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# Association between Depression, Pressure Pain Sensitivity, Stress and Autonomous Nervous System Function in Stable Ischemic Heart Disease: Impact of Beta-Adrenergic Receptor Blockade

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

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## Abstract

**Background: Depression and ischemic heart disease (IHD) are associated with persistent stress and autonomic nervous system (ANS) dysfunction. The former can be measured by pressure pain sensitivity (PPS) of the sternum, and the latter by the PPS and systolic blood pressure (SBP) response to a tilt table test (TTT). Beta-blocker treatment reduces the efferent beta-adrenergic ANS function, and thus, the physiological stress response. Objective: To test the effect of beta-blockers on changes in depression score in patients with IHD, as well as the influence on persistent stress and ANS dysfunction. Methods: Three months of non-pharmacological intervention aiming at reducing PPS and depression score in patients with stable IHD. Beta-blocker users (N = 102) were compared with non-users (N = 75), with respect to signs of depression measured by the Major Depressive Inventory questionnaire (MDI), resting PPS, and PPS and SBP response to TTT. Results: MDI score decreased 30% in non-users (p = 0.005) compared to 4% (p > 0.1) among users (between-group p = 0.003; effect size = 0.4). Resting PPS decreased in both the groups. Among most**

*Corresponding author.

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**vulnerable patients with MDI ≥ 15, reductions in MDI score and resting PPS score correlated in non-users, only (r = 0.69, p = 0.007). Reduction in resting PPS correlated with an increase in PPS and SBP response to TTT. Conclusions: Stress intervention in patients with IHD was anti-depressive in non-users, only. Similarly, the association between the reduction in depression, reduction in persistent stress, and restoration of ANS dysfunction was only seen in non-users, suggesting a central role of beta-adrenergic receptors in the association between these factors.**

## Keywords

**Chronic Stress, Depression, Autonomic Nervous System, Systolic Blood Pressure, Pain Sensitivity, Beta-Blockers, Ischemic Heart Disease**

## 1. Introduction

Depressive disorders and ischemic heart disease (IHD) are both considered as the leading causes of the global burden of disease [1] [2]. A relationship between depression and heart disease is well established, although the biochemical and physiological mechanisms are not well understood [3]. In healthy people, depression and depressive mood are associated with increased risk of developing IHD [4], and for the patient with IHD, depression is associated with a higher risk of adverse cardiac events [5]. Conversely, IHD patients have a 2 - 3 times increased risk of being depressed [6]. Antidepressant drugs tend to reduce the depressive symptoms in people with IHD. Whether this effect is associated with a reduced cardiac morbidity or mortality remains unknown [7].

Increased pressure pain sensitivity of the sternum (PPS) has been observed in patients with stable IHD [8] [9] and can be measured by algometry measuring pain threshold [10]. Increased resting PPS has been demonstrated to be associated with elements of persistent stress [8] [10]-[13] including depressive symptoms in healthy as well as in IHD and breast cancer subjects [8] [11] [13]. An intervention trial using a non-pharmacological approach to stress handling among patients with IHD showed an intended reduction of elevated resting PPS at the baseline. This was associated with a significant reduction in depression score [9], an increase in the PPS response during tilt table test (TTT), and a reduction in the number of autonomic nervous system dysfunction (ANSD) risk factors [9]. Furthermore, the increased response in PPS to tilting test after intervention was associated with reduction in the numbers of ANSD risk factors [9], suggesting that the intervention reduced depression score while ANSD was reversed. The application of the same intervention modality to women with breast cancer was found to improve the depressive and quality of life-related symptoms [13], and in a case of healthy working people, it resulted in a clinically meaningful reduction in the cardiovascular and biochemical factors associated with persistent stress [13].

ANSD is associated with increased risk of morbidity and mortality in case of heart diseases independently of traditional risk factors [14], and may be the uniting link between persistent stress, depression, and IHD [3] [15]-[17]. Traditionally, the adrenergic ANS function has been assessed by the pulse and blood pressure response to TTT. A recent study suggested that the PPS response to TTT might also be used to assess the ANS function [9]. Higher PPS response in tilting test subjected to milder ANSD, with the PPS response being closely related to the pulse and blood pressure response [18]. The beta-adrenergic receptors are considered important in the efferent functioning of the ANS, and thus, also in the efferent physiological and psychological stress response [19] [20]. Accordingly, the function of the beta-adrenergic receptors might link depression with resting PPS, the latter as a measure of persistent stress. A pilot study in consecutive out-clinic patients with stable IHD, including 36 users of beta-blockade medication and 62 non-users, showed no significant difference with respect to the PPS measure for these two groups (unpublished observation). Furthermore, these receptors may be engaged in linking depression and the PPS response to TTT, the latter as a measure of ANS function.

