PHD THESIS

PRESSURE PAIN SENSITIVITY OF THE CHEST BONE, CARDIOVASCULAR RISK FACTORS, AND PERSISTENT STRESS

Søren Ballegaard. MD.

Herlev University Hospital, Department of Medicine O, Endocrine Unit, Herlev, and Faculty of Health Sciences, University of Copenhagen, Denmark.

Department of Sports Science and Clinical Biomechanics; University of Southern Denmark, Odense, Denmark.

PRESSURE PAIN SENSITIVITY OF THE CHEST BONE, CARDIOVASCULAR RISK FACTORS, AND PERSISTENT STRESS

Trykfølsomheden på brystbenet, kardiovaskulære risikofaktorer og vedvarende stress.

A thesis submitted for the degree of

Doctor of Philosophy

Søren Ballegaard. MD.

From

1) Herlev University Hospital, Department of Medicine O, Endocrine Unit, Herlev, and Faculty of Health Sciences, University of Copenhagen, Denmark.

2) Department of Sports Science and Clinical Biomechanics; University of Southern Denmark, Odense, Denmark.

Contact information:

Søren Ballegaard, Department of Medicine O, Endocrine Unit, Herlev University Hospital, 2730 Herlev, Denmark.

E-mail: sba@ullcare.com

Telephone: + 45 4019 2645.

ENGLISH SUMMARY

Background: Clinical observations indicate that pressure pain sensitivity (PPS) of the chest bone might be useful as a biofeedback marker for behavioral adjustment in patients with ischemic heart disease, similar to the use of home measurement of blood sugar as a biofeedback marker in diabetes patients. As such, reducing an elevated PPS has been found to reduce cardiovascular risk factors. The current thesis explores the possible association between PPS and a pre-selected set of cardiovascular risk factors. Recent research has found that these cardiovascular risk factors are also associated with persistent stress.

Objectives: *Firstly*, to test the association between PPS and a pre-selected group of established physiological and psychological cardiovascular risk factors. S*econdly*, to test if a PPS-guided intervention, using daily PPS-guided cognitive reflection and repeated cutaneous sensory nerve stimulation, can reduce an elevated PPS, and subsequently, if this reduction is associated with concomitant reductions in the pre-selected group of cardiovascular risk factors.

Methods: Outcome variables included PPS and a pre-selected set of cardiovascular risk factors: 1) physiological risk factors: blood pressure, heart rate, work of the heart measured as pressure-rate-product, and autonomic nervous system function measured by the tilt-table response; and 2) depression score measured by the Major Depression Inventory. Using these outcome variables, the association between PPS and the included cardiovascular risk factors was tested in a series of clinical and experimental studies. Cross-sectional studies were carried out on healthy people (N =308), and in patients with stable ischemic heart disease (N = 361). In addition, randomized clinical trials with a 3-month follow-up period were conducted on healthy people (N = 42), and on patients with stable ischemic heart disease (N = 213). Furthermore, a short-term experimental physiological study (N = 361) combined with a 3-month prospective randomized intervention study (N= 181) was conducted in the same group of patients with stable ischemic heart disease.

Results: 1) PPS was associated with the pre-selected cardiovascular risk factors: autonomic nervous system function, blood pressure, heart rate, pressure-rate-product and depression score. 2) The intervention studies showed that when compared to a control treatment, the active treatment reduced an elevated PPS, and that this reduction was associated with concomitant and clinically relevant changes in the pre-selected cardiovascular risk factors. The effects were more pronounced if the risk factor in question was elevated at baseline.

Conclusions: PPS was found to be associated with a pre-selected set of established cardiovascular risk factors. The combination of daily PPS-guided cognitive reflection and cutaneous sensory nerve stimulation reduced an elevated PPS measure, and this reduction was associated with significant and clinically relevant changes in the included cardiovascular risk factors. As such the findings suggest that PPS monitoring may be a useful composite measure for this group of cardiovascular risk factors.

DANISH SUMMARY (DANSK RESUME)

Baggrund: Kliniske observationer tyder på at måling af tryk følsomeden på brystbenet (PPS) kan være anvendeligt som et biofeedback mål for adfærdsmæssig justering hos patienter hjertesygdom., svarende til hvad gælder for hjemme blodsukker måling hos diabetes patienter. Således har en reduktion af et forhøjet PPS vist sig at reducere kardiovaskulære risiko faktorer. Den aktuelle afhandling undersøger den mulige kobling mellem PPS og en forudbestemt samling af kardiovaskulære risiko faktorer. Forskning gennemført inden for de senere år har vist, at disse risiko faktorer også er koblede til vedvarende stress.

Formål: *For det første,* at teste, koblingen mellem PPS og en forudbestemt samling af kardiovaskulære risiko faktorer, *For det andet,* at teste hvorvidt en PPS-guided behandling, der består af daglig PPS- guided kognitiv reflektion og kutan sensorisk nerve stimulation kan reducere et forhøjet PPS, og dernæst, hvorvidt denne reduktion er sammenfaldende med en reduktion i de forudbestemte kardiovaskulære risiko faktorer.

Metoder: De anvendte effekt variable omfattede PPS og en bred vifte af kardiovaskulære risikofaktorer: 1) fysiologiske risikofaktorer: blodtryk, puls, hjertets arbejde målt som puls-blodtryk-sproduktet, autonom funktion målt som reaktion på en vippetest, samt depressions score målt ved spørgeskemaet: Major Depression Inventory.

spørges. Med brug af disse effektvariable blev koblingen mellem PPS og de anvendte kardiovaskuläre risikofaktorer testet i en række række kliniske og eksperimentelle studier. Tværsnitsstudier blev gennemført på raske personer (N =308) og på patienter med stabil iskæmisk hjertesygdom (N = 361). Randomiserede kliniske interventionsstudier blev gennemført på raske personer (N = 42) og på personer med stabil iskæmisk hjertesygdom (N = 213). Derudover blev et kort-tids eksperimentelt studie (N = 361) kombineret med et prospektivt randomiseret interventionsstudie (N= 181) på den samme gruppe af hjertepatienter.

Resultater: 1) PPS var koblet til de forudbestemte kardiovaskulære risiko faktorer: autonom funktion, blodtryk, puls, puls-blodtryks-produkt og depressions score. 2) Interventionsstudierne viste, at sammenlignet med en kontrol behandling, medførte den aktive behandling en reduktion i PPS. Og denne reduktion var sammenfaldende med en klinisk relevant reduktion i de forudbestemte kardiovaskulære risiko faktorer. Disse effekter var mere udtalte hvis den pågældende risikofaktor var forhøjet ved behandlingens start.

Konklusioner: PPS var koblet til en forudbestemt samling a fetablerede kardiovaskulære risiko faktorer. Kombinationen af daglig PPS-guided kognitiv reflektion og kutan sensorisk nerve stimulation førte til en reduktion af et forhøjet PPS. Og denne reduktion var sammenfaldende med klinisk relevante reduktioner i de forudbestemte kardiovaskulære risiko faktorer. På den baggrund taler resultaterne for, at PPS kan anvendes som et samlet mål for denne gruppe kardiovaskulære risiko faktorer.

PREFACE & ACKNOWLEDGEMENTS

The practical work of this thesis was carried out while I was employed as Chief Scientific Officer at the small innovation company Ull Care Ltd. in close collaboration with, and under the supervision of, Professor Jens Faber, MD, DMSci, Herlev University Hospital, Department of Endocrinology; Professor Finn Gyntelberg, MD, DMSci, The National Research Center for the Working Environment; Associate Professor Benny Karpatschof, DMSci, Psychological Institute, Copenhagen University; and Professor and Chairman Lars Arendt-Nielsen, MD, PhD, DMSci, Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University. The work was carried out during the period from 2005 to 2012. The writing work of the thesis was conducted in close collaboration and under the guidance of Professor Jan Hartvigsen, PhD, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark.

Firstly, the thesis investigates the possible association between PPS and a pre-selected group of established cardiovascular health risk factors. Secondly, whether a PPS-guided intervention program can reduce an elevated PPS, and subsequently, if this reduction is associated with concomitant and clinically relevant changes in these risk factors. It is based on five consecutive scientific papers, which have all been published in peer-reviewed scientific journals.

ACKNOWLEDGEMENTS

During my scientific work I have enjoyed the support of so many people, whom I cannot thank enough.

First of all, I want to thank my research supervisors Jens Faber, Finn Gyntelberg, Benny Karpatschof and Lars Arendt-Nielsen for their inspiration and encouragement, for fruitful and insightful discussions as well as for their continuous support throughout the PhD work.

Furthermore, they brought invaluable knowledge and insight from within each of their specialties: Jens Faber on the metabolic and endocrine aspects, Finn Gyntelberg on the work-related stress and cardiovascular epidemiological aspects, Benny Karpatschof on the psychometrical and statistical aspects, and Lars Arendt-Nielsen on the pain and algometric aspects of the work. Furthermore, I want to thank Professor Jan Hartvigsen for valuable methodological advice in the study of office workers, for the evaluation of the papers with respect to a potential submission of a PhD thesis to the University of Southern Denmark, and for his excellent and dedicated supervision during the writing of the thesis.

I am deeply grateful to my Japanese Acupuncture Master, Professor Fumitaka Tayama, PhD, Kurume University, Japan, for his passionate, insightful and fruitful education and inspiration within the field of acupuncture theory and practice as well as for scientific teamwork during my one year stay in Japan (1989 – 1990). His teaching represents the basic source of inspiration for the development of the hypotheses of this thesis.

A close collaboration has been maintained for more than 25 years with Benny Karpatschof, MSc,PhD, Psychological Institute, University of Copenhagen, Jørgen Nyboe, MAct, Chief Statistician, Rigshospitalet, University of Copenhagen and Professor Werner Trojaborg, MD, DMSci, Columbia University, New York, USA; and similarly, to Professor Finn Gyntelberg MD, DMSci, The National Research Center for the Working Environment, and Professor Åke Hjalmarson, MD, DMSci, Department of Cardiology, Göteborg University Sweden for more than 15 years. Their exceptional, persistent, devoted and sometimes courageous support was an important underpinning for the developments presented in this thesis.

With respect to the conduct of the pilot studies prior to the work of this thesis: 1) for the study on opera singers and out-clinic patients, I thank my research colleagues and co-authors Benny Karpatschof, Werner Trojaborg, Jørgen Nyboe, Åse Marie Hansen, Gisli Magnusson and Pernille

Bjørn Petersen. For research assistance, I thank Nette V. Olsen, Rikke Grønkjær, Tine B. H. Meincke, Carsten Snedker, Gitte H. Sommer, Arne H. Andreasen and Bente Olsen. I thank Kasper Bech Holten, CEO of the Royal Danish Opera for making possible the recruitment of opera chorus and opera solo singers for the pilot studies on transient stress during an opera performance; 2) for the study on breast cancer women, I thank my research colleagues and co-authors Christen Axelsson, Benny Karpatschof and Peer Schousen. For research assistance, I thank Bernadette Boissevain, Rikke Grønkjær, Nette V. Olsen, and Gitte H. Sommer; 3) for the intervention study on opera students, I thank my research colleagues Benny Karpatschof, Gitte H. Sommer, Finn Gyntelberg, Pernille B. Petersen and Jens Faber. I thank Anne Margrethe Dahl of the Royal Danish Opera Academy for the conduct of all instructions and contacts with the students in the active group as well as for allocation of the active study group for the pilot intervention study on opera students. I thank Eva Hess Thaysen of The Royal Danish Academy of Music for help with the conduct and allocation of the pilot intervention study on opera students (for the control group) and the pilot experimental studies on transient stress in opera students; 4) for the intervention study on Olympic sailors, I thank my research colleagues Pernille B. Petersen, Gitte H. Sommer, Finn Gyntelberg and Jens Faber. I thank the coach of the sailors, Jesper Bank, and the sailors Jonas Warrer and Martin Kirteterp for excellent teamwork during the conduct of the study. I thank Benny Karpatschof for statistical analysis. I thank Jesper Bank and Professor Niels H. Secher MD, DMsci, Department of Anaesthesiology, Rigshospitalet, University of Copenhagen, for critical review of the manuscript.

I want to thank my research colleagues and co-authors during the thesis work for their great spirits, open discussions and constructive dialogue (in alphabetic order): Lars J. Andersen, Lars Arendt-Nielsen, Per Bech, Natasha Bergmann, Jens Faber, Finn Gyntelberg, Gitte S. Harboe, Åke Hjalmarson, Pernille Holmager, Benny Karpatschof, Jesper Kristiansen, Jesper Krogh, and Pernille B. Petersen. For supplementary statistical analysis, I thank Bjarne Ersboel. I thank Lars

Gundorph, CEO of the insurance company Willis Ltd, for active teamwork, and for recruitment of subjects for the studies on office workers. I thank Professor Christian Torp-Petersen, MD, DMSci, for fruitful discussions and for providing the access to recruit patients from the Department of Cardiology, Gentofte Hospital with respect to the studies on patients with stable ischemic heart disease.

I thank Caroline Ballegaard, Charlotte Christiansen and Bente Olsen for enthusiastic and excellent research assistance, and furthermore Caroline Ballegaard for devoted technical assistance for more than 10 years. The staff of the Metabolic Ward from the Department of Endocrinology 54O4, Herlev University Hospital are thanked for their skillful job concerning blood sampling and measurements for the study on office workers and their valuable contribution concerning the practical issues of the study on ischemic heart disease patients: Helle-Marina Oxfeldt, Tine Skogen-Larsen, Ulla Kjærulff-Hansen, Tonni Løve Hansen, Hanne Dorthe Mogensen, Marianne Sørensen and Rikke M. Henkel.

I thank the insurance broker Willis Ltd. for unrestricted financial funding for the study on office workers, and the Johan Schrøder's Family Foundation, The Lundbeck Foundation, Else and Mogens Wedells-Wedellsborg Foundation, and Carpenter Sophus Jacobsen and wife Astrid Jacobsens's foundation for financial support for the study on ischemic heart disease patients. During the conduct of the studies of the thesis, I thank Ull Care A/S for my employment during that period.

From the bottom of my heart, thanks to all the people mentioned above and also to anyone who may have slipped my memory.

"I never did anything alone. What was accomplished was accomplished collectively". This is a quotation by Golda Meir, which seems to fit well with the work of this thesis.

TABLE OF CONTENTS

PAPERS OF THE THESIS

This thesis is based on the five papers listed below, supported by supplementary findings where appropriate. These supplementary findings resulted from analyses that were conducted on existing data and are represented in the thesis as 'supplementary data'.

(1) Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Invest 2012; 72: 459–66.

(2) Bergmann N, Ballegaard S, Holmager P, Kristiansen J, Gyntelberg F, Andersen LJ, Hjalmarson Å, Bech P, Arendt-Nielsen L Faber J. Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease. Scand J Clin Lab Invest 2013; 73: 373–9.

(3) Ballegaard S, Petersen PB, Harboe GS, Karpatschof B, Gyntelberg F, Faber J. The association between changes in pressure pain sensitivity and changes in cardiovascular physiological factors associated with persistent stress. Scand J Clin Lab Invest 2014; 74: 116–25.

(4) Bergmann N, Ballegaard S, Bech P, Hjalmarson Å, Krogh J, Gyntelberg F, Faber J. The effect of daily self-measurement of Pressure Pain Sensitivity followed by acupressure on depression and quality of life versus treatment as usual in ischemic heart disease: A randomized clinical trial. PLOS ONE 2014: 9[5], e97553.

(5) Ballegaard S, Bergmann N, Karpatschof B, Kristiansen J, Gyntelberg F, Arendt-Nielsen L, Bech P, Hjalmarson Å, Faber J. Association between pressure pain sensitivity and autonomic function as assessed by a tilt table test. Scand J Clin Lab Invest. 2015; 75; 345-54.

CHAPTER 1: INTRODUCTION

1.1 CLINICAL OBSERVATIONS LEADING TO THE HYPOTHESES OF THE THESIS

The explorative process, prior to setting the hypotheses to be tested in the five studies of this thesis, contained a series of consecutive steps of observations and developments during the period between 1985 and 2008, which are described below and illustrated in Figure 1.

Transcutaneous electrical nerve stimulation (6) and cutaneous sensory nerve stimulation were found to help angina pectoris patients (7-12), possibly by reducing sympathetic tone (9;12;13). Cutaneous sensory nerve stimulation was found to have an enhancing effect on existing homeostatic mechanisms controlling the cardiovascular system, and possibly mediated by the autonomic nervous system function (14), a finding that was later confirmed by others (15;16).

Inspired by Traditional Chinese Medicine (17), clinical observations during a one-year study program in Japan, and clinical observations of patients with ischemic heart disease, the following intervention strategy was tested prospectively in consecutive patients with advanced angina pectoris (18-20) and in patients with stroke (21). The patients were asked to evaluate the level of soreness (by finger pressure) of the chest bone every morning and evening as a biofeedback marker for stress, and to use this information for behavioral adjustment – a practice similar to the daily blood sugar measurements taken by diabetes patients. Secondly, they were asked to conduct cutaneous sensory nerve stimulation morning and evening on a pre-selected group of tender points on the body surface. The aim was to reduce the soreness of these points for preventative purposes, as well as to reduce the soreness and subsequent angina pain by using it in an ad hoc manner in the event of angina pectoris. In addition, the participants could choose whether or not to participate in a comprehensive self-care-based intervention program that included physical and cognitive exercise in order to obtain and maintain a low level chest bone soreness, as well as receive diet recommendations. The patients reported that: i) the preventative cutaneous sensory nerve

stimulation by finger pressure reduced the tenderness of the chest bone in less than a minute, ii) most often, the soreness of the chest bone was high during an angina attack, and iii) that finger pressure, when used during an angina attack was associated with a reduction of the soreness and a concomitant relief of the angina pain within a few minutes (20).

In a 3-year prospective non-randomized comparative clinical database study, including 168 consecutive patients with advanced angina pectoris, the patients observed that the intervention worked according to the intended aim. Compared to the year before at the start of the intervention, the 3-year number of in-hospital days was reduced by 90%. The use of medication and need for invasive treatment were both reduced by 80% (20).

In order to quantify the chest bone soreness as a pressure pain sensitivity (PPS) threshold in a blinded manner, a device with that quality was developed in collaboration with the Danish Technical University (22).

Subsequently, in a series of pilot studies, PPS was found to be associated with the following cardiovascular risk factors: blood pressure, heart rate, pressure-rate product, autonomic dysfunction and depression score (3;22-24). In addition, the PPS-guided non-pharmacological and self-care-based intervention was found to reduce PPS with concomitant reduction in these cardiovascular risk factors (3;22-24).

Given this background, the studies included in this thesis tested the following hypotheses:

Hypothesis 1: PPS is associated with a pre-selected group of established cardiovascular risk factors; and

Hypothesis 2: The combination of daily PPS-guided cognitive reflection and cutaneous sensory nerve stimulation reduces an elevated PPS with a concomitant decrease in these cardiovascular risk factors.

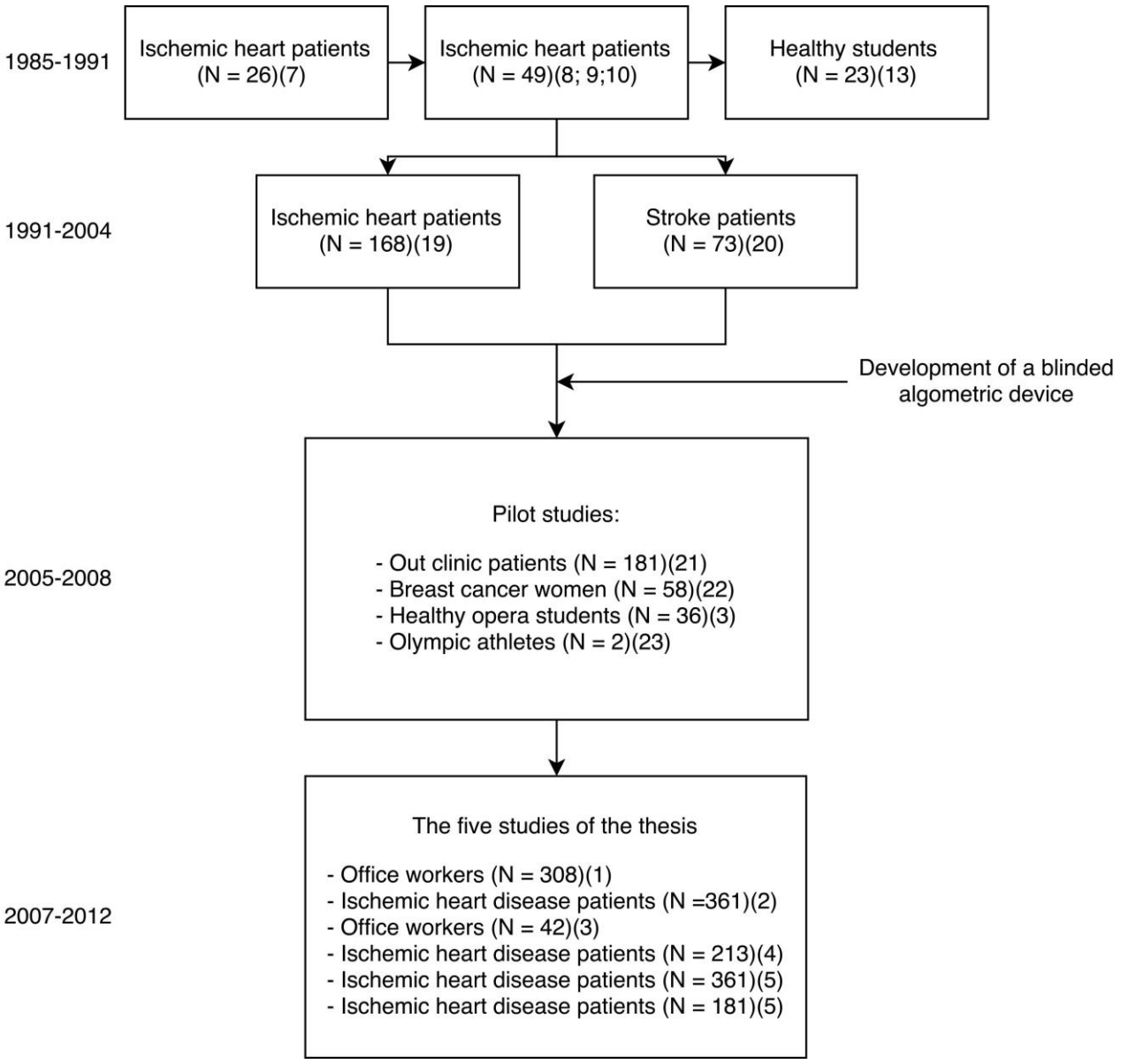

Figure 1: Diagram of the flow of studies and developments leading to the current thesis.

1.2 PRESSURE PAIN SENSITIVITY AND AUTONOMIC NERVOUS SYSTEM

Pressure pain is a conscious experience and therefore involves considerable psycho-social components (25). It has a bi-directional relationship with the sympathetic part of the autonomic nervous system (26).

Modulation of pain sensation is initiated by cognitive and emotional processing in the brain (27) by attention (28) as well as by social factors (29). The cellular sites of modulation are the polymodal receptors, which are identical throughout the evolutionary chain: from fish to higher vertebrates to humans (30;31). Furthermore, it has been suggested that the sensitivity of these receptors serves as a non-cognitive alarm and defence system, thus changing sensitivity during stress in order to enhance survival (32).

Two distinct polymodal receptors have been identified: the A-delta receptor with a low pressure pain threshold, and the C receptor with a high threshold (32;33). It is possible that the molecular site of modulation is the Ca^{2+} permeable channel subgroup TRPV 4 (34). Resent research indicates that TRPV 4 can be stimulated by a variety of exogenous and endogenous substances, including sympathetic input (35).

<u>The physiological background for the PPS measure and PPS-related nerve stimulation</u>

All cutaneous sensory neurons can be classified as A-Beta, A-delta or C fibers. A-beta fibers only conduct non-noxious signals such as touch and vibration to the spinal cord, A-delta fibers and C fibers conduct both noxious and non-noxious signals (27). The mechanisms for the processing and transmitting of these signals are not fully understood, but several integrated neurological pathways are involved (27). Nociceptive alarm impulses (e.g. the PPS measure), reach the dorsal part of the spinal cord by A-delta and C fibers. From here, the impulse reaches the thalamus primarily through

the lateral spinothalamic tract pathway in the spinal cord. If sufficiently powerful, the stimulus activates limbic structures (e.g. mainly, the amygdale) and initiates a stress response (e.g. increases sympathetic tone). The non-noxious impulses, from A-delta and C fibers, reach the thalamus through a different spinal pathway: the anterior spinothalamic tract. And in contrast to the noxious stimulus, the non-noxious impulse leads to a different hypothalamic response mediated by oxytocin: activating homeostatic cardiovascular control (36;37), and reducing the sympathetic tone, if elevated (38).

Against this background, a functional, structural and molecular basis for the suggested hypothesis of an association between PPS and autonomic nervous system function may be present. And similarly, non-noxious stimulation of the cutaneous sensory receptors may stimulate cardiovascular homeostatic control and sympathetic tone.

Measurement of pressure pain sensitivity

The standard in measuring pressure sensitivity is by algometry (39). In algometry, the pressure pain threshold is recorded as the threshold at which the person feels pain when increased pressure is gradually applied to the measurement site by a handheld instrument. Algometry is also the standard measurement method in pain research related to musculoskeletal pain, deep somatic tissue hyperalgesia, and chronification of pain (39;40). As such, algometry has been used to assess and understand hypersensitivity and hyperalgesia in somatoform pain disorders (41): the presence of generalized hyperalgesia in rheumatic arthritis (42), chronic fatigue syndrome (43), and chronic whiplash pain (44), chronic pelvic pain (45), as well as in fibromyalgia (46), and osteoarthritis (47).

1.3. ISCHEMIC HEART DISEASE, AUTONOMIC NERVOUS SYSTEM FUNCTION AND CARDIOVASCULAR RISK FACTORS

Ischemic heart disease was found to be a leading cause of death in the Global Burden of Disease study (48). The cardiovascular system is controlled and influenced by not only a unique intrinsic system, but also by the autonomic nervous system and the endocrine system (49;50).

A broad range of physiological, biochemical and psychological cardiovascular risk factors has been identified, all of which have a close association with the autonomic nervous system: heart rate (51;52), the work of the heart measured as systolic blood pressure x heart rate product (53;54), the metabolic syndrome characteristics (e.g. hypertension, disturbed glucose and lipid metabolism and abdominal fat distribution) (55-58), chronic low-grade inflammation (59) and depression (60), as well as autonomic nervous system dysfunction measured as the vagal function (61).

1.4 THE TERM, CONCEPT, AND MEASUREMENT OF PERSISTENT STRESS

At the time of the initiation of the studies of this thesis, the link between ischemic heart disease and persistent stress was not generally accepted (62). However, the link is now generally acknowledged (64;65). Furthermore, studies conducted by others have shown that the included cardiovascular risk factors are also associated with persistent stress (56;57;61;65), and that persistent stress may lead to impaired pain control and an elevated pain sensitivity (46;66;67). On this background, the possible association between PPS and persistent stress becomes a natural part of the discussion, with possible implications from the current findings. For this purpose, an introduction to the term, the concept and the measurement of persistent stress is included below.

The term ‘stress’ has several meanings and definitions, and was still under debate, when the current studies were initiated (68-70). However, at the time of writing this thesis, the theory proposed by McEwen had received general acceptance (71-74). Stress involves a stressor and a stress response (68;71). The imminent or perceived stimulus that initiates the stress response is called the *stressor*. The stress response is controlled by the autonomic nervous system (68).

It is essential to distinguish between two forms of stress referred to in this thesis: transient stress and persistent stress, both of which are defined below. Other terms are also used for the same concept: acute or chronic stress (69), and allostasis or allostatic overload (75).

Transient stress

Transient stress (or allostasis) may be defined as the physiological state of preparedness, automatically induced in the body through neural/hormonal signals from the brain, when we are acutely challenged or we acutely feel or anticipate a threat/a challenge (68;71).

The transient stress response is essential for survival. It functions as an adaptive response to the challenges of life (71). When the challenge/threat is over, the body gradually returns to its former state of homeostasis (71;76). The ability to effectively and quickly return to homeostasis and subsequently initiate a new transient stress response when needed is called ‘resilience’ (69;72).

Persistent stress

Persistent stress (or allostatic overload) is the result of a prolonged imbalance between the stressor load and the capacity of the adaptive transient stress response (68;69;73;75), and may be defined as

a dysfunction of neurological/hormonal processes in the brain due to a prolonged exposure of the hormones involved in transient stress (68;73).

The persistent stress condition leads to a dysfunction of the adaptive transient stress response and, accordingly, may lead to a variety of physiological, psychological, social, and mental dysfunctions or problems (77;78). It may negatively affect work performance (79) as well as general health (80), and be associated with the development of elements of the metabolic syndrome (56;57;81), as well as ischemic heart disease, depression, and type 2 diabetes (58;82).

Persistent stress has been found to be associated with widespread increased pain sensitivity, leading to both hyperalgesia (pain induced by noxious stimuli) and allodynia (pain induced by non-noxious stimuli) (83;84). The cause has been suggested to be a dysfunction of the intrinsic pain modulation system (47), which mediates pain inhibition in the spinal dorsal root when pain signals ascend from the periphery through C sensory and A-delta fiber neurons (85). Autonomic nervous system dysfunction may be involved in this dysfunction of the pain modulation system (46;86;87).

Measurement of stress

Because it is not possible to measure stress directly, physiological markers such as heart rate, heart rate variability, blood pressure, plasma catecholamines, and plasma or salivary cortisol levels are used alone or in combination with behavioral observations and self-reported responses on personal questionnaires. As such, allostatic overload (i.e. persistent stress in this thesis) was originally developed as a composite measure of chronic stress-related disequilibrium generated from 10 different outcome measures (88).

