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ORIGINAL PAPER

Higher plasma levels of MR-pro-atrial natriuretic peptide are linked to less anxiety: results from the observational DIAST-CHF study

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Abstract
Aims Growing evidence suggests that natriuretic peptides play a role in the neurobiology of anxiety. In the present study, we investigated whether in patients with cardiovascular risk factors higher plasma levels of natriuretic peptides are linked to reduced anxiety.
Methods A total of 1,360 patients from the observational DIAST-CHF study (mean age 65.9 ± 8.2 years, 48.7 % males, mean left ventricular ejection fraction 60.0 ± 8.2 %) with risk factors for diastolic heart failure were included. Study participants underwent physical examination, echocardiography, and assessment of anxiety using the Hospital Anxiety and Depression Scale (HADS). In addition, plasma concentrations of natriuretic peptides were measured.
Results Among the total study population, there were $n = 117$ patients (8.6 %) with HADS anxiety scores above the cut-off (≥11) suggestive of clinically relevant anxiety. In bivariate analyses, we found a significant inverse association between elevated HADS anxiety and log-transformed mid-regional pro-atrial natriuretic peptide (MR-proANP) ($p < 0.001$) and amino-terminal pro-brain natriuretic peptide (NT-proBNP) ($p = 0.008$). Logistic regression models adjusted for sex, age, body mass index, and Framingham score confirmed that plasma MR-proANP ($\exp(\beta) = 0.35$, 95 % confidence interval [95 % CI] 0.14–0.92, $p = 0.032$) concentrations were significantly and inversely associated with clinically relevant anxiety, while NT-proBNP ($\exp(\beta) = 0.67$, 95 % CI 0.41–1.07, $p = 0.094$) failed to reach the significance level in independently predicting anxiety.
Conclusions In our study population of outpatients with cardiovascular risk factors, plasma concentrations of MR-proANP were negatively and independently related to clinically relevant anxiety. Further investigations are required to search for possible anxiolytic effects of this circulating natriuretic peptide in medical outpatients with cardiovascular risk factors for diastolic dysfunction.

Keywords Anxiety · Natriuretic peptide · Cardiovascular risk · Heart failure · Diastolic dysfunction

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Introduction

Atrial and brain natriuretic peptides (ANP and BNP) belong to a family of neurohormonal substances which play an important role in the regulation of cardiovascular homeostasis and body fluid volume. In response to myocardial stretch and increased blood volume, the two peptides are released by cardiac myocytes and have been shown to promote diuresis and vasodilation [1]. Numerous studies have demonstrated elevated serum natriuretic peptide levels in patients with congestive chronic heart failure (CHF) and have stressed the value of ANP and BNP as useful tools in the diagnosis of CHF [2–4]. Moreover, natriuretic peptides have been shown to identify CHF patients at risk of death and serve as long-term predictors of adverse outcome in all stages of CHF [5–8] as well as in primary care or population-based cohorts [9, 10]. Therefore, ANP and BNP have been introduced in routine medical practice as biomarkers for risk stratification and monitoring of treatment effectiveness in CHF patients [7, 11]. A predictive value for increased mortality has also been shown for the N-terminal portions of the respective prohormones: the 98-amino acid NT-proANP and the 76-amino acid NT-proBNP [12, 13].

Besides their cardiovascular effects, it has been reported that the 28-amino acid peptide ANP and its close homolog BNP exert anxiolytic-like behavior [14, 15]. Animal studies in rodents and clinical studies in patients with panic disorder have gathered evidence that administration of ANP leads to a partially suppressed hypothalamo-pituitary-adrenocortical (HPA) system and that this peptide may act as corticotropin-releasing hormone (CRH)-inhibiting factor [16]. The panicogenic effects of cholecystokinin-tetrapeptide (CCK-4) were attenuated by ANP infusions in human patients with panic disorder, pointing to an important neuromodulatory role of ANP and its cognate membrane-bound receptors in the central nervous system [17–19].

Although it has been well established that natriuretic peptides modulate endocrine and emotional stress responses, clinical studies in CHF patients on this issue are rare. One study by Murberg and colleagues in clinically stable patients with congestive heart failure ($n = 119$) found that depressive symptoms and overall well-being were not related to plasma proANP levels [20], while a negative association between NT-proANP and anxiety was shown in a similar-sized sample ($n = 119$) of patients with heart failure or its risk factors [21]. Therefore, the present study was aimed to assess this relationship in a heterogeneous sample of patients with cardiovascular risk factors by testing more putative biomarkers for their role in linking natriuretic peptide concentrations to anxiety. To our knowledge, this is the first investigation on the association of different natriuretic peptide measurements and clinically relevant anxiety in such a large study population.

