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The association between changes in pressure pain sensitivity and changes in cardiovascular physiological factors associated with persistent stress

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Abstract

Objectives. To evaluate the possible association between pressure pain sensitivity of the chest bone (PPS) and cardiovascular physiological factors related to persistent stress in connection with a three-month PPS-guided stress-reducing experimental intervention programme. Methods. Forty-two office workers with an elevated PPS (≥ 60 arbitrary units) as a sign of increased level of persistent stress, completed a single-blinded cluster randomized controlled trial. The active treatment was a PPS (self-measurement)-guided stress management programme. Primary endpoints: Blood pressure (BP), heart rate (HR) and work of the heart measured as Pressure-Rate-Product (PRP); Secondary endpoints: Other features of the metabolic syndrome. Results. PPS decreased and changes in PPS after the intervention period were significantly associated with HR, PRP, body mass index (BMI) and visceral fat index (all correlation coefficients > 0.2, p < 0.05). Compared to the control cluster group, the active cluster group obtained a significant reduction in PPS, Low-density lipoprotein (LDL) cholesterol and total number of elevated risk factors (p < 0.05). On an individual level, significant and clinically relevant between-group reductions were observed in respect to BP, HR, PRP, total and LDL cholesterol, and total number of elevated risk factors (p < 0.05). Conclusions. The stress intervention method applied in this study induced a decrease in PPS which was associated with a clinically relevant decrease in resting blood pressure, heart rate, work of the heart and serum cholesterols.

Key Words: Stress, pressure pain threshold, blood pressure, heart rate, pressure-rate-product, BMI, cholesterol

Introduction

No international consensus on biochemical, psychological, or physiological methods for measuring stress conditions exists [1,2]. This is due to the difficulty of identifying one consistent and single measure of stress, since the individual stress response is complex and involves most body functions [3].

In this context it is essential to distinguish between transient and persistent stress. Transient stress is characterized by increased preparedness, induced through neural and hormonal signals as a response to perception of a challenge like a dangerous or painful situation, or the demand of an acute performance. When the challenge is over, homeostasis is re-established [4,5]. In contrast, persistent stress is caused by prolonged exposure to the same challenges as in transient stress, but without sufficient restitution in between, which may lead to a variety of physiological and psychological dysfunctions [6,7]. Persistent stress may affect work performance [8], as well as general health negatively [9], and seems associated with the development of elements of the metabolic syndrome (i.e. hypertension, disturbed cholesterol and glucose metabolism, and abdominal fat distribution) [10–12], as well as ischemic heart disease, depression, and type 2 diabetes [3,13]. Post Traumatic Stress Syndrome (PTSD) is also regarded as a result of persistent stress, and a direct link between PTSD and cardiovascular disease has been suggested, with the metabolic syndrome, autonomic dysfunction,
insulin resistance and low grade inflammation as the key potential common pathways [14, 15].

Since stress is not directly measurable, physiological markers such as heart rate, blood pressure, plasma catecholamines and plasma or salivary cortisol levels are often used, together with behavioral observations and answers to personal questionnaires. The physiological markers are regarded as the most objective [5]; however, they are also influenced by other factors than stress such as physical activity, smoking, and diurnal variation [6, 7]. Chronic stress is associated with widespread increased pain sensitivity [16], which may be due to activation of cutaneous polymodal nociceptors [17] responding to mechanical stimuli, noxious heat, and inflammatory mediators. These polymodal nociceptors are subject to modulation by cognitive and emotional processing in the brain [18], by attention [19], by social factors [20] and by sympathetic input [21]. This afferent-efferent system is designated the diffuse noxic inhibitory control system (DNIC), which may be regarded as a house-keeper with regard to pain sensation [22].

Pain sensation is measured by algometry, and we have developed a simple device which measures pressure pain sensitivity of the chest bone blindly (PPS) [23]. PPS correlates closely to another pain-algometer which is often used for the evaluation of DNIC [24]. We have previously demonstrated that transient stress results in a short-term change in PPS which correlates closely to changes in blood pressure, pulse rate, work of the heart and saliva cortisol, and that PPS correlates to resting pulse rate and resting work of the heart in patients with chronic disease, mainly ischemic heart disease, thus bridging PPS to chronic stress. These correlations were absent when using index finger as a control measurement site [23]. In analogy, we found in two cross-sectional studies on 308 office workers and 361 patients with stable ischemic heart disease, that resting PPS was related to quality of life, degree of depression and clinical stress symptoms [24, 25].