As the autonomic nervous system controls the efferent stress response, measuring its function and dysfunction may be one way to identify and characterize the stress response. Furthermore, as the

autonomic nervous system also controls pain perception, measuring autonomic nervous system function may link the stress response with the pain response. Tilt-table testing is one of several standard methods for evaluating the response dynamics of the sympathetic branch of the autonomic nervous system (89-91). Tilt-table testing leads to a controllable stimulation of the sympathetic part of the autonomic nervous system mediated by gravity stress and assessed by the response of systolic blood pressure and heart rate (89;91). Autonomic nervous system dysfunction has been found to be linked to hypertension (92), post-traumatic stress disorder (63), and to depression in connection with ischemic heart disease (93). Persistent stress has also been found to be associated with a reduced pain threshold, and thus increased cutaneous sensitivity (85;94), and autonomic nervous system dysfunction has been suggested as the link between the two (46). On this background, measurement of PPS and the PPS response to tilt-table testing may represent possible ways to measure the stress response and autonomic nervous system function.

Structural changes in the central nervous system have been observed in combination with changes in stress resilience (95;96), suggesting that stress resilience is related to central nervous system structures, and is measurable and modifiable (69). Therefore, autonomic nervous system dysfunction, as assessed by a change in tilt-table testing response, might be linked to a state of reduced brain resilience.

Today, the standard way of measuring the physiological link between stress and the autonomic nervous system is heart rate variability, which measures cardiac vagal activity (97-99). In addition, a broad range of stress-related questionnaires have been developed, such as Cohen's Perceived Stress Scale (100), the Karolinska Exhaustion Disorder Scale (101), the Trier Social Stress Test (102), or the Shiron Melamen Burnout Questionnaire (103) .

However, with respect to the aim of the current studies, heart rate variability is influenced by beta-blockade medicine, which is used by the majority of patients with ischemic heart

disease. Therefore, for the current studies, a measure not influenced by beta-blockade medicine was used.

CHAPTER 2: AIMS AND HYPOTHESES OF THE THESIS

The overall aims of the current thesis are to address the following hypotheses:

Hypothesis 1: PPS is associated with a pre-selected group of established cardiovascular risk factors; and

Hypothesis 2: The combination of daily PPS-guided personal reflection and cutaneous sensory nerve stimulation reduces an elevated PPS with a concomitant decrease in these cardiovascular risk factors.

Specifically, this was done by investigating the following research questions based on the five papers of this thesis:

1. Is the PPS measure associated with the following cardiovascular health risk factors:
    a. Physiological variables: blood pressure, heart rate, and workload of the heart measured by the pressure-rate-product and autonomic nervous system function assessed by the tilt-table response.
    b. Psychological variable: depression score assessed by the Major Depression Inventory questionnaire?
2. Is the combination of daily PPS-guided cognitive reflection and daily cutaneous sensory nerve stimulation effective in reducing an elevated PPS, when compared to a control treatment in a randomized design, and:
    a. Is a reduction of an elevated PPS associated with a concomitant reduction in the included cardiovascular risk factors?
        1. Physiological variables: blood pressure, heart rate, pressure-rate-product, and autonomic nervous system function.

2. Psychological variable: depression score assessed by the Major Depression Inventory questionnaire.

CHAPTER 3: MATERIALS AND METHODS

3.1 STUDY DESIGN AND STUDY POPULATIONS

Table I: Study design, study populations and aims of the five studies of the thesis

Study design, study populations and number of participants (N)	Research questions	Thesis paper
Cross-sectional studies		
Healthy office workers, N = 308	1. Is PPS associated with quality of life? 2. Are PPS measurements reliable? 3. Does PPS screening work? 4. Is PPS feasible for home use?	(1)
Healthy office workers, N = 42	1. Is PPS associated with biochemical and physiological cardiovascular risk factors?	(3)
Patients with ischemic heart disease, N = 361	1. Is PPS associated with quality of life? 2. What is the concurrent validity of the new PPS measurements when compared to measures from another algometric device?	(2)
Intervention studies		
Healthy office workers, N = 42	1. Is a reduction in an elevated PPS associated with changes in biochemical and physiological cardiac risk factors? 2. Does PPS screening work? 3. Does a PPS-guided intervention reduce an elevated	(3)

	PPS as well as biochemical and physiological cardiac risk factors? 4. Does PPS work in home use?	
Patients with ischemic heart disease, N = 213	1. Does PPS screening work? 2. Does a PPS-guided intervention reduce an elevated PPS, reduce depression, and improve questionnaire-evaluated quality of life? 3. It PPS feasible for home use?	(4)
Experimental studies		
Patients with ischemic heart disease		
Short-term experimental study, N = 361	1. Is PPS associated with autonomic nervous system function? 2. Does resting PPS work for autonomic nervous system dysfunction screening?	(5)
Prospective randomized intervention study, N = 181	1. Is a reduction in an elevated PPS associated with a reversal of autonomic nervous system dysfunction? 2. Does PPS work for screening? 3. Does a PPS-guided intervention reverse autonomic nervous system dysfunction?	(5)

3.2 PROCEDURES AND ANALYSES COMMON TO ALL FIVE PAPERS

PPS measurement

For research purposes, the following procedure is used**:** the subject is placed in a supine position, and receives the following verbal instruction: “You will gradually experience an increase in pressure, firstly on the index finger and secondly on the chest bone. As soon as you feel discomfort, you say ‘stop’. Accordingly, it is not a matter of how much pressure you can tolerate, but rather when it feels natural for you to withdraw from the pressure”.

The measurement on the index finger is used as a control point and for introducing the procedure. The location for measuring on the sternum is identified by palpation as the most tender point within the area between the third, fourth and fifth inter-costal space, reflecting the area of segmental innervations of the heart (104) (Figure 2). When the researcher observes a noxious withdrawal reflex or a startle reflex during the procedure, the pressure is determined as the PPS measure.

The technique used for PPS measurement at home exclusively relates to the observation of discomfort by the subject.

Figure 2: The PPS measurement device and measurement site

The PPS measurement device is an algometer that transforms the pressure applied into a logarithmic scale of sensitivity levels from 30 to 100. The value of 100 equals the highest measurable level of sensitivity, whereas the value of 30 equals the lowest measurable level of sensitivity. An increase in 30 PPS units equals a 100% increase in sensitivity. The final version of the instrument (Ull Meter ®) was patented (Patent No EP 1750772 B1). In Table II, PPS measures as shown on the instrument are converted into kilogram pressure per square centimeter measurement pad (e.g. the pad used is 2 cm^2), and this is converted to SI units (kPa) (e.g. 1 kg/cm^2 = 98 kPa).

With respect to the use of PPS as a measure for autonomic nervous system function, a pilot study showed that the PPS measure was not influenced by the beta-blockade medication (105). On this background, the change in PPS response to a tilt-table test was regarded as a suitable method to assess the possible association between PPS and the sympathetic part of the autonomic nervous system function as well as the association between PPS and the physiological stress response.

Table II: Conversion table between PPS measure, SI units (kPa), and pressure applied per cm^2

PPS measure as shown on the display	**Pressure in kg/cm^2 (approximately)**	**PPS measure in SI units (kPa) (approximately)**
30	4	400
45	3	300
60	2	200
75	1.5	150
90	1	100

PPS: pressure pain sensitivity.

Table III: Outcome measures for the five papers of this thesis

Outcome categories	**Outcome measure**	**Thesis study**
Physiological cardiovascular risk factors	Heart rate, blood pressure and pressure-rate-product. Autonomic nervous system function assessed by heart rate, systolic blood pressure and PPS response to tilt-table testing	(3;5)
Biochemical cardiac risk factors of the metabolic syndrome	Serum glycated hemoglobin (HbA1c), YKL 40 and lipids; Body Mass Index, Visceral Fat Index	(3)
Quality of Life and depression measure	SF-36 questionnaire scores for physical and mental health	(1;2;4)
	Major Depression Inventory score	(1;2;4)
	WHO (Five) Well-Being Index	(1;2;4)
Composite clinical measures	Number of elevated health risk factors	(3)
	Number of autonomic nervous system dysfunction risk factors	(5)

Statistics common to all five studies

The statistical package for the social sciences (SPSS) for Windows was used in all analyses (IBM Corp., Armonk, NY, USA, version 18 or 19).

Because correlation coefficient analysis was an essential part of the evaluation in this thesis, distinction was made between significant correlation coefficients and clinically relevant correlation coefficients; the former evaluated from significance tests, the latter from the size of the correlation coefficient (r); $r < 0.1$: no correlation; $r \geq 0.1$: weak correlation; $r \geq 0.3$: moderate correlation; and $r \geq 0.5$: strong correlation (106;107).

Given that correlation analysis does not evaluate cause and effect relationships, intervention studies were included in which only the one outcome measure, PPS, was changed.

With respect to the statistic power of the current studies, in general statistic terms, when re-testing a hypothesis, this fortifies the evidence. In the current series of studies, the hypotheses were established in long-term clinical observations, and subsequently tested positively in a series of pilot studies (3;22-24) prior to the studies of the thesis.

3.3 THE INDIVIDUAL PAPERS OF THE THESIS

Paper 1: Cross-sectional study in healthy office workers

Participants

All 433 employees in a large Danish company within the finance sector were invited to participate. Of these, 308 (71%) accepted the invitation.

Variables (see Table III)

In addition, and in order to elucidate a potential influence from demographic confounding factors, supplementary and thus new variables are included in the thesis: 1) Concomitant disease: hypertension, diabetes, ischemic heart disease, and cancer; 2) use of medication; 3) life style: (a) How often do you exercise at least 30 minutes? (1: *daily*; 2: *weekly*; 3: *monthly*; 4: *never*). (b) How often do you use alcohol? (1: *never*; 2: *less than 14 units per week (females), less than 21 units per week (males)*; 3: *more*). (c) How is your use of tobacco? (1: *never smoked*; 2: *stopped > 1 year ago*; 3: *current user, <15 units per day*; 4: *current user >15 units per day*).

Analyses

Non-parametric analyses were used, as PPS data were not normally distributed. To test the association between PPS and quality of life, Spearman correlation analysis was used. This test was also used to test measurement reliability as the correlation between repeated measurements; 5 seconds between measurements conducted by professionals and one full day between measurements when PPS measurements were conducted at home. To test the between-measurement difference throughout the full PPS scale, a Bland-Altmann analysis was used. To test the PPS as a screening tool, Chi-square odds ratio analysis, two step categorization and Receiver Operating Characteristic

curve analyses were used. To test for potential systematic measurement error in long-term use, trend analysis for the 4-month observation period was used.

A supplementary Cohen Kappa coefficient analysis was carried out with respect to the two-step categorization reliability.

Paper 2: Cross-sectional study in patients with stable ischemic heart disease

Participants

All 1,181 patients from the Departments of Cardiology at Gentofte and Herlev Hospitals, who had participated in the local cardiac rehabilitation programs during the period of 1999-2011, were invited to participate via a standard invitation letter. Of these, 361 persons accepted and participated.

Variables (see Table III)

The included outcome measures for quality of life, depression and well-being are shown in Table III.

Analyses

As the criteria for the use of parametric statistics were fulfilled, these were used, including unpaired t-test, one-way ANOVA with post-hoc Bonferroni adjustment and simple linear regression analysis. Multiple linear regression with backward elimination of non-significant variables was performed using PPS and Clinical Stress Questionnaire score as independent variables, and PPS or Clinical Stress Questionnaire score together with age, gender, Major Depression Inventory score, and SF-36 Physical Composite Scale score as independent variables.

Measurement of PPS by two different algometers

The PPS measurement device used in this thesis was tested against another and broadly accepted pressure algometer (Algometer Type II, Somedic AB, Sweden). Using the Somedic algometer, the pressure pain threshold was defined as the algometer pressure applied when the person verbally expressed the experience of pain. In this technique, the applied pressure is held stable at a pre-defined pressure (30 kPa/s), and the subject is informed to say 'stop' when the pressure is regarded as painful. The calculated accumulated pressure is used as the pressure-pain-threshold measure. This is somewhat different from the measurement technique of PPS used in the current studies, in which the pressure threshold was defined as the pressure applied when an objective withdrawal reflex is observed or when the person verbally expresses the experience of pain before a withdrawal reflex is observed. The applied pressure at this point is regarded as the pressure pain threshold. Furthermore, the rate for increasing the applied pressure is approximately 60 kPa/s, allowing a measurement time of 3-5 seconds.

Paper 3: Randomized interventional study in office workers

Participants

Among the 308 office workers included in the first study, 64 people with a resting PPS ≥ 60 were invited to participate in the intervention study, 44 agreed to participate and 42 completed the study.

Variables (see Table III)

In addition, a composite clinical measure was generated from the number of elevated health risk factors using the following points of discrimination: systolic blood pressure ≥ 130 mmHg, diastolic

blood pressure ≥ 85 mmHg, heart rate ≥ 70 beats per minute, pressure-rate-product ≥ 9100 mmHg × beats per minute, total cholesterol ≥ 5.0 mmol/L and HbA1c ≥ 5.0%.

Interventions

In the active intervention group, the participants received a PPS-guided non-pharmacological self-care based intervention: all subjects were instructed by a professional instructor to perform PPS measurements at home twice daily: in the morning before breakfast, and in the evening before going to bed. The purpose of the PPS measure was to serve as a guide for behavioral adjustments according to the measure. Immediately after each PPS measurement and as a mandatory stress-reducing intervention, the participants were instructed to conduct cutaneous sensory nerve stimulation by finger pressure (e.i. acupressure) on specific points on the chest bone and on the back between the shoulder blades using the following procedure: 1) identify the most tender spot within the marked area on the body surface, 2) apply finger pressure without causing pain, 3) hold the pressure for 30 – 60 seconds until the tenderness is noticeably reduced. All subjects received a personal PPS measurement instrument, an instruction manual and were individually instructed in how to measure, how to reflect on the measure, and how to conduct cutaneous sensory nerve stimulation. The participants were offered a second appointment and/or 1-2 phone contacts with the instructor if needed. The participants were instructed to report their PPS measurements each day on their personal login on a website. On the website, each participant was able to track his/her results and changes in PPS during the intervention period. The professional instructor followed the web monitoring of each patient, and if measurements were missing for more than one week or did not show a decrease in PPS, the instructor contacted the participant.

The control group received a one-hour oral instruction in general stress management, but no further information.

Analyses

Non-parametric analyses were used, as PPS data were not normally distributed: Wilcoxon two-sample test for between-group analysis, Mann Whitney one-sample test for within-group analysis, and Spearman's rho for correlation analysis. The use of the block randomization procedure for effect analysis was taken into account by means of a general linear mixed model in a variance component testing context, where subjects were nested within locations and locations were nested within groupings (intervention/control). Fischer's Exact Test evaluated between-group difference with respect to the ratio of elevated health risk factors.

Paper 4: The longitudinal randomized intervention study in patients with ischemic heart disease

Participants

Two hundred and thirteen patients with stable ischemic heart disease, who participated in the cross-sectional study (Study 2) and who had PPS $\geq$ 60 units were included in a 3-month individually randomized controlled study, of which 106 were allocated to the active intervention group, and 107 to the control group.

Variables (see Table III)

The included questionnaire-derived outcome measures for depression, well-being and general physical and mental health are shown in Table III.

Interventions

The active intervention was identical to the one used in the study of office workers (Study 3). In contrast to the study of office workers, the control group participants in this study were told that their stress level was elevated and the associated potential impact on their disease. Furthermore, they received a book on general stress management.

Analyses

As the criteria for the use of parametric statistics were fulfilled, paired and non-paired t-tests were used. Data were analyzed on an intention-to-treat basis; for testing of statistical significance, all randomized patients were included regardless of subsequent adherence to the treatment. Cohen effect size was used to compare the active group with the control group with respect to the Major Depression Inventory score and the WHO (Five) Well-Being Index, using intention-to-treat data.

Paper 5: Experimental physiological study in patients with ischemic heart disease

Participants

Participants in this study also took part in Study 4. This randomized experimental intervention group consisted of the 86 patients in the active group and the 95 patients in the control group who completed a second tilt-table test after the intervention period.

Procedures

The autonomic nervous system function was measured by the systolic blood pressure and heart rate response to a tilt-table test. The PPS response to tilt-table testing was included as an extra variable. The tilt-table test stimulates the autonomic nervous system by orthostatic stress, initiated by passive

repositioning from supine to 70 degrees upright. During tilt-table testing, the subject was positioned on the tilt-table and fastened in a supine position, and the following procedure was carried out: 1) a 10-minute rest period in the supine position (first and second set of recordings) (i.e. resting values); and 2) passive tilting to an angle of 70 degrees and a subsequent 7-minute rest in that position (see Figure 3).

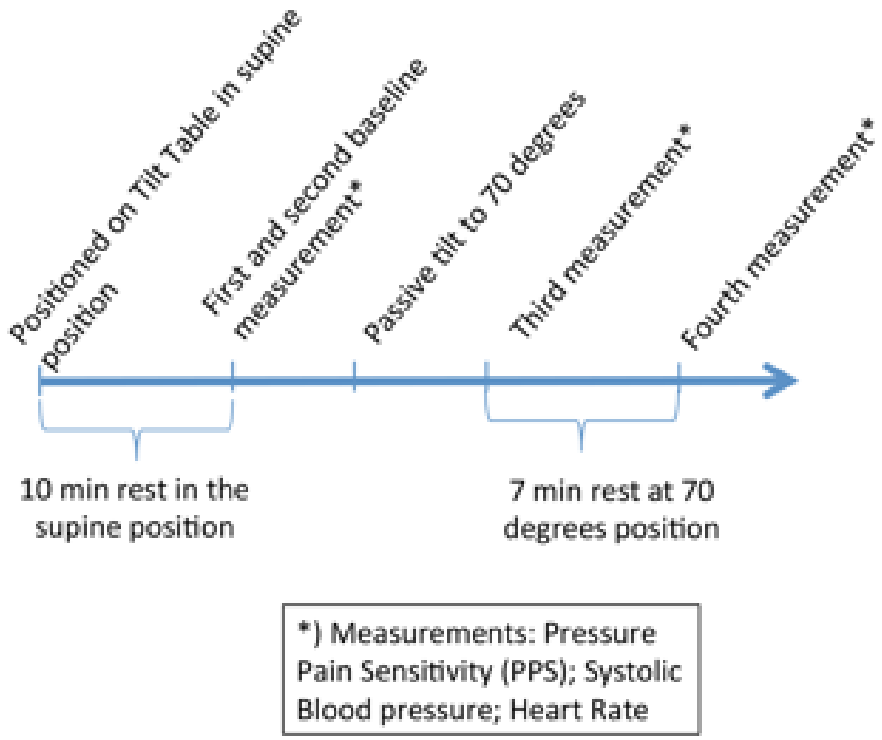

Figure 3: Time line for Tilt Table Test

Variables (see Table III)

In addition, four individual risk factors for autonomic nervous system dysfunction were included in addition to that of verified ischemic heart disease: chest pain at rest, an elevated level of persistent

stress defined as resting PPS ≥ 60 arbitrary units, an elevated resting systolic blood pressure (≥ 130 mm Hg), and overt depression (a Major Depression Inventory score ≥ 20).

Analyses

As the criteria for the use of parametric statistics were fulfilled, Pearson's correlation analysis was used with respect to analyses of associations. Non-parametric Wilcoxon and Mann-Whitney tests were used for between-group and within-group comparisons. Fischer's Exact Tests were used for analysis when frequencies were compared.

CHAPTER 4: RESULTS

4.1 RESULTS FROM THE FIVE INDIVIDUAL PAPERS

Paper 1: The cross-sectional study in office workers

Description of the study sample

The demographic data of the study group are shown in Table III.

Table IV: Demographic data of the office worker study population (Study 1)

Variables	**Study group**
Number of participants (N)	308
Male, n (%)	142 (46)
Age in years, median (interquartile range)	42 (34-47)
Morbidity	
Hypertension, n (%)	35 (11)
Diabetes, n (%)	5 (2)
Heart disease, n (%)	3 (1)
Cancer, n (%)	6 (2)
Depression, n (%)	14 (5)
Life style	
Engagement in 30 minutes of exercise, median and interquartile range	Once weekly: median and interquartile range are identical
Use of alcohol; medians and interquartile ranges	Less than 14 units per week (females)/ Less than 21 units per week (males). Medians and interquartile ranges are identical
Use of tobacco; median and interquartile range	Median: Never smoked; Interquartile range: never smoked – stopped less than a year ago

(N = total number of participants, n = number of subgroup of participants)

Results

Statistically significant, but weak correlations were found between PPS and questionnaire-evaluated health. PPS measurement reliability and categorization agreement were high for research use as well as for home use. With 5 seconds between measurements and conducted by 10 different observers, no significant between-observer differences were found; the categorization agreement was 89%. The Cohen Kappa coefficient was 0.9 with respect to categorization reliability between the repeated measures (supplementary data). A Bland Altmann plot demonstrated similar between-measurement differences throughout the PPS scale. People with a PPS $\geq$ 60 units had an elevated health risk profile based on their responses in questionnaires when compared to people with a PPS $\leq$ 40 (all $p < 0.05$) (all odd ratios > 2). When categorizing a person with PPS $\geq$ 60 units as persistently stressed (27% of subjects), and using the Major Depression Inventory score, and SF-36 Questionnaire score, for risk calculations, the remaining 73% of the subjects with no elevated risk factors were identified with an 80% specificity. Using Receiver Operating Characteristic analyses for sensitivity and specificity evaluation, the area below the Receiver Operating Characteristic curve was > 0.6 and significant in all cases (all $p < 0.01$) (Figure 4). No significant systematic measurement error was found in long-term home use.

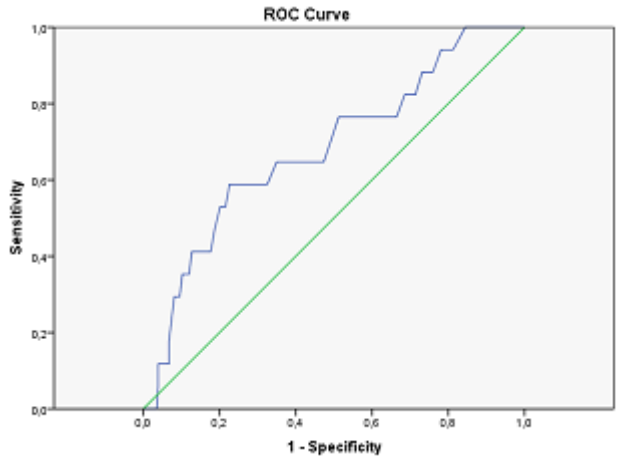

Figure 4: Receiver Operating Characteristic (ROC) curve for Major Depression Inventory score and PPS. The curve shows the connection between Major Depression Inventory score and PPS cut points (MDI score ≥ 20, PPS ≥ 60, respectively) with respect to sensitivity and specificity (for example showing that 0.6 in sensitivity corresponds with a 0.8 in specificity). The size of the area below the curve = 0.68 ($p < 0.01$).

Paper 2: Cross-sectional study in patients with stable ischemic heart disease

Description of the study sample

The study population is presented in Table V.

Results

At baseline, the PPS was found to be significantly and weakly correlated with SF-36 Mental Component Summary, SF-36 Physical Component Summary, Major Depression Inventory score, Clinical Stress Questionnaire score, and Canadian Cardiovascular Society Functional Classification of Angina Pectoris (all $p < 0.05$)(all $r < 0.2$). At the post-intervention measurement, the corresponding correlations were larger: PPS versus Major Depression Inventory score ($r = 0.3$; $p < 0.0001$); PPS versus WHO (Five) Well-Being Index ($r = -0.3$; $p = 0.001$), PPS versus SF-36

Mental Component Summary ($r = -0.2$; $p = 0.02$), and versus SF-36 Physical Component Summary ($r = -0.3$; $p = 0.004$) (N= 183) (Supplementary data).

Table V. Demographic data of the study group with ischemic heart disease (Studies 2, 4, 5).

	Cross-sectional study	Intervention study Active group study (4)	Intervention study Control group study (4)
N	361	106	107
Male, n (%)	286 (79)	64 (74)	70 (74)
Age in years, mean (SD)	63 (7.9)	62 (8.1)	63 (7.9)
Cardiac variables			
Past myocardial infarction, n (%)	229 (63)	58 (67)	59 (62)
Treated with PCI, n (%)	242 (67)	60 (70)	66 (70)
Treated with CABG, n (%)	102 (28)	22 (26)	23 (24)
Cardiac risk factors			
Heart failure, n (%)	111 (31)	26 (30)	36 (38)
Diabetes, n (%)	28 (13)	20 (19)	8 (8)
Have been treated for depression, n (%)	49 (14)	12 (14)	16 (17)

(N = total number of participants; n = number of subgroup participants; PCI = Percutaneous coronary intervention; CABG = coronary artery bypass grafting)

Measurement of PPS by two different algometers and with additional analyses

The internal correlation between repeated measurement with 5 seconds between measurements was $r = 0.89$ (both $p < 0.0001$) (N = 39) for both instruments when measurement was applied on the flat anterior surface of the tibia bone (Figures 5a and 5b). The correlation coefficient between measurements conducted by the two instruments was $r = 0.83$ (Figure 5c), and the mean difference was 18 kPa ($p > 0.1$). In the same experiment, pressure pain threshold of the sternum was conducted using the PPS device and the definition of pressure pain threshold used in this thesis. With 5 seconds between these measurements on the sternum, the internal correlation was $r = 0.97$ ($p < 0.0001$) (Figure 5d). This correlation coefficient is significantly higher than the internal correlation coefficients obtained by the two different instruments on the tibia (both $p = 0.03$). The mean differences between the two repeated measurements on the tibia with 5 seconds between measurements were 48 kPa for the established and new algometer alike. For the new algometer and using the two-criteria measurement techniques for the pressure pain threshold, the mean difference between two repeated measurements on the sternum was 22 kPa, which was significantly less than both pressure pain threshold measurements on the tibia (both $p < 0.0001$).

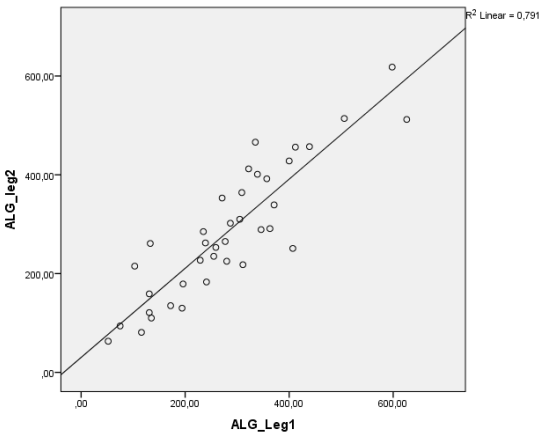

Figure 5a.

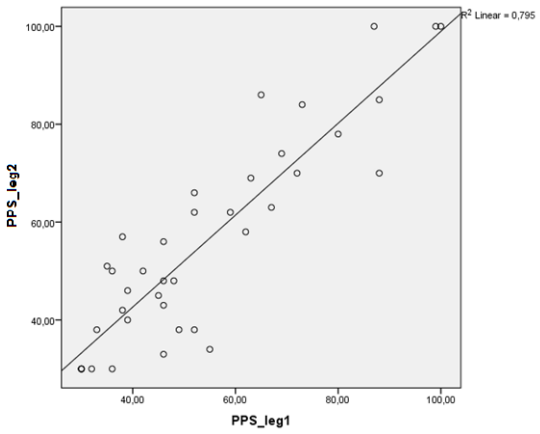

Figure 5b.

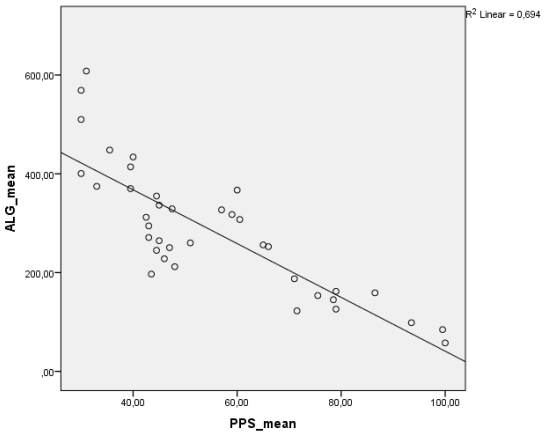

Figure 5c.

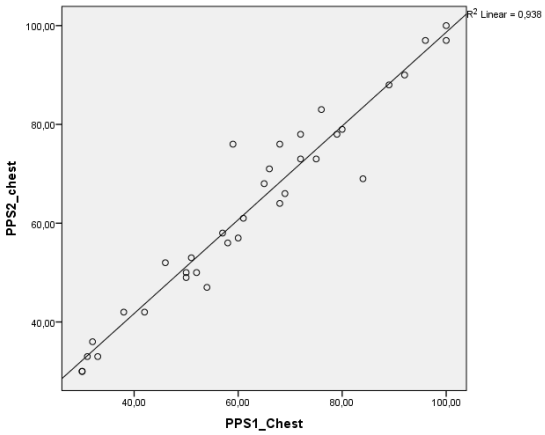

Figure 5d.

Figure 5: Correlations between pressure pain threshold measurements: (5a) measurement on the tibia bone, 5 seconds between measurements using a commonly used algometer, and using verbal determination of pressure pain threshold, only (r = 0.89) (p < 0.0001); (5b) measurement on the tibia bone, 5 seconds between measurements, using the new algometer device and using verbal determination of pressure pain threshold, only (r = 0.89) (p < 0.0001); (5c) mean measurements on the tibia bone when the two algometers of Figures 5a and 5b are compared (r = 0.83) (p < 0.0001); (5d) measurement on the sternum using the new algometer and using the determination technique which includes nociceptive withdrawal reflex in the determination of the pressure pain threshold, (r = 0.96) (p < 0.0001). (Alg_leg 1 and Alg_leg 2: first and second by Sometic algometer; PPS_leg 1 and PPS_leg 2: first and second leg measurement by the new algometer used in this thesis; ALG_mean and PPS_mean: mean measurement by the Sometic and the new algometer, respectively; PPS1_chest and PPS2_chest: first and second measurement on the sternum by the new algometer).

