].

Thus, HRV appears to have a strong association with stress responsiveness, and represents a sensitive marker for arousal and allostatic load [30]. Whereas acute stress results only in short-term changes in HRV, chronic stress is often followed by long-term reduction of parasympathetic activity, resulting in the overactivity of counter-regulatory systems (i.e., the sympathetic control of cardiac rhythms) [31].

Time domain of HRV

The simplest form of HRV analysis is represented by a tachogram, which plots the total number of beats on the x-axis, and the RR intervals on the y-axis **(**Figure 1A). Another way to analyze HRV is to calculate the mean RR interval and its standard deviation derived from short-duration (e.g., 5-min) ECGs. Other types of arithmetic manipulations of RR intervals have been used for HRV calculations, including:

- The standard deviations of the normal mean RR interval (SDANN index);
- The frequency of two consecutive RR intervals differing by more than 50 ms (pNN50 index);
- The root-mean square of the difference of successive RR intervals (RMSSD index);
- The difference between the shortest RR interval during inspiration and the longest during expiration (maximum–minimum or peak-valley quantification of HRV);
- The base of the triangular area under the main peak of the RR interval frequency distribution diagram obtained from 24-h recording.

As these different methods of HRV analysis are largely equivalent, no specific method can be recommended, provided measurement epochs are 5 min or longer.

All these measurements of short-term variation of HRV are highly correlated, estimate high-frequency variances in heart rate and provide information about parasympathetic ANS activity.

Frequency domain of HRV

Besides time domain analysis, another commonly used method of HRV evaluation is frequency domain analysis. The latter evaluation is based on spectral analysis of ECG-derived data.

Whereas time domain analysis uses RR interval data from an ECG **(**Figure 1), spectral analysis detects the frequency of RR interval changes from time and represents the signal as a combination of sine and cosine waves, with different amplitudes and frequencies **(**Figure 2).

Power spectrum of HRV

Power spectral analysis uses fast Fourier transform or auto-regression techniques of ECG-derived data [32]. This type of analysis usually results in the identification of several frequency bands associated with ANS activity. The two major components of the HRV spectrum consist of a high-frequency (HF: 0.18–10.4 Hz) band, which is synchronous with respirations, and a low-frequency (LF: 0.04–0.15 Hz) band, which appears to be mediated both by parasympathetic and sympathetic nerve impulses. While HF is clearly the result of respiratory sinus arrhythmia, the neuroendocrine contributions to LF are unclear, but seem to be affected by centrally generated brainstem rhythms, baroreceptor feedback influences and both sympathetic and parasympathetic input [33]. The power of each spectral component can be expressed in absolute units (ms^2), whereas the total power of a signal, integrated over all frequencies, is equal to the variance of the entire signal. In some cases, the ratio of the low- to high-frequency spectra is used as an index of parasympathetic–sympathetic activity. However, this approach is controversial because of incomplete understanding of the LF components.

As a measure of parasympathetic activity, spectral analysis of HF probably offers no additional information over time-domain measures. On the other hand, the meaning and utility of LF (0.04–0.15 Hz) has been the target of intense investigation. This frequency band is thought to be modulated by both the sympathetic and parasympathetic nervous systems. Even slower modulations of heart rate are reflected in the very-low-frequency band (VLF: 0.0033–0030.04 Hz). VLF is considered to represent the influence of the peripheral vasomotor and renin–angiotensin systems [22]. The remainder of the power spectrum is comprised of the ultra-low-frequency band, which reflects all variance below 0.0033 Hz and consists mainly of circadian rhythms. All of these indices together represent the total power, which is the sum of all the variance in the beat-to-beat signals. The HF:LF ratio is useful to evaluate fluctuations in the balance between the sympathetic and parasympathetic nervous systems.

Measurement of VLF, LF and HF power components is usually made in absolute values (ms^2), but LF and HF may also be converted to normalized units (nu) [34]. Normalized units capture the relative value of each power component in proportion to the total power ± the VLF component. Describing LF and HF as LFnu or HFnu seems to better reflect the balance of the sympathetic and parasympathetic components of the ANS. In addition, normalization tends to decrease the effects of total power changes on the values of LF and HF components.

In general, HRV analysis (by time domain or spectral methods) represents a noninvasive approach of evaluating the activity of the ANS, which is an important component of the stress-response system. The assessment of HRV requires only ECG equipment, computers and commercially available software.

