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Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review

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ABSTRACT

Objective: The goal of this systematic literature review is to determine whether there are differences and similarities in heart rate variability (HRV) between adult patients with Fibromyalgia (FM), Chronic Fatigue Syndrome (CFS), and healthy pain-free control subjects.

Methods: To obtain relevant articles, PubMed and Web of Knowledge were searched for case–control studies. Selection of the literature was based on selection criteria ascertaining studies with adult human patient groups comparing HRV. Risk of bias and levels of evidence were determined.

Results: Sixteen case–control studies were included, 10 comparing FM patients to controls and 6 comparing CFS patients to controls. Methodological quality was moderate to good. Both time domain and frequency domain measurements were used. The majority of the researchers observed lower HRV in FM patients compared to healthy control persons, as well as increased sympathetic activity and a blunted autonomic response to stressors. Resistance training improved HRV in FM patients. In CFS patients HRV was only reduced during sleep.

Conclusion: FM patients show more HRV aberrances and indices of increased sympathetic activity. Increased sympathetic activity is only present in CFS patients at night. Since direct comparisons are lacking and some confounders have to be taken into account, further research is warranted. The role of pain and causality can be subject of further research, as well as therapy studies directed to reduced HRV.

1. Introduction

The autonomous nervous system is part of the peripheral nervous system and is responsible for maintaining important functions, such as involuntary vital parameters (blood pressure, heart rate, respiration, and temperature). The two branches, the sympathetic and parasympathetic branch, have antagonistic influences on most bodily functions, which contributes to the homeostasis in the body. Disruptions in homeostasis (ie, stress) place demands on the body that are met by the activation of, among others, the sympathetic nervous system [1]. In case of chronic stress, the tolerance of the stress response may be exceeded, giving rise to chronic diseases [2]. A large number of these chronic diseases are accompanied by chronic pain and fatigue. This has led to the assumption that abnormal sympathetic activation could be involved in the pathogenesis of chronic pain and fatigue syndromes. This hypothesis is further based on the observations that pain and fatigue are often correlated to symptoms of autonomic dysfunction [3,4].

In consequence, much interest has recently been expressed in the possible role of the autonomic nervous system in the pathogenesis of chronic pain and fatigue syndromes, like fibromyalgia (FM) and the chronic fatigue syndrome (CFS) [5]. Both are considered as related syndromes, supported by the high percentages of overlap between the two syndromes (35–70%) [6], but in the meantime substantial differences have been reported [7,8].

Much of the common symptoms could be attributed to a dysfunction of the autonomic nervous system [9]. Due to sympathetic hyperactivation and/or parasympathetic dysfunction, the body is no longer able to respond to different stressors, which can explain the fatigue, stiffness, sensitive tender points [10,11], exercise intolerance [12], sleeping problems [13], etc.

There are different ways for evaluating autonomic function. The most commonly used, fastest, and least invasive method is measuring heart rate variability (HRV), analyzing the variability of time between successive R waves (R–R interval analysis). There

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are two ways to analyze these R–R intervals. Time domain analysis of heart rate variability uses statistical methods to quantify the variation of the standard deviation or the differences between successive R–R intervals. Frequency domain analysis of heart rate variability enables us to calculate the respiratory-dependent high-frequency and the low-frequency power. High-frequency power is mediated by vagal activity, while low-frequency power has been suggested to represent predominantly sympathetic modulation [14].

This reliable biomarker [15] is based on the fact that heart rate is not constant, but oscillates around an average value. The antagonistic effects of the sympathetic branch and parasympathetic branch of the autonomic nervous system on the sinus node are responsible for this constant variability.

HRV analyses have been used in different populations and the literature provides strong evidence for HRV changes to have an important prognostic value in health and disease. Decreased HRV would indicate poor health [16,17]. Besides HRV as relevant outcome measure for cardiovascular morbidity and mortality, there is growing knowledge regarding HRV in the pathogenesis of chronic pain and fatigue syndromes. Since both FM and CFS are typical chronic pain syndromes with specific similarities and differences and with symptoms that could be attributed to autonomic dysfunction, it seemed interesting to list the present knowledge on the differences and similarities in HRV in patients with FM and patients with CFS compared to healthy individuals. When reduced HRV would seem to play a major role in FM or CFS, this information could be used to steer and assess the effects of the rehabilitation of these patients. In that case, therapy could address autonomic dysfunctions (eg, exercise therapy, relaxation, and breathing exercises) and HRV could be used as an outcome to assess progression and to provide biofeedback.

The present systematic literature review will try to summarize answers to the following research questions:

(1) Are there differences and/or similarities in HRV between adults with FM and adults with CFS?
(2) Are these differences and/or similarities different from healthy adult persons without pain?
(3) What is the clinical relevance of HRV in CFS and FM?

