

Chronic pain-related changes in cardiovascular regulation and impact on comorbid hypertension in a general population: the Tromsø study

Stephen Bruehl^{a,*}, Roy Bjørkholt Olsen^b, Christian Tronstad^c, Knut Sevre^d, John W. Burns^e, Henrik Schirmer^{f,g,h}, Christopher Sivert Nielsen^{i,j}, Audun Stubhaug^{i,h}, Leiv Arne Rosseland^{h,k}

Abstract

Heart rate variability (HRV) and baroreflex sensitivity (BRS) are indexes reflecting the ability to maintain cardiovascular homeostasis amidst changing conditions. Evidence primarily from small studies suggests that both HRV and BRS may be reduced in individuals with chronic pain (CP), with potential implications for cardiovascular risk. We compared HRV and BRS between individuals with CP (broadly defined) and pain-free controls in a large unselected population sample. Participants were 1143 individuals reporting clinically meaningful CP and 5640 pain-free controls who completed a 106-second cold pressor test (CPT). Participants self-reported hypertension status. Resting HRV and BRS were derived from continuous beat-to-beat blood pressure recordings obtained before and after the CPT. Hierarchical regressions for the pre-CPT period indicated that beyond effects of age, sex, and body mass index, the CP group displayed significantly lower HRV in both the time domain (SDNN and rMSSD) and frequency domain (high-frequency HRV power), as well as lower BRS. Results were somewhat weaker for the post-CPT period. Mediation analyses indicated that for 6 of 7 HRV and BRS measures tested, there were significant indirect (mediated) effects of CP status on the presence of comorbid hypertension via reduced HRV or BRS. Results confirm in the largest and broadest sample tested to date that the presence of CP is linked to impaired cardiovascular regulation and for the first time provide support for the hypothesis that links between CP and comorbid hypertension reported in previous population studies may be due in part to CP-related decrements in cardiovascular regulation.

Keywords: Chronic pain, Hypertension, Cardiovascular, Blood pressure, Heart rate variability, Baroreflex sensitivity

1. Introduction

The cardiovascular and pain regulatory systems are structurally and functionally intertwined.^{6,22} In healthy individuals, these interconnections produce blood pressure (BP)-related hypoalgesia, in which elevated BP triggers reduced pain sensation. Although some work suggests that BP-related hypoalgesia in some cases

may remain intact in individuals with chronic pain (CP),^{24,25} multiple other studies indicate that CP is associated with reduced magnitude of BP-related hypoalgesia,^{5,7,9,10,12,37,40} suggesting possible CP-related impairments in cardiovascular regulatory systems potentially relevant to comorbid cardiovascular risk in CP.

Multiple population studies indicate that CP is linked to increased hypertension risk.^{23,35,36,40,54,65} For example, in the Tromsø Study,⁶⁰ CP was associated with a 23% increased risk of comorbid hypertension, even after adjustment for other risk factors.⁴⁰ Mechanisms contributing to this increased hypertension risk remain incompletely understood. Impaired BP-related hypoalgesia in CP suggests possible hypertension-relevant changes, but these are only detectable at the group level (ie, altered group correlations).⁴⁰

Reduced heart rate variability (HRV) and baroreflex sensitivity (BRS) are known markers for hypertension risk assessable at the individual level.^{14,16,28,30,34,52} Heart rate variability and BRS reflect, respectively, the ability of the cardiovascular system to adjust heart rate and BP efficiently in response to situational demands. Limited evidence from small studies suggests that CP is linked to reductions in BRS of potential mechanistic relevance to hypertension risk.^{1,12,21,48,53} Similarly, recent meta-analyses concluded that CP is associated with reduced overall and high-frequency (HF) HRV, the latter reflecting primarily vagal cardiac input crucial for maintaining cardiovascular homeostasis.^{31,62}

Evidence for CP-related reductions in HRV and BRS is limited mostly to studies in relatively small samples (<100 participants), with HRV conclusions strongly influenced by fibromyalgia studies.⁶² An exception is a large study reporting lower HRV in

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

^a Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA, ^b Department of Anesthesiology, Sorlandet Hospital, Arendal, Norway, Departments of ^c Clinical and Biomedical Engineering and, ^d Cardiology, Oslo University Hospital, Oslo, Norway, ^e Department of Behavioral Science, Rush University, Chicago, IL, USA, ^f Division of Medicine and Laboratory Sciences, Akershus University Hospital, Lørenskog, Norway, ^g Department of Clinical Medicine, University of Tromsø, The Arctic University, Tromsø, Norway, ^h Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, ⁱ Department of Aging, Norwegian Institute of Public Health, Oslo, Norway, Departments of ^j Pain Management and Research and, ^k Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

*Corresponding author. Address: Vanderbilt University Medical Center, 701 Medical Arts Building, 1211 Twenty-First Ave South, Nashville, TN 37212, USA. Tel.: (615) 936-1821; fax: (615) 936-8983. E-mail address: Stephen.Bruehl@vanderbilt.edu (S. Bruehl).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 159 (2018) 119–127

© 2017 International Association for the Study of Pain

<http://dx.doi.org/10.1097/j.pain.0000000000001070>

185 temporomandibular disorder (TMD) pain patients compared with 1633 TMD-free controls.³⁸ The only other large study of this issue reported no mean differences in HRV between 731 patients with chronic widespread pain and 843 controls.² No previous study in a large sample has tested for CP-related differences in BRS, and no studies have directly evaluated whether CP-related changes in HRV or BRS impact on risk of comorbid hypertension in the CP population.

The current study tested in a large population-based sample whether HRV and BRS are diminished in individuals with diverse CP conditions relative to pain-free controls. This study builds on previous work in the Tromsø Study which revealed both elevated hypertension risk and group-level impairments in BP-related hypoalgesia among individuals reporting CP.⁴⁰ We hypothesized that resting HRV and BRS, both before and after a stressor, would be significantly lower in individuals reporting clinically significant CP than in pain-free individuals. We also tested whether sex moderated these effects, given the recent work suggesting greater impairments in HRV among women with CP.⁶⁶ We further hypothesized that greater CP severity would be associated with lower HRV and BRS, if these changes reflect pain-specific cardiovascular dysfunction. Finally, to evaluate clinical relevance of CP-related changes in HRV and BRS, we for the first time tested whether reduced HRV and BRS in individuals with CP mediate reported associations between CP and comorbid hypertension.

