Systematic Review

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Heart rate variability in patients with low back pain: a systematic review

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Abstract

Objectives: Heart rate variability (HRV) is an important physiological measure of the capacity for neurogenic homeostatic regulation, and an indirect measure of emotional processing. We aimed to investigate whether HRV parameters are altered in people with chronic low back pain when compared to healthy controls.

Methods: We searched on PubMed, Scopus, CINAHL, Web of Science, Cochrane Library, and PsycINFO from inception to January 2018. The inclusion criteria were: patients with non-specific chronic low back pain, absence of radiculopathy, age from 18 to 65 years, and comparison with healthy controls. Data extraction was performed by two independent review authors. The methodological quality of the studies was assessed using the appraisal tool for cross-sectional studies.

Results: After screening 2,873 potential articles, two studies met the inclusion criteria. Studies were composed of 153 patients with chronic low back pain and 62 healthy controls. An electrocardiogram was used to record HRV and linear methods (time and frequency) were used to analyze the results. The main findings indicate that patients with chronic low back pain have a significant reduction in HRV, with sympathetic predominance compared to healthy controls.

Conclusions: There is limited evidence suggesting that chronic low back pain patients presented a lower vagal activity evidenced by HRV, when compared to healthy controls. The results of this systematic review should be interpreted with caution due to the restricted number of included studies, small sample sizes and different protocols used to measure HRV. The limited evidence about HRV alterations in low back pain also suggests the need of future studies to investigate if HRV parameters can be a useful measure in chronic pain samples or even if it can be used as an outcome in clinical trials aiming to investigate the effectiveness of interventions based on emotion regulation.

Keywords: chronic pain; heart rate determination; low back pain; pain; systematic review.

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Introduction

Low back pain has the highest disability burden worldwide [1]. In most cases, low back pain is associated with a broad range of factors including genetic, physical, psychological, and social [2]. The current evidence shows that chronic pain conditions are associated with morphological and

functional changes in the entire nervous system including the peripheral receptors, the spinal cord, and the brain [3, 4]. Longitudinal studies composed of patients with chronic low back pain showed changes in corticostriatal circuitry and mesolimbic brain structures including an increase in the activity of cognitive-emotional brain areas (i.e., prefrontal cortex, amygdala, insula, and anterior cingulate cortex) [5], an increase in connectivity between the prefrontal cortex and nucleus accumbens [6], and reduction of white matter tract integrity [7]. The brain circuitry identified as being crucial to pain chronification in patients with low back pain is also involved in appetitive and aversive learning [8].

A comprehensive view of the interaction between brain areas and visceral structures was proposed by the neurovisceral integration model [9]. This model describes a complex neural system that integrates signals from inside and outside the body and adaptively regulates physiological cognitive and behavioral responses, perception, and action including sensory and motor changes [10]. In this model the amygdala, which has its control mediated by the prefrontal cortex and outputs to the autonomic nervous system (ANS), can be influenced during threat and uncertainty [11–13]. One method to assess the interconnection of the central nervous system and the heart is the use of heart rate variability (HRV) [9, 12, 14, 15], a non-invasive method used to evaluate ANS modulation of the cardiac sinus node and which describes the oscillations between consecutive electrocardiogram RR intervals [15].

The neurovisceral integration model can be considered as a flexible neural network associated with self-regulation and adaptability [9, 16]. Despite the complexity of this neural system, it is possible that physiological measures, such as HRV, can serve as indices of the degree to which this system provides flexible, adaptive regulation in the presence of challenges (i.e., environmental, and also pain) [17–21]. It has been suggested that higher levels of HRV at rest indicate a context of highly adaptive emotional responses, low HRV is associated with health impairments including cardiovascular disease, mood disorders and increased morbidity [22]. In fact, reduction of HRV has been shown in different chronic pain conditions such as low back pain [23], neck pain [24], fibromyalgia [25, 26], complex regional pain syndrome [27], whiplash-associated disorders [28], and phantom limb pain [29].

Pain is inherently salient, aiming to protect our body from actual or potential tissue damage and people in pain may present physiological and behavioral protective responses [30]. Therefore, pain is an intrinsic threat and can alter the sympatho-vagal balance. It is possible that low HRV, as an index of activity in a set of neural structures involved in physiologic, affective, and cognitive regulation, may serve as a useful marker for a range of physical and psychological disorders including chronic pain. Given this substantial amount of data, the aim of this review was to systematically obtain data on resting HRV in people with chronic low back pain.

