CARDIOVASCULAR MEDICINE

N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure

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Objective: To determine whether the plasma concentration of the putative new cardiac hormone relaxin is predictive of clinical outcome in patients with chronic heart failure (CHF).
Design: Plasma relaxin and N-terminal pro B type natriuretic peptide (NT pro BNP) concentrations were measured in 87 patients admitted in an emergency with CHF caused by left ventricular systolic dysfunction. These were related to death and death or readmission with CHF over the following year.
Setting: Western Infirmary, Glasgow, UK.
Main outcome measures: Plasma concentrations of relaxin and NT pro BNP; time to death or hospitalisation caused by heart failure.
Results: Plasma concentrations of both relaxin and NT pro BNP were greatly increased. Of the 43 patients with NT pro BNP above the group median concentration, 23 (53%) died and 30 (70%) died or were hospitalised with CHF. Among the 44 with concentrations below the median, these numbers were 5 (11%) and 12 (27%), respectively ($p < 0.0001$ and $p < 0.0001$, respectively). Plasma NT pro BNP concentration remained an independent predictor of an adverse clinical outcome in a multivariate analysis. Of the 42 patients with a relaxin concentration above the median, 13 (31%) died and 20 (48%) died or were hospitalised. Below the median, these numbers were 15 of 45 (33%) and 22 of 45 (49%) ($p = 0.76$ and $p = 0.84$, respectively).
Conclusions: NT pro BNP is a powerful and independent predictor of outcome in CHF, whereas relaxin, also secreted by the heart in increased amounts in CHF, is not.

Relaxin is a polypeptide hormone belonging to the insulin family.[1–3] Though known for many years as a hormone of parturition, relaxin has lately been shown to be a powerful systemic arterial vasodilator released from the heart.[1 4 5] One recent study reported increased cardiac relaxin release and increased plasma relaxin concentrations in heart failure.[4] Consequently, it has been postulated that relaxin, like the natriuretic peptides, may be secreted as a compensatory neuroendocrine response in heart failure.[4 5] With other pathophysiologically important neurohumoral mediators there is a clear relation to outcome in heart failure, whereby higher plasma concentrations, indicating greater neurohumoral activation, are associated with a worse prognosis.[6–8] Consequently, we have examined the relation between plasma relaxin concentration and clinical events in patients with chronic heart failure (CHF). As a "positive control", we also examined the prognostic importance of N-terminal pro B type natriuretic peptide (NT pro BNP) in the same patients.[9]

Table 1 Characteristics of patients studied

Number of patients	87
Age (years) (range)	75 (51–93)
Sex (male/female)	51/36
Current angina	38
Previous myocardial infarction	40
Diabetes	13
Chronic obstructive pulmonary disease	24
Atrial fibrillation	25
β Blocker	9
Angiotensin converting enzyme inhibitor	37
Diuretic	60
HMG CoA reductase inhibitor	2
Calcium channel blocker	20
Digoxin	17
Nitrate	12
Aspirin	43
Warfarin	9
Admission New York Heart Association class	
II	21
III	28
IV	38
Creatinine (μmol/l)	*132 (7.2)

HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A.
*Mean (SD)

METHODS

Patients

Patients taking part in a randomised controlled trial of specialist nurse intervention were studied. This trial has been described in detail elsewhere.[10] Briefly, patients admitted to hospital, on an emergency basis, with heart failure caused by left ventricular systolic dysfunction were enrolled in a trial comparing conventional care with conventional care supplemented by specialist heart failure nurse intervention. Patients were followed up for a mean of 12 months after randomisation. Deaths and hospital readmissions were recorded. Readmissions were adjudicated by a blinded end point committee. The primary end point was death or readmission with heart failure. Patients consented to have venous blood collected for measurement of neurohumoral factors.