In the present study we tested if a long-term reduction of an elevated resting PPS as a result of a stress-reducing program was associated with a concomitant decrease in established cardiovascular physiological and biochemical health risk factors previously shown to be associated with persistent stress. Accordingly, a reduction of an elevated PPS measure is a premise for the study, and a test with regard to the possible significant between-group effect of the used intervention is a secondary aim, only.

Methods

Study design

The study design is an experimental prospective interventional feasibility field study using natural, geographically selected cluster randomization. Prior to the start of the study, a pilot study in 36 students from two academic opera singing schools was used to test experimental set-up and form the hypotheses [26]: Is a reduction of an elevated PPS measure associated with a concomitant reduction in cardiophysiological and biochemical variables, which are linked to persistent stress, and in particular if these variables are elevated at baseline?

The randomization was conducted cluster-wise, based on six geographical different locations (i.e. offices). All participants from the one location were randomized to either an active or a control group in order to minimize bias from between-participant communication within each location. Since two locations had the highest number of employees, these two offices were allocated to each study-arm, in order to minimize the level of uneven numbers of office workers in the two study groups. The randomization was conducted for all locations at the same time, and for logistic reasons, it was done before the screening took place and with information of the participants after the screening. Since the numbers of participants at the sites were different, an inequality between numbers in the subsequent active and control groups had to be accepted.

The target group of the intervention, the hypotheses, the data collection and the data analysis focused on the individual participants, rather than the clusters. Furthermore, the study focused exclusively on persons with an elevated stress level, identified by a screening procedure, since we have previously demonstrated that a resting PPS ≥ 60 was associated with significantly elevated health risk factors evaluated from quality of life questionnaires related to persistent stress, when compared to subjects with a PPS < 60 [25]. Such a screening procedure, if effective, would be cost-effective in occupational relations when compared to the situation in which all employees are allocated to the intervention. Therefore subjects with a resting PPS ≤ 60 were excluded from this study.

Participants

All 433 office workers employed at an international insurance company were invited to participate in the study in which only persons with a resting PPS ≥ 60 (arbitrary units) were included. Three-hundred and eight (71%) accepted the invitation, 180 office workers underwent screening for participating in the active intervention group and 128 persons for participating in the control group. Twenty-one percent (n = 64) of the participants had a PPS ≥ 60 after 10 min of rest, of which 42 completed the study; 31 in the active group (18 female/13 males) (median age 36 years) (3 clusters) and 11 in the control group (8 female/3 males) (median age 33 years) (2 clusters). The study population has been described in detail previously [25]. The employees of this company were
chosen as they were accessible as well as they were regarded as representative for modern international office workers in general.

The interventions

The chosen control intervention served as a control with regard to stress management, but with no intentional focus on PPS. Accordingly, if PPS remained unchanged in this group during the observational period, the findings of this group could be used to address the potential influence from time (i.e. the three-month observational period) and unknown confounding factors.

(1) Active groups: Two hours of group instruction lecture in the Ull Care program (for detail, see below), including instruction of home PPS measurement. In addition a personal instructor providing 3 personal face-to-face technical consultations (lasting 30 min each) and 5 telephone consultations (lasting 15 min each) on the technical issues, only; a personal PPS measurement instrument and an Ull Care instruction booklet identifying the key issues of the program, access to both a web page for personal track recording of the PPS measure and a web version of the full Ull Care program (www.ullcare.com).

(2) Control groups: A 1-h group lecture on general stress management.

The Active Intervention: Ull Care®

Ull Care® is a stress-management program using the PPS measure as a biofeedback marker for stress. The main effort is a daily self-care program with a professional back-up dependent on demand. The program includes: (1) Daily mandatory PPS measurement at home as a behavioral guideline for the stress level, thus followed by reflection, as well as by daily acupressure; and (2) request to use supplementary stress reduction modalities based on one’s own preferences (relaxation, breathing and mindfulness exercises, physical exercises, cognitive exercises and diet). The program has been evaluated and found usable previously in open prospective observational clinical data base studies in patients with ischemic heart disease and stroke [33–35].

Procedure

PPS, blood pressure and heart rate were recorded on each office location, after 10 min of rest in supine position and before blood sampling. All data were recorded before and after the three-month period of observation. The subjects were informed not to smoke tobacco, drink coffee or alcohol, take medication or do heavy physical exercise 2 h prior to the examinations.

