High Plasma Levels of N-Terminal Pro-Atrial Natriuretic Peptide Associated With Low Anxiety in Severe Heart Failure

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Objective: Plasma levels of natriuretic peptides are elevated in congestive heart failure (CHF). These peptides show anxiolytic properties in studies of rodents and patients with panic disorder, but their possible effect on anxiety has never been studied in cardiac patients. We therefore assessed associations of the Atrial Natriuretic Pro-Peptide (pro-ANP) with anxiety in patients with CHF and controls. **Method:** This was a cross-sectional study of 119 patients (46 with CHF, 76 controls with cardiovascular risk factors) in a tertiary care center. The study included assessment of CHF severity, ejection fraction, pro-ANP (microtiter assay), and psychosocial status (self-rating questionnaires for anxiety, depression, vital exhaustion, and quality of life). **Results:** The diagnosis and severity of CHF was significantly related to pro-ANP levels, bad physical quality of life, vital exhaustion, and depression. However, there was no significant effect of disease severity on anxiety. In CHF patients, pro-ANP was negatively correlated with anxiety (ρ = -0.30, p = .041). In the whole group, anxiety was independently predicted by vital exhaustion, depression, and younger age (overall adjusted R^2 = 0.48). Pro-ANP plasma levels showed an additional, inverse association with anxiety (β = -0.17, p = .013, adjusted R^2 = 0.50). Predicted mean anxiety scores derived from this model showed a good fit with anxiety scores observed in subgroups defined by CHF severity. **Conclusion:** Pro-ANP plasma levels are independently and inversely related to anxiety. Even in severe CHF with severely compromised quality of life, anxiety tends to decrease with high pro-ANP levels. This might be part of a negative feedback loop limiting psychological distress and its adverse autonomic consequences in severe heart failure. **Key words:** Pro-ANP, congestive heart failure, anxiety.

ANOVA = analysis of variance; **ANP** = atrial natriuretic peptide; **CHF** = congestive heart failure; **HADS** = Hospital Anxiety and Depression Scale; **LVEF** = left ventricular ejection fraction; **MQ** = Maastricht Questionnaire; **NYHA** = New York Heart Association; **pro-ANP** = N-terminal Pro-Atrial Natriuretic Peptide; **PTCA** = percutaneous transluminal coronary angioplasty; **QoL** = quality of life; **SF36** = Short Form 36 Health Survey.

INTRODUCTION

Neuroendocrine activation is typically found in patients with congestive heart failure (CHF). This activation includes, among others, the natriuretic peptides, which are secreted by the cardiac atria and ventricles as a response to volume and/or pressure overload. Plasma levels of the atrial natriuretic peptide (ANP) have long been known to be elevated in heart failure (1). This hormone, and especially the more stable 98-amino acid N-terminal pro-ANP, a cleavage product of ANP activation, shows significant negative correlations with ejection fraction and positive correlations with clinical severity of heart failure (2, 3). ANP has a vasodilator effect and may partly counteract the adverse effects of sympathetic activation in these patients. However, a direct sympathoinhibitory effect of ANP observed in healthy persons (4) could not be confirmed in patients with heart failure (5).

On the other hand, natriuretic peptide receptors have not only been identified in the cardiovascular system and kidneys but also in several brain regions. ANP binds mainly to natriuretic peptide receptor A. Stimulation of this receptor in the brain inhibits the activation of the hypothalamic-pituitary-adrenal axis and the subjective reactions to anxiety-inducing stimuli (6). Studies in rodents and in patients with panic disorder have shown that infusions of ANP suppress the psychological and sympathetic response to behavioral and biochemical triggers of panic and nonpanic anxiety (7, 8). It has therefore been suggested that ANP may be the inhibitory component of a feedback loop involved in the physiology of anxiety.

This might also be important in heart failure, because patients with heart failure suffer from considerable psychological distress, vital exhaustion, and depression. In these patients, high endogenous levels of ANP might help limit emotional arousal, which could otherwise result in a further increase in sympathetic activity and adverse cardiac outcomes.