*Objectives*: The present study was performed in order to explore the interactions between depression, persistent stress, and ANSD in IHD patients with or without treatment with beta-adrenergic blocking medication. The study focused on the functioning of beta-adrenergic receptors in modulating these associations. This was done as a post-hoc analysis of a large stress intervention trial, testing the anti-depressive effect of reducing the level of persistent stress by non-pharmacological means in patients with stable IHD. These patients were divided into beta-adrenergic receptor blockade medication users or non-users.

## 2. Methods

### 2.1. Participants, Design and Setting

The participants were part of a larger study group (N = 213) participating in a prospective randomized intervention trial [9]. The patients were randomized into the active treatment group (N = 106) and control group (N = 107). Dropouts were 20 and 12, respectively. One hundred and eighty-one patients with resting PPS ≥ 60 at baseline completed the three months randomized trial, in which 86 patients were randomized to the active group and 95 to the control group (see Consort **Figure 1**). The study was conducted in the period from June 2011 to May 2012. The cut point, PPS ≥ 60, for categorization of a patient as being persistently stressed was based on previous consecutive studies on risk factors for impaired health [10] [11].

Since both the active and control groups experienced a significant reduction in PPS during the intervention period, and the intervention was non-pharmacological in nature, the groups were combined into one group for the purpose of the present study, and then further divided into groups of non-users (N = 75) and users (N = 106) of beta-blockade medication. Among the users of beta-blockade medication, four used hydrophilic beta-blockers

