Brain natriuretic factor: regional plasma concentrations and correlations with haemodynamic state in cardiac disease

A Mark Richards, Ian G Crozier, Timothy G Yandle, Eric A Espiner, Hamid Ikram, M Gary Nicholls

Abstract

Objective—To document regional plasma concentrations of brain natriuretic factor (BNF) and their relations to concurrent concentrations of atrial natriuretic factor, cyclic guanosine monophosphate, and haemodynamic state.

Design—Regional blood sampling from a systemic artery and vein, renal vein, and coronary sinus together with concurrent haemodynamic indices in patients coming forward for left and right cardiac catheterisation.

Setting—Tertiary referral centre.

Patients—22 consecutive unselected patients coming forward for left and right cardiac catheterisation or electrophysiological studies in the course of standard diagnosis for a range of cardiac disorders.

Main outcome measures—Significant arteriovenous gradients for plasma BNF concentration were found across the lower limb, the kidney, and the heart. These were less than concurrent arteriovenous gradients in plasma atrial natriuretic factor (ANF). Arterial concentrations of plasma BNF were positively related to concurrent concentrations of ANF ($r = 0.72, p < 0.01$) and cyclic guanosine monophosphate ($r = 0.52, p < 0.05$). Arterial plasma concentrations of BNF showed a significant positive correlation with right atrial pressure and pulmonary artery wedge pressure and an inverse relation to cardiac output.

Conclusions—Regional plasma concentrations of BNF indicate cardiac secre-

tion of this peptide and clearance in a number of tissues. Renal clearance is proportionally greater than that found across the limb. Absolute and proportional arteriovenous gradients of this peptide are considerably less than for concomitant concentrations of ANF suggesting slower metabolic clearance of BNF. Plasma BNF concentrations rise with increasing cardiac impairment and are related to indices of cardiac function. These findings are consistent with a role for BNF in the neurohumoral response to cardiac impairment.

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Brain natriuretic factor (BNF) is a recently discovered member of the atrial peptide family. Originally isolated in porcine brain¹ it was later found in cardiac tissue and in plasma.^{2,3} It may be cosecreted from atrial granules⁴ but the primary source of BNF seems to be by synthesis from cardiac ventricular tissue.⁵ Its presence has been confirmed in a number of species including humans.^{5,6} Concentrations of BNF are increased in heart failure and in acute myocardial infarction.^{5,7,8} When given in pharmacological doses to patients with heart failure it exerts considerable haemodynamic effects.⁹

To date little information is available regarding the regional plasma concentrations of BNF, the relation of BNF to concurrent concentrations of atrial natriuretic factor (ANF), and the relation of BNF to haemodynamic state. Hence, we examined plasma concentrations of BNF, ANF, and cyclic

Departments of Cardiology and Endocrinology, Princess Margaret Hospital, Christchurch 2, New Zealand
A Mark Richards
Ian G Crozier
Timothy G Yandle
Eric A Espiner
Hamid Ikram
M Gary Nicholls

Correspondence to Dr A Mark Richards, Department of Cardiology, Princess Margaret Hospital, Cashmere Road, Christchurch 2, New Zealand.

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Patient data

Patient	Age(y)	Sex	HR (beats/min)	RAP (mm Hg)	PAWP (mm Hg)	PAP (mm Hg)	CO (l/min)	MAP (mm Hg)	Diagnosis
1	59	M	70AF	7	13	20	5.22	95	AI(mild)
2	66	M	64	3	10	18	4.85	110	Normal
3	56	M	55	5	9	18	4.42	88	AS/AI(mod)
4	61	M	90	5	14	35	5.20	124	AS(severe)
5	77	M	68	3	7	13	4.10	89	AS(mod)
6	55	M	84	4	6	12	8.39	110	Normal
7	45	F	110	9	29	42	3.90	124	COCM(severe)
8	68	M	50	6	12	19	3.50	77	AS(mod)/IHD (severe)
9	79	F	80AF	10	20	24	3.01	75	AS(mod)/ AI(mod)
10	65	F	78	5	10	24	5.42	98	IHD(severe)
11	68	F	75	4	23	31	3.53	92	MS(severe)
12	67	M	62	5	25	32	3.93	113	AS(severe)
13	72	M	64	7	18	27	4.80	110	AS(mod)/IHD(severe)
14	22	M	56	7	11	16	6.10	88	AS(mild)
15	63	F	52	5	8	18	4.16	102	IHD(mod)/AS(mild)
16	60	F	120AF	8	21	25	4.53	120	AI(mod)