However, the effect of ANP on emotional functioning in CHF has only been studied in one sample: Murberg et al. (9) examined correlations of subjective well-being and depression with plasma levels of pro-ANP but found no such association. To date, no data are available on possible associations between natriuretic peptides and anxiety in cardiac patients.

The aim of the present study was to test the hypothesis that high plasma levels of pro-ANP are associated with relatively low anxiety in CHF patients.

METHODS

The sample of the present study consists of 46 patients who had a clinical diagnosis of CHF and an echocardiographically determined LVEF < 45% and 73 subjects who had at least one cardiovascular risk factor (hypertension, hypercholesterolemia, smoking) but no known heart disease and no clinical signs of heart failure. All 119 patients participated in a study of neuroendocrine activation in the diagnostics of congestive heart failure. The protocol of this study was approved by the institutional ethics committee and all patients gave written informed consent before being included in the study.

As part of the study, the patients completed a set of psychological questionnaires, including the Hospital Anxiety and Depression Scale and the Maastricht Questionnaire for vital exhaustion. The Hospital Anxiety and Depression Scale (HADS) (10–12) is a widely used short self-assessment questionnaire, especially developed for physically ill patients. Its items mainly ask for psychological manifestations of (generalized) anxiety and depressive mood. Each of the two subscales consists of seven items. Possible subscale scores range from 0 to 21. The Maastricht Questionnaire (MQ) (13) asks for levels of vital exhaustion, which have been shown to predict adverse

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outcomes in patients with coronary heart disease. The 21-item version used for this study has a possible range from 0 to 42. One hundred six patients also completed the SF-36 Health Survey, the most frequently used generic multidimensional quality of life (QoL) scale (14, 15), which was introduced into the study shortly after its beginning. T-standardized scores of the physical and psychosocial components will be reported for this instrument.

All patients received routine cardiological workup. In addition, detailed echocardiograms were performed for assessment of systolic and diastolic function, including left ventricular ejection fraction (LVEF). Clinical CHF severity was rated by an experienced cardiologist, who was blind to the patients' pro-ANP levels and questionnaire scores. Ratings were performed according to New York Heart Association (NYHA) criteria.

Venous blood samples were drawn and centrifuged. Heparinated plasma aliquots were then frozen and stored at -80°C, until they were analyzed in a specialized laboratory. Pro-ANP was determined using microtiter immunoassays (Immundiagnostik, Freiburg, Germany). These measurements were performed according to the recommendations of the manufacturer, with values ≤1320 fmol/ml considered normal.

All data were coded and entered into an anonymized database on a personal computer. For the statistical analyses, SPSS for Windows (V.10) standard software was used. Because of considerably skewed distributions of hormone levels, nonparametric statistics (Spearman-Brown correlations, Mann-Whitney *U* tests, Wilcoxon tests, Kruskal-Wallis ANOVA) were used if possible. For multivariate prediction of anxiety, we performed stepwise linear regressions. The analyses including pro-ANP levels as a predictor were computed twice: once with pro-ANP raw values and alternatively with log-transformed pro-ANP values.

RESULTS

Baseline Data and Group Differences

Both patient groups had a similar mean age of 62 years and similar socioeconomic and occupational characteristics (Table 1). As expected, more patients with CHF than control subjects were male. More than 40% of the CHF subjects had severe heart failure, according to New York Heart Association functional classes III-IV, CHF patients had a mean ejection fraction of 28%, which was significantly lower than the normal mean ejection fraction of 64% observed in the control group. As could be expected, more CHF patients than controls were taking beta blockers, ACE inhibitors, diuretics, and digitalis, whereas there was only a small and insignificant difference in the number of patients taking psychotropic drugs. The types of psychotropic drugs taken included antidepressants in two CHF patients and two control subjects. Two patients with CHF were taking neuroleptics and one was taking oxazepam, whereas one control subject received a herbal antidementive/antidepressant.