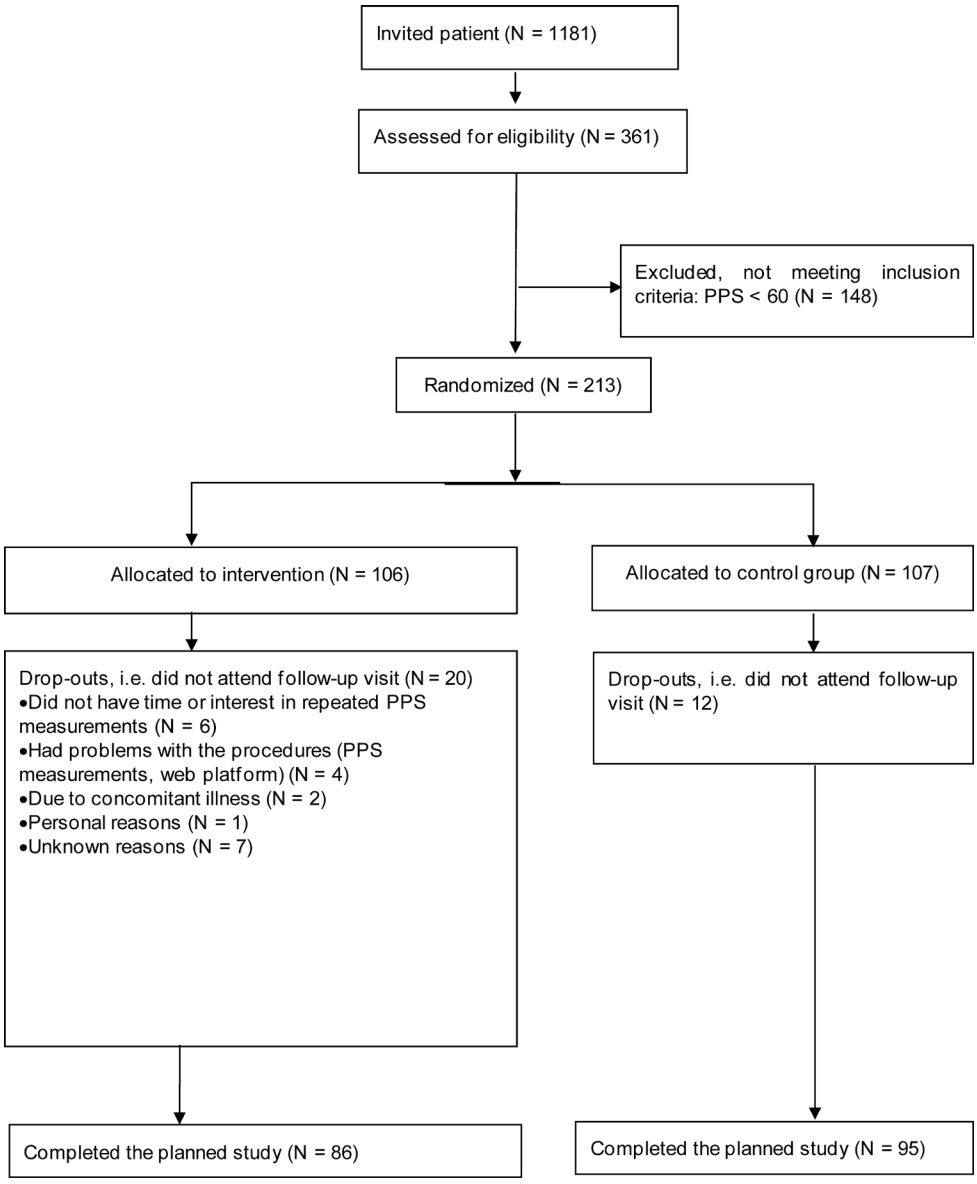


**Figure 1.** Consort diagram.

(e.g., Atenolol), which fails to penetrate the blood-brain barrier, and the remaining 102 used lipophilic beta-blockers that possess the penetrative property. To exclude bias from this difference, the Atenolol users were excluded from the study.

Informed consent was obtained from all the participants after providing oral and written information about the study. The study was conducted at Herlev University hospital, Copenhagen, and was approved by the local ethics committee (ID H-4-2010-135), and registered on www.clinicaltrials.gov (NCT01513824).

## 2.2. Interventions

The stress reduction interventional program was carried out for a three months period, and has previously been reported in detail [9]. It was based on the active group performing a non-pharmacological, self-care stress-reducing program. The program included a home use PPS measurement device, with the instruction to perform daily home PPS measurements and sensory nerve stimulation with the aim to reduce PPS, and with a professional backup, depending on individual demands. The level of persistent stress for the control group was elevated as well, and these patients received the information that their level of persistent stress was elevated and a booklet of general stress management, but no further instructions. The program did not include any medication other than that given at the beginning of the study. Furthermore, it did not include other manoeuvres that might affect the ANS function independently. All medications remained unchanged during the last one month prior to the baseline examination as well as during the entire intervention period.

## 2.3. Outcome Measures

The Major Depressive Inventory (MDI) questionnaire [9] was used to assess the degree of depression. This questionnaire gives a nominal outcome, with a score from 0 to 50. A score ≥20 indicates overt depression, whereas ≥15 is indicative of incipient depression [9]. Resting PPS was used to assess the level of persistent stress [8] [10]-[13] and the PPS and SBP responses to TTT to assess adrenergic ANS function [18].

The variables were recorded before and after three months of non-pharmacological intervention period with the aim to reduce elevated resting PPS. This was performed as a randomized prospective trial that has been previously described in detail [9]. The changes obtained over the time were calculated as post-intervention values (*i.e.*, after three months) minus pre-intervention baseline values. Thus reduction in the variable during the three months resulted in negative values, while an increase resulted in positive values.

In order to evaluate the potential influence of the beta-blockade treatment, the observed changes in effect variables during the three months of intervention for non-users and users were compared. In addition the internal correlations between the changes in the effect variables were compared. The degree of ANSD was measured by the PPS and SBP response due to TTT. However, owing to the very nature of beta-blockade medication, any secondary effect on the SBP response to TTT from a non-medical induced reduction in sympathetic tone would be expected to be blunted by the beta-blockers.

### 2.3.1. Pressure Pain Sensitivity Measurement of the Sternum (PPS)

An algometric instrument (Ull Meter: UllCare Ltd. Lemchesvej 1, DK 2900 Hellerup, Denmark) (Patent No. EP 1750772 B1) was used for measurement of the Pressure Pain Sensitivity of the sternum (PPS) [10], and the same procedure was used when measuring resting PPS and PPS response to TTT. The instrument measures the pressure pain threshold, which is transformed into a logarithmic scale and inverted into a sensitivity scale from 30 to 100 units (a high PPS value indicates high sensitivity, and thus, low pressure pain threshold). For analysis, the mean of two consecutive measurements was used. If the difference between the measurements was more than 10 units, a third measurement was performed, and the result was calculated as the mean of all three recordings. A resting PPS value ≥60 units was used as an arbitrary discrimination point for an elevated level of persistent stress, based on previous findings [10] [11].

### 2.3.2. Tilt Table Test (TTT)

This test induces a transient increase in the sympathetic tone and is usually conducted for diagnostics with respect to adrenergic ANS function [21]. After a 10-minute rest in the supine position, the first and second PPS and SBP measurements were conducted. Then the patient was passively tilted to an angle of 70 degrees and left for at seven minutes rest in that position after which a third PPS and SBP measurement was performed. The average between the first and second PPS and SBP measurements represented the resting PPS and SBP. The dif-

ference between the resting PPS and SBP and third PPS and SBP measurement represented the PPS and SBP response to TTT.

