Physiology & Behavior 152 (2015) 203–216

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Cardiovascular activity and chronic pain severity

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HIGHLIGHTS

- Chronic pain sensation severity affects orienting cardiovascular response.
- Severity of pain sensitization affects early orthostatic cardiovascular response.
- Severity of emotional distress affects late orthostatic cardiovascular response.
- MMPI-2 results demonstrate three-cluster solution for the cardiovascular activities.

ARTICLE INFO

Article history:
Received 26 April 2015
Received in revised form 9 August 2015
Accepted 29 September 2015
Available online 3 October 2015

Keywords:
Chronic pain severity
Emotional distress
Pain magnification
Blood pressure
Orthostatic stress
Orienting behavior

ABSTRACT

Objective: Objective markers of chronic pain severity are needed when examining and treating patients with chronic pain whose suffering may be overstated or underestimated. This study tested a hypothesis that the strength of cardiovascular (CV) reactivity in response to a social evaluative threat and orthostatic challenge is a reliable index of severity of pain-related complaints.
Methods: Measurement of CV reactivity and response styles in 34 men and 16 women with chronic pain from different bodily injuries, were retrieved from a larger database of patients. Measurement of CV reactivity in response to a postural challenge was repeated twice (sessions 1 and 2) on the same day of a medical examination which includes a psychosocial evaluation.
Results: A decrease in systolic blood pressure (SBP) from session 1 to session 2 was found in subjects with low pain severity scores, but not in those with high pain severity scores. High scores for pain catastrophizing/magnification and pain-related emotional distress were independently associated respectively with a SBP increase at an early-point in time and a SBP decrease at a mid-point in time after standing up from lying down. Stronger heart rate reactivity responses to orthostatic challenge indicated greater protection against the presence of these chronic pain symptoms.
Conclusions: This biobehavioral protocol enables measurement of chronic pain suffering and protection in three dimensions: physical, emotional, and cognitive.

1. Introduction

Clinical indices of disease severity, body impairment, and nociception using traditional physical, morphologic, imaging, or serologic examination protocols are only weakly related to self-reports of chronic pain severity, frequency and number of pain episodes, and disabling functional impairments [1–3]. The challenge is especially relevant in children, older adults, and persons with limited education or ability to communicate [4,5] and in individuals with traumatic brain injuries, residual post-concussive syndromes and PTSD, dementia, post-stroke syndromes, neuropathic pain syndromes, somatoform pain disorders, and personality disorders [6–11] whose self-reported suffering related to chronic pain may be intentionally or unintentionally misrepresented as a consequence of "illness behavior" [12].

Prior studies have emphasized the importance of pain in blood pressure (BP) regulation [13–17]. They show that pain modulates the activity of neurons responsible for controlling baroreceptor responses and that pain may increase hypertension risk in people with chronic pain. Neural components mediating baroreceptor and nociceptive signals are functionally intertwined within the nervous system [18–20]. Evidence suggests that nociceptive stimulation increases BP by attenuating the cardiac baroreflex and by increasing sympathetic nervous system activity [21–23]. Resting systolic BP (SBP) and baroreceptor sensitivity were positively related to pain threshold and tolerance in healthy people [24,25]. However, these relationships are not present in young patients with chronic pain [26]. In older patients with chronic pain, the relationships

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http://dx.doi.org/10.1016/j.physbeh.2015.09.029

between resting SBP and the pain sensation measures are already negative, and higher resting SBP is already associated with lower baroreceptor sensitivity [25]. Taken together, these findings suggest that pain chronicity may moderate the relationship between baroreflex mechanisms regulating BP and pain sensation intensity.

Postural (orthostatic) change from lying to standing is a gravity induced biological challenge that triggers several successive evolutionary-developed physiological processes for maintaining BP level. It corresponds to alertness behavior most activated when standing up to protect against light-headedness and fainting [27–29]. Baroreceptors play a primary role in controlling these processes by causing both parasympathetic withdrawal and sympathetic activation [30–32]. Systolic blood pressure fluctuations in earlier response to orthostatic challenge (around the 1st minute after standing up) were found to correlate with pharmacological and non-pharmacological indicators of baroreflex functioning [33]. Deeper and delayed orthostatic fall was associated with lower baroreceptor sensitivity or transfer gain function. Other baroreflex mechanisms like cardiac and vascular baroreflex resetting (vagal withdrawal and sympathetic activation) can also be involved in blood pressure regulation during orthostasis [32] and all these mechanisms may be impaired in patients with chronic pain [34].

A study of orthostatic cardiovascular (CV) responses in chronic pain patients found that the ability to enhance sympathetic activation of blood vessels and the withdrawal of vagal modulation of the sinoatrial node for maintaining BP level is significantly reduced [35]. Poor orthostatic CV reactivity (CVR) is considered to result from inadequate triggering of baroreflex mechanisms that regulate common arousal- and pain-related (analgesic/sedative) systems in those experiencing greater chronic pain [36–38]. A weak orthostatic CVR and its inversion due to (de)conditioning (i.e., higher CV activity when lying down compared with standing posture) is found to be a reliable marker or predictor of difference and change in both somatic and mental health [27,39,40]. This CVR regulated by baroreflex activity may also be associated with the emotional component of chronic pain as a general physiological response to the negative affect associated with stressful events [27,41,42]. A weak or flattened CVR in response to psychological challenges like mental concentrations and social evaluative threat in patients with chronic pain may also use the same baroreflex mechanisms coupling its impairment with severity and/or duration of chronic pain [43,44].

Pain is a complex experience associated with sensory events, emotions, thoughts, and physical and interpersonal actions; and with no valid and reliable method of 'objective' quantification at present [45]. Therefore, we relied mainly on self-report measures as the 'gold standard' to determine the relationships between chronic pain and physiological measures. Sensory or nociceptive experience (pain severity including pain intensity and frequency), experience of negative affect (pain distress or unpleasantness associated with anxiety, depression, irritation, and overall negative mood), experience of negative cognition or thought disorganization (e.g., pain catastrophizing including helplessness, rumination, and magnification), and experience of physical (functional) and psychosocial (interpersonal) behavioral problems have been considered as core experiential dimensions caused by chronic pain [45,46]. Thus the pain experience should be assessed in a complex way and subjective scales should be selected specifically relevant for the subjects and objectives of study. Most recommendations for chronic pain assessment tools have been provided for clinical trials and vary depending on specific patient populations and objectives [47,48]. Instruments that are legally encouraged for use, have a normative database in the specific population of injured workers with chronic pain, and cover all the above mentioned core experiential dimensions of chronic pain were included in this study [49–52]. Some of these instruments measure several dimensions of pain with differing combinations of intensity, affect, interference with functioning and thoughts and certain overlapping was expected, assessed, and controlled for.

This study evaluates group data from injured workers with chronic pain. It aims to test the hypothesis that an altered (reduced, inverted, or unstable) CVR in response to physical (orthostatic) and mental (psychosocial evaluation) stress conditions are related to greater severity of chronic pain-related complaints, i.e., its sensational, emotional, cognitive, and behavioral components. The second objective of this study is to evaluate the independence or uniqueness of these chronic pain's components in their impact on these CV responses. Scales that measure behavior, emotional response styles, and maladaptive behavioral responses in this clinical population are evaluated as possible mediators and moderators of these relationships.

2. Materials and methods

2.1. Data source

This study relies on clinical and laboratory data obtained from mandated medical-legal examinations (MLEs) of injured workers with litigated disability claims. The selected population has several salient characteristics [53], which provide researchers with several advantages in achieving previously mentioned objectives: (i) the litigating process gives unsolicited access to people with remarkably diverse etiological and pathological sources of chronic pain and its severity. This helps generalize the expected findings of a common biomarker of severity, i.e. the CVR indicator of maladaptive neuroplastic change in pain control, to different patients with chronic noncancer pain [18,54]; (ii) the examining doctor is a neutral panel qualified medical examiner (PQME) typically given carte blanche authority to perform whatever diagnostic tests are required short of authorizing hospitalization; and (iii) injured workers are legally required to attend this examination but nonetheless asked to initially give written informed consent regarding no privacy, confidentiality, or future treatment relationship. The MLEs were performed by a PQME according to the California Labor Code mandates for medical–legal examinations. At no point in time was the injured worker ever identified as a research subject participating in a research study. MLEs of injured workers with a litigated injury claim are not voluntary.

The situation under which all subjects were being examined could bias self-reports of pain severity. Validity MMPI-2 scales were used (see below) to control for this bias as recommended in this population [55]. We used these validity scores in mediation and moderation analyses for assessing if an over- or under-reporting strategy of subjects produces/mediates or biases/modifies the expected relationships between CVR and pain scores. It allowed us to additionally evaluate the reliability of CVR metrics when assessing chronic pain severity.

Survey data of MLEs over the past 3 years are retrospectively analyzed to study relationships between subjective measures of pain and functional disability with orthostatic CV measures. The CV measures were included in the PQME's assessment protocol to provide a physiological measure of individual resilience to adversity, i.e., occupational injuries [27,28,56]. The CV measurement procedure was not considered at the time for studying or evaluating chronic pain. The approval for publishing this study was received from the institutional review board (IRB) of the University of California, Los Angeles (UCLA).