Materials and methods

Protocol and registration

A systematic review was undertaken and reported based on the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [31]. The research protocol for the review was prospectively registered on PROSPERO (CRD42018079159). The research question of this systematic review was: Is HRV altered in people with chronic low back pain for the outcomes of frequency, time, and non-linear HRV domains?

Eligibility criteria

Eligibility for inclusion in the review was independently assessed by two reviewers (PMB and VS) after considering full-text articles and applying the inclusion criteria. Disagreements between the reviewers were resolved through discussion or by arbitration of a third reviewer if required (FR). Inclusion criteria were: (i) studies reporting baseline resting HRV in patients with chronic low back pain (those collected before any intervention), (ii) patients with non-specific chronic low back pain (defined as persistent or recurrent pain lasting longer than three months without a specific cause), (iii) absence of radiculopathy, (iv) included participants aged between 18 and 65 years, (v) control group composed of healthy controls, (vi) studies that reported original and peer-reviewed data, and (vii) studies should state in the title or abstract that they used HRV and reported its domain (frequency, time, and/or non-linear). Studies were not included if: (i) HRV was measured as an outcome after an intervention, (ii) studies that reported the inclusion of patients with cardiovascular (e.g. angina, heart disease, heart disease, myocardial infarction, etc.), respiratory, infectious, metabolic, neurological or autoimmune diseases, and (iii) studies without a control group composed of healthy participants.

Search strategy

We searched on PubMed, Scopus, CINAHL, Web of Science, Cochrane Library, and PsycINFO from inception to January 2018. Search strategies included the terms *electrocardiography*, *arterial pulse*, *heart rate*, *heart rate variability*, *HRV*, *autonomic nervous system*, *parasympathetic* and *sympathetic nervous system*, *vagus nerve*, *pain*, *lumbar*, *low back pain*. The search terms have been adapted for use with other bibliographic databases in combination with specific

database filters for controlled trials, when available. There was no restriction for the year of publication or language. A manual search was performed by checking the reference lists of each eligible article by two authors (PMB and VS). Details of the search strategy are illustrated in Appendix.

Study selection and data synthesis

Search results were exported, organized, and de-duplicated within Mendeley software (Elsevier, USA). Two reviewers (PMB and VC) independently performed an initial database search and screened the search results for relevance using title and abstract. Discrepancies were discussed and resolved. The data from each study included were extracted independently by two authors (PMB and VC). Disagreements between the reviewers were resolved through discussion or by arbitration of a third reviewer if required (FR). Data items extracted from studies including study data (authors, country, and year of publication), participant characteristics, and HRV measurement data (duration of recording and HRV parameters).

Risk of bias in individual studies

Methodological quality was determined using the appraisal tool for cross-sectional studies (AXIS tool) which assesses the appropriateness of study design for the stated aims, sample size justification, and reliability of survey instruments and evaluates whether the response rate raises concerns regarding non-response bias. The AXIS tool does not include a numerical scale that can be used to produce quality assessment score; instead, the tool aims to assess the individual characteristics of a study cumulatively [32].

Data analysis

Due to the heterogeneity of the studies included in this systematic review a meta-analysis was not possible. Therefore, the data analysis was descriptive.

Results

Study characteristics

The bibliographic search identified 2,873 potential articles. After the duplicates were removed, 2,187 studies remained. Of the references included for evaluation, 76 studies were selected by title and their abstracts were read; after selection of the abstracts, 12 articles remained for the complete reading. After selection by eligibility according to the inclusion criteria, two studies were selected for this review. Another seven studies were considered for inclusion, obtained from lists of references and citations of relevant articles (Figure 1).

Characteristics of the studies

The studies included in this review had a total of 153 patients with low back pain and 62 healthy controls. The sample of the studies was mainly composed of female