### 2.4. Minimizing Bias

To minimize bias, the following precautions were taken: 1) the PPS device was designed in a manner that made the measurement non-visible to both the instructor and patient until the end of each measurement; 2) the professional instructor measuring PPS and conducting the TTT was blinded to the results of randomization; and 3) before randomization the patients were instructed not to discuss the result of randomization with the research personnel performing the follow-up recordings after the three-month period.

### 2.5. Estimation of Sample Size

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

### 2.6. Statistical Analysis

Non-parametrical statistics were used for group comparison, Wilcoxon two-sample test for between-group analysis, Mann-Whitney one-sample test for with-in the group analysis, and the parametric Pearson's test for correlation analysis. For testing of statistical significance, all randomized patients who concluded the second set of measurements were included. The effect size for depression score was calculated as the difference in mean depression score before and after the intervention for the two groups divided by the standard deviation of the depression score for both groups [22]. A minimum clinical relevant antidepressant effect size for pharmaceutical treatment in the patients with overt depression (MDI score ≥ 20) was found to be 0.3 according to the US Federal Drug Administration [23]. The statistical program, SPSS, version 18 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

#### 2.6.1. Subgroup Analysis

Due to the nature of the intervention, an effect on the depression score may be minor or absent if it is within the normal range at baseline. This issue has previously been discussed in a comprehensive manner [12] [13]. Consequently, a subgroup analysis was included for patients with a depression score at baseline MDI score ≥ 15 [9].

## 3. Results

### 3.1. Baseline

The demographics of the enrolled patients are given in **Table 1**. The beta-blocker non-user and user groups did not differ with regard to age, depression score, resting PPS as well as in changes in the PPS and SBP response to TTT. However, the user group had a male preponderance, had lower resting pulse rate, and a higher frequency of heart failure.

### 3.2. Changes during Three Months Follow-Up (Table 2)

*Depression*: Changes in the depression score differed between the groups: In non-users MDI decreased by 30% ($p = 0.005$) as compared to a non-significant reduction of 4% in the user group (between the groups $p = 0.003$). The anti-depressive effect size was 0.4 for non-users when compared to the users.

In the subgroup of patients with a raised MDI ≥ 15 (N = 33), which is indicative of incipient depression, MDI score in non-users (N = 17) decreased from mean 20.0 (SD: 5.5) before the intervention to 10.9 (SD: 6.9) after intervention ($p = 0.001$), whereas users (N = 16) only demonstrated a non-significant change, from mean 19.6 to 17.8 after the intervention ($p > 0.1$) (between the groups $p = 0.009$). In this subgroup of patients, the anti-depressive effect size was 0.9 for the non-users when compared to users.

*Persistent stress*: Resting PPS was reduced for the total group (N = 177) by a mean of 12 arbitrary units (SD: 21), equal to approximately 15% ($p < 0.0001$). The reduction was independent of the use of beta-blockers, and was similar in both the groups (between the groups $p > 0.1$).

*ANS dysfunction*: The PPS response to a TTT increased by an average of three arbitrary units (SD: 18), equal

**Table 1.** Baseline demographics according to the study groups: non-users or users of beta-blockade medication (−/+Beta-blockage).

| | −Beta-blockade | +Beta-blockade |
|---|---|---|
| *N* | 75 | 102 |
| Male, % | 66 | 78* |
| Age in years, mean (SD) | 62 (9) | 63 (7) |
| Resting PPS, (arbitrary units), mean (SD) | 76.6 (13.0) | 78.3 (13.0) |
| MDI, (arbitrary units), mean (SD) | 9.4 (6.8) | 8.6 (7.5) |
| PPS response to TTT, (arbitrary units), mean (SD) | −5.4 (11.6) | −4.7 (14.2) |
| Systolic blood pressure (SBP) response to TTT, (mmHg), mean (SD) | −3.3 (13.1) | −2.3 (12.3) |
| *Cardiac variables* | | |
| Previous myocardial infarction (%) | 63 | 68 |
| Treated with PCI (%) | 64 | 73 |
| Treated with CABG (%) | 23 | 31 |
| Resting pulse, (beats/min), mean (SD) | 64 (11) | 59 (9)** |
| SBP, (mmHg), mean (SD) | 134 (16) | 1330 (17) |
| Diastolic blood pressure, (mmHg), mean (SD) | 789(9) | 80 (9) |
| *Cardiac risk factors* | | |
| Body Mass Index, ($kg/m^2$), mean (SD) | 27.4 (4.8) | 27.6 (4) |
| Triglyceride, (mmol/l), mean (SD) | 1.3 (0.8) | 1.5 (0.9) |
| Total Cholesterol, (mmol/l), mean (SD) | 4.4 (1.0) | 4.3 (1.0) |
| HDL Cholesterol, (mmol/l), mean (SD) | 1.3 (0.4) | 1.2 (0.4) |
| LDL Cholesterol, (mmol/l), mean (SD) | 2.5 (0.8) | 2.3 (0.8) |
| Current smoker (%) | 2 | 2 |
| *Self-reported co-morbidity* | | |
| Heart failure (%) | 19 | 44*** |
| Chronic obstructive lung disease (%) | 5 | 9 |
| Diabetes (%) | 12 | 15 |
| Previous stroke (%) | 6 | 8 |
| Previous treatment for depression (%) | 16 | 14 |
| *Medication* | | |
| Cholesterol-lowering medication (%) | 85 | 96 |
| Calcium antagonists (%) | 19 | 25 |
| Angiotensin-II antagonist and/or ACE inhibitors (%) | 51 | 59 |
| Diuretics (thiazide or furosemide) (%) | 33 | 35 |