AF, atrial fibrillation; HR, heart rate; RAP, mean right atrial pressure; PAWP, mean pulmonary artery wedge pressure; PAP, mean pulmonary artery pressure; CO, cardiac output; MAP, mean arterial pressure; AI, aortic incompetence; AS, aortic stenosis; COCM, congestive cardiomyopathy; MS, mitral stenosis; IHD, ischaemic heart disease; mod, moderate.

guanosine monophosphate (cGMP, the putative second messenger for both hormones), and haemodynamic state in a series of patients undergoing diagnostic cardiac catheterisation.

Patients and methods

Twenty two patients (16 men, six women) aged 22 to 79 (median 58) years gave written informed consent to participate in the study. The study protocol was approved by the Canterbury Area Health Board ethics committee and complies with the requirements of the Declaration of Helsinki. The patients were undergoing diagnostic cardiac catheterisation that required both arterial and venous cannulation. Left ventricular function varied from normal to severe impairment. The aetiology of cardiac disease was mixed (table). Twelve patients had aortic or mitral valve disease with or without concurrent coronary artery disease. Pure triple vessel ischaemic heart disease was present in one patient. One patient had idiopathic dilated cardiomyopathy. Six patients had normal or near normal left ventricular function and were studied for electrophysiological abnormalities as they presented with supraventricular tachycardia or syncope, or were studied after surgical resection of atrioventricular bypass tracts. The remaining two patients underwent catheterisation as part of an investigation for chest pain and were found to have normal coronary angiography and left ventricular function. Four patients fell within New York Heart Association (NYHA) functional class 1, seven were in class 2, six in class 3, and five in class 4. Renal function, as assessed by plasma creatinine concentrations, was normal in all patients. Patients were stable on a variety of drugs for heart failure and arrhythmia although no patient had taken any cardiac medications for the 24 hours before catheterisation. Patients were studied after fasting and after 10 mg of oral diazepam.

In each case the femoral vein and femoral artery were cannulated. In 16 patients (table, which excludes patients undergoing electrophysiological studies) full right sided haemodynamic measurements were made, including measurement of right atrial, right ventricular, pulmonary artery, pulmonary artery wedge pressures, and cardiac output (by thermodilution in triplicate), with standard Swan-Ganz

catheters and transducers. Systemic arterial pressure and heart rate were also recorded. Blood samples were taken sequentially from the femoral artery, femoral vein, renal vein, coronary sinus, and finally a repeat sample was taken from the femoral artery. Right heart pressures and cardiac output were measured immediately after the sample from the coronary sinus. Right heart studies and blood samples were taken before introduction of any radiocontrast material into the circulation.

Blood was taken into chilled tubes that contained ethylene diamine tetraacetate and immediately centrifuged. Plasma was stored at -20°C before radioimmunoassay for BNF, ANF, and cGMP.¹⁰⁻¹² We used a radioimmunoassay for human BNF previously developed¹⁰ to measure BNF in both normal subjects and in patients with heart failure. Briefly, BNF was extracted from human plasma with Vycor glass powder (mean extraction efficiency 79%). The assay used high performance liquid chromatography purified human ^{125}I his, BNF³² and a specific BNF antiserum purchased from Peninsula Laboratories. The minimum detectable concentration was 0.45 fmol/tube and the IC_{50} 9 fmol/tube. Within and between assay coefficients of variation for the assay were 7% and 10%. The normal range of plasma BNF was ascertained from samples from 48 normal volunteers (40 men) aged 18 to 70 years. Blood samples were taken after 30 minutes lying down. The normal range for BNF established from these data was 3–10 pmol/l. Mean (2SD) BNF plasma concentrations (6.3 (0.3 pmol/l) were significantly lower than mean concomitant ANF concentrations (8.4 (0.6 pmol/l) in this group of normal subjects.

