ORIGINAL ARTICLE

Pressure pain sensitivity: A new method of stress measurement in patients with ischemic heart disease

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Abstract

Background. Chronic stress is prevalent in patients with ischemic heart disease (IHD) and worsens the long-term prognosis. Chronic stress is vaguely defined, but is associated with depressive symptoms, reduced psychological wellbeing, and reduced quality of life (QOL). Stress seems to induce hyperalgesia. The aim of the present study was to evaluate hyperalgesia by pressure pain sensitivity (PPS) in patients with IHD, and compare PPS to questionnaires measuring depressive symptoms, reduced psychological wellbeing, and QOL as markers of stress. Design. A cross-sectional study of 361 subjects with IHD. Methods. PPS was measured on the sternum, and compared to the questionnaires: Clinical stress symptoms score (CSS), Major Depression Inventory (MDI), WHO-5 Wellbeing Index, and SF-36 QOL score. Results. PPS correlated to CSS (r = 0.20, p < 0.001), MDI (r = 0.14, p = 0.02), SF-36 mental component summary score (MCS) (r = −0.10, p = 0.049), SF-36 physical component summary score (PCS) (r = −0.17, p = 0.001), and self-perceived stress level (r = 0.15, p = 0.006). CSS correlated similarly (r = 0.5–0.7, all p < 0.001). Comparing subjects within the lowest vs. highest tertiles of PPS and CSS, the mean MDI score was 4 vs. 15, WHO-5 was 77 vs. 53, SF-36 PCS was 53 vs. 43, and SF-36 MCS was 58 vs. 46; all p < 0.001. Conclusions. PPS reflected to a modest degree markers of chronic stress in IHD. PPS and CSS together might be useful as easy-to-use tools for evaluating these markers in IHD patients.

Key Words: Depression, myocardial ischemia, stress psychological, questionnaires, quality of life, pain

Introduction

Chronic stress is associated with ischemic heart disease (IHD) [1,2]. The INTERHEART study found that people with myocardial infarction (MI) as compared to controls, reported a significantly higher prevalence of four general life-related stress factors (stress at work, stress at home, financial stress, and major life events) [1]. In prospective studies, chronic stress seemed to be associated with new cardiovascular events and deaths from IHD [3–5].

Several meta-analyses evaluated the effect of stress-reducing interventions in IHD patients, and concluded that some, but not all, intervention modalities have a positive effect on stress as evaluated by questionnaires [6–8]. It is still debated whether stress reduction reduces the risk of new cardiovascular events and deaths from IHD. However, a recent randomized study found that cognitive stress-reducing therapy significantly reduced recurrent cardiovascular events including acute MI [9].

Stress is a vaguely defined concept, which is typically measured by physiological parameters or questionnaires. The physiological parameters include plasma norepinephrine, plasma and salivary cortisol, blood pressure, heart rate, mean arterial pressure and the pressure-rate-product, which is a measure for the work of the heart [10]. However, these parameters are mostly accepted as the measurements of acute
stress. The questionnaires cover also persistent stress but serve to elucidate the elements of two main topics: either stressors, including stressful life events, job stress and measurements of negative personal relationships; or stress appraisal, including perceived stress and negative affective reactions to stress.

Studies on psychosocial stress have thus been inconsistent, mostly covering only limited components of the stress concept.

It is well known that stress interacts with the pain system and influences pain sensitivity [11,12]. In animals, chronic stress measured as repeated exposures to swim stress or by social defeat models have been shown to induce hyperalgesia [13]. Hyperalgesia represents an appropriate increase in vigilance to prevent potential harm, and might be explained by the activation of cutaneous polymodal nociceptors in the skin sensitive to pressure, heat and sympathetic stimulation [14]. In healthy humans and in patients with IHD and other stress-related disorders, stress load was coupled to increased pain sensitivity, measurable on the skin of the lower part of the sternum [15]. The change in pain sensitivity can be measured by a variety of devices and pain sensitivity thresholds assessed by handheld devices have gained clinical acceptance as they are easy to use and can provide evidence for local and generalized hyperalgesia. Recently a simple and handheld device has been designed to assess pressure pain sensitivity (PPS) [15]. The PPS measure is found to be correlated to several well-known reactions of stress, like the changes in blood pressure, pulse rate, work of the heart and salivary cortisol during transient stress, as well as the resting pulse rate and work of the heart as measures of persistent stress in out-patients with chronic diseases including IHD [15].

