C-type natriuretic peptide levels in cor pulmonale and in congestive heart failure

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Abstract

Background — C-type natriuretic peptide (CNP) is a recent addition to the family of natriuretic peptides which includes atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Whilst the levels of ANP and BNP are increased in conditions such as congestive heart failure and cor pulmonale, abnormal levels of CNP in these conditions have not been reported.

Methods — Plasma levels of CNP were measured by specific radioimmunoassay in 12 young normal controls, 12 elderly normal controls, 12 patients with NYHA grade III–IV congestive heart failure, and in 16 patients with hypoaemic cor pulmonale.

Results — Mean (SE) plasma levels of CNP were similar in young normal controls (0.46 (0.03) pmol/l), elderly normal controls (0.43 (0.05) pmol/l), and in patients with congestive heart failure (0.33 (0.02) pmol/l). In patients with cor pulmonale, however, plasma levels of CNP were raised (1.39 (0.27) pmol/l) 3-2-fold compared with age-matched controls.

Conclusions — In cor pulmonale the increased plasma levels of CNP were not as great as the previously observed increases in levels of ANP (5-6-fold) or BNP (18-5-fold) in comparable patients. CNP may therefore be less important than ANP or BNP as a circulating counter-regulatory peptide in conditions of overactivity of the renin angiotensin system.

Methods

Subjects

Normal controls

Twelve young male volunteers of mean (SE) age 25.9 (1.9) years and 12 older volunteers (10 men) aged 68.5 (1.3) years were studied. None were taking regular medication and all had a normal clinical history and examination, electrocardiogram, echocardiogram, and haematological and biochemical test results.

Patients with congestive heart failure

Twelve (10 men) patients aged 68.6 (2.3) years with stable NYHA grade III–IV heart failure symptoms were studied. All had a left ventricular ejection fraction (LVEF) less than 40% as assessed by radionuclide ventriculography, and had been taking a constant dose of frusemide (mean dose 80 mg/day, range 40–160 mg) and ACE inhibitors for at least two weeks. Patients with clinical or radiographic evidence of chronic obstructive pulmonary disease (COPD), systemic hypertension, disturbances of cardiac rhythm, or impaired renal function (serum creatinine >170 mmol/l) were excluded. In this group mean LVEF was 21.6 (1.8)%.

Patients with cor pulmonale

Sixteen (12 men) patients aged 68.1 (1.9) years with clinically stable cor pulmonale secondary to COPD were studied. All had spirometric results reflecting COPD (FEV1/FVC <70%), arterial hypoxaemia while breathing air (Pao2,
ASSAY PROCEDURE
Approval was obtained from the Tayside committee for medical ethics. After giving informed consent subjects rested supine for 30 minutes while breathing room air. Venous blood was collected into EDTA tubes with aprotonin (Trasyol; Bayer UK Ltd, Newbury, Berkshire, UK) before centrifugation and plasma was stored at −70°C.

Plasma levels of CNP were measured using a commercially available radioimmunoassay kit (Peninsula Laboratories Inc, Belmont, California, USA) after solid phase extraction from plasma proteins. Mean CNP recovery was 54.7% and the intra-assay coefficient of variation was 11.4%. The anti-CNP antibody used had no cross-reactivity with either ANP or BNP.

DATA ANALYSIS
Comparisons were made by analysis of variance and Duncan’s multiple range testing using a Statgraphics (STSC Software, Maryland, USA) package. Results are expressed as mean(SE).

Results
The plasma CNP concentration was similar in both young (0.46(0.03) pmol/l) and elderly (0.43(0.05) pmol/l) normal subjects. In patients with congestive heart failure the plasma CNP concentration was not significantly different from young or elderly controls at 0.33(0.02) pmol/l. In patients with cor pulmonale, however, the plasma CNP concentration was significantly (p<0.05) increased at 1.39(0.27) pmol/l compared with young or elderly controls and with congestive heart failure patients. To accommodate the one outlying data point in the cor pulmonale group, the trimmed mean of the other 15 values was calculated to be 1.18(0.19) pmol/l, significantly (p<0.05) higher than the other three subject groups. In patients with cor pulmonale plasma levels of CNP did not correlate with PaO2, PaCO2 or FEV1.