Methods

Study design

The participants in this study were 1,360 medical outpatients aged 50–85 years recruited from the population-based Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Heart Failure (DIAST-CHF). The multicenter DIAST-CHF study was part of the nationwide German Competence Network Heart Failure conducted in 2004 and 2005 to assess the prevalence of diastolic dysfunction of the left ventricle in medical outpatients treated by primary care physicians [22–24]. Study participants were recruited if they had at least one cardiovascular risk factor for the development of diastolic heart failure, such as hypertension, diabetes mellitus, coronary heart disease, sleep apnea syndrome, or history of heart failure. Exclusion criteria were unwillingness to give informed consent, insufficient understanding of the German language, and/or unavailability for logistic reasons. The study protocol was approved by all local institutional ethics committees and complies with the Declaration of Helsinki. All patients gave written informed consent before being included in the study.

Classification of patient groups

All patients received routine physical examination and a detailed echocardiogram for the assessment of systolic and diastolic functions including left ventricular end-diastolic diameter (LVEDD) and ejection fraction (LVEF). In order to assess the relationship between natriuretic peptides and anxiety in patients with different grades of left ventricular dysfunction, study participants were classified into four groups [23]: normal systolic function and no signs of an abnormal left ventricular relaxation pattern, indicative of grade 0 diastolic dysfunction, were observed in 223 patients (group 1). An abnormal relaxation pattern with a reversal of the normal *E*/*A* ratio was seen in 817 patients, and these were diagnosed as having grade I diastolic dysfunction (group 2). Moderate to severe diastolic dysfunction (grade II–IV) ranging from pseudonormal to restrictive filling dynamics were documented in 209 patients (group 3). The remaining 111 patients (8.3 %) had a reduced left ventricular ejection fraction (LVEF) below 50 % (group 4). The clinical severity of CHF was rated according to the Framingham sum score [25] and the New York Heart Association (NYHA) criteria by experienced cardiologists, who were blind to the patients' levels of natriuretic peptide and the results from psychometric testing.

Assessment of anxiety

Study participants were requested to complete the German version of the Hospital Anxiety and Depression Scale

(HADS) as part of the study procedure. The HADS is a widely used short self-assessment questionnaire especially developed for physically ill patients. The instrument comprises 14 four-point Likert-scaled items on two subscales, covering cognitive-affective features of depression (HADS-D) and psychological manifestations of generalized anxiety and panic (HADS-A) [26–28]. Each subscale consists of 7 multiple-choice items and hence subscale scores range from 0 to 21. In this study, we used the sum score of the HADS-A subscale with higher scores indicating more severe anxiety. In accordance with the literature, we used a cut-off level ≥11 for distinguishing between anxious and non-anxious subjects [28]. A cut-off ≥8 on the depression subscale indicates that the patients probably have a depressive symptomatology. The HADS including its German version has been validated extensively as a measure of clinically relevant anxiety and/or depression and shows good reliability with a Cronbachs α of 0.80.

Laboratory measurements

From each study participant, venous blood samples were drawn after 15 min of rest in a prone position. Both heparinized and EDTA plasma aliquots were obtained by centrifugation. Samples were then immediately frozen and stored at −80 °C, until they were analyzed in a specialized laboratory. NT-proBNP was measured with a commercially available electrochemiluminescence immunoassay on a Cobas 8000 or Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany) using two monoclonal antibodies [29, 30]. Quantitative determination of BNP in plasma samples was achieved by the ADVIA Centaur BNP assay from Bayer Diagnostics (Munich, Germany), which is an automated two-site sandwich immunoassay based on a direct chemiluminescent technology [31]. Mid-regional NT-proANP was determined in EDTA plasma using an immunoluminometric assay (BRAHMS Seristra Luminescence Immuno Assay, Henningdorf, Germany) [32–34]. ProANP was determined using a microtiter immunoassay (Immundiagnostik, Freiburg, Germany) [21].