Paper 3: The longitudinal randomized intervention study in office workers

Description of the study sanple

Among the study population (N = 42), the baseline mean PPS was 77. Based on the relevant cut-off levels, 42% had an elevated systolic blood pressure, 25% an elevated heart rate, 55% an elevated Body Mass Index, 59% an elevated serum total cholesterol, and 40% an elevated glycated hemoglobin.

Results

The PPS correlated significantly with systolic blood pressure (correlation coefficient r = 0.24), Body Mass Index (r = 0.34), Visceral Fat Index (r = 0.26), as well as total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride (all r > 0.20). Changes in PPS during the intervention period correlated moderately to strongly with the changes in heart rate, pressure-rate-product, Body Mass Index, Visceral Fat Index, YKL-40, and total cholesterol, while for Hb1Ac, the correlation was only significant for the group with elevated Hb1Ac at baseline (all r > 0.3)(Figure 6).

During the intervention, when the elevated PPS measure was reduced, concomitant and clinically relevant and statistically significant reductions were observed for the active group when compared to the control group, with respect to PPS (42%), systolic blood pressure (8%), pressure-rate-product (10%), total cholesterol (13%), LDL cholesterol (16%), and total number of elevated health risk factors (50%) (all $p < 0.05$). With respect to the total number of elevated risk factors, this was reduced in 71% of the people in the active group, compared to 20% in the control group ($p < 0.003$). For people with an elevated cardiovascular physiological risk factor at baseline (e.g. blood pressure, heart rate; pressure-rate-product; total cholesterol and LDL cholesterol), significant reductions and response rates of ≥ 85% were observed for the active group, while no significant changes were observed in the control group.

When adjusted for the use of the block randomization procedure, a significant between-group effect of the intervention was found for PPS, LDL cholesterol and total number of elevated health risk factors.

With respect to compliance, the office workers in the active group recorded their PPS measure on average every second day during the first month, every third day during the second month, and every fourth day during the third month.

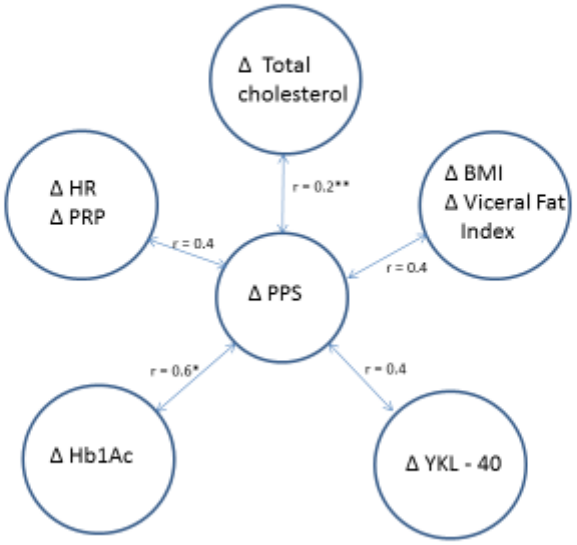

Figure 6: The association between changes in PPS and changes in physiological and biochemical cardiovascular health factors associated with persistent stress. The correlation coefficients (r) between changes in resting PPS (ΔPPS) changes in factors of cardiovascular physiology: heart rate and pressure-rate-product (ΔHR and ΔPRP), fat distribution (ΔBMI and ΔVisceral Fat Index), fat metabolism (Δ Total cholesterol), glucose metabolism (ΔHb1Ac), and low-grade inflammation (ΔYKL-40) (all $p < 0.05$; N = 42). *for people with elevated Hb1Ac at baseline only (N = 17); **correlation is not significant ($p > 0.1$).

Paper 4: Longitudinal randomized intervention study in patients with ischemic heart disease

Description of the study sample

The study population is presented in Table V. No significant between-group differences were found with respect to the primary and secondary effect variables. However, with respect to self-reported diabetes and heart failure, heart failure was significantly more common in the control group, and diabetes in the active intervention group.

Results

When compared to the control group, the Major Depression Inventory score and the PPS were both reduced significantly in the active group, by 22% and 28%, respectively. With respect to the WHO (Five) Well-Being Index, the score increased significantly in the active group and non-significantly in the control group, with a significant between-group difference at 3 months.

The effect size on the active group versus the control group was 0.12 for Major Depression Inventory, 0.11 for WHO (Five) Well-Being Index, and 0.63 for PPS when all patients were included. However, the effect size increased to 0.35 for the subgroup of patients with a Major Depression Inventory score ≥ 15 as a sign of incipient depression.

For the subgroup of patients with a Major Depression Inventory score ≥ 20 as a sign of overt depression, the effect size was 0.9. The mean Major Depression Inventory score for these patients in the active group changed from 26 to 15, and for the control group from 24 to 22 arbitrary units ($p = 0.1$). In these patients, the change in PPS correlated strongly and significantly with the change in Major Depression Inventory score ($r = 0.62$; $p = 0.03$); the change in WHO (Five) Well-Being Index score ($r = -0.74$; $p = 0.006$); and the change in SF-36 Physical Component Summary ($r = -0.85$; $p = 0.002$) (N = 13) (Figure 7) (Supplementary data).

With respect to compliance, 94 patients (89%) reported repeated PPS measurements at home. The mean number of recorded PPS measures was 90 during the 3-month observation period.

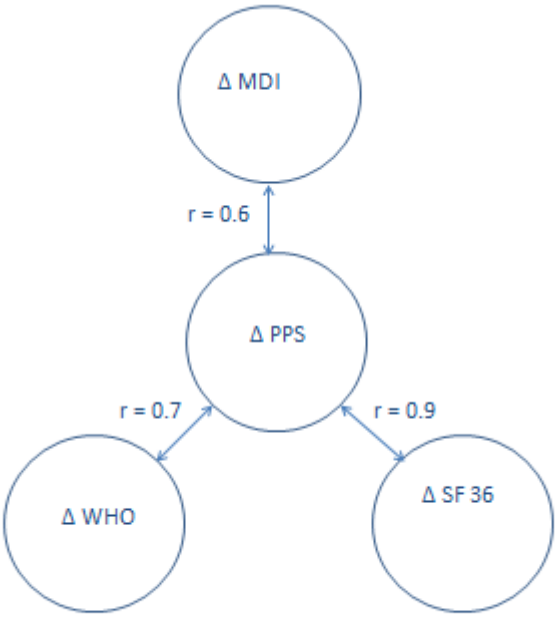

Figure 7: The association between changes in PPS **and changes in psychological cardiovascular health risk factors associated with persistent stress during the intervention trial**. The correlation coefficients (r) between changes in resting PPS (ΔPPS) and changes in factors of cardiovascular quality of life in patients with stable ischemic heart disease, an elevated PPS measurement (i.e. ≥ 60) and an elevated Major Depression Inventory score (i.e. ≥ 20 at baseline (ΔPPS, ΔSF-36, ΔMDI, ΔWHO = changes during intervention period for the four variables, respectively) (N = 13).

Paper 5: Experimental physiological study patients with ischemic heart disease

Description of the study sample

The study population of the short-term experimental study is presented in Table V. The study group of the randomized intervention study consisted of 74% men, and the mean age of the study group was 63 years. All had by definition ischemic heart disease, 65% had had a previous myocardial

infarction, 70% percutaneous coronary intervention, 25% coronary artery bypass graft, 34% heart failure, and 15% had been diagnosed with depression. Eighty-six patients were randomized to the active group and 95 to the control group.

Results

The short-term experimental study

During tilt-table testing, mean PPS was reduced from 65 to 61 units and systolic blood pressure was reduced from 137 mmHg to 131 mmHg, whereas mean heart rate increased from 61 to 67 beats per minute (all $p < 0.0001$). The change in PPS during tilt-table testing correlated positively to the change in systolic blood pressure ($r = 0.44$) and heart rate ($r = 0.49$) (both $p < 0.0001$). The higher the resting PPS, the lower the PPS response to tilt-table testing ($r = - 0.37$; $p < 0.0001$) (Figure 8). When including the four additional risk factors for autonomic nervous system dysfunction (e.g. chest pain at rest, depression, systolic blood pressure $\geq$ 130 mmHg and resting PPS $\geq$ 60), it was found that the higher the number of risk factors, the lower the PPS response to tilt-table testing. The group with no additional autonomic nervous system risk factors had a mean increase of +4 units in PPS during tilt-table testing, compared to – 2, - 5, – 8, and –19 for the groups with one, two, three and four additional risk factors, respectively ($r = - 0.21$; $p < 0.0001$)(Figure 9)

Using resting PPS of 60 units as the discrimination point for an elevated level of persistent stress, there was a significant between-group difference with respect to the PPS response to tilt-table testing, when the group with resting PPS of < 60 (N = 155) (mean change: +1 PPS units) was compared to the group with resting PPS of $\geq$ 60 (N = 206) (mean change: - 7 PPS units) (between-group $p < 0.0001$).

The prospective randomized intervention study

The greater the reduction in resting PPS during the intervention period, the greater the increase in the PPS response to tilt-table testing over 3 months, with a strong correlation between the two ($N = 181$) ($r = 0.52$; $p < 0.0001$) (Figure 10). A reduction in PPS of ≥ 15 was regarded as the minimum clinically relevant difference. When the group of patients who obtained this difference was compared to the group who did not, the former group obtained a mean of +12 PPS units in PPS response to tilt-table testing during the intervention period, compared to – 4 PPS units in the latter group (between-group $p < 0.0001$). Furthermore, the increase in PPS response to tilt-table testing correlated significantly with a concomitant reduction in the number of autonomic nervous system dysfunction risk factors ($r = - 0.23$; $p < 0.003$)

When compared to the control group, the active intervention group had a significant reduction in resting PPS and number of autonomic nervous system dysfunction risk factors, a significant increase in the one-minute PPS response to tilt-table testing, while the 7-minute response reached a p-value of 0.07.

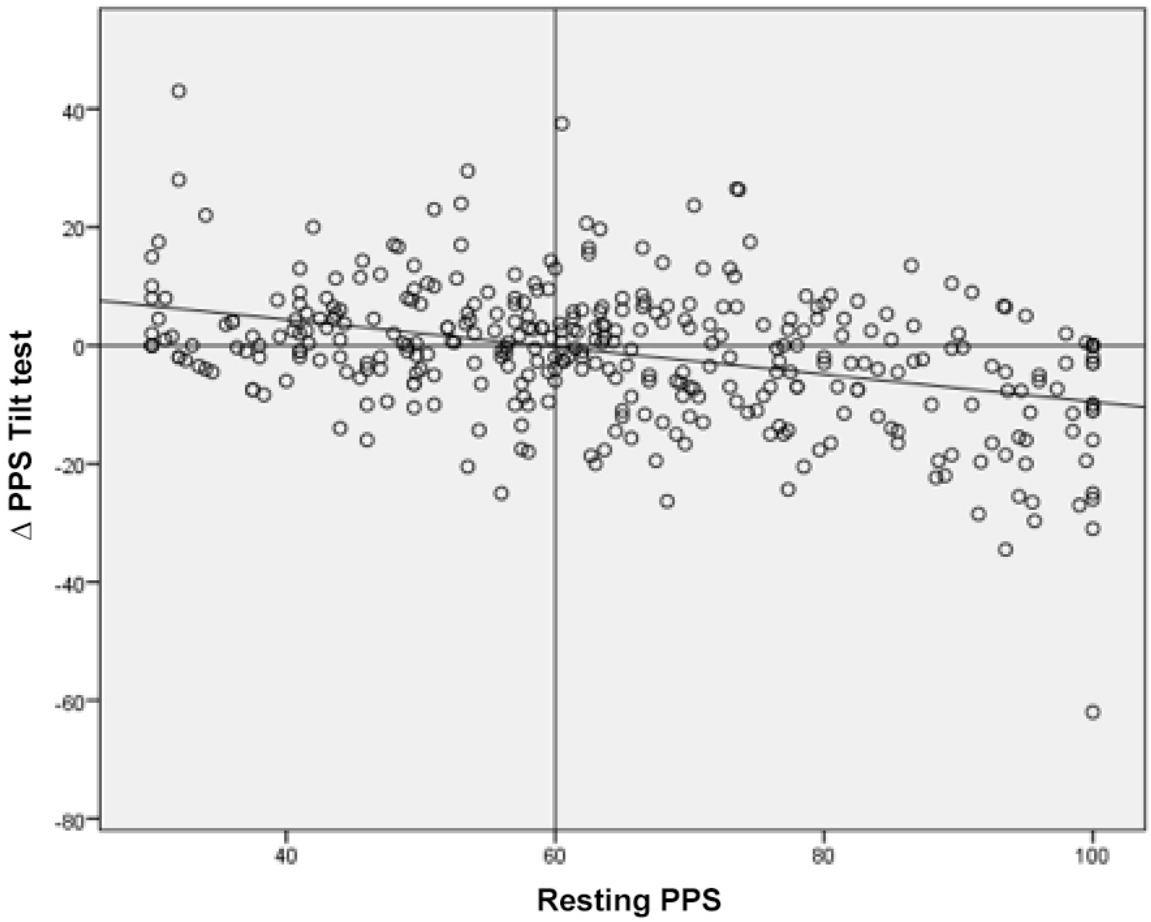

Figure 8: The association between baseline PPS (Resting PPS) and change in PPS during baseline tilt-table testing (Δ PPS Tilt test) (r = - 0.37; p < 0.0001; N = 361).

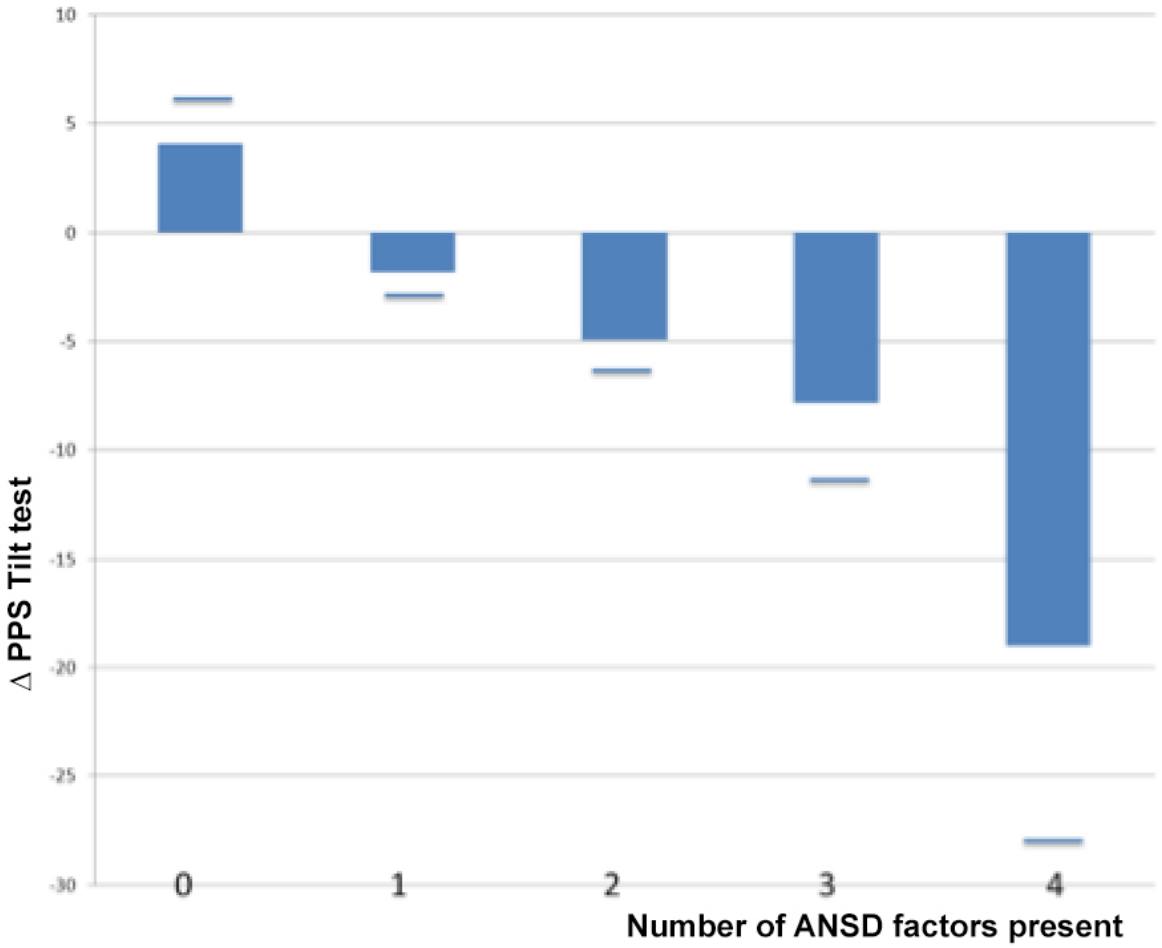

Figure 9: The association between mean change in PPS during tilt-table testing (Δ PPS Tilt test) and number of autonomic nervous system dysfunction (ANSD) risk factors, including chest pain at rest, hypertension (systolic blood pressure ≥ 130), depression (Major Depression Inventory score ≥ 20), and elevated level of persistent stress (resting PPS ≥ 60 units)(r = – 0.21, $p <$ 0.0001; N = 361). The horizontal lines indicate 95% confidence intervals.

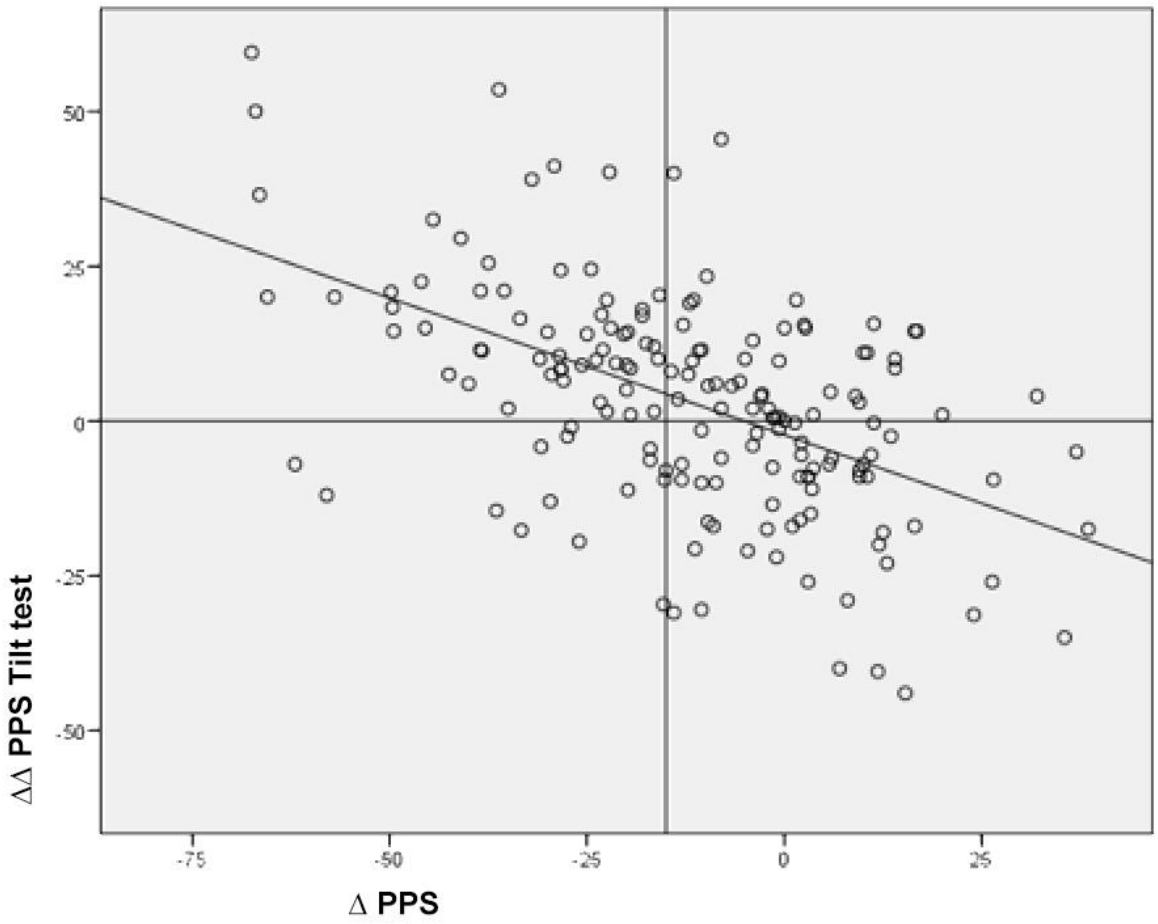

Figure 10: The association between change in resting PPS during the study period (Δ PPS) and change in PPS during tilt-table testing, when baseline and post-intervention tilt-table testing are compared (ΔΔ PPS Tilt test) ($r = -0.52$, $p < 0.0001$; $N = 177$). Vertical line indicates minimal important difference (see text) with respect to reduction in resting PPS during intervention period (15 units).

CHAPTER 5: GENERAL DISCUSSION

The results of this thesis can be summarized as follows:

1) In the cross-sectional studies, the PPS measure was weakly or moderately associated with the included cardiovascular risk factors. However, when measured longitudinally, and in response to an intervention aimed at reducing PPS, these associations were moderate to strong, and especially so in people with an elevated cardiovascular risk factor at baseline. Associations between PPS and cardiovascular risk factors included: physiological measures of autonomic nervous system function, systolic and diastolic blood pressure, heart rate, and pressure-rate-product; and one psychological measure, a depression score.
2) When compared to a control intervention, an active non-pharmacological intervention including daily PPS-guided cognitive reflection and daily cutaneous sensory nerve stimulation resulted in a statistically significant reduction in resting PPS with concomitant statistically significant reductions in autonomic nervous system function, diastolic and systolic blood pressure, heart rate, pressure-rate-product, and depression score.

The PPS measurement device and algometry

Algometry is the standard measurement method in pain research related to musculoskeletal pain, and deep somatic pain (39). As such, it has been used for a long time to assess and understand hypersensitivity and hyperalgesia in somatoform pain disorders (41), and the presence of generalized hyperalgesia in conditions such as rheumatoid arthritis (42), chronic fatigue syndrome (43), chronic whiplash pain (44), chronic pelvic pain (45), and fibromyalgia (46).

The new PPS measurement device used in the current studies showed a strong association with an existing algometric device, when measuring pressure pain threshold. The PPS measure showed similar between-measurement difference along the full PPS scale and no

systematic error in long-term home use. Furthermore, the new device was found to be feasible for individual home-based measurement, a feature that was outside the scope of the existing algometric device. It should be emphasized that the new PPS measurement device rests on established and thoroughly tested technology, an algometric determination of pressure pain threshold. The technical novelties are the blinded measure of the pressure pain threshold, and a measurement pad that allows measurement of the pressure pain threshold of the periosteum of the chest bone rather than the skin superficial to the bone. However, the main novelty is the context in which pressure pain threshold is used.

The association between PPS, autonomic nervous system dysfunction and the persistent stress response

The current findings invite a discussion about the possible association between PPS, autonomic nervous system dysfunction and persistent stress.

In terms of contemporary scientific findings, autonomic nervous system dysfunction may link: i) an elevated PPS, impaired pain control and persistent stress (46;66;67), ii) ischemic heart disease, depression, and persistent stress (64;65), and iii) metabolic syndrome and persistent stress (56;57). From this viewpoint, the current findings of a link between PPS, autonomic nervous system dysfunction, and cardiovascular risk factors associated with persistent stress is not surprising.

However, novel and surprising findings, which support this notion are provided by a third study with ischemic heart disease patients, which is not part of this thesis (105). In this study, it was found that beta-adrenergic receptor blockade medication inhibited the secondary effects on depression score and systolic blood pressure response to tilt-table testing, when resting PPS was reduced during the 3-month intervention. However, the changes in resting PPS and PPS response to

tilt-table testing during the 3 months were not influenced by the medication. This medication inhibits the efferent physiological stress response induced by the autonomic nervous system. Accordingly, these findings show that: i) the regulation of PPS is located above the beta-adrenergic receptors in the autonomic nervous system hierarchy, ii) PPS is directly related to the physiological stress response, iii) a part of the neurological control of the included physiological cardiovascular risk factors are located inferior to the these receptors in this hierarchy, and iv) a part of the neurological pathogenic mechanisms of depression in ischemic heart disease patients is located inferior to these receptors as well (Figure 11).

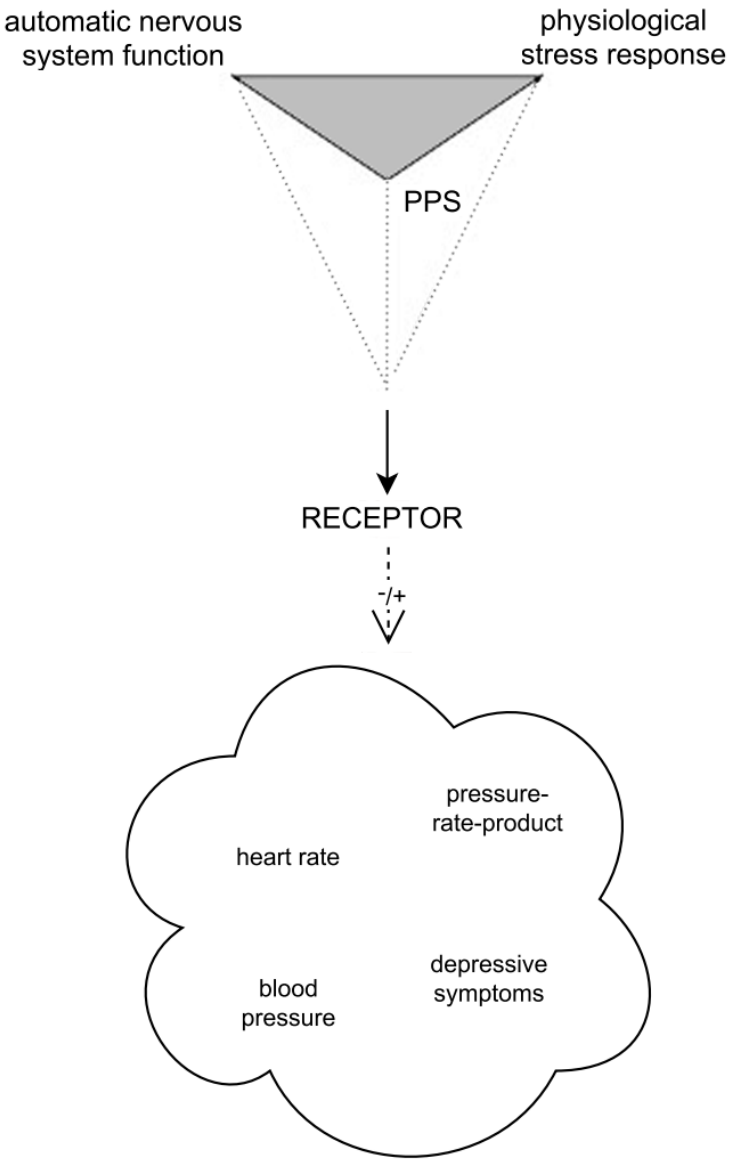

Figure 11. The possible link between PPS, autonomic nervous system function, the physiological stress response, physiological cardiovascular risk factors and depressive symptoms in patients with ischemic heart disease. The internal and direct association between PPS, the physiological stress response and the autonomic nervous system function is illustrated by the triangular relationship between the three. The beta-adrenergic receptor inhibits or facilitates the link between these and the physiological cardiovascular risk factors and depressive symptoms.

The association between PPS and the included cardiovascular risk factors

The results of the studies support the first hypothesis of this thesis: that PPS is associated with cardiovascular risk factors including blood pressure, heart rate, pressure-rate-product, autonomic nervous system function, and depression. However, it should be emphasized that the hypothesis that a reduction of an elevated PPS is associated with concomitant lowering of cardiovascular risk factors does not necessarily imply a cause and effect relationship between PPS and these risk factors. These associations were weak to moderate in the cross-sectional studies, moderate to strong in the intervention studies, and even stronger if the outcome measures were elevated at baseline.

In the cross-sectional studies, the association may have been weakened by the fact that (i) the PPS measure may have reflected both transient and persistent stress; (ii) the association with a risk factor may have required a more persistent stress burden and thus an elevated PPS for a prolonged period of time before the risk factor was elevated as well, such as has been suggested for blood pressure (108); and (iii) the risk factor may have been elevated for reasons other than persistent stress, in which case the risk factor may have been elevated without a corresponding increase in PPS.

In the intervention studies, the association may have been stronger due to people with a low PPS measure at baseline being excluded in these studies , as the intervention was aimed at reducing PPS, if this was elevated. As such, a possible link between cardiovascular risk factors associated with persistent stress and PPS is reinforced, if the intervention succeeds in reducing PPS and this reduction is subsequently associated with a concomitant reduction in the included risk factor.

The intervention used was non-pharmacological, and due to the nature of the intervention, would mediate any effect via existing homeostatic mechanisms. The risk factor would more likely be reduced if it was elevated at baseline, and be more likely to remain unchanged if not

elevated. This may make the association even stronger, if PPS as well as the cardiovascular risk factors were elevated at baseline. This mechanism is in contrast to that of pharmaceutical intervention such as beta-blockade intervention, which lowers heart rate and blood pressure, regardless of whether baseline values are high or low. For that reason, such intervention is contraindicated in people with low resting pulse or low blood pressure.

As such, it makes sense that the associations were weak in the cross-sectional studies, stronger in the interventional studies and even more so, when both outcome measures were elevated at baseline.

The PPS-guided intervention

The current studies show that daily PPS-guided cognitive reflection and daily cutaneous sensory nerve stimulation reduce an elevated PPS, and that this reduction is followed by a concomitant reduction in the included cardiovascular risk factors associated with persistent stress. However, due to the nature of the studies, it is not possible to distinguish between the effect from the PPS-guided cognitive reflection and the effect from repeated cutaneous nerve stimulation. Accordingly, such distinction was not part of the aim of the studies.