The plasma CNP concentration was therefore raised 3.0-fold in patients with cor pulmonale compared with young normal controls and 3.2-fold compared with age and sex matched elderly normal controls. Individual values with sample means are depicted in the figure.

Discussion
These findings indicate that, despite similar activation of the renin angiotensin system in patients with cor pulmonale and congestive heart failure,1,8 circulating CNP levels are raised in cor pulmonale but not in congestive heart failure. We should therefore briefly consider possible explanations for this observation.

Little is known regarding the stimuli for CNP synthesis and release, although plasma levels of CNP are unaffected by the acute pressor effects of angiotensin II in normal subjects.9 Differences in vasodilator therapy between these groups – that is, ACE inhibition in the congestive heart failure group causing a reduction in vascular stretch – are therefore less likely to be a valid explanation. Reduced clearance of CNP is also unlikely to explain these differences, given that renal function was similar in patients with cor pulmonale and congestive heart failure, although how this is affected by hypoxaemia is unknown.

The other obvious difference between the two patient groups is the presence of arterial hypoxaemia. Whether hypoxaemia stimulates CNP release, as is the case with ANP,9,10 is unknown. Alternatively, chronic arterial hypoxaemia may cause sufficient endothelial damage to allow CNP to leak out into plasma in greater quantity.

Plasma levels of CNP in normal subjects in other studies have been somewhat higher than our own even after conversion into the same SI units. The differences may be partially explained by the use of differing assay methodology. Our method gave 54.7% CNP extraction whereas other methods appear to have higher CNP extraction efficiency. The observed pattern of raised CNP levels in patients with cor pulmonale is, however, still valid in comparison with controls and congestive heart failure patients where the assay methodology was identical.

Despite the present finding that plasma levels of CNP are significantly raised in patients with cor pulmonale, it would appear that ANP and BNP are the predominant circulating natriuretic peptides since ANP is increased 5.6-fold and BNP 18.5-fold in comparable patients.7 CNP may therefore act mainly as a paracrine agent within vascular tissue rather
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Effect of exercise on the nasal transmucosal potential difference in patients with cystic fibrosis and normal subjects

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Abstract

Background – Normal subjects have a negative nasal transmucosal potential difference (TPD) at rest which becomes more negative with exercise. Patients with cystic fibrosis have a more negative resting nasal TPD than controls. The present study was designed to determine the effects of exercise on the TPD of patients with cystic fibrosis.

Methods – Seven subjects with cystic fibrosis and seven control subjects had their usual TPD measured at rest, and during and after a 12 minute period on an exercise bicycle designed to produce a pulse rate of 80% of their maximum predicted value.

Results – The normal subjects developed a more negative nasal TPD during exercise which returned towards normal at the completion of the rest period. The patients with cystic fibrosis had higher resting values which became less negative during exercise. At the end of the exercise period there was no difference between the two groups. At the end of the recovery period the results for the patients with cystic fibrosis had returned to their resting values.

Conclusions – Exercise reduces the abnormally high resting values for nasal TPD in patients with cystic fibrosis. Elucidation of the mechanism for this change may help to produce functional improvement for patients with this disease.

Cystic fibrosis is characterised by an increase in thick mucous secretions. A defective transmembrane regulator for chloride transport in epithelial cells, unable to open under the influence of cyclic AMP, has been described. Respiratory epithelial cells from patients with cystic fibrosis also have a high sodium absorption from the mucosal surface which causes a more negative transmucosal potential difference (TPD) than in controls.

Exercise causes an increase in nasal secretion in normal subjects. TPD also increases in normal subjects during exercise, a change probably related to the increase in secretion. The current study was performed to see if the nasal TPD behaved in the same way during exercise in patients with cystic fibrosis and healthy subjects.

Methods

Seven patients with cystic fibrosis (four men) aged 9–24 years and seven age and gender matched healthy controls volunteered for the
C-type natriuretic peptide levels in cor pulmonale and in congestive heart failure.

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