Statistical analyses

Demographic and clinical data are presented as means ± standard deviations or frequencies and percentages, while natriuretic peptide levels are given as medians and interquartile ranges (IQR). Student's *t* test was used to compare HADS-A scores in anxious versus non-anxious study participants. Mann–Whitney *U*-tests were used to compare medians of the non-normally distributed natriuretic peptide concentrations between the two groups of anxious and non-anxious patients. For the comparison between the four groups of patients with diastolic (grade 0, I, and ≥II) and systolic (LVEF < 50 %) dysfunction, univariate analyses of variance (ANOVA) were calculated. Logistic regression models were computed with classification as anxious and non-anxious according to HADS-A as dependent variable adjusted for age, sex, body mass index (BMI), Framingham sum score, systolic blood pressure and each of the natriuretic peptides measured separately. These potential confounders were entered in the models because of well-established effects of sex, age, somatic comorbidity, and heart disease on the prevalence of anxiety [35]. The results from these calculations are reported as multivariate odds ratios (exp(β)-coefficients) and their 95 % confidence intervals. All analyses with natriuretic peptides were computed with log10-transformed values. In all analyses, a p value ≤ 0.05 was used to indicate statistical significance. Data were analyzed on a personal computer with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Anxiety levels in the study population

The mean HADS-A anxiety score in the whole study group was 5.0 ± 3.6 (Table 1). In contrast to depression ($p = 0.111$, see Table 1), ANOVA revealed a significantly lower mean HADS-A score in patients with systolic dysfunction (4.0 ± 2.8) as compared to patient groups with diastolic dysfunction of grade I (5.1 ± 3.6) and grade ≥II (5.2 ± 3.8), respectively ($p = 0.021$). Among all study participants, $n = 117$ patients (8.6 %) had HADS anxiety scores above the cut-off (≥11) suggestive of clinically relevant anxiety. As demonstrated in Table 2, study participants with normal versus elevated HADS anxiety scores differed significantly with respect to sex ($p = 0.002$), BMI ($p < 0.001$), systolic blood pressure ($p = 0.005$), and LVEDD ($p = 0.027$).

Plasma levels of natriuretic peptides in anxious versus non-anxious participants

Next, we assessed whether the means of the various natriuretic peptides tested differed between the two groups of anxious and non-anxious subjects. The results showed no significant group difference with respect to BNP ($p = 0.431$) or NT-proANP ($p = 0.126$) concentrations. However, the two groups differed significantly in circulating MR-proANP (median 74, IQR 54–107 vs 88, IQR 62–130 pmol/l, $p < 0.001$) and NT-proBNP levels (72, IQR 39–174 vs 101, IQR 51–191 pg/ml, $p = 0.008$).

Plasma MR-proANP is an independent predictor for anxiety

Given the association of MR-proANP and NT-proBNP with anxiety in univariate analysis, we finally computed a set of

Table 1 Characterization of the total study population including the four groups of patients with diastolic dysfunction graded as indicated and systolic dysfunction as defined by a reduced ejection fraction (EF) <50 %