2.2. Procedures.

All the data examined in this study are from injured workers with litigated disputed injury claims mandated to be examined by SP as a PQME. 100% presented with chronic pain. MLEs are typically conducted over the course of two days, usually several weeks apart. This enabled a test-retest clinical assessment protocol. Day one (D-1) assessments were conducted by a trained technician who supervised administration of self-report standardized depression, anxiety, and pain questionnaires including self-reports of functional impairments. The trained technician also administered the CV measurement protocol and supervised completion of computer-administered psychodiagnostic and neurocognitive tests by subjects. Day two (D-2) assessments were conducted by the PQME. They included an extensive face-to-face medical-legal neuropsychiatric

and chronic pain medicine examination of a subject's symptomatic distress and functional impairments with respect to an alleged psychiatric injury (see details in [53]). Repeat administration of questionnaires and neurocognitive testing excluding CV measurement protocol was conducted when determined to be clinically necessary. Typically, both D-1 and D-2 required approximately 6 hours or more of subject participation on successive days including allowance for personal time needs.

The history obtained from subjects included completion of a self-reported comprehensive standardized medical assessment of physical and mental states with detailed questions about family, developmental, childhood, educational, functional, employment, and psychosocial history, past medical, surgical, and injury history, current symptoms, and current and past medications needed for diagnosis, pain management, and other conditions. The subjects also completed standardized questionnaires to assess severity of functional impairments with respect to activities of daily living (ADL).

Cases were selected for inclusion in analyses if they contained a complete set of CV readings collected during D-1 together with any measure of individual physical sensation, emotional, cognitive and behavioral response styles surrounding their chronic pain. This includes: pain sensation severity, pain-related emotional distress, pain catastrophizing cognition (helplessness, rumination, magnification), and pain-related disability (see below). Fifty individual (16 women) records out of 205 inspected cases met the inclusion criteria and all were accepted for analyses.

2.3. Demographic, medical, and injury characteristics

General demographic, health, cardiovascular, injury, pain, and disability characteristics of the selected subjects are presented in Table 1. All selected subjects included in the study received "usual treatment" in a health-care delivery system that was legislatively driven and litigious with an emphasis on cost-containment. When subjects were maximally medically improved, whole person impairment (WPI) was quantitatively rated from 0%–100%.

Some participants were taking major classes of anti-hypertensive medications (6%, e.g., angiotensin II receptor antagonist, angiotensin-converting enzyme inhibitor, selective β1 receptor antagonist) and psychotropic medications (20%, e.g., barbiturates, tricyclic, atypical or noradrenergic and specific serotonergic antidepressants, benzodiazepines, selective serotonin or serotonin-norepinephrine reuptake inhibitors, antidepressant, atypical antipsychotic). Diagnostically most participants (84%) were given the DSM IV diagnosis of "Pain Disorder Associated With Both Psychological Factors and a General Medical Condition." Included general medical conditions involve multiple (from 2 to 9) body regions (e.g., head, jaw, neck, hands, arms, elbows, forearms, wrists, fingers, upper back and shoulders, mid back, lower back, chest, abdomen, pubic area, buttock, legs, hamstrings, knees, shins, calves, feet, soles, and/or toes). Other participants had mild traumatic brain injury, generalized anxiety-like disorder due to a general medical condition, or major depressive mood disorder.

2.4. Chronic pain measures

The Ratings Determining Impairment Associated with Pain (RDIP) consists of 26 numerical rating scales assessing pain severity (chronic pain experience as a physical sensation including current, worst, average, aggravated pain intensity and the frequency of pain experience[1]; 5 scales; range from 0 to 20), and its effects on mood (pain emotional distress including feeling anxious, depressed, irritable, and overall affected; 5 scales; range from 0 to 10) and activity (pain activity limitation including social and physical behavior; 16 scales; range from 0 to 30) with a total score ranging from 0 to 60 [49]. This instrument from the AMA Guides for the Evaluation of Permanent Impairment, Fifth Edition is legally encouraged for use and found to be a reliable alternative to a clinician-derived behavioral instrument, the Physical Performance Test [57].

The Pain Catastrophizing Scale (PCS) consists of 13 five-point scales (from 0, not at all, to 4, all the time) assessing pain as a negative cognition (total scores range from 0 to 52) with the tendency (i) to magnify, heighten, or exaggerate the threat value of pain stimulus or pain sensations (range 0–12; a 'magnification' subscale), (ii) to perceive oneself as unable to cope with pain symptoms (i.e., feel helpless in the context of pain; range 0–24; a 'helplessness' subscale), and (iii) to a relative inability to inhibit pain-related thoughts in anticipation of, during, or following a painful encounter (i.e., rumination with excessive focus on pain sensations; range 0–16, a 'rumination' subscale) [58–60]. Raw scores were converted to percentiles, which were further used in analyses. Percentiles of PCS raw scores were suggested to be used in this population [50]. The percentile scores are derived from a large sample of injured workers of both sexes with a mean age of 42.2 years (range 17 to 63 years) who had initiated litigated claims via retained attorneys in response to disputed injuries by employers. Individuals who score between the 50th and 75th percentiles on the PCS are considered at

Table 1
General demographic, health, cardiovascular, injury, pain, and disability characteristics of the study's sample.

Variables		Estimates (mean [SD])
Age (years at examination)		47.4 (10.9)
Sex	Female (N)	16
	Male (N)	34
Race	White (N)	44
	Non-White (N)	6
Ethnicity	Hispanic (N)	21
	Non-Hispanic White (N)	23
	African (N)	6
Education (years)		11.8 (3.5)
Body mass index (kg/cm^2)		31.3 (5.8)
Systolic blood pressure (mm Hg)		126.5 (15.1)
Diastolic blood pressure (mm Hg)		79.7 (8.7)
Mean arterial pressure (mm Hg)		95.3 (10.3)
Pulse pressure (mm Hg)		46.8 (9.7)
Heart rate (bpm)		73.9 (12.0)
Rate pressure product (bpm * mm Hg)		9357.0 (1964.1)
Variables		Estimates (mean [SD])
Period from injury to examination (months)		40.1 (25.5)
Whole Person Impairment score[a]		42.1 (8.2)
Cumulative trauma or distress	Yes (N) [months]	25 (72.0)
	No (N)	25
Pain severity by RDIP		13.8 (4.6)
Pain-related emotional distress by RDIP		6.0 (2.7)
Pain-related activity interference by RDIP		15.6 (7.4)
General pain-related impairment by RDIP		35.3 (12.9)
Pain-related rumination by PCS		60.2 (33.8)
Pain-related helplessness by PCS		63.1 (30.8)
Pain-related magnification by PCS		66.3 (30.4)
General pain-related catastrophizing by PCS		61.6 (32.9)
Functional disability by PDQ		51.0 (22.2)
Psychosocial disability by PDQ		38.4 (14.4)
General disability by PDQ		89.4 (34.6)
Functional disability by ODI (%)		45.6 (13.2)

RDIP — Ratings Determining Impairment associated with Pain [49]; PCS — Pain Catastrophizing Scale (scores are presented in percentiles) [58,59]; PDQ — Pain Disability Questionnaire [51,52]; ODI — Oswestry Disability Index [51,65].

[a] Whole Person Impairment score was clinically evaluated by the medical examiner according to the California Labor Code mandates for medical–legal examinations.

[1] Frequency of pain experience as a 'burdening' component of chronic pain experience has main impacts on calculating the total score of chronic pain severity than other separate scales assessing current, worst, average, and aggravated pain intensity integrated in a 'magnitude' component of chronic pain experience [49] and on significant profile and mediation effects of the total score of chronic pain severity obtained in this study (data not shown).

moderate risk for the development of chronicity. Individuals who score above the 75th percentile would be considered at high risk for the development of chronicity.

Whereas other broader measures of affect (depression and anxiety) include both fluctuations in positive and negative affect dimensions in general, the PCS exclusively measures the extent to which pain exaggerates negative self-esteem or belief (i.e., pain's impact on subject's pessimistic view) in cognitive, behavioral, affective, and social domains [60,61]. Catastrophizing is a personal assessment of impaired coping ability with pain as a stressor that threatens health, well-being, and quality of life in contrast to pain coping self-efficacy. This factor has been shown to contribute to pain-related disability beyond the variance accounted for by pain intensity itself [62]. Though some neurophysiological findings showed independence of pain catastrophizing from the actual pain status, it is not always evident whether a patient's emotional distress (negative affectivity) and catastrophizing (negative cognition) actually overlap and reflect the same domain. Therefore the concept and terms 'catastrophizing', 'magnification', 'helplessness', and 'rumination' with respect to "chronic pain and the brain" disorders have been considered controversial [63,64]. The present study was considered to also test the possible independence between pain catastrophizing and pain emotional distress with a multiple regression analysis. It allows for partitioning the total variance into the variances (reflected in regression coefficients or partial slopes) uniquely explained by each predictor variable (e.g., pain catastrophizing) independently of other, i.e., statistically controlled, predictors (e.g., pain emotional distress).

2.5. Disability measures

The Pain Disability Questionnaire (PDQ) consists of 15 numerical rating scales (ranging from 0 to 10) assessing the association of pain with generalized functional (ability/disability) status (PDQ_f; range from 0 to 90) and psychosocial behavior activity (PDQ_p; range from 0 to 60) with the total ranging from 0 to 150. It was specifically developed to measure the association of chronic functional impairment with musculoskeletal disorders attributed to pain and demonstrates a higher degree of responsiveness compared to other disability scales [51,52]. At present, ratings of pain-related impairment and WPI (whole person impairment) are based on PDQ [49]. A degree of pain control was extracted from item 9 of PDQ and was used as an additional separate covariate in the models of pain and CV relationships.

The Oswestry Disability Index [ODI] (also known as the Oswestry Low Back Pain Disability Questionnaire) is the oldest instrument that researchers and disability evaluators use to measure a patient's permanent functional status and disability associated with low back pain focusing primarily on the physical activities of daily living, with only minimal attention given to psychosocial factors [51,65].