Abbreviations: CHF, chronic heart failure; ELISA, enzyme linked immunosorbent assay; NT pro BNP, N-terminal pro B type natriuretic peptide

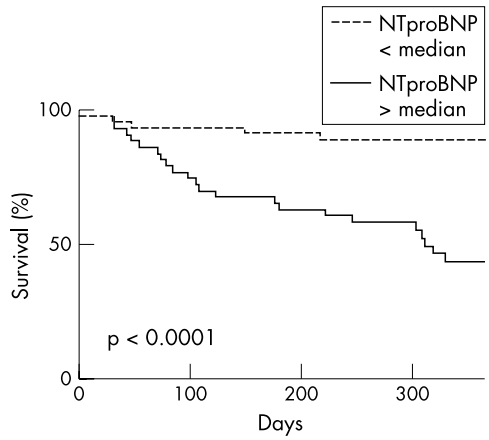

Figure 1 Time to death in patients with plasma N-terminal pro B type natriuretic peptide (NT pro BNP) concentrations above and below the median.

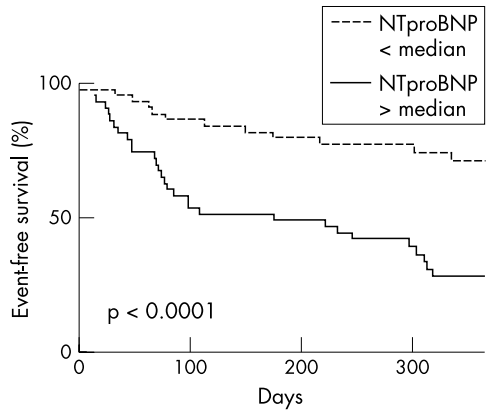

Figure 2 Time to death or hospital admission for heart failure in patients with plasma NT pro BNP concentrations above and below the median.

Assays

NT pro BNP was measured in blood samples taken just before discharge by using a validated and commercially available immunoassay (Roche Diagnostics, Mannheim, Germany).[11] Plasma relaxin was determined with the use of an enzyme linked immunosorbent assay (ELISA) kit (Immundiagnostik, Bensheim, Germany), as reported previously.[4]

Statistical analysis

Event rates were compared for patients with plasma concentrations of NT pro BNP and relaxin above and below the group median. As NT pro BNP concentrations above the median were associated with a significantly worse clinical outcome, multivariate analyses were carried out to determine whether NT pro BNP was an independent predictor of outcome (death and death or hospital admission for CHF). Firstly, a univariate analysis was performed using all relevant baseline data (for example, age, sex, New York Heart Association functional class, left ventricular function, heart rhythm, comorbidity, history of prior CHF hospitalisation, creatinine). Variables significantly ($p < 0.05$) associated with outcome were then examined in a stepwise multivariate analysis.

RESULTS

Of the 165 patients randomly assigned in the study, plasma NT pro BNP and relaxin concentrations were available for 87. Table 1 gives details of these patients.

The median (range) plasma NT pro BNP concentration was much increased at 2994 (134–35 000) pg/ml compared with normal (< 334 pg/ml for female and < 227 pg/ml for male patients). Plasma NT pro BNP was a predictor both of death and of heart failure hospitalisation or death (figs 1 and 2). Of patients with NT pro BNP above the median concentration (n = 43), 23(53%) died and 30 (70%) died or were hospitalised with CHF. For those with NT pro BNP concentrations below the median (n = 44), these proportions were 5 (11%) and 12 (27%) ($p < 0.0001$ for death and $p < 0.0001$ for death or CHF hospitalisation).

In the multivariate analysis, plasma NT pro BNP concentration was a significant, independent predictor of death or CHF hospitalisation (odds ratio 4.15, $p = 0.003$) and of death alone (odds ratio 2.22, $p = 0.03$).

The median (range) plasma relaxin concentration was also greatly increased at 89 (11–644) pg/ml compared with normal (< 2 pg/ml). However, in contrast to NT pro BNP, there was no relation between relaxin and outcome (figs 3 and 4). Of those patients with a relaxin concentration above the median (n = 42), 13 (31%) died and 20 (48%) died or were

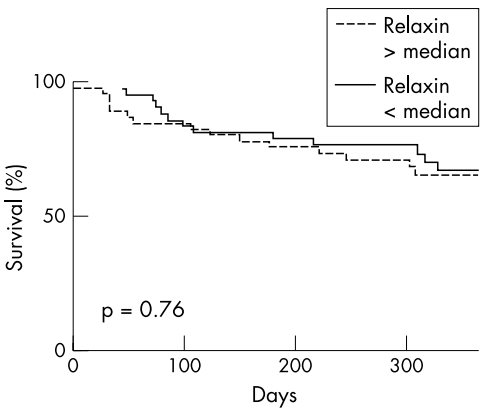

Figure 3 Time to death in patients with plasma relaxin concentrations above and below the median.

