ORIGINAL ARTICLE

Association between pressure pain sensitivity and autonomic function as assessed by a tilt table test

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Abstract

Background. We tested the hypothesis that pressure sensitivity of the sternum (PPS) is associated with autonomic nervous system (ANS) function as assessed by tilt table test (TTT), in patients with stable ischemic heart disease.

Objectives. (1) To evaluate an association between PPS and systolic blood pressure (SBP) and heart rate (HR) responses to TTT; and (2) to test the hypothesis that a reduction of resting PPS raises the PPS, SBP and HR responses to TTT response and lowers risk factors for ANS dysfunction (ANSD).

Methods. Cross-sectional study: In 361 patients with stable ischemic heart disease we measured PPS, SBP, and HR during TTT. Intervention study: We reassessed subjects with persistent stress who concluded a stress intervention trial by a second TTT.

Results. Cross-sectional study: Resting PPS and the PPS response to TTT were correlated (r = -0.37). The PPS response to TTT was correlated with that of SBP (r = 0.44) and HR (r = 0.49), and with the number of risk factors for ANSD (r = -0.21) (all p < 0.0001). Intervention study: A reduction in resting PPS was associated with an increment in PPS response to TTT (r = -0.52, p < 0.0001). The greater this increment, the greater was the reduction in ANSD risk factors (r = -0.23; p = 0.003).

Conclusion. The results are consistent with the hypothesis that PPS at rest and in response to TTT reflects ANS function.

Key Words: Autonomic nervous system dysfunction, depression, pressure pain sensitivity, pressure pain threshold, stress, tilt table test

Abbreviations: ANS, autonomic nervous system; ANSD, autonomic nervous system dysfunction; CSS, Clinical stress score: Questionnaire which assesses clinical stress symptoms; HR, heart rate; MDI, Major Depression Inventory: A questionnaire which assesses depression; MID, minimum important difference; PPS, pressure pain sensitivity of the chest bone measured by an Ull Meter®; SBP, systolic blood pressure; SF 36, Short Form 36: A questionnaire which assesses mental and physical health by 36 questions, two main scores and 8 subscores; SF 36, MCS, SF 36 main score: Mental component summary for mental health; SF 36, PCS, SF 36 main score Physical Component Summary for physical health; TTT, tilt table test; WHO5, WHO Quality of Life questionnaire assessing quality of life by 5 questions.

Introduction

Autonomic nervous system (ANS) dysfunction is associated with increased risk of ischemic heart disease morbidity and mortality, independent of other risk factors [1]. ANS controls sudomotor (sweating), cardiovagal, and adrenergic functions [2] and tilt table test (TTT) is used to evaluate ANS [2–4]. TTT leads to a controllable stimulation of ANS, as assessed by systolic blood pressure (SBP) and heart rate (HR) [2–4].
We developed a device that measures pressure pain sensitivity over the sternum (PPS), with a high PPS measure indicating high sensitivity and a low pressure pain threshold [5]. The results obtained by this algometer are in close agreement with another pain algometer, developed for the evaluation of pain sensitivity threshold [6]. The PPS value is measured at the chest bone, and the values are increased both by transient and persistent stress [5–7]. During transient stress, such as imposed by an opera performance or cycling PPS, Hr, and SBp values change in parallel [5–7].

In patients with stable ischemic heart disease (IHD), we examine whether stress (transient or persistent) as measured by PPS is associated with functional assessed by PPS, SBp, and Hr responses to TTT, and by the number of risk factors for ANSD in both a cross-sectional and an interventional protocol.

Methods

Design

The study included: (1) A cross-sectional evaluation of an association between resting PPS and the PPS response to TTT, an association between the PPS and the HR and SBP responses to TTT, and the association between the responses to TTT and ANSD; and (2) an interventional, prospective, randomized controlled study on the changes in (i) PPS, HR and SBP during TTT, and (ii) number of ANSD risk factors, when an elevated resting PPS is sought reduced by a self-care-based, PPS measure device supported non-pharmacological stress management intervention program.