2.6. Covariates

Besides demographic variables (age, sex, and BMI) and a period from injury to examination (duration of chronic pain or pain chronicity; months), several scales estimating quality of life (mental, physical, and functional health status; 36-Item Short Form Health Survey [SF36]), mood and sleep problems (e.g., Patient Health Questionnaire [PHQ-9] and Pittsburgh Sleep Quality Index [PSQI]), personality traits or dispositions (e.g., Personality Psychopathology Five and Broad Personality Characteristics subscales of Minnesota Multiphasic Personality Inventory-2 [MMPI-2]) and individual response styles (e.g., Validity scales of MMPI-2) were serially included in statistical models to evaluate their possible confounding, mediating, or moderating effects on relationships between pain and CV measures. A full list of scales and their subscales, which were used as covariates, is presented in Supplementary data (Table 1S). Administration of multiple questionnaires provided the assessment of consistency of responding. At the time of the interview, some subjects were also examined with other psychosocial instruments with overlapping questions, which were not considered in the present study (see supplementary Table 2S). Those questionnaires were not selected for this pilot study, because they were either less standardized, or presented only occasionally in the database of this sample: i.e., they were included in the MLE later or were canceled earlier (as redundant) by SP, than the time when cardiovascular protocol was accepted by him for the MLE.

Current use of specific antihypertensive agents, psychotropic drugs, and other pain medicines including opioids was recorded, but not considered as covariates in the present study, because these drugs did not constitute sufficient groups for the control of their specific effects as fixed factors. Their possible effects were considered as a random factor in the present study. Moreover, a large population and prospective study showed no significant moderating effect of these drugs on relationships between similar measures of affective condition and orthostatic and orienting CV responses [27]. All subjects included in the study had been under pain control treatment. Degree of pain control by medication or a non-drug method of treatment was examined as a possible covariate.

2.7. Cardiovascular measures

Systolic and diastolic blood pressures (SBP and DBP) and heart rate (HR) were recorded in the left arm with a digital automated sphygmomanometer (HEM-7220-ZCS, OMRON Corp., Kyoto, Japan) during a specially designed 2 × 2 CV measurement protocol, which integrated previously suggested procedures for the measurement of CV changes in response to orthostatic and psychosocial challenges [27,40]. In the present design the MLE protocol, including a complex of cognition, emotion and behavior evaluation tests, having to recall traumatic injuries followed by periods of being unable to work introduces a psychosocial evaluation stress or challenge to the subject. This satisfies meeting the respective formal criteria: i.e., the combination of (i) elements of uncontrollability and (ii) high levels of social-evaluative threat [66]. This methodological conceptualisation was based on our previous findings of the stressfulness of a similar interview in a general population [27]. It was confirmed by a measure of cardiac metabolic activity (rate-pressure product) that indicated higher values before and lower values after the interview comparable to those in response to orthostatic stress. Other studies have also indicated that higher values of rate-pressure product can be similarly induced by physical and mental stressors [67,68]. Moreover, both interview and orthostatic responses were also concordant in predicting mean scores and changes of mood across 4-years [27]. This allowed not having to introduce another social threat task to assess CVR in response to psychosocial evaluation stress.

The CV measurement protocol was administered on the first day (Day 1) of the MLE. It consisted of two sessions. Session 1 was an initial ('orienting') measurement session conducted in the morning shortly after the subject's arrival. Session 2, the afternoon session, was conducted at the end of Day 1 upon completion of computer administered psychodiagnostic testing, i.e. the MMPI-2 and completion of self-report questionnaires (i.e., 'after habituation or sensitization to examination'). CV changes between the two sessions were considered to represent an individual's capability for regulating (increasing or inhibiting) arousal associated with orienting/habituation behavior in response to a psychosocial challenge, which may be impaired in chronic pain [69–71]. The time between the two sessions was estimated for a possible moderation effect.

At both sessions, the subject was challenged with the same orthostatic procedure: postural change from a period of lying down with eyes closed for 6–8 min to standing up with eyes open for the next 6–8 min. CV activity was measured 4 times during the lying posture and then 4 times after standing up with intervals of at least 1 min between the readings at each session based on clinical concern that cardiovascular activity stabilized. Standing posture was taken a minute after the last CV reading during lying. Impairments in baroreflex regulation of CV arousal during this orthostatic process was indexed by CV changes (i) between postures

averaged across respective CV readings of both sessions and (ii) within postures (i.e., between CV readings) of both sessions. CV changes between and within postures were considered to represent an individual's capability for regulating (increasing and inhibiting) arousal associated with level of alertness in response to posture changes, which may be impaired in chronic pain [35].

The subject remained still, and neither the subject nor the technician talked during the CV measurements. No direct pain measurements were performed in any positions. In both positions the cuff was at the same level as the subject's heart. Sixteen single readings of SBP, DBP and HR with date and time of records were obtained for each subject. Additional CV measures (mean arterial pressure [MAP = DBP + (SBP − DBP) / 3], pulse pressure [PP = SBP − DBP], rate-pressure product [RP = HR * SBP]) were calculated and included in the analyses.

Different CV or hemodynamic variables (SBP, DBP, HR, MAP, PP, and RP) were selected to evaluate relationships between pain measures and the reactivity of CV system with respect to different psychophysiological and physiological mechanisms. For example, SBP and DBP variations were previously found to be independently related to positive or negative affect regulation, to psychosocial (interviewing) or physical (orthostatic) challenge, and to low or high intensity exercise, respectively [27,41,72]. Variation of HR reactivity was found to be significantly related to bodily sensation associated with an approach-avoidance motivational dimension and was also used as a psychosomatic fitness measure [73–75].

Reactivity of other CV measures (MAP, PP, and RP) were evaluated to detect the transfer of independent CV activities to integrative hemodynamic processes. For example, RP detects reciprocal or unidirectional integrative change in mechanisms determining SBP and HR responses to challenges and distinguishes conditions with more energy cost or more energy economic cardiac metabolism. From a wide variety of hemodynamic measurements, RP reactivity or RP reserve has been previously found to be the strongest predictor of cardiovascular mortality and mood change [27,76–78]. The MAP can be conceptualized as the sum of central venous pressure and the product of systemic vascular resistance and cardiac output. The PP is proportional to stroke volume and inversely proportional to the compliance of the aorta and peripheral resistance. MAP and PP responses can exhibit, respectively, absolute and relative reciprocal or unidirectional integrative change in mechanisms determining cardiac and vascular responses to challenges.

2.8. Statistical analysis

Descriptive and inferential analyses were performed by SPSS (SPSS Science, Chicago, IL) using Pearson product–moment correlation, General Linear Models by Type III method (GLM) and an additional SPSS macro command set to evaluate significance and confidential intervals of moderation (by Johnson–Neyman technique) and mediation (by bootstrapping) effects of regression analyses [79]. Differences at $p < .05$ were regarded as significant. All parameter estimates are expressed as non-standardized (B) regression coefficients and their standard errors (SE). Where necessary, a partial η^2 was reported as a measure of strength of association (effect size), which is comparable to R^2 expressing the percentage of explained variance. Sex as categorical, and age and BMI as quantitative variables were included in all models to adjust for these factors.

To provide evidence for conceptual validity of effects (i.e., to decrease the risk of making Type I and Type II errors; (74)), the main hypothesis and related findings of relationships between CV and pain variables were tested in a first group of analyses using three different statistical models or analytic approaches (see Figure 1S in Supplementary data): profile and trend analyses using the GLM procedure (trend analyses are presented in Text 1S in Supplementary data), and mediation analysis using the bootstrap procedure.

The GLM procedure of the first group of analyses was conducted with repeated readings (measures) of CV (SBP, DBP, HR, MAP, PP, and RP) treated as continuous dependent variables representing multiple measurements to test interaction effects between 3 within-subject factors (factor 1: 2 Sessions as 2 points of orthostatic challenge nested within [before and at the end of] psychosocial challenge; factor 2: 2 Postures as 2 points of orthostatic lying-to-standing challenge; and factor 3: 4 Readings as 4 points of CV readings during each posture) and subjective pain-related ratings also treated as continuous independent variables. The GLM Repeated Measures procedure provided multivariate analyses of interaction effects of these within-subject challenge factors and subjective pain measures on CV changes (e.g., Session * Pain severity, Posture * Readings * Pain distress, Posture * Pain chronicity or Session * Posture * Readings * Pain catastrophizing) as profile analyses. These profile analyses tested the 'parallelism' null hypothesis [80], which asked whether CV changes between sessions, postures, or readings showed the same pattern (i.e., similar profile) with respect to individual differences in the subjective variables. The multivariate approach to repeated measures does not require the compound symmetry and sphericity assumptions. All multivariate F values were obtained by the Pillai's Trace statistic, which is equivalent to partial η^2 and R^2 measures of effect size, and tolerant of the violation of homogeneity of variance-covariance matrices.

Simpler post-hoc regression models within the first group of analyses were used to inspect those relationships, which were found significant by more complex (profile) analyses to detect the CV changes (differences between separate pairs of CV readings) with maximum impact in the effects. In addition, significant relationships were evaluated for cut-off points for respective pain severity, pain distress, and pain catastrophizing scales, and the period of pain chronicity/duration giving the best-fitting models (selected by Akaike Information Criterion) for presenting these relationships in figures with possible clinical implications.

Mediation models of the first group of analyses were applied to evaluate causality relationships between CV reactivity, pain measures, and disability scales by using bias corrected and accelerated (BCa) bootstrap procedure with 1000 bootstrap resamples to generate non-parametric 95% confidence intervals (CI) of regression coefficients from empirical sampling distribution. The bootstrap procedure was suggested as a robust alternative to inference based on parametric assumptions (such as normally distributed errors) to confirm findings obtained by parametric analyses and is recommended for reporting inferences in scientific reports [75].