For between-group significance: *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.

to approximately 55% ($p < 0.03$) with no difference between the non-users and users of beta-blocking agents. However, the SBP response to TTT remained unaltered (mean increase of 1 mmHg (SD: 18)), with no significant difference between the two groups (between the groups $p > 0.1$).

### 3.3. Relations between Depression, Persistent Stress, and ANSD (Table 2)

*Depression versus persistent stress*: No significant associations were found between the changes in MDI score

**Table 2.** Results for the non-users and users of beta-blockade medication (−/+Beta-blockade). Change is calculated as Post-intervention value–Pre-intervention value.

| Variable | Number total N (number of Non-users/users) | −Beta-blockade | +Beta-blockade | Significance p value (between-group) |
|---|---|---|---|---|
| *Change during three months of intervention* | | | | |
| MDI, mean (SD) | 177 (75/102) | −2.8 (5.2)* | −0.4 (4.1) | p = 0.003 |
| MDI, mean (SD) for patients with MDI ≥ 15 at baseline | 33 (17/16) | −9.1 (6.5)* | −1.8 (6.2) | p = 0.009 |
| Resting PPS, mean (SD) | 177 (75/102) | −10 (17)* | −14 (24)* | n.s |
| PPS response to TTT, mean (SD) | 177 (75/102) | 3.0 (16) | 2.8 (19) | n.s |
| SBP response to TTT , mean (SD) | 177 (75/102) | 2.4 mmHg | 0.7 mmHg | n.s. |
| *Correlations between changes during 3 months of intervention* | | | | |
| Change in MDI score versus change in resting PPS | 177 (75/102) | −0.09 | −0.08 | n.s |
| Change in MDI score versus change resting PPS for patients with MDI ≥15 at baseline | 33 (17/16) | −0.69* | −0.04 | p = 0.05 |
| Change in MDI score versus change in PPS response to TTT | 177 (75/102) | −0.02 | 0.37* | p = 0.02 |
| Change in MDI score versus change in PPS response to TTT for patients with MDI ≥ 15 at baseline | 33 (17/16) | −0.43 | 0.54* | p = 0.02 |
| Change in resting PPS versus change in PPS response to TTT | 177 (75/102) | 0.37* | 0.59* | n.s |
| Change in resting PPS versus change in SBP response to TTT | 177 (75/102) | 0.32* | + 0.13 | P = 0.004 |

For between-group significance: Exact "p" value is presented; n.s. = non significant. For within group significance: *= $p < 0.05$.

and resting PPS, neither in the total group nor in the two subgroups of beta-blocker users and non-users. In contrast to the total groups of patients, the reductions in MDI score in the subgroup of patients with MDI ≥ 15 (N = 33) were significantly associated with reductions in resting PPS in the non-user group (r = 0.69, intra-group p = 0.007), but not in the user group (r = 0.04, p > 0.1) (between the groups p = 0.05).

*Depression versus ANSD*: Looking at the total group (N = 177), the reduction in MDI during the three months of intervention was associated with a reduction in the PPS response to a TTT (r = 0.19; p = 0.02). This positive correlation was driven only by the beta-blocker users with a significant and positive association (r = 0.37) while no correlation was found in the non-user group (r = 0.02) (p > 0.01). Considering the most depressed patients, the subgroup of the patient having MDI ≥ 15, the beta-blocker users demonstrated an even stronger positive association between the reductions in MDI and PPS responses to a TTT (r = 0.54, p = 0.04). In contrast, this association now was negative with regard to the non-users (r = −0.43, p > 0.1) (between the groups p = 0.02) (**Figure 2**), indicating that in the non-users with an elevated MDI score, the reduction in MDI over time was associated with an increase in the PPS response to a TTT.