Patients

The cross-sectional study included 361 patients with stable IHD. Patients were recruited from a database on subjects with established IHD at the departments of Cardiology, Gentofte and Herlev University Hospitals, Denmark. All subjects had been rehabilitated between 1999 and 2011. Inclusion criteria were: (1) IHD (myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), (2) completed cardiac rehabilitation more than 6 months ago, and (3) ≤75 years as described [6] (Table I). The interventional study included the 213 patients who had elevated PPS ≥ 60 (58%) at

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<tr>
<th>Table I. Baseline demographics according to study groups.</th>
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<tr>
<td>Cross-sectional study</td>
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<td>Age in years, mean (SD)</td>
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<td>WHO-5 wellbeing score, mean (SD)</td>
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Except for the prevalence of known diabetes no significant differences between the active and control group were found.
baseline: The patients were randomized to active treatment ($n = 106$) or control group ($n = 107$). Dropout was 20 and 12, respectively [8]. As there were no significant between-group differences at baseline apart from prevalence of diabetes, the two groups were treated as one group for the aim of the present study. Written informed consent was obtained from all the participants after oral and written information about the study as approved by the local ethics committee (ref no. H-4-2010-135), and registered at www.clinicaltrials.gov (NCT01513824).

Procedures

Tilt table test. TTT stimulates the autonomic nervous system by orthostatic stress, initiated by passive repositioning from supine to 70 degrees upright [2]. ANS function is assessed from the HR and SBP response to TTT [2,4]. During TTT, the subject was positioned at the tilt table and fastened in a supine position, and the following procedure carried out: (1) 10-min rest in the supine position (first and second set of recordings); and (2) passively tilted to an angle of 70 degrees for 7-min rest in that position. A third and a fourth set of measurements were performed in the beginning and end of this period (Figure 1). The measurement of HR and SBP response to TTT is recommended to be after 10 min [2]. We added measurements right after the upright tilt position was obtained, as clinical observations suggest an immediate change in PPS during transient stress in opera students [5].

Pressure pain sensitivity. An algometric instrument (Ull Meter®: UllCare Ltd, Lem Chesvej 1, DK 2900 Hellerup, Denmark) was used for measurement of PPS [5]. The instrument measures the pressure pain threshold, and that value is transformed to a logarithmic scale and inverted into a sensitivity scale from 30–100 units. The mean of two measurements was used. If the between-measurement difference was more than 10 units, a third measurement was performed and the result was calculated as the mean of the three recordings. A resting PPS ≥ 60 units was used as an arbitrary discrimination point for an elevated level of persistent stress [5].

Systolic blood pressure (SBP), heart rate (HR) and pressure-rate-product (PRP). Blood pressure and heart rate were recorded using a Thusaue automatic blood pressure monitor (W0840 002 001, Microlife ref. BP-3AA1-2, BP 243-92307, Levallois-Perret Cedex, France). For analysis the mean of two measurements was used. If the between-measurement difference was more than 10%, a third measurement was carried out and the result was calculated as the mean of the three recordings.

Outcome variables

Cross sectional study outcome variables: (1) Resting PPS versus changes in PPS, SBP and HR during TTT: With regard to TTT, the following effect variables were used: Changes in PPS, SBP, and HR during a 7-min period of TTT as recommended by international standards [9]. In order to test if similar changes could be obtained using a shorter observation period, changes after 1 min in upright position were included. (2) The PPS, HR and SBP response versus numbers of ANSD risk factors.

Four individual risk factors for ANSD were included in addition to the verified iHD: Chest pain at rest [9], an elevated level of persistent stress defined as resting PPS ≥ 60 arbitrary units [7], an elevated resting SBP defined as SBP ≥ 130 mm Hg [10], and depression defined as an MDI (Major Depression Inventory) score ≥ 20 [11]. All participants filled out the MDI questionnaire, which assesses the degree of depression, before and after the intervention period.

Intervention study outcome variables: (1) Change in resting PPS during intervention versus the change in PPS, HR and SBP response to TTT; and (2) change in PPS, HR and SBP response to TTT and the change in number of ANSD risk factors.