2. Methods

2.1. Design

The Tromsø Study is a prospective epidemiologic study of health problems, symptoms, and chronic diseases initiated in 1974. Seven surveys have been conducted 6 to 7 years apart to date, with the seventh completed in October 2016. Tromsø 6 provided the data for the current study,¹⁷ which was approved by the Data Inspectorate of Norway and the Regional Committee of Medical and Health Research Ethics, North Norway. Each participant provided a written informed consent before participation.

2.2. Sample

Tromsø 6 was performed in 2007 to 2008; 19,762 participants of both sexes were invited and 12,982 (65.7%) aged 30 to 87 years participated. Sampling procedures are detailed elsewhere.¹⁷ All participants in Tromsø 6 were asked to participate in the cold pressor test (CPT), although some were turned away due to capacity problems. The total pool of participants undergoing the CPT who were potentially qualified for the current study was $n = 10,566$. From this group, a final pool of potential participants ($n = 8204$) was selected based on the availability of valid continuous BP data sufficient to derive HRV and/or BRS values as described below. Given the study hypotheses, we were interested in comparing the subgroup of individuals experiencing no persistent pain with those experiencing clinically meaningful CP. As in Olsen et al,⁴¹ clinically meaningful CP was operationalized as participants reporting that: (1) they were currently experiencing persistent pain that had lasted for 3 months or more, (2) the pain was experienced daily, and (3) the pain was reported as having a usual severity of at least a 3/10 on a 0 to 10 pain intensity scale (0 = “No Pain” and 10 = “Worst Pain Imaginable”). From the pool of potential participants, $n = 1143$ individuals reporting clinically meaningful CP as defined above were selected for the “Chronic Pain” group, whereas $n = 5640$ individuals reporting no persistent pain were selected as the “Pain-Free” group. The $n = 1421$ individuals not meeting the criteria for either group were excluded from the final

study sample. Characteristics of the final sample are summarized by the participant type in **Table 1**.

2.3. Apparatus

2.3.1. Cold pressor test

Heart rate variability and BRS values are reported for seated rest periods both before and after a CPT to permit the assessment of values at a true resting baseline and again during resting recovery after a cardiovascular and pain stressor (detailed in Olsen et al⁴¹). In brief, the CPT used a 3°C circulating water bath (Julabo PF40-HE; JULABO Labortechnik GmbH, Seelbach, Germany) connected to a 13 L external plexiglass container with a flow rate of 22 L/min. The procedure began by having participants seated in a comfortable chair with instructions to relax for 30 seconds, whereas baseline continuous BP and pulse wave readings were recorded. Then, participants were asked to submerge their dominant hand up to the wrist in the cold water, with instructions to continue until their pain tolerance was reached or the full test was completed (maximum of 106 seconds). After the CPT was completed, a 50-second posttest resting assessment period followed. The mean (SD) duration of the CPT in this study was 90.7 (26.65) seconds in the pain-free group, and 85.2 (30.62) seconds in the chronic pain group ($t[6723] = 5.64, P < 0.001$).

2.3.2. Assessment of heart rate variability and spontaneous baroreflex sensitivity

Although the gold standard for derivation of HRV and BRS is the use of electrocardiograph (ECG) recordings to determine the R-R

Table 1
Descriptive characteristics.

Characteristic	Group	
	Pain-free (n = 5640)	Chronic pain (n = 1143)
Sex (% female)§	47.8	61.2
Age, y	57.19 ± 12.10	57.00 ± 11.21
BMI§	26.79 ± 4.03	27.82 ± 4.62
Reporting hypertension (%)§	24.4	30.5
Usual pain intensity (0-10)	—	5.36 ± 1.65
Number of pain locations (1-14)	—	4.10 ± 2.64
Pre-CPT SDNN§	3.54 ± 0.56	3.47 ± 0.59
Pre-CPT rMSSD§	3.31 ± 0.59	3.24 ± 0.61
Pre-CPT HF power§	10.12 ± 1.14	9.97 ± 1.17
Pre-CPT BRS†	2.31 ± 0.71	2.19 ± 0.69
Post-CPT SDNN§	3.94 ± 0.55	3.88 ± 0.56
Post-CPT rMSSD‡	3.41 ± 0.63	3.35 ± 0.62
Post-CPT HF power*	11.07 ± 1.08	11.00 ± 1.08
Post-CPT BRS§	2.30 ± 0.73	2.20 ± 0.65

Values presented are percentage or mean ± SD. All cardiovascular measures were significantly non-normal in distribution, so were subjected to log transformations. Descriptive statistics reflect these log transformed values that were used in all analyses.

* $P < 0.10$.

† $P < 0.05$.

‡ $P < 0.01$.

§ $P < 0.001$.

BMI, body mass index; BRS, baroreflex sensitivity; CPT, cold pressor test; HF, high frequency; HRV, heart rate variability; SDNN, standard deviation of R-R intervals; rMSSD, root mean square of the successive differences of the R-R intervals.

intervals reflected in both measures, R-R intervals can be estimated using pulse wave data obtained by plethysmography in the course of acquiring continuous noninvasive beat-to-beat BPs.⁵⁰ A systematic review showed that most investigations demonstrated good agreement between HRV estimates based on ECG recordings and estimates derived from plethysmography-based methods during resting conditions such as in the current study.⁵⁰ For consistency of terminology with the larger literature and since their interpretation is the same, values below based on pulse-wave approximations of R-R interval will be referred to as HRV.

Heart rate variability and BRS were derived in this study based on noninvasive beat-to-beat BP and pulse wave data (as an estimate of R-R interval) acquired using a Finometer Pro (Finapres Medical Systems, Amsterdam, the Netherlands). This plethysmography-based device assesses BP by continuous examination of the arterial pressure wave in the middle finger of the nondominant hand. This method has been found to provide reliable and accurate BP values that correlate well with intraarterial BP measurements.²⁷ For preprocessing, artifact correction and data formatting of Finometer data, as well as BRS derivation, Matlab R2015 was used. The Finometer data were cleaned for technical errors using threshold-based rejection of recordings containing nonphysiological values, with sporadic artifacts removed using the procedure described by Deegan et al.¹⁵

Heart rate variability data were processed using the RHRV module (version 4.0) within the R statistical package (<http://rhrv.r-forge.r-project.org/>). Detailed information on processing of the HRV signal and rationale for selection of HRV measures presented below is provided in online supplement 1 (available as supplemental digital content at <http://links.lww.com/PAIN/A487>). The current analyses focused on several HRV measures commonly reported in the pain literature. In the time domain, we report the SD of the R-R intervals (SDNN), a measure of overall HRV, and the root mean square of the successive differences of the R-R intervals (rMSSD). The latter is a measure of short-term variability in HRV, and is believed to reflect primarily vagal cardiac input.^{31,32,59} To derive HRV values in the frequency domain, we used wavelet transform methods (applying the Haar wavelet function; eg, Thurner et al⁶¹), which are free from assumptions of stationarity in biological signals and provide a better temporal resolution, thereby being more suitable for data obtained over shorter assessment periods as in the current study. In the frequency domain, we report only HF power (0.15-0.4 Hz band), which reflects primarily vagal cardiac input. Low frequency power and the low frequency/HF power ratio are not reported because of the questions about their interpretation^{4,49} and concerns regarding unreliability due to the short assessment periods used in this study.