Others have found corresponding results showing that stress reduction by other means had an effect on individual cardiovascular risk factors. Those studies found that cognitive therapy reduced the risk of new myocardial infarctions (109), and group-based psychotherapy prolonged life (110), mental stress reduction improved quality of life and reduced blood pressure in ischemic heart disease patients (111), a combination of mental and physical stress reduction as seen in Yoga and Qicong reduced blood pressure and serum cholesterols (112;113), and listening to music was found to reduce blood pressure and heart rate (114). In line with these findings, stress reduction

therapies have been recommended in the treatment of hypertension (115;116) and ischemic heart disease (117).

With respect to the included daily repeated cutaneous sensory nerve stimulation, previous studies suggest that it may increase exercise performance and reduce angina attack rate in patients with ischemic heart disease (7;9;10), mediated by a reduced sympathetic tone (9). Furthermore, it has been found that such cutaneous sensory nerve stimulation enhances cardiovascular homeostatic mechanisms (14). Similar effects have been obtained by transcutaneous electrical nerve stimulation (118;119) and by electrical spinal cord stimulation (120;121). Other researchers have found that cutaneous sensory nerve stimulation reduced low back and neck pain (122;123). A recent review concludes that it may improve patient outcomes, but rigorous trials are needed (124). Given this background, the current findings may suggest that the daily repeated cutaneous sensory stimulation has an independent effect, lowering the sympathetic tone, if elevated.

Strengths and limitations

The main points of methodological strength of the included studies are: (1) inclusion of pre-selected and pre-tested effect variables; (2) the use of a prospective randomized design; (3) the potential influence from the many possible confounders being taken into account in large scale studies in patients with stable ischemic heart disease by obtaining extensive background information; (4) the inclusion of a large-scale and strictly experimental physiological study of patients with stable ischemic heart disease that due to the nature of the study excluded patient expectation-related bias; (5) the hypotheses and research questions were tested in pilot studies prior to the studies of the thesis; and (6) with respect to the conduct of the PPS measurement, it is considered a strength that the PPS measure in the cross-sectional study in the 308 office workers was conducted by10

different observers, who, before the study, had received 3 months of education in both the theory and practice of PPS measurement.

It is debatable whether the determination of the pressure pain threshold used in the current thesis represents a methodological weakness. When compared to a standard algometric procedure, the current technique was not found to be inferior.

Some important general methodological aspects should be raised: (a) How much and for how long does PPS need to be elevated before the included variables become affected in a measurable way? (b) How much and for how long does an elevated resting PPS need to be reduced before the included effect variables are influenced by this reduction in a measurable way? (c) Are the included effect variables elevated for reasons other than stress? (d) Does a reduction of an elevated resting PPS only affect the included variable, if this variable is influenced by stress and is elevated as well?

We have addressed these challenges in various ways:

a) In the cross-sectional study in ischemic heart disease patients, the group was divided into tertiles with respect to time since ischemic heart disease diagnosis and the most recently completed cardiac rehabilitation. No significant impact of time was found. However, only patients who had undergone cardiac rehabilitation for more than 6 months were included. As such, it cannot be ruled out that a potential impact of time can be identified in the time period immediately after disease onset or the most recent cardiac rehabilitation.

(b) By pooling data from two consecutive measurements with months between measurements in cross-sectional studies, the potential influence from confounding factors may be elucidated. Personal potential confounding factors are thought to be stable within the individual during these time periods. Such data showed consistent results in office workers and ischemic heart

disease patients, thus suggesting that the observed associations between PPS and cardiovascular health risk factors are not subject to significant influence from a variety of potential confounding factors within and between the included study groups.

A statistical limitation arising from the use of correlation analysis in the study of associations and reliability should be discussed. It can be argued that other statistical analytical methods might have been used: such as Cohens Kappa coefficient in the analysis of categorization agreement, intra-class correlation analyses when comparing PPS measures conducted by different observers, and Bland Altman analysis when comparing two different algometric devices. We used Pearson's parametric and Spearman's non-parametric correlation analyses. Scatter plots have been included to show linearity and homoscedasticity. The observed correlation coefficients were often moderate to strong, which minimizes the potential bias from the use of correlation analysis. As a supplementary analysis, the Cohen Kappa coefficient was 0.9 with respect to categorization agreement in the study of office workers, which is considered a "strong to almost perfect agreement" (125). Since correlation analysis cannot be used to evaluate cause and effect relationships, intervention studies have been included in which only one outcome measure was reduced, that is, PPS. Concomitant and meaningful changes in the other variables underscore the cause and effect relationship between PPS and the included cardiovascular risk factors. And this analysis has a higher priority in the evaluation than the correlation analysis. With respect to the risk of mass significance, the tested associations were established during long-term clinical observations and tested positive in a series of pilot studies prior to the studies of this thesis. Thus, the studies of this thesis were designed to re-test the associations between pre-defined variables, which minimize the risk of mass-significance. On this basis, it is likely that these limitations do not affect the overall conclusions significantly.

Other methodological limitations include:

(1) In the studies involving office workers, we did not specifically address the presence of a chronic pain syndrome among the participants. However, we asked for information on daily use of medication, and no use of pain-relieving medication was reported. With respect to co-morbidity, the presence of hypertension, diabetes, cancer, and heart disease was not different from that of the general Danish population, neither was their lifestyle. Accordingly, we regard the study population to be fairly representative of Danish office workers. In the intervention study, the relatively small sample size is a limitation with respect to an evaluation of the investigated intervention. However, with respect to the screening aim of the study and possible association between a reduction in an elevated PPS measure and concomitant changes in relevant cardiovascular risk factors, this limitation seems of minor importance.

(2) In the clinical intervention study in patients with ischemic heart disease, it is a limitation that the intervention study ended up being underpowered, when evaluating the effect on depression. In contrast to the study of office workers, the controls in the heart study had some treatment in order to diminish stress: they were informed that they had an elevated stress level, and received a book on general stress management. The book explained that an elevated stress level was a risk factor in patients with ischemic heart disease. In addition, the book gave information on stress reduction methods. The purpose for the information given to the control group was to strengthen the separate effect of the biofeedback method used with the PPS measure in combination with sensory nerve stimulation provided to the actively treated group. However, it should be emphasized that the inclusion of these two specific aspects of the comprehensive intervention program used in the early studies on patients with ischemic heart disease (18-20) and stroke (21)was chosen because other scientists have demonstrated that the other elements of the intervention program used; e.g. diets

(126), physical exercise (127) and cognitive exercises or counselling (109;110) each have a positive effect on ischemic heart disease prognosis.

CHAPTER 6: GENERAL CONCLUSIONS

1) Hypothesis 1 of the thesis is confirmed by the current five studies of this thesis: PPS is associated with established cardiovascular risk factors. These factors include blood pressure, heart rate, pressure-rate-product, autonomic nervous system function and depression score.

2) Hypothesis 2 of the thesis is confirmed by the current five studies of this thesis: the combination of daily PPS-guided cognitive reflection and daily cutaneous sensory nerve stimulation reduces an elevated PPS measure and this reduction is associated with concomitant clinically relevant improvements in the included cardiovascular risk factors: blood pressure, heart rate, pressure-rate-product, autonomic nervous system function and depression score. As such the PPS measure may represent a useful monitoring tool as a composite measure for the included risk factors.

3) Including contemporary findings from research outside the studies of this thesis, it may furthermore be concluded that PPS is associated with persistent stress. As such, the PPS may represent a useful monitoring tool for persistent stress.

CHAPTER 7: PERSPECTIVES AND IMPLICATIONS

Potential research implications of the PPS measure

- Clinical studies on the use of PPS as a measure of physiological stress, transient as well as persistent.
- Large-scale prospective randomized studies that address the observed association between PPS and cardiovascular risk factors. Such studies may include other means of assessment for the autonomic nervous system such as heart rate variability.
- Inclusion of PPS in ongoing and/or new large prospective population cohort studies in order to gain further understanding of the epidemiological applicability.
- Studies elucidating the distribution of PPS across different population groups, age groups, and between the sexes.
- Large-scale clinical studies that evaluate the usefulness of the combined PPS measurement and intervention on relevant clinical variables in healthy people and people with ischemic heart disease, hypertension and stroke.
- Small to medium size clinical studies evaluating the usefulness of the combined PPS measurement and intervention on other non-communicable diseases such as cancer, diabetes, depression, chronic obstructive lung disease, and chronic non-malignant pain.
- Experimental physiological studies that explore the physiological background for the PPS measure, which may include studies exploring the involvement of neurological receptors in the PPS measure and potentially identifying the engaged receptors, studies elucidating the link between PPS, the hypothalamus, and regulation of the cardiovascular system.
- Studies elucidating the usefulness of the PPS measure in top athletes and the general sport populations.

- Studies using other intervention modalities for the reduction of an elevated PPS measure such as physical exercise and sports, music, singing and dancing, meditation, mindfulness, yoga, Tai Qi, Qigong, psychological counseling and group therapy, psychotherapy and cognitive therapy.
- Neuro-scientific studies exploring the possibility of pharmaceutical reduction of an elevated PPS measure.

Potential implications of the PPS measure for practical use

In contrast to pharmaceutical treatment, the PPS measure is not associated with any known risks, side effects or complications. Furthermore, the PPS measure and the PPS–guided intervention were found to work well in combination. This suggests potential practical applications.

The PPS measure may be a practical tool for people interested in measuring their level of physiological stress. This interest may be of particular interest for people having stressful job positions and life situations. Also people having regular returning stress demands in their job like performing artists, surgeons, flight traffic controllers, and soldiers in combat may also benefit. Active sports participants in competitions may find the PPS measure useful as actually demonstrated in the paper on Olympic sailors (24).

In clinical practice, patients with chronic diseases of any kind may find the PPS measure useful.

Ethical aspects of the PPS measure.

The PPS measure may be a useful tool for research and a number of practical purposes as discussed above. However, for any kind of physiological measurement, a risk of adverse effects is potentially

present. Although the PPS measure is harmless in itself, it may still be used inappropriately. As an example of such inappropriate use: employers may want to screen and monitor their employees' PPS values, which might be used for determining the suitability of employees for jobs.

For some people, knowledge related to their level of stress may introduce fear and worry if they have a high PPS value. If no possibility for lowering the value existed, this might be an ethical problem. However, several methods are available for stress reduction. Accordingly, measurement of PPS is not unethical.

CHAPTER 8: FUNDING AND DISCLOSURES

Søren Ballegaard (SB) invented the PPS instrument used to measure PPS. He is also a shareholder of the company that owns the PPS instrument. In order to avoid bias, SB was not involved in the patient contact and collection of data in the studies of this thesis, as all measurement and collection of data took place in locations to which SB had no access. With regard to statistical analyses, SB participated in these, but all analyses were performed a second time by an independent expert in statistics.

The studies on office workers received financial support from Willis Limited. The studies on patients with ischemic heart disease received financial support from the Johan Schrøder's Family Foundation, The Lundbeck Foundation, Else and Mogens Wedells-Wedellsborg Foundation, and Carpenter Sophus Jacobsen and wife Astrid Jacobsens's Foundation. During the conduct of the studies that comprise this thesis, the PhD candidate was employed by Care A/S. No public or private funding was involved with regard to preparing the manuscript of the thesis. No other disclosures were reported.

LITERATURE LIST

(1) Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Invest 2012 Oct;72(6):459-66.

(2) Bergmann N, Ballegaard S, Holmager P, Kristiansen J, Gyntelberg F, Andersen LJ, et al. Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease. Scand J Clin Lab Invest 2013 Aug;73(5):373-9.

(3) Ballegaard S, Petersen PB, Harboe GS, Karpatschof B, Gyntelberg F, Faber J. The association between changes in pressure pain sensitivity and changes in cardiovascular physiological factors associated with persistent stress. Scand J Clin Lab Invest 2014;74:116-25.

(4) Bergmann N, Ballegaard S, Bech P, Hjalmarson A, Krogh J, Gyntelberg F, et al. The effect of daily self-measurement of pressure pain sensitivity followed by acupressure on depression and quality of life versus treatment as usual in ischemic heart disease: a randomized clinical trial. PLOS ONE 2014;9(5):e97553.

(5) Ballegaard S, Bergmann N, Karpatschof B, Kristiansen J, Gyntelberg F, Arendt-Nielsen L, et al. Association between pressure pain sensitivity and autonomic function as assessed by a tilt table test. Scand J Clin Lab Invest 2015 Sep;75(5):345-54.

(6) Mannheimer C, Carlsson CA, Ericson K, Vedin A, Wilhelmsson C. Transcutaneous electrical nerve stimulation in severe angina pectoris. Eur Heart J 1982 Aug;3(4):297-302.

(7) Ballegaard S, Jensen G, Pedersen F, Nissen VH. Acupuncture in severe, stable angina pectoris: a randomized trial. Acta Med Scand 1986;220(4):307-13.

(8) Ballegaard S, Pedersen F, Pietersen A, Nissen VH, Olsen NV. Effects of acupuncture in moderate, stable angina pectoris: a controlled study. J Intern Med 1990 Jan;227(1):25-30.

(9) Ballegaard S, Meyer CN, Trojaborg W. Acupuncture in angina pectoris: does acupuncture have a specific effect? J Intern Med 1991 Apr;229(4):357-62.

(10) Ballegaard S, Karpatschoff B, Holck JA, Meyer CN, Trojaborg W. Acupuncture in angina pectoris: do psycho-social and neurophysiological factors relate to the effect? Acupunct Electrother Res 1995 Apr;20(2):101-16.

(11) Ballegaard S. Acupuncture and the Cardiovascular System: a Scientific Change. Acupuncture in Medicine 1998;16(1):2-9.

(12) Ballegaard S. Acupuncture in Cardiovascular Disease. In: Stein RA, Oz MC, editors. Complementary and Alternative Cardiovascular Medicine. 1. ed. Humana Press Inc.; 2004. p. 167-87.

(13) Chauhan A, Mullins PA, Thuraisingham SI, Taylor G, Petch MC, Schofield PM. Effect of transcutaneous electrical nerve stimulation on coronary blood flow. Circulation 1994 Feb;89(2):694-702.

(14) Ballegaard S, Muteki T, Harada H, Ueda N, Tsuda H, Tayama F, et al. Modulatory effect of acupuncture on the cardiovascular system: a cross-over study. Acupunct Electrother Res 1993 Apr;18(2):103-15.

(15) Longhurst J. Acupuncture's Cardiovascular Actions: A Mechanistic Perspective. Med Acupunct 2013 Apr;25(2):101-13.

(16) Longhurst JC, Tjen AL. Acupuncture regulation of blood pressure: two decades of research. Int Rev Neurobiol 2013;111:257-71.

(17) Beijing College of Traditional Medicine. Essentials of chinese acupuncture. Beijing: Foreign Languages Press; 1980.

(18) Ballegaard S, Norrelund S, Smith DF. Cost-benefit of combined use of acupuncture, Shiatsu and lifestyle adjustment for treatment of patients with severe angina pectoris. Acupunct Electrother Res 1996 Jul;21(3-4):187-97.

(19) Ballegaard S, Johannessen A, Karpatschof B, Nyboe J. Addition of acupuncture and self-care education in the treatment of patients with severe angina pectoris may be cost beneficial: an open, prospective study. J Altern Complement Med 1999 Oct;5(5):405-13.

(20) Ballegaard S, Borg E, Karpatschof B, Nyboe J, Johannessen A. Long-term effects of integrated rehabilitation in patients with advanced angina pectoris: a nonrandomized comparative study. J Altern Complement Med 2004 Oct;10(5):777-83.

(21) Magnusson G, Ballegaard S, Karpatschof B, Nyboe J. Long-term effects of integrated rehabilitation in patients with stroke: a nonrandomized comparative feasibility study. J Altern Complement Med 2010 Apr;16(4):369-74.

(22) Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Invest 2009;69(6):713-21.

(23) Axelsson CK, Ballegaard S, Karpatschof B, Schousen P. Pressure pain sensitivity as a marker for stress and pressure pain sensitivity-guided stress management in women with primary breast cancer. Scand J Clin Lab Invest 2014 Aug;74(5):399-407.

(24) Ballegaard S, Petersen BP, Harboe GS, Gyntelberg F, Faber J. Association between Pressure Pain Sensitivity, Performance Stability and Overall Performance in Olympic Sailors. Sports Medicine & Doping Studies 2016;6(2):177.

(25) Cowen R, Stasiowska MK, Laycock H, Bantel C. Assessing pain objectively: the use of physiological markers. Anaesthesia 2015 Jul;70(7):828-47.

(26) Schlereth T, Birklein F. The sympathetic nervous system and pain. Neuromolecular Med 2008;10(3):141-7.

(27) Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009 Oct 16;139(2):267-84.

(28) Jasmin L, Rabkin SD, Granato A, Boudah A, Ohara PT. Analgesia and hyperalgesia from GABA-mediated modulation of the cerebral cortex. Nature 2003 Jul 17;424(6946):316-20.

(29) Sapolsky RM. The influence of social hierarchy on primate health. Science 2005 Apr 29;308(5722):648-52.

(30) Sneddon LU. Evolution of nociception in vertebrates: comparative analysis of lower vertebrates. Brain Res Brain Res Rev 2004 Oct;46(2):123-30.

(31) Sneddon LU, Braithwaite VA, Gentle MJ. Do fishes have nociceptors? Evidence for the evolution of a vertebrate sensory system. Proc Biol Sci 2003 Jun 7;270(1520):1115-21.

(32) Kumazawa T. The polymodal receptor: bio-warning and defense system. Prog Brain Res 1996;113:3-18.

(33) Kumazawa T. Primitivism and plasticity of pain--implication of polymodal receptors. Neurosci Res 1998 Sep;32(1):9-31.

(34) O'Neil RG, Heller S. The mechanosensitive nature of TRPV channels. Pflugers Arch 2005 Oct;451(1):193-203.

(35) Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. TRPV4 calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol 2004 Feb;286(2):C195-C205.

(36) Gutkowska J, Jankowski M. Oxytocin revisited: its role in cardiovascular regulation. J Neuroendocrinol 2012 Apr;24(4):599-608.

(37) Vargas-Martinez F, Uvnas-Moberg K, Petersson M, Olausson HA, Jimenez-Estrada I. Neuropeptides as neuroprotective agents: Oxytocin a forefront developmental player in the mammalian brain. Prog Neurobiol 2014 Oct 13;123C:37-78.

(38) Lee HJ, Macbeth AH, Pagani JH, Young WS, III. Oxytocin: the great facilitator of life. Prog Neurobiol 2009 Jun;88(2):127-51.

(39) Arendt-Nielsen L, Yarnitskyy D. Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. J of Pain 2010.

(40) Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010 Oct;6(10):599-606.

(41) Egloff N, Camara RJ, von KR, Klingler N, Marti E, Ferrari ML. Hypersensitivity and hyperalgesia in somatoform pain disorders. Gen Hosp Psychiatry 2014 May;36(3):284-90.

(42) Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 2012 Feb;41(4):556-67.

(43) Nijs J, Meeus M, Van OJ, Ickmans K, Moorkens G, Hans G, et al. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. Eur J Clin Invest 2012 Feb;42(2):203-12.

(44) Van OJ, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. Eur J Pain 2013 Mar;17(3):299-312.

(45) Kaya S, Hermans L, Willems T, Roussel N, Meeus M. Central sensitization in urogynecological chronic pelvic pain: a systematic literature review. Pain Physician 2013 Jul;16(4):291-308.

(46) Chalaye P, Goffaux P, Bourgault P, Lafrenaye S, Devroede G, Watier A, et al. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. Clin J Pain 2012 Jul;28(6):519-26.

(47) Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. Pain 2010 Jun;149(3):573-81.

(48) Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation 2014 Apr 8;129(14):1493-501.

(49) Thomas GD. Neural control of the circulation. Adv Physiol Educ 2011 Mar;35(1):28-32.

(50) Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World J Cardiol 2015 Apr 26;7(4):204-14.

(51) Lanza GA, Fox K, Crea F. Heart rate: a risk factor for cardiac diseases and outcomes? Pathophysiology of cardiac diseases and the potential role of heart rate slowing. Adv Cardiol 2006;43:1-16.

(52) Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008 Sep 6;372(9641):817-21.

(53) Villella M, Villella A, Barlera S, Franzosi MG, Maggioni AP. Prognostic significance of double product and inadequate double product response to maximal symptom-limited exercise stress testing after myocardial infarction in 6296 patients treated with thrombolytic agents. GISSI-2 Investigators. Grupo Italiano per lo Studio della Sopravvivenza nell-Infarto Miocardico. Am Heart J 1999 Mar;137(3):443-52.

(54) De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003 Sep;24(17):1601-10.

(55) Bjorntorp P, Holm G, Rosmond R, Folkow B. Hypertension and the metabolic syndrome: closely related central origin? Blood Press 2000;9(2-3):71-82.

(56) Folkow B. Mental stress and its importance for cardiovascular disorders; physiological aspects, "from-mice-to-man". Scand Cardiovasc J 2001 Jul;35(3):163-72.

(57) Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology 2005 Jan;30(1):1-10.

(58) Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005 Dec 12;165(22):2644-50.

(59) Song CL, Bin L, Diao HY, Wang JH, Shi YF, Lu Y, et al. Diagnostic Value of Serum YKL-40 Level for Coronary Artery Disease: A Meta-Analysis. J Clin Lab Anal 2016 Jan;30(1):23-31.

(60) Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 2009;12(1):1-21.

(61) Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007 Feb;74(2):224-42.

(62) Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. Circulation 2005 Jul 19;112(3):332-40.

(63) Wentworth B.A., Stein M.B., Redwine L.S., Xue Y., Taub P.R., Clopton P., et al. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? Cardiol Rev 2013;21(1):16-22.

(64) Steptoe A, Kivimaki M. Stress and cardiovascular disease. Nat Rev Cardiol 2012 Jun;9(6):360-70.

(65) Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 2009 Jan;12(1):1-21.

(66) Vierck CJ, Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain 2006 Oct;124(3):242-63.

(67) Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain 2000 Aug;123 (Pt 8):1703-9.

(68) Fink G. Stress: Definition and history. In: Fink G, editor. Stress Science:Neuroendocrinology.San Diego: Academic Press; 2010. p. 3-9.

(69) Oken BS, Chamine I, Wakeland W. A systems approach to stress, stressors and resilience in humans. Behav Brain Res 2015 Apr 1;282:144-54.

(70) Eurofound. EWCO Comparative analytical resport on work related stress. 2010.
Ref Type: Online Source

(71) McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 1998 May 1;840:33-44.

(72) McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007 Jul;87(3):873-904.

(73) McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 2008 Apr 7;583(2-3):174-85.

(74) McEwen BS. Stress, sex, and neural adaptation to a changing environment: mechanisms of neuronal remodeling. Ann N Y Acad Sci 2010 Sep;1204 Suppl:E38-E59.

(75) McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993 Sep 27;153(18):2093-101.

(76) Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005 Feb;29(1):3-38.

(77) McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004 Dec;1032:1-7.

(78) Karasek R. The stress-disequilibrium theory: chronic disease development, low social control, and physiological de-regulation. Med Lav 2006 Mar;97(2):258-71.

(79) Loeppke R, Taitel M, Haufle V, Parry T, Kessler RC, Jinnett K. Health and productivity as a business strategy: a multiemployer study. J Occup Environ Med 2009 Apr;51(4):411-28.

(80) Boles M, Pelletier B, Lynch W. The relationship between health risks and work productivity. J Occup Environ Med 2004 Jul;46(7):737-45.

(81) Goetzel RZ, Carls GS, Wang S, Kelly E, Mauceri E, Columbus D, et al. The relationship between modifiable health risk factors and medical expenditures, absenteeism, short-term disability, and presenteeism among employees at novartis. J Occup Environ Med 2009 Apr;51(4):487-99.

(82) Holmes SD, Krantz DS, Rogers H, Gottdiener J, Contrada RJ. Mental stress and coronary artery disease: a multidisciplinary guide. Prog Cardiovasc Dis 2006 Sep;49(2):106-22.

(83) Spezia Adachi LN, Caumo W, Laste G, Fernandes ML, Ripoll RJ, de SA, et al. Reversal of chronic stress-induced pain by transcranial direct current stimulation (tDCS) in an animal model. Brain Res 2012 Dec 13;1489:17-26.

(84) Richebe P, Rivat C, Cahana A. Stress-induced hyperalgesia: any clinical relevance for the anesthesiologist? Anesthesiology 2011 Jun;114(6):1280-1.

(85) Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, et al. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. J Pain 2012 May;13(5):450-8.

(86) Tietjen GE, Brandes JL, Peterlin BL, Eloff A, Dafer RM, Stein MR, et al. Allodynia in migraine: association with comorbid pain conditions. Headache 2009 Oct;49(9):1333-44.

(87) Rayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, et al. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. PLoS One 2013;8(6):e63903.

(88) Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A 2001 Apr 10;98(8):4770-5.

(89) Novak P. Quantitative autonomic testing. J Vis Exp 2011;(53).

(90) Jaradeh SS, Prieto TE. Evaluation of the autonomic nervous system. Phys Med Rehabil Clin N Am 2003 May;14(2):287-305.

(91) Opie LH. Normal and abnormal cardiac function. Heart disease 7th edition. A textbook of cardiovascular Medicine.New York: Saunders Ltd; 2001. p. 703-4.

(92) Pikkujamsa SM, Huikuri HV, Airaksinen KE, Rantala AO, Kauma H, Lilja M, et al. Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. Am J Hypertens 1998 May;11(5):523-31.

(93) Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med 2005 May;67 Suppl 1:S29-S33.

(94) Spezia Adachi LN, Caumo W, Laste G, Fernandes ML, Ripoll RJ, de SA, et al. Reversal of chronic stress-induced pain by transcranial direct current stimulation (tDCS) in an animal model. Brain Res 2012 Dec 13;1489:17-26.

(95) Friedman AK, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, et al. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science 2014 Apr 18;344(6181):313-9.

(96) de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci 2005 Jun;6(6):463-75.

(97) Tak LM, Riese H, de Bock GH, Manoharan A, Kok IC, Rosmalen JG. As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. Biol Psychol 2009 Oct;82(2):101-10.

(98) Prinsloo GE, Rauch HG, Derman WE. A brief review and clinical application of heart rate variability biofeedback in sports, exercise, and rehabilitation medicine. Phys Sportsmed 2014 May;42(2):88-99.

(99) Quintana DS, Heathers JA. Considerations in the assessment of heart rate variability in biobehavioral research. Front Psychol 2014;5:805.

(100) Lee EH. Review of the psychometric evidence of the perceived stress scale. Asian Nurs Res (Korean Soc Nurs Sci) 2012 Dec;6(4):121-7.

(101) Beser A, Sorjonen K, Wahlberg K, Peterson U, Nygren A, Asberg M. Construction and evaluation of a self rating scale for stress-induced exhaustion disorder, the Karolinska Exhaustion Disorder Scale. Scand J Psychol 2014 Feb;55(1):72-82.

(102) Frisch JU, Hausser JA, Mojzisch A. The Trier Social Stress Test as a paradigm to study how people respond to threat in social interactions. Front Psychol 2015;6:14.

(103) Wiegner L, Hange D, Bjorkelund C, Ahlborg G, Jr. Prevalence of perceived stress and associations to symptoms of exhaustion, depression and anxiety in a working age population seeking primary care--an observational study. BMC Fam Pract 2015 Mar 19;16:38.

(104) Williams PL, Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE. In: Ferguson MWJ, editor. Gray's Anatomy. The anatomical basis of Medicine and Surgery. 38 ed. New York: Churchill Livingstone; 1995. p. 538-46.

(105) Ballegaard S. Association between Depression, Pressure Pain Sensitivity, Stress, Autonomic Nervous System Function in stable Ischemic Heart Disease: Impact of Beta-adrenergic Receptor Blockade. Journal of Behavioural and Brain Science 2016;6:317-28.

(106) correlation coefficient evaluation. PrFont34Bin0BinSub0Frac0Def1Margin0Margin0Jc1Indent1440Lim0Lim1http://explorable.com/statistical-correlation.html . 2013.
Ref Type: Internet Communication

(107) Cohen J. A power primer. Psychol Bull 1992 Jul;112(1):155-9.

(108) Timio M, Saronio P, Venanzi S, Gentili S, Verdura C, Timio F. Blood pressure in nuns in a secluded order: A 30-year follow-up. Miner Electrolyte Metab 1999 Jan;25(1-2):73-9.

(109) Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 2011 Jan 24;171(2):134-40.

(110) Orth-Gomer K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). Circ Cardiovasc Qual Outcomes 2009 Jan;2(1):25-32.

(111) Younge JO, Gotink RA, Baena CP, Roos-Hesselink JW, Hunink MG. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2015 Nov;22(11):1385-98.

(112) Hartley L, Dyakova M, Holmes J, Clarke A, Lee MS, Ernst E, et al. Yoga for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2014;(5):CD010072.

(113) Hartley L, Lee MS, Kwong JS, Flowers N, Todkill D, Ernst E, et al. Qigong for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2015;(6):CD010390.

(114) Bradt J, Dileo C. Music for stress and anxiety reduction in coronary heart disease patients. Cochrane Database Syst Rev 2009;(2):CD006577.

(115) Hackam DG, Quinn RR, Ravani P, Rabi DM, Dasgupta K, Daskalopoulou SS, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2013 May;29(5):528-42.

(116) Grassi G, Ram VS. Evidence for a critical role of the sympathetic nervous system in hypertension. J Am Soc Hypertens 2016 May;10(5):457-66.

(117) Hering D, Lachowska K, Schlaich M. Role of the Sympathetic Nervous System in Stress-Mediated Cardiovascular Disease. Curr Hypertens Rep 2015 Oct;17(10):80.

(118) Chauhan A, Mullins PA, Thuraisingham SI, Taylor G, Petch MC, Schofield PM. Effect of transcutaneous electrical nerve stimulation on coronary blood flow. Circulation 1994 Feb;89(2):694-702.