Mann-Whitney *U* tests showed that CHF patients had significantly higher plasma levels of pro-ANP than the control group; median and maximum pro-ANP values in the CHF group were about 25 times as high as the corresponding values found in the control group. Pro-ANP levels above the recommended cutoff were observed in 93.5% of the CHF patients and in 5.5% of the control subjects ($p < .00005$).

On the psychological questionnaires, CHF patients scored significantly worse than the control subjects on the physical components of quality of life, vital exhaustion, and depression. In contrast, there was only a minimal and statistically insignificant difference in anxiety scores.

TABLE 1. Baseline Data of the CHF Patients and Control Subjects

	CHF	Controls	Significance (*p*)
N	46	73	
Age (years)[a]	62.4 ± 14.2	62.4 ± 9.0	NS
Men (%)	87.0	50.7	<.0005
Married (%)	75.8	73.6	>.20
More than basic school (%)	30.3	38.9	>.20
Qualified professionals (%)	31.3	32.8	>.20
Active employment (%)	18.2	25.0	>.20
NYHA functional class (%)			<.0005
0 (no heart disease)		100	
I	15.2	0	
II	41.3	0	
III	23.9	0	
IV	19.6	0	
Ejection fraction (%)[a]	27.9 ± 9.2	64.4 ± 4.3	<.0005
Ischemic CMP (%)	54.4	0	<.0005
Diabetes	32.6	43.8	>.20
pro-ANP (fmol/ml)[b]	564–7592–46750	173–500–1939	<.0005
Beta blockers (%)	50.0	29.0	.024
ACE inhibitors (%)	75.0	30.6	<.0005
Diuretics (%)	72.7	37.5	<.0005
Digitalis (%)	50.0	2.7	<.0005
Psychotropic drugs (%)	11.4	4.1	.132
HADS anxiety[a]	6.4 ± 4.0	5.8 ± 4.0	.308
HADS depression[a]	6.2 ± 4.3	4.7 ± 4.1	.027
MQ vital exhaustion[a]	19.4 ± 10.7	13.7 ± 10.7	.004
SF36 physical component[a]	34.0 ± 10.4	44.1 ± 11.3	<.005
SF36 psychosocial component[a]	46.0 ± 11.7	49.8 ± 10.5	.119

[a] Mean ± standard deviation.
[b] Minimum–median–maximum.

Associations of Pro-ANP, Disease Severity, and Questionnaire Scores

In the whole group, pro-ANP showed high correlations with ejection fraction (ρ = -0.75) and NYHA functional class (Spearman-Brown's ρ = 0.80), thus reflecting severity of cardiac dysfunction and clinical disease severity.

Among all measures of cardiac disease severity, plasma levels of pro-ANP were most closely related to (bad) self-rated physical QoL (ρ = -0.48, $p < .0005$). In addition, pro-ANP showed significant positive associations with vital exhaustion (ρ = 0.32, $p < .0005$) and depression (ρ = 0.23, p = .011). Slightly weaker associations were observed between the other cardiac severity markers and physical QoL whereas both ejection fraction and NYHA functional class showed associations similar to pro-ANP with vital exhaustion and depression.

Interestingly, none of the physical severity markers was associated with anxiety (ρ = 0.05–0.09, all $p > .30$). This lack of correlation was due to a nonlinear association between pro-ANP and anxiety, which was clearly distinct from the continuous associations of pro-ANP with QoL, depression, and vital exhaustion. On the subgroup level, there was no correlation between anxiety and pro-ANP in the control subjects (ρ = 0.09, p = .46) but a significant negative correlation existed between anxiety and pro-ANP (ρ = -0.30, p = .041) in the CHF group.

In the next step, we classified patients by functional CHF severity. Patients without known heart disease and those with a history of CHF but no current symptoms (NYHA I, N = 7) were classified as asymptomatic (NYHA 0-I, N = 80); those with dyspnea at moderate exercise (NYHA II, N = 19) as moderate heart failure; and those with dyspnea at minimal exercise or at rest (NYHA III-IV, N = 20) as severe heart failure (Table 2). The resulting three subgroups had median pro-ANP plasma levels of 541 fmol/ml, 5885 fmol/ml, and 11342 fmol/ml, respectively ($p < .0005$). There were also differences in several of the baseline variables (Table 2). Of these, most were also significantly related to pro-ANP levels. However, of all baseline variables that differed significantly among subgroups, age was the only variable which was also significantly associated with anxiety, whereas anxiety was independent of ejection fraction, cardiac or psychotropic medications, and the presence of ischemic vs. nonischemic heart failure.