A second group of analyses inspected the models with significant relationships between CV changes and pain measures for possible mediation mechanisms of those relationships with respect to dispositional affect, behavioral, and cognitive coping or response styles. All mediation effects were evaluated for confidential intervals of regression coefficients by the bootstrap procedure included in the SPSS macro command set.

A third group of analyses inspected the models with significant relationships between CV changes and pain measures for possible confounding or moderation mechanisms with respect to the coping and response styles (e.g., "abnormal illness behaviors") by the same SPSS macro command set. The Johnson–Neyman (J–N) technique included in the SPSS macro command set was used to detect regions of significant relationships in the cases of significant moderation effects. Since some questionnaires were included in the medical-legal examination protocol later than others, degrees of freedom varied in the different analyses.

Heterogeneity of subjects in some domains (e.g., demographics, associated medical conditions, specific drug use) was considered as random factors in the present study. The heterogeneity was expected to decrease the effect size of the linear relationships of interest, but could not be fully controlled in this retrospective study.

3. Results

3.1. Relationships between demographic, pain, and disability variables

Pain severity, distress, and catastrophizing, as well as PDQ_f, PDQ_p, and ODI did not significantly differ between men and women or

subjects differing in ethnicity, age, or BMI. Pain severity and pain catastrophizing scores were higher in White subjects compared to Non-Whites (respective Bs[SE] = 4.67[1.97] and 28.46[14.07], ts[p] = 2.37[.023] and 2.02[.049], η^2 = .12 and .08). Although all obtained relationships were found to be similar for the overall Pain Catastrophizing Scale and its 3 subscales, of these three Catastrophizing subscales pain magnification was found to be the most independent from other pain-related (pain severity and pain distress) measures in the present sample (Pearson's correlation coefficients for pain distress scores with scores of total catastrophizing scale and rumination, helplessness, and magnification subscales were 0.58, 0.58, 0.56, 0.45, respectively). Therefore pain magnification effects were chosen to demonstrate relationships of the pain catastrophizing measure to other variables in further analyses. The pain activity limitation subscale of RDIP and ODI highly correlated with PDQ_f (rs = .88 and .86, p < .001) showing similar relationships with the pain measures (data not shown), and therefore were considered redundant measures of functional disability in this sample.

3.2. Relationships between pain severity, pain-related disability, and CV changes

3.2.1. Profile analysis

Significant Session * Pain Severity interactions were obtained for SBP, DBP, MAP, and RP responses (Table 2). Fig. 1 (CV values averaged across two postures) and 2aS present this pain-related effect on between-session CV changes with 9 as a cut-off point of chronic pain severity. Post-hoc analyses found that individuals with lower pain severity showed a decrease of CV arousal level from session 1 to session 2 compared to those with higher pain severity. Moreover, parameter estimates showed that individuals with lower pain severity also had significantly higher absolute SBP and MAP levels at session 1 compared to those with higher pain severity (respective Bs[SE] = 13.86[5.84] and 8.53[4.17], t[p] = 2.74[.023] and 2.05[.047], η^2 = .12 and .10). All these pain severity effects on CV change between sessions were greater during the lying position compared to standing (e.g., for SBP: respective Pillai's Trace = 0.31, F(1, 40) = 18.02, p < .001 compared to Pillai's Trace = 0.10, F (1, 40) = 4.62, p = .038).

3.2.2. Mediation analysis

Mediation analysis confirmed the findings of the profile analysis by showing, e.g., that the pain severity measure significantly mediated relationships between SBP changes and both PDQ measures (Bs[SE] = 0.52[0.21] and 0.28[0.14], 95% CIs = 0.15–1.05 and 0.05–0.63 for respective PDQ_f and PDQ_p). A lower SBP level at session 1 compared with SBP level at session 2 corresponded with higher ratings of chronic pain severity, which in turn were associated with higher ratings of impaired functional and psychosocial abilities.

Table 2
Session (2 points of psychosocial challenge) × Chronic Pain Severity (continuous and dichotomized) interaction effects on a profile (change) of cardiovascular (CV) activity[a] obtained from systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), and rate-pressure product (RP) readings.

CV measures	Chronic pain severity					
	Continuous		Categorical, low/high		Categorical, low/high[b]	
	Pillai's Trace[c]	F (1, 40)	Pillai's Trace[c]	F (1, 40)	Pillai's Trace[c]	F (1, 35)
HR	.02	0.76	.03	1.20	.02	0.53
DBP	.12	5.29*	.26	14.07***	.26	12.35***
SBP	.15	6.90*	.22	11.56**	.17	6.95*
MAP	.15	7.10*	.28	15.69***	.25	11.75**
PP	.07	2.86	.06	2.54	.02	0.75
RP	.14	6.33*	.24	12.43***	.16	6.75*

[a] After adjustment to Sex, Age, and BMI variables.
[b] After an additional adjustment to two other pain measures (pain distress and magnification) as continuous covariates.
[c] Pillai's Trace value is equivalent to partial η^2 and R^2 measures of effect size.
* p < .05.
** p < .005.
*** p < .001.

3.3. Relationships between pain distress, pain-related disability, and CV changes

3.3.1. Profile analysis

Significant Posture * Readings * Pain Emotional Distress interactions were obtained for SBP, PP, and RP responses (Table 3). Fig. 2 (CV values averaged across two sessions) and 2bS present these pain-related effects on between- and within-posture CV changes with 6.3 as a cut-off point of the pain distress measure. Post-hoc analyses showed that individuals with lower pain distress significantly differed from those with higher pain distress by a SBP profile during a transition from a late lying period to early and mid periods of standing (Pillai's Trace = 0.32, F(3, 38) = 6.03, p = .002; marked by a circle in Fig. 2a). This effect was mirrored by PP and RP profiles with an area restricted to the early and mid-periods of standing posture (respective Pillai's Trace = 0.10, F(3, 40) = 4.31, p = .044; Pillai's Trace = 0.26, F (3, 39) =6 .74, p = .003; marked by circles in Fig. 2b and c). Higher distress was associated with a relative decrease of CV reactivity at mid-point after standing up compared to an opposite profile of CV change associated with a lower distress.

3.3.2. Mediation analysis

Mediation analysis confirmed the findings of the profile analysis by showing, e.g., that the pain distress measure significantly mediated relationships between the SBP changes during a mid-period of standing and both PDQ measures (Bs[SE] = 1.05[0.52] and 0.89[0.43], 95% CIs = 0.29–2.48 and 0.27–1.91 for respective PDQ_f and PDQ_p). A relatively lower mid-response of SBP to orthostatic challenge corresponded with higher ratings of chronic pain distress, which in turn were associated with higher ratings of impaired functional and psychosocial abilities.

3.4. Relationships between pain magnification/catastrophizing, pain-related disability, and CV changes

3.4.1. Profile analysis

Significant Posture * Readings * Pain Magnification interactions were obtained for SBP, MAP, PP, and RP responses (Table 4). Fig. 3 (CV values averaged across two sessions) and 2cS present these pain-related effects on between- and within-posture CV changes with 50 as a cut-off point of the pain magnification measure. Post-hoc analyses showed that individuals with lower pain magnification significantly differed from those with higher pain magnification by a SBP profile during a transition from the late lying period to early and mid periods of standing (Pillai's Trace = 0.34, F(3, 43) = 7.43, p < .001; marked by a circle in Fig. 3a). This effect was to some extent mirrored by MAP, PP, and RP profiles (respective Pillai's Trace = 0.15, F(1, 45) = 7.74, p = .008; Pillai's Traces = 0.18 and 0.23, Fs (2, 44) = 4.74 and 6.43, ps = .014 and .004; marked by respective circles in Fig. 3b–d). Higher magnification was associated with a relative increase of CV reactivity at early point (i.e. immediately) after standing up compared to an opposite profile of CV change associated with a lower magnification.

3.4.2. Mediation analysis

Mediation analyses confirmed the findings of the profile analysis by showing, e.g., that the pain magnification measure significantly mediated relationships between the SBP changes during an early period of standing and both PDQ measures (Bs[SE] = 0.43[0.35] and 0.28[0.21], 95% CIs = 0.04–1.47 and 0.03–0.91 for respective PDQ_f and PDQ_p). A relatively higher early response of SBP to an orthostatic challenge corresponded with higher ratings of chronic pain magnification, which in turn were associated with higher ratings of impaired functional and psychosocial abilities.