The aim of the present study was to evaluate hyperalgesia by PPS in patients with stable IHD, and compare PPS to questionnaires measuring depressive symptoms, reduced psychological wellbeing, reduced quality of life (QOL), and number of clinical stress signs (CSS) as markers of stress [16,17].

Study population and methods

A total of 361 patients with established and stable IHD were included in this study. The patients were recruited from a database on subjects with established IHD at the departments of Cardiology, Gentofte University Hospital, and Herlev University Hospital, Copenhagen, Denmark (HjerteRask). All patients were rehabilitated during the period of 1999–2011.

The inclusion criteria were: (i) Documented IHD (defined as MI, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]), (ii) completed cardiac rehabilitation more than six months ago, and (iii) age of 75 years or younger.

The exclusion criteria were: (1) Hospitalization due to psychiatric disease prior to IHD, (2) scheduled cardiac surgery, (3) changes in heart medication within the last month, (4) chronic competing disorder that clearly impaired the patients’ QOL (such as, severe lung disease or cancer in progress), and (5) chronic pain syndromes due to arthritis and fibromyalgia among others.

In accordance to the inclusion and exclusion criteria, 1129 patients were invited by letter. Out of 640 responders, 386 accepted to participate and provided written informed consent. Finally, 361 participants completed according to the protocol.

In order to study if those patients who did not respond differed in morbidity from those who participated, a response analysis was made. The response analysis was based on the data of 200 non-responders and 200 responders obtained from the registry of the Danish National Board of Health, which recorded all primary hospital discharge diagnoses in Denmark. The group that participated was significantly younger and included more women. However, there was no difference between participants and non-participants according to the number of heart-related hospitalizations, number of patients treated with CABG or PCI, or number of patients with diabetes mellitus.

A website was established for the study (www.songheart.org), and all participants answered questionnaires on a website with their personal login data, which was first opened after the study ended in order to avoid bias.

The questionnaires included the following:

- A demographic questionnaire including information on IHD, co-morbidity and medical treatment.
- Three validated and reproducible questionnaires, accepted as markers of stress [16]:
  - MDI, which assesses depressive symptoms on a score from 0–50, where 0 equals to no signs of depression.
  - SF-36, which assesses general physical (PCS) and mental (MCS) QOL. A score of 100 equals best possible QOL.
- The CSS questionnaire [17]: CSS is a newly developed score of 56 clinical stress symptoms experienced during the last four weeks (see Appendix).
- Information on self-perceived stress obtained on a 7-point Likert scale from non-stressed to very stressed during the last three months.

The PPS measurement device has been already described in details [15]. In short, the instrument is a hand-held device by which a gradually increasing pressure is applied to the skin on a 1 cm² area. The
pressure is ended when the patient (after instructions) signals that the pain threshold has been reached.

The PPS measurement procedure

The patient was placed in a supine position and was accustomed to the feeling of pressure from the PPS algometer by repeated measurements on the tibia bone (typically six measures). After 10 minutes of rest, the most sensitive area on the sternum at the level of intercostal spaces 3–5 was identified by palpation. The most tender point was selected for PPS measurement. A gradually increasing pressure performed by the instructor was applied for 2–5 seconds until the pain threshold was reached. The PPS algometer automatically transformed the pain threshold into a logarithmic scale of sensitivity levels (from 30–100 PPS units). An increase in 30 PPS units corresponded to a 100% increase in sensitivity. PPS was measured twice. In case of more than five units’ deviation, a third measurement was performed, and the mean value of all three measurements was used. In order to avoid bias, the PPS algometer was designed in such a way that the reading was only visible for the participant or the researcher after the measurement was finished.