Minimizing bias

The following special precautions were taken to minimize bias: (i) Block randomization was used in order to minimize effect bias from the between-participant communication within each location; (ii) the reading of the PPS instrument was not visible during measuring; (iii) recordings of blood pressure and heart rate were done after measuring PPS as the PPS measurement is not fully automatically conducted but involves the researcher applying pressure from the instrument to the chest bone of the subject; (iv) the intervention was conducted at home by the individual participant; and (v) the professionals conducting the physiological measurements and blood sampling were blinded with regard to the randomization of the participant.

Outcome measures

PPS was the experimental key endpoint, since a change in PPS was the premise for the study design.

Study endpoints

Primary endpoints were: Cardiac physiological measures: Blood pressure (BP), heart rate (HR), work of the heart measured as Pressure-Rate-Product (PRP).

Secondary endpoints were: Results of blood tests (with regard to glucose metabolism, fat metabolism, inflammation and stress response), body composition, BMI and total number of elevated risk factors. Compliance was measured by the frequency of which the participants put their PPS measurements into their web journal. All endpoints were regarded as individual endpoints, in order to study the possible association between PPS and the included physiological and biochemical risk factors, when an intervention with the target to reduce an elevated PPS measure was introduced. And as such, the study could only meet its primary aim if PPS on an individual basis was reduced after intervention; consequently, the analysis of a potential significant between-group effect of the intervention for the used variables is the secondary aim of the study, only.

Pressure pain sensitivity (PPS)

An algometric instrument (Ull Meter, UllCare Ltd, DK 2900 Hellerup, Denmark) was used for measurement of the pressure pain sensitivity on the sternum [23]. For analysis, the mean of two consecutive measurements was used; if the between-measurement difference was more than 10 arbitrary units, a third measurement was performed and the result was calculated as the mean of all three. Measurements were carried out with the participants in the supine position after 10 min of rest.
Pressure pain sensitivity and intervention

Blood pressure, heart rate and Pressure-Rate-Product

Blood pressure (mm Hg) and heart rate (beats/min) were recorded by Thuasne automatic blood pressure monitor, model W0840 002 001 (Microlife ref. BP3-AA1-2, BP 243 - 92307 Levallois-Perret Cedex, France). For analysis, the mean of two consecutive 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 all three. The measurements were conducted in the supine position after 10 min of rest. Pressure-Rate-Product (PRP) (mm Hg x beats/min) was calculated as systolic blood pressure (SBP) x heart rate.

Elevated cardiovascular physiological measure and Minimal Important Difference

The following points of discrimination were used when defining an elevated cardiac risk factor: Resting heart rate (HR) (≥ 70 beats/min) [27], resting blood pressure (BP) (≥ 130/85 mmHg) [28], and consequently resting Pressure-Rate-Product (PRP) (≥ 9100 mmHg x beats/min), total cholesterol (≥ 5.0 mmol/L) [29], and Hb1Ac (≥ 5.0%). A Minimal Important Difference (MID) from before to after intervention was defined as ≥ 10% reduction, if elevated at baseline. As in the pilot study, the total number of elevated risk factors is used as a composite secondary endpoint.

Body mass index (BMI)

The weight and height of each participant were measured; body mass index (kg/m²) was calculated as weight/height².

Body composition

Visceral fat (arbitrary units) were measured using a bioelectrical impedance tetra polar device, which includes both metal footpads and hand electrodes (Body Composition Monitor, Omron BF-500 [Omron Medizintechnik, Mannheim, Germany]) [30].

Blood analyses

Blood analyses were conducted on blood samples obtained after overnight fasting for the evaluation of: (1) Glucose metabolism: Hemoglobin A1c (HbA1c) (routine laboratory method), (2) Fat metabolism: Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations (routine laboratory methods); (3) Low grade inflammation: YKL-40 (as measured by ELISA, Quidel, CA, USA). YKL-40 reflects the innate immune system and as such is a marker of low grade inflammation, and seems to be independently associated with the development of cardiovascular disease [31,32].

Statistics

Non-parametric statistics were used due to the small number of participants and a skewed distribution of the included variables (Wilcoxon two-sample test for between-group analysis, Mann-Whitney one-sample test for within group analysis, and Pearson’s test for correlation analysis). Response rate was calculated as the number of persons in the active group with a reduction of minimum one measurement unit in the effect variable divided by the total number of persons in the active group completing the trial. Between-group difference with regard to ratio of elevated risk factors, Fischer’s exact test was used. Two-sided analysis was used in the intervention part and one-sided statistics in the test of association between PPS and cardiovascular physiological variables, as the latter previously has been tested positively [23,26].