From lowest to highest CHF severity there was a significant, linear decrease in physical QoL ($p < .0005$) and a significant linear increase of vital exhaustion ($p < .0005$) and depression (p = .023) (Figure 1). In contrast, anxiety increased from 5.7 ± 4.0 in the asymptomatic group to 7.6 ± 4.6 in moderate CHF but returned to an almost normal mean (± SD) score of 5.9 ± 3.3 in the most severely ill subgroup (NS vs. asymptomatic group).

Determinants of Anxiety

In bivariate analyses examining all sociodemographic, cardiac, and psychological baseline data as well as current medications, four variables were significantly correlated with anxiety and pro-ANP levels and might have influenced their association. These four variables were vital exhaustion, depression, age, and sex.

Of these, vital exhaustion, depression, and age were retained as significant independent predictors of anxiety in a stepwise multivariate regression model (adjusted R^2 = 0.48). Patients had higher anxiety scores if they were vitally exhausted (β = 0.45, $p < .0005$); younger (β[age] = -0.24, p = .001); and more depressed (β = 0.29, p = .003).

Z-standardized mean anxiety scores observed in the three disease severity subgroups and estimated anxiety scores derived from the regression model are shown in Figure 2. Although observed scores were fairly well predicted by the

TABLE 2. Baseline Data by Grouped NYHA Classes

	NYHA 0–I	NYHA II	NYHA III–IV	Significance (p)
N	80	19	20	
Age (years)[a]	62.0 ± 9.2	58.5 ± 13.8	67.6 ± 14.5	.035
Men (%)	14.3	21.1	5.0	>.20
Married (%)	75.0	71.4	80.0	>.20
More than basic school (%)	40.8	14.3	33.3	.161
Qualified professionals (%)	32.9	28.6	33.3	>.20
Active employment (%)	27.6	21.4	0	.066
Ejection fraction (%)[a]	61.7 ± 9.7	26.8 ± 6.5	25.8 ± 9.8	<.0005
Ischemic CMP (%)	5.0	47.4	60.0	<.0005
Diabetes (%)	42.5	21.1	45.0	.196
pro-ANP (fmol/ml)[b]	398–541–756	3055–5885–9260	6009–11342–15742	<.0005
Beta blockers (%)	32.9	47.4	44.4	>.20
ACE inhibitors (%)	35.4	78.9	66.7	.002
Diuretics (%)	39.2	63.2	88.9	<.0005
Digitalis (%)	6.3	52.6	50.0	<.0005
Psychotropic drugs (%)	5.0	5.3	16.7	.199

[a] Mean ± standard deviation.
[b] 25th percentile–median–75th percentile.

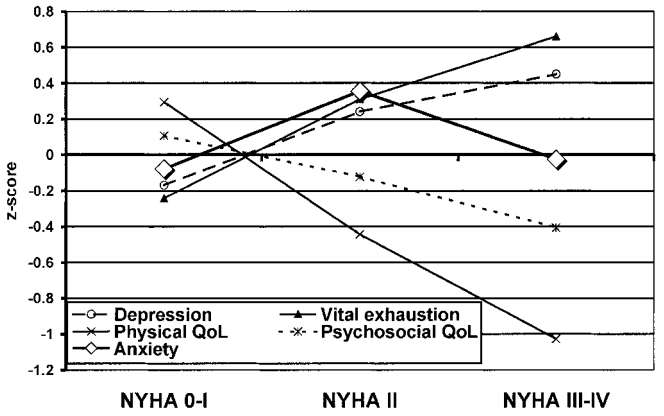

Fig. 1. Z-standardized psychological and quality-of-life scores by severity of congestive heart failure. NYHA = New York Heart Association functional class; NYHA 0 = no known heart disease; QoL = Quality of Life.