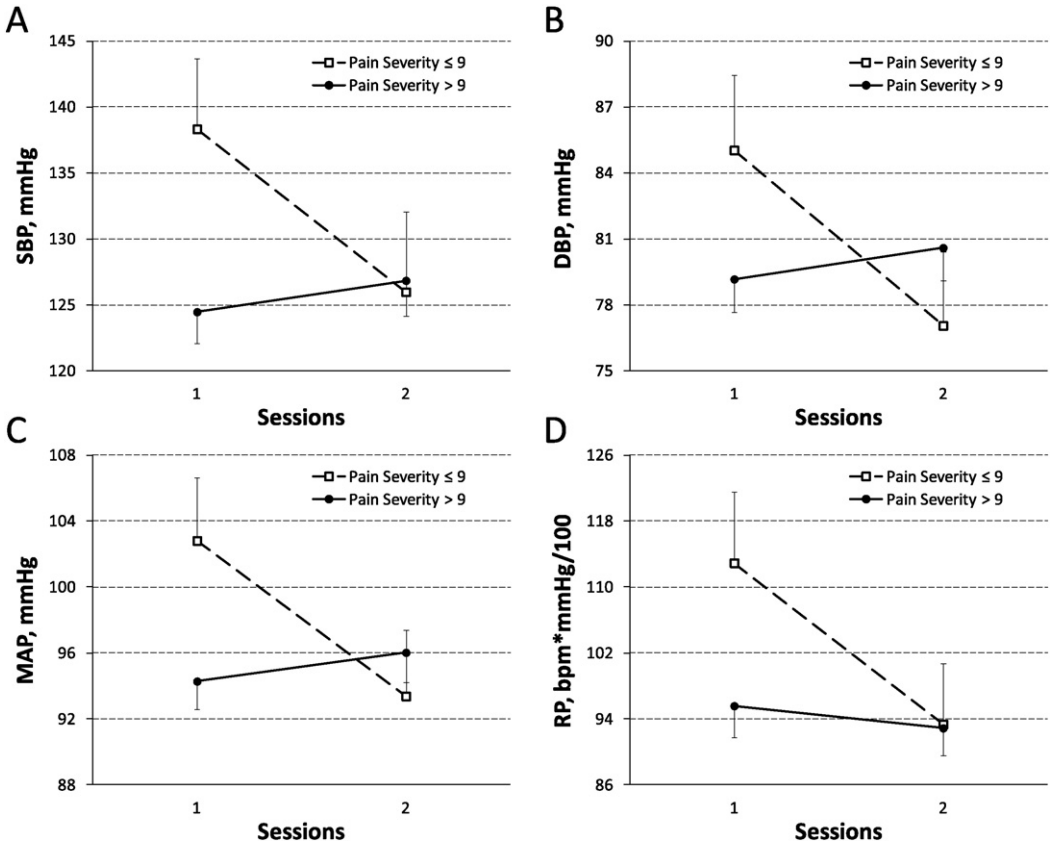

Fig. 1. Between-session cardiovascular (A — systolic blood pressure, SBP; B — diastolic blood pressure, DBP; C — mean arterial pressure, MAP; D — rate–pressure product, RP) changes, which were found to be significant between groups of individuals with high and low pain severity scores (cutoff point = 9) assessed by the RDIP scale. Presented data were averaged for posture and reading factors within each session.

3.5. Relationships between pain chronicity (months), pain-related disability, and CV changes

3.5.1. Profile analysis

Significant Posture * Pain Chronicity interactions were obtained for HR and RP responses (Table 5). Fig. 4 (CV values averaged across two sessions) and 2dS present these pain-related effects on between-posture CV changes with 37 months as a cut-off point of the pain chronicity measure. Individuals with a relatively shorter pain duration (for about 3 years) had significantly weaker HR and RP contrasts between the lying and standing postures compared with those with longer pain duration (more than 3 years) showing the stronger orthostatic HR and RP contrasts.

Table 3
Posture (lying/standing challenge) × Readings (4 points) × Pain Emotional Distress (continuous and dichotomized) interaction effects on a profile (change) of cardiovascular (CV) activity[a] obtained from systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), and rate-pressure product (RP) readings.

CV measures	Pain emotional distress					
	Continuous		Categorical, low/high		Categorical, low/high[b]	
	Pillai's Trace[c]	F (1, 39)	Pillai's Trace[c]	F (3, 38)	Pillai's Trace[c]	F (3, 33)
HR	.01	0.10	.02	0.24	.03	0.34
DBP	.02	0.31	.04	0.53	.06	0.66
SBP	.22	3.60*	.42	9.16**	.41	7.73**
MAP	.06	0.76	.14	2.15	.17	2.20
PP	.18	2.81*	.26	4.34*	.16	2.04
RP	.11	1.55	.21	3.34*	.24	3.42*

[a] After adjustment to Sex, Age, and BMI variables.
[b] After an additional adjustment to two other pain measures (pain severity and magnification) as continuous covariates.
[c] Pillai's Trace value is equivalent to partial η^2 and R^2 measures of effect size.
* $p < .05$.
** $p < .001$.

3.5.2. Mediation analysis

While a direct effect of pain chronicity on PDQ measures was positive (longer pain duration determined more impaired functional and psychosocial abilities; Bs[SE] = 0.47[0.15] and 0.35[0.12], 95% CIs = 0.17–0.77 and 0.11–0.59 for respective PDQ_f and PDQ_p), a longer pain duration through a relatively higher HR response to orthostatic challenge corresponded with lower ratings of disability considering the existence of an autonomic mechanism with protective effect (Bs[SE] = −0.14[0.10] and −0.09[0.07], 95% CIs = −0.44 — −0.02 and −0.34 — −0.003 for respective PDQ_f and PDQ_p). Additional two-mediator models indicated that the protective effect of this autonomic mechanism on the behavioral abilities was transferred through a general pain-killing effect (longer pain chronicity → higher HR response to orthostasis → lower pain severity, distress, or magnification → lower pain disability; data not shown), though direct effects of the chronicity on these pain measures and further to disability were inductive (data not shown).

3.6. Associations between CV changes and pain measures with respect to coping styles

A series of mediation and moderation analyses were conducted to further specify uniqueness of the indicated CV mechanisms associated

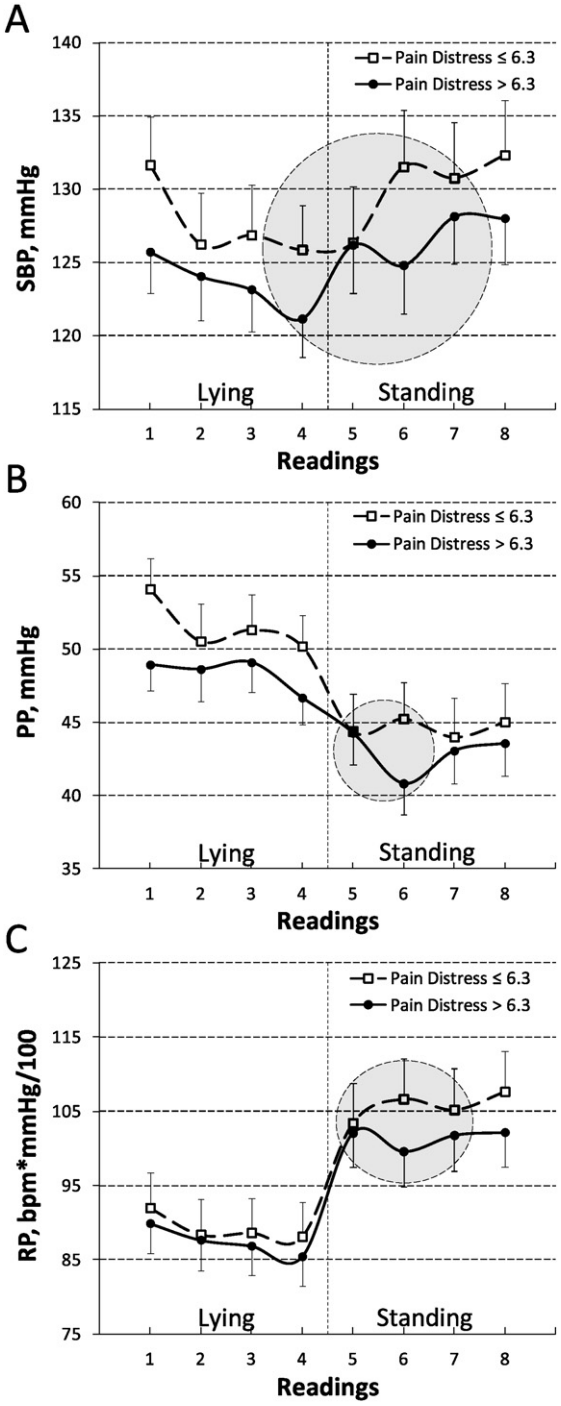

Fig. 2. Orthostatic cardiovascular (A — systolic blood pressure, SBP; B — pulse pressure, PP; C — rate–pressure product, RP) changes, which were found to be significant between groups of individuals with high and low pain-related emotional distress scores (cutoff point = 6.3) assessed by the RDIP scale. Patterns showing maximum significant difference between the groups are included in circles. Presented data were averaged for two sessions.

with pain measures (severity, distress, and catastrophizing) with regard to emotional and behavioral coping and response styles (data only reported for SBP). No significant mediation, confounding, or moderation effects on the relationship between pain measures and SBP changes were obtained for time difference between sessions, the extent of pain control, the period from injury to examination (pain chronicity; months), and the presence and longevity of cumulative trauma associated with the work injury accident.

Table 4
Posture (lying/standing challenge) * Readings (4 points) * Pain Magnification (continuous and dichotomized) interaction effects on a profile (change) of cardiovascular (CV) activity[a] obtained from systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), and rate-pressure product (RP) readings.

CV measures	Pain magnification					
	Continuous		Categorical, low/high		Categorical, low/high[b]	
	Pillai's Trace[c]	F (1, 43)	Pillai's Trace[c]	F (3, 38)	Pillai's Trace[c]	F (3, 33)
HR	.03	0.36	.06	0.92	.22	3.18*
DBP	.05	0.74	.05	0.80	.14	1.89
SBP	.32	6.67***	.37	8.51***	.33	5.73**
MAP	.17	2.82*	.18	3.09*	.27	4.29*
PP	.22	4.12*	.20	3.50*	.16	2.23
RP	.23	4.35*	.29	5.84**	.21	3.16*

[a] After adjustment to sex, age, and BMI variables.
[b] After an additional adjustment to two other pain measures (pain severity and distress) as continuous covariates.
[c] Pillai's Trace value is equivalent to partial η^2 and R^2 measures of effect size.
* $p < .05$.
** $p < .005$.
*** $p < .001$.

