The role of N-terminal pro-B-type natriuretic peptide in psychosocial functioning of depressed coronary heart disease patients

Dissertation

zur Erlangung des humanwissenschaftlichen Doktorgrades

in der Medizin

der Georg-August-Universität Göttingen

vorgelegt von

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aus Frankfurt am Main

Göttingen, 2019

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Tag der mündlichen Prüfung: 03.12.2019

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Hiermit erkläre ich, die vorliegende Arbeit eigenständig angefertigt und keine anderen als die von mir angegeben Quellen und Hilfsmittel verwendet zu haben.

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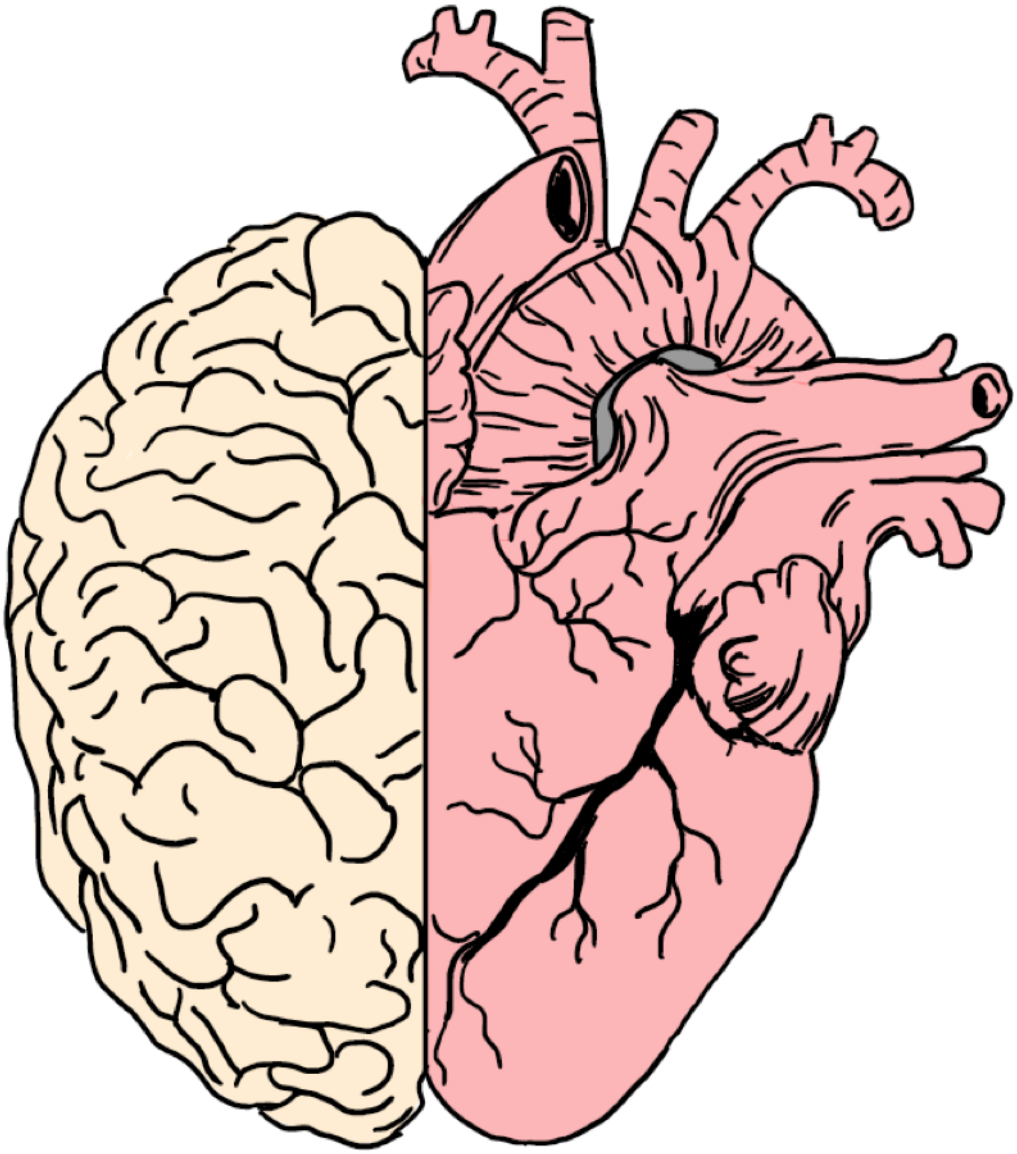

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List of abbreviations

ACTH	Adrenocorticotropic Hormone
ANP	Atrial Natriuretic Peptide
AP	Angina Pectoris
BNP	B-type Natriuretic Peptide
CAD	Coronary Artery Disease
CCK-4	Cholecystokinin Tetrapeptide
cGMP	Cyclic Guanosine Monophosphate
CHD	Coronary Heart Disease
CNP	C-type Natriuretic Peptide
CRH	Corticotropin-Releasing Hormone
DIAST-CHF	Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Heart Failure
DNP	D-type Natriuretic Peptide
DS-14	14-Item Type D Scale
EHIS	European Health Interview Study
FQCI	Freiburg Questionnaire for Coping with Illness
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	Glycated Hemoglobin
HPA axis	Hypothalamic-Pituitary-Adrenal axis
IL-1	Interleukin-1
IL-6	Interleukin-6
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
MQ	Maastricht Questionnaire
mRNA	Messenger Ribonucleic Acid
NE	Norepinephrine
NPPB-gene	Natriuretic Peptide B-gene
NPR-A	Natriuretic Peptide Receptor-Type A
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
NYHA	New York Heart Association

PHQ	Patient Health Questionnaire
RAAS	Renin-Angiotensin-Aldosterone-System
SF-36	Medical Outcomes Short Form Health Survey
SPIRR-CAD	Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease
STEMI	ST Elevation Myocardial Infarction
TNF-α	Tumor Necrosis Factor-alpha

Abstract

Patients suffering from coronary heart disease (CHD) are often affected by mental health issues, such as depression, anxiety and low quality of life. This affects the progression of their heart condition negatively. Natriuretic peptides might play a role in the patients' mental adaptation to CHD. Studies on A-type natriuretic peptide (ANP) found an anxiolytic effect of this peptide in humans. B-type natriuretic peptide (BNP) was also shown to have anxiolytic properties in an animal model but results in humans were so far inconclusive. To determine the role of BNP with regard to mental health in CHD patients, data from a large multicenter trial were analyzed. Based on previous studies it was hypothesized that high levels of BNP would be negatively associated with the patients' physical state, but positively with their mental health.

The hypotheses were tested with cross-sectional data of 529 mildly to moderately depressed CHD patients. N-terminal proBNP (NT-proBNP) was assessed at baseline together with a variety of psychometric tests and somatic data from medical records. Mental health was assessed repeatedly over 24 months using standardized questionnaires. The association of NT-proBNP and anxiety was subsequently assessed in more detail using longitudinal data of 308 patients with baseline NT-proBNP measures and anxiety measures from baseline to 24-months follow-up.

Linear regression models adjusted for sex, age, and physical functioning showed significant negative associations of baseline NT-proBNP with depression, anxiety, vital exhaustion, negative affectivity, and depressive coping but positive associations with self-rated mental health, despite worse physical functioning. Linear regression models of the longitudinal data adjusted for sex, age, body mass index, and physical functioning showed that baseline NT-proBNP was a significant predictor for anxiety at baseline, 1, 6, 12, 18, and 24 months. Surprisingly, a linear mixed model analysis showed a significant time*NT-proBNP*sex interaction when NT-proBNP as fixed factor was dichotomized into the lowest vs. the three highest quartiles. In this sample, women with very low levels of NT-proBNP had persisting high levels of anxiety while in all other groups anxiety decreased over the investigated period of two years. The results indicate that (NT-pro)BNP is associated with the patients' overall mental health and anxiety over two years. However, different pathways for men and women seem to be present. These results are discussed, and possible mechanisms are suggested.

Zusammenfassung

Patienten, die an koronarer Herzkrankheit (KHK) leiden, sind häufiger von psychischen Problemen wie Depression, Angstzuständen und niedriger Lebensqualität betroffen. Dies beeinflusst den Verlauf ihrer Herzerkrankung negativ. Natriuretische Peptide könnten eine Rolle dabei spielen, wie KHK-Patienten psychisch auf ihre Erkrankung reagieren. Studien an A-Typ natriuretischem Peptid (ANP) fanden eine anxiolytische Wirkung dieses Peptids beim Menschen. B-Typ natriuretisches Peptid (BNP) zeigte auch in einem Tiermodell anxiolytische Eigenschaften, Ergebnisse beim Menschen waren bisher jedoch nicht eindeutig. Um die Rolle von BNP in der psychischen Gesundheit von KHK-Patienten zu bestimmen, wurden Daten aus einer großen multizentrischen Studie analysiert. Vor dem Hintergrund der bestehenden Studienlage wurde die Hypothese aufgestellt, dass hohe BNP-Werte negativ mit dem körperlichen Zustand der Patienten, aber positiv mit ihrer psychischen Gesundheit korrelieren.
Die Hypothese wurde mit Querschnittsdaten von 529 leicht bis mittelgradig depressiven KHK-Patienten getestet. N-terminales proBNP (NT-proBNP) wurde zu Studienbeginn zusammen mit einer Vielzahl von psychometrischen Test- und somatischen Daten aus der Krankenakte erhoben. Die psychische Gesundheit der Patienten wurde regelmäßig über 24 Monate hinweg mit standardisierten Fragebögen untersucht. Im Anschluss wurde der longitudinale Zusammenhang von NT-proBNP und Angst detaillierter anhand von Daten von 308 Patienten mit NT-proBNP Messungen zu Studienbeginn und Angstmessungen von Studienbeginn (Baseline) bis zum letzten Testzeitpunkt nach 24 Monaten untersucht.
Lineare Regressionsmodelle, adjustiert für Geschlecht, Alter und körperliche Funktionsfähigkeit, zeigten signifikante negative Zusammenhänge von NT-proBNP mit Depression, Angst, vitaler Erschöpfung, negativer Affektivität und depressiver Krankheitsbewältigung sowie positive Korrelationen mit selbsteingeschätzter psychischer Gesundheit trotz schlechterer körperlicher Funktionsfähigkeit. Lineare Regressionsmodelle der Längsschnittdaten, adjustiert für Geschlecht, Alter, Body Mass Index und körperliche Funktionsfähigkeit, zeigten, dass die Baseline NT-proBNP Werte ein signifikanter Prädiktor für Angstwerte der Baseline, 1, 6, 12, 18 und 24 Monaten war. Überraschenderweise zeigte ein gemischtes lineares Modell eine signifikante Zeit*NT-proBNP*Geschlecht-Interaktion, wenn NT-proBNP als fester Faktor in das niedrigste

vs. die drei höchsten Quartile dichotomisiert wurde. In dieser Stichprobe hatten Frauen mit sehr niedrigen NT-proBNP-Werten anhaltend hohe Angstwerte, während in allen anderen Gruppen die Angstwerte über den Testzeitraum von zwei Jahren abnahmen. Die Ergebnisse deuten darauf hin, dass (NT-pro)BNP mit der allgemeinen psychischen Gesundheit der Patienten und dem Verlauf der Angst über zwei Jahre zusammenhängt. Allerdings scheinen unterschiedliche Wirkmechanismen für Männer und Frauen zu bestehen. Diese Ergebnisse werden diskutiert und mögliche Mechanismen erläutert.

1 Introduction

Since pre-Christian time, the heart has been considered the home of emotions, connecting heart and psyche with each other. This is also manifest in everyday language where the heart is associated with feelings, such as "warm-hearted", "change of heart", or "heartbroken". With increasing anatomical insight and technical advancements in medicine the heart was viewed more and more as a mere pump and the heart-psyche-interaction got limited to the heart receiving signals, e.g. to increase the heart rate in states of physical or mental stress.

This view began to be challenged with the discovery of the endocrine function of the heart. Experiments showed that the dilation of the atrium by a balloon and the intravenous injection of extracts from atrial myocytes induced diuresis and natriuresis (Henry et al. 1956; de Bold et al. 1981; de Bold and Salerno 1983). In subsequent years a polypeptide named atrial natriuretic factor, later atrial natriuretic peptide (ANP), was isolated and sequenced from rat and human atria.

The first connection to the central nervous system was laid in 1984 when ANP expression was found in the hypothalamus (Tanaka et al. 1984). Another member of this peptide family, B-type natriuretic peptide (BNP), was first discovered in porcine brain and is thus also referred to as brain natriuretic peptide (Sudoh et al. 1988). These discoveries were a first step towards scientific evidence for a bidirectional interaction of heart and psyche. Years after the first findings, a possible role of ANP in panic attacks and an anxiolytic effect of ANP were described in multiple studies (Kellner et al. 1995; Ströhle et al. 2001; Wiedemann et al. 2001). The anxiolytic function of ANP is another step towards a biological explanation for the long-thought bidirectional heart-psyche-interaction. While ANP has been studied more extensively, little is known about the role of BNP in emotion regulation and its effect on anxiety.

In the following, a brief overview of coronary heart disease (CHD) and mental health issues in CHD patients will be given. Subsequently, natriuretic peptides will be explained, with a focus on BNP and their role in CHD and recent findings about the bidirectional association of all three factors, i.e. the role of ANP and BNP with regard to mental health of CHD patients will be depicted.