Correlation between PPS and cardiovascular physiological factors

To test the possible association between PPS and cardiovascular physiological factors related to persistent stress, the following challenges need to be addressed: (i) A PPS measure may reflect both acute and chronic (persistent) stress [23], and an association to a physiological parameter or a cardiovascular risk factor may require a more persistent stress burden and thus PPS elevation for a prolonged time, as it, for example, has been suggested with regard to blood pressure [36]; (ii) both PPS as well as cardiovascular physiological risk factors such as blood pressure and serum cholesterol might only be influenced in a positive way by stress intervention if these variables are elevated at baseline; (iii) the used cardiovascular factor may be elevated for other reasons than persistent stress; in this case, the risk factor may be elevated without a corresponding elevated PPS; (iv) an intervention with the aim to reduce stress may only affect the stress component of the cardiovascular physiological factor; (v) in order to elucidate the effect of time, while eliminating potential bias from unknown confounding factors, data from pre- to post-observation period may be pooled as these, yet unknown confounding factors are expected to remain stable within an individual during the observation period, a hypothesis which is tested by correlation analysis of pre- and post-observation period values for each effect variable. In conclusion, the correlation between PPS and the used cardiovascular physiological factors may be (1) conditional (example: If the level of persistent stress has been elevated for a certain period of time), (2) partial (example: The link...
is related to the stress component of the physiological variable, only), (3) heterogeneous (example: Be influenced by a heterogeneous distribution of yet unknown confounding factors [social-economic variables and gender as such examples] within or between the study groups), (4) multi-factorial (example: The link is mediated by the central cardiovascular regulatory systems as the common nominator), and (5) and/or non-linear (example: One variable needs to change to certain degree in order to induce changes in another variable, as is observed in pharmaceutical treatments).

In the present study, these challenges are met as follows: (1) Only patients with an elevated resting PPS measure were included in this study; (2) pooled data from before and after treatment were used in order to eliminate the possible bias from the correlations being partial, conditioned, heterogeneous or non-linear, as well as the possible bias from person related psycho-social and psychological factors, as such factors were considered stable within the observation period; and (3) furthermore, with bias from these factors being eliminated, the effect of time could be addressed by having a control group which was expected to have unchanged PPS during the observational period. As statistical correlation analysis for repeated data samples does not exist, the statistical significance of observed correlation coefficients is based on independent samples, as this methodological shortcoming was considered of minor clinical importance.

Cluster analysis

The cluster randomized design was taken into account in the analysis by means of a general linear mixed model in a variance components setting where subjects are nested within groupings (intervention/control). Subjects within locations and locations are the variance components and are assumed random. Groupings are a fixed effect. A possible effect of intervention is then correctly tested against locations within groupings in the balanced case. Since this case is unbalanced, a Satterthwaite approximation is used to find the correct variance and degrees of freedom to use [37]. In order to perform the analysis in a non-parametric manner each variable was rank transformed before analysis. This analysis was performed using the GLM procedure, SAS 9.3. The statistical program SPSS, version 18 (SPSS Inc, Chicago, IL, USA) was used for all other analyses.

Results

Baseline data

Data for the study group are presented in Table I. Forty-two percent of the 42 subjects completing the trial had elevated systolic BP (≥130 mm Hg), 23% elevated diastolic BP (≥85 mm Hg), 25% elevated resting HR (≥70 beats/min), 27% elevated PRP (≥9100 mmHg beats/minute), 55% elevated BMI (≥25), 59% elevated serum total cholesterol (≥5.0 mmol/L), and 40% elevated Hb1Ac (≥5.0%) with no significant differences between the active and the control group, or between groups of subjects who completed or dropped out.

Correlations between PPS and cardiovascular physiological and metabolic factors

For all used cardiovascular physiological factors and metabolic syndrome characteristics the correlation between pre- and post-observation period variables

Table I. Physiological and biochemical data on the office worker population divided into active and control group. For each group is shown baseline and follow-up data. Within-group differences are shown for each group. In addition between-group differences are shown in respect to effect, measured as difference between before and follow-up values. No significant between group differences were observed at baseline (all p > 0.1). All values are shown as median (Inter quartile range).