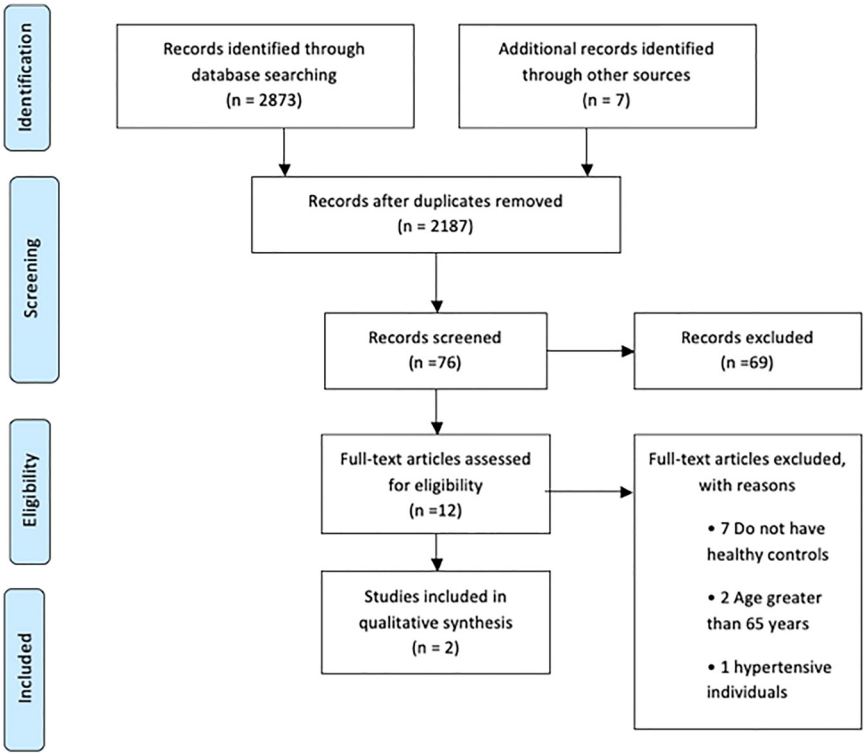

Figure 1: Selection of studies for inclusion in the systematic review.

participants. The studies were published in 2007 [33] and 2011 [34] and were conducted in Sweden and India, respectively. The study of Kalezic et al. [33], excluded patients who were taking medications that could interfere in ANS activity, and patients with neurological or rheumatic disorder, depression, or dizziness [33]. To perform data collection, the authors recommended that participants not use any type of medication. The study of Shankar et al. [34], did not present data on the exclusion of patients due to the use of medications, other diseases, or previous surgeries. The characteristics of the studies included are presented in Table 1.

Risks of bias analysis

Methodological quality analysis determined that both studies assessed obtained 16 out of 20 items in the AXIS tool (Supplementary Material). Neither study took measures to justify the sample size, address and categorize or describe non-responders, or report any funding sources or conflicts of interest.

Method of measuring HRV

Both studies used an electrocardiogram to record RR intervals, for periods of 1 [34] or 5 min [33] with patients at rest and awake and both analyzed HRV using linear methods (time and frequency). Kalezic et al. [33], did not describe the position in which the measure was obtained. Shankar et al. [34], measured the RR intervals during respiration or expiratory-to-inspiratory ratio (E:I) with the patients for 1 min in a supine position. After a verbal command, patients were asked to breathe deeply and continuously at a rate of six breaths per minute (5 s of inspiration and 5 s of expiration).

HRV parameters measured

Kalezic et al. [33] performed HRV frequency domain analysis, presenting normalized values for low frequency – LF (n.u.) and high frequency – HF (n.u.). The authors found a higher mean value for LF (n.u.) (mean=0.54 [SD=0.14]) in patients with low back pain when compared with healthy controls (mean=0.43 [SD=0.15]). Regarding the HF values, patients with low back pain presented a mean value of 0.44 (SD=0.14) and healthy controls presented a mean value of 0.35 (SD=0.12). Overall, this study found higher mean values for LF and lower ones for HF in patients with chronic low back pain compared to healthy controls. These differences were detected in low frequency spectral power ($p<0.001$) and, high frequency spectral power ($p<0.001$).

Regarding the variables of the HRV time domain, Kalezic et al. [33] assessed the SDNN (mean of the standard

Table 1: Table of characteristics of included studies.

Author	Year	Country	Low back pain	Sample	Protocol	Measures	Main findings
Kalezic et al. [33]	2007	Sweden	≥3 months	Controls: (n=32) *Women: 15 (46.8%)* *Mean (age)=36* *SD (age)=9* Low back pain: (n=93) *Women: 48 (51.6%)* *Mean (age)=38;* *SD (age)=7*	ECG 5 min at rest	LFnu (NR), HFnu (NR), SDNN	Patients had an increase in LFnu and a smaller increase in HFnu compared to controls.
Shankar et al. [34]	2011	India	≥6 months	Controls: (n=30) *Women: 17 (56.6%)* *Mean (age)=35.9* *SD (age)=4.15* Low back pain: (n=60) *Women: 40 (66.6%)* *Mean (age)=35.3* *SD (age)=5.7*	ECG 1-min supine recording with student physiograph machine (INCO)	E:I ratio, 30:15 ratio	Patients had a lower E:I ratio compared to healthy controls at rest.