A minimal important difference (MID) in PPS, when pre-treatment values were compared to post-treatment values, was arbitrarily set to a 15-unit reduction, which equals a 50% increase in applied physical pressure. Patients, who obtained this effect as minimum, were defined as responders, and those who did not were defined as non-responders.

Intervention study: The Stress Reduction Intervention

A total of 181 patients with resting PPS ≥ 60 at baseline concluded the 3-month randomized controlled trial, in which 86 persons were randomized to the
active group and 95 persons to the control group (Table I). The cut-off point PPS ≥ 60 for categorization of a person as being persistently stressed was based on previous consecutive studies on risk factors for impaired health [5,7]. The intervention stress reduction program (e.g. UlCare®) was carried out during a 3-month period and was based on the active group performing a non-pharmacological, self-care stress-reducing program including a PPS measurement device with the instruction to perform daily home PPS measurements, instruction in daily sensory nerve stimulation with the aim to reduce PPS, and with a professional back-up, depending on individual demands [8]. The control group received the information that their level of persistent stress was regarded as elevated and a booklet of general stress management [12], but no further instruction. The program did not include any medication other than that given at study entrance. Furthermore, it did not include other maneuvers that might affect the ANS function independently. In addition, all participants were instructed not to change any medication during the observation period.

Minimizing bias

The following precautions were made to minimize bias: (1) The PPS device was designed in a manner that made the measurement non-visible to both instructor and patient until the end of each measurement; (2) blood pressure and heart rate were recorded after the PPS measurement as the PPS measurement is not fully automatically conducted, but involves the researcher applying pressure from the instrument to the chest bone of the patient; (3) the professional instructor measuring PPS and conducting TTT was blinded to the results of randomization; and (4) the patients were instructed before randomization not to reveal the result of randomization to the research personal performing the follow-up investigations after the three-month period.

Statistics

Non-parametric statistics were used, namely, Wilcoxon two-sample test for between-group analysis, Mann-Whitney one-sample test for with-in group analysis, and Pearson’s test for correlation analysis. Fisher’s Exact Probability Test was used for analysis of change in the frequency of ANSD risk factors after intervention. The statistical program, SPSS, version 18 (SPSS Inc, Chicago, IL, USA) was used for all analyses.

To control for potential bias from regression towards the mean in respect of the correlation between resting PPS and changes in PPS during TTT, the following measures were taken:

(A) In respect of testing for regression towards the mean for the correlation between resting PPS and change in PPS during the individual TTT: If change in PPS during TTT reflects a regression towards the mean phenomena, the correlation between first PPS measurement and change in PPS between first and second measurement should be the same as the correlation between first PPS and difference between first and third PPS measurement. The patient rests between first and second measurement. The third measurement is conducted after 1 min of TTT.

(B) In respect of the test for regression towards the mean for changes during intervention period: (i) By comparing active versus control treatment in respect of change in resting PPS and change in PPS response to TTT during the 3 months of intervention, it is possible to elucidate the potential bias from regression towards the mean. Any statistical between-group difference will suggest that an observed correlation between change in resting PPS and change in PPS response to TTT has an independent physiological background on top of any regression towards the mean effect. (ii) As for pre-treatment TTT, the post-intervention TTT includes two PPS measurements after 10 min of rest, and a third measurement after 1 min of tilting. If changes in PPS during TTT during 3 months of intervention reflect a regression towards the mean phenomena, only, the correlation between change in resting PPS during the three months of intervention and difference between first and second PPS measurement should be similar to the corresponding correlation between first and third measurement. (iii) With regard to 3-month changes in resting PPS versus 3-month changes in PPS response to TTT; if these changes should be exclusively a regression towards the mean phenomena, similar correlations should be found for the correlation between 3-month changes in resting PPS versus changes in PPS during post-intervention TTT, when first and second PPS measurement is compared to first and third PPS measurement; and similarly when 3-month changes for the difference between first and second PPS measurement is compared to the 3-month difference between first and third measurement.