1.1 Coronary heart disease

Acute and chronic ischemic heart diseases are the most common cause of death worldwide (Robert-Koch-Institut 2015; Nowbar et al. 2019). In Germany approximately 130.000 people die every year from CHD (interchangeably used with coronary artery disease (CAD)) and its complications such as myocardial infarction and heart failure (Deutsche Herzstiftung e.V. 2018). CHD can manifest in three stages: 1) silent, 2) stable, and 3) unstable. While the silent stage is asymptomatic, the second stage is characterized by stable angina pectoris (AP). Patients often report AP as a tight, strangling feeling in their chest, or as pain or pressure behind the sternum. However, discomfort can also be located in the back, arms, or the epigastric region and intensity varies from sharp pain to only slight discomfort or no pain at all. In stable AP, symptoms occur during physical exercise or emotional stress and usually disappear within five minutes. The third stage includes unstable AP, i.e. symptoms of AP at rest or sleep, which last longer and can get worse over time. Unstable AP can also lead to ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI).

The pathogenesis of all forms of CHD is the hardening of the coronary arteries, called atherosclerosis. This inflammatory process is initiated by low density lipoproteins (LDL), fluctuations of blood pressure, or the effects of tobacco, among other factors, which injure the walls of the coronary arteries. Inflammation activates macrophages (a subgroup of immune cells), which produce growth factors and cytokines (e.g. interleukin-1 (IL-1), interleukin-6 (IL-6), or tumor necrosis factor-alpha (TNF-α)). Cytokines then induce the proliferation of smooth muscle cells in the coronary arteries, which disturb the regulation of the width of the blood vessels. Moreover, cytokines facilitate the development of unstable plaques. These are highly inflammatory accumulations of cholesterol in the vascular walls, that decrease blood flow to the heart muscle and can thrombose or embolize when ruptured. The resulting decrease in oxygenation of the heart muscle can lead to myocardial infarction or sudden cardiac death (Lusis 2000; Herrmann-Lingen et al. 2014).

The sclerosis and narrowing of the coronary arteries can present in many different ways and with varying intensity. Cardinal symptoms of CHD are stable and unstable AP and symptoms often start when the stenosis reaches a critical level around 75%. Of-

ten symptoms are triggered by physical or mental stress but also arise when a plaque ruptures, leading to acute coronary syndrome (Herrmann-Lingen et al. 2014).
Due to improved health behaviors (e.g. non-smoking, physical activity, healthy diet) and improved cardiometabolic risk profiles of patients (blood pressure, glycated hemoglobin (HbA_{1c}), LDL) as well as improved care of acute myocardial infarction, the incidence rate and mortality has decreased in Germany. The most recent European Health Interview Survey (EHIS), conducted in 2014/2015, estimates the overall 12-month-prevalence of CHD in Germany at 3.7% for women and 6.0% for men. These rates increase up to 16.0% in women and 24.1% in men 75 years of age and older. The life-time prevalence of CHD is 6.6% for women and 9.6% for men (Robert-Koch-Institut 2015; Busch and Kuhnert 2017).

1.2 Mental health and coronary heart disease

CHD not only affects the heart and the body, but also the mental state and quality of life of patients. Anxiety, depression and psychological distress are very common in CHD patients and influence the course of the disease (Herrmann-Lingen and Buss 2002; Barth et al. 2004; van Melle et al. 2004; Albus et al. 2018). It is likely that the mental health of CHD patients is also influenced by neurobiological processes that modulate psychological adaptation.
Cardiac patients have a prevalence of 20-50% for depressive symptoms and up to 29% for major depressive disorder (Bankier et al. 2004; Albus et al. 2018). Depression alone, but especially the combination of depression and anxiety, increases the risk of mortality in CHD (Parissis et al. 2008; Watkins et al. 2013). Even in people without a diagnosed heart disease depression significantly increases the risk for CHD and myocardial infarction by about 30%, independent of other risk factors (Gan et al. 2014). This increase in morbidity and mortality in depressed people can be explained by a combination of multiple factors (Herrmann-Lingen et al. 2014). First, on a physiological level, inflammatory processes can facilitate plaque destabilization, as described above, and heightened coagulation increases the risk of thrombosis. Moreover, depression leads to changes in the hormonal stress axis (Wiedemann et al. 2000) and disrupts the autonomic balance, which is associated with reduced heart rate variability and arrhythmia (Carney and Freedland 2008). Second, depressed CHD patients are less likely

to adhere to medical advice, including medication, and are less motivated to join rehabilitation programs. Third, the decreased energy level during depressive episodes and the anti-depressive effects of nicotine and overeating often hamper necessary lifestyle changes, such as smoking cessation, a healthy diet, and physical activity.

Patients often experience the comorbid depression as more burdensome than the somatic changes of CHD. Especially patients with maladaptive personality traits such as type D personality are at high risk of developing a depression. This personality type is characterized by the combination of negative affectivity and social inhibition (the inability to communicate emotions in relationships) and has been associated with increased mortality in CHD patients (Grande et al. 2012). 35-60% of cardiac patients also commonly describe states of excessive fatigue, decreasing energy and feeling dejected or defeated. These symptoms are summarized as vital exhaustion, which is a strong risk factor for future myocardial infarction, independent of other risk factors (Appels and Mulder 1988; Kop 1999). The somatic and mental consequences of CHD collectively reduce the patients' quality of life, a subjective, multidimensional construct that can be divided into a physical and a mental domain (Ware and Sherbourne 1992). In patients with a cardiac disease quality of life is markedly decreased and correlates more with the subjective New York Heart Association (NYHA) class than with somatic markers of disease severity, such as left ventricular ejection fraction (LVEF) (Schowalter et al. 2013).

Due to the vital meaning of the heart, cardiac diseases are commonly accompanied by states of anxiety. This is important and potentially lifesaving as it urges patients to seek medical help and adhere to health behaviors. This is supported by the finding that in CHD patients without myocardial infarction or with less severe CHD, anxiety was found to be a protective factor against mortality and major adverse events (Meyer et al. 2010; Meyer et al. 2015a). However, other studies found contrary results, with anxiety being an independent risk factor for increased morbidity and mortality (Roest et al. 2010; Watkins et al. 2013), probably by increasing heart rate, blood pressure, and the increased likelihood of arrhythmia (MacMahon and Lip 2002; Herrmann-Lingen et al. 2014). The physiological effects during states of anxiety (e.g. increased heart rate) can in turn further increase acute anxiety leading into a vicious circle.

1.3 Natriuretic peptides

A- and B-type natriuretic peptide are known to counteract the volume overload in chronic hypertension and heart failure. They lower the blood pressure by inducing vasodilation and stimulating the excretion of water and sodium and have a wide range of neuromodulatory effects. BNP is stored with ANP in atrial granules. Moreover, volume overload stretches the ventricular walls, which increases the transcription of BNP (Potter et al. 2006; Hodes and Lichtstein 2014). In addition to mechanical stretch of the myocardium, there are multiple factors that trigger BNP release, including the sympathetic nervous system, vasopressin, endothelin, and angiotensin II (Luchner and Schunkert 2004; Meyer and Herrmann-Lingen 2017).

These factors activate the transcription factor GATA-4, which binds to the promoter of the BNP-encoding gene, which activates the natriuretic peptide B (NPPB)-gene located on chromosome 1p36.2. Subsequently, the mRNA transcript is expressed as 134 amino acid prepro-BNP. Once secreted, a 26 amino acid sequence is cleaved from the N-terminus, resulting in $\text{proBNP}_{1\text{-}108}$. In a last step, furin (a membranous serine-protease) cleaves proBNP into the biologically inactive 76 amino acid long N-terminal proBNP (NT-proBNP) and the active $\text{BNP}_{77\text{-}108}$ (Potter et al. 2006; Volpe et al. 2016; Meyer and Herrmann-Lingen 2017).

Both ANP and BNP bind to the NPR-A receptor which increases the intracellular cyclic guanosine monophosphate (cGMP) production inducing vasodilation of the smooth muscle cells and a shift of intraventricular fluid to reduce blood pressure (Stoevesandt 2008). Natriuretic peptides are a natural antagonist of the renin-angiotensin-aldosterone-system (RAAS) and inhibit the release of renin in the kidney. Moreover, they inhibit the sympathetic nervous system, the release of aldosterone in the adrenal gland, and the release of vasopressin in the pituitary gland; hormones that increase the blood volume and thus blood pressure (Luchner and Schunkert 2004; Hodes and Lichtstein 2014; Volpe et al. 2016). As vasopressin and the sympathetic nervous system promote the release of natriuretic peptides, this system acts as a humoral feedback-loop (Inoue et al. 1988).

In addition, natriuretic peptides inhibit the hypothalamic-pituitary-adrenal axis (HPA axis) in the locus coeruleus, the pituitary gland, the hypothalamus, and the adrenal cortex. The resulting inhibition of norepinephrine (NE), corticotropin-releasing hormone

(CRH), cortisol, and adrenocorticotropic hormone (ACTH) counteracts the physiological response to physical and psychological stress (Hodes and Lichtstein 2014). In addition, natriuretic peptides stimulate vagal afferents, which contribute to internal stress regulation (Hansson 2002; Yuan and Silberstein 2016). BNP is used more commonly as a diagnostic and prognostic marker of cardiac dysfunction than ANP, as it is mainly released from the ventricles. BNP plasma levels correlate with the severity of the disease, however for clinical diagnostics and research purposes the levels of the more stable N-terminal prohormone (NT-proBNP) are used (Ponikowski et al. 2016) since it does not show severe fluctuations in response to exercise or time of day (Ponikowski et al. 2016).

1.4 Current state of research on natriuretic peptides and mental health in coronary heart disease patients

As described above, natriuretic peptides reduce sympathetic tone and affect the activity of the HPA axis (Wiedemann et al. 2000; Luchner and Schunkert 2004), thus antagonizing the neurohumoral activation induced by reduced heart function and the sympatho-excitatory effects of anxiety. Yet, their role in mental health is still not well understood. Multiple studies associated ANP with anxiety and showed its anxiolytic-like function. Early study results revealed an increased secretion of ANP in lactate-induced panic attacks (Kellner et al. 1995) and an attenuation of symptoms of cholecystokinin tetrapeptide (CCK-4)-induced panic in panic disorder patients pretreated with ANP and healthy participants that exercised for 30 minutes (Ströhle et al. 2001; Ströhle et al. 2006). Moreover, an independent negative relation of plasma pro-ANP and anxiety was found in a mixed sample of patients with heart failure and controls (Herrmann-Lingen et al. 2003), and in alcohol dependence and withdrawal (Koopmann et al. 2014; von der Goltz et al. 2014). The association of ANP and anxiety is especially striking as the emotional and physiological arousal that accompanies states of anxiety is specifically detrimental for a weakened heart, as in CHD or heart failure patients.

In contrast to the variety of studies dealing with the role of ANP in CHD, only few studies addressed the association of BNP with psychosocial factors. Anxiolytic effects of BNP were first shown in an animal model (Bíró et al. 1996). In patients at risk

for heart failure or diagnosed with heart failure, no consistent results were found. One study reported an inverse relation of BNP and anxiety; however, BNP was not an independent predictor (Meyer et al. 2015c). Other studies found a positive association (Tsuchihashi-Makaya et al. 2009) or no association of BNP and self-rated anxiety (Brouwers et al. 2012). In a sample of 85 CHD patients, no association between anxiety disorder and NT-proBNP was found (Bankier et al. 2009).

Studies on BNP and depression point towards a positive association (Bunevicius et al. 2006; Politi et al. 2007; Brouwers et al. 2014). However, these studies used different patient populations, including patients with major depressive disorder, brain tumor, and heart failure. Results on other measures of mental health are scarce. Studies found a positive association of ANP with vital exhaustion (Herrmann-Lingen et al. 2003), no association of BNP with type D personality (Pelle et al. 2010), and a negative association of BNP with quality of life (Laederach-Hofmann et al. 2007).

2 Research question

The cardiovascular system is complexly involved in the interaction of heart and psyche. The heart not only receives psychobiological signals, e.g. via the sympathetic nervous system, the vagus nerve, and stress hormones, but is also an endocrine organ itself. Natriuretic peptides relieve the heart by decreasing its pre- and afterload, but studies also point towards an anxiolytic effect. A replication of these findings would support an adaptive model of heart-psyche-interaction, which contributes to psychological adaptation in cardiac disease. The goal of the present work is to explore the role of (NT-pro)BNP with regard to the mental health of mildly to moderately depressed CHD patients.

The relationship between CHD and psychosocial state seems to be reciprocal. CHD limits the physical functioning of patients and thereby decreases their quality of life. Moreover, depression and anxiety, as common comorbidities of CHD, further impact the patients' quality of life negatively. Depression, anxiety, and low quality of life in turn increase the risk for future adverse cardiac events and worsen the cardiac prognosis. Natriuretic peptides seem to play an important role in counteracting this vicious circle on a physiological as well as psychological level. Therefore, the goal of the presented secondary analyses is to shed more light onto the relationship of (NT-pro)BNP with the psychosocial status in CHD patients to broaden the understanding of this natriuretic peptide and its role in emotion regulation.

In line with the hypothesis that (NT-pro)BNP has a positive effect on the psychological well-being of CHD patients, a negative association of anxiety, depression and vital exhaustion with NT-proBNP is expected. As NT-proBNP is a marker of illness severity, higher levels of NT-proBNP are expected to correlate negatively with patients' physical quality of life, but positively with patients' psychological quality of life. With better well-being and higher psychological quality of life, patients with high levels of NT-proBNP are expected to show more functional coping with their illness. Based on previous findings with ANP, baseline BNP is expected to be associated with a decline of anxiety over time.

3 Methods

To test the proposed hypotheses, NT-proBNP was entered in a cross-sectional model as predictor of anxiety, depression, quality of life, vital exhaustion, coping with illness, and social inhibition and negative affectivity, i.e. type D personality. Subsequently, the longitudinal association of anxiety and NT-proBNP was assessed in more depth with baseline NT-proBNP samples and six anxiety measures. Measurements were taken at baseline and after 1, 6, 12, 18, and 24 months.