<table>
<thead>
<tr>
<th></th>
<th>Active group (n = 31)</th>
<th>Control group (n = 11)</th>
<th>p-value for change between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After intervention</td>
<td>Baseline</td>
</tr>
<tr>
<td>PPS (resting) (arbitrary units)</td>
<td>77 (16)</td>
<td>45 (30)***</td>
<td>77 (21)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 (15)</td>
<td>117 (17)***</td>
<td>122 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80 (13)</td>
<td>75 (11)***</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 (14)</td>
<td>66 (11)</td>
<td>63 (25)</td>
</tr>
<tr>
<td>PRP (mm Hg × beats/min)</td>
<td>8591 (2706)</td>
<td>7638 (1920)***</td>
<td>7722 (2330)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 (4.0)</td>
<td>24.8 (4.7)</td>
<td>24.7 (5.3)</td>
</tr>
<tr>
<td>Visceral fat (arbitrary units)</td>
<td>7 (3)</td>
<td>6 (3)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.0 (0.3)</td>
<td>5.0 (0.2)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4 (1.1)</td>
<td>4.6 (1.4)***</td>
<td>5.0 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.4 (0.8)</td>
<td>1.4 (0.5)</td>
<td>1.5 (0.5)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.3 (1.4)</td>
<td>2.7 (1.3)***</td>
<td>3.0 (1.3)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.0 (0.6)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.8)</td>
</tr>
<tr>
<td>YKL-40 (µg/L)</td>
<td>44 (22)</td>
<td>49 (40)</td>
<td>41 (22)</td>
</tr>
<tr>
<td>Elevated Risk factor (number)</td>
<td>2 (2)</td>
<td>1 (2)***</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

***p < 0.001; ns = non significant.
Pressure pain sensitivity and intervention

Physiology (resting PPS) was not significantly influenced by unknown confounding factors during the observation period, which makes pooling of pre- and post-observation period data for analysis possible.

Pooling the data from baseline and after three months follow-up (n = 42), PPS correlated significantly to systolic BP (r = 0.24; p = 0.01), BMI (r = 0.34; p = 0.003), visceral fat index (r = 0.26; p = 0.02), serum total cholesterol (r = 0.23; p = 0.04), LDL cholesterol (r = 0.21; p = 0.05), and triglyceride (r = 0.23; p = 0.04). Correlations to diastolic BP and PRP only showed trends (both p = 0.06).

Changes in PPS during the intervention period correlated to changes in HR (r = 0.42; p = 0.003) (n = 42), PRP (r = 0.30; p = 0.03), BMI (r = 0.44; p = 0.01), visceral fat index (r = 0.39; p = 0.02), YKL-40 (r = 0.44; p = 0.01), and total cholesterol (r = 0.2; p > 0.1), while for Hb1Ac the correlation was only significant for the group with elevated Hb1Ac at baseline (r = 0.57, p = 0.01) (n = 17) (Figure 1).

When further reviewing the correlation between changes in PPS and heart rate (Figure 2), it was found that among the 11 participants in the active group with an elevated HR (≥ 70) at baseline, 10 experienced a reduction in HR after intervention (p < 0.01) and all 11 experienced a decline in PPS. In contrast, among the participants with a normal HR and an elevated PPS, a reduction in PPS after the intervention was not associated with a corresponding decline in HR (p > 0.1). Among subjects with a normal heart rate at baseline a significant number of participants had an elevated heart rate at the follow-up examination (p = 0.002) (Fisher Exact Probability Test). Concerning PRP, systolic and diastolic blood pressure and serum cholesterol similar patterns were observed: Significant reduction for the subjects in the active group with elevated baseline values, whereas no significant changes were observed in the active group without elevated baseline values nor among the subjects in the control group with elevated baseline values (both p > 0.1).

