ORIGINAL ARTICLE

Lowered Parasympathetic Activity in Apparently Healthy Subjects with Self-Reported Symptoms of Pain: Preliminary Results from a Pilot Study

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■ **Abstract**

Objectives: The aim was to evaluate differences in the autonomic nervous system (ANS) activity, indexed by heart rate variability (HRV) in apparently healthy subjects with self-reported symptoms of pain (SRSP) within an exploratory analysis.

Methods: HRV data from 14 apparently healthy male individuals were analyzed to address potential differences in subjects with and without SRSP. SRSP was assessed using the four pain-related items from the symptom checklist (SCL-90R). Subjects were stratified based on the presence of SRSP.

Results: Parasympathetic activity, indexed by pNN50, RMSSD, and high frequency (HF) spectrum of HRV, was lower in subjects with SRSP. Low frequency (LF) HRV and the LF/HF ratio were greater in subjects with SRSP. However, analysis of variance revealed no significant differences between the groups. Pearson correlations showed a correlation of pNN50, HF, LF, and LF/HF ratio and the presence and frequency of SRSP. Measures of parasympathetic activity (pNN50 and HF) were inversely associated with more SRSP, indicating that subjects with more frequent SRSP show decreased parasympathetic activity.

Conclusions: Consistent with evidence on changes in HRV in patients with clinical conditions of chronic or recurrent pain, this is the first study to show that healthy individuals who report symptoms of pain may have lower parasympathetic activity revealed by measures of HRV. ■

Key Words: self-reported pain, autonomic nervous system, heart rate variability, parasympathetic activity

INTRODUCTION

Evidence supports the existence of extensive interactions between the neural systems involved in the autonomic control of cardiovascular processes and systems modulating the perception of pain.[1–3] Heart rate variability (HRV, ie, the beat-to-beat variation in the heart rate) is driven by the autonomic nervous system (ANS) and

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allows teasing out the relative contributions of sympathetic and parasympathetic activity underlying autonomic reactivity in the control of the heart.

A large variety of health conditions are associated with changes in ANS function, indexed by HRV.[4] Addressing the field of pain, reduced HRV is reported in patients with complex regional pain syndrome,[5] patients with fibromyalgia,[6] patients with chronic neck pain,[7] irritable bowel syndrome,[8] or headache.[9,10] Furthermore, lower HRV is associated with extended pain-related sick leave in employees.[11] Thus, measures of HRV are of interest in the study of pain-related diseases[12] and potential outcome measure for the relief of pain due to therapeutic interventions, resulting in a re-increase of HRV measures.[13–15]

To our knowledge, no study has investigated the relation of changes in HRV and the frequently presence of symptoms of pain in apparently healthy subjects. Within this article, we present a first exploratory analysis of such an association in 14 apparently healthy male adults.

METHODS

The study was approved by the Institutional Review Board, and all participants provided written informed consent prior to their assessment. Self-rated health (SRH) was measured using the question "How do you rate your current health status?" on a 0 "very bad" to 6 "excellent" scale. Only subjects indicating a SRH $\geq$ 3 "fair" were considered for inclusion in the present analysis. A total of 14 healthy male individuals were included in the trial. None of the subjects reported current medication intake or suffering from chronic or acute disease.

HRV was measured while subjects were sitting on a comfortable chair for 5 minutes. A Polar RS800CX portable device was used to record interbeat-intervals (IBI) at sampling frequency of 1000 Hz, providing a temporal resolution of 1 ms for each R–R interval. The device's transmitter, consisting of a stable polyamide case with electrodes attached to an elastic belt fixated to the chest of the subjects device-specific software (Polar ProTrainer 5, Polar Electro, Kempele, Finland), was used to transfer recordings to a personal computer. IBI data were imported and analyzed with "Kubios HRV - Heart Rate Variability Analysis Software" (Biosignal Analysis and Medical Imaging Group, University Kuopio, Finland, Version 2.0[16]). For further analysis, the square root of the mean squared difference of successive NN intervals (RMSSD, ms), the proportion of pairs of successive NNs that differ by more than 50 ms (pNN50, %), absolute spectral power expressed as normalized units (n.u.) of high frequency (HF n.u.; 0.15 to 0.4 Hz), and low frequency components (LF n.u.; 0.04 to 0.15 Hz) were obtained, and the LF/HF ratio was computed. Data on HRV measures were skewed and successfully log-transformed for further analysis, in particular Pearson's correlation test and analysis of variance (ANOVA). The HF component reflects cardiac vagal (ie, parasympathetic) activity, while the LF component is associated with baroreflex activity.[17–19] RMSSD and pNN50 are closely related to the HF component of the power spectrum and thus, are strongly associated with cardiac vagal activity, reflecting a parasympathetic influence.