2. Methods

This systematic review is reported following the PRISMA-guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses), which is an updated statement addressing the conceptual and methodological issues of the original QUOROM Statement [18].

2.1. Eligibility criteria

To be included in the present systematic review, articles had to report the results of clinical studies (S) evaluating heart rate variability (O) in patients with CFS or FM (P) compared to healthy controls (C).

2.2. Information sources and search strategy

To identify relevant articles PubMed (http://www.ncbi.nlm.nih.gov/entrez) and Web of Science (http://isiwebofknowledge.com) were searched in February 2012. Keywords were derived from the PICOS-question and were converted to possible Mesh-terms.

The search strategy was based on a combination of the following Mesh-terms or free-text words: ("Fatigue Syndrome, Chronic" [Mesh]) OR "Fibromyalgia" [Mesh] OR "Myalgic encephalomyelitis" AND "Heart Rate" [Mesh] AND ("Heart rate variability" OR "Electrocardiography" [Mesh]). In addition reference lists of relevant published articles were searched to make the search as complete as possible.

2.3. Study selection

To be included in the review, the following inclusion criteria had to be fulfilled: (1) subjects were adults (> 18 years); (2) in all subjects were diagnosed with "chronic fatigue syndrome" or "fibromyalgia"; (3) control subjects were healthy individuals; (4) results of HRV, interpreted as variability of time between successive R waves, were described and compared; (5) the article was written in Dutch or English; and (6) was a full-text report of original research.

For the fourth criterion, only studies using time domain analysis and/or frequency domain analysis to evaluate HRV were included. The former calculates the average R–R interval and standard deviation (SDNN) expressed in milliseconds (ms) on short-term (eg, 5 min). Sometimes the average sum of the squares of the differences between consecutive R–R intervals (RMSSD) is used or the percentage that represents the differences between successive R–R intervals that are larger than 50 ms (PNN50). The analysis of the frequency domain, expressed in Hertz (cycli per second), is based on analysis of the ECG data and the frequency of changes in R–R intervals and expresses the signal as a combination of sine and cosine waves, with different amplitudes and frequencies. This frequency domain analysis can be divided into four frequency components. These are the high-frequency band (HF) with frequencies of 0.15–0.4 Hz, the low-frequency band (LF) with frequencies between 0.04 Hz and 0.15 Hz, the very low-frequency band (VLF) with frequencies between 0.0033 Hz and 0.04 Hz, and the ultra low-frequency (ULF) band with frequencies below 0.0033 Hz (Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology, 1996).

First, all search results were screened based on the title and abstract. The full-text article was retrieved if the citation was considered potentially eligible and relevant. In the second phase, each full-text article was once again evaluated whether it fulfilled the inclusion criteria. If any of the five inclusion criteria were not fulfilled, then the article was excluded from the literature review.

2.4. Qualification of searchers

Literature was searched and screened by F.D.B., master in the ~~physiotherapy and~~ rehabilitation sciences. She was trained by the first author (M.M.), who obtained the degree of PhD with a dissertation regarding chronic pain and central sensitization and has published three systematic reviews [19,20,21].

2.5. Data items and collection

Information was extracted from each included study and presented in an evidence table (Table 2) regarding: (1) study design; (2) sample size; (3) characteristics of participants, and inclusion and exclusion criteria; (4) outcome measure; (5) main results; (6) and remarks. One review author (F.D.B.) extracted the data from included studies and the first author checked the extracted data.

2.6. Risk of bias in individual studies

In order to establish the validity of the remaining publications, risk of bias in the publications was controlled by using the