*Persistent stress versus ANSD*: Reductions over three months in resting PPS were associated with an increase in the PPS response to TTT both in the total group (r = −0.50, p < 0.0001) (N = 177) (**Figure 3**) and in the two subgroups (r = −0.37 among the beta-blocker non-users, and r = −0.59 among users, both intra-group p < 0.002). Thus, this association was present for both the groups, and not inhibited in the user group. In contrast, the change in SBP due to TTT demonstrated a different pattern. During the three months of intervention, the reduction in resting PPS was only associated with an increase in the beta-blocker non-user group (r = −0.32; p = 0.007), and not in the user group (r = 0.13, p > 0.1) nor in the total group (N = 177) (r = −0.03; p > 0.1). The different pattern for users and non-users was highly significant, *i.e.*, between the groups (p = 0.004). This means, that in the case of the non-users, the larger magnitude of the reduction in resting PPS, the larger the increase in SBP response to tilting.

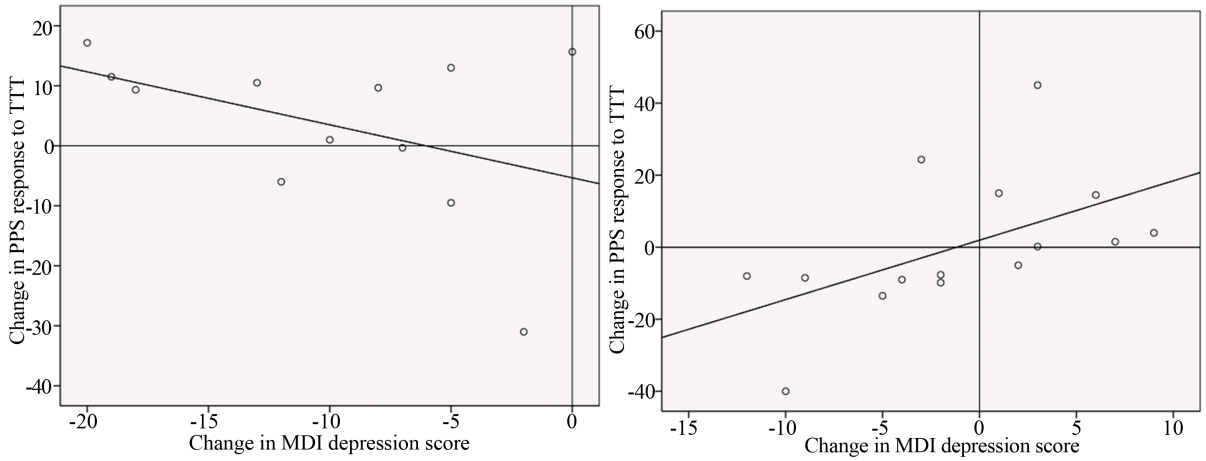


**Figure 2.** Correlation between the changes in MDI depression score and changes in PPS response to a tilt table test during three months of intervention for non-users (**Figure 2(a)**) and users (**Figure 2(b)**) of beta-blockade medication for the subgroup of patients with elevated depression score (MDI score ≥ 15) (between-group difference p = 0.02) (N = 27). (a) Correlation between the changes in MDI depression score and changes in PPS response to a tilt table test for the non-users of beta-blockade medication (r = −0.43) (p > 0.1) (N = 12); (b) Correlation between the changes in MDI depression score and changes in PPS response to tilt table test for the users of beta-blockade medication (r = +0.54) (p = 0.04) (N = 15).

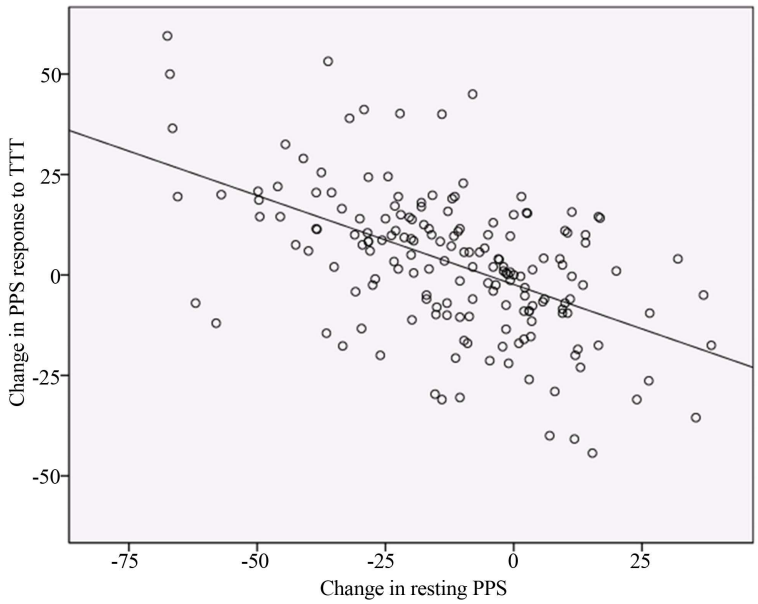


**Figure 3.** Correlation between the changes in resting PPS and changes in PPS response to tilt table test during three months of intervention (change is calculated as post-intervention value–pre-intervention value) (r = −0.50) (p < 0.0001) (N = 177).