Self-reported symptoms of pain (SRSP) within the past 4 weeks were derived from four items of the German version[20,21] symptom checklist.[22] These items included item 1 ("headaches"), item 12 ("pain in heart or chest"), item 27 ("pains in lower back"), and item 42 ("soreness of muscles"). All items were scored on a 5-point scale: 0 = *not at all*, 1 = *a little bit*, 2 = *moderately*, 3 = *quite a bit*, and 4 = *extremely*. A total pain index (TPI) was calculated by the sum of the item values (0 to 16). Subjects were stratified to groups according to the distribution of the TPI into a group of subjects with no or nearly no SRSP (TPI = 0 to 1) and subjects with more than one SRSP (TPI > 1). Statistical analysis was performed using SPSS 21.0 (21, IBM Chicago, IL, U.S.A). Effect size calculation and power analysis were performed using G*Power 3.[23]

RESULTS

Subjects' mean age was 24.3 $\pm$ 2.0 years. Six subjects reported more than one symptom of pain (TPI > 1). Mean TPI among these subjects was 3 $\pm$ 0.9 (maximum = 4). The groups did not differ in age. Subjects with SRSP showed lower pNN50, RMSSD, HF n.u., and greater LF n.u. and LF/HF ratio than subjects without SRSP. However, ANOVA revealed no significant differences between subjects with SRSP (TPI > 1) and subjects without SRSP (TPI = 0 to 1) on any of the variables (Table 1).

Pearson correlations (r) on log-transformed variables showed a significant correlation of TPI and pNN50 ($r = -0.548$, $P = 0.043$), HF n.u. ($r = -0.579$, $P = 0.030$), LF n.u. ($r = 0.614$, $P = 0.020$), and LF/HF ratio ($r = 0.593$, $P = 0.025$). Correlations indicated a

Table 1. Values of HF and LF According to Self-Reported Symptoms of Pain

Group	Age (years)	RMSSD†	pNN50†	LF n.u†	HF n.u†	LF/HF ratio
TPI 0 to 1	24.75 (2.38)	89.10 (108.02)	24.12 (21.59)	65.72 (10.72)	34.28 (10.72)	2.33 (1.63)
TPI > 1	23.67 (1.36)	41.22 (22.01)	11.15 (10.31)	75.96 (7.34)	24.04 (7.34)	3.43 (1.10)
P-value	0.340	0.284	0.129	0.067	0.099	0.086
F-value	0.989	1.258	2.659	4.072	3.200	3.497
ES (SMD)	0.557	0.614	0.767	1.163	1.115	0.726
Required N	104	86	56	26	28	62

†Data were log-transformed for analysis.
All values are means and standard deviations in brackets (SD); Stratified groups by total pain index (TPI); RMSSD, square root of the mean squared difference of successive NN intervals; pNN50, the proportion of pairs of successive NNs that differ by more than 50 ms; HF, high frequencies; LF, low frequencies; *P*- and *F*-values refer to analysis of variance (ANOVA); ES, effects size of standardized mean difference; Required N, required n total N for two-tailed t-test given power of 0.80.

positive association of the presence of SRSP with higher LF n.u. and LF/HF ratio and a negative association of the presence of SRSP and lower pNN50 and HF n.u. No significant correlation of TPI and RMSSD ($r = -0.324$, $P = 0.258$) was observed. Effect sizes on standardized mean differences and required sample sizes to reveal significant differences are given in Table 1 (Figure 1).

DISCUSSION

The present study aimed to investigate a possible relation of the ANS activity and the presence of symptoms of pain in apparently healthy young male adults. While there is a huge amount of the literature on the evidence of changes in ANS activity in patients with chronic or recurrent conditions of pain, little alternations of ANS function due to the presence of symptoms of pain in apparently healthy individuals have not been investigated so far. Self-rated symptoms of pain (SRSP) within this study were assessed by four pain-related items of the symptom checklist (SCL-90R). ANS activity, indexed by HRV, was measured for 5 minutes while subjects were sitting on a comfortable chair.