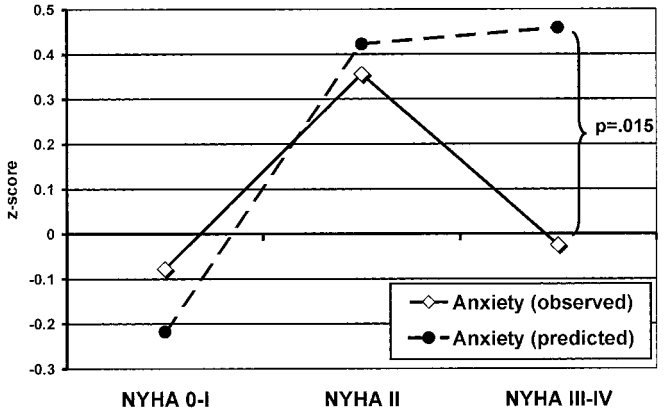

Fig. 2. Observed and predicted z-standardized anxiety scores by severity of congestive heart failure. NYHA = New York Heart Association functional class; NYHA 0 = no known heart disease. Prediction based on vital exhaustion, depression, and age.

regression model in the first two subgroups with no or only moderate CHF, observed anxiety scores were significantly lower ($p = 0.015$) than predicted in patients with severe CHF.

Pro-ANP was then added to the stepwise regression model and further improved the model fit (adjusted $R^2 = 0.50$). The four independent, significant predictors included in this model and their regression coefficients are displayed in Table 3. As can be seen, vital exhaustion and depression are still positively related and age is negatively related to anxiety.

In addition, pro-ANP shows an independent, inverse association with anxiety.

This result was virtually unchanged, when log-transformed pro-ANP values were used instead of raw values ($\beta = -0.16$, $p = .020$) or when the eight patients taking psychotropic drugs were excluded (β[pro-ANP] = -0.19, $p = .009$). There was no additional effect of sex, diagnosis of heart failure, NYHA class, or ejection fraction.

When predicted z-standardized anxiety scores derived from the four-predictor model were compared with the observed mean anxiety scores, there was a clearly better fit, with no significant difference between observed and predicted anxiety scores in any of the subgroups (Figure 3). Especially the decrease of anxiety scores observed in the patients with severe CHF is at least partially reflected by the model, indicating that high pro-ANP was most probably related to this decrease.

DISCUSSION

To our knowledge, this is the first study investigating the association between a natriuretic peptide and anxiety in cardiac patients. Our results confirm earlier findings that ANP and pro-ANP reflect physical severity of heart failure. In addition, we could now also show that the subjective perception of physical impairment, vital exhaustion, and (to a lesser degree) depression are positively correlated with pro-ANP levels. It might therefore be surprising that no such correlation was found between pro-ANP and anxiety, especially because anxiety, depression, and vital exhaustion showed relevant covariance in this sample as well as in most patient groups reported in the literature. Contrary to naïve expectations, pro-ANP even showed a significant negative correlation with anxiety in the subgroup with known CHF.

This finding is important for several reasons.

First, it adds to our knowledge about physiological factors affecting emotional well-being and quality of life in heart disease. The literature on this subject has, until now, mainly focused on psychosocial risk factors and – to a lesser degree – physical correlates of bad quality of life. In this tradition, centrally stimulated levels of neurohormones have been studied with respect to their potentially hazardous cardiovascular effects. More recently, adverse effects of peripheral mediators (such as proinflammatory cytokines) on emotional function have also been suspected in coronary patients (16). However, none of the previous studies has examined the neuropsychological consequences of hormones secreted by the heart itself nor has there been a full physiological understanding of the negative feedback loops limiting the increase in emotional arousal occurring as a result of heart disease. Although suc-