3.1 Study design

The data used to assess the assumed association of NT-proBNP with measures of mental health stem from a multicenter randomized controlled study, the Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD) trial. Patients ($N = 570$) had clinical evidence of CHD (coronary stenosis $> 50\%$ in recent angiogram or history of percutaneous intervention) and a least mildly elevated depression scores (Hospital Anxiety and Depression Scale (HADS), Zigmond and Snaith 1983; Herrmann-Lingen et al. 2011). The cut-off on the HADS depression subscale was set to > 7, to include all possible cases and have a low proportion of false negatives, as recommended by Zigmond and Snaith (1983). To test whether stepped psychotherapy is more effective in reducing depressive symptoms, patients were randomized to usual care plus one information session or usual care plus a stepwise individual and group psychotherapy intervention (see Appendix for Consort flow chart). Details on the design of the study have been published in Albus et al. 2011. The primary results of the SPIRR-CAD trial have been reported in Herrmann-Lingen et al. 2016. The trial protocol was approved by the ethics committees of all participating centers and the trial was conducted in accordance with the Helsinki declaration and Good Clinical Practice. All patients gave written informed consent before being included in the study.

3.2 Assessments

To test the association of NT-proBNP and mental health measures, baseline ($N = 529$) and 24-months follow-up ($N = 308$) data of patients with valid NT-proBNP samples at baseline were used. At baseline, blood was drawn from a cubital vein in rest-

ing patients and immediately centrifuged. Until analysis at a central lab, the blood samples were stored at - 80° C. Serum concentrations were measured using an electrochemiluminescence immunoassay, using two monoclonal antibodies (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany; Prontera et al. 2005).

As the SPIRR-CAD trial took place in Germany, all materials were provided in German. Socio-demographic information on age, sex, marital status, highest educational level, and the patients' current employment situation was included. The patients' medical status was taken from their medical records. Anxiety was measured using the anxiety subscale of the German version of the HADS (Herrmann-Lingen et al. 2011). Depression scores from the HADS depression subscale were not used for the main analyses as this scale was used as an inclusion criterion and baseline scores are therefore severely skewed. Instead, the 9-item Patient Health Questionnaire (PHQ) was analyzed (Spitzer et al. 1999; Löwe et al. 2002). To assess different dimension of coping with illness the 5-dimensional Freiburg Questionnaire of Coping with Illness (FQCI) was used (Muthny 1989). Vital exhaustion was measured using the 21-item Maastricht Questionnaire (MQ) (Appels et al. 1987). The two dimensions of type D personality, i.e. social inhibition and negative affectivity were assessed with the 14-item Type D Scale (DS-14) (Denollet 2005). Different dimensions of quality of life were assessed with the Medical Outcomes Short Form Health Survey (SF-36), including the z-standardized mental health and physical health component scores (Ware and Sherbourne 1992).

3.3 Data analysis

The association of NT-proBNP with all psychosocial variables was analyzed at baseline as well as longitudinally from baseline to the 24-month follow up. In both analyses, descriptives were calculated for the socio-demographic questions. All raw data of the questionnaires and NT-proBNP levels were tested for normality using a Kolmogorov-Smirnov test of normality. The test showed severe skewness for NT-proBNP levels (Figure 1), thus data were log-transformed to approximate a normal distribution (Figure 2).

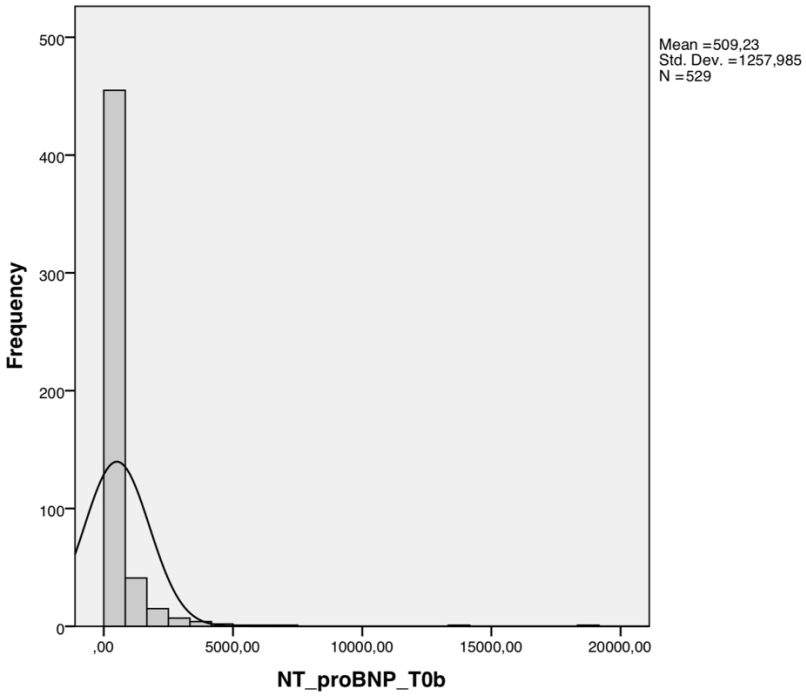

Figure 1: Frequency distribution of NT-proBNP measures at baseline.

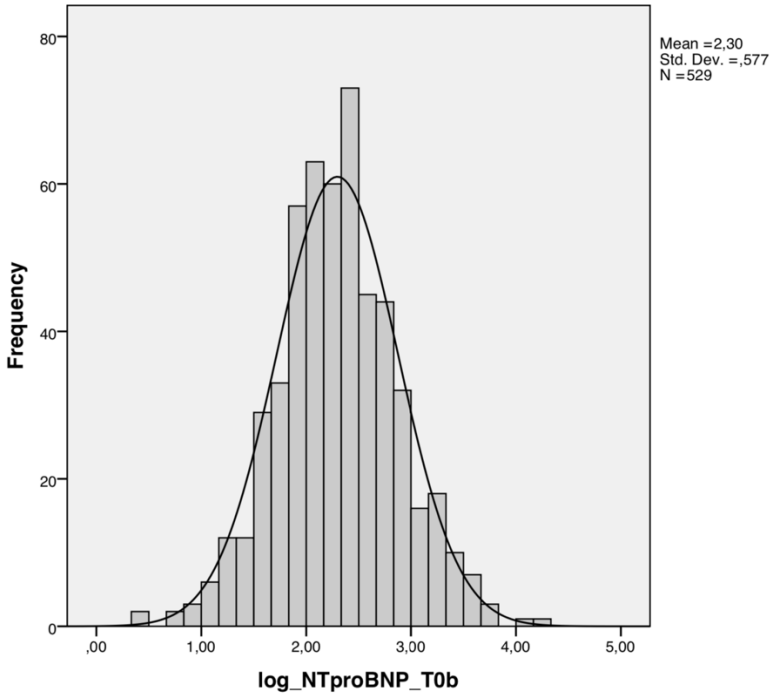

Figure 2: Frequency distribution of log-transformed NT-proBNP measures at baseline.

The association of NT-proBNP levels with illness severity and psychosocial functioning was assessed with bivariate Pearson's correlation analysis or Spearman's rho, where applicable. The independent associations of NT-proBNP with the psychometric scales were assessed with separate linear regression models. To adjust for additional factors, the regression models were adjusted for sex and additional confounding factors that were significantly associated with NT-proBNP and the psychometric scale in the correlation analysis.

Longitudinal associations of NT-proBNP and anxiety were analyzed in more depth using multilevel linear mixed models with the six anxiety measures as level-1 variable, nested within participants as level-2 variable. Model A included random intercepts for participants, NT-proBNP as continuous variable, and sex, randomization arm, time, and the interactions with time as fixed effects. Model B included NT-proBNP as dichotomized variable comparing the lowest quartile versus the highest three quartiles. Subgroup analysis was done using Student's t-test for continuous measures and χ^2 analysis for categorical measures. Non-parametric data were compared using Mann-Whitney-U and Wilcoxon signed-rank tests. All data were analyzed using SPSS (Version 24 and 25, IBM Corp., Armonk, NY, USA) and R (Version 3.5.1.).

4 Summary of the main findings

The cross-sectional analysis in publication 1 (Fangauf et al. 2018) showed that 75% of the patients scored above the clinically relevant cut-off of 7 on the anxiety subscale of the HADS. A significant positive association was found between log-transformed NT-proBNP measures and age, Charlson comorbidity index and the bodily pain subscale of the SF-36. This scale is scored inversely with higher scores indicating less pain. Log-transformed NT-proBNP measures showed significant negative associations with BMI, ejection fraction, and the physical functioning subscale of the SF-36. Results of the associations with mental health measures confirmed the expected negative association of NT-proBNP with anxiety, depression, negative affectivity, vital exhaustion, and depressive coping. Positive correlations were found with trust in physicians (a subscale of the Freiburg Questionnaire of Coping with Illness) and the mental health subscale of the SF-36. These analyses confirmed the hypothesis that NT-proBNP is consistently negatively correlated with physical health, but positively correlated with psychological quality of life. Separate linear regression models for these significant psychometric scales were constructed and adjusted for sex, age, and physical functioning. All models showed significant independent associations of log(NT-proBNP) and all tested psychometric scales. These results support the hypothesis that in coronary patients BNP is associated with better mental health, despite the physical limitations due to the cardiac disease.

The longitudinal analysis in publication 2 (Fangauf et al. 2019) broadens the results of the first publication on NT-proBNP and anxiety. At 24-months follow-up, 49% of the patients still scored above the clinically relevant cut-off of 7 on the anxiety subscale of the HADS, however the anxiety score decreased significantly from baseline to 24-months in both men and women. The results show a consistent negative association of baseline NT-proBNP with anxiety measures over the 24 months, independent of age, sex, BMI, and self-reported physical functioning. NT-proBNP could thus potentially be prognostically relevant not only for morbidity and mortality, but also for the mental state of cardiac patients. While the results confirm the hypothesis that baseline NT-proBNP would be associated with a decline of anxiety over 24 months, model A of the multilevel linear mixed model analysis showed no significant interaction of time with any of the tested factors. Model B, however, revealed a significant interaction

of time with NT-proBNP and, surprisingly, a significant sex-effect, showing that in women with very low levels of NT-proBNP anxiety did not decrease significantly over the time tested as it did in the rest of the sample. The persisting high levels of anxiety of this subgroup might be the result of an insufficient up-regulation of BNP despite the weakened state of their heart due to CHD.

5 Publications

5.1 Publication 1: Associations of NT-proBNP and parameters of mental health in depressed coronary artery disease patients

Fangauf SV, Herbeck Belnap B, Meyer T, Albus C, Binder L, Deter H-C, Ladwig K-H, Michal M, Ronel J, Rothenberger A, et al. (2018): Associations of NT-proBNP and parameters of mental health in depressed coronary artery disease patients. Psychoneuroendocrinology 96, 188–194

Psychoneuroendocrinology 96 (2018) 188–194

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Associations of NT-proBNP and parameters of mental health in depressed coronary artery disease patients

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ARTICLE INFO

Keywords:
Natriuretic peptide
Coronary artery disease
Mental health
Anxiety
Depression
Quality of life

ABSTRACT

Natriuretic peptides (NP) are involved in the regulation of blood pressure and blood volume, and are elevated in patients with coronary artery disease (CAD). They are used as markers for illness severity, but their role in mental health is not well understood. Recently, A-type NP (ANP) has been associated with reduced anxiety in studies on cardiac patients; however, this study is the first to assess this effect for B-type NP (BNP) and for further dimensions of well-being and mental health. Depression, anxiety, and distress are more common in CAD patients than in the general population and are most likely not only influenced by psychological adaptation but also by neurobiological processes. We used baseline N-terminal proBNP (NT-proBNP) samples and psychometric assessments of 529 at least mildly depressed (Hospital Anxiety and Depression Scale, depression score ≥ 8) CAD patients from the multicenter Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD) trial. Psychosocial status was assessed using standardized self-rating questionnaires on anxiety, depression, coping with illness, vital exhaustion, type D personality, and quality of life. Separate linear regression models for each psychometric scale revealed significant negative correlations of NT-proBNP with anxiety, depression, vital exhaustion, depressive coping, and negative affectivity. Moreover, patients with higher levels of NT-proBNP experienced less bodily pain and had a better self-rated mental health, despite worse physical functioning. Linear regression adjusted for age, sex, and physical functioning (Short Form Health Survey [SF-36]) revealed NT-proBNP to be a significant predictor for all tested measures of the patients' psychosocial status. These results indicate that NT-proBNP is not only positively associated with greater disease severity in mildly to moderately depressed CAD patients but also with better psychosocial status and mental well-being. Possible mechanisms of this effect are discussed.

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https://doi.org/10.1016/j.psyneuen.2018.06.001
Received 9 March 2018; Received in revised form 30 May 2018; Accepted 2 June 2018

1. Introduction

Considering that coronary artery disease (CAD) is one of the most common sources of disability and mortality worldwide (Franco et al., 2011) and that depression and anxiety increase the morbidity and mortality in patients with CAD, surprisingly little is known about the neurobiological factors influencing patients' mental health and quality of life. This is considerable since depression as well as anxiety and psychological distress are common in CAD patients with a prevalence of 20–50% for depressive symptoms, up to 29% for major depressive disorder, and approximately 45% for anxiety disorders (Bankier et al., 2004; Herrmann-Lingen and Buss, 2002; Ladwig et al., 2014; Todaro et al., 2007). Anxiety is regarded as an independent risk factor for increased morbidity and mortality in CAD and post-myocardial infarction (MI), probably caused by increases in heart rate and in frequency of arrhythmias (MacMahon and Lip, 2002; Roest et al., 2010; Watkins et al., 2013). However, other studies found contrary results with anxiety acting as a protective factor with regard to mortality and major adverse events in healthy persons or CAD patients without a history of MI, attributed to an increase in help-seeking and health behavior in anxious patients (Meyer et al., 2015a, 2010; Mykletun et al., 2007).