Baroreflex sensitivity values (in milliseconds per mm Hg) were derived using the sequence technique based on procedures described previously.^{3,42} The sequence technique assesses spontaneous BRS in the time domain and has been used in numerous previous studies.^{18,29,43,44,55-58} This technique focuses on the identification of spontaneous ramps in BP (ie, progressive increases or decreases in BP) that are associated with concordant changes in the R-R interval. Thus, BRS reflects the functional efficiency in maintaining stable BP in response to changing conditions. Sequence method BRS derived using R-R intervals estimated using the pulse wave from finger plethysmographic devices (like the Finometer used in the current study) has been found to correspond well with BRS measures derived using ECG recordings when obtained under resting conditions.⁶⁴ The sequence method results in spontaneous BRS values that are

stable across test days.²⁹ Baroreflex sensitivity was derived in the current study from consecutive heartbeats with increasing or decreasing systolic BP and subsequent R-R intervals. The slope of the regression line between the 2 was calculated. Analyzable sequences were considered to be those with at least 3 intervals, nonzero slopes, and displaying correlation coefficients of $r > 0.85$. Baroreflex sensitivity values used in the analyses were then calculated as the mean values of the significant slopes obtained within each assessment period. As an interpretive example, a larger positive BRS slope value would indicate greater increases in the R-R interval (slowing of heart rate) after a preceding rise in BP, indicating greater responsiveness of baroreflex circuits to BP changes and better ability to maintain homeostasis. To enhance the reliability of the BRS index, analyses were restricted to those participants with at least 3 valid BRS sequences during the given recording period (pre-CPT and post-CPT).

2.4. Chronic pain assessment

For CP group participants, usual CP intensity was rated on a 0 to 10 numeric rating scale, anchored with “No Pain” and “Worst Pain Imaginable.” CP participants also reported all body locations in which they experienced CP (from a list of 14 locations; Yes/No format). The number of reported pain locations was summed, creating a variable reflecting the total number of CP locations ranging from 1 to 14. Pain locations assessed were the head, jaw, neck, back, shoulder, arm, hand, hip, leg, foot, chest, stomach, genitals, and skin.

2.5. Procedure

All participants completed 2 self-administered questionnaires, including questions related to CP (https://en.uit.no/prosjekter/prosjekt?p_document_id=104991). Height and weight were measured in centimeters and kilograms, respectively. Body mass index was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

Throughout laboratory testing, participants remained seated in a quiet room and all tests were conducted by a single study technician. The procedures began with participants resting quietly for at least 5 minutes as the CPT procedures were described and the Finometer Pro device placed and calibrated. After this, the study protocol began with recording of continuous cardiovascular data for a 30-second pre-CPT resting assessment period, followed by the CPT task, and a subsequent 50-second post-CPT resting assessment period. Cardiovascular data from the pre-CPT and post-CPT periods were examined in the current study to permit the examination of HRV and BRS both at resting prestressor baseline and during a poststressor resting recovery period. This approach was taken in an effort to provide an internal replication of results from the pre-CPT resting baseline period. Because of evidence that correspondence between pulse waves (used to derive HRV and BRS in the current work) and ECG measures of R-R interval may be poor under nonresting conditions,⁶⁴ cardiovascular values obtained during the CPT task itself were expected to be less reliable and therefore were not analyzed.

2.6. Statistical analyses

Analyses were conducted using SPSS for Windows version 24. All BRS and HRV measures were found to be highly skewed to the right end of the distribution. Tests for violation of normality were significant for all measures (Kolmogorov-Smirnov test; all P 's < 0.001). To address the nonnormality of the cardiovascular

measures, all analyses were conducted using log transformed HRV and BRS values.

Missing data were assumed to be at random, with all available cases meeting the validity criteria included in the primary analyses. These validity criteria were <10% removed beats from a recording during RHRV prefiltering for HRV variables or at least 3 analyzable sequences for BRS. Final sample sizes with fully validated data available for analysis of each class of variables were as follows: pre-CPT HRV variables (pain free: $n = 5432$; CP: $n = 1108$), pre-CPT BRS (pain free: $n = 1291$; CP: $n = 236$), post-CPT HRV variables (pain free: $n = 5157$; CP: $n = 1041$), and post-CPT BRS (pain free: $n = 2953$; CP: $n = 599$). Test-retest reliability between pre-CPT and post-CPT measures was generally high for HRV measures (intraclass correlations = 0.73–0.82). For BRS, the comparable intraclass correlation was 0.44.

Preliminary analyses used χ^2 tests for group differences on dichotomous variables, independent samples t -tests for group differences on continuous variables, and Pearson correlations to evaluate associations between potential confounds and cardiovascular outcomes. Preliminary analyses in the full sample revealed that lower values on HRV and BRS measures were consistently and significantly associated with greater age and body mass index (P 's < 0.001). Age had previously been shown in meta-analyses to significantly influence HRV values.^{31,62} For consistency with planned mediation analyses, which used a regression-based approach, primary analyses used a series of hierarchical linear regressions with the targeted HRV and BRS measures as the dependent variables. In each regression, age and body mass index were entered in the first step to control for their potential confounding effects, main effects of CP status and sex were entered in the second step, and a multiplicative CP status \times sex interaction was entered in the third step (to evaluate moderation by sex of the hypothesized CP effects). In the subsample with CP only, associations between cardiovascular measures and pain severity measures (usual pain intensity ratings and number of painful body sites) were evaluated using partial correlations, controlling for age, sex, and body mass index.