	Total study population (n = 1,360)	Group 1 EF ≥ 50 DD = 0 (n = 223)	Group 2 EF ≥ 50 DD = I (n = 817)	Group 3 EF ≥ 50 DD ≥ II (n = 209)	Group 4 EF < 50 (n = 111)	F value	p value
Sex (male, %)	48.7	45.3	46.0	45.5	81.1	17.6	<0.001
Age (SD, years)	65.9 ± 8.2	60.1 ± 7.2	67.4 ± 7.6	64.6 ± 8.2	65.9 ± 8.2	60.9	<0.001
Hypertension (%)	80.3	69.5	81.3	84.7	86.5	7.5	<0.001
Hyperlipoproteinemia (%)	40.8	37.2	40.1	44.5	45.9	1.2	0.293
Diabetes mellitus (%)	24.3	17.0	23.9	27.8	35.1	5.0	0.002
Current smoking (%)	10.3	13.1	10.3	9.1	7.2	2.7	0.044
Body mass index (kg/m^2)	28.9 ± 4.9	27.5 ± 5.1	29.1 ± 4.7	29.4 ± 4.9	29.8 ± 5.5	8.2	<0.001
6-min walking distance (m)	518 ± 106	568 ± 80	506 ± 109	524 ± 103	489 ± 109	21.8	<0.001
Framingham sum	0.71 ± 1.08	0.43 ± 0.77	0.71 ± 1.08	0.80 ± 1.16	1.11 ± 1.26	10.8	<0.001
Atrial fibrillation (%)	4.6	4.9	2.4	3.8	20.7	26.5	<0.001
History of MI (%)	9.3	5.8	7.1	8.6	33.3	29.8	<0.001
Systolic BP (mmHg)	147.2 ± 21.0	141.9 ± 20.9	148.7 ± 21.0	147.8 ± 20.3	145.6 ± 21.2	6.5	<0.001
Diastolic BP (mmHg)	83.2 ± 11.7	82.3 ± 11.8	84.3 ± 11.8	80.9 ± 11.7	81.0 ± 10.6	7.1	<0.001
Heart rate (bpm)	70.2 ± 11.6	67.2 ± 10.5	72.4 ± 11.6	64.8 ± 9.6	70.1 ± 12.2	31.5	<0.001
NYHA class	2.0 ± 0.7	2.2 ± 0.6	1.9 ± 0.6	2.1 ± 0.7	1.9 ± 0.8	0.98	0.402
LA (mm)	41.0 ± 6.0	40.2 ± 5.9	40.2 ± 5.4	42.4 ± 6.0	46.2 ± 7.7	40.1	<0.001
LVESD (mm)	31.1 ± 6.3	30.6 ± 4.7	30.2 ± 5.6	30.4 ± 5.0	39.9 ± 8.7	94.9	<0.001
LVEDD (mm)	49.3 ± 6.2	49.8 ± 5.1	48.2 ± 5.9	49.5 ± 5.2	55.9 ± 7.6	56.2	0.027
LVEF (%)	60.0 ± 8.2	62.2 ± 6.4	61.3 ± 6.3	61.8 ± 6.7	42.8 ± 7.1	292	<0.001
MR-proANP (pmol/l)	104 ± 69	90 ± 44	95 ± 62	119 ± 69	165 ± 114	42.3	<0.001
NT-proBNP (pg/ml)	195 ± 368	119 ± 131	142 ± 226	229 ± 331	665 ± 892	82.0	<0.001
BNP (pg/ml)	89 ± 112	77 ± 90	74 ± 87	105 ± 105	189 ± 209	38.8	<0.001
NT-proANP (pmol/l)	4329 ± 1968	3911 ± 1416	4085 ± 1548	4655 ± 1894	6124 ± 3816	24.1	<0.001
HADS-A score	5.0 ± 3.6	4.8 ± 3.7	5.1 ± 3.6	5.2 ± 3.8	4.0 ± 2.8	3.3	0.021
HADS-A ≥ 11 (%)	8.6	9.0	8.6	12.0	1.8	9.6	0.023
HADS-D score	4.2 ± 3.6	3.7 ± 3.8	4.2 ± 3.5	4.5 ± 3.6	4.2 ± 3.3	3.3	0.111
HADS-D ≥ 8 (%)	16.8	13.5	16.3	22.0	17.1	6.0	0.111

Results are presented as means and standard deviations. Raw data of natriuretic peptide concentrations are given

ANP atrial natriuretic peptide, *BNP* brain natriuretic peptide, *BP* blood pressure, *DD* grade of diastolic dysfunction, *HADS-A* anxiety subscale of the Hospital Anxiety and Depression Scale, *LA* left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVES* left ventricular ejection fraction, *MI* myocardial infarction, *SD* standard deviation

Table 2 Comparison of the anxious versus non-anxious patient group

	Non-anxious group ($n = 1243$)	Anxious group ($n = 117$)	p value
Sex (male, %)	50.0	45.0	0.002
Age (SD, years)	66.2 ± 8.2	62.6 ± 7.4	<0.001
Hypertension (%)	80.0	82.9	0.458
Hyperlipoproteinemia (%)	40.6	42.7	0.657
Diabetes mellitus (%)	23.7	29.9	0.164
Current smoking (%)	29.4	33.8	0.277
Body mass index (kg/m^2)	28.9 ± 4.9	29.8 ± 5.3	0.049
6-min walking distance (m)	518 ± 106	514 ± 107	0.653
Framingham sum	0.67 ± 1.05	1.14 ± 1.27	<0.001
Atrial fibrillation (%)	4.7	2.6	0.309
History of MI (%)	9.3	9.4	0.957
Systolic BP (mmHg)	147.7 ± 21.1	142.0 ± 19.4	0.005
Diastolic BP (mmHg)	83.2 ± 11.7	83.4 ± 12.2	0.857
Heart rate (bpm)	70.2 ± 11.6	69.9 ± 11.6	0.809
NYHA class	1.9 ± 0.7	2.2 ± 0.5	0.154
LA (mm)	41.1 ± 6.0	40.1 ± 6.0	0.076
LVESD (mm)	31.1 ± 6.4	30.8 ± 5.3	0.464
LVEDD (mm)	49.4 ± 6.3	48.3 ± 5.0	0.027
LVEF (%)	59.9 ± 8.3	61.0 ± 7.0	0.167
HADS-A score	4.3 ± 2.9	12.6 ± 1.6	<0.001