Thirty-nine consecutive participants underwent a supplementary examination where pressure pain threshold was recorded by the PPS algometer, as well as by a broadly accepted pressure algometer (Algometer Type II, Somedic AB, Sweden), normally used to measure diffuse noxious inhibitory control (DNIC) [18,19]. Measurement site was the fascia of the anterior tibia for both instruments. Each instrument was used for two consecutive measurements, with five seconds interval. Measurement site was identical for both instruments, and the order of measurement was random. The correlation coefficient between measurements conducted by the two instruments was: $r = 0.83$, $p < 0.001$.

Written informed consent was obtained from all the participants. The study was approved by the local ethical committee, and was registered on www.clinicaltrials.gov (NCT01513824).

Statistical analysis

Parametric statistics including unpaired $t$-test, one way ANOVA with post-hoc Bonferroni adjustment and simple linear regression analysis were used. Multiple linear regression with backward elimination of non-significant variables were performed by using PPS and CSS as dependent variables, and CSS or PPS together with age, gender, MDI and SF-36 PCS as independent variables. The effect of a combined measure of PPS and CSS was evaluated: Patients within the lowest tertile of both PPS and CSS (low PPS–low CSS group) were compared to those within the highest tertile of both PPS and CSS (high PPS–high CSS group). As the MDI was considered a measure of depression severity with a cut-off score for very mild depression at a MDI total score of 15 or higher, it was planned to perform an item response analysis for the included participants, as well as the participants with an MDI score of 15 or higher. The parametric item response theory analysis was used to evaluate this model’s requirement that the symptoms with lower prevalence had to be preceded by the symptoms with higher prevalence [16]. For this purpose, we used the RUMM (Rasch Unidimensional Measurement Model) 2030 program [20]. The model was tested through the fit of the model to the actual scoring, using Conditional Maximum Likelihood approach, including test for item homogeneity across variables like severity of depression, gender, and age [21]. The rejection level of the model according to the Rasch analysis was $p < 0.05$. The level of $p < 0.05$ was also regarded as the level of statistical significance in other tests where the statistical package SPSS version 19 was used.

Results

Thirty-two percent of the invited patients completed the protocol. The study population consisted of 21% women and 79% men, and the median age was 64 years (range: 33–75 years). All had by definition IHD, 63% reported having had a previous MI, 67% had been treated with PCI, and 28% had had a CABG. Median time from the diagnoses of IHD was six years (range: 0–33 years), and the median time from most recently ended cardiac-rehabilitation was three years (range: 0–13 years).

Concerning co-morbidity, the following were registered: 31% had diagnosed heart failure. Seven percent suffered from asthma and 5% from mild chronic obstructive lung disease. Seven percent had previously experienced a stroke, 13% had diabetes and 14% had been diagnosed with depression. Twenty-five percent experienced angina pectoris corresponding to Canadian Cardiovascular Society Functional Classification of Angina Pectoris (CCS) class I, 10% to CCS class II, 1.4% to class III and 0.8% to class IV. Nine percent reported dyspnoea at an activity level equivalent to New York Heart Association (NYHA) class III. None had dyspnoea at rest (NYHA class IV).

Medication. 60% of the patients were treated with beta-blockers, 96% with antiocoagulants or drugs affecting platelet (thrombocyte) function, 88% with cholesterol-lowering medicine, 24% with calcium-antagonists, and 57% with Angiotensin-II antagonist and/or Angiotensin converting enzyme inhibitors (ACE inhibitors). Two percent were treated with insulin and 8% with oral anti-diabetic drugs. Five percent used anti-depressive medication.
Use of healthcare in the last 12 months. 19% of the patients reported that they had been admitted to the hospital due to heart diseases, 31% had visited a cardiology specialist as an out-patient, and 38% had visited their general practitioner due to heart diseases.