3.6.1. Pain severity

Sex-role behavior style evaluated by MMPI-2 5 (Mf) scale partially mediated the association between pain severity and SBP change between sessions detected by the respective profile analysis (B[SE] = 0.22[0.14], 95% CI = 0.01–0.61). Low pain severity scores corresponded with lower scores on the Masculinity–Femininity scale (i.e., with bias to a masculine gender role), which in turn were associated with higher SBP level at session 1 and its steeper decrease by session 2.

Maladaptive affect-regulation profile (high scores of affective and physical complaints), borderline and antisocial behaviors, maladaptive thinking profile (e.g., irrational and maladaptive beliefs), as well as a "fake bad" response style (over-reporting or exaggeration of negative symptoms) estimated by MMPI-2 decreased effect size of relationship between pain severity and SBP change between sessions (data not shown).[2] Ethnicity was also found to be a significant moderating factor with African-American origin as a confounding factor of the relationship, but only when SBP was measured during a standing position (B[SE] = 1.39[0.67], 95% CI = 0.03–2.75).

3.6.2. Pain distress

The association between SBP change to standing up and pain-related emotional distress detected by the respective profile analysis was totally mediated by (i) depression severity as indexed by CES-D and PHQ-9 scales (respective Bs[SE] = 0.07[0.04] and 0.09[0.05], 95% CI = 0.01–0.18, 0.01–0.22), and (ii) clinical anxiety severity in general, and its 'subjective anxiety' and 'neurophysiologic arousal' dimensions as indexed by BAI (respective Bs[SE] = 0.11[0.05], 0.08[0.04], and 0.16[0.05], 95% CIs = 0.03–0.22, 0.01–0.20, 0.06–0.27) included separately in the analysis. Lower SBP level at mid-point after standing up corresponded with higher depression and anxiety, which in turn was associated with high scores of pain-related emotional distress.

Low scores of affective and physical complaints, and high scores of behavioral disinhibition, sensation seeking, masculine, and extraverted

[2] In particular, the J-N technique showed that the confounding effects were associated with lower scores of a positive mood CES-D subscale (cutoff = 3), higher scores of GAD-7 anxiety (cutoff = 6), higher scores of subjective anxiety subscale of BAI (cutoff = 10), high scores of MMPI-2 F-K (raw cutoff = 16), F (T cutoff = 82), TRIN (66), Fp (72), 1 (Hs) (83), 3 (Hy) (81), 6 (Pa) (68), RC3 (65), RC4 (53), OBS (66), HEA (76), CYN (65), ASP (62), Mt. (72), Ho (67), PSYC (65), Pd4 (62), Sc1 (74), Sc3 (79), Pa1 (76), Pa2 (64), Ma1 (57), HEA2 (88), CYN1 (63), CYN2 (61), ASP1 (61), LSE2 (59) scales, and low scores of MMPI-2 K (41), S (41), Do (37), Pa3 (41) scales.

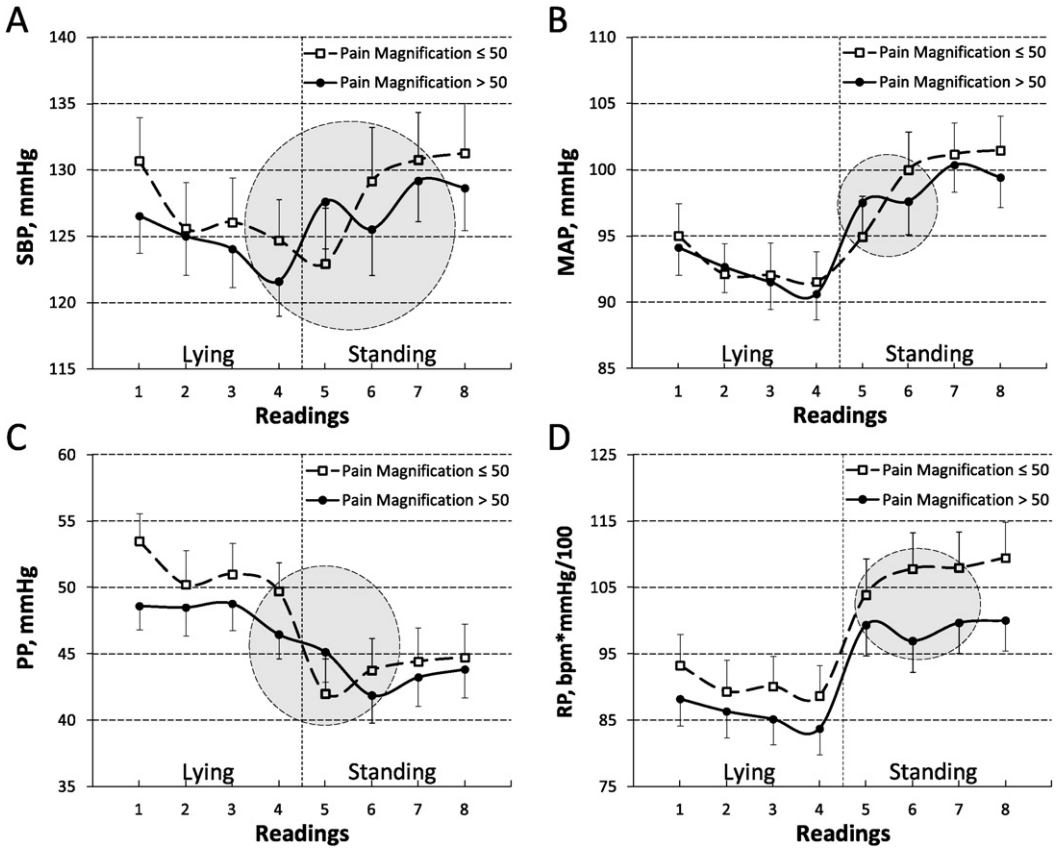

Fig. 3. Orthostatic cardiovascular (A — systolic blood pressure, SBP; B — mean arterial pressure, MAP; C — pulse pressure, PP; D — rate-pressure product, RP) changes, which were found to be significant between groups of individuals with high and low pain magnification scores (cutoff point = 50) assessed by the PCS scale. Patterns showing maximum significant difference between the groups are included in circles. Presented data were averaged for two sessions.

behavior styles, as well as low scores of "fake bad" or high scores of "fake good" response style (denial of problems) decreased effect size of relationships between orthostatic mid-point SBP level and pain-related emotional distress (data not shown).[3]

3.6.3. Pain catastrophizing/magnification

Relationship between high SBP level at early point after standing up and high pain magnification was totally mediated by disturbances in all emotional, cognitive, and behavioral domains associated with the deficit in the core motivational and ego-mastery mechanisms of coping with challenges indexed by high scores of negative mood subscale of CES-D (B[SE] = 0.61[0.32], 95% CI = 0.09–1.36), cognitive dimension subscale of BDI-II (B[SE] = 0.61[0.32], 95% CIs = 0.09–1.37), PTSD as indexed by the PCL-C scale (B[SE] = 0.68[0.36], 95% CI = 0.04–1.46), low scores of defensiveness, high scores of demoralization, dysfunctional negative emotions, obsessiveness, severe depression, low self-esteem, high work interference, high scores of negative treatment indicators, manifest anxiety and depression, low ego-strength, low dominance, high scores of college maladjustment, PTSD, low social imperturbability, lack of ego mastery, high scores of self-doubt, low motivation as indexed by the MMPI-2K, RCd, RC7, OBS, DEP, LSE, LSE1, WRK, TRT, TRT1, A, Es, Do, Mt., Pk, Pd3, Sc4, and Sc5 scales (Bs[SE] = 0.54–1.23[0.28–0.39], 95% CIs = 0.09–2.16) included separately in the analysis. Higher SBP level at an early point after standing up corresponded with a higher deficit in the core motivational and ego-mastery mechanisms, which in turn was associated with high scores of pain-related magnification.

High scores of affective and physical complaints and high scores of behavioral inhibition, and sensation avoidance behavior style decreased the effect size of relationships between orthostatic early SBP level and pain magnification (data not shown).[4] Race was also found to be a significant moderating factor with Non-White origin of subjects as a confounding factor of the relationship (B[SE] = 2.20[0.85], 95% CI = 0.49–3.91).

4. Discussion

This study confirmed the hypothesized relationship between cardiovascular reactivity and chronic pain in a heterogeneous population as predicted by previous studies conducted in more homogeneous groups. Three different physiological mechanisms regulating blood pressure changes in response to psychosocial evaluation and orthostatic challenges were found to be independently related to the subjective

[3] In particular, the J-N technique showed that the confounding effect was associated with high scores of SF36-PF (cut-off = 29), SF36-BP (29), SF36-GH (33), SF36-VT (36), SF36-SF (25), SF36-RE (26), SF36-MH (23), SF36-PCS (33), SF36-MCS (25) scales, lower scores of negative mood CES-D subscale (cutoff = 9), clinical depression as indexed by BDI-II scale (cutoff = 15), and 'subjective anxiety' subscale of BAI (cutoff = 7), low scores of MMPI-2 FBS (T cutoff = 81), RBS (44), 1 (Hs) (83), 3 (Hy) (82), 7 (Pt) (76), D5 (64), DEP2 (65), LSE1 (56), RC1 (76), HEA (78), HEA1 (72), Hy4 (79), and higher scores of 9 (Ma) (53), RC9 (45), GM (45), AGGR (54), DISC (49), Ma1 (46), Ma3 (54), ANG1 (53). Confounding effect was also associated with lower scores of chronic pain severity as indexed by RDIP scale (cut-off = 14).