Depression alone, but especially in comorbidity with anxiety, increases the risk of mortality in patients with CAD (Lichtman et al., 2014). Similar to depression in symptomology is vital exhaustion, a state of excessive fatigue, decreased energy, and the feeling of being dejected or defeated. Vital exhaustion is highly prevalent in cardiac patients (35–60%), and it predicts future MI independently of other risk factors (Appels and Mulder, 1988; Kop, 1999).

Cardiac patients typically have elevated levels of A- and B-type natriuretic peptides (ANP and BNP, respectively). ANP and BNP are secreted by the cardiac atria and ventricles when they are stretched, such as in patients with heart failure or CAD (Kim et al., 2006). They induce natriuresis and diuresis leading to a decrease of blood pressure and of pre- and afterload of the heart. Plasma levels of BNP correlate with the severity of the cardiac disease. They are synthesized in the cardiac myocytes as preprohormones and cleaved into proANP/proBNP. These prohormones are then cleaved in equal parts into the biologically inactive N-terminal and the active ANP/BNP. Due to longer half-lives of the N-terminal peptides (NT-proANP/NT-proBNP), their concentrations are commonly measured for clinical diagnostics and research purposes (McMurray et al., 2012). Both ANP and BNP bind to the NPR-A receptor, which is expressed in kidney and heart tissue but also in the brain, e.g., brain stem nuclei (Abdelalim et al., 2006).

Interestingly, research found that natriuretic peptides seem to be associated with emotion regulation and attenuate the activity of the hypothalamic-pituitary-adrenal (HPA) axis (Wiedemann et al., 2000). They also reduce sympathetic tone, thus counteracting the neurohumoral activation typically seen in heart failure (Luchner and Schunkert, 2004). The association of natriuretic peptides and emotion regulation is compelling as the emotional and physiological arousal that accompanies states of anxiety and stress may be especially detrimental for patients with ischemic cardiomyopathy.

Most research on natriuretic peptides and emotion examined the relationship of ANP and anxiety, showing that lactate-induced panic attacks are accompanied by an increased secretion of ANP (Kellner et al., 1995), whereas pretreatment with ANP attenuated symptoms in cholecystokinin tetrapeptide (CCK-4)-induced panic (Ströhle et al., 2001). Moreover, plasma proANP showed an independent negative correlation with anxiety (Herrmann-Lingen et al., 2003). Apart from studies regarding anxiety, research on the relation of natriuretic peptides and other aspects of psychosocial functioning is sparse. Data are contradictory on whether ANP and BNP are related to depression (Brouwers et al., 2014; Herrmann-Lingen et al., 2003; Murberg et al., 1997; Pelle et al., 2010). However, vital exhaustion was positively associated with NT-proANP in one study (Herrmann-Lingen et al., 2003).

Similarly, distress also has a negative influence on cardiac diseases. Patients with type D personality, a combination of experiencing negative emotions and an inhibition to engage in social contact, are especially vulnerable to the effects of distress (Denollet and Conraads, 2011). Numerous studies reported type D personality to be a determinant for impaired health status, higher rates of rehospitalization and mortality in patients with chronic heart failure (Denollet and Brutsaert, 1998; Schiffer et al., 2010). Also, it may act as a prognostic risk factor in patients with CAD (Grande et al., 2012). However, other studies found no effect on adverse outcomes (Coyne et al., 2011; Meyer et al., 2014) or associations with BNP (Pelle et al., 2010).

Interestingly, the reduced quality of life in cardiac patients correlates more closely with subjective markers of disease severity (e.g., New York Heart Association (NYHA) class) and emotional status compared to objective cardiac markers (e.g., left ventricular ejection fraction (LVEF), BNP) (Ladwig et al., 2014). In contrast to the multiple studies on proANP, so far only one observational study has assessed the association of NT-proBNP with anxiety. An inverse association was found in patients with cardiovascular risk factors which failed to reach significance as an independent predictor when adjusted for age, sex, body mass index (BMI), and Framingham score (Meyer et al., 2015b).

In the present study, we examined the relationship of NT-proBNP and psychosocial status in mildly depressed patients with CAD to broaden our understanding of this natriuretic peptide and its association with emotions. We tested the hypothesis that BNP (as reflected by its proxy NT-proBNP) is a relevant biological factor related to mental health in CAD patients. In particular, we hypothesized that NT-proBNP would be negatively correlated with anxiety, depression, vital exhaustion, type D personality, non-functional coping, and physical quality of life, but positively correlated with functional coping strategies and psychological quality of life.

2. Methods

2.1. Study design

In a secondary analysis, we used data from the Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD) trial, a randomized controlled trial comparing usual care plus a stepwise psychotherapy intervention to usual care plus one individual information session. The design and main results have been described in more detail elsewhere (Albus et al., 2011; Herrmann-Lingen et al., 2016). The trial was conducted at ten different study sites in Germany in accordance with Good Clinical Practice and the Helsinki Declaration. All ethics committees of the participating centers approved the trial protocol and all patients gave their written informed consent.

2.2. Participants

The study enrolled 570 patients aged 18–75 with CAD (coronary stenosis > 50% as determined by a recent coronary angiogram or history of percutaneous coronary intervention) and a depression score ≥ 8 on the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Exclusion criteria were severe heart failure (LVEF < 20% or NYHA class IV), severe depressive episodes according to the Structured Clinical Interview for DSM-IV (SCID) (Wittchen et al., 1997), other severe or life-threatening physical or mental diseases, and insufficient ability to speak German. Data from 529 patients (93%) with valid baseline NT-proBNP and HADS measurements were included in the present analysis.

2.3. Assessments

At baseline, all centers assessed the patients' medical history and their socio-demographic data (e.g., age, gender, marital status, and highest educational level) from their medical records and standardized clinical interviews. The patients' psychosocial status was assessed using

the German versions of standardized self-rating questionnaires.

To assess anxiety symptoms, we used the HADS (Herrmann-Lingen et al., 2011; Zigmond and Snaith, 1983), a questionnaire with two 7-item subscales with clinically relevant cut-off scores of eight points each (range 0–21).

We used the 9-item depression scale of the Patient Health Questionnaire (PHQ-9) (Löwe et al., 2002; Spitzer et al., 1999) to assess depressive symptoms. Each item assesses one of the nine DSM-IV criteria for major depression and scores range from 0 to 27. Scores higher than ten indicate a moderate level of depression.

The Freiburg Questionnaire of Coping with Illness (FQCI) (Muthny, 1989) was used to examine the patients' coping styles with their illness on five scales, namely depressive coping, active problem-oriented coping, distracting and encouraging oneself, religiosity and quest for meaning, and minimization and wishful thinking. All items are rated on a scale ranging from 1 = "not at all" to 5 = "very much", and a sum score is calculated for each subscale. Two additional items assess trust in physicians.

The 21-item Maastricht Questionnaire (MQ) (Appels et al., 1987) assesses vital exhaustion. Symptoms of feeling exhausted, dejected, and defeated are rated ranging from 0 = "not present" to 2 = "present" with a cut-off point of > 19 (range 0–42) signifying vital exhaustion.

To measure the two components of type D personality, namely social inhibition and negative affectivity, we used the 14-item type D scale (DS-14) (Denollet, 2005) with seven items on each subscale. The negative affectivity subscale covers feelings of irritability, dysphoria, and worry, while the social inhibition subscale asks for a lack of social confidence, discomfort in social interactions, and reticence. Answers range from 0 to 4 with a cut-off for the presence of type D ≥ 10 on each of the two scales (range 0–28).

The Medical Outcomes Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992) assesses physical and mental health-related quality of life with higher scores signifying better quality of life. This questionnaire has eight subscales (general mental health, role limitations because of emotional problems, social functioning, role limitations because of physical problems, bodily pain, vitality, general health perceptions, and physical functioning). The mental and physical quality of life subscales can be summarized as z-standardized mental health component and physical health component scores, respectively.

Blood was drawn from a cubital vein in resting patients, centrifuged, aliquoted, and stored at -80 °C until being analyzed. A central core lab measured serum concentrations of NT-proBNP using an electrochemiluminescence immunoassay on a Cobas 8000 or Cobas e411 (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) using two monoclonal antibodies (Prontera et al., 2004).

2.4. Data analysis

All raw data from the questionnaires and NT-proBNP measurements were tested for normality revealing that NT-proBNP levels were severely skewed. To reduce the skewness and approach normal distribution, data were log-transformed. We calculated bivariate Pearson's correlation coefficients (and Spearman's rho where applicable) between log(NT-proBNP) and baseline parameters (age, BMI) and markers of illness severity (NYHA class, LVEF, Charlson comorbidity index (CCI)). We calculated additional bivariate correlations for log(NT-proBNP) with each questionnaire and subscale. To examine independent associations of NT-proBNP with the patients' psychosocial and subjective health status, separate linear regression models were constructed for each psychometric scale that correlated significantly ($p < .05$) with log (NT-proBNP). We adjusted the regression analyses for sex and those possibly confounding factors that showed significant associations with log(NT-proBNP) and the psychometric scales in the bivariate analysis. All data were analyzed using SPSS (Version 24, IBM Corp., Armonk, NY, USA).

Table 1
Baseline Characteristics.

	N/valid N	%
Male sex	417/529	78.8
Married	331/502	62.6
Socioeconomic status		
Low	217/529	41.0
Medium	206/529	38.9
High	106/529	20.0
NYHA class		
I	184/507	34.8
II	237/507	44.8
III	86/507	16.3
Beta-blocker medication	465/529	87.9
	M	*SD*
Age, y (N = 529)	59.3	9.4
LVEF (N = 308)	56.7	14.4
BMI (N = 515)	28.4	4.8
CCI (N = 529)	2.1	1.4
NT-proBNP, median (IQR), ng/l (N = 529)	188.2	382.6
HADS anxiety (N = 529)	10.4	3.8
PHQ depression (N = 501)	9.9	5.4
DS-14 negative affectivity (N = 314)	15.77	4.8
DS-14 social inhibition (N = 314)	11.74	5.5
MQ vital exhaustion (N = 499)	25.5	10.6
SF-36 physical component summary (N = 456)	37.7	9.9
SF-36 mental component summary (N = 456)	38.0	11.2
FQCI depressive coping (N = 480)	11.9	3.8
FQCI trust in physicians (N = 483)	3.6	1.0
FQCI religiosity and quest for meaning (N = 484)	12.81	3.6

BMI = body mass index (kg/m^2), CCI = Charlson comorbidity index, DS-14 = fourteen item Type D scale, FQCI = Freiburg Questionnaire of Coping with Illness, HADS = Hospital Anxiety and Depression Scale, IQR = interquartile range, LVEF = left ventricular ejection fraction, MQ = Maastricht Vital Exhaustion Questionnaire, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, PHQ = Patient Health Questionnaire, SF-36 = Short Form Health Survey.

3. Results

3.1. Baseline characteristics and correlation analysis

Patients in our study had a mean age of 59.3 years, were predominately male (78.8%), 53.9% were non-working, and most (79.9%) had a low or medium socioeconomic status (Table 1). Study participants had a median NHYA class of II and a median of two comorbidities. 87.9% (465 patients) took beta-blockers.

Most of the patients had elevated anxiety scores with 75% scoring above the clinically relevant cut-off (≥ 8, HADS anxiety subscale). 59.4% of the patients met the criteria for type D personality.

The median NT-proBNP concentration was 188.2 ng/l (Table 1).

There were significant associations of log(NT-proBNP) with age, Charlson comorbidity index, ejection fraction, and self-reported physical functioning (all $p < 0.01$), and with BMI, bodily pain (Fig. 1), but not with beta-blocker medication ($r_s = .085$, $p = .052$) or NYHA class ($r_s = .065$, $p = .142$). We found significant negative correlations of log (NT-proBNP) with most measures of distress, signifying better mental health scores in patients with higher NT-proBNP concentrations (Fig. 2).

3.2. Multiple regression analysis

Separate multiple linear regression models were constructed for each significant psychometric scale of the correlation analysis to predict the patients' psychosocial status from their NT-proBNP level. The regression models were adjusted for age, sex, and physical functioning (subscale of SF-36) since these factors showed significant correlations with all psychometric scales. Beta-blocker medication, CCI, NYHA class, and BMI did not correlate significantly (all p-values > .05), therefore

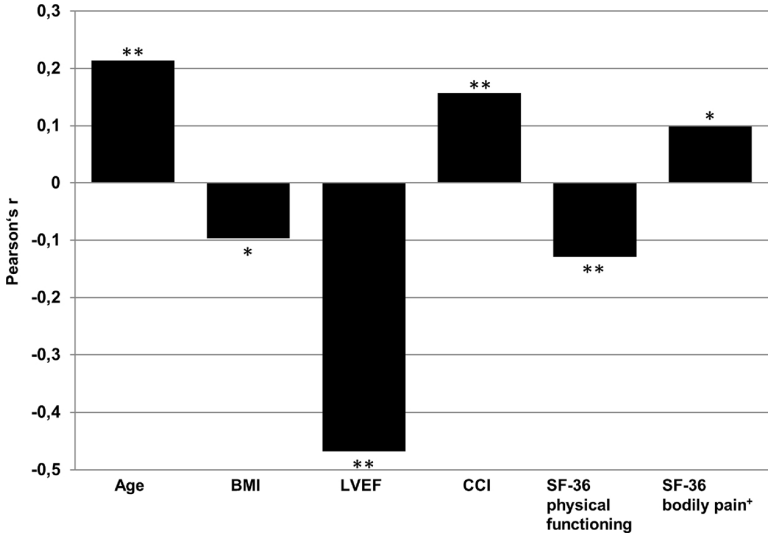

Fig. 1. Pearson's correlation coefficients of log(NT-proBNP) with medical status and self-rated physical health [* $p < .05$, ** $p < .01$, *** $p < .001$, $^{+}$ higher score = less pain, BMI = body mass index (kg/m^2), CCI = Charlson comorbidity index, LVEF = left ventricular ejection fraction, SF-36 = Short Form Health Survey].

they were not included in the regression models. LVEF showed weak but significant correlations with vital exhaustion (r = .131, p = .025), bodily pain (r = -.123, p = .037), and negative affectivity (r = .189, p = .001) but not with anxiety, depression, coping or other subscales of quality of life (all p-values > .05).