Statistical analysis of data consisted of paired *t* tests and calculation of Fisher correlation coefficients. *p* Values <0.05 (two tailed test) were taken to indicate statistical significance.

Results

Figure 1 shows mean regional plasma concentrations of BNF and ANF. No significant differences were found in initial compared with final femoral arterial values of either BNF or ANF indicating that plasma concentrations of these peptides remained stable for the sampling period. Initial femoral arterial values were used for all analyses of hormone arteriovenous gradients. Significant arteriovenous gradients in plasma BNF concentrations were found between the femoral artery and vein and between arterial and coronary sinus and arterial and renal vein concentrations (fig 1). The fall in BNF concentrations from femoral artery to vein ($n = 22$) was slight (a decrement of only 2 pmol/l (–6%)) but statistically significant ($p < 0.01$). In 13 patients in whom coronary sinus sampling was successful, cardiac secretion of BNF was indicated as coronary sinus concentrations of BNF were on average more than double concurrent arterial values. A fall in BNF concentrations

Figure 1 Plasma concentrations (mean (SEM)) of BNF and ANF in femoral artery (Fem a), femoral vein (Fem v), coronary sinus (C sinus), and renal vein (Ren v) in patients with a range of cardiac disease.

across the renal circulation (an average decrement of 7 pmol/l (-21%), $p < 0.01$) was found and this was consistently greater than concurrent falls between femoral artery and vein.

At all four sampling positions, mean plasma ANF concentrations were significantly greater than concurrent BNF concentrations (fig 1, $p < 0.01$, $p < 0.001$, $p < 0.05$, $p < 0.0001$ for arterial, coronary sinus, renal venous, and femoral venous plasma). Absolute and proportional arteriovenous gradients for plasma ANF concentrations were significantly greater than those found in concurrent BNF concentrations. Plasma ANF fell by 35% between the femoral artery and vein ($n = 22$), increased by 528% between artery and coronary sinus ($n = 13$), and fell by 60% between artery and renal vein ($n = 16$). Cyclic GMP concentrations showed a small rise from femoral artery to vein (6.6 (0.7) to 7.5 (0.7 pmol/ml, $p < 0.01$) and no significant change from arterial to coronary sinus concentrations (5.8 (0.9) to 6.1 (0.9 pmol/ml, NS). By contrast, there was a sharp decline in cGMP concentrations across the renal circulation (5.9 (0.7) to 3.1 (0.4) pmol/ml, $p < 0.001$).

Arterial concentrations of BNF ($n = 22$) were related to concomitant plasma ANF concentrations ($r = 0.72$, $p < 0.001$) and with cGMP ($r = 0.52$, $p < 0.05$). As expected ANF and cGMP were also positively related ($r = 0.82$, $p < 0.0001$).

Figure 2 shows the significant inverse rela-

tion of plasma BNF concentrations (arterial) to concurrent cardiac output and the positive relation with pulmonary artery wedge pressure. Plasma BNF was also significantly related to mean pulmonary artery pressure ($r = 0.55$, $p < 0.05$) and mean right atrial pressure ($r = 0.51$, $p < 0.05$) with these relations resembling that found between BNP and pulmonary artery wedge pressure. No relation with systemic arterial pressure was found. Similar relations occurred between plasma ANF concentrations and haemodynamic indices. Plasma ANF was inversely related to cardiac output ($r = -0.45$, $p = 0.10$, NS) and positively related to right atrial ($r = 0.53$, $p < 0.05$), pulmonary wedge ($r = 0.53$, $p < 0.05$), and mean pulmonary artery pressures ($r = 0.55$, $p < 0.05$). As in the case of plasma BNF, plasma ANF concentration showed no significant correlation with systemic arterial pressure.