We hypothesized a conceptual model in which previously reported associations between CP and the presence of comorbid hypertension were mediated by lower levels of HRV and BRS in participants with CP. As expected, preliminary analyses indicated that the CP group reported a hypertension diagnosis significantly more often than the pain-free control group (Table 1). This indicated that mediation analyses were justified (ie, there was an effect to be mediated). A series of statistical mediation models was therefore tested (Fig. 1 for the general conceptual model). Because the various HRV and BRS measures were significantly intercorrelated (Table 2), each mediation model evaluated included only a single HRV or BRS measure to avoid issues of multicollinearity. As described by Preacher and Hayes,⁴⁵ assuming that there is an

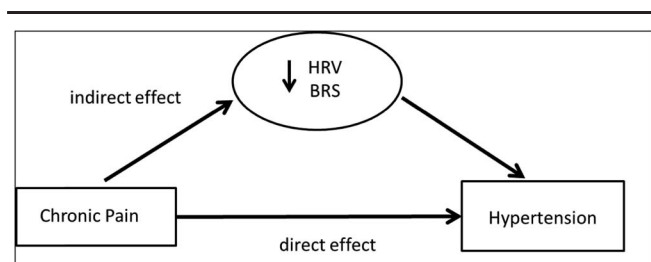


Figure 1. Conceptual figure of sequential mediation models testing the indirect effect of chronic pain status on the presence of comorbid hypertension via heart rate variability or baroreflex sensitivity measures.

effect to be mediated, the presence of mediation is supported if the indirect effects of CP status on hypertension status via HRV or BRS measures were significant. Custom SPSS dialog (the Indirect Procedure; <http://www.afhayes.com/public/indirect.zip>) was used to conduct the mediation analyses. As portrayed in Figure 1, these analyses determined the significance for both the direct effect of CP status on comorbid hypertension status and its indirect effect on hypertension status via HRV or BRS measures. To limit the number of analyses, mediation analyses were limited to those HRV or BRS measures (hypothesized mediators) showing significant associations with CP status in primary analyses. To address potential confounds in a manner similar to primary analyses, all mediation analyses included age, sex, and body mass index as covariates.

In theory, both direct and indirect effects might be significant in the case of partial mediation. The significance of indirect effects was tested using bootstrap estimates that make no assumptions about the distribution of the variables.⁴⁵ This bootstrap methodology was used to test each mediation model in a series of 1000 random subsamples repeatedly drawn from the full sample, generating 95% confidence intervals (bias corrected) around the indirect effect test statistic. If the 95% confidence intervals for the indirect effect generated by the model do not include zero, this indicates that the hypothesized indirect (mediated) effect is significant at the $P < 0.05$ level. Based on previously published empirical power estimates for the bias-corrected bootstrap methodology employed in the current study¹⁹ and assuming small effect sizes for associations between CP status and cardiovascular measures and between cardiovascular measures and hypertension status, a sample size of 462 participants was required to achieve a power of 0.80 to reject the null hypothesis regarding mediation. The current sample size was therefore adequately powered for all mediation analyses conducted.

3. Results

3.1. Sample characteristics

Sample characteristics are summarized in Table 1. Although the CP and pain-free groups were similar in age, the CP group had a significantly higher percentage of women. The CP group also displayed a significantly higher mean body mass index compared to the pain-free group. In addition, subjects in the CP group were significantly more likely to report a diagnosis of hypertension. Ratings of usual pain intensity in the CP group revealed daily pain of moderate intensity, experienced at 4 body locations on average (out of 14 possible locations).

3.2. Heart rate variability and baroreflex sensitivity measures as a function of chronic pain status

Unadjusted mean (\pm SD) values for HRV and BRS measures across groups are presented in Table 1. In all cases, values in the CP group were lower than in the pain-free group. Hierarchical regressions were conducted to examine the effects of CP status on HRV and BRS measures, controlling for potential confounds, as well as to determine whether sex moderated these effects (CP status \times sex interaction). For brevity, results are presented only for the hypothesized effects of interest, although it is noted that results for step 1 in regressions (entry of age and body mass index control variables) were significant at $P < 0.001$ for all HRV and BRS measures.

For the pre-CPT assessment period, regressions revealed significant CP status main effects beyond the influence of age,

Table 2
Intercorrelations between HRV and BRS measures pre-CPT and post-CPT.

Cardiovascular measure	Pre-CPT SDNN	Pre-CPT rMSSD	Pre-CPT HF power	Pre-CPT BRS	Post-CPT SDNN	Post-CPT rMSSD	Post-CPT HF power
Pre-CPT rMSSD	0.85	—	—	—	—	—	—
Pre-CPT HF power	0.91	0.83	—	—	—	—	—
Pre-CPT BRS	0.26	0.34	0.28	—	—	—	—
Post-CPT SDNN	0.58	0.58	0.58	0.38	—	—	—
Post-CPT rMSSD	0.59	0.70	0.62	0.48	0.79	—	—
Post-CPT HF power	0.64	0.65	0.68	0.44	0.91	0.86	—
Post-CPT BRS	0.58	0.63	0.62	0.27	0.89	0.87	0.50

All correlations were $P < 0.001$.

BRS, baroreflex sensitivity; CPT, cold pressor test; HF, high frequency; rMSSD, root mean square of the successive differences of the R-R intervals; SDNN, standard deviation of R-R intervals.

sex, and body mass index on both HRV time domain measures (SDNN: $\beta = -0.033$, $t[6534] = -2.89$, $P = 0.004$; rMSSD: $\beta = -0.036$, $t[6534] = -3.00$, $P = 0.003$). For the pre-CPT HRV frequency domain measure, HF Power, results also revealed significant effects of CP status ($\beta = -0.040$, $t[6530] = -3.52$, $P < 0.001$). A significant CP status main effect on pre-CPT spontaneous BRS was observed as well ($\beta = -0.055$, $t[1521] = -2.13$, $P = 0.033$). The entry of the CP status \times sex interaction into the model in step 3 was not significant in any of these pre-CPT analyses (all P 's > 0.35). Based on the unadjusted mean values and SDs, the corresponding effect sizes for the significant pre-CPT measures were as follows: SDNN: $d = 0.13$; rMSSD: $d = 0.11$; HF HRV: $d = 0.13$; and BRS: $d = 0.17$. By convention,¹³ all of these would be interpreted as small effect sizes.