[4] In particular, the J-N technique showed that the confounding effect was associated with high scores of CES-D and BDI-II somatic complaints subscales (respective cutoffs = 11 11 and 10), higher scores of depression and anxiety as indexed by PHQ-9 and GAD-7 scales (respective cut-offs = 14 and 11), higher scores of BAI 'subjective anxiety' and 'neurophysiological arousal' subscales (respective cut-offs = 11 and 8), poor sleep efficiency as indexed by PSQI scale (cutoff = 2), higher level of daytime sleepiness as indexed by ESS scale (cutoff = 12), high functional disability as indexed by ODI scale (cutoff = 44), lower emotional role as indexed by SF36-RE scale (cutoff = 26), higher scores of MMPI-2 1(Hs) (T cutoff = 84), 2(D) (78), 3(Hy) (84), 7(Pt) (75), RC1 (80), HEA (81), R (66), D1 (72), D2 (65), D4 (73), low scores of DISC (44) and RBS (43).

Table 5
Posture (lying/standing challenge) × Pain Chronicity (months; continuous and dichotomized) interaction effects on a profile (change) of cardiovascular (CV) activity[a] obtained from systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), heart rate (HR), and rate-pressure product (RP) readings.

CV measures	Pain chronicity			
	Continuous		Categorical, low/high	
	Pillai's Trace[b]	F (1, 45)	Pillai's Trace[b]	F (1, 45)
HR	.19	10.35**	.19	10.66**
DBP	.03	1.55	.08	3.66
SBP	.00	0.06	.00	0.00
MAP	.02	0.83	.03	1.40
PP	.01	0.37	.04	1.94
RP	.14	7.30*	.10	4.88*

[a] After adjustment to sex, age, and BMI variables.
[b] Pillai's Trace value is equivalent to partial η^2 and R^2 measures of effect size.
* $p < .05$
** $p < .005$.

experience of pain in three different domains: (i) as a negative somatic sensation that challenges physical well-being and related functional abilities (physical activity; e.g. activities of daily living); (ii) as a negative emotional feeling that challenges psychosocial well-being (symptomatic distress and negative affective reactivity); and (iii) as negative thinking that challenges cognitive functioning (motivational well-being and volitional activity). Cardiovascular indicators related to these mechanisms were found to be tolerant of "fake-bad" response styles (exaggeration and over-reporting of negative symptoms, e.g., high scores on MMPI-2 TRIN, F, Fp, FBS and F-K scales and low scores on MMPI-2 K and S scales) and of "fake-good" response-styles (understatement of negative symptoms and/or denial of problems, e.g., Non-White origin of subjects and low scores on MMPI-2 FBS and RBS scales).

In contrast to the present study most previous studies of chronic pain (i) have included populations of patients, whose pain was associated with very specific diagnoses or impairments (e.g., [1,2,35,37,44]), that restricted generalization of findings; (ii) have investigated mainly one dimension of pain (e.g., sensational [13,26]), which did not test the specificity of detected markers with respect to other pain dimensions or domains (e.g., emotional and cognitive); (iii) have conducted group-wise analyses between patients and healthy controls [13], which did not specify, whether the indicator is related to any specific pain dimension (i.e., sensational, emotional and cognitive) or to a general pain-related impairment when compared to healthy controls; (iv) have obtained measures without control for psychosocial context and habituation to it, where stressfulness could modulate pain experience and the impact of pain on physiological processes (e.g., [3]); and (v) have not demonstrated the tolerance of findings and indicators with respect to patients' credibility and response styles (e.g., [37]).

4.1. Main findings

Findings in this report show that higher pain sensation severity is associated with reduced cardiovascular arousal in response to a significant event, the beginning of a medical-legal examination as a social evaluative threat. Previous studies suggest that transient increases in blood pressure are associated with a central sympathetically mediated hypoalgesic effect to an acute pain stimuli as a component of a stress response [81]. This mechanism does not seem impaired in those subjects showing a nonextinguished arousal response (high cardiovascular (re)activity at session 1) in the presence of a chronic pain syndrome. It corresponds with a recent finding that patients with a longer duration of chronic neck pain demonstrate a lower cardiovascular responsiveness to an acute psychosocial stressor [44]. This allows for considering the association between higher pain severity and the absence of orienting behavior [27]. As a consequence, upon completion of the examination day (re-testing in session 2) the absence of cardiovascular habituation (e.g., absence of systolic blood pressure decrease) was found in those subjects. It was especially observed in systolic and mean arterial pressures measured during a quiet non-demanding condition (lying with closed eyes). The same impairment was found in diastolic blood pressure and rate-pressure product changes. This dysregulation was also found to be an objective predictor of pain-related functional disability indicated by Pain Disability Questionnaire and tolerant to maladaptive response styles and to effects from other pain-related dimensions (emotional distress and cognitive distortion or catastrophizing). Orthostatic profiles (patterns) were similar in both sessions (see Tables 3 and 4, and Fig. 2S). This allows considering that the effect of pain severity on cardiovascular change between sessions (i.e., in response to long psychosocial evaluation) does not significantly affect predicted relationships between other pain dimensions (emotional distress and cognitive distortion or catastrophizing) and cardiovascular responses to orthostatic challenge.

Altered regulation of cardiovascular response to the orthostatic challenge (stress) were found to be related to individual styles of behavioral coping (emotional and cognitive) with chronic pain-related stress. The relative increase of cardiovascular reactivity instead of a decrease at an early point of orthostatic challenge (i.e., 0–2 min after standing up) was associated with greater pain magnification (a component of pain-related catastrophic thinking), and was an additional objective predictor of the degree of functional disability. It was observed in systolic blood pressure and rate-pressure product, and mirrored in mean arterial and pulse pressure changes. This impairment of cardiovascular response may be attributed to the dysregulation of early cardiac and

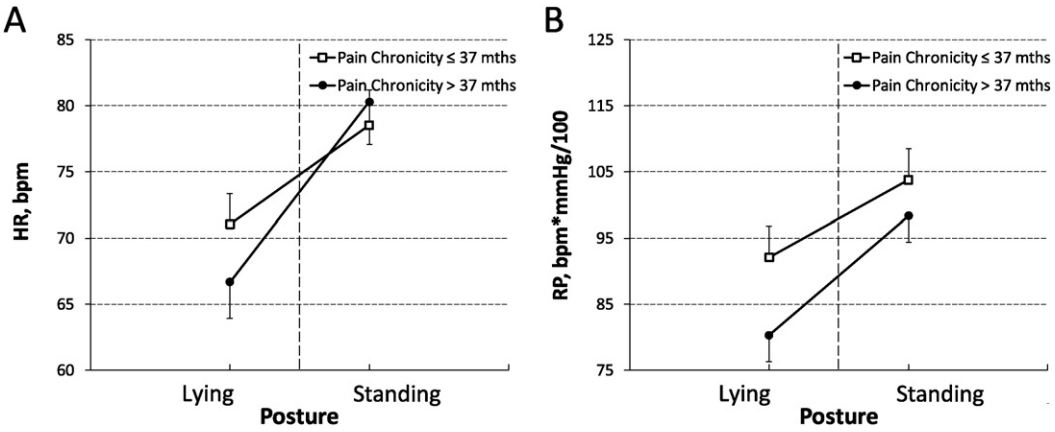

Fig. 4. Orthostatic cardiovascular (A — heart rate, HR; B — rate–pressure product, RP) changes, which were found to be significant between groups of individuals with high and low pain chronicity (cutoff point = 37 months) assessed by the period from injury to examination. Presented data were averaged for two sessions and for 4 readings within each posture.

vascular baroreflex functioning after standing up from lying [33,82,83]. In addition, the appearance of a relative decrease of cardiovascular response instead of its increase at mid-point during the orthostatic challenge (i.e., 2–3 min after standing) was associated with higher emotional distress and was another objective predictor of functional disability. It was also observed in systolic blood pressure and rate-pressure product, and mirrored in pulse pressure change. This impairment in cardiovascular response may be attributed to the dysregulation of later cardiac and vascular baroreflex functioning after standing up from lying [33,82,83]. The pain magnification and the emotional distress effects on orthostatic cardiovascular responses were found to be independent of each other. Additionally analysis showed that the control of their co-occurrence or confounding misrepresentation in self-ratings could double the effect size of their counterparts.

Upright posture requires a rapid and effective skeletal muscle pump, neurocardiac, neurovascular, and neurohumoral compensations to maintain blood pressure, cerebral blood flow, and consciousness. The integrative response is the combination of several compensatory responses. For example, within-subject changes in pulse pressure predicts within-subject changes in cardiac output in response to physical exercise [84]. Thus pain distress effect on a coupled drop of systolic and pulse pressures and on drop in cardiac metabolic activity with no effect on diastolic pressure in response to orthostatic stress can be associated with the impairment of cardiac component of baroreflex in blood pressure regulation. Indeed the gravitational stimulus increases the involvement of baroreflex pathway in the control of blood pressure in healthy subjects, but its reduced strength (i.e., reduced efficiency of the cardiac baroreflex control) was found during the active standing in patients with a chronic pain syndrome coupled with a high negative affectivity [34,85–87]. This may determine instability of systolic and pulse pressure levels in such subjects during orthostasis indicated in the present study. However, the pain magnification effect on a coupled rise of systolic and mean arterial pressures and on a lesser drop in pulse pressure (in response to orthostatic stress) can be associated with a centrally enhanced sympathetic driving of the heart and vessels permanently retained by this negative cognition that affects baroreflex regulation of blood pressure when actively standing [35].