Role of HRV in risk assessment of disease

One of the major reasons for widespread interest in HRV analysis relates to its ability to predict important health outcomes, like survival after myocardial infarcts [35]. Several prospective studies have shown that reduced HRV predicts sudden death in patients after myocardial infarcts, independent of other prognostic indicators such as ejection fraction [36]. Reduced HRV also appears to be a marker of fatal ventricular arrhythmia. Moreover, a number of studies have suggested that reduced HRV may also predict risk of reduced survival even among individuals free of CHD [37,38].

Autonomic dysfunction has been documented in many conditions, some of them closely associated with FM, such as irritable bowel syndrome [39,40], chronic fatigue syndrome [41] and migraine headaches [42]. A growing number of reports have demonstrated decreased parasympathetic activity in irritable bowel syndrome patients, usually associated with either increased cholinergic activity or decreased sympathetic activity [43]. Similar to FM, patients with irritable bowel syndrome [39] or chronic fatigue syndrome [44] have abnormal sympathetic response to orthostatic stress, including dysautonomia with orthostatic intolerance [45].

HRV & sleep

Not only wakefulness, but also sleep, is modulated by the ANS [46]. Whereas nonrapid eye movement sleep is characterized by parasympathetic predominance, rapid eye movement sleep and wakefulness show increased levels of sympathetic activity [47]. Such changes can be repeatedly observed during the whole sleep cycle. While slow-wave sleep is associated with increased HF power, early non-rapid eye movement stages show increases in sympathovagal modulation (LF). Different levels of sympathovagal balance can be observed during all sleep stages. The important role of the ANS is further demonstrated by HRV changes preceding arousals from deep sleep and the onset/offset of rapid eye movement sleep by up to 20 heart beats [47].

Many chronic pain patients characteristically complain of nonrefreshing sleep interrupted by multiple arousals, including patients with chronic fatigue syndrome [48] or FM [49]. These symptoms suggest a role of autonomic dysfunction in the pathogenesis of these chronic pain disorders. Indeed, several HRV studies of FM [50,51] and chronic fatigue syndrome [52] patients have provided supportive evidence for this assumption.

Effects of emotions & pain on HRV

Although the sensory and affective components of pain are tightly coupled, they have separate neural underpinnings [53]. Specifically, the unpleasantness of pain plays an important role as a homeostatic emotion [54]. Physiologically, HRV is not only a measure of autonomic, humoral and intrinsic influences on heart rate, but can also serve as an objective index of emotionality [55]. Affective states are associated with physiological arousal, which depends on autonomic activation. HRV is not only a measure of autonomic regulation of arousal, but also provides information about the ability of the nervous system to organize an affective homeostatic response in accordance with the situational demands. In addition, recent findings indicate that HRV can be used as a predictor of thermal pain sensitivity [56].

ANS dysfunction & HRV changes in FM

Autonomic dysfunction has been consistently demonstrated in FM patients [50,51,57–60]. The dysautonomia of FM is characterized by persistent ANS hyperactivity at rest and hyporeactivity during stress. Such abnormalities have been detected in FM patients during and after exercise [61], hypoglycemia [57] and tilt-table testing [60,62]. ANS hyporeactivity appears to be correlated with persistent fatigue and other clinical symptoms associated with FM, including low blood pressure, dizziness and faintness. Sympathetic hyperactivity may be responsible for these patients' frequent complaints of cold extremities (Raynaud's phenomenon) [59,63]. Similar findings have been reported in other chronic pain syndromes like irritable bowel syndrome and interstitial cystitis, all of which also show signs of sympathetic hyperactivity.

Heart rate variability analysis has been used to detect abnormal ratios of sympathetic–parasympathetic balance in FM patients [50,64]. One study showed that under resting conditions, the heart rate of FM patients was higher, and HRV was lower compared with

controls [64]. More specifically, FM patients seemed to have higher LF and lower HF components of power spectral density than controls. Importantly, quality of life, physical function, anxiety, depression and perceived stress were moderately to highly correlated with LFnu, HFnu, and LF:HF ratio. However, there was no association between HRV parameters and measures of tenderness or FM symptoms.