Results

Analysis for possible regression towards the mean

(A) Test for regression towards the mean with regard to the correlation between resting PPS and change in PPS during the individual TTT: For baseline measurements the correlation coefficient between first PPS measurement and change in
PPS between first and second measurement was $r = -0.07$ ($p > 0.1$) ($n = 361$) versus $r = -0.34$ ($p < 0.0001$) for the correlation between first PPS and difference between first and third PPS measurement. There is a significant difference between the two correlation coefficients ($p < 0.0001$). For post-intervention measurement, the correlation coefficient between first PPS measurement and change in PPS between first and second measurement was $r = -0.01$ ($p > 0.1$), compared to $r = -0.42$ ($p < 0.0001$) ($n = 181$) for the correlation between first PPS and difference between first and third PPS measurement. There is a significant difference between the two correlation coefficients ($p < 0.0001$).

(B) In respect of testing for regression towards the mean for changes during intervention period: (1) When the group of patients who received active treatment ($n = 86$) was compared to the group who received control treatment ($n = 95$) in respect of the effect of the three months intervention, the active group obtained: (i) A significant reduction in resting PPS (mean change from 82–60 PPS units in active group, compared to mean change from 81–72 in the control group) (between-group $p < 0.0001$) ($n = 181$); (ii) a significant increase in the PPS response to TTT, as measured during the first minute of TTT (mean change in PPS from −4.5 PPS units to +0.9 PPS units in the active group, compared to mean change in PPS from −2.9 PPS units to −1.6 PPS units in the control group (between-group $p = 0.015$). When the PPS response was measured during the entire 7-min length of TTT; the corresponding changes were from −5.1 to −0.6 in the active group, compared to −4.4 to −3.0 in the control group (between-group $p = 0.07$). The within-group difference was significant in the active group ($p = 0.008$) and not significant in the control group ($p > 0.1$). Furthermore a significant between-group difference was found between reduction in number of ANSD risk factors (mean number from 2.0–1.2 in the active group, compared to mean number from 1.9–1.6 in the control group; between-group $p < 0.0001$).

(2) For the correlation between change in resting PPS and the change in PPS during post-intervention TTT, correlation between change in resting PPS and difference between first and second PPS measurement was: $r = 0.14$ ($p = 0.06$) versus $r = -0.34$ ($p < 0.0001$) for the correlation between change in resting PPS and difference between first and third measurement. There is a significant difference between the two correlation coefficients ($p < 0.0001$).

(3) In respect of 3-month changes in resting PPS versus 3-month changes in PPS response to TTT, the correlation coefficient between 3-month changes in resting PPS and 3-month changes in difference between first and second PPS measurement was: $r = 0.25$ ($p = 0.001$) versus $r = -0.41$ ($p < 0.0001$) for the correlation between 3-month change in resting PPS versus 3-month change in difference between first and third PPS measurement. There is a significant difference between the two correlation coefficients ($p < 0.0001$).

Cross-sectional study

During TTT, mean PPS was reduced significantly from 65–61 units (SD: 19 units and 20 units, respectively); mean SBp decreased from 137–131 mm Hg (SD: 18 and 26 mm Hg, respectively), whereas mean HR increased from 61–67 beats per min (SD: 10 and 14 beats per minute, respectively) (all $p < 0.0001$ ($n = 361$).

The change in PPS during TTT correlated positively to the change in SBp ($r = 0.44$) and HR ($r = 0.49$; both $p < 0.0001$ ($n = 361$); that is for example the higher the increase in PPS the higher was the increase in SBP and HR. Similarly, changes in SBP correlated positively to changes in HR during TTT ($r = 0.58$, $p < 0.0001$).

The higher the resting PPS, the lower was the PPS response to TTT ($r = -0.37$; $p < 0.0001$) (Figure 2). Resting PPS did not correlate to the SBP or HR response to TTT (both $r < 0.05$ and both $p > 0.1$).