**Effect of intervention**

At baseline, no significant between-group differences were observed. When compared to the control group, the individuals of the active group demonstrated a significant decrease in PPS (mean change in active group [95% confidence limits]: −25 [−14 to −25] versus control group: −9 [+1 to −20] (p = 0.003), SBP −13 mm Hg [−3 to −21] vs. −4 mm Hg [2 to −14] (p = 0.04); DBP −8 mm Hg [−2 to −1] vs. −2 mm Hg [5 to −6] (p = 0.02); HR−2 beats per min [3 to −6] vs. 5 beats per min [10 to −4] (p = 0.05); PRP −1000 mm Hg × beats per min [−400 to −2100] vs. −100 mm Hg × beats per min [1100 to −500] (p = 0.005); LDL cholesterol −0.5 mmol/L [−0.3 to −0.9] vs. −0.1 mmol/L [0.1 to −0.7] (p = 0.05); Total cholesterol −0.6 mmol/L [−0.4 to −10] vs. 0.0 mmol/L [0.1 to −0.8] (p = 0.02)).
In respect to the total number of elevated cardiovascular physiological risk factors (systolic blood pressure, diastolic blood pressure, heart rate, PRP, and/or serum total cholesterol), the median number in the active group was reduced from 2 at baseline to 1 after intervention (71% obtained a reduction) \( (p < 0.0001) \). In the control group the median number increased from 1 at baseline to 2 after intervention (20% obtained a reduction) \( (p > 0.1) \) (between-group difference: \( p < 0.003 \) ) (Table I). These changes corresponded to median reductions in the active group of 42% in PPS (response rate 90%) (e.g. response rate = the number of persons in the active group with a reduction in the effect variable divided by the total number of persons in the active group completing the trial), 10% in PRP (response rate 81%), 13% in total cholesterol (response rate 86%), and 16% in LDL cholesterol (response rate 90%) (all \( p < 0.001 \)). Participants in the active group who had elevated cardiovascular physiological risk factors at baseline demonstrated rather robust reductions: Elevated BP at baseline: 13 out of 14 participants (93%) showed a reduction in BP \( (p < 0.001) \); elevated HR: 10 out of 11 (91%) demonstrated a reduction \( (p < 0.01) \); elevated PRP: 10 of 10 (100%) demonstrated a reduction \( (p < 0.002) \); elevated total serum cholesterol: 11 out of 13 (85%) \( (p < 0.001) \); elevated LDL cholesterol: 14 out of 16 (88%) \( (p < 0.001) \) demonstrated reduction. In the control group, no significant differences were observed between pre- and post- treatment values (Table I).

When adjusted for cluster randomization a significant between-group difference in effect was found for PPS, LDL cholesterol and total number of elevated health risk factors (all \( p < 0.05 \) ) (Table II).

Among the participants in the active group no side-effects, complications or instrument failures were reported during the full length of observation period. In respect to compliance, their PPS measurements were recorded in the webjournal on average every other day during the first month of intervention, every third day during the second month and every fourth day during the third months.

### Table II. Cluster randomization adjustments showing: Individual and between-group significance, average cluster sample size, cluster intra class correlation coefficients, and between-cluster group significance test (one sided \( p \)-values).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Individual significance test</th>
<th>Average cluster sample size</th>
<th>Cluster intra class correlation coefficient</th>
<th>Cluster significance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta_PPS</td>
<td>0.002</td>
<td>8.4</td>
<td>0.18</td>
<td>0.01</td>
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<tr>
<td>Delta_SYS</td>
<td>0.02</td>
<td>8.4</td>
<td>0.41</td>
<td>0.20</td>
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<tr>
<td>Delta_DIA</td>
<td>0.04</td>
<td>8.4</td>
<td>0.42</td>
<td>0.05</td>
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<tr>
<td>Delta_HR</td>
<td>0.04</td>
<td>8.4</td>
<td>0.79</td>
<td>0.45</td>
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<tr>
<td>Delta_PRP</td>
<td>0.004</td>
<td>8.4</td>
<td>0.77</td>
<td>0.35</td>
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<tr>
<td>Delta_LDL</td>
<td>0.05</td>
<td>7.5</td>
<td>0.06</td>
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<tr>
<td>Delta_KOL</td>
<td>0.02</td>
<td>7.5</td>
<td>0.44</td>
<td>0.06</td>
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<tr>
<td>Delta_Sum_Risk</td>
<td>0.001</td>
<td>7.5</td>
<td>0.15</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### Discussion

In this prospective observer-blinded cluster randomized controlled interventional trial, in otherwise healthy office workers, it was found that a reduction of an elevated PPS was associated with statistically significant and clinically relevant reductions in resting blood pressure, heart rate, work of the heart (PRP), serum total and LDL cholesterol levels, and total number of elevated cardiovascular risk factors. The results suggest a causal association between PPS and a variety of important cardiovascular physiological factors and metabolic syndrome characteristics associated with persistent stress: Heart rate, blood pressure, work of the heart (PRP), total cholesterol, LDL cholesterol, triglyceride, BMI, visceral fat, the inflammation marker YKL-40, and long-term glucose levels. Accordingly, PPS may be able to identify a group of office workers who will benefit from a stress-reducing intervention program. In continuation of this, the study results suggest we should use any interventional method to reduce an elevated resting PPS.