Central sensory and affective pain processes may share common sensory mechanisms. However, pain magnification in particular and pain catastrophizing in general may not be related to central nociceptive processing although playing an important role in the development of chronic pain [63,88,89]. Indeed, a previous study found an interaction effect of higher catastrophizing about pain and lower cardiovascular (e.g., systolic and diastolic blood pressures) reactivity to an anger or sadness recall interview with the greatest pain [37]. In previous studies, pain-related emotional distress was also found to be directly and indirectly connected with both pain catastrophizing and pain severity [1,60,90–92]. One of mechanisms for these effects may be associated with the common central role of dopaminergic systems modulating pain sensation and its affective and cognitive processing [93].

Duration or chronicity of painful condition was found to affect pain-related disability in two different ways: negatively (longer pain duration → stronger orthostatic HR response as indicator of pain-killing, -coping, or -protective mechanism → lower severity of pain symptoms in general → lower pain-related disability) and positively (longer pain duration → higher severity of pain symptoms in general → higher pain-related disability). The same stronger orthostatic HR response associated with a larger vagus withdrawal capacity due to higher baseline vagus activity was described as an indicator of a general resilience or protective mechanism against trauma in a recent study [75]. Level of activity of this mechanism can be inherited (e.g., by *MTHFR* mutation) or acquired (e.g., by regular physical activity).

Taken together the main findings from this report suggest that impairment of cardiovascular auto-regulation associated with the severity of behavior disability may be estimated during specific 'behavior transition' periods claiming changes in energy metabolism. It is consistent with the concept of evolutionary correspondence between the strength of cardiovascular reactivity to challenges and metabolic demands for coping with challenges [27]. Altered cardiovascular response to a stressful (medical) examination was considered to be associated with the physical component of pain affecting orienting behavior in response to arousing event. Fluctuations of cardiovascular response to orthostasis were associated with the effect of emotional and cognitive motivational components of pain on arousal or alertness regulation when standing from lying. Chronic fluctuations in response to orthostatic stress (i.e., fast interchanges between profound increases and excessive decreases of blood pressure level) may cause a cerebral ischemic reperfusion injury leading to cell death and tissue damage in vulnerable people [94–96]. Resulting brain damage may trigger further neuropsychiatric syndromes. These are detected as mediation factors in the present study. They may then trigger maladaptive affect-regulation (affective and physical complaints), maladaptive thinking (irrational beliefs) or both response styles. This depends on human vulnerabilities (see below). Confirming this hypothesis requires further in depth investigation of neurophysiological and neurohumoral mechanisms associated with these changes in blood pressure regulation with the application of more sophisticated neuroimaging and neuroimmune methods and techniques [47,97,98]. Cardiac chronotropic response to orthostatic stress is considered to be an indicator of a general protective vagus mechanism counteracting pain impairment effects on physical, emotional and cognitive functioning during illness chronicity.

4.2. Findings of mediation and moderation analyses

Additional mediation analyses suggested possible mechanisms that contribute to the relationships between cardiovascular reactivity regulation and individual pain severity levels, pain-related emotional distress and magnification/catastrophizing. For example, higher scores on the Masculinity–Femininity scale of the MMPI-2 (i.e., scoring higher in a feminine direction of human traditional sex-typed behavior) partly mediated the relationship between impaired cardiovascular reactivity and severity of chronic pain. Some researchers consider that the extent of male or female role playing in societies is under the influence of sex steroid hormones presenting during prenatal development [99–101]. Our finding and this consideration are in accord with other findings that estrogens and anti-androgens could facilitate chronic pain development and inhibit mechanisms for coping with it [102–104]. It is also concordant with other studies showing that elevations on the Masculinity–Femininity scale of the MMPI-2 predicted (i) a higher number of chronic pain conditions at 30-year follow-up and (ii) the presence of chronic pain symptoms [105,106]. However, in contrast to chronic pain, elevations on this scale predicted a longer acute pain non-experience after surgery (i.e., longer duration of anesthesia post-effect) [107]. Another part of the relationship between the impaired orienting cardiovascular response and chronic pain severity was left unexplained by the mediation analysis. This suggests additional uncovered physiological mechanisms (e.g., associated with race or ethnic differences in sensitivity to pain and its chronicity), which could also be involved in chronic pain development or coping with it [21,108].

Moderation analyses found that the relationship between self-reports of pain severity and cardiovascular change between sessions could be confounded or biased in part of the present clinical sample by individual response styles associated with: (i) "faking bad" (exaggeration of negative symptoms); (ii) borderline and antisocial personality traits; (iii) maladaptive affect-regulation profiles including deep concerns about physical symptoms, somatization and conversion reactions; and (iv) maladaptive thinking profiles. The latter includes poor impulse control, high irritability, low tolerance for frustration, low self-confidence, lack of ego mastery, social alienation, and disorganized, bizarre, or disoriented thinking, and irrational beliefs. Moreover, the observed effect of pain severity on between-session cardiovascular changes was independent of both defensive response styles and affective states.

Other findings showed that pain-related emotional distress appeared to be managed by an approach motivation mechanism for coping with pain using the 'maladaptive affect-regulation profile.' This includes intentional and unintentional help-seeking strategies. Previously this personal profile was found in patients managing chronic pain with medication-overuse, but without other substance addiction problems [109,110]. Self-reports related to this 'affective' pain dimension could be confounded or biased by a "fake-good" response style. Such subject may present with denial of impaired behaviors and negative events and a "macho" masculine sex role (e.g., stoic denial of aches, pains, complaints, or weaknesses; denial of psychological fears or problems), antisocial behavior, risk-taking behavior, impulsivity, sensation seeking traits, behavioral disinhibition, amorality, extroversion, and high suspiciousness of others with feelings of hostility and resentment.

In contrast to pain-related distress, our findings suggest that the process of pain magnification/catastrophizing seemed to be managed by an avoidance motivation mechanism for coping with pain that is associated with general withdrawal strategies. This is found in persons with maladaptive thinking spectrums (demoralization, low self-esteem, low ego-strength and -mastery, low dominance and motivation, high self-doubt, maladjustment, and work interference, obsessiveness, negative treatment indicators) and with the presence of posttraumatic stress disorder symptoms. Previously, this personality profile was found in patients with substance addiction problems [109]. Moderation analyses also detected that self-reports associated with this spectrum could be confounded by affective symptoms and physical complaints, as well as Non-White origin of subject who had lower scores of both pain severity and pain catastrophizing.

Thus, MMPI-2 results in chronic pain subjects in our study demonstrate a three-cluster solution for pain-related response styles when coping with the effects of chronic pain. It may be described as a masculine-feminine (sex role), with maladaptive affect-regulation (social approach motivation, excessive 'energy', and non-cognitive or somatic-emotional symptoms), and maladaptive thinking (social avoidance motivation, low 'energy', and cognitive-emotional symptoms).

4.3. Limitations and perspectives

Although the medical-legal examination in this study was considered as a psychosocial stressor it was not previously used as a situation with social evaluative threat. Nevertheless, the present results support a previous finding that flattened cardiovascular reactivity to a social evaluative threat can indicate a chronic pain experience [44]. The study was conducted in a relatively small sample. The present findings have also not distinguished whether cardiovascular arousal was caused by experiencing or by coping with pain. Other questionnaires which were used in the examination, but which were not included in the study might have additional confounding effects thereby diminishing the observed effect sizes of relationships between cardiovascular and subjective measures. It thus requires caution in the interpretation of results. We therefore propose the confirmation of these findings in other studies. Some methodological inconsistency in chronic pain measurement can obscure the interpretation of association of pain severity and cardiovascular measures between studies. Severity of chronic pain can be evaluated as a current pain magnitude or intensity, e.g., by a visual analog scale, or as a long-lasting trait by assessment of frequency of pain experience and pain duration [111]. Association of cardiovascular reactivity with chronic pain severity assessed as a current or acute condition may be closer to the acute pain effect [112], but may be more related to the pain duration or burdening effects if assessed as a chronic trait [44,57].

In a mixed clinical group of chronic pain subjects results from this study nonetheless suggest for the first time that properties of a scientifically validated cardiovascular metric can be used to assess chronic pain in three main dimensions/domains (as a physical sensation, as emotional distress, and as catastrophic thinking) as it relates to whole person impairment and to disability. It is this understanding which may potentially benefit clinicians seeking to assess symptomatic distress from chronic pain (irrespective of its origin) and chronic pain-related functional impairment or disability in patients with limited education or ability to communicate. The identified autonomic markers of pain impairment effects along with an autonomic marker of the protection effect against pain may also help pain medicine practitioners when selecting and monitoring interventions for specific pain control. For example, in some instances, patients may benefit from interventions that improve emotional well being or cognitive control of pain with little actual impact on pain intensity. One of the most vital benefits, that identification of these indicators offer, is to impact decision-making regimens when individualizing treatment. Therefore, results from this study suggests that clinical recognition of pain severity associated with frequency and magnitude of pain episodes versus pain related emotional distress versus pain magnification/catastrophizing introduces the option of targeting a treatment intervention or combination of interventions that are most relevant for managing human suffering in the chronic pain patient on an individual basis.

5. Conclusion

In sum, we suggest that preliminary results from this study identify a translational physiologic assessment protocol that enables a more accurate three-dimensional understanding of suffering in chronic pain subjects. If this assessment protocol is confirmed it will help clinicians to bypass uncontrollable and debilitating biopsychosocial stressful life events confounding clinical pain assessment.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgment

We thank Professor David Shapiro for his valuable suggestions and Evan Perlo and Peggy Gorelick for their technical assistance. This work was partly supported by private financial contributions from SP, and awards from the Russian Institute for Advanced Study, Sholokhov Moscow State University for the Humanities and from the Russian Humanitarian Scientific Foundation (№ 14-06-00304a) granted to DMD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.physbeh.2015.09.029.

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