Discussion

These data confirm that plasma BNF concentrations are raised in cardiac disease in proportion to the severity of haemodynamic dysfunction. BNF is inversely related to cardiac output and positively related to both right ventricular and left ventricular filling pressures. This information is consistent with previous reports indicating an inverse relation between plasma BNF concentrations and cardiac index in acute myocardial infarction.⁸ To our knowledge these are the first data relating BNF to haemodynamic state in a group with a range of chronic stable cardiac dysfunction although a positive relation between plasma BNF concentrations and NYHA functional class has been previously reported.⁷ The relation between plasma BNF concentrations and haemodynamic indices parallel those seen between ANF and haemodynamic state. This information complements the powerful body of published evidence linking ANF concentrations to haemodynamic state in heart disease.¹³⁻¹⁵ The two peptides may play a complementary part in the overall neurohumoral response to cardiac dysfunction.

At all sites inspected in our patients, mean plasma BNF concentrations were less than plasma ANF concentrations. It is known that in normal volunteers plasma BNF is significantly lower than concurrent plasma ANF.^{5,10} In severe cardiac impairment, however, BNF may exceed ANF concentrations.^{7,9,10} Hence, in a group such as ours in which a broad range of cardiac dysfunction is present, including a significant proportion of the patients with normal haemodynamic indices, the higher mean plasma ANF concentrations are not unexpected.

We have established a significant arteriovenous gradient for BNF across the lower limb and human kidney. To our knowledge this is the first finding of renal extraction of BNF. Our data concerning coronary sinus concentrations of BNF confirm previous reports of cardiac secretion of this peptide.⁵ All arteriovenous gradients for plasma BNF were simi-

Figure 2 Plasma BNF concentrations (arterial) plotted against concurrent cardiac output (upper panel) and pulmonary artery wedge pressures (PAWP, lower panel) in 16 patients undergoing diagnostic cardiac catheterisation.

lar in direction but less in magnitude both in proportional and absolute terms than those found for plasma ANF concentrations. These findings are consistent with a slower clearance of BNF in most tissues, perhaps reflecting a reduced affinity of BNF for clearance receptors.¹⁶ Accordingly, our recent studies incorporating infusion of exogenous BNF show a much reduced disappearance rate ($t_{1/2}$) of BNF from venous plasma at about one seventh the rate found for ANF.¹⁷ This is consistent with our finding of a six fold difference in proportional femoral arteriovenous decrement for BNF (6%) compared with ANF (35%).

Plasma cGMP concentration is significantly correlated with both plasma ANF and BNF concentrations consistent with its purported second messenger role for both agonists. It is impossible to discern from our present data what proportion of plasma cGMP is attributable to the effect of one or other or the combined influence of the two natriuretic peptides. Also, other factors, including endothelium derived relaxing factor influence concentrations of plasma cGMP to an uncertain degree. Femoral venous concentrations of cGMP were subtly but significantly greater than those found in femoral arterial blood. This is consistent with spillover of intracellular second messenger concentrations into the venous effluent from the tissue concerned. To our knowledge this finding has not previously been recorded in a group of patients with a range of cardiac disease. A noticeable renal clearance of cGMP was found to be entirely consistent with the well documented renal clearance of cGMP, that is similar to glomerular filtration rate.¹⁸

In conclusion, in a group of patients with a range of cardiac disease, plasma BNF concentrations were raised above normal in proportion to the degree of haemodynamic impairment. Plasma BNF and plasma ANF concentrations were closely correlated and the two peptides may complement each other in the overall neurohumoral response to cardiac dysfunction. BNF is clearly secreted from the heart and cleared across a similar array of organs as is ANF, but arteriovenous gradients are far less than those found in concurrent ANF concentrations suggesting a much slower clearance of BNF. Clearly, further observational and interventional studies are required to better define the roles, and the relative importance, of BNF and ANF in pressure and volume homeostasis in health and disease.

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