(119) Murray S, Collins PD, James MA. Neurostimulation treatment for angina pectoris. Heart 2000 Feb;83(2):217-20.

(120) Murray S, Carson KG, Ewings PD, Collins PD, James MA. Spinal cord stimulation significantly decreases the need for acute hospital admission for chest pain in patients with refractory angina pectoris. Heart 1999 Jul;82(1):89-92.

(121) Taylor RS, De VJ, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. BMC Cardiovasc Disord 2009 Mar 25;9:13.

(122) Matsubara T, Arai YC, Shiro Y, Shimo K, Nishihara M, Sato J, et al. Comparative effects of acupressure at local and distal acupuncture points on pain conditions and autonomic function in females with chronic neck pain. Evid Based Complement Alternat Med 2011;2011.

(123) Hsieh LL, Kuo CH, Lee LH, Yen AM, Chien KL, Chen TH. Treatment of low back pain by acupressure and physical therapy: randomised controlled trial. BMJ 2006 Mar 25;332(7543):696-700.

(124) Lee EJ, Frazier SK. The efficacy of acupressure for symptom management: a systematic review. J Pain Symptom Manage 2011 Oct;42(4):589-603.

(125) McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22(3):276-82.

(126) Dalen JE, Devries S. Diets to prevent coronary heart disease 1957-2013: what have we learned? Am J Med 2014 May;127(5):364-9.

(127) Skinner JS, Cooper A, Feder GS. Secondary prevention for patients following a myocardial infarction: summary of NICE guidance. Heart 2007 Jul;93(7):862-4.

Scandinavian Journal of Clinical & Laboratory Investigation, 2012; 72: 459–466

informa
healthcare

ORIGINAL ARTICLE

The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace A feasibility study

SØREN BALLEGAARD[1], PERNILLE B. PETERSEN[1], FINN GYNTELBERG[2] & JENS FABER[3,4]

[1]*Ull Care, Hellerup,* [2]*The National Research Center for the Working Environment, Copenhagen,* [3]*Department of Medicine O, Endocrine Unit, Herlev University Hospital, Herlev, and* [4]*Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark*

Abstract

Objectives. To examine the association between pressure pain sensitivity (PPS) at the sternum as a measure of persistent stress assessed by questionnaires in a working population. ***Methods.*** In 308 office employees PPS measurement was compared to Quality of life questionnaires: SF-36 for general physical and mental health, the Major Depression Inventory (MDI); 50 specific clinical symptoms for persistent stress; subjective evaluation of present and long-term stress level on a 7-point ordinal scale. Repeated measures were used to validate the PPS method. ***Results.*** A significant correlation between PPS and a persistent stress condition evaluated from SF-36, MDI and a number of clinical symptoms were found (all $p < 0.01$). Persons with PPS ≥ 60 units had an elevated health risk profile based on the questionnaires, when compared to persons with PPS ≤ 40 (all $p < 0.05$) (all odds ratios > 2). When categorizing a person with PPS ≥ 60 as persistently stressed (27% of subject), and using SF-36, MDI and the number of stress signs for risk calculation, the remaining 73% of the subjects, with no elevated health risk factors, were identified with an 80% specificity. During home measurements, with a full day between measurements, between-measurement correlation coefficient was 0.87 and categorization reproducibility 87% (both $p < 0.001$). ***Conclusions.*** In office workers, the PPS measurement correlated to several QOL questionnaires and was found useful for persistent stress screening. Validation studies demonstrated sufficient reproducibility including during self measurement at home.

Key Words: *Psychological stress, physiological stress, SF 36 questionnaire, Depression questionnaire, stress test, depression*

Introduction

Presently, no international consensus on biochemical, psychological, or physiological methods for measuring a transient and persistent stress condition 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]. Measuring stress in a place of work is a challenge. Using physiological markers might be preferable, but they have shortcomings. Thus physiological markers like catecholamine levels in urine or corticol in sputum are influenced by other factors than stress. The most important are physical exercise, use of tobacco, alcohol and coffee and tea drinking during work. Furthermore, corticol levels have major diural fluctuations making interpretation of the results difficult. In addition, sample collection is very resource demanding under field conditions. Accordingly, questionnaires addressing general mental and physical health may represent one possible workplace measure of the complex and comprehensive influence of stress on human functions. The SF 36 questionnaire and the Major Depression Inventory have been internationally recognized as stress measurement methods and have been found useful for stress evaluation in workplace situations [4–7].

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 threat or challenge is over, homeostasis is

Correspondence: Søren Ballegaard, Ull Care, Lemchesvej 1, 2900 Hellerup, Denmark. Tel: + 45 3940 4142. E-mail: sba@ullcare.com

(Received 27 January 2012; accepted 19 April 2012)

ISSN 0036-5513 print/ISSN 1502-7686 online © 2012 Informa Healthcare
DOI: 10.3109/00365513.2012.695023

re-established [8,9]. In contrast, *persistent stress* is caused by prolonged exposure to the same challenges as in transient stress, but without sufficient restitution in between, which leads to a variety of physiological and psychological dysfunctions [10,11]. Persistent stress may affect work performance, as well as general health negatively [12], and may lead to features of the metabolic syndrome [13–15], and ischemic heart disease [3,16]

In observations of normal persons during an acute stress load, as well as in patients with chronic diseases like ischemic heart disease, stroke and breast cancer, stress perception has been coupled to increased pain sensitivity on specific locations of the skin of the chest bone [17–19; Axelsson et al; unpublished data). This hypersensitivity seems to be explained by the presence of cutaneous polymodal nociceptors, which respond to pressure, heat and acidity [20] and are sensitive to sympathetic stimulation [21]. They may lead to activation of a noxious withdrawal reflex (NWR) [22]. The NWR is regarded as a reliable and objective tool for exploring pain control systems in humans [23]. From the evolutionary survival purpose of the stress response, it makes sense that the human warning system sensitivity (Pressure pain sensitivity) and defence system sensitivity (withdrawal reflex sensitivity) increase in order to protect the vital heart region.

In search of a method to measure the integrated response of stress, we have developed a new handheld algometric device, which makes it possible to quantify the level of sensitivity at a distinct point on the body, the sternum within the area between the third, fourth and fifth intercostals space reflecting the area of the segmental innervation of the heart [24], and we have designated the measure as Pressure Pain Sensitivity (PPS). We have then shown that the PPS measure seems well correlated to several well-known reactions to stress, like changes in blood pressure, pulse rate, work of the heart and salivary cortisol during transient stress, the resting pulse rate and work of the heart as measures for persistent stress in 181 consecutive out-patient clinic patients with chronic diseases as well as to the presence of the NWR in both situations [17].

In the present study we hypothesized that PPS may be used to estimate the level of persistent stress in the working population. In a group of office workers our aims thus were: To examine the association between PPS and standardized questionnaires on quality of life (QOL) which have been found useful in work-life stress evaluation; to evaluate the PPS measure as a screening tool for identifying persons with a level of persistent stress that may need intervention; and to evaluate if the PPS measure could be used as a home measurement device with respect to compliance and possible long-term adaptation of the measure.

Material and methods

Subjects and study design

Four-hundred and thirty-three persons employed in a large Danish company within the finance sector were invited to participate in the study, and 308 (71%) accepted to participate. The participants were characterized according to their job-description as 16 senior managers, 30 managers, 130 office workers and 132 office assistants.

PPS was measured in the workplace in the supine position by a professional instructor on all participants and they answered the set of included questionnaires: SF-36, Major Depression Inventory, clinical symptoms and demographics. Subjects with a resting PPS at baseline ≥ 60 ($n = 60$) were educated to self-measurement of PPS and to perform measurements twice daily for 3 months.

The following precautions were taken to minimize bias: Reading of the instrument was not visible during measuring neither for subject nor researcher; and the PPS measuring researcher had no access to the answers of the used questionnaires.

Measurement variables

Pressure Pain Sensitivity. PPS of the sternum was recorded using an instrument (Ull Meter), which mathematically transformed the pain threshold into a logarithmic scale of sensitivity levels (from 0–100 PPS units). An increase in 30 PPS units corresponds to a 100% increase in sensitivity. The method is previously described in details [17]. The measurement site is the sternum within the area between the third, fourth and fifth intercostals space (Figure 1) reflecting the area of the segmental innervation of the heart [24].

SF-36 questionnaire. The SF-36 questionnaire was used as an internationally validated questionnaire to assess general mental and physical health (Quality Of Life: QOL) by two main scores: Mental Component Summary (MCS) and Physical Component Summary (PCS) [25,26]. A score of 100 indicates perfect well-being. The SF-36 has been used in large population studies as an assessment tool of the long-term adverse health effects from work-related stress [4], and early retirement from the labour market [27].

Major Depression Inventory. The Major Depression Inventory (MDI) is a validated questionnaire for measurement of depression [28], and a measure above 20 indicates overt depression. The link between stress and depression is well established [5–7].

Clinical symptoms. On a symptom check-list (Table I), the participants registered the possible occurrence of 59 different clinical symptoms, found to be associated with persistent stress, experienced within the last 4 weeks. The choice and use of these symptoms

Figure 1. Measurement site for PPS measurement. The level of the nipples corresponds to the 4th intercostal space.

is based on an explorative testing in 250 cardiac nurses, and it was found that the number of these clinical symptoms correlated significantly to the PPS measure ($r = 0.3$; $p < 0.001$) (unpublished). A large part of these symptoms are also found on the stress symptoms checklist used by Washington State University [29]. These symptoms were not pointed out as possible stress symptoms, but were intentionally described as general health complaints, and were put in a random order with respect to impact on quality of life.

Elevated health risk factor. An elevated health risk factor was defined with the following point of discrimination for each of the used questionnaires, the SF-36 scales: (MCS and PCS scales) $\leq$ the 25 % percentile for the general Danish population, matched for age and gender [25], the MDI score: a score ≥ 20 [28], the clinical symptoms: > 10 symptoms.

Lifestyle and medical history. The following questions were used on a 7-step ordinal scale: Perceived present level of stress; perceived average level of stress during the last 3 months. A four point ordinal scale (1: daily; 2: weekly; 3: monthly; 4: never) was used with respect to: Use of acupressure, relaxation, attention to diet, and daily physical exercise of minimum 30 min. Use of alcohol was recorded as: 1, never; 2, less than 14 units per week for females and less than 21 units per week for males; 3, more. Use of tobacco was recorded as: 1, never smoked; 2, stopped more than one year ago; 3, current user but less than 15 units per day; 4, current user more than 15 units per day. With respect to disease, the subjects were asked if they had present or previous hypertension, diabetes mellitus, cancer or heart disease.

Statistics

(i) To test the hypothesis that a high PPS is associated with an elevated health risk profile with respect to the used questionnaires a correlation analysis was used. Furthermore, an odds ratio analysis was made with respect to the likelihood of having an elevated health risk, evaluated from the included questionnaires, if PPS was high. (ii) To test if PPS could be used as a screening tool, two step categorizations were made for included questionnaires; ('elevated health risk factor group' versus 'no elevated risk factor group'). In order to test the sensitivity and specificity of using PPS ≥ 60 as a diagnostic discrimination point for an elevated level of persistent stress measured as an elevated health risk factor with respect to SF 36, MDI and number of clinical symptoms. Receiver Operation Characteristic curves (ROC) were made as a way to evaluate the true positive rate (sensitivity) as a function of the false positive rate (100 minus specificity). In this analysis we used the same discrimination points for 'elevated

Table I. Clinical symptoms: The participants were asked to mark if they had experienced any of the following within the past 4 weeks.

1. Back pain	21. Fatigue	41. Irritability/'short fuse'
2. Headache	22. 'Butterflies' in my stomach	42. Increased use of stimulants (coffee, cigarettes, alcohol)
3. Ringing in the ears	23. 'Lump in my throat'	43. Increased use of prescription drugs
4. Hot flushes	24. Forgetfulness	44. Increased use of over the counter drugs or natural medicines
5. Lack of energy	25. Difficulty concentrating	45. Dizziness
6. Anxiousness	26. Restlessness	46. Increased sick leave
7. Stomach pains/stomach ache	27. Reduced sense of humour	47. Reduced initiative
8. Decreased tolerance for noise or odor	28. Reduced empathy	48. Joint pains
9. Loss of appetite or comfort eating	29. Social withdrawal	49. Cold hands/feet
10. Muscle tension	30. Low spirits	50. Reduced judgement
11. Frequent infections	31. Grinding teeth	51. Circular thinking or myriad of thoughts
12. Worsening of chronic illness	32. Cannot get worries out of my mind	52. Nausea or vomiting
13. Increased frequency of making mistakes	33. Vision related difficulties	53. Pressure/pain in the chest
14. Rapid heartbeat	34. Anxiety/fear	54. Irregular heart rhythm
15. Anger outbursts, that I cannot control	35. Reduced tolerance to others	55. Increased sensitivity to light and touch
16. Clumsiness	36. Difficulty in thinking clear	56. Irregular motion
17. Reduced zest of life	37. Cry easily	57. Tender muscles
18. Reduced sex drive	38. Insomnia/difficulty sleeping	58. Reduced sexual endurance (men)
19. Feeling of reduced time for relaxation and pleasure	39. Overly aggressive	59. Irregular toilet visits
20. Impatience	40. Indecision/difficulty making decisions	

Table II. Demographic data. All values are baseline values and shown as median with inter quartile limits.

Numbers	308	83 (27%)	141 (46%)	84 (27%)
PPS		34 [30–37]	48 [45–52]	69 [63–76]
Age (years)	42 [34–47]	42 [36–49]	42 [34–46]	39 [32–45]*
Gender distribution (% females)	54%	55%	51%	56%
SF-36*				
Physical function	100 [94–100]	100 [95–100]	98 [90–100]	95 [93–100]*
Bodily pain	84 [62–84]	84 [72–100]	84 [62–84]	72 [62–84]***
General health perceptions	85 [72–92]	87 [77–97]	84 [72–92]	80 [62–92]***
Vitality	70 [55–80]	75 [60–85]	75 [55–80]	60 [48–80]*
Mental health	84 [76–88]	88 [77–92]	84 [76–88]	80 [67–88]***
Physical component summary	54 [51–57]	56 [52–58]	54 [52–57]	53 [50–56]*
Mental component summary	55 [50–58]	56 [52–58]	56 [50–59]	53 [46–58]*
MDI Depression score	5 [3–9]	4 [2–8]	5 [3–8]	6 [4–10]***
Clinical symptoms (number)	6 [4–11]	6 [4–10]	6 [4–10]	8 [5–14]*

The SF-36 results have been compared to norm data for correction of age and gender when calculating differences. Only significant items are given.
*Significance test between group 1 and 3; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

health risk factor' for MDI, SF-36 and clinical symptoms questionnaires as presented above.

Group comparison, analysis of variance, simple correlation and odds-ratio (OR) evaluations were performed using non-parametric analyses: Mann-Whitney U, Kruskal-Wallis, Spearman and Chi- square tests. Non-parametric tests were used since PPS data were not normally distributed. A multivariate linear regression analysis was performed (in subjects with PPS >30, compromising 77% of the material) to examine whether PPS was independently associated with the following co-variables: Age, sex, physical and mental components summary (SF-36), MDI depression score and clinical symptoms. Standardized coefficient (β) is given for the linear regression analysis. All values are two tailed, and a *p*-value below 0.05 was considered statistically significant.

The statistical software package SPSS version 18 (SPSS Inc, Chicago, II) was used for all analyses.

Results

Data for the PPS and the questionnaires on SF-36 (QOL), depression and clinical symptoms are given in Table II. No between-group differences were found with respect to the presented lifestyle questions, PPS values within different job groups or with respect to presence of disease (all $p > 0.1$).

The office workers had a mental health and physical health as the normal Danish population, evaluated from the SF-36 questionnaire. The median MDI score was 5, (inter quartile range 3–9), and 14 participants had a score above 20, which is indicative for overt depression. Median number of clinical symptoms was 6 (inter quartile range 4–11).

The subjects were divided into three groups based on PPS values: PPS ≤ 40, PPS between 40 and 60, and PPS ≥ 60, the latter value regarded as cut off for an elevated stress level (Table II). Twenty-seven percent of the participants had a PPS ≥ 60. With this 3-step increase in PPS interval levels 5 out of 8 subscales (physical function, bodily pain, general health perception, vitality, mental health) and both main scales (physical- and mental component summary) of the SF-36 questionnaire demonstrated significantly decreasing scores, i.e. worsening of health. Increased PPS was also associated with a significant increase in depression score (MDI) and number of clinical symptoms. Similarly, significant correlations were found between PPS and SF-36 score, MDI score and number of clinical symptoms (Table III). The correlation between PPS and NWR was significant as well ($r = 0.38$, $p < 0.001$).

In contrast to the data obtained by the questionnaires, no significant correlations were found between PPS and the subjects' own perception of stress using ordinal scales from 1–7 (both $p > 0.1$). The mean stress scores for the 3 groups based on PPS were '3, 2 and 3' for the personal perception of the present level of stress, and '4' for all of the three groups with respect to the personal perception of the average level of stress during the past 3 months (both $p > 0.1$).

Comparing the groups with PPS ≤ 40 and ≥ 60, respectively, the odds ratio for having an elevated health risk profile was twice as high for the high PPS

Table III. Correlation between PPS and results from the questionnaires.

	Correlation coefficient	*p*-value (two-tailed)
Age	−0.19	0.001
SF-36* scores:		
Physical function	−0.10	0.104
Bodily pain	−0.15	0.019
General health perceptions	−0.20	0.001
Vitality	−0.17	0.008
Mental health	−0.13	0.041
Physical component summary	−0.13	0.041
Mental component summary	−0.19	0.003
MDI depression score	0.21	0.001
Number of clinical symptoms	0.19	0.003

Table IV. Numbers of persons having questionnaire results below the 25% percentile (SF-36) or more than 10 clinical symptoms, as well as Odds Ratio (OR) for the group with PPS ≥ 60 compared to the group with PPS ≤ 40.

Questionnaires	Limits for registration	Low risk PPS ≤ 40	High risk PPS ≥ 60	OR [95% CL]	*p*-value
SF-36					
Physical component summary	<25% percentile	13%	29%	2.7 [1.2–6.2]	0.019
Mental component summary		21%	40%	2.5 [1.2–5.1]	0.013
Major depression Inventory	≥20	4%	9%	2.4 [0.6–9.5]	ns
Clinical symptoms	>10	22%	39%	2.2 [1.0–4.6]	0.036

group (PPS ≥ 60), when compared to the low PPS group (PPS ≤ 40), which was statistically significant for the main SF-36 scales and the number of clinical symptoms (Table IV). With respect to MDI the statistical analysis of the odds ratio was not possible because of the low number of subjects with an MDI score ≥ 20, (3 and 7 in the two groups, respectively).

Validation of the PPS measurement

Reliability of the PPS measurement was tested in two different situations: (i) with 5 seconds or (ii) a full day between measurement. When PPS measurements were *repeated* with 5 seconds between measurement in the 308 office workers and managers, and conducted by 10 different instructors, a significant correlation between first and second measurement was found ($r = 0.90$, $p < 0.001$); mean between-measurement difference was 1.3 PPS units (SD 7.4, $p < 0.01$). A Bland Altman plot demonstrated similar between-measurement difference throughout the full PPS scale (Figure 2). When PPS measurements were *repeated* with a full day between measurements (from morning until evening) for the 60 office workers who had the instrument for home measurement during 3 months, morning and evening PPS value correlated significantly ($r = 0.87$, $p < 0.001$), mean difference 2.1 units (SD = 8.9, $p < 0.01$) the evening value being the highest.

Agreement: the ability to reproduce the two-step PPS-based categorization (PPS ≥ 60; PPS < 60), was tested in two ways: (i) the categorization agreement, i.e. professional measurement with 5 seconds between measurements was 89% in the 308 study participants undergoing professional measurement from 10 different instructors; (ii) the home measurement conducted by the individual participant and with one full day between PPS measurements: Categorization agreement was 87% in the 60 office workers measuring for 3 months (1854 person days) at home.

In addition, the two-step PPS-based persistent stress categorization was tested against a two-step categorization (elevated versus not elevated health risk factor) with respect to the SF-36 and MDI scores, as well as the number of clinical symptoms. It was found that the mean PPS measure was significantly

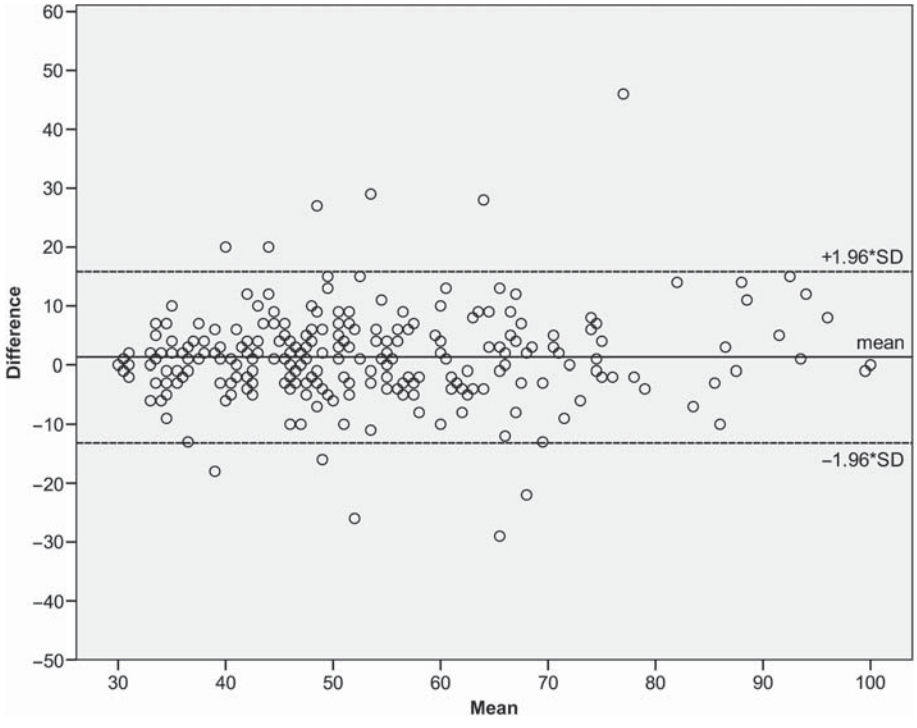

Figure 2. Bland Altman plot for PPS measurement in 282 office workers, done twice with 5 seconds between measurements.

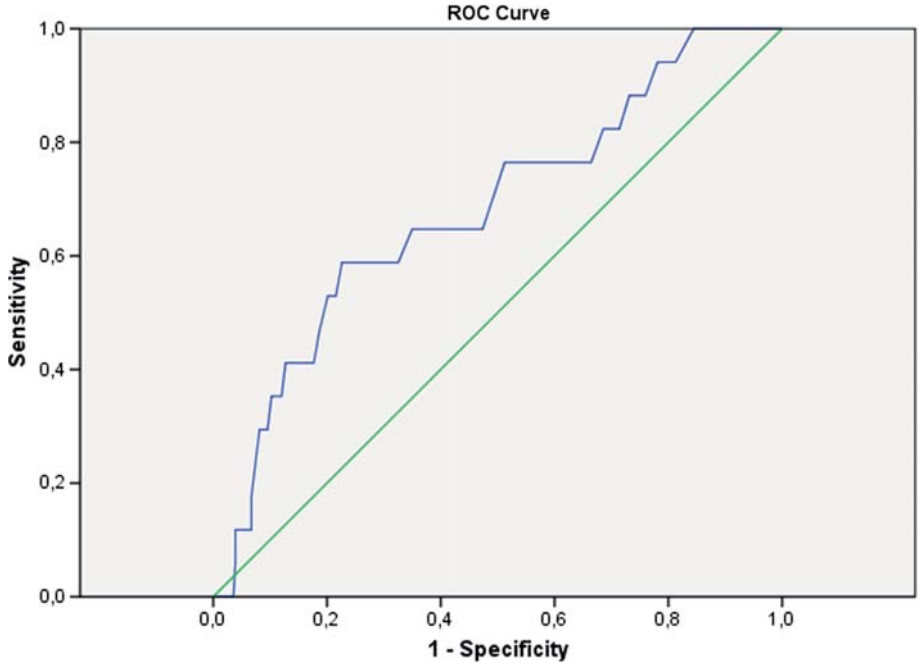

Figure 3. ROC curve for MDI score ≥20 and PPS score ≥60. The curve shows the connection between MDI and PPS cut-off points for persistent stress with respect to sensitivity and specificity (showing that 0.6 in sensitivity corresponds with a 0.8 specificity). The size of the area below the curve is = 0.68 ($p < 0.01$).

higher in the 'elevated health risk factor group', when compared to the 'not elevated risk factor group' for all effect variables: SF-36 MCS scale (mean PPS 57/49, $p = 0.004$); SF-36 PCS scale (mean PPS 56/49, $p = 0.004$), MDI score (mean PPS 61/51, $p = 0.012$); number of clinical symptoms (mean PPS 58/49, $p < 0.001$).

Using ROC analysis for specificity and sensitivity evaluation of the two-step PPS measure categorization (PPS ≥60; PPS <60) against similar two-step categorization (elevated risk profile/no elevated risk profile) for SF-36 and MDI scores, and number of clinical symptoms, the area below the ROC curve was >0.6 and significant in all cases; SF-36 MCS scale (area 0.62, $p < 0.004$), SF 36 PCS scale (area 0.62, $p < 0.004$), MDI (area 0.68, $p < 0.01$), and number of clinical symptoms (area 0.65, $p < 0.001$). Figure 3 shows the ROC curve for PPS ≥60 versus MDI ≥20: With a specificity of 0.8, the sensitivity was 0.6 for MDI and 0.4 for MCS, PCS and number of clinical symptoms. Similarly, a sensitivity of 0.8 resulted in a specificity of 0.4 for MDI and MCS scales and 0.3 for PCS and clinical symptoms.

A possible systematic measurement error in long-term home use due to hypothesized pain threshold adaptation was addressed by calculating the mean PPS differences between morning and evening measures during 4 calendar months for the 60 office workers during home measurement. From morning to same evening, the differences were; +2.0, +2.0, +1.0, and +3.1, evening being the highest (including 232, 785, 624 and 213 person days, respectively); from evening to next morning, the corresponding numbers were: −2.0, −1.0, −3.0, and −2.4, respectively (p for trend during the 4 calendar months: both $p > 0.1$). These results indicated that the PPS measure increased slightly during day time and decreased during the night, and that these day-to-day measurement fluctuations did not change during the 3 months of observation (covering 4 calendar months).

Discussion

The study demonstrates that in office workers, the PPS measure seems well correlated with several measures for QOL and depression, which all are accepted as associated with persistent stress. Further, the practical PPS measurement seemed feasible and led to a meaningful result of a stress screening at a workplace. Finally, the individuals with elevated PPS measure had sufficient compliance during home measurements and no measurement adaptation over time was found.

Among many ways of measuring persistent stress the questionnaires MDI and SF-36 have been accepted as usable tools although they measure only parts of the integrated and complex reaction to a persistent stress load [4,27,30]. PPS correlated to both MDI score, SF-36 physical and mental components, and also with the scoring of clinical symptoms of stress. The fact that PPS correlates to all of these measures opens up the possibility that PPS can be used as a quick and integrated measure of persistent stress. Further our results suggest that home-based measurements might be feasible during follow-up studies with or without stress intervention.

PPS correlates also to other markers for increased sensitivity; the noxious or startle reflex both being part of an integrated bio-warning and defence function of the polymodal sensor cell [17,31] and both may be regarded as biological markers for the Diffuse Noxious Inhibitory Control System (DNIC), which through the polymodal sensory cells exhibit an ongoing repression on sensory perception. Pressure pain hypersensitivity has been found due to a DNIC dysfunction in patients with fibromyalgia, low back pain and knee arthritis [32–34], and a hypersensitive startle reflex is part of the Post Traumatic Stress Syndrome [35]. Accordingly, a link between PPS and persistent stress may be explained by a dysfunction of the DNIC system.

With respect to the PPS validation, the PPS measure was found to be reproducible both in the short term (5 seconds) as well as long term (>10 hours) when measured in clinical settings by professionals and at home as self-measurements in a working population group. The two-step categorization, using PPS = 60 as the point of discrimination was found to be reproducible as well. The results matched the level of contemporary non invasive diagnostic measures, such as repeated audiometric measurements ($r = 0.70$) [36], armpit versus rectal temperature ($r = 0.43$) [37] and home blood pressure measurement versus 24 h ambulatory blood pressure monitoring ($r = 0.57$–0.75) [38].

The ROC analysis revealed significant and similar size of the areas below the curve for the chosen two-step categorizations of PPS, QOL, depression (MDI) as well as clinical symptoms, with values of 0.62–0.68. For comparison, ROC curve areas for some commonly used medical procedures are as follows: 0.53–0.58 for ambulatory 12 lead ECG recording in the prediction of significant coronary artery disease [39], 0.65 for fasting glucose measured preoperatively to Coronary Artery Bypass Grafting in the prediction of 1-year survival [40], and 0.68 for exercise ECG in the prediction of significant coronary artery disease as evaluated by coronary angiography [41]. For an 80% specificity of the PPS-based two-step categorization, the sensitivity was between 0.4 and 0.6. Thus, a low PPS seems to identify individuals with normal QOL according to the SF-36 questionnaire. Furthermore, a low PPS indicates absence of depression. Also, a low PPS score is strongly associated with a low number of clinical symptoms. In this way, the PPS may be a useful tool for population screening and much quicker than questionnaire methods. With respect to sensitivity, the ROC analysis revealed that using the chosen cut-off point, the sensitivity was 40% for the SF-36 questionnaire and clinical symptoms and 60% for depression. This indicates that using the chosen cut-off points and the choice of a high specificity, the PPS measure categorization seems to identify many people without elevation of the chosen measures for persistent stress. It may be discussed whether a high specificity or a high sensitivity is most feasible for practical use. A high specificity leads to a high rate of true negative, which in this study meant that with a 80% probability 70% of the working group could be excluded having no need for further educational or interventional efforts. However, among the remaining 30%, half of them were 'false positives' with respect to persistent stress as measured by the included questionnaires. Such a result may be acceptable if the purpose is to screen a workplace for persistent stress-related conditions.