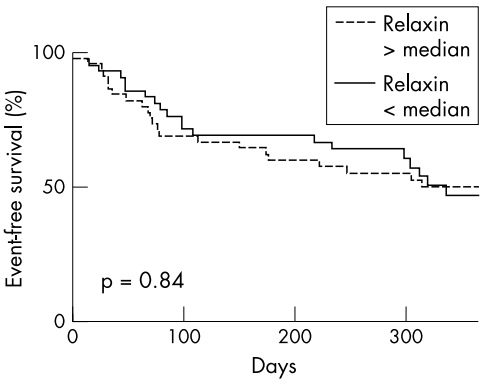

Figure 4 Time to death or hospital admission for heart failure in patients with plasma relaxin concentrations above and below the median.

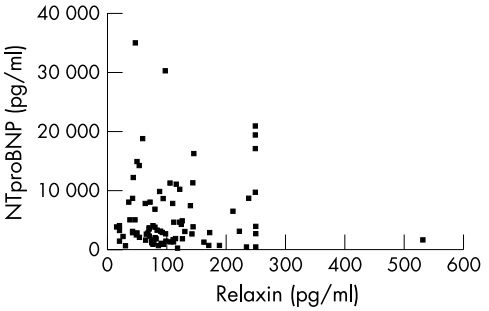

Figure 5 Correlation plot for NT pro BNP and relaxin concentrations.

hospitalised. These proportions for patients with a plasma relaxin concentration below the median (n = 45) were 15 (33%) and 22 (49%) (p = 0.76 for death and p = 0.84 for death or CHF hospitalisation). Plasma relaxin concentration was not a significant predictor of outcome in the univariate analysis.

There was no correlation between plasma concentrations of relaxin and those of NT pro BNP (fig 5).

DISCUSSION

Our study confirms that heart failure caused by left ventricular systolic dysfunction is associated with a large increase in the plasma concentration of the two new neurohumoral markers NT pro BNP and relaxin. As yet, there are very few reports of plasma NT pro BNP concentrations in heart failure[11–16] and only one other describing relaxin concentrations.[4]

In the present study NT pro BNP was also predictive of both death and death or readmission with worsening CHF. Though the predictive value of other natriuretic peptides in CHF has been extensively reported, we know of only one other study describing the prognostic importance of NT pro BNP in CHF.[15 17–22] In a substudy of the Australia-New Zealand carvedilol trial, Richards and colleagues[15] found that NT pro BNP was a strong predictor of all cause mortality, as well as admission to hospital with CHF. In that study, NT pro BNP had more predictive power for these outcomes than left ventricular ejection fraction. We also found NT pro BNP to be an independent predictor of adverse clinical outcome. Consequently, there are now two studies confirming that this very stable peptide,[23 24] which is easy to assay,[13 23 24] has prognostic as well as diagnostic value in CHF. NT pro BNP also gives prognostic information after myocardial infarction and in acute coronary syndromes.[25 26]

Dschietzig and colleagues[4] have recently shown that cardiac relaxin production and plasma relaxin concentrations are increased in CHF; the latter finding was confirmed in the present study. As relaxin is a powerful vasodilator secreted by the heart,[5] our hypothesis was that, like the natriuretic peptides, plasma concentrations may be related to prognosis. We were not able to confirm this.

Though plasma concentrations of most neurohumoral factors are predictive of outcome, not all are (for example, arginine vasopressin).[27] We found no correlation between plasma NT pro BNP and relaxin concentrations, suggesting different release mechanisms. The atria may be a more important source of relaxin than the ventricles, whereas the opposite is true for NT pro BNP.[4 28] As a biochemical marker of left ventricular dilatation and wall stress, NT pro BNP, perhaps not surprisingly, is therefore a powerful prognostic factor.[15] Furthermore, net cardiac relaxin release is not pronounced except in moderate to severe CHF and even then is not always observed.[4] These reasons may explain why relaxin was not predictive of outcome. However, it remains possible that relaxin does have some weak predictive effect that was not observed because of the modest size of our study.

In summary, even though relaxin has been shown to be a potent vasodilator released by the failing heart, it is not a powerful prognostic indicator in CHF.

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