For the post-CPT assessment period, hierarchical regressions revealed significant CP status main effects (beyond the influence of age, sex, and body mass index) only for the HRV time domain measures (SDNN: $\beta = -0.030$, $t[6192] = -2.53$, $P = 0.011$; rMSSD: $\beta = -0.033$, $t[6192] = -2.66$, $P = 0.008$) and spontaneous BRS ($\beta = -0.041$, $t[3547] = -2.47$, $P = 0.014$). The main effect of CP status for post-CPT HF power was nonsignificant ($\beta = -0.017$, $t[5593] = -1.35$, $P = 0.177$). As for the pre-CPT measures, the entry of the CP status \times sex interaction into the model in step 3 did not reveal significant sex moderation effects for any of the post-CPT measures (all P 's > 0.36). The corresponding effect sizes for the significant post-CPT measures were as follows: SDNN: $d = 0.11$; rMSSD: $d = 0.09$; and BRS: $d = 0.14$. Each of these would be interpreted as a small effect size.¹³

3.3. Associations between heart rate variability, baroreflex sensitivity, and pain-related outcomes

Partial correlations (controlling for age, sex, and body mass index) in the CP subgroup between HRV and BRS measures and ratings of usual pain intensity and number of body locations affected by pain are summarized in **Table 3**. The usual pain intensity showed small but significant (inverse) associations with all measures during the pre-CPT period except spontaneous BRS. In the post-CPT period, only SDNN showed a significant inverse association with usual pain intensity, again of small magnitude. Associations with the number of body sites affected by pain were generally larger in magnitude than for pain intensity, but still small in absolute terms. In all cases, these associations were inverse with significant correlations noted for pre-CPT SDNN, rMSSD, HF power, and post-CPT rMSSD. Overall, the pattern of correlations above indicated that HRV was lower in individuals with CP, which was more severe in intensity or extent.

3.4. Statistical mediation tests

Given the small effect sizes noted for CP-related differences in HRV and BRS, the next question explored was whether these small effects were clinically meaningful. We pursued this question by testing a series of statistical mediation models (the general conceptual model is portrayed in **Fig. 1**), in which CP-related differences in HRV measures or BRS mediated the association between CP status and comorbid hypertension status reported in our previous related work⁴⁰ and other population studies.^{23,35,36,40,54,65} In preliminary analyses, a hypertension diagnosis was significantly more common in those with CP compared with pain-free controls (**Table 1**). Moreover, across both study subgroups, significantly lower values were observed for all HRV and BRS measures in individuals reporting a hypertension diagnosis (all P 's < 0.001). In light of these preliminary findings, mediation tests appeared justified for the following hypothesized mediators: pre-CPT SDNN, pre-CPT rMSSD, pre-CPT HF power, pre-CPT BRS, post-CPT SDNN, post-CPT rMSSD, and post-CPT BRS.

Table 4 summarizes the results of statistical mediation analyses. For each mediation model tested, path coefficients are provided for the IV (CP status) \rightarrow mediator (individual HRV or BRS measure) path, the mediator \rightarrow DV (hypertension status)

Table 3
Partial correlations (controlling for age, sex, and BMI) between HRV and BRS measures, chronic pain intensity, and number of chronic pain sites in the chronic pain subgroup.

Cardiovascular measure	Usual pain intensity	Number of pain sites
Pre-CPT SDNN	-0.07†	-0.11§
Pre-CPT rMSSD	-0.08‡	-0.10§
Pre-CPT HF power	-0.08‡	-0.10§
Pre-CPT BRS	-0.03	0.06
Post-CPT SDNN	-0.07†	-0.04
Post-CPT rMSSD	-0.04	-0.09‡
Post-CPT HF power	-0.06*	-0.04
Post-CPT BRS	0.00	-0.01

All analyses used log transformed values for cardiovascular measures due to significant non-normality. For HRV variables, $n = 945$ to 1083 ; For BRS, $n = 233$ to 593 .

* $P < 0.10$.
† $P < 0.05$.
‡ $P < 0.01$.
§ $P < 0.001$.

BMI, body mass index; BRS, baroreflex sensitivity; CPT, cold pressor test; HF, high frequency HRV, heart rate variability; rMSSD, root mean square of the successive differences of the R-R intervals; SDNN, standard deviation of R-R intervals.

Table 4

Summary of significance of direct and indirect (mediated) effects for sequential mediation models in which the association between chronic pain status and the presence of comorbid hypertension is mediated by each HRV or BRS measure.

Hypothesized mediator	Path coefficients			Indirect effect via HRV or BRS measure, Bootstrap 95% confidence intervals	
	IV → mediator	mediator → DV	Direct effect IV → DV	Lower	Upper
Pre-CPT SDNN	−0.05†	−0.29‡	0.17*	0.0037	0.0289*
Pre-CPT rMSSD	−0.06†	−0.18‡	0.17*	0.0027	0.0217*
Pre-CPT HF power	−0.12†	−0.10‡	0.19*	0.0037	0.0249*
Pre-CPT BRS	−0.11*	−0.05	0.19	−0.0148	0.0406
Post-CPT SDNN	−0.05*	−0.22‡	0.19*	0.0022	0.0232*
Post-CPT rMSSD	−0.05†	−0.20‡	0.19*	0.0027	0.0248*
Post-CPT BRS	−0.08†	−0.15*	0.10	0.0021	0.0317*

To reduce the number of analyses, mediation models were only tested for hypothesized mediators showing a significant association with chronic pain status. All mediation models controlled statistically for the effects of age, sex, and BMI.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

BRS, baroreflex sensitivity; CPT, cold pressor test; HF, high frequency; HRV, heart rate variability; rMSSD, root mean square of the successive differences of the R-R intervals; SDNN, standard deviation of R-R intervals.

path, and the direct effect of IV → DV. The indirect effects were significant (P 's < 0.05) for the path between CP status and comorbid hypertension status via pre-CPT SDNN, pre-CPT rMSSD, pre-CPT HF power, post-CPT SDNN, post-CPT rMSSD, and post-CPT BRS. The indirect effect through pre-CPT BRS was not significant, possibly due to diminished statistical power related to the lower sample size available for this measure. In light of significant direct effects noted in all but one of these mediation models that revealed significant indirect effects, results suggest partial mediation of links between the presence of CP and the presence of comorbid hypertension by the lower HRV and BRS values associated with CP.

4. Discussion

Recent meta-analyses conclude that HRV is significantly reduced in individuals experiencing CP.^{31,62} These meta-analyses indicate that most HRV studies reflect relatively small samples (<100 individuals) and conclude that this literature is heavily influenced by fibromyalgia studies.⁶² One large previous HRV study reported findings consistent with these overall meta-analysis conclusions (185 TMD pain patients, 1633 TMD-free controls).³⁸ Although several small studies had also suggested that BRS was significantly lower in individuals with several specific CP conditions,^{1,12,21,48,53} no large studies with general population samples had previously investigated this issue. Whether findings of reduced HRV and BRS among individuals with CP would extend to an unselected population sample with diverse CP conditions and a broad age range (ages 30–87) was unknown. The current work tested for hypothesized associations between the presence of CP, broadly defined, and reductions in HRV and BRS in the largest sample reported to date.