Various stressors, including tilt-table testing, have been used to test ANS function in FM [60]. During these tests, HRV monitoring showed abnormal sympathetic responsiveness (decreased power spectral density of LFnu) of these patients. In addition, the circadian power spectrum of RR intervals was diminished in FM patients, indicating global ANS hyporesponsiveness [50].

ANS abnormalities may also be involved in the disrupted sleep patterns of FM patients, in particular, increased arousals and awakenings [50,51]. Normally, HRV of healthy individuals shows a predominance of HF components during slow-wave sleep, which shifts towards LF bands before the onset of rapid eye movement sleep and/or awakenings, suggesting increased sympathetic activity prior to arousals [47]. As FM patients show a predominance of LF bands during sleep [50], sympathetic hyperactivity may contribute to the frequent arousals reported in this chronic pain syndrome. Thus, FM patients seem to lack the circadian variations of HRV seen in healthy controls; most importantly, the nocturnal rise of HF spectral components and the prevalent LF band oscillations.

These findings indicate chronic ANS hyperactivity, as well as insufficient sympathetic responses of FM patients to stressors [50].

Additionally, HRV seems to be sensitive to change in FM symptoms and function. Several studies have demonstrated that resistance exercise training can increase muscle strength and decrease pain perception in individuals with FM [65,66]. Such improvements were substantial in one study – upper and lower body muscle strength increased by more than half and pain perception decreased by more than a third [67]. In addition to increased muscle strength, resistance exercise was also able to improve HRV (total power and RMSSD). Importantly, power spectrum analysis of beat-to-beat intervals was not only able to distinguish FM patients from normal controls in these studies, but also correlated with improvements of pain and function of FM participants.

Conclusion

Autonomic dysfunction of FM patients seems to be strongly associated with reduced total power of HRV, low vagal tone, decreased baroreceptor sensitivity and increased sympathetic activity [60,68]. Such ANS abnormalities have not only been associated with greater risk of developing hypertension [69], but also greater mortality, mostly from cardiovascular causes [70]. Interestingly, several epidemiological studies have reported significantly increased mortality of FM patients compared with matched controls [71,72], but the decreased long-term survival of FM patients was not associated with cardiovascular diseases but with malignancies and infections. ANS dysfunction may have contributed to this poor outcome. Future studies will be necessary to assess whether ANS abnormalities play an important role in the increased mortality of FM patients.

Despite widespread use of spectral methodology, true standards for normal and abnormal HRV values are currently unavailable. However, this finding is not surprising, since under resting conditions the range of sympathovagal balance can be extremely wide and can be affected by many factors such as age, gender, physical fitness and disease conditions. During rest and stressful conditions, such as tilt-table testing, cold pressor test or active standing, most clinical studies have shown abnormal ANS responsiveness of FM patients. Such dysfunction of the

ANS can be readily assessed by power spectrum analysis of beat-to-beat variability. Although some FM clinical trials have shown HRV sensitivity to treatment effects [67,73,74], less evidence is available for HRV as a predictor of clinical pain [56]. Thus, HRV seems to be a useful noninvasive tool for the evaluation of ANS abnormalities in FM and other chronic illnesses. Future studies are needed to assess the sensitivity and specificity of HRV as a useful surrogate (biomarker) of ANS dysfunction in FM, which may be relevant for clinical trials as well as medical practice.

Executive summary

- A definition of fibromyalgia (FM) requires the presence of chronic widespread pain and 11 or more so-called tender points, all of which may be prone to patient as well as investigator bias.
- Biomarkers are defined as characteristics that can be objectively measured and evaluated as indicators of normal or pathological processes.
- Besides excellent specificity, ideal biomarkers should be easy to obtain and show high sensitivity to change.
- Multiple biomarkers have been considered for FM, including measures of central sensitization, substance P and abnormal pain inhibitory/facilitatory mechanisms.
- Abnormalities of the stress-response systems, including the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, are a hallmark of FM.
- Heart rate variability (HRV) represents a noninvasive measure of sympathovagal balance that requires only electrocardiogram recordings and computerized analysis by commercially available software.
- Analysis of FM patients' electrocardiogram recordings has shown significant reductions in HRV compared with normal subjects.
- HRV may be a useful biomarker of abnormal sympathovagal balance in FM.