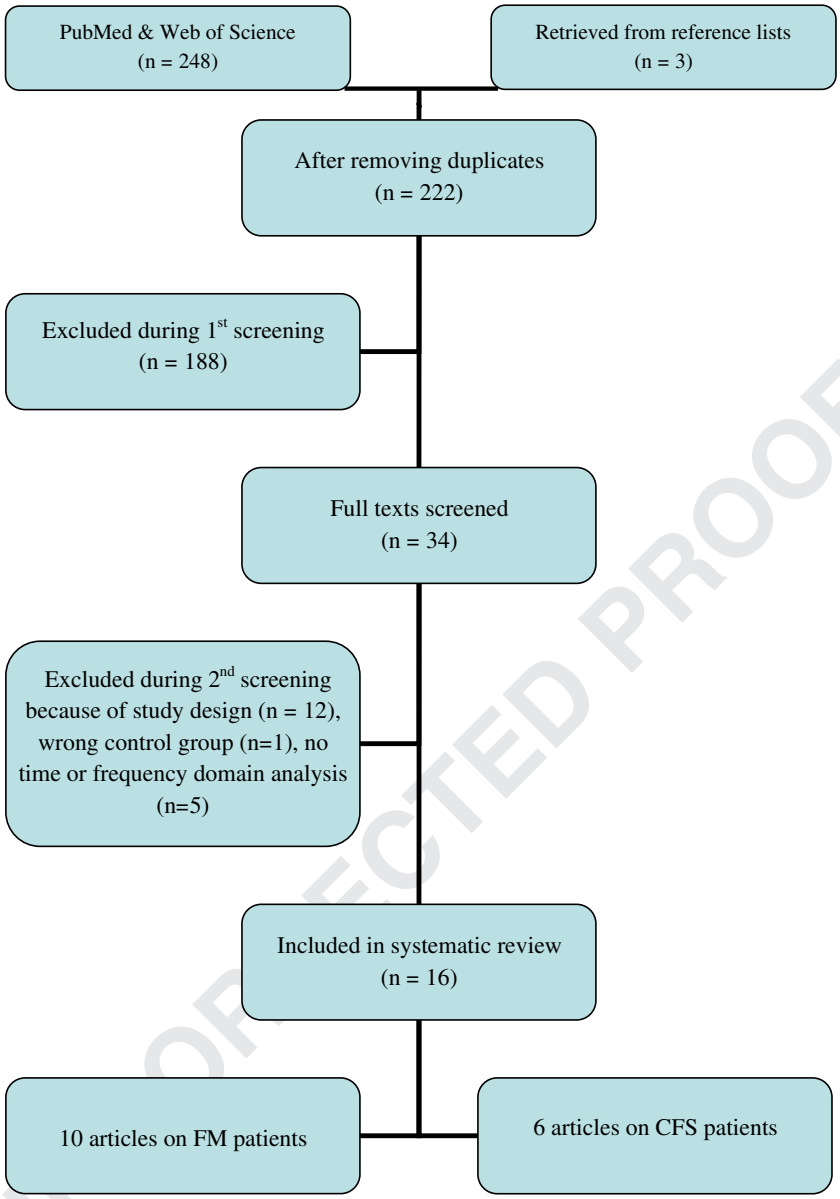

Fig. 1.

"Checklist for case–control studies," provided by the Dutch Institute for Healthcare Improvement (CBO) and the Dutch Cochrane Centre. Articles were scored on description of the groups, exclusion of selection bias, accounting for confounding factors, blinding of assessors, and equal exposure (= assessments) of both groups.

Methodological quality was assessed by two independent, blinded researchers (F.D.B. and D.G.), ie, they were not acquainted with each other's evaluation of the search results. D.G. is a PhD candidate working on chronic pain and fibromyalgia and was trained by M.M.

After rating the selected articles, the results of both researchers were compared and differences were analyzed. In case of disagreement, the reviewers screened the manuscript a second time and the point of difference was discussed. Both reviewers got the opportunity to argue and to convince the other in order to obtain a consensus. When consensus could not be reached a third opinion was provided by the last author (M.M.).

After pooling the results, the overall quality of evidence for each outcome was rated with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [22]. GRADING the evidence was done by the first author (M.M.).

3. Results

3.1. Study selection

As shown in Figure 1, a total of 248 studies were identified. After the two screening phases 16 case–control studies remained. None of the studies compared CFS patients to FM patients.

3.2. Risk of bias and level of evidence

The risk of bias and the level of evidence of the different studies are reported in Table 1.

In most cases (92% or 88 of the 96 items), the two researchers agreed. After a second review and a comparison of the eight differences, the reviewers reached a consensus for seven items. The remaining point of discussion was solved after a third opinion.

Table 1
Methodological quality of the included studies

	1	2	3	4	5	6	Total
Cohen et al. [23]	+	+	+	+	+	+	6/6
Figueroa et al. [24]	+	+	+	+	?	–	4/6
Boneva et al. [25]	+	+	?	+	?	–	4/6
Burton et al. [26]	+	+	+	+	?	–	4/6
Cohen et al. [32]	+	+	+	+	?	–	4/6
Dogru et al. [29]	+	+	+	+	?	–	4/6
Lerma et al. [37]	+	+	+	+	?	–	4/6
Martinez-Lavin et al. [10]	+	+	+	+	?	–	4/6
Martinez-Lavin et al. [36]	+	+	+	+	?	–	4/6
Raj et al. [31]	+	+	+	+	?	–	4/6
Yamamoto et al. [28]	+	+	+	+	?	–	4/6
De Becker et al. [33]	+	+	?	+	?	–	3/6
Duprez et al. [27]	+	+	?	+	?	–	3/6
Kulshreshtha et al. [30]	+	+	?	+	?	–	3/6
Reyes del Paso et al. [35]	+	+	?	+	?	–	3/6
Yataco et al. [34]	+	+	–	+	?	–	3/6

Items: 1: Description patients; 2: Description control subjects; 3: Selection bias; 4: Exposure comparable; 5: Blind assessor; 6: Accounted for confounders; +: Yes; –: No; ?: Lack of information.