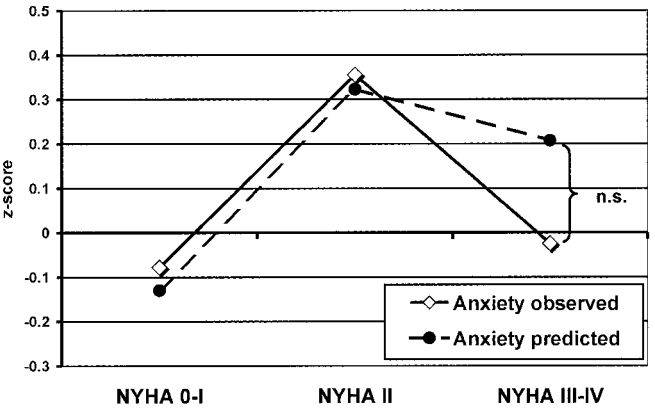

Fig. 3. Observed and predicted z-standardized anxiety scores by severity of congestive heart failure. NYHA = New York Heart Association functional class; NYHA 0 = no known heart disease. Prediction based on vital exhaustion, depression, and age *plus pro-ANP plasma levels*.

TABLE 3. Multivariate Predictors of Anxiety in the Whole Sample (Stepwise Linear Regression)

	Beta	Significance (*p*)	Model R^2 (adjusted)
Vital exhaustion	.49	<.0005	.37
Age	−.22	.002	.44
Depression	.29	.003	.48
Pro-ANP	−.17	.013	.50

cessful coping will play a major part in this adaptation process, direct physiological effects might also be involved. The heart might hereby not only be the target organ of psychoneuroendocrine efferents but rather play an active part in the regulation processes – not only of body fluid content and vascular resistance but also of emotional and neurohumoral activation. This would make sense from a biological point of view: the emotional and physiological arousal often found in anxiety states would impose an additional burden on the failing heart and thereby exert a deleterious effect; and a possible anxiolysis produced by ANP in response to atrial overload could partly reverse, or at least limit, this effect.

Second, this finding also helps one get a more differentiated impression of the different psychological and psychosomatic states experienced by patients with heart failure.

The subjective reports of physical quality of life show an impressively high correlation with CHF severity. Interestingly, the correlation is highest with pro-ANP, as a marker of functional CHF severity, and much lower with LVEF. On the other hand, there is no, or even a negative, correlation of CHF severity with anxiety. In terms of the magnitude of their correlations with pro-ANP (or CHF severity in general), vital exhaustion, depression, and overall psychosocial quality of life lie somewhere between self-rated physical status and anxiety: vital exhaustion is closest to the physical impairment of CHF. Depression, as measured by the HADS depression scale, which does not rely on physical indicators of depression, is closer to anxiety, although the associations of anxiety and depression scores with pro-ANP were clearly distinct. This may help to understand why depression, but not generalized anxiety, is independently associated with adverse cardiovascular outcomes in patients with documented heart disease (17) and why some authors (18, 19) even found opposite effects of anxiety and depression scores on prognosis. Despite the known adverse effects of anxiety on, eg, autonomic cardiac control (20), higher anxiety may in part also reflect lower ANP levels, which mean less severe heart failure and a better prognosis.

In addition, some unexpected earlier findings from our group found a possible explanation: patients with coronary artery disease and a history of PTCA (which has been shown to reduce ANP levels during exercise) (21) had higher anxiety than their counterparts without previous PTCA (22). They might also have had lower ANP levels. Furthermore, in that study, 1242 men with documented CHD and recent ventriculograms showed associations between ejection fraction and anxiety that were very similar to the association found between clinical heart failure severity and anxiety in the present study. Anxiety was somewhat higher in patients with slightly reduced ejection fraction compared with those who had normal systolic function. However, the *lowest* anxiety scores were observed in patients with moderate to severe left ventricular dysfunction (22). Finally, in the same study, the subgroup that also showed left ventricular hypertrophy had surprisingly low anxiety. The impaired ventricular compliance associated with left ventricular hypertrophy typically leads to atrial dilatation and increased ANP secretion (23), which could serve as a possible explanation of the low anxiety scores. However, these possible associations are still speculative.