All models revealed log(NT-proBNP) to be significantly associated with all tested measures of the patients' psychosocial status ($p < .05$, Table 2), except for trust in physicians which was not significant. For anxiety and vital exhaustion, all factors (log(NT-proBNP), age, sex, and physical functioning) were significant predictors, while for depression, depressive coping, and mental health all factors except sex were significant predictors. For negative affectivity and bodily pain, only log (NT-proBNP) and physical functioning were significant predictors. Since previous studies had also adjusted for BMI, we performed an additional analysis including BMI as a predictor, which did not change the previous results.

In a sensitivity analysis, we also included LVEF as predictor for those psychometric variables with which it was significantly associated in bivariate analyses, i.e., vital exhaustion, negative affectivity, and the pain subscale of the SF-36. Although the sample size for these analyses was substantially reduced (n = 308) due to incomplete availability of LVEF data, the association between (absence of) pain and log(NT-proBNP) remained significant (beta = 0.179, p = 0.002). In contrast, the associations of log(NT-proBNP) with vital exhaustion (beta = -0.079) and negative affectivity (beta = -0.075) were reduced and lost statistical significance, although the direction of the associations remained unchanged.

Table 2
Multiple regression models. Predictor: log(NT-proBNP) adjusted for age, sex and physical functioning (SF-36).

Dependent variable	B	Std. Error	β	p
HADS anxiety	−.865	.282	−.135	.002
PHQ-9 depression	−.811	.367	−.087	.028
FQCI depressive coping	−.723	.296	−.110	.015
MQ vital exhaustion	−2.599	.716	−.141	.000
DS-14 negative affectivity	−1.027	.381	−.123	.007
SF-36 mental health	3.416	1.375	.105	.013
SF-36 bodily pain	8.183	1.765	.179	.000

DS-14 = fourteen item Type D scale, HADS = Hospital Anxiety and Depression Scale, MQ = Maastricht Vital Exhaustion Questionnaire, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PHQ = Patient Health Questionnaire, SF-36 = Short Form Health Survey.

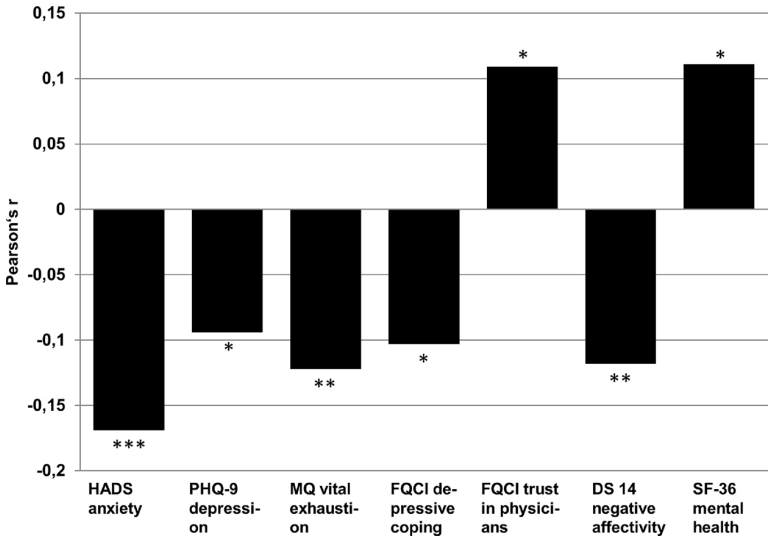

Fig. 2. Pearson's correlation coefficients of log(NT-proBNP) with psychological status and self-rated mental health [* $p < .05$, ** $p < .01$, *** $p < .001$, DS-14 = 14-item Type D scale, FQCI = Freiburg Questionnaire of Coping with Illness, HADS = Hospital Anxiety and Depression Scale, MQ = Maastricht Vital Exhaustion Questionnaire, PHQ = Patient Health Questionnaire, SF-36 = Short Form Health Survey].

4. Discussion

In this secondary analysis from a large multicenter trial, we confirmed that NT-proBNP levels in patients with CAD and at least mild depressive symptoms are associated with markers of their medical and psychosocial health status. As hypothesized, NT-proBNP showed significant inverse correlations with anxiety which persisted after multivariate adjustment. Although counterintuitive from a cardiological perspective, these findings are biologically plausible and in line with previous research (e.g., Meyer and Herrmann-Lingen, 2017).

While natriuretic peptides indicate more severe heart disease and represent powerful and independent prognostic indicators for CAD events among subjects with stable CAD (Bibbins-Domingo et al., 2007), they are not causally involved in heart disease but rather understood as one element of adaptive counter-regulation. By stimulating excretion of water and sodium they reduce the hemodynamic load on the heart (Hodes and Lichtstein, 2014). In addition, they may stimulate vagal afferents (Hansson, 2002) which are known to contribute to internal stress regulation, an effect that is being used in therapeutic vagus nerve stimulation (Yuan and Silberstein, 2016). Natriuretic peptides reduce sympathetic tone (Luchner and Schunkert, 2004) and activity of the renin angiotensin aldosterone system (RAAS; Hodes and Lichtstein, 2014), thereby partly antagonizing the neuroendocrine activation typically found in heart failure.

An anxiolytic-like effect of ANP and BNP has been shown in animal models (e.g., Bíró et al., 1996; von der Goltz et al., 2014). This effect may be mediated by reduced corticotropin-releasing hormone (CRH) secretion in limbic structures (Hodes and Lichtstein, 2014; Wiedemann et al., 2000), which also reduces pituitary and adreno-cortical hormone secretion and sympathetic tone. Several studies of human probands and patients with panic disorder or alcohol withdrawal (Koopmann et al., 2014; Ströhle et al., 2006, 2001) show that exogenous ANP application or exercise-induced increases in ANP levels reduce clinical symptoms of anxiety or CCK-4-induced panic attacks. In two previous studies, we also found inverse associations of pro-ANP with anxiety in cardiac patient samples (Herrmann-Lingen et al., 2003; Meyer et al., 2015b). Biologically, it appears plausible and would make sense for natriuretic peptides to buffer against anxious arousal in situations of more severe heart disease.

While most previous studies on associations of natriuretic peptides and anxiety mainly looked at (pro)ANP, a link between NT-proBNP and anxiety has been reported in two publications. In a study by Bankier and colleagues (2009), interview-diagnosed anxiety disorders and NT-proBNP showed no significant association in a relatively small sample of 85 CAD patients. In contrast, Meyer and coworkers (2015b) found a weak negative correlation between NT-proBNP and self-rated symptoms of (generalized) anxiety in patients with cardiovascular risk factors including some patients with CAD or heart failure. However, that association was no longer significant after adjustment for confounders. Our study is therefore the first one showing an independent inverse association of NT-proBNP with anxiety.

The more surprising finding in the present study is that NT-proBNP was also independently associated with lower levels of depression, negative affectivity, depressive coping, vital exhaustion, bodily pain, and higher levels of self-rated mental health. At the same time NT-proBNP indicated more severe physical illness and reduced physical quality of life which could be expected to rather impair emotional well-being and mental quality of life. However, associations between morphological or humoral measures of cardiac disease severity usually show only weak and sometimes no associations with mental well-being.

For example, Juenger et al. (2002) showed that chronic heart failure patients in general had severely reduced quality of life, but within the heart failure sample, systolic left ventricular function was unrelated to any of the dimensions of quality of life measured by the SF-36. Another study showed that also diastolic dysfunction was unrelated to depression and mental quality of life in patients with cardiovascular risk factors (Edelmann et al., 2011). In that study, NT-proBNP was even unrelated to physical quality of life in adjusted analyses. The negative association of NT-proBNP with measures of distress beyond anxiety – despite the presence of more severe physical illness – may suggest not only an anxiolytic but a more general stress-buffering effect of natriuretic peptides which has already been described for patients with alcohol withdrawal (Koopmann et al., 2014).

Associations between natriuretic peptide levels and depressive symptoms or vital exhaustion have been reported in a few previous studies and results were inconclusive: Murberg et al. (1997) found a negative but insignificant association of pro-ANP and depressive symptoms on the Zung depression scale in 119 patients with heart failure. A positive association of pro-ANP with depression and vital exhaustion was observed in patients with congestive heart failure and healthy controls (Herrmann-Lingen et al., 2003). However, this association may have mainly been driven by the difference in both depressive symptoms/vital exhaustion and pro-ANP between healthy probands and heart failure patients which may have obscured a relatively weak depression-buffering effect of BNP per se.

Bunevicius et al. (2017) found a positive association between NT-proBNP and depressive symptoms (rho = 0.240, p = 0.026) in patients awaiting surgery for brain tumors. However, the source and mode of action of BNP in those patients remained unclear, as most cases of elevated NT-proBNP occurred in patients without heart disease and NT-proBNP levels significantly differed across different tumor entities. Previous results on the effects of natriuretic peptides in the brain point towards peripheral BNP usually becoming active in the brain as no BNP mRNA was detected in the brain (Langub et al., 1995), but BNP was found in the human cerebral cortex (McKenzie et al., 1994) and the hypothalamus of monkeys (Abdelalim et al., 2006). BNP might have a neuroprotective function as it was found to increase cerebral blood flow and reduce inflammation in studies on mice (Hodes and Lichtstein, 2014). By this mechanism, it could have a beneficial effect in brain disease, although that effect may be too weak to compensate for physical and emotional sequelae of brain tumors.

4.1. Limitations

While there are some reasons to believe that the association between NT-proBNP and mental health could be causal in a way that BNP improves well-being, the cross-sectional design of our study does not allow us to draw such causal conclusion. It is also conceivable that psychosocial stress in turn reduces the release of BNP.

Although this study was conducted on a fairly large sample, it has to be noted that the majority of our study participants were male white Germans with CAD, at least mild symptoms of depression, and accompanying elevations in other dimensions of distress. Thus, the results might not be readily generalizable to women or other races and ethnicities, to non-depressed CAD patients, nor those with other physical illnesses such as brain diseases, or healthy subjects.

Previous studies showed that the incidence and possibly also the pathophysiology of CAD differ between men and women (Wakabayashi, 2017). However, our findings were stable when adjusting for sex in the multivariate analyses. For gender-specific analyses, future studies need to recruit more equally and our results also need replication in patients with other illnesses or from other racial/ethnic backgrounds.

Symptoms of anxiety and depression were only assessed by self-report. Interview-based diagnoses of anxiety disorders or depressive episodes might yield different results. Finally, longitudinal observations and experimental designs such as those used for ANP will be important for identifying the causal mechanisms behind the observed associations.

4.2. Conclusion

Our results suggest that BNP, like ANP, may have anxiolytic-like properties. Furthermore, this is the first study to show that (NT-pro)

BNP is associated with well-being and better mental health of CAD patients in multiple dimensions, including depression, coping with illness, and quality of life. The results point towards a more general stress-buffering function of BNP ultimately shielding the heart not only from fluid overload but also from excessive neuroendocrine activation, and possibly from psychosocial distress increasing such activation. Experimental and longitudinal studies are needed to further assess the psychoprotective function of this natriuretic peptide.

Declarations of interest

Christoph Herrmann-Lingen reports that he is receiving royalties from Hogrefe Huber Publishers for the German version of the Hospital Anxiety and Depression Scale. During the last three years he has received lecture honoraria from Servier, Heel, and Novartis and an honorarium from Pfizer for serving on an advisory board. The remaining authors report no conflicts of interest.

Source of funding

This study has been funded by a grant from the German Research Foundation (DFG; # HE 3115/10-1, HE 3115/10-2, AL 559/2-1, AL 559/2-2) to Drs. Herrmann-Lingen and Albus, and a grant from the German Ministry of Education and Research to the German Center of Cardiovascular Research (DZHK), partner site Göttingen.

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5.2 Publication 2: Longitudinal relationship between B-type natriuretic peptide and anxiety in coronary heart disease patients with depression

Fangauf SV, Meyer T, Albus C, Binder L, Deter H-C, Ladwig K-H, Michal M, Ronel J, Rothenberger A, Söllner W, et al. (2019): Longitudinal relationship between B-type natriuretic peptide and anxiety in coronary heart disease patients with depression. Journal of Psychosomatic Research 123, 109728

Journal of Psychosomatic Research 123 (2019) 109728

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Longitudinal relationship between B-type natriuretic peptide and anxiety in coronary heart disease patients with depression

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ARTICLE INFO

Keywords:
Anxiety
Coronary heart disease
Depression
Natriuretic peptide

ABSTRACT

Objective: Patients with coronary heart disease (CHD) suffer from physical limitations, but also from psychological distress. Natriuretic peptides may be involved in the neurobiological processes that modulate psychological adaptation, as they are increased in heart disease and seem to have an anxiolytic-like function. Longitudinal data on this association are scarce.