The final score of each study is presented in Table 1, with the explanation for the loss of points.

Methodological quality was moderate to good (varying between 3/6 and 6/6). Most of the time studies lost points on *"blinding of assessors"* and *"accounting for confounders."* Only one study explicitly stated the blinding of the researcher performing the analyses [23], others did not mention this, which is understandable given the nature of the assessment (ECG, Holter, etc.). Only one study was awarded for accounting for confounders [23] as it controlled for breathing rate, frequency, and physical activity, as presented in Table 2. Nevertheless, all or most studies matched their groups for age, gender, and BMI.

3.3. Study characteristics

For each study, the characteristics for which data were extracted (study size, participants, outcome measure, main results, and remarks) are presented in Table 2.

3.4. Outcome measures

The studies in this review used HRV assessment as an outcome measure for the function of the autonomic nervous system.

Most of the studies combined both *time and frequency domain analysis* [10,24–32].

Four studies used only *frequency domain analysis* [23,33–35] and two only *time domain analysis* [36,37].

To improve readability an overview of the abbreviations is presented in Table 3.

The HF component and PNN50, SDNN, and RMSSD are seen as indicators of parasympathetic activity [29,38], while the LF component represents the activity of the sympathetic nervous system, although some studies suggest that it reflects both the sympathetic and parasympathetic nervous system [23,32,38]. The LF/HF ratio is used as indicator of the balance between the sympathetic and parasympathetic nervous system [25,26,29,34].

The results of the frequency domain analysis are hard to compare because of different measurement units: ms², natural logarithms of ms², normalized units, and percentages. The latter are used to present the LF or HF power relative to the total power.

As none of the studies compared CFS patients to FM patients, direct comparisons could not been made. Therefore patient groups will be discussed in comparison to healthy controls. In the discussion these results will be brought together.

3.5. HRV FM patients

3.5.1. 24 h monitoring

As presented in Table 2, Martinez-Lavin et al. reported for the first time that FM patients have significant lower HRV and parasympathetic activity (SDNN and PPNN50) compared to healthy controls [36]; these results were later confirmed [31,37]. While RMSSD was similar to that of healthy controls in two studies [29,36] and lower in the study of Lerma et al. during 24-h recording, but not at night [37].

HF is overall lower and LF/HF higher, for LF results are conflicting [29,31,35]. In the study of Dogru et al. differences were not revealed during daytime, but only during 24-h monitoring and during night [29].

3.5.2. Supine rest

All studies using time domain analysis reported reduced HRV in FM patients in supine position [24,30].

Frequency domain analyses unraveled differences compared to normal controls, but the direct of the differences in conflicting, due to the different units used to express the variables. Despite the studies expressing LF in percentage [23,30,32], the others found lower LF components in FM patients [24,31,35], but HF is overall lower and the ratio LF/HF higher [23,30–32,35].

3.5.3. Reaction to stressors

Although there are some small differences in the response to upright tilt, FM patients react similarly to control subjects, but reactions are again different between the different studies due to the different measure units [10,32], although more positive tilts (presyncopes) were observed and HRV reactivity was smaller in one study [31].

During *mental stress*, no task effects are observed in FM patients, indicating the lack of or a reduced cardiovascular response to stress [35].

Resistance training (16 wk) seems to increase HRV in FM [24].

> Moderate evidence supports decreased parasympathetic activity expressed by reduced SDNN, PPNN50, and HF and higher LF/HF on 24-h monitoring. For RMSSD and LF, evidence is conflicting. In supine condition moderate evidence is available for decreased absolute LF, but increased relative LF, because TP is lower in FM.

3.6. HRV CFS patients

Although some studies point to altered autonomic activity in patients with CFS as well, results are more in line with those observed in healthy controls.

3.6.1. Monitoring during sleep

As presented in Table 3, the results of HRV analysis collected in two sleep studies, point towards a decrease in HRV and vagal modulation of heart rate in subjects with CFS [25,26].

3.6.2. Supine rest

None of the studies revealed differences in supine position [27,28,33,34].