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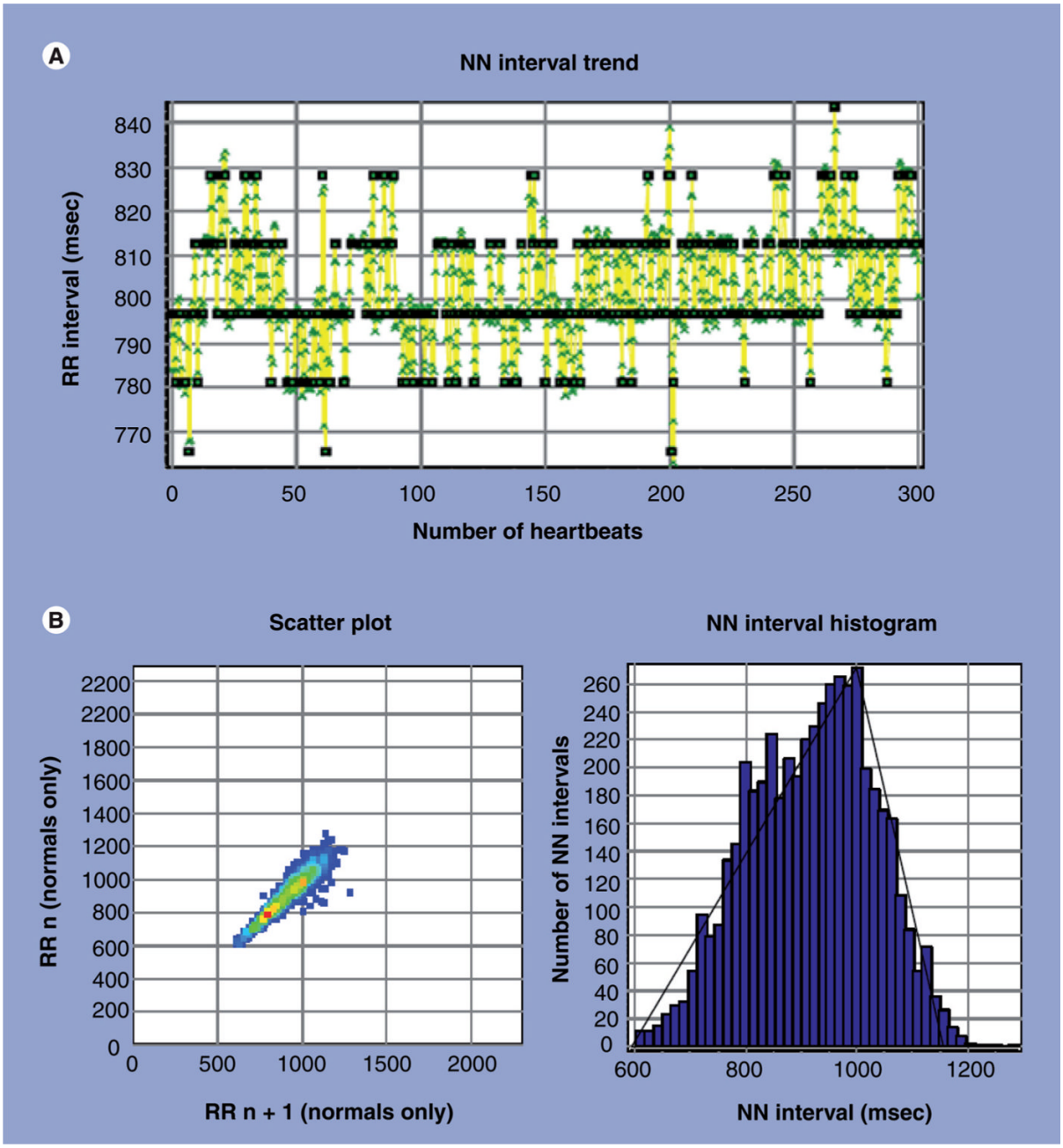

Figure 1. Time domain analysis of heart beats of a normal female measured during 300 s in supine position at rest

(A) Tachogram of RR intervals. **(B)** Poincaré scatter plot of heart beats on the left, histogram of heart beat intervals on the right. Whereas Poincaré plots illustrate the variability of adjacent heart beats, the histogram shows the normal distribution of heart beat intervals over 300 s at rest.

NN: Normal beats; RR: Beat-to-beat.