Methods: To assess the relationship between NT-proBNP and anxiety (Hospital Anxiety and Depression Scale (HADS)), we used secondary data from a multicenter trial from baseline to 24 months. Patients (N = 308, 80.8% male, mean age 60.1 years) had stable CHD and moderate levels of depression (HADS ≥8).

Results: Multiple linear regression adjusted for age, sex, BMI, and physical functioning revealed NT-proBNP as a significant predictor for anxiety at baseline, 1, 6, 12, 18, and 24 months (all $p < .05$). Linear mixed model analysis with the six anxiety measures as level-1 variable and NT-proBNP as fixed factor revealed a significant time*NT-proBNP interaction ($t(1535.99) = -2.669$, $p = .01$) as well as a significant time*NT-proBNP*sex interaction ($t(1535.99) = 3.277$, $p = .001$), when NT-proBNP was dichotomized into lowest vs. the three highest quartiles.

Conclusion: Our results indicate a stable negative association of baseline NT-proBNP with anxiety over two years. In men and women, different pathways modulating this relationship appear to be in effect. Female patients with very low NT-proBNP levels, despite their cardiac disease, show persistently higher levels of anxiety compared to women with higher levels of NT-proBNP and compared to men.

Trial name: A Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-

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[1] See acknowledgement for other members of the study group.

https://doi.org/10.1016/j.jpsychores.2019.05.006
Received 18 December 2018; Received in revised form 15 May 2019; Accepted 19 May 2019

CAD).
Trial registration:www.clinicaltrials.govNCT00705965; www.isrctn.com ISRCTN76240576.

1. Introduction

Patients with coronary heart disease (CHD) have an increased prevalence of psychological distress and mental disorders. It was reported that 20–50% of CHD patients show symptoms of depression and 20–30% fulfill the criteria for major depression [1–3]. Since mental diseases, in particular depression, worsen the progression and prognosis of CHD, it is important to diagnose and treat these comorbidities appropriately. Studies reported that CHD patients with comorbid depression show higher numbers of complications and have a 1.6–2.5-fold increased risk of recurrent coronary events and all-cause death [1,4]. While depression is an established cardiac risk factor [5], the impact of anxiety is less clear, as there is conflicting evidence, whether anxiety increases or reduces the risk of mortality. In multiple studies anxiety was found to be independently associated with an increased risk of mortality in healthy individuals and CHD patients, while others reported no such association [6]. In a study by Meyer and colleagues, higher anxiety scores were associated with reduced mortality in 4864 patients undergoing an exercise test, including both CHD patients without myocardial infarction (MI) and patients without CHD [7].

The role of anxiety in cardiac disease may be confounded by the neurohumoral effects of natriuretic peptides. These peptides are typically elevated in heart failure and not only induce natriuresis, diuresis and vasodilation, but also attenuate the activity of the hypothalamic-pituitary-adrenal (HPA) axis and reduce sympathetic tone [8,9]. They might thus be regarded as antagonists to the sympatho-exitatory effect of anxiety. A-type natriuretic peptide (ANP) was found to exert anxiolytic effects in rodents and humans and has been negatively associated with anxiety in both cardiac patients and patients with alcohol withdrawal [10–14]. While the effect of ANP on anxiety has been assessed in multiple studies, only few studies concerned the relationship between B-type natriuretic peptide (BNP) and psychological measures, even though BNP and its N-terminal prohormone (NT-proBNP) are frequently used as markers of illness severity and prognosis in patients with heart failure. Recent studies also suggest a role of BNP in emotion regulation, however these findings are inconsistent, and longitudinal data are scarce.

In a recently published cross-sectional analysis, we found a link between high serum concentrations of NT-proBNP and lower levels of anxiety, depression and further measures of mental health [15]. Patients with higher levels of NT-proBNP had a better overall mental health status, despite their somatic symptoms and worse physical functioning. To further assess the significance of NT-proBNP in the emotion regulation of CHD patients, we aimed at analyzing the longitudinal association of NT-proBNP and anxiety.

2. Methods

2.1. Study design

This is a post-hoc analysis of data from the Stepwise Psychotherapy Intervention for Reducing Risk in Coronary Artery Disease (SPIRR-CAD) trial to assess the longitudinal association of baseline NT-proBNP with anxiety. SPIRR-CAD, a randomized controlled trial, comparing usual care plus one individual information session to usual care plus a stepwise psychotherapy intervention, was conducted in ten tertiary care centers in Germany. The design of the study, recruitment path and main results are described in more detail elsewhere [16,17]. Briefly, the study tested whether a stepwise psychotherapy intervention added to usual care improves depressive symptoms more than a single information session. Primary endpoint was the change in depressive symptoms (Hospital Anxiety and Depression Scale (HADS)) from baseline to 18 months. The results showed that depressive symptoms decreased significantly in both groups with no significant difference between the groups or sexes. There was, however, a significant interaction with type D personality, i.e. patients with type D personality showed greater improvements in the stepwise psychotherapy group than in the usual care plus one information session group. The SPIRR-CAD trial further assessed multiple secondary endpoints, including additional biomarkers (high sensitivity C-reactive protein, cortisol, interleukin 10, CD-40 L, fibrinogen, creatinine, and thyroid-stimulating hormone). As these were not the focus of the present post-hoc analysis, they were not analyzed. All ethics committees of the study sites approved the trial protocol and the study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice. All patients gave written informed consent before enrollment. The present analysis used data at all time points of the SPIRR-CAD trial i.e., baseline (T0), 1 month (T1), 6 months (T2), 12 months (T2b), 18 months (T3) and 24 months (T4).

2.2. Participants

The main study enrolled 570 patients, 308 (54%) of whom had valid baseline NT-proBNP measures and HADS-anxiety measures at all six time points. Patients were eligible to participate when showing angiographic (coronary stenosis > 50%, as determined by a recent coronary angiogram) or clinical (history of percutaneous coronary intervention) evidence of CHD and a depression score ≥ 8 on the HADS-depression subscale. Inclusion in the study further required sufficient knowledge of the German language, and patients had to be free of symptoms of severe heart failure (left ventricular ejection fraction (LVEF) < 20% or New York Heart Association (NYHA) class IV) or other life-threatening mental or physical diseases at baseline. Due to ethical concerns, patients with severe depressive episodes (according to Structured Clinical Interview for DSM-IV (SCID)) had to be excluded from the study. Included patients were between 18 and 75 years of age.

2.3. Assessments

The patients' medical history, medication and sociodemographic data were collected from medical records and standardized interviews. Anxiety was assessed using the German version of the HADS questionnaire. This commonly used screening instrument has 14 items to assess symptoms of depression and anxiety in non-psychiatric hospitalized patients with seven items on each subscale [18,19]. It was developed to exclude symptoms that might equally arise from mental or somatic disease, such as fatigue. The scale shows good internal consistency and has been validated in numerous studies in CHD patients. According to the original publication, a cut-off of ≥8 should be used for each subscale to include all possible cases and have a low proportion of false negatives. A cut-off of ≥11 should be used to only include cases of high symptomatology, thereby reducing the possibility of a misclassification of false positive cases [19].

To measure NT-proBNP levels, blood was drawn from a cubital vein in resting patients at baseline. The patients' blood was immediately centrifuged and stored at −80 °C until analyzation at a central lab using an electro-chemiluminescence immunoassay (Elecsys, Roche Diagnostics GmbH, Mannheim, Germany). NT-proBNP is commonly used for research purposes and clinical diagnostics due to its longer half-live and higher stability as compared to BNP. Given that the

precursor pro-BNP is hydrolytically cleaved in an equal stoichiometric ratio into the active BNP molecule and its biologically inactive N-terminal fragment, the NT-proBNP analyte can be used as a valid proxy for serum BNP concentration.

2.4. Data analysis

All raw data were tested for normality and log-transformed to approach normal distribution if they were severely skewed, such as laboratory measures of NT-proBNP. Pearson's correlations were calculated to characterize the sample in terms of sociodemographic data. To control for confounding factors, multiple regression models with baseline NT-proBNP as independent and anxiety as dependent variables were calculated adjusting for sex, age, body-mass index (BMI), and physical functioning, as determined from the corresponding subscale of the SF-36 questionnaire (Medical Outcomes Short Form Health Survey; 20). To assess the longitudinal association of NT-proBNP and anxiety, multilevel linear mixed models were calculated. The models included the six assessments of anxiety as level-1 variable, nested within participants as level-2 variable. In model A, we included random intercepts for participants, as well as NT-proBNP as continuous measure, sex, randomization arm, time, and the interactions with time as fixed effects. In model B, we entered the same factors into the model, however we dichotomized NT-proBNP into lowest vs. highest three quartiles. Differences between subgroups (e.g., sexes, quartiles of NT-proBNP) were assessed using χ^2 analysis for categorical measures and Student's *t*-test for continuous measures. For comparisons of non-parametric data, Mann-Whitney-*U* and Wilcoxon signed-rank tests were performed. All data were analyzed using SPSS (Version 25, IBM Corp., Armonk, NY, USA) and R (Version 3.5.1.).

3. Results

3.1. Baseline characteristics

The mean age of the sample was 60.1 (SD = 8.9) years. The majority of patients were male (80.8%), non-working (53.9%), and married (75.0%) and most patients had a medium or low socioeconomic status (Table 1). Patients had a mean HADS-depression score of 10.2, but the majority did not have a major depressive disorder (MDD) according to SCID (68.2%). The mean anxiety score on the HADS-anxiety subscale was 10.2 (SD = 3.7) at baseline and 76.9% had clinically relevant scores ≥8. After 24 months, approximately half of the patients (49%) still had elevated anxiety scores, whereas the mean score had dropped to 7.7 (SD = 4.2). Separate analysis by sex showed that the prevalence of anxiety at baseline was 74.3% for men and 88.1% for women, which decreased to 47.4% and 55.9%, respectively, after 24 months. This reduction in the HADS-anxiety scores was significant in both male (t(248) = 9.91, p < .001) and female study participants (t(58) = 6.34, p < .001).

Comparison of the included versus the excluded sample revealed that included patients were significantly older (mean (SD) = 60.1 (8.9) versus 58.0 (10.1)), had lower levels of NT-proBNP (median = 165.5 ng/l versus 261.3 ng/l) and higher LVEF (mean (SD) = 58.8 (13.8) versus 53.7 (14.6)). Moreover, they had a higher socioeconomic status (22.7% versus 15.1%) and a significantly higher percentage was married (75.0% versus 54.5%). The samples did not differ on baseline anxiety or other descriptive variables.

Comparison of patients with versus without MDD showed significantly different levels of NT-proBNP (F(3, 304) = 3.35, p = .02). Patients without MDD displayed higher NT-proBNP levels (median (IQR) = 188.55 (318.15)) than patients with mild or moderate MDD (median(IQR) = 123.9 (196.80) vs. 113.25 (203.33)). Patients in partial remission (N = 7) were not included in this analysis due to their small number.

3.2. Correlation analysis

Correlation analysis revealed significant negative associations between baseline log(NT-proBNP) and HADS-anxiety measures at all time points (Table 2). The associations remained significant at all time points in a multiple regression analysis adjusted for age, sex, BMI, and physical functioning (subscale of the SF-36 questionnaire) (all p < .05).

3.3. Multilevel linear mixed model

The results of model A (continuous measure of NT-proBNP) revealed no significant interaction of any of the factors with time (all p > .05). In model B (lowest vs. three highest quartiles of NT-proBNP), we found a significant time*NT-proBNP interaction (t(1535.99) = −2.669, p = .01), as well as a significant time*NT-proBNP*sex interaction (t(1535.99) = 3.277, p = .001). Fig. 1 and 2 show the different time course of anxiety for patients in the lowest versus the three highest quartiles of NT-proBNP, separately for the two genders. The mean values illustrate the significantly different course of anxiety in women with NT-proBNP levels < 86 ng/l versus ≥86 ng/l (Fig. 1), and the similar course in men with low versus high NT-proBNP (Fig. 2).

3.4. Sex-specific analysis

To further explore the unexpected sex difference that was found in model B, we performed an exploratory analysis to compare NT-proBNP levels of men and women at baseline. Overall, the median level of NT-proBNP did not differ significantly between men and women (U = 7118.5, Z = −0.396, p = .71). Comparing the male (N = 249) and female (N = 59) sample, χ^2 analysis and Student's *t*-test showed a

Table 1
Baseline characteristics.

	N/ valid *N*	%
Male sex	249/308	80.8
Married	225/300	75.0
Socioeconomic status		
low	113/308	36.7
medium	125/308	40.6
high	70/308	22.7
SCID major depression		
none	210/308	68.2
mild	39/308	12.7
moderate	52/308	16.9
Partial remission	7/308	2.3
NYHA class		
I	114/298	38.3
II	137/298	46.0
III	47/298	15.8
Beta-blocker medication	265/308	86.0
	M	*SD*
Age, y (N = 308)	60.1	8.9
LVEF (N = 176)	58.8	13.8
BMI (N = 303)	28.7	4.8
CCI (N = 308)	2.0	1.5
T0 NT-proBNP, median (IQR), ng/l (N = 308)	165.5	277.1
T0 HADS depression (N = 308)	10.2	2.5
T0 HADS anxiety (N = 308)	10.2	3.7
T1 HADS anxiety (N = 308)	9.2	4.1
T2 HADS anxiety (N = 308)	8.4	4.0
T2b HADS anxiety (N = 308)	8.4	4.1
T3 HADS anxiety (N = 308)	7.7	4.0
T4 HADS anxiety (N = 308)	7.7	4.2

BMI = body-mass index (kg/m^2), CCI = Charlson comorbidity index, HADS = Hospital Anxiety and Depression Scale, IQR = interquartile range, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, SCID = Structured Clinical Interview for DSM-IV.