3.6.3. Upright tilt

De Becker et al. did not compare HRV reactivity during tilting, but compared patients and controls in supine and upright position and only found a higher LF component in upright position in CFS

Table 2
Evidence table of the included studies

Reference	Sample	Inclusion criteria	Mean age	Outcomes	Results CFS ↔ CON	Remarks
A. CFS studies						
Boneva et al. [25]	30 CFS (4♂, 26♀) 38 CON (7♂, 31♀)	CFS: CDC 1994 CON: non-fatigued and healthy CFS and CON matched: age, gender, race, and BMI	CFS: 49.5 ± 7.8 y CON: 50.5 ± 8.8 y	ECG: during sleep	– Time domain = – LF, VLF, and TP < (ms²) – HRV ♀ < ♂	Not controlled for breathing rate and depth and physical activity
Burton et al. [26]	20 CFS (3♂, 17♀) 20 CON (5♂, 15♀)	CFS: CDC 1994 CON: non-fatigued and healthy CFS and CON matched: age, gender, BMI, and activity level	CFS: 41 ± 11.4 y CON: 36 ± 13.2 y	Polar monitor: during sleep	– RMSSD < – HF < (%) – LF/HF > – LF =	Not controlled for breathing rate and depth
De Becker et al. [33]	21 CFS (6♂, 15♀) 13 CON (5♂, 8♀)	CFS: CDC 1988 CON: healthy CFS and CON matched: age and gender	CFS: 31.7 ± 10.6 y CON: 28.1 ± 5.2 y	ECG and Holter: 10' supine and upright tilt	– *Supine and upright*: – HF, LF/HF: = (nu) – *Upright*: LF > – Reactivity not compared	Not controlled for physical activity
Duprez et al. [27]	38 CFS (9♂, 29♀) 38 CON (9♂, 29♀)	CFS: CDC 1988 CON: healthy normotensive CFS and CON matched: age and gender	CFS: 34.8 ± 8.0 y CON: 35.6 ± 10.5 y	ECG: supine and 10' standing	– *Supine*: LF, HF, TP = (ms²) – *Supine to upright*: = CON HF ↘	Not controlled for physical activity
Yataco et al. [34]	19 CFS (5♂, 14♀) 11 CON (4♂, 7♀)	CFS: CDC 1988 CON: healthy, no medication CFS and CON matched: age and gender	CFS: 29 ± 12 y CON: 34 ± 9 y	ECG and Holter: 20' supine to upright tilt	– *Supine*: LF, HF, LF/HF = – *Supine to upright*: = CON HF ↘, LF and LF/HF ↗	Not controlled for breathing rate and depth and physical activity
Yamamoto et al. [28]	39 CFS (7♂, 32♀) 31 CON (5♂, 26♀)	CFS: CDC 1994, no medication with cardiovascular or orthostatic effects CON: healthy, sedentary CFS and CON matched: age, gender, race and BMI	CFS: 40.1 ± 9.6 y CON: 42.4 ± 7.7 y	ECG: 20' supine to head up tilt (HUT)	– *Supine*: = – *HUT*: SDNN, HF, Fractal power < (amplitudo) – *Supine to HUT*: SDNN, HF ↘ = CON Fractal power = ↔ CON ↘	Not controlled for breathing rate and depth
Reference	Sample	Inclusion criteria	Mean age	Outcomes	Results FM ↔ CON	Remarks
B. FM patient						
Dogru et al. [29]	50♀FM 38♀CON	FM: ACR 1990 CON: healthy FM and CON matched: age, hip circumference, BMI	FM: 38 ± 7 y CON: 36 ± 8 y	Holter: 24 h	– *24 h and night*: HF <, LF and LF/HF > (nu) – *Daytime*: = – RMSSD = – LF/HF_{Day}/ LF/HF_{Night} <	Not controlled for breathing rate and depth
Figueroa et al. [24]	10♀FM 9♀CON	FM: ACR 1990 CON: healthy FM and CON matched: age and BMI	FM: 50 ± 10 y CON: 49 ± 8 y	ECG: 20' supine and post-training (16 wk)	– *Supine*: RMSSD, TP, LF < LF/HF, HF = (Ln ms²) – *Post-training (FM)*: TP and RMSSD > baseline	Not controlled for physical activity
Cohen et al. [23]	22♀FM 22♀CON	FM: ACR 1990 CON: healthy; FM and CON matched: age, smoking and time ECG	FM: 47 ± 7.1 y CON: 47 ± 7 y	ECG: 20' supine	– TP < – HF <, LF and LF/HF > (%)	Not related to tenderness and symptoms

Table 2 (*continued*)