Figure produced from unpublished data.

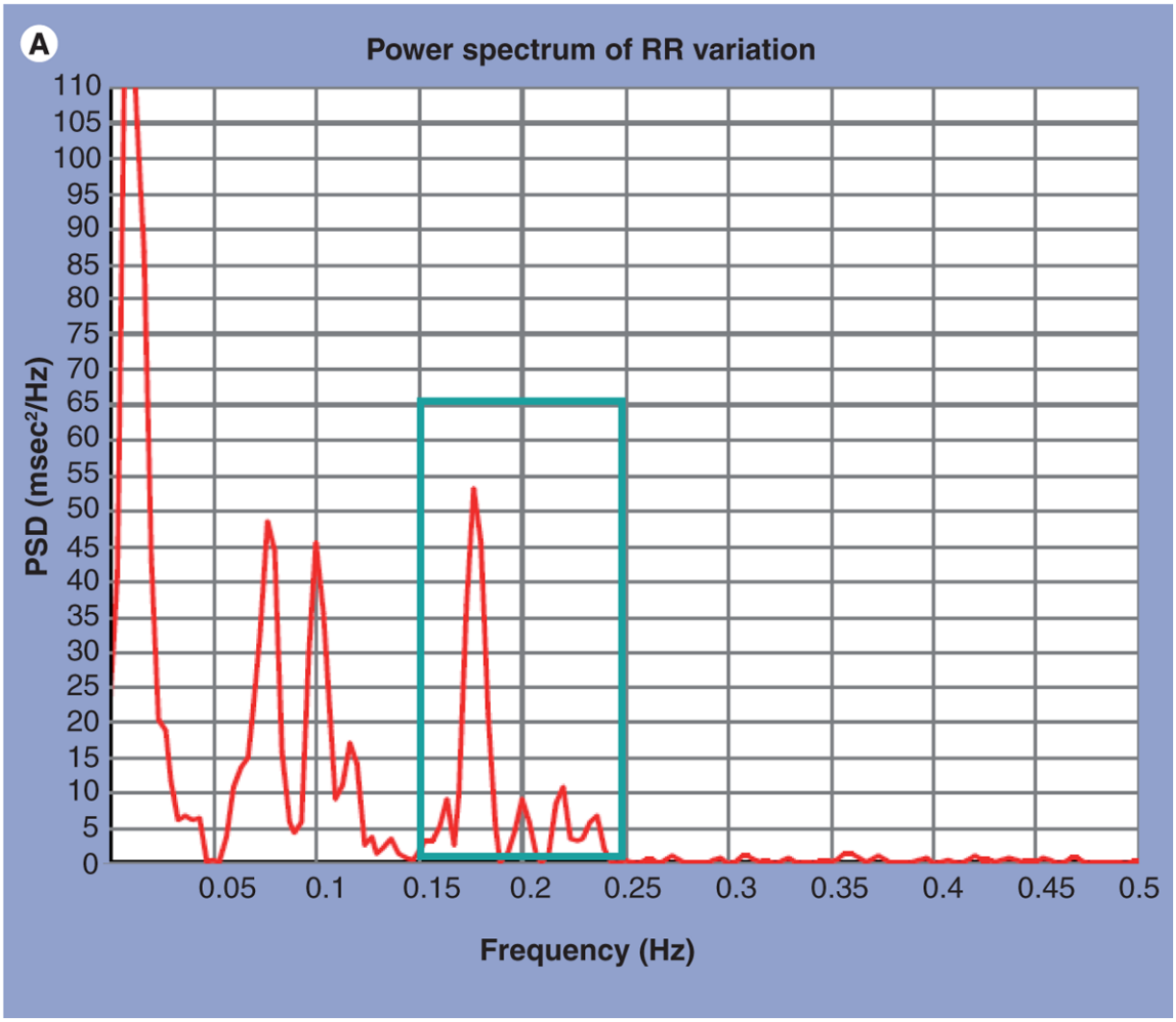

Figure 2B

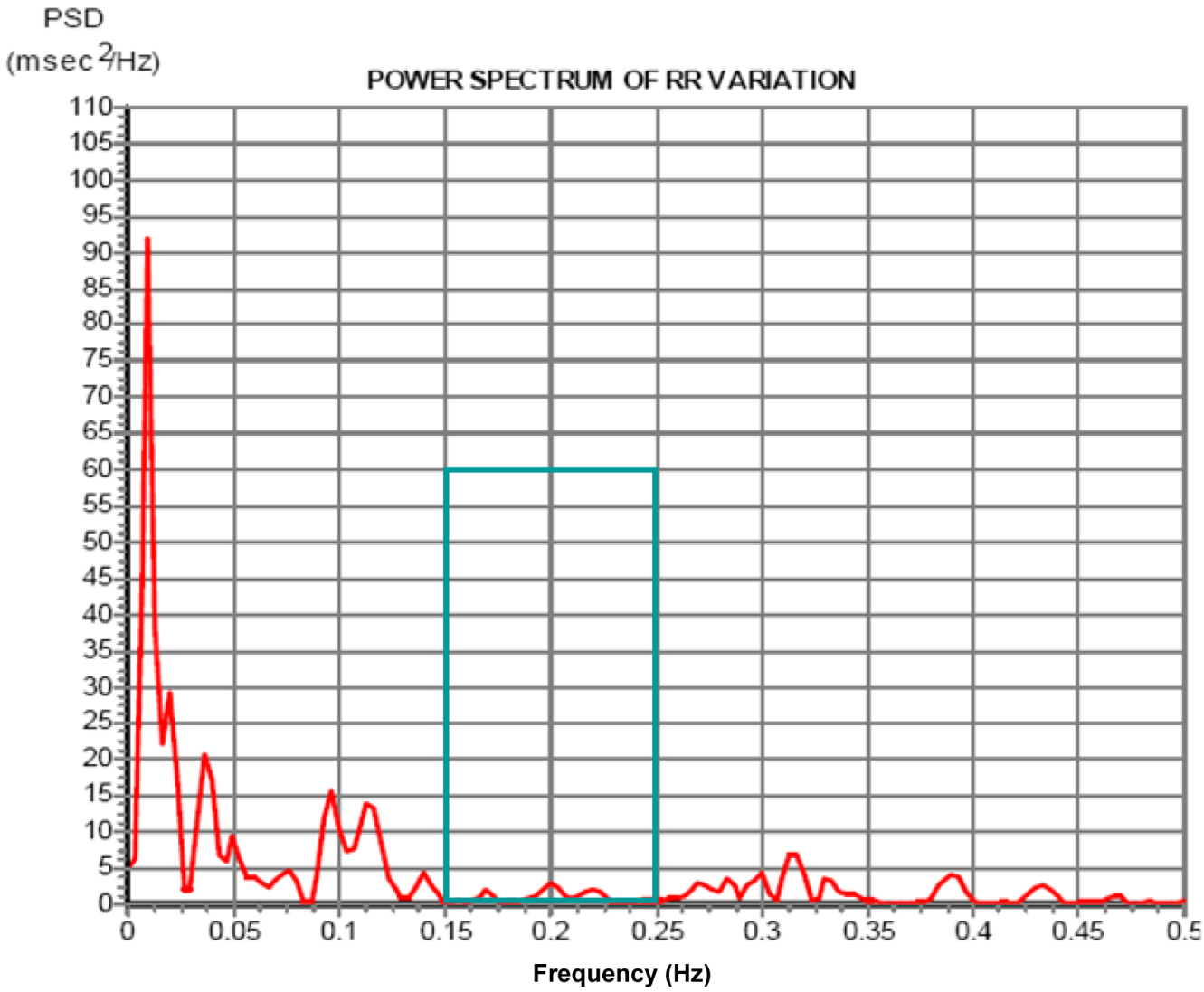

Figure 2. Frequency domain analysis of heart beat intervals during 300 s in supine position at rest

(A) shows the power spectrum of heart beat variability over 300 s measured in a normal female participant in supine position at rest. Frequency variations range from 0 to 0.5 Hz. The area outlined by the box shows RR variations related to respirations (respiratory arrhythmia), which reflects parasympathetic tone. **(B)** illustrates the changes seen in HRV of FM patients over the same time span. Note the overall reduced power (variability) of the high- and low-frequency spectrum.

FM: Fibromyalgia; HRV: Heart rate variability; Hz: Hertz; PSD: Power spectrum density; RR: Beat to beat.

Figure produced from unpublished data.