In total, 62 (17%) of the patients had an MDI score of 15 or more; whereas, 31 (9%) had an MDI score of 20 or more. The patients with an MDI score of 15 or more had a mean PPS score of 69.9, SD 20; whereas, those with an MDI under 15 had a mean PPS score of 63.8, SD 19, p = 0.025.

The item response theory accepted (p = 0.23) that the total score of the MDI was sufficient as the rank ordering of prevalence was the same for all participants (n = 361) and for the group with an MDI score of 15 or more (n = 62). The most prevalent item was ‘lack of energy’, then came ‘sleep troubles’, ‘restlessness’, ‘lack of interests’, and ‘sadness’. These five items had a mean score of approximately 1 for all participants and a mean of 2.8 for those with an MDI of 15 or more.

The patients were divided into tertiles based on PPS and CSS. Increasing PPS was associated with increasing CSS (p = 0.044) and decreasing SF-36 PCS (p = 0.008). Increasing CSS was associated with increasing PPS (p = 0.002) and MDI score (p < 0.001), as well as self-perceived stress-level (p < 0.001), decreasing WHO-5 score (p < 0.001), and SF-36 PCS and MCS (both p < 0.001).

A correlation analysis demonstrated several significant correlations (Table I): Increasing PPS correlated to increasing CSS, MDI, self-perceived stress level, decreasing SF-36 PCS including several of the sub-items, and decreasing SF-36 MCS including the sub-item social function. CSS was associated with all questionnaires evaluated.

In a multiple linear regression analysis with backward elimination of non-significant variables, PPS was independently associated with CSS (β = 0.124, p = 0.026), SF-36 PCS (β = −0.109, p = 0.049) and gender (β = −0.231, p < 0.001). Whereas, CSS was independently associated with PPS (β = 0.077, p = 0.040), MDI (β = 0.621, p < 0.001) and SF-36 PCS (β = −0.192, p < 0.001).

Patients with both the lowest PPS and CSS tertile were compared to those with both highest PPS and CSS tertile (Table II). The low-low group had considerably different values for all parameters tested compared to the high-high group (all p < 0.001).

There was no difference between having/not having had a cardiac infarction, PCI or CABG and the results of PPS or questionnaires.

To evaluate if stress-level was influenced by time, participants were divided into tertiles based on the time since IHD diagnosis, and time since most recently ended cardiac rehabilitation, respectively. No changes were found according to mean PPS, CSS, stress questionnaire-scores or self-perceived stress level between the different time durations.

Correlation was found between Angina class and the following: PPS (r = 0.162, p = 0.002), CSS (r = 0.378, p < 0.001), MDI (r = 0.309, p < 0.001), WHO-5 (r = −0.327, p < 0.001), SF-36 PCS (r = −0.459, p < 0.001), SF-36 MCS (r = −0.269, p < 0.001), all subgroups of SF-36, and self-perceived stress-level (r = 0.212, p < 0.001). NYHA class did not correlate significantly to PPS, but did correlate to CSS (r = 0.362, p < 0.001), MDI (r = 0.318, p < 0.001), WHO-5 (r = −0.249, p < 0.001), SF-36 PCS (r = −0.394, p < 0.001), SF-36 MCS (r = −0.163, p < 0.001), all subgroups of SF-36, and self-perceived stress-level (r = 0.113, p = 0.032).

No differences in stress-levels were seen between participants according to +/- beta-blocker, cholesterol lowering medication or Angiotensin II-inhibitors/ACE-inhibitors.