Reference	Sample	Inclusion criteria	Mean age	Outcomes	Results CFS ↔ CON	Remarks
Cohen et al. [32]	19♂FM 22♂CON	FM: ACR 1990 CON: healthy FM and CON matched: age, smoking, and time ECG; no comorbidities, no drugs influencing ANS last 4 wk	FM: 45.8 ± 7.1 y CON: ?, matched	Holter: 20' supine to upright tilt	– *Supine*: TP < HF <, LF/HF and LF > (%) – *Upright vs supine*: = CON HF↘, LF and LF/HF↗	Not controlled for physical activity
Kulshreshtha et al. [30]	42♀ FM 42♀ CON	FM: ACR 1990 CON: healthy FM and CON: right-handed, no history of smoking, alcoholism or drug intake, no comorbidity, refrained central working drugs 4 wk prior and analgesics 1 day before test	FM: 39.95 ± 6.4 y CON: 38.23 ± 5.7 y	ECG: 15' supine	– SDNN, RMSDD, PNN50 < – LF, LF/HF, TP = (%) – HF <	Not controlled for physical activity
Lerma et al. [37]	22♀ FM 22♀ CON	FM: ACR 1990; CON: healthy; FM and CON: fertile, but not in menstrual period, free of medication influencing ANS or sleep	FM: 32.4 ± 7.9 y CON: 30.4 ± 7.4 y	Holter: 24 h	– *24 h*: SDNN, PNN50, RMSDD < – *At night*: SDNN <	Not controlled for breathing rate and depth and physical activity
Martinez-Lavin et al. [10]	19♀FM	FM: ACR 1990, 20–60 y, no comorbidities, major depression or medication influencing ANS	FM: 46 ± 10.5 y	ECG: 15' supine to upright tilt	– *Upright vs supine:* SDNN =, LF↘, HF↗, TP↘ (=CON, except LF↔) (nu)	Not controlled for breathing rate and depth and physical activity
	19♀CON	CON: no fatigue, pain or medication; FM and CON matched: age and gender, 8–9 AM	CON: 45 y		– No supine comparison	
Martinez-Lavin et al. [36]	30 FM	FM: ACR 1990, 20–60 y, no comorbidities, major depression or medication influencing ANS	FM: 38.6 ± 10.5 y	ECG: 24 h	– RMSSD = – SDNN, COVR, PNN50 <	Not controlled for breathing rate and depth and physical activity
	30 CON 93%♀	CON: no fatigue, pain or medication FM and CON matched: age and gender	CON: ±2 y matched			
Raj et al.[31]	17♀FM 15♀CON	FM: ACR 1990 CON: not ACR; FM and CON: no comorbidities, no highly dosed antidepressants	FM: 25–50 y CON: 25–50 y	Holter: 24 h and 30' supine to 30' 70° upright tilt (if no presyncope, isoproterenol was infused)	– *24 h*: SDNN, RMSDD, PNN50 < LF, TP =HF <, LF/HF > (Ln ms²) – *Supine*: LF, TP, HF < LF/HF > – *Upright*: = – *Positive tilts*: > – *Reactivity HRV*: <	Not controlled for breathing rate and depth and physical activity
Reyes del Paso et al. [35]	35 FM (3♂, 32♀) 29 CON (2♂, 27♀)	FM: ACR 1990 CON: healthy FM and CON matched: age, gender, BMI, educational and professional status, no comorbidities, 6 PM	FM: 50 ± 6.7 y CON: 49.4 ± 9.4 y	ECG: 15' rest, during mental stress and in recovery	– *Rest*: LF, HF, TP < LF/HF > (ms²) – *No task effects*; except LF/HF ↘ and in recovery ↗ ↔ CON LF/HF = – TP, LF, HF < in depressed FM	Not controlled for breathing rate and depth

CFS = chronic fatigue syndrome; CDC = Centers for Disease Control and Prevention; FM = fibromyalgia; ACR = American College of Rheumatology criteria; CON = healthy controls; ANS = autonomic nervous system; HRV = heart rate variability; LF power = low-frequency power (ms²); HF power, high-frequency power (ms²); TP = Total power (ms²); RMSSD = root of the mean squares of differences between adjacent R–R intervals; SDNN = standard deviation on R–R intervals; COVR = coefficient of variation; PNN50 = number of pairs of adjacent R–R intervals differing by > 50 ms divided by the total number of R–R intervals; nu = normalized units; Ln = natural logarithm.

patients, indicating increased sympathetic activity when they are exposed to stress but not at rest.

Studying the reaction to upright tilt, all investigations found similar responses of LF (↗), HF (↘), LF/HF (↗) and SDNN (↘) in CFS patients compared to healthy controls [27,28,34]. Only fractal power was quite stable CFS patients, while it decreased in controls [28].