## 4. Discussion

### 4.1. Non-Users

In patients with IHD, the non-users of adrenergic beta-receptor blockade medication showed a clinically relevant anti-depressive effect from a three months non-pharmacological intervention program. This was not the case among the beta-blocker users. In the subgroup of patients with an elevated depression score (MDI score ≥ 15), the difference was even more pronounced. Statistically significant between-group differences were found between the non-users and users with respect to the correlations between the changes in depression score versus the changes in resting PPS as the measure of persistent stress. The same between-group differences were found

between the changes in depression score and the changes in the PPS response to TTT as the measure of ANS function. Furthermore, the reduction in resting PPS was significantly associated with an increase in SBP response to TTT only in case of the non-users, with a significant difference to the user group.

Virtually in the group of non-users, there was a decrease in the levels of perceived depression (*i.e.*, a decrease in the MDI score) and persistent stress (*i.e.*, a decrease in resting PPS), with partial restoration of ANSD (*i.e.*, an increase in the PPS and SBP response to TTT).

### 4.2. Users

In contrast, users demonstrated a different pattern in which no reduction was observed in the perceived level of depression. However, the level of persistent stress was reduced, and the ANSD was restored as measured by the PPS response to a TTT. When measuring the ANS function by the means of SBP response to TTT, no restoration of ANSD was obtained.

These overall findings suggested that the level of persistent stress was reduced in the case of the non-users, and this reduction was associated with restoration of ANSD, which probably led to the further reduction of the perceived level of depression. However, the reduction in the level of persistent stress remained stable in case of the users, but the beneficial effect on the perceived level of depression disappeared. Also, while measuring the restoration of ANSD, the present findings demonstrated a potential distortion between the PPS and SBP response to TTT. Thus, the change over time in the PPS response to TTT remained similar for both the users and non-users, whereas the association between the reduction in resting PPS and change in SBP response to TTT vanished among the users. Accordingly, the present data might suggest that the beta blockage medication inhibits the efferent effects of the reduction of an elevated PPS measure at the level of transmission at the beta-receptor, and thus, the effect of ANSD restoration on the SBP response to TTT and depression reduction. Consequently, the regulation of resting PPS and PPS response to TTT seems to be superior in the ANS hierarchy than the SBP response to TTT and the individually perceived level of depression, both of which seems to be inferiorly located to the beta-receptor in the ANS hierarchy. These speculations obviously call for further studies.

It is known that the beta blocker treatment may induce depression as one of its side effects [24]. The findings of the present study suggest another role of beta blockade in depression. Beta-blockers may inhibit the anti-depressive effect of a non-pharmacological stress-reducing program that is a novel and potentially clinical important observation. Whether it is a general phenomenon that beta-blocker treatment counteracts the effect of more specific anti-depressive treatment inclusive of pharmacological treatment is not known to the best of our knowledge. However, as mentioned above, the present findings suggest that the beta-adrenergic receptor may be engaged in the association between the depression and persistent stress in patients with IHD, which has also been suggested by other researchers [3] [4] [15]-[17]. This interpretation is furthermore supported by the present findings of a positive correlation between the reduction in both resting PPS and depression score only among the non-users.

The demonstrated positive association between the reduction in depression score during the three months of intervention and a similar reduction in the PPS response to TTT was counter-intuitive but was only found among the beta-blocker users. Such an association might simply be due to the fact that beta-blocker treatment abolished the effect on depression score when resting PPS was reduced, and thus, distorted the association. In the subgroup of patients with an elevated MDI score, the reduction over time was associated with an increase in the PPS response to TTT, and thus, to a lesser degree of ANSD. This is another clue to the suggestion that the beta-adrenergic receptors are engaged in the association between the ANS function and depression. It also might be an argument for the fact that the anti-depressive effect from alleviation of ANS dysfunction and concomitant reduction of an elevated level of persistent stress in IHD patients is mediated by the beta-adrenergic receptor.

Our findings suggest an internal association between the persistent stress, depression, and ANS dysfunction in patients with stable IHD. When an elevated level of persistent stress was reduced by non-pharmaceutical means, the use of beta-blockers had an inhibiting effect on the concomitant reduction in depression score. In addition, the use of beta-blockers was similarly found to inhibit the associations between the alleviation of ANS dysfunction and reduction of the depression score. This latter association was significantly stronger than the association between the reductions in the level of persistent stress and depression score. The use of beta-blockers did not influence the reduction of persistent stress, the restoration of ANS dysfunction or the association between the two. Accordingly, the present findings may suggest that the association between depression and stress is indirect,

with ANS as the intermediate link.