Table 2
Correlation analysis.

HADS-anxiety measure		Baseline	1 month	6 months	12 months	18 months	24 months
log(NT-proBNP)	Pearson correlation	−0.198	−0.159	−0.151	−0.223	−0.129	−0.152
	p-value (2-tailed)	0.000	0.005	0.008	0.000	0.024	0.007

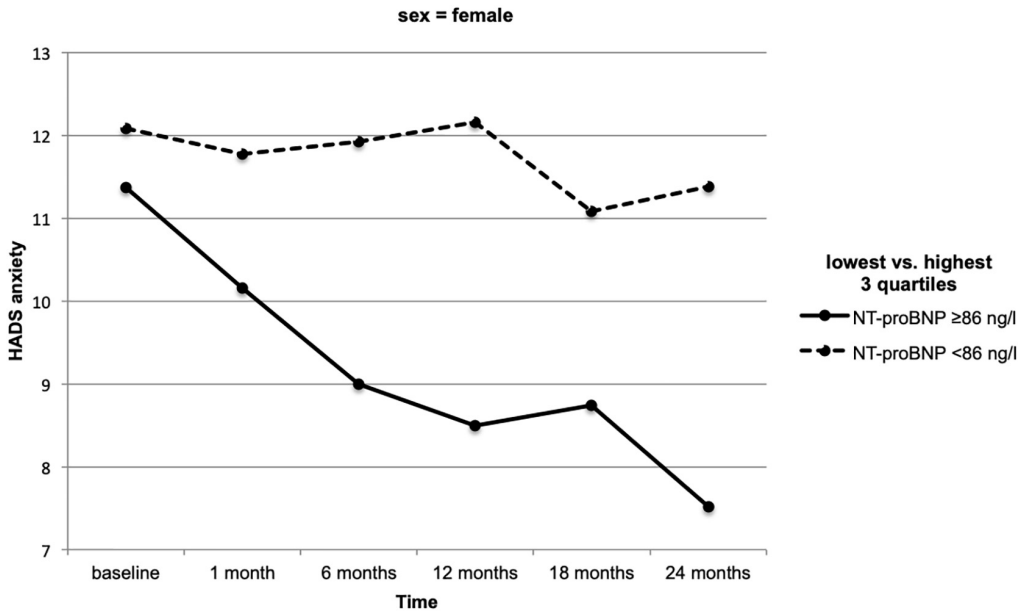

Fig. 1. Mean scores of HADS anxiety over 24 months in women with the lowest versus the 3 highest quartiles of baseline NT-proBNP. HADS = Hospital Anxiety and Depression Scale, NT-proBNP = N-terminal pro-B-type natriuretic peptide.

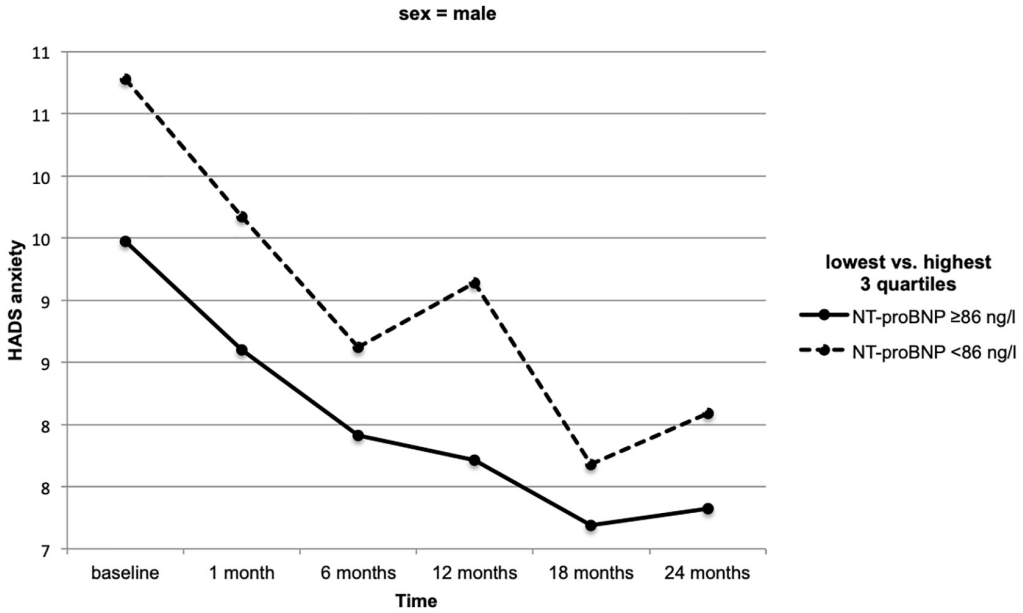

Fig. 2. Mean scores of HADS anxiety over 24 months for low and high baseline NT-proBNP in men. HADS = Hospital Anxiety and Depression Scale, NT-proBNP = N-terminal pro-B-type natriuretic peptide.

significant difference in NYHA class ($\chi^2 = 6.79$, $p = .03$) and LVEF ($t(174) = -2.27$, $p = .03$), with women having both a higher LVEF and a higher NYHA class. Men and women did not differ in age, BMI, and Charlson comorbidity index. As the sample of women was relatively small, more extensive analyses were not possible.

4. Discussion

In the present secondary analysis of the SPIRR-CAD trial, we investigated the longitudinal association of anxiety and NT-proBNP in mildly to moderately depressed coronary artery disease patients. The

results indicate that higher baseline levels of NT-proBNP were associated with persistently lower levels of HADS-anxiety scores over 24 months. To our knowledge, this is the first study with such a large sample and a follow-up of two years. Our results extend the findings of previous studies on natriuretic peptides and anxiety showing an inverse relationship [10,12,15,21], however, they are in contrast to studies in patients with heart failure that found positive or no associations of (NT-pro)BNP and HADS anxiety [22,23]. As these studies were conducted in a different patient population and either cross-sectional, or had a short follow-up period, they are not readily comparable to our findings. Brouwers and colleagues used anxiety as a predictor for the course of NT-proBNP over 9 months. In 94 heart failure patients they found no significant influence of baseline anxiety levels on the course of BNP. This supports our hypothesis that BNP affects the course of anxiety. Even though the present results do not prove causality, they support this notion. We hypothesize that an insufficient up-regulation of BNP, despite cardiac disease, results in more enduring anxiety than in patients with higher levels of this natriuretic peptide.

The results of linear mixed model A did not confirm a linear association between baseline NT-proBNP and anxiety over time and did not render a significant interaction effect. Model B, with dichotomized NT-proBNP values, detected a significant time*NT-proBNP and time*NT-proBNP*sex interaction term. The results show a significantly different course of anxiety for women with very low versus higher levels of NT-proBNP. While women with higher levels of NT-proBNP had a continuous decrease in anxiety over 24 months, women with very low levels of NT-proBNP did not exhibit such change and remained at a high level of anxiety over the entire course of the study, irrespective of their treatment assignment. Male patients with very low levels of NT-proBNP also exhibited higher levels of anxiety; however the course of anxiety over 24 months did not differ from that observed in men with higher levels of NT-proBNP. These results point towards a non-linear association between NT-proBNP and anxiety with higher levels of anxiety, if the body is unable to up-regulate NT-proBNP despite a cardiac disease.

While the negative association between NT-proBNP and anxiety is in line with previous literature, the interaction with the patients' sex was unexpected. The results cannot be explained by the patients' age, BMI, comorbidity, or medication as these parameters did not differ between men and women. Further research with a more balanced representation of both sexes is needed to elaborate why this effect was only present in women.

Previous studies described sex differences in NT-proBNP levels, psychological conditions and cardiac disease separately, but the interaction of these factors has not been studied. Overall, female CHD patients seem to have a high prevalence of depression and anxiety (as women in epidemiological and other clinical samples). However, few studies present data separated by sex, and, in addition, women are still underrepresented in most studies on cardiac diseases. A recent systematic review concluded that women experience more depressive symptoms than men shortly after a cardiac event as well as longitudinally [24]. Moreover, women have naturally higher levels of BNP than men, possibly mediated by circulating free testosterone [25,26]. However, we found no significant difference in NT-proBNP levels for women compared to men. This might be due to 71% of women in our sample being post-menopausal, a state associated with decreasing levels of NT-proBNP [25,27]. Even though NT-proBNP is an established marker of disease severity in heart failure and other cardiac illnesses, the multitude of factors that influence its level (including age, sex steroids, and BMI) call its prognostic value as an isolated predictor into question and warrants further sex-specific interventions.

4.1. Limitations

As the present results are a secondary analysis of the SPIRR-CAD trial, in which NT-proBNP and anxiety were not primary endpoints and patients had moderate to high levels of depression, a study with a less pre-selected sample of heart patients would be more suitable. While the present results stem from a large multicenter trial, they have to be interpreted under the consideration that the number of women in this sample was small, with the majority being male white Germans. The results are thus not readily generalizable to female cardiac patients or other races and ethnicities. Moreover, the inclusion criteria demanded stable CHD and a HADS-depression score ≥ 8, thus we cannot assess the additional effects of the cardiac disease and the depressive symptoms on the association of anxiety and NT-proBNP. Additionally, many patients also had elevations in other dimensions of distress. The results thus cannot be generalized to patients with other somatic or mental illnesses or healthy subjects. Due to the nature of our data, we cannot attribute the course of anxiety to changes in NT-proBNP. As 46% of the sample did not have valid measures for all 6 time points and had to be excluded for the present analysis, there is the possibility of a selection bias. Selected patients had higher ejection fraction and thus also lower levels of NT-proBNP, however with a long follow-up of two years it is common that mostly less severely ill patients have valid measures for all time points.

4.2. Conclusion

Our results show a stable negative association of baseline NT-proBNP and anxiety over two years. However, different pathways in men and women appear to modulate this relationship. Especially women who were not able to up-regulate their BNP at baseline despite their cardiac disease, exhibit persistently higher levels of anxiety, compared to women with higher levels of BNP and compared to men. In contrast, baseline anxiety did not predict the change in anxiety, arguing for a probable causal effect of BNP on anxiety rather than vice versa. However, measuring NT-proBNP levels at multiple time points (in parallel to anxiety scores) and using cross-lagged-model statistics could help clarify this issue. Nevertheless, our results suggest an anxiolytic-like function of BNP, acting as a humoral feedback signal shielding the diseased heart from the adverse effects of overshooting anxiety.

Conflicts of interest and source of funding

During the last three years, Christian Albus received lecture honoraria from Boehringer Ingelheim, Bayer Vital, Daiichi Sankyo, and MSD Sharp & Dohme.

Rolf Wachter reports having been an investigator or consultant for, or received fees from Bayer, Berlin Chemie, Bristol-Myers-Squibb, Boehringer Ingelheim, Boston Scientific, CVRx, Gilead, Johnson & Johnson, Medtronic, Novartis, Pfizer, Sanofi, and Servier outside the submitted work. He received research grants from Boehringer Ingelheim, the European Union, and the German Federal Ministry of Education and Research.

Christoph Herrmann-Lingen reports that he is receiving royalties from Hogrefe Huber Publishers for the German version of the Hospital Anxiety and Depression Scale. During the last three years he has received lecture honoraria from Servier, Heel, and Novartis.

The remaining authors report no conflicts of interest.

This study has been funded by a grant from the German Research Foundation (DFG; # HE 3115/10-1, HE 3115/10-2, AL 559/2-1, AL 559/2-2) to Drs. Herrmann-Lingen and Albus, and a grant from the German Federal Ministry of Education and Research to the German Center of Cardiovascular Research (DZHK), partner site Göttingen. The sponsors were not involved in the study design, data collection, analysis, interpretation or writing of the report.

Acknowledgements

Additional members of the SPIRR-CAD Study Group:

Berlin: Andrea Köpsel, Dipl. Psych., Daniela Kronfeldt, MD, Kristina Orth-Gomér, MD, Burkert Pieske, MD, Miriam Rudat, PhD, Sabine

Siebenhüner, MD; Bad Nauheim: Jochen Jordan, PhD; Cologne: Martin Hellmich, PhD, Frank Lambertus, MD, Ursula Paulus, PhD, Andreas Stöhr, PhD, Frank Vitinius, MD; Dresden: Silvia Wolff-Stephan, PhD, Matthias Israel, MD, Michael Mueck-Weymann†, MD, PhD, Katja Petrowski, PhD; Freiburg: Stephanie Bursch, Dipl. Psych., Kurt Fritzsche, MD; Göttingen: Alexandra Bosbach, Dipl. Psych., Katja Jamrozinski, PhD, Halina Lackschewitz, PhD, Regina Stötzel, MD, Ulrike Mälzig, MD; Hannover: Martina de Zwaan, MD, Christian Krauth, PhD, Cornelia Reichert, PhD, Barbara Schwandt, PhD, Christiane Waller, MD; Heidelberg: Bernhard Hain, MD, Jana Jünger, MD, Jobst-Hendrik Schultz, MD; Mainz: Manfred E. Beutel, MD, Jörg Wiltink, MD; Munich: Christina Henningsen, Dipl. Psych.; Nuremberg: Rüdiger Behnisch, MD, Anita Kraiss, Dipl. Psych.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2019.05.006.

