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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.

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?

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].

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).

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.

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.

Qualification of searchers

Literature was searched and screened by F.D.B., master in the rehabilitation sciences and physiotherapy. 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 [19-21].

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.

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 "Checklist for case–control studies," provided by the Dutch Institute for Healthcare Improvement (CBO) and the Dutch