ANP atrial natriuretic peptide, *BNP* brain natriuretic peptide, *BP* blood pressure, *DD* grade of diastolic dysfunction, *HADS-A* anxiety subscale of the Hospital Anxiety and Depression Scale, *LA* left atrium, *LVEDD* left ventricular end-diastolic diameter, *LVES* left ventricular ejection fraction, *MI* myocardial infarction, *SD* standard deviation

multivariate logistic regression models with clinically elevated HADS-A scores versus normal scores as the dependent variable adjusted for sex, age, BMI, and Framingham sum score, where each natriuretic peptide was included separately as an additional variable (Table 3). Data from these models confirmed that elevated MR-proANP was significantly and independently associated with lower anxiety ($\exp(\beta) = 0.35$, 95 % CI 1.4–0.92, $p = 0.032$). Moreover, by adding MR-proANP as an additional variable in this model, the corrected R^2 of the entire model as a measure of the goodness-of-fit slightly increased from 0.041 to 0.045. In similar models, NT-proBNP also tended to predict less anxiety ($\exp(\beta) = 0.67$, 95 % CI 0.41–1.07, $p = 0.094$), whereas the other natriuretic peptides were not linked to anxiety. Similar results were obtained when systolic blood pressure was additionally included in these models (data not shown).

Discussion

The present sub-study of the DIAST-CHF trial was conducted to assess the relationship between circulating natriuretic peptides and anxiety in medical outpatients with cardiovascular risk factors for diastolic dysfunction or overt heart failure. Our study design offered the opportunity to explore the interconnection of natriuretic peptides and anxiety in patients with mild or moderate diastolic heart failure since in these subgroups the natriuretic peptide levels were not generally high as compared to patients with reduced systolic function.

The main finding of this sub-study was an inverse association between MR-proANP and anxiety, corroborating a previous study in 119 patients with heart failure which reported higher plasma levels of NT-proANP to be related to lower anxiety [19]. Although we observed that, in our study population of 1,360 study participants, all four natriuretic peptide markers tended to be lower in anxious versus non-anxious patients, the association was neither significant for BNP nor for NT-proANP. The initial association of NT-proBNP with anxiety lost significance in the multivariate model. The weak association between NT-proBNP and anxiety observed in our sample may explain why Brouwers and colleagues in their cohort of only 94 patients with systolic heart failure found no effect of plasma NT-BNP levels on HADS-A scores [36]. In contrast to BNP, however, we found that low plasma MR-proANP concentrations were significantly associated with clinically relevant anxiety in both univariate and multivariate models, when adjusted for sex, age, body mass index, and Framingham score.

The inverse relationship between MR-proANP (and less clearly NT-proBNP) and anxiety was not unexpected, given the anxiolytic activity of peripherically administered ANP in human patients with panic disorder [17] as well as in rodents following intracerebroventricular ANP administration in paradigms such as the elevated plus maze [37, 38]. The inhibitory action of elevated plasma ANP levels in panicogenic challenge with sodium lactate or CCK-4 suggests a humoral feedback loop in the central nervous

Table 3 Results from logistic regression models with clinically significant versus insignificant HADS-A screening as dependent variable and the plasma concentrations of natriuretic peptides as independent variable adjusted for age, sex, body mass index (BMI), and Framingham sum

	Exp(β)	95 % confidence interval	Wald value	*p* value
Model 1				
Dependent variable HADS-A ≥ 11				
(Total model $p < 0.001$, $R^2 = 0.041$)				
Sex	1.793	1.196–2.686	8.000	0.005
Age	0.932	0.909–0.956	28.984	<0.001
BMI	1.009	0.972–1.047	0.21	0.647
Framingham sum	1.481	1.262–1.737	23.205	<0.001
	Exp(β)	95 % CI	Wald value	*p* value
Model 2				
Dependent variable HADS-A ≥ 11				
(Total model $p < 0.001$, $R^2 = 0.045$)				
Sex	1.784	1.189–2.678	7.817	0.005
Age	0.943	0.917–0.970	17.019	<0.001
BMI	1.004	0.966–1.043	0.036	0.850
Framingham sum	1.509	1.283–1.774	24.706	<0.001
MR-proANP	0.352	0.136–0.916	4.583	0.032
	Exp(β)	95 % CI	Wald value	*p* value
Model 3				
Dependent variable HADS-A ≥ 11				
(Total model $p < 0.001$, $R^2 = 0.043$)				
Sex	1.837	1.223–2.759	8.575	0.003
Age	0.940	0.914–0.966	19.987	<0.001
BMI	1.006	0.969–1.045	0.109	0.742
Framingham sum	1.509	1.283–1.774	24.759	<0.001
NT-proBNP	0.665	0.412–1.073	2.798	0.094