Results indicated that compared with pain-free controls, the CP group exhibited significantly lower HRV values in both the time domain (SDNN and rMSSD) and the frequency domain (HF power). Group differences were smaller in the post-CPT resting period, likely reflecting residual influence of the CPT, which is known to be a significant cardiovascular stimulus.³⁹ Results in this study indicating significantly lower SDNN, an index of overall HRV, in the CP group are consistent with published meta-analytic results.⁶² Findings of significantly lower values in CP participants

compared with nonpain participants in the current study for both rMSSD and HF HRV are also consistent with the conclusions of previous meta-analyses,^{31,62} with both measures known to reflect primarily vagal cardiac input.³² Unlike recent work reporting significantly greater reductions in SDNN and HF HRV in young women with functional abdominal pain relative to men with functional abdominal pain and healthy controls,⁶⁶ the current work did not find evidence for similar sex moderation in patients with CP broadly defined. This may have been due to the much younger age of the sample in the previous study (young adults) compared with the current general population sample, or possibly to the nonselective CP definition used in the current work.

The effect sizes for HRV values in the current study can be compared with the only similar previous work reporting significant CP-related differences in a relatively large sample.³⁸ In the current work, effect sizes were largest for the pre-CPT resting baseline, with $d = 0.13$ for SDNN, $d = 0.11$ for rMSSD, and $d = 0.13$ for HF HRV. The previous relatively large study of the same cardiovascular measures,³⁸ comparing TMD pain patients to healthy controls, showed effect sizes of $d = 0.18$ for SDNN, $d = 0.17$ for rMSSD, and $d = 0.25$ for HF HRV. As per the guidelines recommended by Cohen,¹³ all effect sizes in the current work represent small effects, with all but rMSSD in the study by Maixner et al.³⁸ also representing small effects. Although there is a general correspondence in the magnitude of HRV differences across these 2 studies, effects sizes were in all cases larger in the TMD study. This may be due in part to the shorter assessment periods for HRV in the current study compared with Maixner et al.³⁸ Meta-regression results suggest an association between shorter HRV assessment periods and smaller effects sizes for CP-related reductions in HRV.³¹

This study is the first to evaluate in a large population sample whether spontaneous resting BRS is significantly decreased in individuals with CP. Results revealed small but statistically significant reductions in BRS in the CP group relative to pain-free controls. Given the known involvement of vagal afferents in baroreflex circuits,⁴⁶ and the fact that both HF HRV and rMSSD primarily reflect vagal cardiac input, findings of lower BRS, HF HRV, and rMSSD in the CP participants all highlight the importance of altered vagal inhibitory function in CP. The pain

relevance of vagal function is shown by evidence that stimulation of vagal activity by electrical stimulation^{11,20} or by activation of baroreceptors tied to vagal afferent circuits⁴⁷ both produce analgesia.

Vagal inhibitory activity as indexed by BRS and HRV measures is relevant not only to pain itself, but also to understanding possible contributors to the comorbid hypertension that has been linked to CP.^{8,23,35,36,40,54,65} Reduced HRV and BRS are known markers for hypertension risk.^{14,16,28,30,34,52} Results of mediation analyses conducted in the current large population sample for the first time suggest that reduced overall HRV (SDNN), vagally mediated HRV specifically (rMSSD, HF Power), and BRS (all tested individually) may mediate associations observed between the presence of CP and the presence of comorbid hypertension. Findings of significant direct effects of CP on comorbid hypertension in the context of significant indirect (mediated) effects suggest partial, rather than full, mediation by CP-related reductions in HRV and BRS.

Reasons for lower HRV and BRS in individuals with CP are not known. One possible contributor is poor conditioning related to lower activity levels that are likely to be more prevalent among those with CP, although the fact that HRV and BRS differences between groups were apparent even when controlling for differences in body mass index, a possible surrogate for general activity levels, might argue against this possibility. It is also possible that mood disorders, such as depression, that are often comorbid with CP⁶³ could contribute to the reduced HRV and BRS associated with CP.^{26,33,51} Finally, we have speculated in the past that ongoing pain itself might disrupt functionally interrelated cardiovascular and pain inhibitory circuits, for example, by depleting opioidergic or alpha-2 adrenergic inhibitory capacity, leading to sympathetically driven BP increases triggered by ongoing pain without adequate compensatory inhibition.⁶ Confirming whether such changes contribute to reduced HRV and BRS, as well as increased hypertension prevalence in those with CP, awaits future exploration.

A recent meta-analysis highlighted the dearth of studies examining associations between HRV measures and CP intensity.⁶² In the current work, small but significant inverse associations, primarily for the resting pre-CPT assessment period, were noted between HRV measures (SDNN, rMSSD, HF power) and both CP intensity and number of CP sites. These parallel findings may best be interpreted as indicating that individuals with more severe CP exhibit greater deficits in HRV. This finding is quite similar to results of 1 smaller study which reported significant correlations between greater CP intensity and lower SDNN in 731 patients with chronic widespread pain.² In contrast to HRV, the association between BRS and pain severity measures was not significant, despite observed associations between the presence of CP (as a dichotomous measure) and lower mean BRS.

Several potential study limitations should be noted. First, short HRV and BRS assessment periods were necessitated in the current work due to the high throughput of patients and time constraints in this very large sample. Short assessment periods may have reduced the reliability of the HRV and BRS measures reported in this work, although test-retest reliability in this study was found to be acceptable for time domain HRV measures and HF power. Meta-analytic results confirm that shorter assessment periods are associated with smaller HRV effect sizes.³¹ Thus, the current results may have underestimated the true difference between the CP and nonpain groups on HRV measures. A second potential limitation is that HRV and BRS values were derived from the Finometer pulse wave rather than actual R-R

intervals (ECG), although these 2 methods correspond well under resting conditions as in the current work.⁵⁰ Reliance on pulse waves may have caused HF HRV in particular to be overestimated.⁵⁰ This, however, should have affected both groups equally, and if anything, might have worked against hypotheses of lower HF HRV in those with CP compared with controls. Both reliance on pulse waves and the short assessment periods may have contributed to the somewhat lower BRS values in the current work compared with past studies. The use of self-reported hypertension diagnoses and CP status also are potential weaknesses, with more detailed assessment of both not feasible due to the scale of the data collection procedures. A final limitation is that mediation results indicate statistical mediation only; all data were collected during the same session. Prospective work assessing HRV and BRS at baseline with subsequent assessment of new-onset hypertension would ideally be conducted to fully support a causal interpretation of the current findings.