ECG, electrocardiogram; E:I, expiration:inspiration ratio; VFC, heart rate variability; HFnu, normalized high-frequency power; LFnu, normalized power of low frequency; NA, not applicable; SDNN, standard deviation of all normal R–R intervals recorded in a time interval (ms).

deviations of all normal sinus RR intervals) variable (i.e. the standard deviation of the normal-to-normal range). The study presents a difference in SDNN mean values between low back pain participants (53.5; SD=23.02) and healthy controls (50.0; SD=24.07). However, the SDNN differences were not statistically significant.

Deep breathing test – E:I ratio (sinus respiratory arrhythmia) and orthostatic ratio (30:15 ratio)

Shankar et al. [34] presented the E:I ratio results expressed in terms of a ratio of a mean of six maximal RR intervals during expiration to an average of six minimum RR intervals during inspiration; the 30:15 ratio was calculated considering the relation between the maximum RR interval around 30 beats and the minimum RR interval around 15 beats after standing. Values were expressed as mean and standard deviation [34]. The E:I ratio was 1.33 (SD=0.14) in participants with low back pain and 1.44 (SD=0.15) in healthy controls. Participants with chronic low back pain had a lower E:I ratio as compared to the control group, and this difference was statistically significant (p=0.002). For the 30:15 parameter, the mean value in the low back pain participants was 1.17 (SD=0.08) and in the healthy controls was 1.25 (SD=0.16) (p=0.012).

Discussion

This study aimed to identify the resting HRV in patients with chronic low back pain. The main findings of the present study suggest a predominance of sympathetic nervous system activity measured by HRV parameters in patients with chronic low back pain in comparison to healthy participants. We found a predominance of sympathetic tone with a lower activation of parasympathetic tone characterized by increased BF (n.u.) and a lower E:I ratio in participants with chronic low back pain, which suggests low vagal tone or may an increased sympathetic flow in patients with pain.

Changes in resting HRV characterized by lower vagal tone have also been reported in other chronic pain conditions such as rheumatoid arthritis [35], fibromyalgia [36], shoulder and neck pain [37], irritable bowel syndrome [38], whiplash-associated disorders [39], chronic prostatitis [40], chronic pelvic pain [41], complex regional pain syndrome [27], head/orofacial pain and chronic migraine [42, 43], and chronic fatigue syndrome [44]. Reyes del Paso et al. [45] in a study composed of 54 patients with fibromyalgia, identified lower mean values in all domains of HRV frequency, indicating a general decrease in HRV, when compared to healthy controls on baseline. Hallman and Lyskov [24] aimed to investigate autonomic nervous system regulation, physical activity, and daily stress perception in 55 patients with chronic neck and shoulder pain. The authors found shorter RR intervals and HRV reduction when compared to the control group. These findings characterize a lower activation of parasympathetic tone in the chronic pain group.

Tracy el al. [46]. aimed to identify changes in HRV in a wide range of chronic pain conditions including fibromyalgia, temporomandibular disorders, chronic neck and shoulder pain, chronic low back pain, and others. The authors reported that chronic pain conditions were associated with a reduction of HRV, in particular in HF domain and time domain measurements. Regarding HF, the authors observed a moderate decrease in patients with chronic pain when compared to healthy controls, and the effect size was considered small (ES=−0.39). In the time domain, the most common HRV measures were RMSSD (root mean square of successive RR interval differences), SDNN (Standard Deviation of the average NN intervals) and RRI (wave interval RR). RMSSD was shown to be strongly associated with parasympathetic cardiac influence. In the review carried out by Tracy et al. [46], there were no significant differences in RMSSD between individuals with chronic pain and controls. Their results also showed that chronic pain is associated with a decrease in SDNN. This finding was attributed to a lower activation of parasympathetic tone. The main difference between this review and the study of Tracy et al. [46] was that we sought to identify HRV changes exclusively in patients with low back pain when compared to healthy volunteers. However, studies that met the inclusion criteria included only patients with chronic low back pain.