The present findings are in line with others suggesting ANS to be an important link between depression and persistent stress [3] [15], as well as between depression and IHD [4]. It has been found that pharmacological anti-depressive treatment was unable to relieve ANS dysfunction [25]. In combination with the present findings, this might explain the lack of effect of the anti-depressive medication on cardiovascular variables in the IHD patients [7].

### 4.3. Strengths and Weaknesses

The strengths of the study were: i) the large number of persons studied, ii) the use of a well established experimental procedure with a fully controllable stimulation of ANS, and iii) the previously tested PPS discrimination point for an elevated level of persistent stress [3] [23]. It should be noted that the present study addresses only the link between depression and IHD from the perspective of stress and ANS function. Furthermore, due to the non-randomized design with respect to the use of beta-blocker, the patients who used beta-receptor blocking medication differed from the non-users with respect to gender (more males) and prevalence of heart failure that might represent a potential bias. However, we did not believe that these differences confounded the outcomes of the present study. Thus, the patients with heart failure were stable and up-titrated in anti-congestive medication, and in general, had a high performance, being in New York Heart Association class I-II. Further, there were no differences with respect to a degree of depression, resting PPS, and PPS and SBP response to TTT at the baseline. The present study is a post-hoc study, and the results should be accordingly interpreted with caution. This limitation was addressed by adding the change into the analysis regarding the SBP response to TTT. It was found that when an elevated resting PPS was reduced, the association to the secondary effect on the SBP response to TTT was significantly influenced by the beta-blockade medication. For e.g., the correlation was found to be positive and significant among the non-users that was absent among the users of beta-blockade medication, with a significant between-group difference. Such a secondary effect on SBP response to TTT was mediated by a change in the sympathetic tone that was influenced by the very nature of the beta-blocker medication. The finding of a confirmation of this association supports the overall conclusions as well as the association between PPS and physiological stress.

It should also be underlined that with respect to the possible influence of beta-blockers on PPS measure, the study was a hypothesis confirming study, based on our previous observation as mentioned in the introduction. However, with respect to the possible influence from beta-blockade medication on depression, the study is hypothesis generating, only. In order to study an association that includes a reduction of the depression score, the reduction may be minor or absent if the depression score is within normal range at baseline. This has already been discussed in a comprehensive manner [26]. In the present study, the effects of beta-blockers that are observed in the group as a whole are more pronounced when analysed in the subgroup of patients with an elevated depression score at baseline. This may be regarded as a strength.

With respect to a possible clinical relevance of the achieved anti-depressive effects in the non-user group the effect size was 0.4 for the group as a whole with a mean MDI depression score of 9.4 at baseline, whereas the effect size was 0.9 among the subgroup of patients with a score $\geq 15$ at baseline. This may be compared to the minimum clinical relevant antidepressant effect for pharmacological treatment of patients with overt depression (e.g. MDI score $\geq 20$ at baseline) which was 0.3 according to the US Federal Drug Administration [26]. As such, it may be concluded that the achieved clinical effect size by this non-pharmacological intervention was clinically relevant for IHD patients in general, and even more so for the patients with an elevated depression score.

The future studies based on the present findings might accommodate the fact regarding the existence of beta-adrenergic receptors in the brain at a location at which an improved ANS function may exercise an anti- depressive effect. Although a confirmation of the existence of beta-adrenergic receptors in the brain has proven to be unusually difficult, it seems likely that such receptors are located in the brain [26] and with possible links to depression related areas in the hippocampus and prefrontal cortex [27].

Little is known about stress resilience, for e.g., when and how stress shifts from being beneficial and protective to becoming deleterious [28]. The adult human brain is highly resilient and adaptable and engaged in adaptive structural plasticity in the hippocampus, amygdala, and prefrontal cortex [29]. However, the full understanding of the biological factors involved and identification of useful markers of resilience are missing [30]. As such, the resting PPS measure and the PPS response to a TTT may represent new ways to measure stress and

stress resilience, and the tested intervention may represent an intervention, which alleviates ANS dysfunction while relieving the depression in the IHD patients [3] [23].

## 5. Conclusion

In conclusion, the study suggests that the beta-adrenergic receptor represents a new and clinically relevant key to the understanding of the association between depression, persistent stress, and ANS dysfunction in IHD.

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## Disclosures

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. As such he had no access to the study site (Herlev Hospital) during the entire study period. No other disclosures were reported.

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