When resting PPS of 60 units was used as the discrimination point for an elevated level of persistent stress, the changes in PPS during TTT for the group with resting PPS < 60 ($n = 155$), was (mean ± SD) +1 ± 11 units compared to −7 ± 18 units for the group with resting PPS ≥ 60 ($n = 206$; between-group $p < 0.0001$).

![Figure 2. Cross-sectional study: The association between baseline resting PPS and change in PPS during baseline TTT (delta PPS Tilt test); $r = -0.37$; $p < 0.0001$ ($n = 361$).](image-url)
Concerning comorbidity in respect of ANSD risk factors; 31% had chest pain at rest, 63% had elevated systolic blood pressure according (resting SBP ≥ 130 mm Hg), 9% had depression (MDI score ≥ 20), and 58% had PPS ≥ 60. On including these four additional risk factors for ANSD, it was observed that the higher the number of ANSD risk factors, the lower was the PPS response to tilting \((r = -0.21, p < 0.0001)\) \((n = 361)\) (Figure 3). The mean change in PPS during TTT was + 4 units for those subjects with no extra risk factor \((n = 28)\), − 2 units for one additional risk factor \((n = 148)\), − 5 units for two \((n = 134)\), − 8 units for three \((n = 46)\), and − 19 units for four additional risk factors \((n = 5)\) (Figure 3). No significant correlations were found between number of ANSD risk factors and changes in SBP or HR during TTT (both \(r < 0.01, p > 0.1\) ) \((n = 361)\).

**Intervention study**

The obtained changes in resting PPS during the 3-month intervention period correlated negatively to the PPS response to TTT performed after 3 months and after the intervention \((r = -0.38; p < 0.0001)\) \((n = 181)\) (Figure 4); i.e. the greater the reduction in resting PPS over time, the more positive was the PPS response to TTT at 3 months. A total of 79 patients obtained a reduction in PPS ≥ 15 units over 3 months (responders), which was regarded as the minimum relevant clinical difference (MID); 53 out the 86 patients in the active group (61%) and 26 out of the 95 patients in the control group (27%) (between-group \(p < 0.0001\) ) (Odds ratio for becoming a responder: 4.1 (95% confidence limits 2.2–7.7). The 79 responders demonstrated a significant increase in PPS during TTT at 3 months follow-up examination (mean ± SD): + 4 ± 11 units (intragroup \(p < 0.0001\) ), whereas the 101 non-responders (i.e. persons obtaining a change < 15 PPS units in resting PPS) demonstrated a significant decrease in PPS during TTT: − 6 ± 13 (intragroup \(p < 0.0001\) ) (\(p\) value for difference between responders and non-responders < 0.0001).

The change in PPS response to TTT from baseline to post-intervention at 3 months was calculated (e.g. the PPS response to TTT at 3 months minus the same response at baseline). As such, the change in PPS response to TTT during the 3 months of intervention correlated to the change in resting PPS during the same period \((r = -0.52, p < 0.0001; n = 181)\) (Figure 5); that is, the greater the reduction in PPS over 3 months, the greater the increase in the PPS response to TTT over 3 months. This correlation

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![Figure 3](image1.png)  
**Figure 3. Cross-sectional study:** The association between mean change in PPS during TTT and number of ANSD risk factors, including chest pain at rest, hypertension (SBP ≥ 130), depression (MDI score ≥ 20), and elevated level of persistent stress (resting PPS ≥ 60 units); \(r = -0.21, p < 0.0001\) \((n = 361)\). The horizontal lines indicate 95% confidence intervals.

![Figure 4](image2.png)  
**Figure 4. Intervention study:** The association between change in resting PPS during intervention period and change in PPS response to TTT (Delta PPS Tilt test after intervention); \(r = -0.38, p < 0.0001\) \((n = 177)\). Vertical line indicates minimal important difference (see text) with respect to reduction in resting PPS (defined as 15 PPS units).

