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Paper

Rheumatoid arthritis patients with active disease and no history of cardiac pathology have higher Brain Natriuretic Peptide (BNP) levels than patients with inactive disease or healthy control subjects.

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ABSTRACT

Background Rheumatoid arthritis (RA) is associated with increased incidence cardiac failure. It is yet unclear how much the increased incidence is secondary to ischaemic damage, or whether inflammatory cytokines might have a direct effect on the myocardium

Objectives To establish if patients with active rheumatoid arthritis but no history of cardiac disease have higher serum levels of brain natriuretic peptide (BNP), than patients with less active RA, or disease-free controls.

Methods 90 patients with RA and 31 healthy control subjects were recruited. Each was screened to exclude previous history of cardiac disease. RA disease activity was measured using the DAS28 assessment, and other demographic, physical and laboratory tests performed. Serum BNP levels were measured in all subjects.

Results There was no difference in the age, percentage females or BMI between the RA and control subjects. Median BNP in the RA patients was 80.0 pg/ml (IQR 38.0-132.0) compared with 48.5 (26.0-86.0) in the control subjects ($p=0.017$). There was a significant correlation between DAS28 and serum BNP in the RA group, $r=0.37$, $p<0.01$. RA patients were divided into three groups according to DAS28 scores. Patients with very active disease (DAS28>5.1) had significantly higher BNP levels than patients with moderately active disease (3.2<DAS28<5.1) or inactive disease (DAS28<3.2) (both $p<0.01$). Median BNP of RA patients with inactive disease did not differ from Controls.

Conclusion RA patients with no history of cardiac disease have higher serum BNP levels than healthy control subjects. RA patients with active RA have higher BNP levels than RA patients with moderately active or inactive disease, raising the possibility of a directly depressive effect of inflammatory cytokines on the myocardium

BACKGROUND

Rheumatoid arthritis (RA) is now viewed as a systemic autoimmune condition rather than simply an inflammatory arthropathy, with much of the increased mortality attributable to accelerated atherosclerosis and ischaemic heart disease. Alongside coronary artery disease, the incidence of congestive cardiac failure (CCF) is increased in RA[1]. There are several possible explanations for this, including ventricular failure secondary to ischaemic myocardial damage, but inflammatory cytokines produced in RA, such as TNF alpha, have also been shown to have a directly injurious effect on cultured myocytes, including the induction apoptosis and fibrosis[2]. A recent study has shown that serum concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), a hormone produced by the cardiac ventricles in response to stretch and elevated in cardiac failure, are correlated with levels of inflammatory markers and disease activity in RA, and higher than matched controls[3]. However, the study included significant numbers of patients and controls with a history of cardiovascular disease, which might have caused subclinical myocardial impairment. In this study, we tested the hypothesis that serum BNP levels are elevated in RA patients without any previous history of coronary artery disease or cardiac impairment, and that patients with clinically active disease as measured by the Disease Activity Score (DAS28) had higher serum BNP levels than patients with well-controlled disease.

METHODS

Subjects were over 18 years of age and were recruited at rheumatology outpatient clinics in the Erne Hospital, Enniskillen, Northern Ireland. All gave written informed consent.

Control subjects did not have rheumatoid arthritis, any other systemic inflammatory arthritis, or any other condition which might be associated with systemic inflammation (such as chronic chest disease). They were recruited from

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patients referred to a general rheumatology clinic with complaints such as lateral epicondylitis, minor osteoarthritis of the hands and muscular back pain. RA patients fulfilled the ACR classification criteria for rheumatoid arthritis[4], and were excluded if they had a history or either cardiac failure, coronary artery disease or unexplained chest pain, or other chronic inflammatory conditions such as COPD or renal failure. The hospital chart was also examined for any previous diagnosis or investigation of coronary artery disease or cardiac failure. Patients receiving loop diuretics or spironolactone were excluded even if there was not a definite diagnosis of cardiac failure. Patients were also excluded if they were taking medication which might interfere with measurement of BNP levels, such as glitazones or beta-blockers. Thiazide diuretic therapy for hypertension was not counted as a diuretic under exclusions.

The Disease Activity Score based on 28 joint assessment (DAS28) is a validated tool for estimating RA disease activity[5]. Patients with a score of 5.1 or greater are considered as having very active disease, while those with a score of less than 3.2 have inactive disease. A number of other demographic data, treatment history and laboratory tests was collected as outlined in table 1.

Serum BNP was measured on an Abbott Axsym analyzer using a MEIA [Microparticle enhanced immunoassay]. The lower limit of detection for the CRP assay used was <5 mg/l.

Statistical analysis was performed using the SigmaStat 3.1 program (Systat Software Inc). Groups were compared using rank sum order, Spearman's rank correlation and stepwise regression as appropriate.

The study protocol was approved by the National Research Ethics Service (Study Number (08/NIR01/39).

RESULTS

31 healthy control subjects and 90 subjects with RA were recruited. All were Caucasians. There was no significant difference in the age, percentage of females, body mass index (BMI) or use of NSAIDs between control subjects and RA patients. There was however a significantly greater median level of serum BNP in the RA group as compared with the controls (Table 1).

Serum BNP levels in the RA subjects correlated with DAS28 ($r=0.37$, $p<0.01$). We also observed a correlation between increasing age and BNP, although this only reached significance in the RA group ($r= 0.41$, $p<0.01$). There was no significant correlation with disease duration in the RA patients, or BMI in either group. When stepwise regression was performed, neither the introduction of BMI, age or ESR to the equation significantly added to the ability of DAS28 to predict BNP levels.