Some additional caveats must also be kept in mind when interpreting the present results.

This is the first study describing a statistical association of pro-ANP and anxiety in cardiac patients. Further research is needed before our findings can be generalized. It will also be necessary to study the interplay of pro-ANP (and ANP) with other neurohumoral markers such as brain natriuretic peptide, endothelin, catecholamines, etc.

Our study should not be interpreted as demonstrating a causal effect of pro-ANP on anxiety. The cross-sectional evaluation performed in this study suggests a biologically plausible mechanism, although it doesn't prove it. In addition, pro-ANP is a cleavage product of ANP activation without known cerebral effects and, rather, should be considered an indicator for medium-term plasma levels of (C-terminal) ANP. ANP, however, has a definite potential for exerting an anxiolytic effect. It has been shown to pass the blood-brain barrier and reduce anxiety even after peripheral application (7, 8, 24).

Nevertheless, the use of pro-ANP instead of ANP in the present study was well justified. Pro-ANP is produced during activation of ANP in a 1:1 molar ratio. It has a longer plasma half-life and is therefore more likely to reflect medium-term ANP secretion. It is thereby less likely to be influenced by acute exercise, such as climbing stairs and walking throughout hospital floors. It is also more stable in blood specimens and has therefore been shown to be a better marker of—especially less severe—CHF than ANP itself (25).

Our results seem to be in contrast to those reported by Murberg et al. (9). In their study of 119 patients with stable CHF, depression scores showed no association with plasma pro-ANP, whereas in our study they did. However, the association observed in our study was weak and partly caused by the group difference between patients with and without CHF. The symptoms measured by the different depression scales used in the two studies might show a varying overlap with anxiety (which was not measured by Murberg et al.). A possible positive association between depression and pro-ANP might have been masked by confounding symptoms of anxiety in the Murberg et al. study. It is worth mentioning that Murberg et al. found an insignificant (ρ = -0.15) negative association of pro-ANP with neuroticism, which can be sus-

pected to show a relevant correlation with anxiety. Interestingly, in our study, the global psychosocial score of the SF36 showed only an insignificant association with pro-ANP. It therefore seems necessary to use instruments that clearly differentiate between symptoms of anxiety and depression, such as the HADS, in order to find the suspected differential ANP effect. With a nonspecific measure of psychological distress, the different associations of anxiety and depression with pro-ANP might otherwise be counterbalanced, resulting in a lack of correlation.

A final point of concern are the high absolute plasma levels observed in the CHF patients. In patients with panic disorder, an infusion of ANP that raised plasma levels four- to five-fold to those of baseline levels seems to produce marked anxiolytic effects (8). In contrast, the patients from the present study, even those with moderate CHF, had mean pro-ANP plasma levels that were 10- to 25-fold above those of the control persons, some of whom also had levels above the normal range. One might expect a stronger anxiolytic effect of these extremely high levels. However, the chronic psychosocial distress caused by the experience of heart failure will be more difficult to antagonize than short anxiogenic stimuli. Second, earlier studies have shown blunted renal and cardiovascular responses to chronically elevated ANP levels in CHF (1). ANP resistance might also occur in the brain and account for the relatively modest effect observed in our sample as well as for the poor sympathoinhibitory effect of ANP observed in another study (5).

Future research will have to confirm or disprove our still preliminary findings. Should the results be confirmed, therapeutically administered neutral endopeptidase inhibitors, such as candoxatril (26) or synthetic natriuretic peptides, which have recently be shown to produce a short-term cardiovascular benefit and a reduction in dyspnea (27), might also be useful in treating anxiety in patients with heart failure. For example, patients with implanted defibrillators and frequent shock delivery who often suffer from severe heart failure as well as severe anxiety might be candidates for this new treatment option. However, it would be premature to recommend these treatments without further study. Our speculations are also not meant to minimize the importance of successful coping and psychosocial interventions in CHF patients but could possibly help obtain a more complete understanding of the processes involved and help develop a broader range of therapies.

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