The SF-36 PCS was associated with the use of healthcare within the last 12 months, being lower among the patients who were submitted to the hospital

<table>
<thead>
<tr>
<th>Pressure pain sensitivity</th>
<th>Clinical stress signs</th>
</tr>
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<tbody>
<tr>
<td>correlation coefficient (p-value)</td>
<td>correlation coefficient (p-value)</td>
</tr>
<tr>
<td>1</td>
<td>0.197 (&lt;0.001)</td>
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<tr>
<td>Clinical stress signs</td>
<td>Major Depression Inventory</td>
</tr>
<tr>
<td>0.197 (&lt;0.001)</td>
<td>0.141 (0.007)</td>
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<tr>
<td>SF-36 physical component score</td>
<td>Physical functioning</td>
</tr>
<tr>
<td>−0.170 (0.001)</td>
<td>−0.154 (0.003)</td>
</tr>
<tr>
<td>Role physical</td>
<td>General health</td>
</tr>
<tr>
<td>−0.102 (0.054)</td>
<td>−0.177 (0.001)</td>
</tr>
<tr>
<td>Vitality</td>
<td>Social functioning</td>
</tr>
<tr>
<td>−0.067 (0.206)</td>
<td>−0.129 (0.014)</td>
</tr>
<tr>
<td>Mental health</td>
<td>self-perceived stress level</td>
</tr>
</tbody>
</table>

0.454 (<0.001)
due to heart diseases ($p = 0.001$), or had visited a cardiology specialist as an out-patient ($p = 0.032$). Furthermore, subjects reporting to have visited their general practitioner due to heart diseases during the last 12 months rated significantly higher on the CSS ($p = 0.009$) and lower on both the WHO-5 ($p = 0.006$), SF-36 PCS ($p = 0.047$), and the SF-36 MCS ($p = 0.012$). No differences in PPS measure were found.

**Discussion**

The present study showed that the concept of measuring PPS was modestly, but statistically significantly associated to the number of clinical stress signs (CSS), depressive symptoms (MDI), both mental and physical wellbeing (SF-36 QOL score), as well as to the self-perceived stress level in IHD, all markers of the chronic stress concept anticipated being present in a chronic somatic disease like IHD [16,17].

As anticipated, the different questionnaires correlated internally as they contained common elements. For example, three of the five items in WHO-5 were also included in the SF-36 MCS. However, PPS showed an independent association to CSS and SF-36 PCS, while CSS showed an independent association to PPS, MDI and SF-36 PCS.

**Transient or persistent stress**

Evaluation of chronic work-related stress burden in office workers had demonstrated a correlation between increasing PPS and increasing chronic stress by means of MDI, the CSS score, and several elements of SF-36 including both PCS and MCS [17]. However, the PPS measure may also reflect acute stress. Regarding this, we have already demonstrated a close correlation between PPS and blood pressure, heart rate, mean arterial pressure and pressure-rate product in acute stress in opera singers during performance [15]. Thus, PPS at the chest bone seemed to reflect both an acute and chronic stress burden.

**PPS and CSS associations to questionnaires**

We found modest associations between the PPS and questionnaires evaluated. In contrast, CSS score demonstrated a rather substantial and significant association to PPS, as well as all questionnaires evaluated. This was independent of the way in which the data was presented.

In our data analyses, we evaluated the use of a combination of PPS measurement and CSS scoring, dividing subjects into an anticipated low stress group (low PPS–low CSS) and a high stress group (high PPS–high CSS). This analysis demonstrated a difference in all parameters tested. Thus, we suggest that the combination of PPS and CSS may be useful and easy-to-use tools for evaluating these markers of stress in patients with IHD.

The PPS measure seemed to be reproducible and measurable both by a professional and the subject itself with high precision [17]. This pointed at the possibility of monitoring chronic stress by a combination of PPS-measurement and CSS-scoring, as well as a bio-feedback guided stress management approach. However, this had to be evaluated in a prospective trial.

While measuring PPS on patients with a previous CABG, we applied the pressure on a scare. No significant difference in mean PPS was found between the subjects with/without a previous CABG.