The stress-reducing intervention program used in this study was associated with a clinically relevant change in several cardiovascular physiological factors in the active group, and without any risk to the person in connection with home use of the PPS measurement device during a three-month period. A variety of factors known to be associated with persistent stress, such as markers of cardiac physiology, fat distribution and metabolism, glucose metabolism, and vascular inflammation were all correlated in a meaningful way to PPS, when a reduction of an elevated PPS was reduced experimentally. This may suggest a common mechanism behind the observed correlations. This is in accordance with the findings of others, suggesting a link between persistent stress, cardiovascular physiology and the metabolic syndrome \([11,12,38,39]\), indicating a common physiological disturbance in hypertension, obesity, diabetes mellitus, metabolic syndrome and persistent stress \([40,41]\).
For BP, HR, PRP, serum total and LDL cholesterol, and total number of elevated cardiovascular physiological risk factors, they all decreased significantly and concomitantly with PPS in the active group during the intervention period. They were, however, not reduced significantly and concomitantly with a reduction in PPS neither among the control group nor among subjects in the active group who had elevated baseline PPS, but a normal BP, HR, PRP, serum total and LDL cholesterol. One may question if our observation presents the ‘regression towards the mean’? However, among the group with normal HR at baseline, a significant number had elevated HR at the follow-up examination, when compared to baseline. Furthermore, the total number of elevated risk factors was reduced in the active group and increased in the control group, with a significant between-group difference. These observations counteract the ‘regression towards the mean’ hypothesis. On this background it may be suggested that the observed effects of a reduction in PPS may be related to a stimulation of existing cardiovascular homeostatic mechanisms.

We have previously stated [23] that the observed stress-induced hyperalgesia of the chest region, probably mediated by specific cutaneous polymodal nociceptor sensor cells, represents a meaningful survival response by unconsciously increasing the warning system sensitivity (i.e. the PPS measure) and defense system reactivity (i.e. the withdrawal reflex) [19,42]. This notion is supported by the previous finding that PPS is correlated to another marker for increased sensitivity, the startle and noxious withdrawal reflex [23,25], and by the fact that a hypersensitive startle reflex is part of the diagnostic criteria for the PTSD [43].

Limitations and strengths

The present study has some limitations: (i) The small number of participants; (ii) the cluster randomization that led to an uneven distribution of subjects in the active and the control groups; (iii) furthermore, the between-cluster variation for some of the outcome measured weakened the statistical power with regard to the intervention effect analysis. However, this underlines the potential usefulness of the PPS measure to identify persons, across clusters, who have elevated health risk factors, and who may benefit from the intervention on an individual level; (iv) for the correlation analysis as well as for the effect analysis, baseline data were only recorded for the PPS ≥ 60 group. Although it may be argued that it may be relevant to study also persons with a PPS measure < 60, this was not an aim of the present study; (v) the time offered by a professional coach was not the same between the active and the control group, which in itself may have a positive intervention effect, but this study did not intend to test the intervention method in itself; (vi) it may also be discussed if the conducted efforts to minimize bias were sufficient. However, with respect to test the possible link between changes in PPS and changes in cardiovascular physiological and biochemical variables, they should be considered comprehensive and sufficient; (vii) it may be a weakness that at the follow-up examination, no significant between-group differences were found. However, in respect to the number of elevated risk factors, an increase was found in the control group and a reduction in the active group, suggesting that in real-life conditions, such an outcome as that of the present study may still be attractive, stressing the need of a control group as included in this study; (viii) body composition was measured by bioimpedance and not by the golden standard Dual X-ray absorptiometry (DXA). This was due to the nature of the study being a field study. However, the methodology used with a tetrapolar bioimpedance device correlates acceptably to DXA, and is a especially suited for repeated measurements on the same person [30].

Conclusions

This study supports previous findings of an association between PPS, stress and cardiovascular physiological markers. The PPS measure seems to be a suitable tool for identifying persons with persistent stress who may respond to a stress-reducing intervention programme.

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Disclosures

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