RA patients were divided into three groups according to DAS28 scores as described under Methods. Patients with active disease (DAS28>5.1) had significantly higher BNP levels than patients with moderately active disease or inactive disease ($p<0.01$). Median BNP of RA patients with inactive disease did not differ from Controls (Table 2).

DISCUSSION

This study demonstrates that even in subjects with no history, signs or symptoms of cardiac disease, RA patients have significantly higher BNP levels than control subjects, and that RA patients with active RA have significantly higher levels than those with moderately active or well-controlled disease. This difference is not explained by differences in age, BMI or disease duration. Although we cannot entirely exclude past ischaemic damage as a cause of cardiac strain in these patients, the higher BNP levels in the most active RA group suggests that the inflammatory milieu might be a exerting a direct effect on the myocardium, separate from any ischaemic damage. There was also a trend towards shorter disease duration and lower BMI in the most active group (data not shown), again suggesting that the higher BNP levels were linked with current inflammation rather than established damage.

There have been a small number of studies examining BNP in the setting of RA, demonstrating that RA patients have higher levels than matched controls. Most of these studies have included patients with a history of significant established ischaemic heart disease, increasing the likelihood of ischaemic ventricular damage contributing to BNP elevation.

A recent paper by Solus et al[3] showed correlations between disease activity, CRP, TNFalpha and IL-6 with NT-proBNP. However 20% of the longstanding RA patients had a history of angina, MI, stroke or coronary artery procedure, compared with just 8% of controls, increasing the risk that their findings in RA patients were related to previous damage, and that their findings between the two groups might have been influenced by more subclinical damage in the RA group. A 10-year longitudinal study in Norway also showed a link between CRP

TABLE 1.

Patient, disease and treatment characteristics

	Controls (n=31) (median, IQR)	**All RA (n=90) (median, IQR)**	**P value**
Age (yrs)	59.0 (50.3-65.0)	62.0 (53.0-70.0)	0.30
% female	77.4%	80.0%	0.83
BMI (kg/m2)	27.6 (25.2-31.6)	25.9 (23.3-31.4)	0.13
ESR (mm/hr)	12.0 (6.8-18.0)	21.0 (13.0-42.0)	<0.001
CRP (mg/l)	<5	8.0 (5.0-23.5)	<0.001
Regular NSAID use (%)	32.3%	46.7%	0.23
Treatment for hypertension	29.0%	34.7%	0.36
Serum BNP (pg/ml)	48.5 (26.0-86.0)	80.0 (38.0-132.0)	0.017

Table 2.

Serum BNP levels in Control subjects and RA patients grouped by disease activity

	Controls	Inactive RA	Moderately Active RA	Very Active RA
n	31	25	33	32
BNP (IQR) (pg/ml)	48.5 (26.0-86.0)	42 * (24.3-90.0)	76** (35.0-115.0)	101.0 (77.5 – 277.5)

Inactive RA – DAS28<3.2, Moderately Active RA – 3.2<DAS28<5.1, Very Active RA – DAS28>5.1

**Serum BNP Inactive v Active, p<0.01 ** Serum BNP Moderately Active v Active, p<0.01*

and NT-proBNP both at baseline and at 10 years, but again did not exclude those with ischaemic heart disease[6].

Although we did not perform echocardiographs on patients, and therefore might still have included patients with subclinical ischaemic damage or diastolic dysfunction, we believe our exclusion of any suspicion of previous heart disease increases the chances that our findings are predominantly due to direct action of inflammatory proteins on the myocardium. Moreover, even in patients with incident heart failure, RA patients are more likely to have preserved left ventricular ejection fraction[7]. The chances of detecting significant heart failure on echocardiograph in a group of RA patients without any history, symptoms, signs or treatment of the disease is very small; median ejection fraction in a group of RA patients without clinical cardiovascular disease was recently found to be 67%, only slightly lower than a control group with 71% (even if achieving statistical significance in the study[8]), and other groups have identified definite left ventrolic systolic dysfunction in only 5% of RA patients in the outpatient setting, many of whom had a history of ischaemic heart disease and would therefore have been excluded from this study[9].

We might have examined other markers of inflammation, such as IL-6 or TNF alpha, but consciously chose DAS28 as our main outcome for disease activity, so as to make the study as relevant as possible to clinical practice. Other control groups, such as patients with psoriatic arthritis (PsA), might also have been chosen, but the different cytokine profile in PsA would make interpretation difficult, until the cytokines chiefly responsible for direct myocardial damage have been positively identified.

Further insights might be gained by re-measuring BNP levels in the same patients once disease activity had been treated; others have shown that the use of ACE inhibitors improves endothelial function in RA[10] and reduces ESR (11). Whether or not early, prophylactic use of ACE inhibitors in RA, as in diabetes mellitus, improves long term morbidity and mortality remains to be seen.

We believe this study adds weight to the argument that chronic inflammation not only accelerates atherosclerosis, but might also have a directly stressful effect on the myocardium in patients without any history of ischaemic heart disease. It provides yet more evidence that prompt and effective suppression of inflammatory activity in RA is essential not only to preserve synovium and cartilage, but also endothelium and myocardium.

In summary, elevated serum levels of BNP are associated with ventricular strain and increased risk of cardiac events and death in the general population. We found that RA patients with active disease have high levels of BNP as compared both with inactive RA and healthy control subjects, despite no history or ischaemic heart disease or cardiac failure.

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The authors have no conflict of interest

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