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6 General discussion

Cardiovascular morbidity and emotional distress have been pathologically linked by a large body of epidemiological evidence. However, most studies focused on the role of depression in pathways linking the regulation of cardiovascular homeostasis and stress, while the impact of anxiety has often not been taken into account. As natriuretic peptides are present both in the vascular system and the brain, they are of particular interest in this respect since they exert peripheral vasoactive effects and affect emotion. This dissertation presents the results of two post-hoc analyses investigating the association of BNP and mental health in patients with coronary heart disease. The goal was to assess the possible role of (NT-pro)BNP in mental health of depressed CHD patients from the multicenter SPIRR-CAD trial. The hypothesis that BNP, like ANP, shows anxiolytic-like effects was assessed using cross-sectional and longitudinal data. Moreover, the scope of the cross-sectional analysis was broadened by additional measures of mental health, including quality of life, depression, vital exhaustion, coping with illness, and type D personality. The general discussion will provide reflections on the results in the context of current findings of the field, after which strengths and limitations of the studies are summarized. Finally, implications for future research are discussed, followed by the conclusion.

While natriuretic peptides are not known to be causally involved in heart disease, they were shown to be powerful indicators of the severity of heart disease, prognostic markers for CHD progression, and part of adaptive counter-regulation by reducing the hemodynamic load of the heart (Bibbins-Domingo et al. 2007; Hodes and Lichtstein 2014). Our results extend these findings and show a role of NT-proBNP in various measures of mental health. Such broader effect of natriuretic peptides has previously been detected in patients during alcohol withdrawal (Koopmann et al. 2014), whereas extensive studies in cardiac patients are missing. Although counterintuitive, our results support the view of BNP as a general stress-buffering agent as part of adaptive counter-regulation, even though NT-proBNP was also significantly associated with lower levels of physical quality of life and more severe physical illness, which could expectedly impair mental quality of life and emotional well-being. However, previous studies showed that in cardiac patients, somatic measures of cardiac disease are, if at all, only weakly associated with mental health (Jünger et al. 2002; Edelmann et al. 2011). Our results

extend this finding to self-report measures of physical well-being and quality of life, which do not seem to strongly affect the patients' mental health.

An independent inverse association of NT-proBNP and anxiety has not been shown before but was confirmed by a recent analysis of the multicenter Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Heart Failure (DIAST-CHF) study, which revealed a significant negative association of NT-proBNP with HADS anxiety in a sample of N = 1463 patients with cardiovascular risk factors (Sadlonova et al. 2019). Further results of the DIAST-CHF cohort showed significant negative associations of anxiety with vasodilatory peptides, i.e. mid-regional proANP (Meyer et al. 2015c; Sadlonova et al. 2019) and adrenomedullin (Meyer et al. 2015d), as well as with the vasoconstrictive peptides arginine-vasopressin (Sadlonova et al. 2019) and endothelin (Meyer et al. 2015b). The various results of associations of vasoactive peptides with emotion suggest a complex regulation system. Moreover, these peptides influence the release of each other, acting as complex humoral feedback loops. The tentative effects of BNP on anxiety and mental health could be mediated via cGMP signaling pathways in the brain. When BNP binds to the natriuretic peptide receptor-type A (NPR-A) the increased cGMP production can modulate synaptic activity in various brain regions including the cerebellum, the amygdala, and the hippocampus. Behavioral studies have indicated that cGMP signaling, and especially the dysfunction of cGMP signal transduction, is involved in anxiety, depression, addiction, and schizophrenia (Kleppisch and Feil 2009). These long-term effects of cGMP could be mediated via the regulation of gene expression in the respective brain areas. However, these effects have only been shown for cGMP stimulated by nitric oxide and not yet by natriuretic peptides (Kleppisch and Feil 2009).

6.1 Strengths and limitations

To date, this is the most extensive analysis of the association of NT-proBNP with mental health measures in CHD patients. Internationally, few studies have described the association of BNP and mental health in heart disease patients or other populations. In contrast to previous studies, the current data stem from a large sample of a multicenter trial with a long follow-up period of 2 years. Moreover, the current study not only assessed depression or anxiety, but a wider range of mental health measures

and various somatic parameters.

Due to recruitment in German tertiary care centers, the majority of participants were caucasian Germans and the sample mainly consisted of male participants. As the primary goal of the SPIRR-CAD trial was to test the effects of stepped psychotherapy on symptoms of depression in CHD patients, the design did not primarily aim to assess the association between and confirm directionality of NT-proBNP and mental health measures. The cross-sectional analyses in publication 1 cannot show directionality of the observed associations. However, the results indicate that BNP could have anxiolytic effects as predicted, and even broader effects on emotions. This is shown by the fact that NT-proBNP not only correlated significantly with anxiety, but also with various other measures of mental health. Although it seems plausible that BNP not only protects against the adverse effects of anxiety, this conclusion cannot be drawn from the presented results. In addition, the discovered sex-effect in the longitudinal analysis needs replication. As the attrition rate was high, the sample of the longitudinal analysis was small. Especially the number of women was rather low limiting the generalizability of the results. The persisting high levels of anxiety in women with very low levels of NT-proBNP has not been described before and should be studied experimentally in more detail in the future. Naturally, women have higher levels of BNP compared to men, however we did not find significant differences in NT-proBNP between men and women in our sample (Redfield et al. 2002; Chang et al. 2007). The proposed insufficient up-regulation of BNP in parts of the female sample could have been influenced by menopause, which decreases the levels of BNP (Redfield et al. 2002; Glisic et al. 2018). However, as the majority of our female sample was postmenopausal and the female sample was too small for a subgroup analysis, this remains a hypothesis.

To test the primary outcomes of SPIRR-CAD, the inclusion criteria required mild to moderate levels of depression (HADS-depression subscale > 7) and a large number of patients additionally had elevated levels in other dimensions of distress. Moreover, the sample showed significant differences in NT-proBNP levels between patients with major depressive disorder versus without. Due to the pre-selection of the SPIRR-CAD sample, we cannot assess a possible additional effect of depression or a moderating effect of depression on the association of NT-proBNP and mental health. The longi-

tudinal analysis of NT-proBNP and anxiety also entails a possible selection bias, as described in publication 2.

6.2 Research implications

As discussed above, the design of SPIRR-CAD does not allow causal conclusions about the role of NT-proBNP in emotion regulation. Future studies should test this relation experimentally as primary outcome and with a longitudinal design using multiple measures of all tested variables. The apparent differing effects in male and female participants should be investigated further. Therefore the design of future studies should be balanced to include equal amounts of men and women and the sample size should be powered to find subgroup effects. The vasodilatory effects of ANP and BNP have led to the development of synthetic analogues (anaritide and nesiritide, respectively). While they have been tested and approved as potential treatment of decompensated heart failure, their effectiveness and safety have been questioned and their effect on the patients' mental health has yet to be assessed (Potter et al. 2006). While previous studies and the present thesis have focused on ANP and BNP, the physical and mental effects of C- and D-type natriuretic peptide (CNP and DNP, respectively), and urodilatin are poorly defined and need to be studied to understand the complex functions of natriuretic peptides. Especially CNP could possibly be involved in emotion regulation, as it had anxiogenic effects in studies in mice and healthy men (Montkowski et al. 1998; Kellner et al. 2003). The opposing effects on anxiety of ANP and BNP versus CNP might explain why the sacubitril and valsartan containing medication Entresto® does not seem to affect the patients' mental state. This could be expected as sacubitril inhibits neprilysin, which slows down the degradation of natriuretic peptides and by that increases their levels. It seems however that the levels of all natriuretic peptides are increased and their anxiolytic and anxiogenic effects cancel each other out. CNP is mainly expressed in the brain and was shown to be able to increase the permeability of the blood-brain-barrier (Bohara et al. 2014). This could also influence the effect of BNP in the brain, as it was found in the hypothalamus and the cerebral cortex, but no BNP mRNA was observed in the brain (McKenzie et al. 1994; Langub et al. 1995; Abdelalim et al. 2006).

6.3 Final conclusion

Natriuretic peptides, as part of the neurobiological process in CHD, could modulate the psychological adaptation of patients. CHD patients have an increased risk for depression, anxiety and low quality of life, which have a negative effect on the progression and prognosis of the heart disease. The observed negative associations of NT-proBNP with anxiety support the notion that natriuretic peptides could play a crucial role in counteracting this vicious circle. More surprisingly, the results showed negative associations of NT-proBNP with a wider range of mental distress measures at baseline. The longitudinal analysis revealed that women with very low levels of NT-proBNP at baseline show persisting high levels of anxiety, which could be explained by insufficient up-regulation of NT-proBNP despite CHD. Diagnosis and treatment of mental comorbidities are important, as they affect CHD. In conclusion, especially patients with an insufficient up-regulation of NT-proBNP might be at risk for unfavorable outcomes and inadequate adaptation.

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Appendix

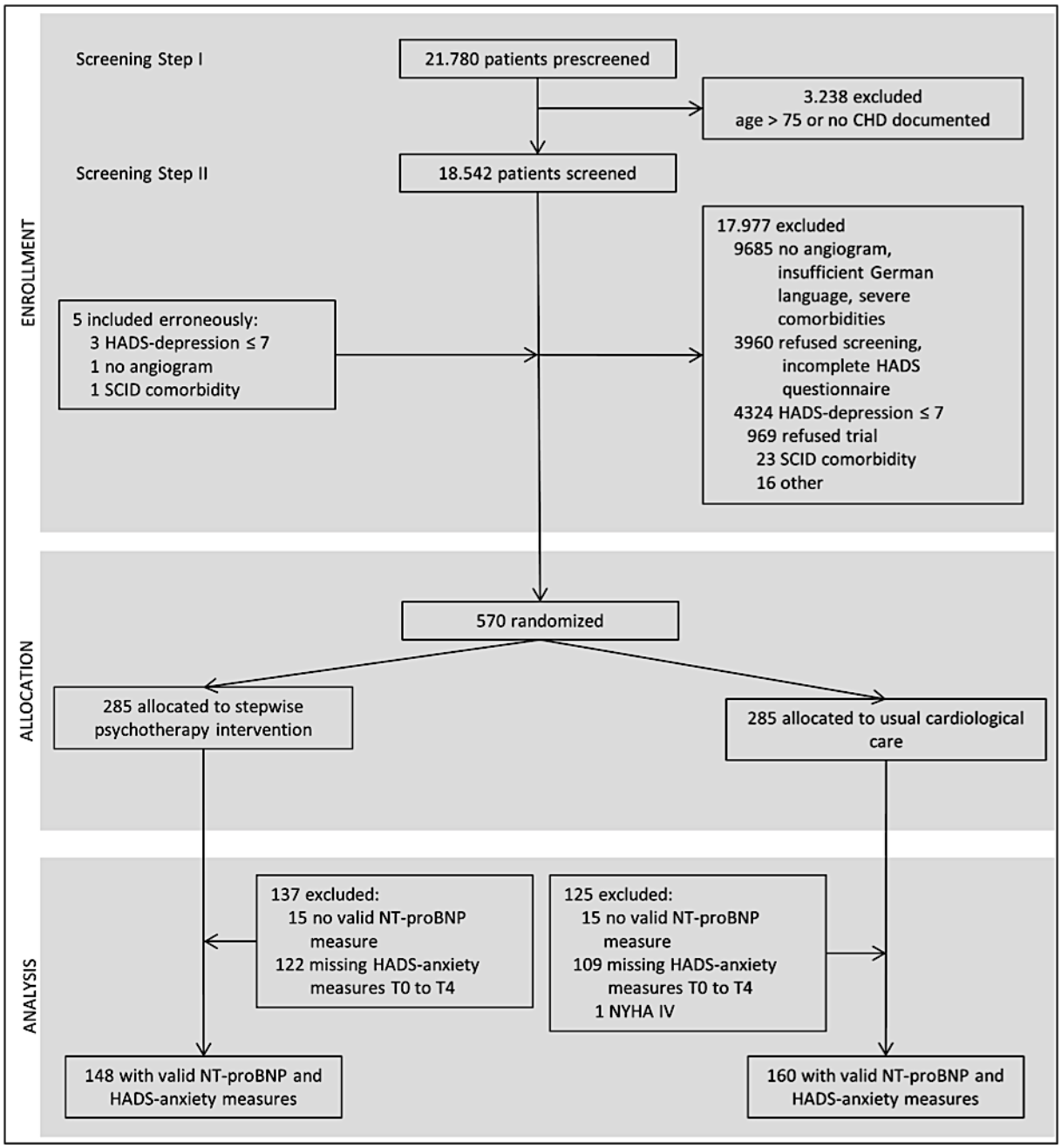

Figure 3: Consort flow chart.

Own contribution

Due to the fact that SPIRR-CAD was a multicenter and interdisciplinary research project, I would like to specify the individual contributions. I conceptualized the research questions under the supervision of my thesis committee. For both publications, I analyzed the data using SPSS and R and interpreted the results. Apart from the Consort flow chart, which was kindly provided by Chr. Herrmann-Lingen, I prepared all tables and figures, and wrote both manuscripts. I submitted and revised both manuscripts for publication.

Christoph Herrmann-Lingen was the senior scientist, who granted me access to the data set and supervised the entire process of literature search, data analysis, and interpretation of the results. Moreover, he critically revised all manuscripts for important intellectual content. Aribert Rothenberger and Rolf Wachter supervised the data analysis and critically revised both manuscripts for important intellectual content.

Birgit Herbeck Belnap helped to draft the manuscript of publication 1 and revised it. Thomas Meyer helped to interpret the data of publication 1 and helped to draft manuscript 2 and revised it. Christian Albus, Lutz Binder, Hans-Christian Deter, Karl-Heinz Ladwig, Matthias Michal, Joram Ronel, Wolfgang Söllner, and Cora S. Weber contributed to the study design, supervised the data acquisition, and provided important intellectual content to the scientific content of this work.

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