The findings of this review are in accordance with the results of other studies composed of people with chronic low back pain. For example, Telles et al. [47] investigated 62 patients with chronic low back pain and found a predominance of LF-HRV parameter (sympathetic activity) in their participants. Regarding time domain measures, the study showed that participants with chronic low back pain presented lower values for pNN50 (mean number of times per hour in which the change in consecutive normal sinus), SDNNi (mean of the standard deviations of all the NN intervals), and RMSSD parameters at baseline. These measures are strongly associated with vagal tone, suggesting that individuals with low back pain have lower parasympathetic activity [48]. Roy et al. [49] evaluated HRV

in a sample of 20 participants with low back pain. It was observed that participants had a predominance of LF activity at baseline, thus characterizing higher sympathetic activity and consequently lower parasympathetic activity. In the study by Zhang et al. [50] with a total of 36 individuals with acute low back pain, the authors observed a predominance of LF in relation to HF. These studies were not included in the present review because they did not have a control group with healthy participants, which makes it difficult to interpret baseline data since, to date, there are no normal values reported in the literature.

Resting HRV measurement may be an important clinical measure in chronic pain conditions. Gockel et al. [23] in a group of 46 patients with low back pain, sought to identify the association of HRV parameters with pain intensity and disability. The authors found that HRV was associated not only with greater pain intensity but also with high levels of disability, presenting evidence that HRV was lower among participants with moderate disability compared to those with minimal disability. The values of RMSSD and HF parameters were lower in participants with a higher degree of disability, suggesting that the parasympathetic heart rate modulation was significantly lower in this sample. Koenig et al. [51] recruited 61 patients, a group with chronic post-traumatic neck pain and healthy controls, to verify if the reduction in HRV measurements was associated with high levels of catastrophizing. The authors observed that individuals with chronic neck pain have lower HF compared to healthy controls and report higher levels of catastrophizing. Maladaptive emotional responses such as catastrophizing, for example, may represent poorly adaptive emotional regulation and predict disease and mortality [28].

This study is not without limitations. Although the studies have good methodological quality, it is not possible to generalize the results due to the small number of studies included, the small sample sizes, the different protocols used to measure HRV and the different parameters. We did not include studies reporting participants with clinical history of cardiovascular, respiratory, infectious, metabolic or autoimmune diseases. We decided to include studies even though the they did not reported a detailed description of the sample characteristics. We are aware that sample characteristics, including demographic and clinical, might have an impact on HRV. However, description of study participants is an oft-under-reported aspect of HRV research and recommendation on how to report sample characteristic is novel [52, 53]. We tried to decrease the impact of this limitation on our results contacting the authors to obtain more details and including studies with age and sex matched healthy volunteers in the control group. Another limitation is the absence of studies with acute or subacute low back pain. Finally, it was not possible to perform a meta-analysis, as the studies used different protocols and measures. It is recommended that further studies investigate the domains of HRV in patients with low back pain and its association with pain intensity, disability and psychological and behavioral changes. We also consider that there is an important gap in the literature in relation to prospective studies to identify whether HRV can be considered a biomarker for pain chronification, pain intensity or pain-related disability.

Conclusion

There is limited evidence in the literature suggesting that patients with chronic low back pain have a significant reduction in HRV, with lower parasympathetic activation and consequently sympathetic predominance, when compared to healthy controls. The results of this systematic review should be interpreted with caution due to the restricted number of included studies, small sample sizes and different protocols used to measure HRV.

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Informed consent: Not applicable.
Ethical approval: Not applicable.

Appendix: Search strategy

ID	Search
#1	Dorsalgia
#2	MeSH descriptor: [Back Pain] explode all trees
#3	backache
#4	MeSH descriptor: [Low Back Pain] explode all trees
#5	MeSH descriptor: [Coccyx] explode all trees
#6	coccydynia
#7	MeSH descriptor: [Sciatica] explode all trees
#8	MeSH descriptor: [Sciatic Neuropathy] explode all trees
#9	MeSH descriptor: [Spondylosis] explode all trees
#10	lumbago
#11	back disorder
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

- #13 MeSH descriptor: [Electrocardiography] explode all trees
- #14 Arterial Pulse
- #15 MeSH descriptor: [Heart Rate] explode all trees
- #16 Heart Rate Variability
- #17 HRV
- #18 MeSH descriptor: [Autonomic Nervous System] explode all trees
- #19 MeSH descriptor: [Parasympathetic Nervous System] explode all trees
- #20 MeSH descriptor: [Sympathetic Nervous System] explode all trees
- #21 MeSH descriptor: [Vagus Nerve] explode all trees
- #22 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
- #23 #12 and #22

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