![Figure 5](image3.png)  
**Figure 5. Intervention study:** The association between change in resting PPS during intervention period and change in PPS response to TTT during intervention period: \(r = -0.52, p < 0.0001\) \((n = 177)\). Vertical line indicates minimal important difference (see text) with respect to reduction in resting PPS during intervention period (defined as 15 PPS units).
A significant increase in PPS response to TTT over the 3-month period was found. The mean change in PPS units was +12 ± 16 for responders (intra-group p < 0.0001) and +23 ± 16 for non-responders (intra-group p = 0.02). The correlation coefficient was 0.50 for active and control group, respectively (both p < 0.0001). On performing the same analysis in the subgroups of responders and non-responders, the responders demonstrated a significant increase in PPS response to TTT over the 3-month period (mean change ± SD): +12 ± 16 PPS units (intra-group p < 0.0001) in contrast to a significant decrease for non-responders: −4 ± 17 (intra-group p = 0.04) (between-group p < 0.0001). In the active group 38 of the 86 patients (44%) obtained an increase in the PPS response to TTT compared to 20 out of the 95 patients in the control group (20%) (between-group p > 0.0001). The odds ratio to obtain a positive PPS response to TTT is: 3.1 (95% confidence limits: 1.6–6.0). However, among patients in the responder group, an increase in the PPS response to TTT was found in 72% and 73% of the patients in the active and control group, respectively (between-group p > 0.1).

The change in resting PPS during the 3 months of intervention did not correlate to the change in SBP and HR response to TTT during the three months (both r < −0.05, both p > 0.1). The SBP and HR response to TTT did not change significantly during the three months of intervention (both p > 0.1).

The number of ANSD risk factors decreased significantly during the intervention period (p < 0.0001), and the reduction in number of ANSD risk factors correlated significantly to the change in PPS response to TTT over time (r = −0.23, p = 0.003) (n = 181); i.e. the greater the increase in PPS response to TTT during the three months of intervention, the greater the reduction in numbers of ANSD risk factors. For responders, the mean frequency of ANSD risk factors was reduced by 0.7 compared to 0.1 for non-responders (p < 0.0001). The reduction in number of ANSD risk factors did not correlate significantly to the change in SBP or HR response to TTT during the 3 months of intervention (r = 0.08, and r = 0.02, respectively (both p > 0.1). The correlation coefficient for the association between reduction in number of ANSD risk factors and the change in PPS response to TTT during the 3 months was significantly different from that of SBP (p = 0.005) and that of HR (p = 0.02).

**Results from one-minute TTT**

At the baseline examination the changes in one-minute PPS response to TTT correlated significantly to resting PPS (r = −0.39, p < 0.0001) (n = 361), and to number of ANSD risk factors (r = −0.21, p < 0.0001). Similarly, the change in one-minute PPS response to TTT during the 3 months of intervention correlated significantly to change in number of ANSD risk factors (r = −0.18, p = 0.01) and change in resting PPS (r = 0.50, p < 0.0001). One-minute PPS response to TTT did not correlate significantly to the corresponding changes in HR (r = 0.00; p > 0.1) or SBP (r = −0.01; p > 0.1) (n = 361).

**Discussion**

The present study demonstrated that the pain sensitivity threshold on the chest bone, measured as PPS both during rest and as the response to a TTT, seems to reflect the adrenergic function of the autonomic nervous system as assessed by the tilt table test. As such, the present study demonstrated several novel findings:

1. The PPS response to TTT was negative in subjects with stable IHD.
2. An elevated resting PPS was associated with a negative PPS response to TTT.
3. The PPS response to TTT varied in parallel with that of SBP and HR during TTT.
4. The higher the number of four independent risk factors for ANSD (chest pain at rest, hypertension, depression, and elevated resting PPS) present in a patient with stable IHD, the more negative was the PPS response to TTT, implying that the magnitude of the negative PPS response to TTT seems to reflect the degree of ANS dysfunction.
5. A reduction in an elevated resting PPS after a period of 3 months of non-pharmacological stress intervention was associated with an increase in the PPS response to TTT as well as a reduction in the number of ANSD risk factors, with an internal correlation between the reduction in numbers of ANSD factors and the increase in PPS response to TTT.