**PPS in patients with IHD and healthy subjects**

The absolute value of the PPS measurement in IHD was higher than in healthy subjects. In a previous study, we found a median PPS of 48 (IQR 39–61) in 308 healthy working officers [17]. However, in the present study, the IHD patients had a median PPS of 64 (IQR 50–79). We have previously suggested a cut-off level at 60 in PPS as an increased sign of stress [17]. Given this, 58% of the IHD patients and 27% of healthy subjects had a PPS value above 60, which could suggest increased stress level in IHD patients. The healthy subjects had a mean age of 42 years as compared to 64 years in the IHD patients, which may weaken the comparison. In both groups,
increasing age was associated with a small and insignificant decrease in PPS, so the difference in age between the groups did not explain the difference in PPS.

**Time dependence**

No effect of time since rehabilitation could be found on the stress-level in patients suggesting that the perception of stress among subjects with IHD is not obviously associated with a more recent episode of IHD, at least if this is more than 6 months ago.

**Patophysiology**

Chronic stress seems to induce a central pain sensitization [11,12]. This has been hypothesized to be caused by a defect in the diffuse noxious inhibitory control system (DNIC) [18]. This afferent/efferent system operates via the sensory nociceptive nervous system, and a defect in DNIC seems to lead to a state of more diffuse hyperalgesia as seen in many chronic pain conditions such as chronic osteoarthritis or fibromyalgia [19,22]. Although pressure algometry is the golden standard in pain research an inherent limitation will always be the fact that the measure is based on a subjective sensation of pain. In the present study we compared two hand held devices and found a close correlation.

**Limitations**

As usually seen in epidemiological research, we had a rather low attendance rate: 32% of the invited population and 56% of those who responded to our invitation participated in the study. However, a response analysis showed that there was no difference between participants and non-participants with regard to the severity of the heart disease, as well as the number of people with diabetes. This suggested that the study sample was representative, even though variables with significant impact might have been missed.

**Conclusions**

PPS reflected, to a modest degree, markers of chronic stress in IHD as depressive symptoms, reduced well-being, and reduced QOL. PPS and CSS together might be useful as easy-to-use tools for evaluating these markers in IHD patients.

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**Disclosures**

Søren Ballegaard invented the Ull-meter used to measure PPS. He is also a shareholder of the company that owned the Ull-meter. In order to avoid bias, he was not involved in the patient contact, collection of data or statistical analysis. No other disclosures were reported.

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**References**


Appendix

Clinical stress signs score (CSS). The participants were asked to mark if they had experienced any of the following within the past 4 weeks.

1. Back pain
2. Headache
3. Ringing in the ears
4. Hot flushes
5. Lack of energy
6. Stomach pains/stomach ache
7. Decreased tolerance for noise or odor
8. Loss of appetite or comfort eating
9. Muscle tension
10. Frequent infections
11. Worsening of chronic illness
12. Increased frequency of making mistakes
13. Rapid heart beat
14. Anger outbursts, that I cannot control
15. Clumsiness
16. Reduced zest of life
17. Reduced sex drive
18. Feeling of reduced time for relaxation and pleasure
19. Impatience
20. Fatigue
21. ‘Butterflies’ in my stomach
22. ‘Lump in my throat’
23. Forgetfulness
24. Difficulty concentrating
25. Reduced sense of humour
26. Reduced empathy
27. Social withdrawal
28. Low spirits
29. Grinding teeth
30. Cannot get worries out of my mind
31. Vision related difficulties
32. Anxiety/fear
33. Reduced tolerance to others
34. Difficulty in thinking clear
35. Cry easily
36. Insomnia/difficulty sleeping
37. Overly aggressive
38. Indecision/difficulty making decisions
39. Irritability/‘short fuse’
40. Increased use of stimulants (coffee, cigarettes, alcohol)
41. Increased use of prescription drugs
42. Increased use of over the counter drugs or natural medicines
43. Dizziness
44. Increased sick leave
45. Reduced initiative
46. Joint pains
47. Cold hands/feet
48. Circular thinking or myriad of thoughts
49. Nausea or vomiting
50. Pressure/pain in the chest
51. Irregular heart rhythm
52. Increased sensitivity to light or touch
53. Irregular motion
54. Tender muscles
55. Reduced sexual endurance (men)
56. Irregular or more often toilet visits