system which buffers the psychopathological and neuroendocrine consequences of heart failure. In line with this hypothesis, expression of ANP mRNA and its corresponding receptors have been reported in areas of the CNS known to regulate emotional states, such as the amygdala and limbic cortex [39]. In summary, these data suggest that ANP functions as a neuromodulator linking cardiovascular effects to changes in anxious affect. However, it is unclear whether ANP exerts its anxiolytic effects by peripheral receptors leading to a direct suppression of sympathetic nerve function and/or epinephrine release, by stimulating afferent vagal activity from the baroreceptor system or by other mechanisms [17].

Seier and co-workers reported that lactate-induced panic attacks enhance the release of ANP, which in turn could suppress the secretion of glucocorticoids from the adrenal glands and attenuate the sympathetic stimulation to the heart [40]. Since ANP and BNP activate the same NPR-A receptor, similar effects of ANP and BNP can be expected. Accordingly, a recent meta-analysis has reported cardioprotective effects for intravenous ANP or BNP administration in patients with myocardial infarction, suggesting that infusion of these natriuretic peptides may be regarded as an effective adjunct therapy for the protection of cardiac function [41]. The possible anxiolysis elicited by elevated natriuretic peptide levels may contribute to their cardioprotective function in patients with heart failure, as it protects against the emotional and physiological arousal frequently found in anxiety states by attenuating the deleterious effects of sympathetic overactivation on the heart [19]. Patients with reduced left ventricular ejection fraction also had significantly dilated atria and the highest proportion of atrial fibrillation, but showed the lowest mean level of anxiety. Their low anxiety is of particular interest, because it cannot simply be explained by better overall health. Some other factor needs to account for this effect, supporting a potential causal role of MR-proANP or ANP.

The high-molecular preproANP is cleaved by two endoproteases, corin and furin, to the active hormone and the N-terminal pro-peptide in a molar ratio of 1:1 [1]. Due to their longer half-lives, the inactive amino-terminal fragments have generally higher plasma concentrations and are known to be less affected by body position

and physical exercise than the active hormones [2]. However, the analytical performance of the various commercially available immunoassays needs to be determined under clinical settings. Since the MR-proANP and the NT-proANP assays are employed to measure the same pro-peptide, the discrepancy between the two tests in explaining anxiety is most probably due to differing performances of the two assays. The descriptive data show that also the NT-proANP assay yielded lower values in anxious patients, however, without reaching significance. Similarly, the insignificant finding for BNP may be due to its shorter plasma half-life as compared to that of NT-proBNP. In summary, our data are still compatible with a general effect of natriuretic peptides on anxiety which only differs in magnitude depending on the measure used.

Several potential limitations concerning our study findings need to be addressed. Our study presents a post-hoc analysis of previously unpublished associations between natriuretic peptides concentrations and results from psychological assessment and is, therefore, not suitable for the establishment of a cause–effect relationship. Another limitation in our study is the lack of repeated measurements of natriuretic peptides which precluded analysis of time-dependent covariates in a longitudinal study design. The clinical utility of our findings still remains to be determined. However, our investigation has also some strengths which include mainly a large and heterogeneous study population with well-defined, complete clinical and echocardiographic data including grading of diastolic dysfunction. In addition, we used well-validated, commercially available immunoassays, because of their diagnostic accuracy and proven prognostic value for left ventricular dysfunction.

Conclusion

In conclusion, our study provides evidence that clinically relevant anxiety is associated with low plasma levels of natriuretic peptides, especially MR-proANP. Given the previously assumed anxiolytic effects of natriuretic peptides, a possible causal effect of high peptide levels on low anxiety should be tested in further studies. Especially, those studies using natriuretic peptides for the treatment of severe heart failure should test whether patients may gain psychological benefit from therapeutic application of natriuretic peptides in addition to the established cardioprotective effects.

Conflict of interest CH-L receives royalties from Hans Huber Publishers, Berne, for the German version of the HADS. The other authors declare that they have no conflict of interest.

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