**PPS and autonomic nervous system function evaluated from TTT**

TTT causes a transient increase in sympathetic tone in the initial 5–10 minutes in a healthy population associated with small changes of HR and SBP, typically an unaltered or small increase of HR and an unaltered or small decrease of SBP [4]. In the present population of patients with stable IHD, we found small but significant changes during TTT, with reductions both of PPS and SBP, increase of HR, and a strong internal correlation among the three. Tilt table test is widely used in research and clinical settings for assessment of adrenergic autonomic (dys)function in cardiovascular conditions such neutralally mediated syncope, the postural tachycardia syndrome or orthostatic hypotension [13], as well as in non-cardiovascular conditions such as diabetes [14], fibromyalgia [15] and vitamin B-12 deficiency [16].

Pain sensation, as measured by PPS, reflects the sensation mediated by the subcutaneous sensory nociceptive C-fibers, and with the polymodal sensor cell as the sensory unit. These sensors have a widespread distribution in the body [17], and are sensitive to sympathetic drive [18]. Increased PPS (or reduced pain threshold) of the chest bone is seen during acute stress, which we have demonstrated in opera solo
singers immediately after the peak of their performance (conducted using backstage measurements), and with a lower PPS before and after one hour of the performance [17]. In this condition, PPS varied in parallel to SBP and HR [17], probably reflecting the transient dynamics of the sympathetic drive [19]. As such these findings are in line with the present study, suggesting that PPS reflects transient changes in sympathetic drive.

Increased pain sensation is also found during conditions with a persistent stress burden, as in people suffering from chronic diseases as IHD [6], migraine [20], post traumatic stress syndrome (PSTD) [21], as well as in patients with a chronic pain syndrome, such as fibromyalgia and irritable bowel syndrome [22]. The latter situations are governed by a state of pronounced generalized pain sensation, which is thought to be due to a disturbance in the afferent-efferent pain sensation system: The diffuse noxious inhibitory control system (DNIC) [23], and associated with depression, anxiety, and reduced quality of life [24]. We have previously measured PPS as a measure of pain sensation in both people with stable IHD [6] and in otherwise healthy office workers [7] and found an association between increased PPS on the one side and depression, increased number of clinical stress symptoms and reduced quality of life on the other. Taken together these data suggest that PPS at rest reflects persistent stress.

Increased pain sensation and persistent stress have further been linked to ANSD in chronic pain conditions, such as fibromyalgia, irritable bowel syndrome, and migraine [20,25] as well as in post traumatic stress syndrome [26]. In the present study, resting PPS was associated with the PPS response to TTT; i.e. the higher the resting PPS, the more negative the PPS response to TTT. We also observed that patients with an increased persistent stress burden by means of an elevated resting PPS (i.e. ≥60 units) demonstrated a lower and negative PPS response to TTT when compared to those subjects with a resting PPS below 60 units. This suggests that a reduced or even negative PPS response to TTT is associated with a high level of persistent stress. The SBP and HR response to TTT is generally accepted as one way to assess ANS function [1]. We found a close link between the PPS, SBP and HR response to TTT. Accordingly, the present findings may suggest a bridging between ANS function and the PPS response to TTT, suggesting that the resting PPS and the PPS response to TTT might be used as a measure of ANS function.

The ANSD is regarded as an independent prognostic factor in heart disease in regard to survival and myocardial infarction risk [1]. In the present study, we found that an increase in the number of four generally accepted signs of ANSD (chest pain at rest, depression, elevated blood pressure, and persistent stress by means of PPS measurement at rest [7,27]), was associated with an incremental reduction in the PPS response to TTT (Figure 2); as such a positive PPS response of + 4 PPS units was seen in patients having none of the risk factors, and a negative PPS response of − 19 PPS units was seen in patients having all four risk factors. Furthermore, when an elevated resting PPS was reduced, the PPS response to TTT became positive, which was associated with a reduction in the number of ANSD risk factors. Against this background, the present data support the hypothesis that pain sensation as measured by PPS, both in the resting state and after tilting, reflects ANS dynamics as well as ANSD.