In summary, this study found that in a large unselected population sample of very wide age range, the presence of CP (broadly defined) was associated with decreased HRV and BRS relative to the absence of CP, independent of potential confounds. Effect sizes were small, but clinically meaningful. Results consistently supported a model in which risk of hypertension in the CP population derives in part from diminished HRV and BRS associated with CP.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

This project was supported by The Norwegian Research Council, South-Eastern Norway Regional Health Authority and The Norwegian Council on Cardiovascular Diseases, The Norwegian Health Association.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/A487>.

Article history:

Received 12 June 2017

Received in revised form 7 September 2017

Accepted 18 September 2017

Available online 6 October 2017

References

- Adlan AM, Paton JF, Lip GY, Kitas GD, Fisher JP. Increased sympathetic nerve activity and reduced cardiac baroreflex sensitivity in rheumatoid arthritis. *J Physiol* 2017;595:967–81.
- Barakat A, Vogelzangs N, Licht CM, Geenen R, MacFarlane GJ, de Geus EJ, Smit JH, Penninx BW, Dekker J. Dysregulation of the autonomic nervous system and its association with the presence and intensity of chronic widespread pain. *Arthritis Care Res (Hoboken)* 2012;64:1209–16.
- Bertinieri G, di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, Mancia G. A new approach to analysis of the arterial baroreflex. *J Hypertens Suppl* 1985;3:S79–81.
- Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Front Physiol* 2013;4:26.
- Bragdon EE, Light KC, Costello NL, Sigurdsson A, Bunting S, Bhalang K, Maixner W. Group differences in pain modulation: pain-free women

- compared to pain-free men and to women with TMD. *PAIN* 2002;96:227–37.
- [6] Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neurosci Biobehav Rev* 2004;28:395–414.
- [7] Bruehl S, Chung OY, Diedrich L, Diedrich A, Robertson D. The relationship between resting blood pressure and acute pain sensitivity: effects of chronic pain and alpha-2 adrenergic blockade. *J Behav Med* 2008;31:71–80.
- [8] Bruehl S, Chung OY, Jirjis JN, Biridepalli S. Prevalence of clinical hypertension in patients with chronic pain compared to nonpain general medical patients. *Clin J Pain* 2005;21:147–53.
- [9] Bruehl S, Chung OY, Ward P, Johnson B, McCubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. *PAIN* 2002;100:191–201.
- [10] Bruehl S, Dengler-Criss CM, Smith CA, Walker LS. Hypoalgesia related to elevated resting blood pressure is absent in adolescents and young adults with a history of functional abdominal pain. *PAIN* 2010;149:57–63.
- [11] Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception—an experimental study. *Brain Stimul* 2013;6:202–9.
- [12] Chung OY, Bruehl S, Diedrich L, Diedrich A, Chont M, Robertson D. Baroreflex sensitivity associated hypoalgesia in healthy states is altered by chronic pain. *PAIN* 2008;138:87–97.
- [13] Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale: Lawrence Erlbaum, 1988. p. 75–108.
- [14] Dauphinot V, Kossovsky MP, Gueyffier F, Pichot V, Gosse P, Roche F, Barthélémy JC. Impaired baroreflex sensitivity and the risks of new-onset ambulatory hypertension, in an elderly population-based study. *Int J Cardiol* 2013;168:4010–14.
- [15] Deegan BM, O'Connor M, Lyons D, O'Laughlin G. A new blood pressure and heart rate signal analysis technique to assess orthostatic hypotension and its subtypes. *Conf Proc IEEE Eng Med Biol Soc* 2007;2007:935–8.
- [16] Ducher M, Fauvel JP, Cerutti C. Risk profile in hypertension genesis: a five-year follow-up study. *Am J Hypertens* 2006;19:775–80.
- [17] Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of the Tromsø study (Tromsø 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. *Scand J Public Health* 2013;41:65–80.
- [18] France CR. Baroreflex sensitivity during noxious stimulation in vasovagal reactors to blood donation. *Int J Psychophysiol* 1995;19:13–22.
- [19] Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. *Psychol Sci* 2007;18:233–9.
- [20] Frøkjær JB, Bergmann S, Brock C, Madzak A, Farmer AD, Ellrich J, Drewes AM. Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. *Neurogastroenterol Motil* 2016;28:592–8.
- [21] Furlan R, Colombo S, Perego F, Atzeni F, Diana A, Barbic F, Porta A, Pace F, Malliani A, Sarzi-Puttini P. Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *J Rheumatol* 2005;32:1787–93.
- [22] Ghione S. Hypertension-associated hypalgesia: evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. *Hypertension* 1996;28:494–504.
- [23] Gureje O, Akinpelu AO, Uwakwe R, Udofia O, Wakil A. Comorbidity and impact of chronic spinal pain in Nigeria. *Spine* 2007;32:E495–500.
- [24] Hagen K, Stovner LJ, Vatten L, Holmen J, Zwart JA, Bovim G. Blood pressure and risk of headache: a prospective study of 22,685 adults in Norway. *J Neurol Neurosurg Psychiatry* 2002;72:463–6.
- [25] Heuch I, Heuch I, Hagen K, Zwart JA. Does high blood pressure reduce the risk of chronic low back pain? The Nord-Trøndelag Health Study. *Eur J Pain* 2014;18:590–8.
- [26] Hoffmann A, Ettinger U, Reyes Del Paso GA, Duschek S. Executive function and cardiac autonomic regulation in depressive disorders. *Brain Cogn* 2017;118:108–17 [epub ahead of print].
- [27] Hofhuizen C, Lansdorp B, van der Hoeven JG, Scheffer GJ, Lemson J. Validation of noninvasive pulse contour cardiac output using finger arterial pressure in cardiac surgery patients requiring fluid therapy. *J Crit Care* 2014;29:161–5.
- [28] Huikuri HV, Ylitalo A, Pikkujämsä SM, Ikäheimo MJ, Airaksinen KE, Rantala AO, Lilja M, Kesäniemi YA. Heart rate variability in systemic hypertension. *Am J Cardiol* 1996;77:1073–7.
- [29] Iellamo F, Legramante JM, Raimondi G, Castrucci F, Massaro M, Peruzzi G. Evaluation of reproducibility of spontaneous baroreflex sensitivity at rest and during laboratory tests. *J Hypertens* 1996;4:1099–104.
- [30] Kilit C, Pasali Kilit T, Onrat E. Autonomic modulation in hypertension without hypertrophy. *Acta Cardiol* 2015;70:721–7.
- [31] Koenig J, Falvay D, Clamor A, Wagner J, Jarczok MN, Ellis RJ, Weber C, Thayer JF. Pneumogastric (vagus) nerve activity indexed by heart rate variability in chronic pain patients compared to healthy controls: a systematic review and meta-analysis. *Pain Physician* 2016;19:E55–78.
- [32] Koenig J, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF. Heart rate variability and experimentally induced pain in healthy adults: a systematic review. *Eur J Pain* 2014;18:301–14.
- [33] Koenig J, Kemp AH, Beauchaine TP, Thayer JF, Kaess M. Depression and resting state heart rate variability in children and adolescents—a systematic review and meta-analysis. *Clin Psychol Rev* 2016;46:136–50.
- [34] Lantelme P, Khettab F, Custaud MA, Rial MO, Joanny C, Gharib C, Milon H. Spontaneous baroreflex sensitivity: toward an ideal index of cardiovascular risk in hypertension? *J Hypertens* 2002;20:935–44.
- [35] Lee S, Tsang A, Huang YQ, Zhang MY, Liu ZR, He YL, Von Korff M, Kessler RC. Arthritis and physical-mental comorbidity in metropolitan China. *J Psychosom Res* 2007;63:1–7.
- [36] Leveille SG, Zhang Y, McMullen W, Kelly-Hayes M, Felson DT. Sex differences in musculoskeletal pain in older adults. *PAIN* 2005;116:332–8.
- [37] Maixner W, Fillingim R, Kincaid S, Sigurdsson A, Harris MB. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. *Psychosom Med* 1997;59:503–11.
- [38] Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, Knott C, Slade GD, Ohrbach R, Diatchenko L, Fillingim RB. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain* 2011;12:T75–91.
- [39] Mouro L, Bouhaddi M, Regnard J. Effects of the cold pressor test on cardiac autonomic control in normal subjects. *Physiol Res* 2009;58:83–91.
- [40] Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Hypertension prevalence and diminished blood pressure-related hypoalgesia in individuals reporting chronic pain in a general population: the Tromsø study. *PAIN* 2013;154:257–62.
- [41] Olsen RB, Bruehl S, Nielsen CS, Rosseland LA, Eggen AE, Stubhaug A. Chronic pain and cardiovascular stress responses in a general population: the Tromsø study. *J Behav Med* 2014;37:1193–201.
- [42] Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. *J Hypertens* 2000;18:7–19.
- [43] Parati G, DiRienzo M, Mancia G. Dynamic modulation of baroreflex sensitivity in health and disease. *Ann N Y Acad Sci* 2001;940:469–87.
- [44] Persson PB, DiRienzo M, Castiglioni P, Cerutti C, Pagani M, Honzikova N, Akselrod S, Parati G. Time versus frequency domain techniques for assessing baroreflex sensitivity. *J Hypertens* 2001;19:1699–705.
- [45] Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods* 2008;40:879–91.
- [46] Randich A, Maixner W. Interactions between cardiovascular and pain regulatory systems. *Neurosci Biobehav Rev* 1984;8:343–67.
- [47] Rau H, Elbert T. Psychophysiology of arterial baroreceptors and the etiology of hypertension. *Biol Psychiatr* 2001;57:179–201.
- [48] Reyes Del Paso GA, Garrido S, Pulgar A, Martín-Vázquez M, Duschek S. Aberrances in autonomic cardiovascular regulation in fibromyalgia syndrome and their relevance for clinical pain reports. *Psychosom Med* 2010;72:462–70.
- [49] Reyes del Paso GA, Langewitz W, Mulder LJ, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology* 2013;50:477–87.
- [50] Schäfer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability? A review on studies comparing photoplethysmographic technology with an electrocardiogram. *Int J Cardiol* 2013;166:15–29.
- [51] Schumann A, Andrack C, Bär KJ. Differences of sympathetic and parasympathetic modulation in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2017;79:324–31.
- [52] Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension* 1998;32:293–7.
- [53] Spaziani R, Bayati A, Redmond K, Bajaj H, Bienenstock J, Collins SM, Kamath MV. Vagal dysfunction in irritable bowel syndrome assessed by rectal distension and baroreceptor sensitivity. *Neurogastroenterol Motil* 2008;20:336–42.