The present study has several limitations: The lack of international consensus on how to measure stress makes a comprehensive validation of any new measure a challenge. We included questionnaires which are internationally recognized with respect to measuring some of the consequences from persistent stress: Quality of life, mental and physical health, as well as a newly-developed clinical symptom score related to stress. A significant correlation between PPS and number of these clinical symptoms has also been confirmed in a recent prospective, block-randomized trial in Opera singing students (unpublished). The impact of time on the development of persistent stress is a source of bias in the present study, which has not been addressed.

It is concluded that in office workers, the PPS measurement correlated to several QOL questionnaires and was found useful for persistent stress screening. Validation studies demonstrated sufficient reproducibility including during self measurement at home.

Declaration of interest: Dr Soeren Ballegaard is a shareholder of the company Ull Care A/S, who holds the patent of the instrument, the Ull meter, used in this study to measure pressure pain sensitivity. Accordingly, Søren Ballegaard has not taken part in the examination of the subjects, the calculation of data, and the evaluation of the results.

References

[1] Ekman R, Lindstedt G. Molekyler på liv og død. In: Ekman R, Arnetz B, editors. Stress: molekylerne, individen, organisationen samhället. Sverige: Liber Press; 2002. pp. 69–89.
[2] Noble RE. Diagnosis of stress. Metabolism 2002;51:37–9.
[3] Holmes SD, Krantz DS, Rogers H, Gottdiener J, Contrada RJ. Mental stress and coronary artery disease: a multidisciplinary guide. Prog Cardiovasc Dis 2006;49:106–22.
[4] Stansfeld SA, Bosma H, Hemingway H, Marmot MG. Psychosocial work characteristics and social support as predictors of SF-36 health functioning: the Whitehall II study. Psychosom Med 1998;60:247–55.
[5] Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the 'kindling' hypothesis. Am J Psychiatry 2000;157:1243–51.
[6] Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2001;2:73–86.

[7] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301: 386–9.
[8] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci 1998;840:33–44.
[9] Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38.
[10] McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann NY Acad Sci 2004;1032:1–7.
[11] Karasek R. The stress-disequilibrium theory: chronic disease development, low social control, and physiological de-regulation. Med Lav 2006;97:258–71.
[12] Boles M, Pelletier B, Lynch W. The relationship between health risks and work productivity. J Occup Environ Med 2004;46:737–45.
[13] Goetzel RZ, Carls GS, Wang S, Kelly E, Mauceri E, Columbus D, Cavuoti A. The relationship between modifiable health risk factors and medical expenditures, absenteeism, short-term disability, and presenteeism among employees at novartis. J Occup Environ Med 2009;51:487–99.
[14] Folkow B. Mental stress and its importance for cardiovascular disorders; physiological aspects, 'from-mice-to-man'. Scand Cardiovasc J 2001;35:163–72.
[15] Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology 2005;30:1–10.
[16] Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005;165:2644–50.
[17] Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Invest 2009;69:713–21.
[18] Ballegaard S, Borg E, Karpatschof B, Nyboe J, Johannessen A. Long-term effects of integrated rehabilitation in patients with advanced angina pectoris: a nonrandomized comparative study. J Altern Complement Med 2004;10:777–83.
[19] Magnusson G, Ballegaard S, Karpatschof B, Nyboe J. Long-term effects of integrated rehabilitation in patients with stroke: a nonrandomized comparative feasibility study. J Altern Complement Med 2010;16:369–74.
[20] Kumazawa T. Primitivism and plasticity of pain – implication of polymodal receptors. Neurosci Res 1998;32:9–31.
[21] Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. TRPV4 calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol 2004;286:C195–C205.
[22] Belmonte C, Viana F. Molecular and cellular limits to somatosensory specificity. Mol Pain 2008;4:14.
[23] Skljarevski V, Ramadan NM. The nociceptive flexion reflex in humans – review article. Pain 2002;96:3–8.
[24] Williams PL, Bannister LH, Berry MM, Collins P, Dyson M, Dussek JE. In: Ferguson MWJ, editor. Gray's anatomy. The anatomical basis of medicine and surgery. 38th edn. New York: Churchill Livingstone; 1995. pp. 538–46.
[25] Bjørner JB, Thunedborg K, Kristensen, TS, Modvig J, Bech P. The Danish SF-36 Health survey: translation and preliminary validity studies. J Clin Epidemiol 1998;51:991–9.
[26] Nishiyama S, Momomura S, Ishiwata S, Daida H, Hara K, Nishimura S, Nakamura M, Yamashina A, Shirai T, Yutaro N, Yamazaki T. [Health-related quality of life in Japanese patients with ischemic heart disease: a multicenter cooperative investigation assessed using SF-36]. J Cardiol 2005;46:211–20.
[27] Harkonmaki K, Rahkonen O, Martikainen P, Silventoinen K, Lahelma E. Associations of SF-36 mental health functioning and work and family related factors with intentions to retire early among employees. Occup Environ Med 2006;63:558–63.
[28] Bech P. Klinisk psykometri. København: Munkgaards forlag; 2010. pp. 69–72.
[29] The Leadership Center at Washington State University. Stress – how to handle it. Available at: http://access.ewu.edu/Documents/Student%20Activities/Clubs/Stress/handleit.pdf
[30] Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 2009;12:1–21.
[31] Kumazawa T. The polymodal receptor: bio-warning and defense system. Prog Brain Res 1996;113:3–18.
[32] Ge HY, Nie H, Graven-Nielsen T, Danneskiold-Samsoe B, Arendt-Nielsen L. Descending pain modulation and its interaction with peripheral sensitization following sustained isometric muscle contraction in fibromyalgia. Eur J Pain 2011. [ePub Ahead June 28].
[33] Kavchak AJ, Fernandez-de-Las-Penas C, Rubin LH, Arendt-Nielsen L, Chmell SJ, Durr RK, Courtney CA. Association between altered somatosensation, pain, and knee stability in patients with severe knee osteoarthrosis. Clin J Pain 2011. [ePub Ahead Dec 2].
[34] O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but do not predispose for, low back pain. Eur Spine J 2011;20:2120–5.
[35] American Psychiatric Association. Diagnostic and statistical manual of mental disorders DSM-IV-TR (4th ed.). Washington, DC: American Psychiatric Association; 2000.
[36] Stewart MG. Outcomes and patient-based hearing status in conductive hearing loss. Laryngoscope 2001;111:1–21.
[37] Edwards B, Waterhouse J, Reilly T, Atkinson G. A comparison of the suitabilities of rectal, gut, and insulated axilla temperatures for measurement of the circadian rhythm of core temperature in field studies. Chronobiol Int 2002; 19:579–97.
[38] Scisney-Matlock M, Grand A, Steigerwalt SP, Normolle D. Reliability and reproducibility of clinic and home blood pressure measurements in hypertensive women according to age and ethnicity. Blood Press Monit 2009;14:49–57.
[39] Mahmoodzadeh S, Moazenzadeh M, Rashidinejad H, Sheikhvatan M. Diagnostic performance of electrocardiography in the assessment of significant coronary artery disease and its anatomical size in comparison with coronary angiography. J Res Med Sci 2011;16:750–5.
[40] Anderson RE, Klerdal K, Ivert T, Hammar N, Barr G, Owall A. Are even impaired fasting blood glucose levels preoperatively associated with increased mortality after CABG surgery? Eur Heart J 2005;26:1513–8.
[41] Froelicher VF, Lehmann KG, Thomas R, Goldman S, Morrison D, Edson R, Lavori P, Myers J, Dennis C, Shabetai R, Do D, Froning J. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. Ann Intern Med 1998;128:965–74.

Scandinavian Journal of Clinical & Laboratory Investigation, 2013; 73: 373–379

informa
healthcare

ORIGINAL ARTICLE

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

NATASHA BERGMANN[1], SØREN BALLEGAARD[2], PERNILLE HOLMAGER[1], JESPER KRISTIANSEN[3], FINN GYNTELBERG[3], LARS J. ANDERSEN[4], ÅKE HJALMARSON[5], PER BECH[6], LARS ARENDT-NIELSEN[7] & JENS FABER[1,8]

[1]*Department of Endocrinology, Herlev University Hospital, Herlev, Denmark,* [2]*Ull Care A/S, Hellerup, Denmark,* [3]*The National Research Centre for the Working Environment, Copenhagen, Denmark,* [4]*Department of Cardiology, Herlev University Hospital, Herlev, Denmark,* [5]*Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden,* [6]*Psychiatric Research Unit, Psychiatric Centre North Zealand, University of Copenhagen, Hillerød, Denmark,* [7]*Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark, and* [8]*Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark*

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

Correspondence: Natasha Bergmann, Department of Medicine O, Endocrine Unit, Herlev University Hospital, 2730 Herlev, Denmark. Tel: + 45 61671390. Fax: + 45 44884142. E-mail: n.c.bergmann@hotmail.com

(Received 6 November 2012; accepted 11 March 2013)

ISSN 0036-5513 print/ISSN 1502-7686 online © 2013 Informa Healthcare
DOI: 10.3109/00365513.2013.785588

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.
  - WHO-5, which assesses psychological well-being. A score of 100 equals best possible psychological well-being.
  - 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 cm^2 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 models' 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 anticoagulants 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 ($\beta = 0.124$, $p = 0.026$), SF-36 PCS ($\beta = -0.109$, $p = 0.049$) and gender ($\beta = -0.231$, $p < 0.001$). Whereas, CSS was independently associated with PPS ($\beta = 0.077$, $p = 0.040$), MDI ($\beta = 0.621$, $p < 0.001$) and SF-36 PCS ($\beta = -0.192$, $p < 0.001$).

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 I. Pearson's correlation analysis with respectively pressure pain sensitivity and clinical stress signs as dependent.

	Pressure pain sensitivity correlation coefficient (*p*-value)	Clinical stress signs correlation coefficient (*p*-value)
Pressure pain sensitivity	1	0.197 (<0.001)
Clinical stress signs	0.197 (<0.001)	1
Major Depression Inventory	0.141 (0.007)	0.694 (<0.001)
WHO	−0.090 (0.088)	−0.619 (<0.001)
SF-36 physical component score	−0.170 (0.001)	−0.406 (<0.001)
Physical functioning	−0.154 (0.003)	−0.397 (<0.001)
Bodily pain	−0.125 (0.017)	−0.478 (<0.001)
Role physical	−0.102 (0.054)	−0.510 (<0.001)
General health	−0.177 (0.001)	−0.483 (<0.001)
SF-36 mental component score	−0.104 (0.049)	−0.534 (<0.001)
Vitality	−0.067 (0.206)	−0.671 (<0.001)
Social functioning	−0.129 (0.014)	−0.461 (<0.001)
Role emotional	−0.096 (0.069)	−0.471 (<0.001)
Mental health	−0.100 (0.059)	−0.633 (<0.001)
self-perceived stress level	0.156 (0.004)	0.454 (<0.001)

Table II. Comparisons between a low stress group defined as the lowest tertile of pressure pain sensitivity and clinical stress signs and a high stress group defined as the highest tertile of both pressure pain sensitivity and clinical stress signs.

	The lowest tertile of pressure pain sensitivity and lowest tertile of Clinical stress signs, (PPS < 56, CSS < 5), mean (SD)	The highest tertile of pressure pain sensitivity and highest tertile of Clinical stress signs (CSS) (PPS > 73 + CSS > 10), mean (SD)	*p* value
N	56	40	
Pressure pain sensitivity	42 (7.7)	91 (8.5)	$p < 0.001$
Clinical stress signs score	2.1 (1.4)	18 (6.1)	$p < 0.001$
Major Depression Inventory	3.55 (4.14)	15.2 (10.2)	$p < 0.001$
WHO-5	77.2 (11.3)	53.1 (18.9)	$p < 0.001$
SF-36 physical component summary score	53.0 (5.34)	42.7 (9.44)	$p < 0.001$
SF-36 mental component summary score	58.1 (4.57)	45.8 (10.2)	$p < 0.001$

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 be a defect in the diffuse noxious inhibitory control system (DNIC) [18]. This afferent/efferent system operates via the sensory nociceptive nerve-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.

Acknowledgements

We are thankful to the staff of the Metabolic Ward for their contribution: Helle-Marina Oxfeldt, Tine Skogen-Lassen, Ulla Kjærulff-Hansen, Tonni Løve Hansen, Hanne Dorthe Mogensen, Marianne Sørensen og Rikke Mirsbach Henkel.

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.

Declaration of interest: This work was supported by the Johan Schrøder's Family and Business Foundation. Natasha Bergmann holds pre-graduate scholarships sponsored by the Lundbeck Foundation, Else and Mogens Wedell-Wedellsborg's Foundation, and Carpenter Sophus Jacobsen and Wife Astrid Jacobsen's Foundation.

References

[1] Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953–62.

[2] Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol 2008;51:1237–46.

[3] Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. Am J Cardiol 1991;68:1171–5.

[4] Kivimaki M, Leino-Arjas P, Luukkonen R, Riihimaki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. BMJ 2002;325:857.

[5] Aboa-Eboule C, Brisson C, Maunsell E, Bourbonnais R, Vezina M, Milot A, Dagenais GR. Effort-reward imbalance at work and recurrent coronary heart disease events: a 4-year prospective study of post-myocardial infarction patients. Psychosom Med 2011;73:436–47.

[6] Whalley B, Rees K, Davies P, Bennett P, Ebrahim S, Liu Z, West R, Moxham T, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev 2011;CD002902.

[7] Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009;169:1158–65.

[8] Van DT, Hermans D, Van AC, Van den Bergh O. Stress reduction through psychoeducation: a meta-analytic review. Health Educ Behav 2012;39:474–85.

[9] Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs. standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 2011;171:134–40.

[10] Chandola T, Heraclides A, Kumari M. Psychophysiological biomarkers of workplace stressors. Neurosci Biobehav Rev 2010;35:51–7.

[11] Richebe P, Rivat C, Cahana A. Stress-induced hyperalgesia: any clinical relevance for the anesthesiologist? Anesthesiology 2011;114:1280–1.

[12] Choi JC, Chung MI, Lee YD. Modulation of pain sensation by stress-related testosterone and cortisol. Anaesthesia 2012;67:1146–51.

[13] McEwen BS, Kalia M. The role of corticosteroids and stress in chronic pain conditions. Metabolism 2010;59 (Suppl. 1):S9–15.
[14] Kumazawa T. Primitivism and plasticity of pain – implication of polymodal receptors. Neurosci Res 1998; 32:9–31.
[15] Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Invest 2009;69: 713–21.
[16] Bech P. Clinical psychometrics, Oxford, UK: Wiley Blackwell; 2012.
[17] Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. Scand J Clin Lab Invest. 2012;72:459–66.
[18] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–72.
[19] Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain 2010; 149:573–81.
[20] Andrich D, Sheridan BE, Luo G. RUMM2030. Version5.1, RUMM Laboratory Pty Ltd, Perth, WA. 2010.
[21] Allerup P. Statistical analyses of data from the iEA reading literacy study. In: Rost J, Langeheine R, editors. Applications of latent trait and latent class models in the social sciences. New York: Waxmann; 1997. pp. 50–9.
[22] Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295–302.

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

Scandinavian Journal of Clinical & Laboratory Investigation, 2014; 74: 116–125

informa
healthcare

ORIGINAL ARTICLE

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

SØREN BALLEGAARD[1], PERNILLE B. PETERSEN[1], GITTE S. HARBOE[1], BENNY KARPATSCHOF[4], FINN GYNTELBERG[2] & JENS FABER[3,5]

[1]*Ull Care, Hellerup,* [2]*The National Research Center for the Working Environment, Copenhagen,* [3]*Department of Medicine and Endocrinology O, Herlev University Hospital, University of Copenhagen, Herlev,* [4]*Department of Psychology, University of Copenhagen, and* [5]*Faculty of Health Sciences, University of Copenhagen, Denmark*

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,

Correspondence: Søren Ballegaard, Lemchesvej 1, 2900 Hellerup, Denmark. Tel: +45 3940 4142. E-mail: sba@ullcare.com

(Received 9 July 2012; accepted 3 November 2013)

ISSN 0036-5513 print/ISSN 1502-7686 online © 2014 Informa Healthcare
DOI: 10.3109/00365513.2013.862847

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 (PSS) [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.

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 × beats/min) was calculated as systolic blood pressure (SBP) × 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 × 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/m^2) was calculated as weight/height^2.

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 locations and locations 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 ($\geq$130 mm Hg), 23% elevated diastolic BP ($\geq$85 mm Hg), 25% elevated resting HR ($\geq$70 beats/min), 27% elevated PRP ($\geq$9100 mmHg $\times$ beats/minute), 55% elevated BMI ($\geq$25), 59% elevated serum total cholesterol ($\geq$5.0 mmol/L), and 40% elevated Hb1Ac ($\geq$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).

	Active group ($n = 31$)		Control group ($n = 11$)		p-value for change between groups
	Baseline	After intervention	Baseline	After intervention	
PPS (resting) (arbitrary units)	77 (16)	45 (30)***	77 (21)	65 (26)	0.003
Systolic blood pressure (mmHg)	127 (15)	117 (17)***	122 (16)	117 (12)	0.04
Diastolic blood pressure (mmHg)	80 (13)	75 (11) ***	76 (19)	73 (19)	0.02
Heart rate (beats/min)	66 (14)	66 (11)	63 (25)	65 (16)	0.05
PRP (mm Hg $\times$ beats/min)	8591 (2706)	7638 (1926)***	7722 (2330)	7725 (3024)	0.005
BMI (kg/m^2)	24.5 (4.0)	24.8 (4.7)	24.7 (5.3)	25.3 (5.0)	ns
Visceral fat (arbitrary units)	7 (3)	6 (3)	5 (4)	5 (3)	ns
HbA1c (%)	5.0 (0.3)	5.0 (0.2)	5.0 (0.5)	5.0 (0.5)	ns
Total cholesterol (mmol/L)	5.4 (1.1)	4.6 (1.4)***	5.0 (0.9)	5.2 (1.1)	0.02
HDL cholesterol (mmol/L)	1.4 (0.8)	1.4 (0.5)	1.5 (0.5)	1.5 (0.6)	ns
LDL cholesterol (mmol/L)	3.3 (1.4)	2.7 (1.3)***	3.0 (1.3)	2.9 (1.2)	0.05
Triglyceride (mmol/L)	1.0 (0.6)	1.0 (0.7)	1.0 (0.8)	1.1 (0.7)	ns
YKL-40 (µg/L)	44 (22)	49 (40)	41 (22)	42 (32)	ns
Elevated Risk factor (number)	2 (2)	1 (2)***	1 (2)	2 (2)	0.003

***$p < 0.001$; ns = non significant.

were significant (all correlation coefficients >0.6; all $p<0.001$), thus supporting the hypothesis that they are 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 participant had an elevated heart rate at the follow-up examination ($p=0.002$) (Ficher Exact Probalitiy 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 $p>0.1$).

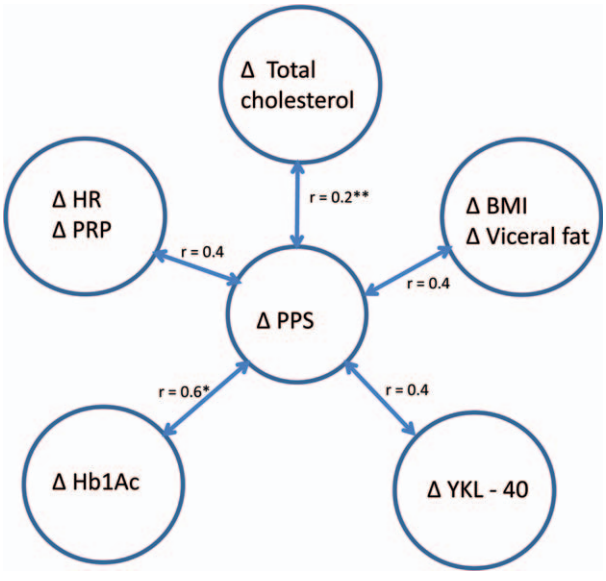

Figure 1. The correlation coefficients (r) between changes in resting PPS (Δ PPS) and changes in factors of cardiovascular physiology (Δ heart rate [HR] and Δ Pressure-Rate-Product [PRP]), fat distribution (Δ body mass index [BMI] and Δ Visceral fat), fat metabolism (Δ cholesterol), glucuose metabolism (Δ Hb1Ac), and low grade inflammation (ΔYKL-40) (all $p<0.05$; $n=42$). *for persons with elevated Hb1Ac at baseline, only ($n=17$); **correlation is not significant ($p>0.1$).

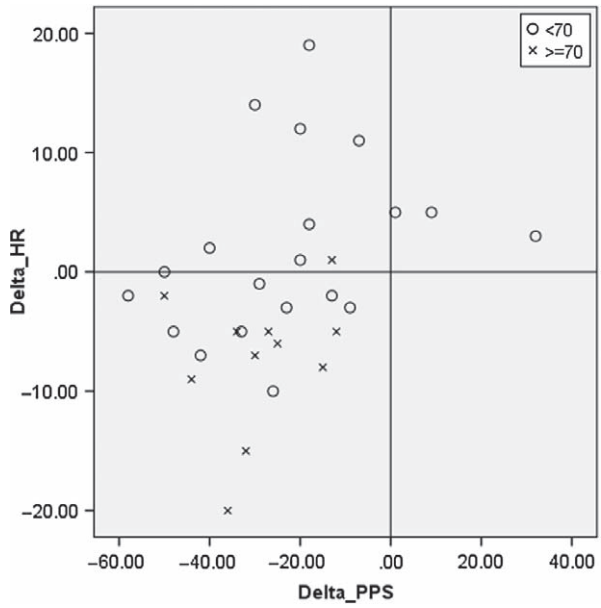

Figure 2. Changes in resting PPS (delta PPS) versus changes in resting heart rate (delta HR) for the active intervention group. Two groups are viewed: (1) baseline HR elevated ≥ 70 beats per minute (crosses); (2) baseline HR not elevated (circles). Among the 11 patients with elevated HR at baseline, 10 experienced a reduction in heart rate after intervention ($p<0.01$), whereas those 20 persons with HR <70 did not experience any significant change in HR ($p>0.1$).

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 $\times$ beats per min [-400 to -2100] vs. -100 mm Hg $\times$ 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 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.

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].

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).

Variable	Individual significance test	Average cluster sample size	Cluster intra class correlation coefficient	Cluster significance test
Delta_PPS	0.002	8.4	0.18	0.01
Delta_SYS	0.02	8.4	0.41	0.20
Delta_ DIA	0.04	8.4	0.42	0.05
Delta_ HR	0.04	8.4	0.79	0.45
Delta_PRP	0.004	8.4	0.77	0.35
Delta_LDL	0.05	7.5	0.06	0.01
Delta_KOL	0.02	7.5	0.44	0.06
Delta_Sum_Risk	0.001	7.5	0.15	0.01

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 tetra polar bioimpedans 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.

Acknowledgements

In the pilot study, we wish to thank Anne Margrethe Dahl, the Royal Danish Opera Academy for conducting all instructions and contacts to the students in the active group as well as for allocation of study for the active group. We wish to thank Eva Hess Thaysen, The Royal Danish Academy of Music, for help with conducting and allocating the study for the control group. We wish to thank Charlotte Christiansen for help with carrying out the study in office workers. The lab technicians from Department of Endocrinology 54O4, Herlev University Hospital are thanked for their skillful job concerning blood sampling and measurements. We wish to thank the insurance broker Willis Ltd for an unrestricted financial funding. For statistical analysis with regard to Cluster Randomization design we thank Bjarne Ersboell, Department of Applied Mathematics and Computer Science, Technical University of Denmark.

Disclosures

Dr Søren Ballegaard is shareholder of the company Ull Care A/S, who holds the patent of the instrument, Ull meter, used in this study to measure pressure pain sensitivity. No other author holds financial interest.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Ekman R, Lindstedt G. Molekyler på liv og død [Molecules in Life and Death]. In: Ekman R, Arnetz B, editors. Stress, Molekylerne, Individen, Organisationen, Samhället [Stress, the Molecules, the Individual, the Organisation, the Society]. Sverige: Liber Press, 2002. pp. 69–89.

[2] Noble RE. Diagnosis of stress. Metabolism 2002;51:37–9.

[3] Holmes SD, Krantz DS, Rogers H, Gottdiener J, Contrada RJ. Mental stress and coronary artery disease: a multidisciplinary guide. Prog Cardiovasc Dis 2006;49: 106–22.

[4] McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann NY Acad Sci 1998;840:33–44.

[5] Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev 2005;29:3–38.

[6] McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann NY Acad Sci 2004;1032:1–7.

[7] Karasek R. The stress-disequilibrium theory: chronic disease development, low social control, and physiological de-regulation. Med Lav 2006;97:258–71.

[8] Loeppke R, Taitel M, Haufle V, Parry T, Kessler RC, Jinnett K. Health and productivity as a business strategy: a multiemployer study. J Occup Environ Med 2009;51: 411–28.

[9] Boles M, Pelletier B, Lynch W. The relationship between health risks and work productivity. J Occup Environ Med 2004;46:737–45.

[10] Goetzel RZ, Carls GS, Wang S, Kelly E, Mauceri E, Columbus D, Cavuoti A. The relationship between modifiable health risk factors and medical expenditures, absenteeism, short-term disability, and presenteeism among employees at novartis. J Occup Environ Med 2009;51: 487–99.

[11] Folkow B. Mental stress and its importance for cardiovascular disorders; physiological aspects, 'from-mice-to-man'. Scand Cardiovasc J 2001;35:163–72.

[12] Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. Psychoneuroendocrinology 2005; 30:1–10.

[13] Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs. Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005;165:2644–50.

[14] Dedert EA, Calhoun PS, Watkins LL, Sherwood A, Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. Ann Behav Med 2010;39:61–78.

[15] Wentworth BA, Stein MB, Redwine LS, Xue Y, Taub PR, Clopton P, Nayak KR, Maisel AS. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? Cardiol Rev 2013;21:16–22.

[16] Spezia Adachi LN, Caumo W, Laste G, Fernandes ML, Ripoll RJ, de SA, Fregni F, Torres IL. Reversal of chronic stress-induced pain by transcranial direct current stimulation (tDCS) in an animal model. Brain Res 2012;1489:17–26.

[17] Richebe P, Rivat C, Cahana A. Stress-induced hyperalgesia: any clinical relevance for the anesthesiologist? Anesthesiology 2011;114:1280–1.

[18] Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 2009;12:1–21.

[19] Kumazawa T. The polymodal receptor: bio-warning and defense system. Prog Brain Res 1996;113:3–18.

[20] Ge HY, Nie H, Graven-Nielsen T, Danneskiold-Samsoe B, Arendt-Nielsen L. Descending pain modulation and its interaction with peripheral sensitization following sustained isometric muscle contraction in fibromyalgia. Eur J Pain 2012;16:196–203

[21] Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. TRPV4 calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol 2004;286:C195–205.

[22] Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, Marchand S, Latif L, Fregni F. Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. J Pain 2012;13:450–8.

[23] Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Invest 2009;69: 713–21.

[24] Bergmann N, Ballegaard S, Holmager P, Krisitansen J, Gyntelberg F, Andersen L, Hjalmarson Å, Bech P, Arendt-Nielsen L, Faber J. Pressure Pain Sensitivity as a new measure of stress in pateints with ischemic heart disease. Scand J Clin Lab Invest 2013;73:373–9.

[25] Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Invest 2012;72:459–66.

[26] Ballegaard S, Petersen PB, Karpatschof B, Gyntelberg F, Faber J, Harboe GS. The effect of stress reduction on pressure pain sensitivity and cardiovascular physiological factors associated with persistent stress: two independent consecutive prospective controlled interventional trials. J Psychother Psychosomat 2013. In press.

[27] Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008;372:817–21.

[28] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. Lancet 2005;366:1059–62.

[29] De BG, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger C, V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003;24:1601–10.

[30] Bosy-Westphal A, Later W, Hitze B, Sato T, Kossel E, Gluer CC, Heller M, Muller MJ. Accuracy of bioelectrical impedance consumer devices for measurement of body composition in comparison to whole body magnetic resonance imaging and dual X-ray absorptiometry. Obes Facts 2008;1:319–24.

[31] Rathcke CN, Vestergaard H. YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 2006;55:221–7.

[32] Rathcke CN, Vestergaard H. YKL-40 – an emerging biomarker in cardiovascular disease and diabetes. Cardiovasc Diabetol 2009;8:61.

[33] Ballegaard S, Johannessen A, Karpatschof B, Nyboe J. Addition of acupuncture and self-care education in the treatment of patients with severe angina pectoris may be cost beneficial: an open, prospective study. J Altern Complement Med 1999;5:405–13.

[34] Ballegaard S, Borg E, Karpatschof B, Nyboe J, Johannessen A. Long-term effects of integrated rehabilitation in patients with advanced angina pectoris: a nonrandomized comparative study. J Altern Complement Med 2004;10:777–83.
[35] Magnusson G, Ballegaard S, Karpatschof B, Nyboe J. Long-term effects of integrated rehabilitation in patients with stroke: a nonrandomized comparative feasibility study. J Altern Complement Med 2010;16:369–74.
[36] Timio M, Saronio P, Venanzi S, Gentili S, Verdura C, Timio F. Blood pressure in nuns in a secluded order: a 30-year follow-up. Miner Electrolyte Metab 1999;25:73–9.
[37] Conover WJ, Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. Am Statistician 1981;124–9.
[38] Dimsdale JE. Psychological stress and cardiovascular disease. J Am Coll Cardiol 2008;51:1237–46.
[39] Farmer JA. Hypertension and the metabolic syndrome. Curr Cardiol Rep 2004;6:427–33.
[40] Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T. Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol 2010;61: 509–21.
[41] Koschke M, Boettger MK, Schulz S, Berger S, Terhaar J, Voss A, Yeragani VK, Bar KJ. Autonomy of autonomic dysfunction in major depression. Psychosom Med 2009; 71:852–60.
[42] O'Neil RG, Heller S. The mechanosensitive nature of TRPV channels. Pflugers Arch 2005;451:193–203.
[43] American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders DSM-IV-TR (4th ed). 2000. Washington, DC: APA.