> Moderate evidence indicates similar HRV in supine position and similar HRV responses, increase in sympathetic activity, and decrease in parasympathetic activity to upright tilt in CFS patients. Only during sleep, preliminary evidence points towards a decrease in HRV and vagal modulation in CFS patients.

3.7. Clinical relevance

Few studies looked at the clinical relevance or correlates of reduced HRV.

According to Cohen et al., [23] HF, LF, and LF/HF are moderately correlated to physical functioning, the Short Form Health Survey 36 (assessing bodily pain, functioning, and quality of life) anxiety, depression, and stress in patients with FM. This is in line with the findings of greater HRV reductions in depressed FM patients and higher cardiovascular reactivity to stress in anxious FM [35].

Furthermore, an increase in HRV (due to resistance training) in patients with FM was correlated to a 39% decrease in pan intensity [24].

Interestingly, correlations found in FM patients are different from those seen in healthy controls. In the FM group, there are correlations between HRV parameters indicative of sympathetic predominance and the severity of pain, constipation, and depression. In contrast, healthy controls display an opposite behavior. They had positive correlations between HRV markers indicative of parasympathetic predominance (either reduced sympathetic activity, increased vagal activity, or both) with the total score of the Fibromyalgia Impact Questionnaire and the severity of fatigue, anxiety, and depression [37].

In subjects with CFS, decreases in HRV are predominantly found during sleep, and additionally, indices of HRV would serve as good predictors of sleep quality [25,26].

> Moderate evidence highlights the relevance of HRV and sympathetic dominance in FM, based on the correlations between HRV indices and measures of symptoms and functioning. In CFS HRV seems related to sleep quality.

4. Discussion

The goal of the present systematic literature study was to compare HRV between CFS patients and FM patients in comparison to healthy controls and to describe the clinical relevance. As none of the studies directly compared CFS and FM patients, we reviewed the knowledge on HRV in patients with FM and in patients with CFS discuss them together in the discussion.

Although there are some inconsistencies and the level of evidence is moderate to low, mainly due to the included study designs (case–control), it seems that HRV and autonomic activity is altered in *FM patients*. HRV is reduced and autonomic activity is dominated by sympathetic activity. The response to acute stressors is analogous to that of healthy subjects, but the magnitude of the changes is always smaller in FM patients, indicating a reduced reactivity of the autonomic nervous system.

Results of frequency domain analyses were often hard to compare between the different studies due to differences in measurement units. The included studies used ms², natural logarithms of ms², percentages, and normalized units. Given the reduced total power in FM patients, using relative or absolute measurements results in different outcomes compared to controls. Especially for LF absolute and relative results were inconclusive. Relative results pointed, however, in the direction of increased sympathetic tone.

In *CFS patients*, fewer studies were performed. Nevertheless, it seems that, besides lower HRV at night [25,26], patients were similar to healthy controls. This points to an overnight increase in the sympathetic activity in CFS patients, consistent with the observation in FM patients by [36]. Besides this similarity, CFS patients are, during the day, more similar to healthy controls than FM patients.

In both patient groups, indices of HRV are related to different clinical characteristics, like physical functioning, depression, sleep quality, quality of life, and pain [23–26,37] and are thus relevant. However, based on the present studies it is not known whether altered HRV could be a cause or a consequence.

This offers new opportunities for further research. Longitudinal studies could for example confirm the results of Figueroa et al. if improved indices of HRV lead to clinical improvements. Optimization of HRV was effected by resistance training, as it seems that 16 wk of resistance training enhances HRV in FM, correlated to pain reduction. Previous studies have indeed shown that deconditioning, due to prolonged bed rest and inactivity, results in decreased HRV [39,40] and reversely, regular physical activity leads to an increase in HRV, mainly due to an increase in parasympathetic tone [41]. It is therefore important to compare FM and CFS patients with an inactive control group. Nevertheless, we do not think that reduced HRV in FM is solely due to deconditioning, since reduced HRV is mainly present in FM and to a lesser extent in CFS patients, who are expected to be less active and fit than the FM patients. Barely four studies in this systematic literature review have recruited inactive control subjects [23,28,29,35] and Burton et al. matched both groups for activity level. On the other hand, Boneva et al. reported lower HRV not to be fully accountable for by CFS subjects' decreased physical activity as differences were still present after statistically controlling for activity level [25], by using self-reported activity levels as covariate and by comparing only with physical activity-matched controls. Others did not mention fitness levels of control subjects or did not use physical activity outcome measures as confounding factors.