**Effect of intervention aiming at reducing PPS**

The second part of our study was an interventional part, in which we encouraged the patients with stable IHD to increase their empowerment regarding stress handling by using PPS measurements at home on a daily basis as a biofeedback-guided stress-handling approach. For the purpose of the present study, we merged the active and the control group, which could be done due to no between-group differences at baseline, and because we only used behavioral therapy and no pharmacological intervention. Thus, the therapy did not interfere with pain sensation or response to TTT. We measured resting PPS and response to TTT before and after a 3-month period. The resting PPS decreased rather pronounced during the 3-month period; mean = 15 units, and with a significant between-group difference (more pronounced in the active group). The scale on the PPS instrument varies from 30–100, and a decrease of 15 units corresponds to a 50% increase in the absolute pressure placed on the sternum [5]. We regard this finding as a clinically relevant reduction in pressure sensitivity. The decrease in resting PPS was associated with a recovery of the PPS response to TTT. This was confirmed when comparing the reduction in resting PPS over 3 months with (i) the PPS response to TTT at 3-months follow-up, and (ii) the change in the PPS response to TTT over the 3-month period. Furthermore, those patients with a reduction in resting PPS greater than 15 units (defined as responders) during the study period, demonstrated a positive response in PPS to TTT at 3 months follow-up when compared to those who did not obtain this effect (defined as non-responders). In addition, although the number of responders was significantly higher in the active group when compared to the control group, but among the responders, no significant between-group difference was found in regard to increase in the PPS response to TTT, suggesting that the increase in PPS response to TTT was obtained from the reduction of resting PPS, rather from the choice of method to reduce the resting PPS. Saying so, the odds ratio for obtaining
the MID effect in resting PPS was four times and significantly higher in the active group when compared to the control group. Furthermore, a strong correlation was found between change in resting PPS and change in PPS response to TTT during the observation period.

The number of ANSD risk factors decreased during the intervention period, and the between-group difference was statistically significant when the active and control groups were compared. This change correlated to the change in PPS response to TTT over the 3-month intervention period. These data support the finding at baseline that resting PPS and the PPS response to TTT might reflect ANS dynamics and the burden of ANSD in patients with stable IHD. The findings also suggest that reducing an elevated resting PPS may improve ANSD.

Strengths and limitations

The strengths of this study were: (i) The large number of participants studied; (ii) the use of a well-established experimental procedure with a fully controlled stimulation of ANS, such as TTT; and (iii) the previously tested used PPS discrimination point for an elevated level of persistent stress [5,7]. A limitation of this study may be that a similar study has not been conducted, thus excluding the possibility to relate the present findings to findings by other research groups. It may be questioned if the correlation between changes in PPS and changes in PPS response to TTT as well as the correlation between change in resting PPS during the months of intervention and the change in PPS response to TTT during the same period are subject to ‘regression towards the mean bias?’ We have addressed this issue comprehensively, and found no significant impact.

Conclusions

Resting PPS seems to reflect the autonomic nervous system function and thus its dysfunction in patients with stable ischemic heart disease. A reduction of an elevated PPS in a prospective manner over 3 months was associated with a restoration of autonomic nervous system dysfunction as measured by a table tilt test, as well as a reduction in number of risk factors.

Acknowledgements

We are thankful to the staff of the Metabolic Ward for their contribution: Helle-Marina Oxfeldt and Tine Skogen-Lassen. We also thank the staff at the Rehabilitation Unit at Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark, for providing us with their database on patients with IHD who had completed cardiac rehabilitation. We thank Prof. Niels H. Secher, MD, DMSci, Department of Anaesthesiology, Rigshospitalet, Denmark, for a critical review of the manuscript.

Funding

This work was supported by the Johan Schroder’s Family and Business Foundation. Natasha Bergmann holds a pre-graduate scholarship sponsored by the Lundbeck Foundation.

Declaration of interest: Søren Ballegaard invented the PPS instrument used to measure PPS. He is also a shareholder of the company that owns the PPS instrument. To avoid bias, he was not involved in the patient contact, collection of data, or statistical analysis. No other disclosures were reported. The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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