OPEN ACCESS Freely available online

PLOS ONE

The Effect of Daily Self-Measurement of Pressure Pain Sensitivity Followed by Acupressure on Depression and Quality of Life versus Treatment as Usual in Ischemic Heart Disease: A Randomized Clinical Trial

Natasha Bergmann[1]*, Søren Ballegaard[2], Per Bech[3], Åke Hjalmarson[4], Jesper Krogh[1], Finn Gyntelberg[5], Jens Faber[1,6]

1 Herlev University Hospital, Department of Endocrinology, Herlev, Denmark, **2** Ull Care A/S, Hellerup, Denmark, **3** Psychiatric Research Unit, Psychiatric Centre North Zealand, Hillerød, Denmark, **4** Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, **5** The National Research Centre for the Working Environment, Copenhagen, Denmark, **6** Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark

Abstract

Background: Depressive symptoms and reduced quality of life (QOL) are parts of the chronic stress syndrome and predictive of adverse outcome in patients with ischemic heart disease (IHD). Chronic stress is associated with increased sensitivity for pain, which can be measured by algometry as Pressure Pain Sensitivity (PPS) on the sternum.

Aim: To evaluate if stress focus by self-measurement of PPS, followed by stress reducing actions including acupressure, can decrease depressive symptoms and increase psychological well-being in people with stable IHD.

Design: Observer blinded randomized clinical trial over 3 months of either intervention or treatment as usual (TAU). Statistical analysis: Intention to treat.

Methods: Two hundred and thirteen participants with IHD were included: 106 to active treatment and 107 to TAU. Drop-out: 20 and 12, respectively. The active intervention included self-measurement of PPS twice daily followed by acupressure as mandatory action, aiming at a reduction in PPS. *Primary endpoint:* change in depressive symptoms as measured by Major depression inventory (MDI). *Other endpoints*: changes in PPS, Well-being (WHO-5) and mental and physical QOL (SF-36).

Results: At 3 months PPS decreased 28%, to 58, in active and 11%, to 72, in TAU, $p<0.001$. MDI decreased 22%, to 6.5, in active group vs. 12%, to 8.3 in TAU, $p=0.040$. WHO-5 increased to 71.0 and 64.8, active group and TAU, $p=0.015$. SF-36 mental score sum increased to 55.3 and 53.3, active and TAU, $p=0.08$.

Conclusions: PPS measurements followed by acupressure reduce PPS, depressive symptoms and increase QOL in patients with stable IHD.

Trial Registration: ClinicalTrials.gov NCT01513824

Citation: Bergmann N, Ballegaard S, Bech P, Hjalmarson Å, Krogh J, et al. (2014) The Effect of Daily Self-Measurement of Pressure Pain Sensitivity Followed by Acupressure on Depression and Quality of Life versus Treatment as Usual in Ischemic Heart Disease: A Randomized Clinical Trial. PLoS ONE 9(5): e97553. doi:10.1371/journal.pone.0097553

Editor: Melvin G. McInnis, University of Michigan, United States of America

Received December 16, 2013; **Accepted** April 17, 2014; **Published** May 21, 2014

Funding: This work was supported by the Johan Schrøder's Family and Business Foundation. Natasha Bergmann held a pre-graduate scholarship sponsored by the Lundbeck Foundation. Grants from Else and Mogens Wedell-Wedellsborg's Foundation, and Carpenter Sophus Jacobsen and Wife Astrid Jacobsen's Foundation were used to cover travel expenses. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Søren Ballegaard invented the instrument used to measure PPS (Ullmeter, patent numbers: PA 2004-00349; PA 2004-00550) and is a shareholder of the firm that owns the PPS instrument (Ullcare A/S). In order to avoid bias, he was not involved in patient contact, collection of data or statistical analysis and was prohibited admittance to the research site during the entire period of the study. His authorship does not alter the authors' adherence to PLOS ONE policies on sharing data and materials. The other authors have no competing interests to declare and no relation to Ullcare A/S including employment, consultancy, patents, products in development or marketed products.

* E-mail: n.c.bergmann@hotmail.com

Introduction

The bidirectional interaction between depression and ischemic heart disease (IHD) has been documented numerous times and is generally accepted [1]. After an acute myocardial infarction (MI) the risk of being depressed is approximately 3 times increased as compared with the general population [2]. In out-patients the 12-month odds ratio of major depression has been found to be 2.3 times higher in individuals with cardiac disease as compared with those with no medical illness [3]. In initially healthy people clinical depression as well as depressive mood is associated with a

significantly increased risk of developing IHD [4]. Further, depression after a MI doubles both the risk of a cardiac re-event during the first 2 years post MI, as well the risk of 2 years mortality [5].

Depression, quality of life and general well-being is all part of the chronic stress concept [6]. Stress is vaguely defined but is generally accepted as a risk factor for a poor outcome in IHD [7]. Chronic stress is associated with cardiovascular re-events and death from IHD and patients with MI have been shown to have higher stress levels when measured both as stress at work, stress at home, financial stress and major life-event stress [7,8].

Chronic stress and depression is associated with widespread increased pain sensitivity, leading to both hyperalgesia (pain induced by noxious stimuli) and allodynia (pain induced by non-noxious stimuli) [9,10]. The increase in pain sensitivity might be due to the neuroplastic effects of chronic stress on pain circuitry i.e. the diffuse noxious inhibitory control system (DNIC) [9,11]. DNIC is an endogenous pathway mediating inhibition of lamina I neurons in the spinal dorsal root when pain signals ascend from the periphery through sensory C fiber neurons distributed wide spread over the body in the epidermis and up through the spinal cord [11]. Patients with hypersensitivity to pain have been shown to have an impaired DNIC modulation [12,13]. Theoretically an intervention aiming at restoring this afferent-efferent disturbance may be beneficial for treating the increased pain sensitivity and at the same time lowering the stress-level and depressive symptoms. It has previously been theorized that therapies such as acupuncture may exert their effects through activation of DNIC [11].

The gold standard in measuring pain sensitivity is by algometry. Recently a simple and handheld algometric device has been designed to asses pressure pain sensitivity (PPS) [14]. The PPS measure has in patients with IHD been found to be significantly correlated to the major depression inventory score (MDI), WHO-5's well-being index as well as to the SF-36 quality of life (QOL) score [15].

Several studies have evaluated the effect of various stress-reducing interventions in patients with IHD and some have shown to improve the prognosis and to reduce the risk of new cardiovascular events [16,17]. We hypothesize that an intervention built on an increased focus on stress and the ability to perform stress reduction should be beneficial for patients with IHD. In analogy to people with diabetes measuring blood glucose levels, a therapy based on a daily semi-objective stress-measurements based on PPS followed by stress-reducing actions theoretically leads to increased empowerment and may have a positive effect on stress-parameters.

Acupressure, i.e. applying a continuous pressure for approximately one minute at specific hyperalgesic points at the body, has been shown to reduce both local and spreading pain in chronic low back pain and neck pain syndromes [18,19] and we have observed that acupressure results in an acute reduction in pain sensitivity and PPS [20].

Thus we hypothesized that the combination of daily self-measurements of PPS aiming at increased empowerment followed by acupressure aiming to restore DNIC, together would resolve in a reduction of the following elements of chronic stress: Depressive symptoms measured by MDI, general well-being measured by WHO-5, and physically and mentally QOL measured by SF-36 QOL-score.

Aiming to test this hypothesis we performed an observer blinded randomized clinical trial with blinded outcome assessment over 3 month in which the active group measured PPS twice daily followed by acupressure as mandatory action. Our primary end point was changes in MDI.

Methods

Ethics Statement

The original protocols and a CONSORT checklist are available as supporting information (see Protocol S1 (Danish), Protocol S2 (English), Checklist S1). The study was approved by the local ethical committee (The Regional Ethical Committee of the Copenhagen Region, Denmark, Kongensvaenge 2, DG-3400 Hilleroed, www.regionh.dk/vek, identifier: H-4-2010-135, and amendment 31962) and the Danish Data Protection Agency (identifier: 2011-41-7022), and was registered on www.clinicaltrials.gov (identifier: NCT01513824). All participants gave their written informed consent after oral and written information about the study. The study was performed according to the declaration of Helsinki.

Study Population

361 patients with IHD participated in a cross-sectional study on the associations between PPS and stress in patients with IHD [15]. From previous studies it seems that PPS≥60 indicates an increased chronic stress level [21]. Participants from the cross-sectional study with PPS≥60, were enrolled in the RCT. Two hundred and thirteen of the 361 patients from the cross-sectional study fulfilled the criteria of having PPS above 60 (see consort, Fig. 1). All participants fulfilled the following additional inclusion criteria and none of the exclusion criteria: *Inclusion criteria*: 1) documented IHD defined as having had a MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), 2) completed cardiac rehabilitation more than six months prior to inclusion, 3) age 75 years or younger at inclusion; *exclusion criteria*: 1) hospitalization due to psychiatric disease prior to IHD, 2) scheduled cardiac surgery, 3) changes in heart medication within the last month prior to inclusion, 4) a chronic competing disorder clearly impairing the patients QOL, 5) chronic pain syndromes such as fibromyalgia or severe arthritis [15].

Randomization

After the baseline visit the participants were allocated randomly with a 1:1 ratio to either the intervention arm or to treatment as usual (TAU). Randomization was stratified according to age, sex, MDI, diabetes, and chronic heart failure. The randomization was performed and carried out by an external statistician using a computerized randomization sequence with a block size of 16, which was unknown to the investigators. The participants received the allocation result by a confidential e-mail generated automatically. One hundred and six participants were allocated to active intervention and 107 to TAU.

Study Design

A single center, two-armed, parallel-group, observer-blinded randomized clinical superiority trial. The participants were enrolled at the trial cite in Copenhagen (Denmark).

Intervention Procedure

Active group. All subjects were instructed by a professional instructor (who had undergone education in PPS instruction and measurement and performing acupressure by passing a 4 week course plus a practical examination) to perform PPS measurements twice daily, in the morning (before breakfast) and in the evening (before going to bed). After the measurement, if the PPS level and thus the stress-level was high, the participant should perform acupressure as a mandatory stress-reducing procedure, as well as reflection on both the PPS level and on ones general feeling of need for stress handling on a voluntary basis.

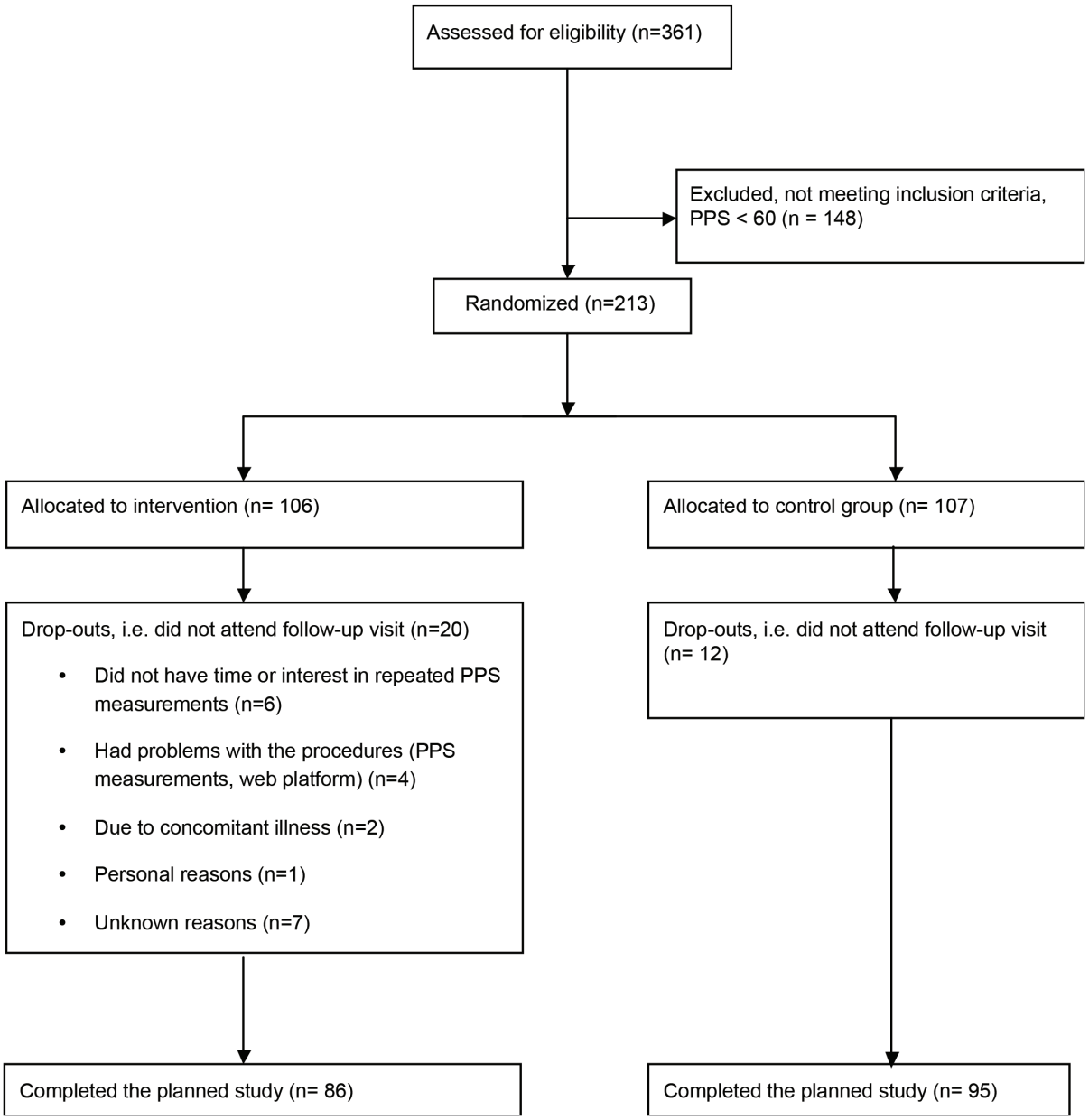

Figure 1. Consort.
doi:10.1371/journal.pone.0097553.g001

All subjects received a personal PPS measurement instrument, together with an instruction manual and were individually instructed during a 45 minutes period at their private homes on how to use the PPS device. This included education in performing acupressure. The acupressure procedure has previously been described in "Magnusson et al," [22]. In brief acupressure is performed by applying finger pressure for one minute sufficiently enough to feel the pressure but without causing pain. The pressure is applied on two points of the body: at the sternum, at the level of the fourth intercostal space and on the back 1.5 inch lateral to the spinal process of the fourth and fifth thoracic vertebra [22].

The participants were offered a new appointment and/or 1–2 phone contacts with the instructor if they had problems with self-measurements of PPS after the visit, or had other questions.

The participants were instructed to report their PPS measurements each day on their personal login on the website www.songheart.org. On the website each participant was able to track results and changes in PPS during the intervention period.

Both the active and the TAU group was informed at baseline, that their stress level was elevated and received a booklet on general stress handling principles [23].

Predefined Endpoints

Primary end-point. Change in MDI from baseline to follow up after three months.

Secondary endpoints. Changes in stress-level as measured by PPS as well as changes in well being as measured by WHO-5.

Tertiary endpoints. Changes in quality of life as measured by SF-36 physical (PCS) and mental (MCS) QOL scale.

Predefined subgroup analysis. The stress-reducing effects in participants with the highest depression/stress level measured as the subgroup of participants with MDI≥15 at baseline and the

subgroup of participants having the highest 50% of both PPS and Clinical stress signs score (CSS) at baseline.

Outcome Measures

PPS. Before and after three months all participants came to the metabolic ward in the morning. The PPS level was measured by a professional after 5–10 min of resting in a supine position. The PPS measurement procedure has previously been described in details [14,15]: The most sensitive area on the sternum was identified by palpation. The instructor applied a gradually increasing pressure with the PPS algometer on the most sensitive point until the pain threshold was reached. The PPS algometer transforms the pressure applied into a logarithmic scale of sensitivity level from 30 to 100. One hundred equals the highest sensitivity level, and thus the highest stress-level, 30 equals lowest measurable stress-level. An increase in 30 PPS units equals a 100% increase in sensitivity [14].

Questionnaires. A website was established for the study (www.songheart.org) and each participant received a personal profile with login. The day prior to the visit at the metabolic ward, the participants answered the following questionnaires on their www.songheart.org profile: 1) MDI, assessing depressive symptoms on a score form 0–50, zero being equivalent to no signs of depressive symptoms, 2) WHO-5, assessing psychological well-being with 100 equivalent to best psychological well-being, 3) SF-36, assessing PCS and MCS QOL with 100 equivalent to best QOL. At baseline a fourth questionnaire was included, measuring CSS as well as a demographic questionnaire. The CSS score is a newly developed score of 56 clinical stress symptoms experienced during the last four weeks [15]. The demographic questionnaire included questions on social status, employment status, cardiac medical history, co-morbidity and medication. This questionnaire should be answered before the baseline visit.

Blinding

The professional instructor measuring PPS was blinded with regard to all results of online questionnaires as well as to the results of the randomization. Further the PPS device was designed in a way making the measure non-visible before the end of each measurement for both instructor and patient. The patients were instructed before randomization not to reveal the result of the randomization to the research personal performing the follow up investigations at three months. Statistical analysis was performed prior to the unveiling of the randomization codes.

Estimation of Sample Size

In the original and approved protocol, sample size was calculated based on an anticipated effect size of 0.4, alpha of 0.05 and beta of 0.20 which corresponded to a sample size of 300 patients.

Statistical Analysis

Data were evaluated by parametric statistics including paired and non-paired t-test on an intention to treat basis (ITT). Both the observed and values are reported. For testing of statistical significance we included all randomized patients in our analysis regardless of subsequent adherence to treatment. We imputed missing values treating the outcomes as dependent variables using multiple imputations. For this we used a linear regression model with the following predictor variables: Allocation, sex, and age. The imputation was conducted using 100 imputations and 20 iterations. The pooled estimates from these imputations were subsequently used for analysis [24].

Cohens effect size was used to compare active to TAU group using ITT data. The effect size was evaluated according to Hedgen and Olkin as the difference in mean change score from baseline to follow up between active group and TAU divided by the pooled standard deviation [25,26]. In relation to clinically significant effects, the following have been proposed: Effect size$<$ 0.19, minor clinically significant effect; 0.20–0.39 small effect; the interval between 0.40 and 0.69, medium effect and $>$0.70, a large effect [27].

Analyses were performed using the statistical package SPSS version 19. All statistical tests were two-sided and p-values below 0.05 were considered statistically significant.

Results

Table 1 shows the demographic characteristics of the participants from the active and TAU group respectively as well as together. There were no significant differences between the two groups regarding age, gender, psychometric measurements, social status, employment status, cardiac variables or risk factors, nor medication. However a group difference was found regarding co-morbidities on self-reported heart failure and self-reported diabetes mellitus (Table 1).

Twenty dropouts (19%) were reported in the active group and 12 (11%) in the TAU group, $p = 0.18$. (Fig. 1) Drop outs were similar to those who completed with regard to sex, age, MDI and WHO-5 scores.

Adaptation of the Interventional Procedure

Ninety four in the active group reported repeated PPS measurements at home, in mean 90 measurements over three months (range 6–192).

Primary Endpoint, MDI

MDI was significantly reduced by 22% after three months in the active group and by 12% in the TAU group. The reduction was significantly greater in the active group as compared with the TAU group, which resulted in a difference between the two groups at three months, $p = 0.040$ (Table 2).

Other Endpoints

WHO-5, increased by 6.4% in the active group and by 3.7% in the TAU group from baseline to follow up ($p = 0.015$ and $p = 0.158$, respectively), which resulted in significantly different levels between active group and TAU at 3 months ($p = 0.016$) (Table 2).

PPS was significantly reduced by 28% after three months in the active group and 11% in the TAU group (both $p<0.001$), and at 3 months the PPS values had become different between the two groups ($p<0.001$).

SF-36 PCS was improved in both groups although not reaching statistically difference at three months, $p = 0.14$. SF-36 MCS improved in the active group ($p = 0.004$), however, the difference after three month compared with TAU values only tended to be significant ($p = 0.09$) (Table 2).

Subgroup Analyses

Two subgroup analyses were performed: One on subjects with MDI$\geq$15 at baseline and another on subjects having both the PPS and CSS within the upper half at baseline (Table 3).

Fourty-two participants had MDI$\geq$15 at baseline and 21 were randomized to active and 21 to TAU group, and 18 subjects in each group completed the study (Table 3). Fifty-nine patients had both PPS$>$81 and CSS$\geq$8 at baseline, corresponding to the

Table 1. Distribution of baseline factors according to treatment group.

	Full sample	Active group	Treatment as usual	P-value
N	213	106	107	
Male (n, %)	156 (73%)	78 (74%)	78 (73%)	NS*
Age in years (mean, SD)	62 (8.1)	62 (8.1)	62 (8.2)	NS
Psychometrics				
MDI (mean, SD)	8.9 (7.4)	8.4 (7.7)	9.4 (7.0)	NS
WHO-5 (mean, SD)	65 (19)	67 (19)	63 (19)	NS
PPS (mean, SD)	81 (13)	81 (13)	81 (13)	NS
SF-36 PCS (mean, SD)	48 (8.4)	48 (9.1)	48 (7.6)	NS
SF-36 MCS (mean, SD)	52 (9.3)	53 (9.3)	52 (9.3)	NS
CSS (mean, SD)	9.7 (7.1)	9.2 (6.5)	10 (7.6)	NS
Social status				
Married or cohabiting (n, %)	175 (82%)	83 (78%)	92 (86%)	NS
Have children (n, %)	190 (92%)	97 (91%)	96 (90%)	NS
Employment status				
Employed (n, %)	106 (50%)	54 (51%)	52 (49%)	NS
Unemployed (n, %)	4 (2%)	3 (3%)	1 (1%)	NS
Retired (n, %)	92 (47%)	46 (44%)	52 (48%)	NS
Cardiac variables				
Selfreported time (years) since diagnosed with IHD (mean, SD)	7.5 (5.8)	8.2 (6.5)	6.8 (5.0)	NS
Treated with PCI (n, %)	147 (69%)	73 (69%)	74 (69%)	NS
Treated with CABG (n, %)	52 (24%)	27 (25%)	25 (23%)	NS
Resting pulse (mean, SD)	61 (11)	61 (11)	60 (11)	NS
MAP (mean, SD)	98 (10)	98 (9.7)	97 (11)	NS
Cardiac risk factors				
BMI (mean, SD)	27.6 (4.3)	27.8 (4.3)	27.4 (4.4)	NS
Triglyceride (mean, SD)	1.5 (0.9)	1.4 (0.7)	1.5 (1.0)	NS
Current smoker (n, %)	22 (10%)	9 (9%)	13 (12%)	NS
Self reported co-morbidity				
Heart failure (n, %)	72 (34%)	29 (27%)	43 (40%)	P = 0.047
Chronic obstructive lung disease (n, %)	13 (6%)	5 (5%)	8 (8%)	NS
Diabetes (n, %)	28 (13%)	20 (19%)	8 (8%)	P = 0.013
Previous cerebral insults (n, %)	15 (7%)	7 (7%)	8 (8%)	NS
Have been treated for depression (n, %)	32 (15%)	12 (11%)	20 (19%)	NS
Medication				
Beta-blockers (n, %)	125 (60%)	65 (61%)	60 (57%)	NS
Cholesterol-lowering medication (n, %)	188 (90%)	94 (89%)	94 (88%)	NS
Calcium antagonists (n, %)	47 (23%)	26 (25%)	21 (20%)	NS
Angiotensin-II antagonist and/or ACE inhibitors (n, %)	115 (55%)	56 (53%)	59 (55%)	NS
Diuretics (thiazide or furosemide) (n, %)	74 (36%)	40 (39%)	34 (33%)	NS
Anti-depressive medication (n, %)	12 (6%)	4 (4%)	8 (8%)	NS

*NS: p>0.05 between active group and TAU.

doi:10.1371/journal.pone.0097553.t001

highest 50% of PPS as well as of CSS. Twenty-nine were allocated to active treatment and 30 to TAU, of whom 24 and 26 respectively completed the study (Table 3).

Effect Size

The effect of active vs. TAU for the whole group was 0.12 for MDI, 0.11 for WHO-5 and 0.63 for PPS. Effect size for the subgroup with MDI≥15 was 0.35 for MDI, 0.21 for WHO-5 and 0.43 for PPS and for the subgroup with both the highest PPS and

Table 2. Results of questionnaires and PPS before and at three months follow up in.

	Statistical analyses	Treatment as usual (TAU), baseline (mean, SD)	Treatment as usual (TAU),follow up (mean, SD)	Baseline vs. follow up, P	Active group, baseline (mean, SD)	Active group, follow up (mean, SD)	Baseline vs. follow up, P	3 month analysis TAU vs. active, P	Effect size
MDI	ITT	9.40 (6.99)	8.31 (6.74)	0.025	8.36 (7.70)	6.48 (6.58)	0.001	0.040	0.12
	PP	9.34 (6.21)	8.32 (6.23)		7.93 (6.72)	6.12 (5.35)			
WHO-5	ITT	62.5 (19.0)	64.8 (20.9)	0.158	66.7 (19.1)	71.0 (18.3)	0.015	0.016	0.11
	PP	63.3 (18.4)	65.2 (19.2)		67.2 (19.1)	71.2 (15.4)			
PPS	ITT	80.9 (13.3)	72.1 (20.5)	<0.001	80.8 (13.3)	58.4 (22.1)	<0.001	<0.001	0.63
	PP	80.6 (13.3)	71.8 (17.5)		82.4 (12.3)	59.7 (20.6)			
SF-36 physical component summary	ITT	47.8 (7.68)	47.7 (9.61)	0.85	48.2 (9.14)	49.5 (9.99)	0.04	0.14	0.14
	PP	47.6 (7.90)	47.7 (8.56)		48.8 (8.50)	50.5 (6.47)			
SF-36 mental component summary	ITT	51.9 (9.31)	53.3 (9.72)	0.094	52.7 (9.35)	55.3 (9.34)	0.004	0.08	0.13
	PP	51.9 (9.23)	53.3 (6.92)		53.1 (9.28)	55.1 (7.84)			

Only statistical analyses using ITT data are presented.

ITT: intention to treat; PP: per protocol; TAU: treatment as usual; MDI: major depression inventory; PPS: pressure pain sensitivity; CSS: Clinical stress signs.

doi:10.1371/journal.pone.0097553.t002

Table 3. Subgroup analyses.

MDI ≥15*	Statistical analyses	TAU: baseline (mean, SD)	TAU: follow up (mean, SD)	TAU: Baseline vs follow up, P	Active group: baseline (mean SD)	Active group: follow up (mean, SD)	Active group: baseline vs follow up, P	Three month follow up TAU vs active, P	Effect size
MDI	ITT	20.5 (6.59)	16.1 (8.31)	<0.001	21.4 (6.19)	14.2 (7.55)	0.005	0.44	0.35
	PP	19.4 (4.91)	15.5 (8.19)		19.3 (4.18)	12.6 (6.86)			
WHO-5	ITT	39.8 (18.4)	51.1 (22.9)	0.015	41.3 (15.4)	56.8 (16.7)	<0.001	0.36	0.21
	PP	39.8 (17.5)	51.3 (22.7)		41.6 (17.3)	57.1 (16.1)			
PPS	ITT	85.0 (12.7)	78.7 (16.5)	0.017	86.1 (12.7)	71.9 (20.4)	<0.001	0.23	0.43
	PP	83.8 (12.5)	78.1 (14.3)		85.1 (13.1)	72.8 (20.0)			
SF-36 physical component summary	ITT	42.4 (8.91)	43.2 (8.76)	0.60	45.0 (10.7)	45.7 (9.93)	0.66	0.40	0.01
	PP	42.2 (8.88)	43.0 (8.43)		48.9 (9.61)	48.3 (8.32)			
SF-36 mental component summary	ITT	42.0 (11.3)	46.3 (8.71)	0.14	38.9 (8.58)	48.5 (11.5)	0.001	0.48	0.52
	PP	41.7 (11.0)	44.9 (7.39)		39.9 (10.0)	45.5 (10.4)			
High PPS and high CSS (PPS>81 and CSS≥8)**		**TAU: baseline (mean, SD)**	**TAU: follow up (mean, SD)**	**TAU: Baseline vs follow up, P**	**Active group: baseline (mean SD)**	**Active group: follow up (mean, SD)**	**Active group: Baseline vs follow up, P**	**Three month follow up TAU vs active, P**	**Effect size**
MDI	ITT	13.3 (9.8)	12.5 (8.6)	0.55	14.3 (9.9)	9.11 (8.30)	<0.001	0.15	0.52
	PP	12.1 (7.18)	12.1 (7.22)		12.3 (7.90)	8.25 (7.52)			
WHO-5	ITT	56.1 (21.7)	56.6 (19.9)	0.09	54.3 (22.9)	67.0 (19.6)	<0.001	0.066	0.62
	PP	57.7 (20.0)	56.7 (18.9)		55.2 (22.3)	68.6 (18.2)			
PPS	ITT	94.3 (5.62)	83.8 (15.3)	<0.001	96.4 (5.31)	77.3 (22.1)	<0.001	0.223	0.46
	PP	92.8 (6.19)	83.3 (13.1)		95.9 (6.06)	74.8 (23.5)			
SF-36 physical component summary		42.4 (7.93)	41.9 (9.50)	0.99	43.3 (9.41)	47.3 (9.75)	0.009	0.044	0.47
		42.2 (7.64)	42.3 (9.15)		47.6 (7.80)	51.8 (5.87)			
SF-36 mental component summary		48.6 (11.8)	49.5 (9.38)	0.64	47.3 (9.42)	52.9 (8.92)	0.004	0.199	0.51
		49.8 (11.0)	49.7 (9.05)		48.47 (9.42)	52.1 (10.2)			

Results of questionnaires and PPS before and at three months follow up in subjects from active and treatment as usual groups. Only statistical analyses using ITT data are presented.
ITT: intention to treat; PP: per protocol; TAU: treatment as usual; MDI: major depression inventory; PPS: pressure pain sensitivity; CSS: Clinical stress signs.
*) Forty-two participants had MDI≥15 at baseline. Twenty-one were randomized to active and 21 to TAU group. Thirty-six participants, 18 active and 18 controls completed the study.
**) Fifty-nine patients had PPS>81 and CSS≥8 at baseline, corresponding to the highest 50% of both PPS and of CSS. Twenty-nine
were allocated to active treatment and 30 to TAU, of whom 24 and 26, respectively, completed the study.
doi:10.1371/journal.pone.0097553.t003

CSS, the effect size was 0.52 for MDI, 0.62 for WHO-5 and 0.46 for PPS.