- [54] Stang PE, Brandenburg NA, Lane MC, Merikangas KR, Von Korff MR, Kessler RC. Mental and physical comorbid conditions and days in role among persons with arthritis. *Psychosom Med* 2006;68:152–8.
- [55] Tank J, Baevski RM, Fender A, Baevski AR, Graves KF, Ploewka K, Weck M. Reference values of indices of spontaneous baroreceptor reflex sensitivity. *Am J Hypertens* 2000;13:268–75.
- [56] Tank J, Jordan J, Diedrich A, Stoffels M, Franke G, Faulhaber HD, Luft FC, Busjahn A. Genetic influences on baroreflex function in normal twins. *Hypertension* 2001;37:907–10.
- [57] Tank J, Schroeder C, Stoffels M, Diedrich A, Sharma AM, Luft FC, Jordan J. Pressor effect of water drinking in tetraplegic patients may be a spinal reflex. *Hypertension* 2003;41:1234–9.
- [58] Tank J, Toka O, Toka HR, Jordan J, Diedrich A, Busjahn A, Luft FC. Autonomic nervous system function in patients with monogenic hypertension and brachydactyly: a field study in north-eastern Turkey. *J Hum Hypertens* 2001b;15:787–92.
- [59] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–65.
- [60] The Tromsø Study. Available at: www.tromsostudy.com. Accessed May 5, 2017.
- [61] Thurner S, Feurstein MC, Teich MC. Multiresolution wavelet analysis of heartbeat intervals discriminates healthy patients from those with cardiac pathology. *Phys Rev Lett* 1998;80:1544–7.
- [62] Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. *PAIN* 2016;157:7–29.
- [63] Velly AM, Mohit S. Epidemiology of pain and relation to psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2017. doi: 10.1016/j.pnpbp.2017.05.012 [epub ahead of print].
- [64] Viehweg J, Reimann M, Gasch J, Rüdiger H, Ziemssen T. Comparison of baroreflex sensitivity estimated from ECG R-R and inter-systolic intervals obtained by finger plethysmography and radial tonometry. *J Neural Transm (Vienna)* 2016;123:481–90.
- [65] Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *PAIN* 2005;113:331–9.
- [66] Walker LS, Stone A, Smith CA, Bruehl S, Garber J, Puzanovova M, Diedrich A. Driving without brakes? Young women with functional abdominal pain have low heart rate variability and reduced parasympathetic control of physiological arousal. *PAIN* 2017;158:1509–16.