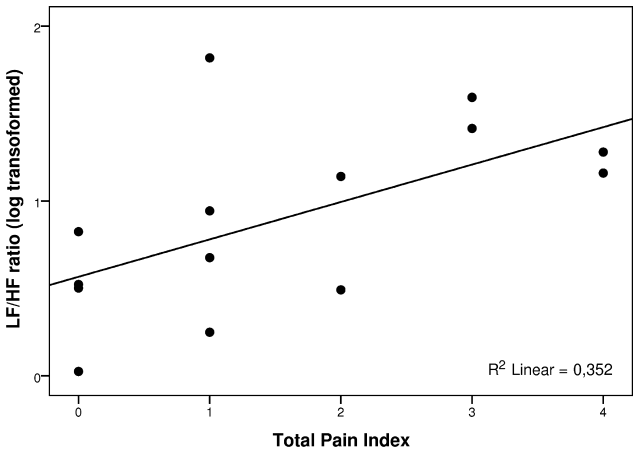

Figure 1. Correlation between low frequency/high frequency (LF/HF) ratio and total pain index.

This exploratory analysis revealed two interesting findings. First, ANS activity in subjects with SRSP and without SRSP shows differences. Second, a correlation between HRV and SRSP was observed. Within the present study, subjects with SRSP showed lower pNN50, lower RMSSD, lower HF n.u. and greater LF n.u., and greater LF/HF ratio compared with pain-free or nearly pain-free subjects. However, none of the differences achieved the set level of significance ($P < 0.05$) due to a possible lack of power within this small sample of subjects. Results were subjected to an *a posteriori* power analysis and effect size calculation to determine the required sample size for future studies (Table 1). Based on these findings, a sample size of 26 to 28 participants is necessary to reveal difference on the frequency domain measures, whereas the time domain measure is less sensitive and requires larger samples.

The RMSSD, the pNN50 components, and the HF spectrum of HRV are vagally mediated and strongly associated with parasympathetic activity. Consistent with findings on clinical subjects with recurrent or chronic pain, HRV and in particular parasympathetic activity in healthy subjects that report symptoms of pain is lowered. Pearson correlations revealed a significant relation of all HRV measures except for RMSSD and the frequency of reported pain symptoms (TPI). The observed negative relation of pNN50 and HF n.u., and the observed positive relation of LF n.u. and LF/HF ratio indicate that subjects with more frequent SRSP show lower pNN50 and HF n.u. on one hand and higher LF n.u. and a greater LF/HF ratio on the other hand. Again, the pNN50 components and the HF spectrum are both an index of parasympathetic activity, supporting the aforementioned decrease in parasympathetic activity in subjects with SRSP.

However, several limitations within the current study need to be addressed. First, the sample consisted of 14 apparently healthy young male adults and therefore these findings might not be generalizable to other

populations. Possible age and gender differences should be addressed within future studies. In particular, age is an important factor in HRV. Future studies should address the relation of the presence of pain symptoms and changes in HRV in older age groups. Furthermore, as all mean HRV measures revealed differences between the groups, but ANOVA failed to achieve significance, the study possibly lacks power. Future studies that investigate a relation of HRV and the presence of self-reported pain in bigger samples are strongly encouraged. Second, we only assessed the frequency of symptoms of pain by self-reports based on four items of a general screening instrument, limited to four pain locations. Future studies of interest are those that assess the severity of symptoms in a variety of locations and the possible contribution of the perceived severity of pain symptoms on changes in ANS function.

To conclude, consistent with evidence on changes in HRV in patients with clinical conditions of chronic or recurrent pain, this is the first study to show that apparently healthy individuals who report symptoms of pain may as well have lower parasympathetic activity revealed by measures of HRV. However, due to the pilot character of the study and the small sample size, further studies are needed to explore the nature of the effects found. Future studies should address different measures to assess SRSP (ie, different locations), corresponding pain-related concepts (ie, catastrophizing), and pain-related behavior (ie, coping, analgesic self-medication) to further investigate their relation to ANS alteration. Furthermore, long-term recordings (ie, 24 hours) of HRV are of potential interest for future studies.

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