Discussion

In the present randomized interventional trial we found, that in patients with stable IHD the combination of daily self-measurements of PPS followed by acupressure and reflection on PPS as a surrogate for current stress-level resulted in a modest but statistically significant improvement in PPS, MDI and WHO-5.

This beneficial effect of the intervention program was more pronounced in subgroups of patients with higher baseline levels of components of the chronic stress syndrome, such as elevated MDI, as well as the combination of an elevated PPS and CSS. These subgroup analyses, however, were hampered by a limited sample size.

The primary endpoint was a reduction in MDI. MDI was chosen as a well validated often used psychometric questionnaire on depressive symptoms. It is well known that patients with IHD as well as other chronic diseases have increased levels of depressive symptoms which leads to a poor outcome [28]. The intervention resulted in a reduction in MDI of 22% in the active group while the TAU group only demonstrated a reduction of 12%, resulting in a significant difference between the active and the TAU group at follow up. This corresponded to a small effect size of 0.12. When looking at the subgroups, however, the reduction in MDI was much greater resulting in an effect size of 0.35 in the MDI$\geq$15 subgroup representing participants with the most depressive symptoms and 0.52 for the high PPS high CSS group representing the participants with an elevated chronic stress level. These effect sizes are clinically significant [27]. Thus our findings point to a greater effect of our intervention among more psychologically vulnerable subjects. These data on effect size should be compared to the effect size of antidepressants found in placebo-controlled clinical trials of treatment resistant patients with overt depression of approximately 0.40, although our patients did not have overt depression [29]. Further, a meta-analysis on exercise training, a well-known and beneficial treatment, on depressive symptoms among patients with a chronic illness, demonstrated an effect size of 0.30 in patients with mild-to-moderate depression [30].

Similar to a positive effect on MDI we found a beneficial effect of the intervention on general well-being as measured by WHO-5′s well-being index. The intervention resulted in an increase in WHO-5 with a small effect size, however subgroup analysis demonstrated a substantially increase in well-being, although the difference at three months between the active and the TAU group, did not reach statistically significance probably due to a limited number of subjects in the subgroup analyses.

The intervention was based on the concept that self-measurement of pain sensation threshold measured by PPS resulted in an awareness of ones current stress-level, leading to reflection as well as to action i.e. increased empowerment, aiming at improving overall well-being.

Acupressure was the only mandatory action for reducing pain sensation in the intervention program. General advice about stress reduction was presented for both the active and the TAU group in the form of a booklet on stress-coping [23].

Parts of the intervention program have been used with success previously in patients with advanced angina pectoris in a non-randomized fashion [31,32]. The intervention procedure was accepted by the participants of the active group, in terms of repeated PPS measurements reported the website. The participants reported in mean 90 measurements over the three month period. This is probably a lower bound since the participants might have performed PPS measurements without reporting them on the website. The current study serves as proof of concept concerning repeated PPS measurements at home followed by acupressure and reflection in general as a stress-reducing intervention.

PPS measures pain sensitivity threshold like other algometers within pain research. We have recently demonstrated a close correlation between PPS and another pressure pain algometer [15].

An inherent weakness of pressure pain algometry is the fact that there is no objective measure of pain threshold since it is the subject itself that reacts to discomfort and ends the measurement. Therefore a potential bias to repeated measurements is habituation both mentally and physically. If present this could result in a progressive reduction in PPS over time. We have performed validation studies in which we have found a very close association between two measurements performed within 5 seconds as well as with one day between measurements [31]. This suggests that a drift towards lowering of the PPS value due to repeated measurements is probably of minor importance.

In the present study the PPS measure was reduced with 22 units in the active group. The PPS device is constructed such that a reduction of 30 units equals a doubling of the pressure applied to the sternum. This quite robust change also speaks against a drift in PPS sensation due to habituation.

The instructors measuring PPS at baseline as well as after three months were blinded to the randomization results, the answers of the questionnaires, the results of the PPS home measurements and to the concrete PPS result while measuring at baseline and follow up visits. The latter is due to the construction of the PPS device, which first shows the result of the pressure when ending the pressure, thus revealing only the final result.

Chronic illness in general is associated with both stress and depressive symptoms which includes IHD [33]. Chronic stress and depression are associated with increased pain sensitivity, clinically presenting with widespread hyperalgesia [10]. A 28% reduction in pain sensitivity from baseline to follow up as found in the present study may be of clinical relevance.

Whether the reduction in pain sensitivity is the primary event leading to reduced feeling of depressive symptoms and increased well-being as found by an improvement in MDI and WHO-5 results, or the intervention works primarily by changing depressive symptoms and well-being and thereafter leads to a reduction in pain sensitivity is not clear. Concerning the mandatory intervention, acupressure, it is a well known clinical observation, that acupressure on a distinct sore point of the body leads to pain reduction locally with a spreading effect into the surroundings, which also has been demonstrated in females with chronic neck pain [18]. Further, the use of acupressure in low back pain has been proven in a RCT setting [19]. We have observed an acute reduction in PPS due to acupressure over the sternum, and it is postulated that acupressure works by reducing pain sensitivity by restoring DNIC [11]. If this is the primary effect of our intervention, the primary event will be reduced pain sensitivity. On the other hand the reflection on ones stress level based on repeated PPS measurements could also be the leading event resulting in increased empowerment which might result in a reduction of depressive symptoms and increased well-being as the primary effect. Several studies have found that psychological interventions including cognitive, behavioral and educational approaches all aiming at enhanced empowerment has been effective in reducing depression and anxiety in patients with IHD [16,34]. Cognitive stress-reducing therapy has also been found to reduce recurrent cardiovascular events [17]. These

studies imply that the empowering part of the intervention may be the primary effect.

Strengths and Limitations

Limitations. We aimed at 300 and included 213 participants. The power analysis was based on an effect size of 0.40, but we only obtained an effect size of 0.12. This means that the study ended up underpowered. However looking at both primary endpoint (MDI) and the other endpoints we found a rather clear tendency towards a beneficial effect on all parameters studied during intervention. This indicates that all bights the effect size was rather small, it seems real and is not a result of a type 1 error. Although the study was underpowered we did find significant changes probably avoiding a rather large risk of a type 2 error.

The randomization procedure included DM and chronic heart failure yes/no, however, the randomization ended up with significantly more diabetics in the active group and in contrast less patients with chronic heart failure compared with the TAU group. Given the small number of diabetics and patients with heart failure the consequence of this randomization failure is probably mild or absent.

The study was single blinded. This was intentionally since the intervention was of an open nature i.e. the participants should reflect on the PPS measurements and also because sham PPS measurement giving false values did not seem ethically acceptable. However, the single-blinded design may have caused bias to the results of the intervention and may have affected the responses from the participants regarding the questionnaires. With regard to the PPS measurements they were performed by professionals who did not have knowledge about the allocation to active or control group. Further the PPS device was designed in a way making the measure non-visible before the end of each measurement for both instructor and patient. Thus the results from PPS measurements can be regarded as double blinded.

Strengths. Rather few in- and exclusion criteria make our study representative to most patients with IHD, further the intervention technique used is easy to adapt and use, and without side effects.

Statistical evaluation was performed by an ITT analysis using all randomized subjects (n = 106). This is the most correct, however not always used in RCT [35].

Conclusions

Self-measurements of PPS followed by acupressure as a mandatory action and otherwise individual reflection, in subjects with stable IHD resulted in a reduction in PPS, reduced amounts of depressive symptoms and increased well-being. This effect seemed more pronounced among the most psychologically vulnerable subjects. Due to the study ending up being underpowered further studies which are properly powered should be performed in order to establish the impact of this new type of intervention.

Perspectives

The concept of biofeedback guided stress handling, i.e. increased patient empowerment, based on frequent self-measurement of PPS might be broadened out to other chronic illnesses like diabetes, as well as to otherwise healthy subjects on work places where the employees demonstrate signs of increased stress due to a high psychological stress demand.

Supporting Information

Protocol S1 Trial Protocol (Danish).
(PDF)

Protocol S2 Trial Protocol (English).
(PDF)

Checklist S1 CONSORT Checklist.
(DOC)

Acknowledgments

We thank the staff at Department of Cardiology, Gentofte Hospital, Denmark for providing us with their database on patients with cardiovascular disease that have been appointed to rehabilitation. We are thankful to the staff of the Metabolic Ward for their very valuable contribution concerning the practical issues: Helle-Marina Oxfeldt, Tine Skogen-Lassen, Ulla Kjærulff-Hansen, Tonni Løve Hansen, Hanne Dorthe Mogensen, Marianne Sørensen og Rikke Mirsbach Henkel.

Author Contributions

Conceived and designed the experiments: SB, PB, AH, FG, JF. Performed the experiments: NB, JF. Analyzed the data: NB, JK, JF. Wrote the paper: NB, SB, JK, PB, AH, FG, JF.

References

1. Grippo AJ, Johnson AK (2009) Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 12: 1–21. 907251419.
2. Lichtman JH, Bigger JTJ, Blumenthal JA, Frasure-Smith N, Kaufmann PG, et al. (2009) AHA science advisory. Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee to the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care Outcomes Research. Endorsed by the American Psychiatric Association. Prog Cardiovasc Nurs 24: 19–26. PCV28.
3. Egede LE (2007) Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry 29: 409–416.
4. Rugulies R (2002) Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med 23: 51–61.
5. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, et al. (2011) Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. Gen Hosp Psychiatry 33: 203–216.
6. Bech P (2012) Clinical psychometrics, Wiley Blackwell, Oxford.
7. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, et al. (2004) Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 364: 953–962.
8. Rosengren A, Tibblin G, Wilhelmsen L (1991) Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. Am J Cardiol 68: 1171–1175.
9. Spezia Adachi LN, Caumo W, Laste G, Fernandes ML, Ripoll RJ, et al (2012) Reversal of chronic stress-induced pain by transcranial direct current stimulation (tDCS) in an animal model. Brain Res 1489: 17–26.
10. Richebe P, Rivat C, Cahana A (2011) Stress-induced hyperalgesia: any clinical relevance for the anesthesiologist? Anesthesiology 114: 1280–1281.
11. Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, et al (2012) Effects of motor cortex modulation and descending inhibitory systems on pain thresholds in healthy subjects. J Pain 13: 450–458.
12. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, et al (2010) Sensitization in patients with painful knee osteoarthritis. Pain 149: 573–581.
13. Arendt-Nielsen L, Yarnitsky D (2009) Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 10: 556–572.
14. Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, et al (2009) A simple and objective marker for stress. Scand J Clin Lab Invest 69: 713–721.
15. Bergmann N, Ballegaard S, Holmager P, Kristiansen J, Gyntelberg F, et al (2013) Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease. Scand J Clin Lab Invest 73: 373–379.
16. Whalley B, Rees K, Davies P, Bennett P, Ebrahim S, et al (2011) Psychological interventions for coronary heart disease. Cochrane Database Syst Rev CD002902.

17. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, et al (2011) Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). Arch Intern Med 171: 134–140.
18. Matsubara T, Arai YC, Shiro Y, Shimo K, Nishihara M, et al (2011) Comparative effects of acupressure at local and distal acupuncture points on pain conditions and autonomic function in females with chronic neck pain. Evid Based Complement Alternat Med 2011.
19. Hsieh LL, Kuo CH, Lee LH, Yen AM, Chien KL, et al (2006) Treatment of low back pain by acupressure and physical therapy: randomised controlled trial. BMJ 332: 696–700.
20. Ballegaard S, Petersen PB, Harboe GS, Karpatschof B, Gyntelberg F, et al (2013) Changes in pressure pain sensitivity an cardiovascular factors associated with persistent stress. psychotherapy and psychosomatics 82, supplement 1: 9.
21. Ballegaard S, Petersen PB, Gyntelberg F, Faber J (2012) The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Invest 72: 459–466.
22. Magnusson G, Ballegaard S, Karpatschof B, Nyboe J (2010) Long-term effects of integrated rehabilitation in patients with stroke: a nonrandomized comparative feasibility study. J Altern Complement Med 16: 369–374.
23. Netterstrøm B (2002) Stress. DR multimedie.
24. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, et al (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338: b2393.
25. Hedges LV OI (1985) Statistical methods for meta-analysis.
26. Bech P (2007) Dose-response relationship of pregabalin in patients with generalized anxiety disorder. A pooled analysis of four placebo-controlled trials. Pharmacopsychiatry 40: 163–168.
27. Bayer L, Blais MA (2010) Understanding Rating Scales and Assessment Instruments. In: Handbook of clinicla rating scales and assessment in psychiatry and mental health. New York: Human press.
28. Barth J, Schumacher M, Herrmann-Lingen C (2004) Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 66: 802–813.
29. Bech P, Gefke M, Lunde M, Lauritzen L, Martiny K (2011) The Pharmacopsychometric Triangle to Illustrate the Effectiveness of T-PEMF Concomitant with Antidepressants in Treatment Resistant Patients: A Double-Blind, Randomised, Sham-Controlled Trial Revisited with Focus on the Patient-Reported Outcomes. Depress Res Treat 2011: 806298.
30. Herring MP, Puetz TW, O'Connor PJ, Dishman RK (2012) Effect of exercise training on depressive symptoms among patients with a chronic illness: a systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 172: 101–111.
31. Ballegaard S, Johannessen A, Karpatschof B, Nyboe J (1999) Addition of acupuncture and self-care education in the treatment of patients with severe angina pectoris may be cost beneficial: an open, prospective study. J Altern Complement Med 5: 405–413.
32. Ballegaard S, Borg E, Karpatschof B, Nyboe J, Johannessen A (2004) Long-term effects of integrated rehabilitation in patients with advanced angina pectoris: a nonrandomized comparative study. J Altern Complement Med 10: 777–783.
33. Herring MP, Puetz TW, O'Connor PJ, Dishman RK (2012) Effect of exercise training on depressive symptoms among patients with a chronic illness: a systematic review and meta-analysis of randomized controlled trials. Arch Intern Med 172: 101–111.
34. Van DT, Hermans D, Van AC, Van den Bergh O (2011) Stress Reduction Through Psychoeducation: A Meta-Analytic Review. Health Educ Behav.
35. Abraha I, Montedori A (2010) Modified intention to treat reporting in randomised controlled trials: systematic review. BMJ 340: c2697.

Scandinavian Journal of Clinical & Laboratory Investigation, 2015; Early Online: 1–10

informa
healthcare

ORIGINAL ARTICLE

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

SØREN BALLEGAARD[1], NATASHA BERGMANN[1], BENNY KARPATSCHOF[2], JESPER KRISTIANSEN[3], FINN GYNTELBERG[3], LARS ARENDT-NIELSEN[4], PER BECH[5], ÅKE HJALMARSON[6] & JENS FABER[1,7]

[1]*Department of Endocrinology, Herlev University Hospital, Herlev,* [2]*Department of Psychology, University of Copenhagen,* [3]*The National Research Centre for the Working Environment, Copenhagen,* [4]*Center for Sensory-Motor Interaction; Department of Health Science and Technology, Aalborg University,* [5]*Psychiatric Research Unit, Psychiatric Centre North Zealand, University of Copenhagen, Hillerød, Denmark,* [6]*Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, and* [7]*Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark*

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].

Correspondence: Søren Ballegaard, Department of Endocrinology, Herlev University Hospital, Herlev, Denmark. Tel: +45 3940 4142. E-mail: sba@ullcare.com,

(Received 18 December 2013; accepted 26 February 2015)

ISSN 0036-5513 print/ISSN 1502-7686 online © 2015 Informa Healthcare
DOI: 10.3109/00365513.2015.1028095

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 ANS function 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 measurement 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

Table I. Baseline demographics according to study groups.

	Cross-sectional study	Intervention study Active group	Intervention study Control group
n	361	86	95
Male, *n* (%)	286 (79)	64 (74)	70 (74)
Age in years, mean (SD)	63 (7.9)	62 (8.1)	63 (7.9)
Psychometrics			
Major depression inventory, mean (SD)	8.3 (7.1)	8.2 (7.0)	9.1 (6.1)
WHO-5 wellbeing score, mean (SD)	66 (18)	67 (19)	63 (18)
Pressure pain sensitivity, mean (SD)	65 (20)	82 (12)	80 (13)
SF-36 physical component, mean (SD)	49 (9.0)	49 (8.3)	48 (7.7)
SF-36 mental component, mean (SD)	53 (9.8)	53 (9.4)	52 (9.0)
Clinical stress score, mean (SD)	8.3 (6.8)	8.4 (6.1)	9.8 (7.0)
Cardiac variables			
Past myocardial infarction, *n* (%)	229 (63)	58 (67)	59 (62)
Treated with percutaneous coronary intervention, *n* (%)	242 (67)	60 (70)	66 (70)
Treated with coronary artery bypass grafting, *n* (%)	102 (28)	22 (26)	23 (24)
Resting pulse, mean (SD)	61 (10)	61 (11)	61 (10)
Mean arterial pressure, mean (SD)	100 (11)	98 (10)	98 (11)
Cardiac risk factors			
Body mass index, mean (SD)	27.7 (4.2)	27.9 (4.5)	27.2 (4.5)
Triglyceride, mean (SD)	1.5 (0.9)	1.4 (0.8)	1.5 (1.0)
Current smoker, *n* (%)	35 (10)	7 (8)	12 (13)
Self-reported comorbidity			
Heart failure, *n* (%)	111 (31)	26 (30)	36 (38)
Chronic obstructive lung disease, *n* (%)	19 (5)	4 (5)	5 (5)
Diabetes, *n* (%)	47 (13)	17 (20)	7 (7)
Previous stroke, *n* (%)	24 (7)	4 (5)	7 (7)
Have been treated for depression, *n* (%)	49 (14)	12 (14)	16 (17)
Medication			
Beta-blockers, *n* (%)	216 (60)	53 (62)	52 (55)
Cholesterol-lowering drugs, *n* (%)	319 (88)	77 (90)	86 (91)
Calcium antagonists, *n* (%)	85 (24)	24 (28)	18 (19)
Angiotensin-II antagonists and/or ACE inhibitors, *n* (%)	207 (57)	45 (52)	52 (55)
Diuretics, *n* (%)	108 (30)	34 (40)	30 (32)

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, Lemchesvej 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].

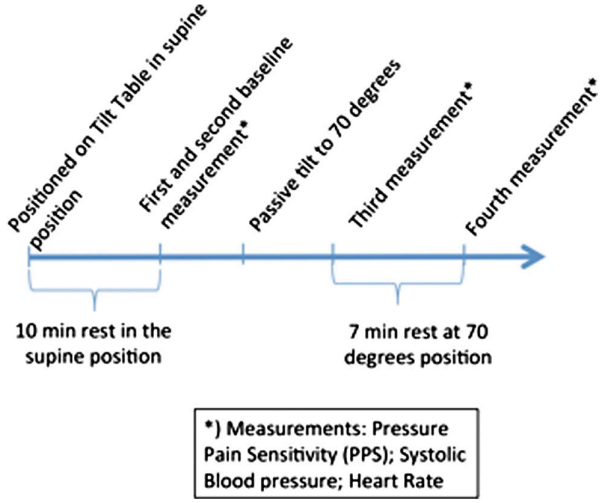

Figure 1. Time line for tilt table test (TTT).

Systolic blood pressure (*SBP*), *heart rate* (*HR*) *and pressure-rate-product* (*PRP*). Blood pressure and heart rate were recorded using a Thuasne 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 $\geq$ 60 for categorization of a person as being persistently stressed was based on previous consecutive studies on risk factor for impaired health [5,7]. The intervention stress reduction program (e.g. UllCare®) 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 $p \leq 0.0001$) ($n = 361$).

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 $\pm$ SD) $+1 \pm 11$ units compared to -7 ± 18 units for the group with resting PPS ≥ 60 ($n = 206$; between-group $p < 0.0001$).

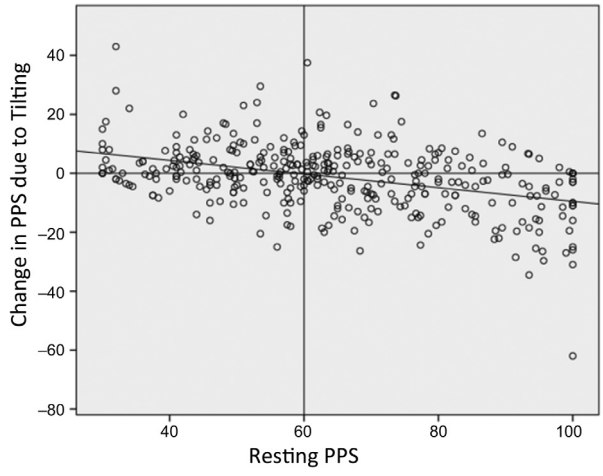

Figure 2. *Cross-sectional study*: The association between baseline resting PPS and change in PPS during baseline TTT (delta PPS Tilt test); $r = -0.37$; $p < 0.0001$) ($n = 361$).

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 $r < 0.01$, both $p > 0.1$) ($n = 361$).

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

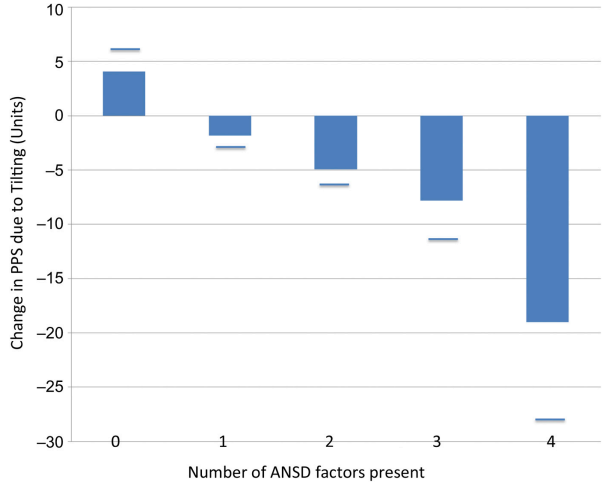

Figure 3. *Cross-sectional study*: The association between mean change in PPS during TTT and number of ANSD risk factors, including chest pain at rest, hypertension (SBP≥130), depression (MDI score≥20), and elevated level of persistent stress (resting PPS≥60 units); $r = -0.21$, $p < 0.0001$) ($n = 361$).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

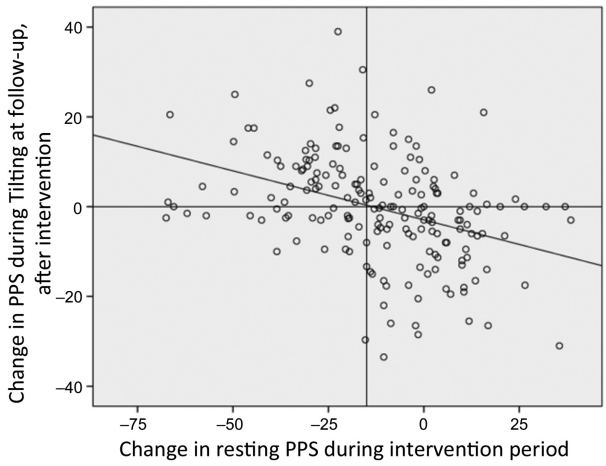

Figure 4. *Intervention study*: The association between change in resting PPS during intervention period and change in PPS during post-intervention TTT (Delta PPS Tilt test after intervention); $r = -0.38$; $p < 0.0001$) ($n = 177$). Vertical line indicates minimal important difference (see text) with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

examination (mean ± SD): + 4 ± 11 units (intra-group $p < 0.0001$), 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 (intra-group $p < 0.0001$) (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

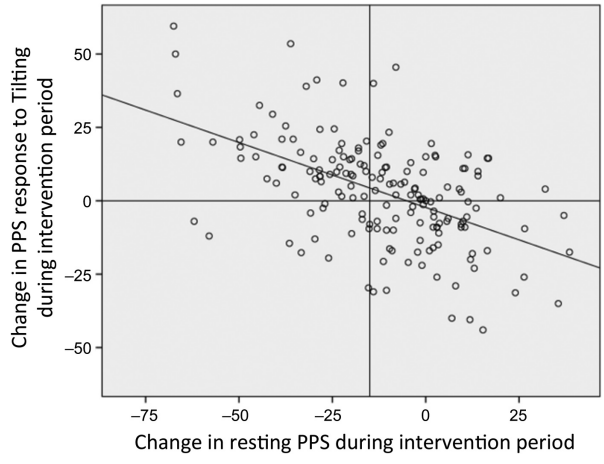

Figure 5. *Intervention study*: The association between change in resting PPS during intervention period and change in PPS response to tilting during intervention period: $r = -0.52$, $p < 0.0001$) ($n = 177$). Vertical line indicates minimal important difference (see text) with respect to reduction in resting PPS during intervention period (defined as 15 PPS units).

coefficient was 0.50 and 0.54 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): $+12 \pm 16$ 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 $p > 0.0001$). (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 neutrally 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 Schrøder'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 patents associated with 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.

References

[1] Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 2007; 74:224–42.
[2] Novak P. Quantitative autonomic testing. J Vis Exp 2011;53.
[3] Jaradeh SS, Prieto TE. Evaluation of the autonomic nervous system. Phys Med Rehabil Clin N Am 2003;14:287–305.
[4] Opie LH. Normal and abnormal cardiac function. Heart disease. A textbook of cardiovascular medicine, 7th edition. New York: Saunders Ltd; 2001. pp 703–4.
[5] Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Invest 2009;69:713–21.
[6] Bergmann N, Ballegaard S, Holmager P, Kristiansen J, Gyntelberg F, Andersen LJ, Hjalmarson Å, Bech P, Arendt-Nielsen L, Faber J. Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease. Scand J Clin Lab Invest 2013;73:373–379.
[7] Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Invest 2012;72:459–66.
[8] Bergmann N, Ballegaard S, Bech P, Hjalmarson Å, Krogh J, Gyntelberg F, Faber J. The effect of daily self-measurement of pressure pain sensitivity followed by acupressure on depression and quality of life versus treatment as usual in ischemic heart disease: a randomized clinical trial. PLoS One 2014;9:e97553.
[9] Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, Katos MC, McCord J, Miller TD, Morise A, Newby LK, Ruberg FL, Scardo KA, Thopson PD. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122:1756–76.
[10] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. Lancet 2005;366:1059–62.
[11] Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression

Inventory, using the Present State Examination as the index of diagnostic validity. J Affect Disord 2001;66:159–64.
[12] Netterstrøm B. Stress. 1. København: DR Multimedie; 2002.
[13] Freeman R, Chapleau MW. Testing the autonomic nervous system. Handb Clin Neur 2013:115–36.
[14] Cozzolino D, Furlan R, Gruosso D, Di MC, Miraglia Del GE, Torella R, Riugliano D. Effects of a mixed meal on hemodynamics and autonomic control of the heart in patients with type 1 diabetes. J Clin Endocrinol Metab 2010:194–200.
[15] Staud R. Autonomic dysfunction in fibromyalgia syndrome: postural orthostatic tachycardia. Curr Rheumatol Rep 2008:463–6.
[16] Beitzke M, Pfister P, Fortin J, Skrabal F. Autonomic dysfunction and hemodynamics in vitamin B12 deficiency. Auton Neurosci 2002;97:45–54.
[17] Kumazawa T. Primitivism and plasticity of pain – implication of polymodal receptors. Neurosci Res 1998;32:9–31.
[18] Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. TRPV4 calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol 2004;286:C195–205.
[19] Lockwood AH. Medical problems of musicians. N Engl J Med 1989;320:221–7.
[20] Tietjen GE, Brandes JL, Peterlin BL, Eloff A, Dafer RM, Stein MR, Drexler E, Martin VT, Huchinson S, Aurora SK, Recober A, Herial NA, Utley C, White L, Khuder SA. Allodynia in migraine: association with comorbid pain conditions. Headache 2009;49:1333–44.
[21] Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 2009;12:1–21.
[22] Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain 2004;107:7–15.
[23] Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009;10:556–72.
[24] Veltri A, Scarpellini P, Piccinni A, Conversano C, Giacomelli C, Bombardieri S, Bazichi L, Dell'Osso L. Methodological approach to depressive symptoms in fibromyalgia patients. Clin Exp Rheumatol 2012;30(6 Suppl. 74):136–42.
[25] Chalaye P, Goffaux P, Bourgault P, Lafrenaye S, Devroede G, Watier A, Marchand S. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. Clin J Pain 2012;28:519–26.
[26] Rayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, VanMeter JW, Bareniuk JN. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. PloS One 2013;8:e63903.
[27] Kontos MC, de Lemos JA, Ou FS, Wiviott SD, Foody JM, Newby LK, Chen A, Roe MT. Troponin-positive, MB-negative patients with non-ST-elevation myocardial infarction: an undertreated but high-risk patient group. Results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get With The Guidelines (NCDR ACTION-GWTG) Registry. Am Heart J 2010;160:819–25.