Besides the issue of the physical activity level, a lot of other factors are known to be capable of modulating HRV. Unfortunately, the majority of the studies did even so not account for breathing rate or frequency, although it is clear that breathing rate if of importance when studying HRV [42]. In healthy individuals, the ECG at rest shows periodic variations in R–R intervals, caused by respiratory sinus arrhythmia due to parasympathetic influences on the sinus node. Respiratory sinus arrhythmia becomes apparent during expiration and ispresent to a lower extent or absent during inspiration. It is indeed shown that deep breathing increases R–R variation both in patients and controls, although effects are smaller in FM patients [43,44]. In the present review, six of the included studies controlled for breathing rate and frequency [23,24,27,30,32,33].

Acute stress situations, on the other hand, are known to reduce HRV [35]. This can be extended to chronic stress. Chronic stress causes reduced parasympathetic activity [45] and explains why many chronic illnesses are characterized by reduced HRV, for example in chronic low back pain patients [46]. Consequently, pain can be the explanation for the differences in results between CFS and FM patients. HRV aberrances are predominantly present in

Table 3
Abbreviations for heart rate variability (HRV) outcome measures included in the review

Abbreviation	Complete term	Indicative of
TP	Total power	Total variance in heart rate pattern
LF	Low-frequency band	Sympathetic activity or both
HF	High-frequency band	Parasympathetic activity
LF/HF	Ratio LF/HF	Balance sympathetic/parasympathetic
SDNN	Standard deviation on average R–R interval	Parasympathetic activity
RMSSD	Root of mean squares of differences between adjacent R–R intervals	
PNN50	Number of pairs adjacent R–R intervals differing by >50 ms/total number of R–R intervals	

the FM group, possibly due to the chronic stressor "pain." Similarly, Mostoufi et al. did not report differences in HRV between FM and control subjects with chronic benign pain [38].

Inversely, it is even suggested that the lack of cardiovascular responses to stress may contribute to deficits in pain inhibition occurring in FM patients [47,48], eg, blood pressure is of relevance for stress-induced hypo-algesia [35,49].

However, the majority of CFS patients also suffer chronic widespread pain or comorbid FM and pain inhibition is even so failing [50,51], but the pain component was not assessed or mentioned in the CFS studies. This underlines again the lack of comparative studies.

As HRV is clearly subject to several factors, it is important to account for these possible cofounders. Both coronary or cardiac disorders and a number of psychiatric situations, like depression, contribute to a decreased HRV [52,53]. Therefore all participants should undergo a physical and psychiatric examination to exclude eventual differential diagnoses or comorbidities. Several of the included studies controlled for these comorbidities, like major depressions [10,25,28,29,36]. However, depression is a diagnosis that blends with fibromyalgia in some cases and it may be difficult to dissect out depression completely. But then again, the differences between CFS and FM may indicate that depression is not the leading actor in the reduced HRV.

Medication use was controlled or taken into account in the majority of the studies. However most studies stated that participants could not take medication influencing the autonomic nervous system and it is not always clear from these studies that none of the medications patients were taking contributed to increased sympathetic nervous system activity, or reduced parasympathetic nervous system activity. Because many FM patients take Amitriptyline and other tricyclics and these may quicken heart rates and reduce R–R intervals.

Also age and gender are of importance [53], but in most studies patient and control group were matched for age and gender and the samples are representative for the complete population.

In general, there are a lot of influencing factors that should be controlled during HRV analysis. Not all studies controlled for all of these factors and this should be remedied in further research. Furthermore blinding was lacking in most of the studies. Whether this is relevant can be discussed given the nature of the assessment. Recording the data by ECG of Holter is not subject to blinding of the assessors, but while manually preparing (excluding noise etc.) the data for analyses, bias can occur due to the lack of blinding.

Finally, it was not possible to exclude bias due to the time of HRV measurement, since only two studies mentioned the time [10,35] and only two studies matched the control group for timing of ECG [23,32].

Besides improving the current study designs where necessary, it could be interesting to study causality of HRV, as earlier mentioned. A direct comparison between CFS, FM, and CFS/FM patients would give a decisive answer to the possible differences in HRV between CFS and FM. And finally, the last step is setting up studies regarding the therapeutic approach of this clearly clinically relevant problem. Reduced HRV is not only related to functioning, sleep, and quality of life in CFS and FM patients, but also to poorer health and cardiovascular mortality and morbidity [16,17].

5. Conclusion

In general, the results of FM studies point towards significantly lower HRV with lower parasympathetic and increased sympathetic activity. When exposed to physical and mental stress, a blunted response is observed and there is a nocturnal increase in sympathetic activity compared to healthy subjects. Training improves HRV in FM. In CFS patients, differences with controls were only observed at night. Possibly, pain is the discriminating factor, although causality cannot be decided based on the included studies. Further research should unravel these remaining questions with very well-controlled methods of HRV analyses.

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