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B-type natriuretic peptide is an independent predictor of endothelial function in man

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ABSTRACT

BNP (B-type natriuretic peptide) has been reported to be elevated in preclinical states of vascular damage. To elucidate the relationship between plasma BNP and endothelial function, we have investigated the relationship between BNP and endothelial function in a cohort of subjects comprising healthy subjects as well as at-risk subjects with cardiovascular risk factors. To also clarify the relative contribution of different biological pathways to the individual variation in endothelial function, we have examined the relationship between a panel of multiple biomarkers and endothelial function. A total of 70 subjects were studied (mean age, 58.1 $\pm$ 4.6 years; 27% had a history of hypertension and 18% had a history of hypercholesterolaemia). Endothelium-dependent vasodilatation was evaluated by the invasive ACH (acetylcholine)-induced forearm vasodilatation technique. A panel of biomarkers of biological pathways was measured: BNP, haemostatic factors PAI-1 (plasminogen-activator inhibitor 1) and tPA (tissue plasminogen activator), inflammatory markers, including cytokines [hs-CRP (high sensitive C-reactive protein), IL (interleukin)-6, IL-8, IL-18, TNFα (tumour necrosis factor α) and MPO (myeloperoxidase] and soluble adhesion molecules [E-selectin and sCD40 (soluble CD40)]. The median BNP level in the study population was 26.9 pg/ml. Multivariate regression analyses show that age, the total cholesterol/HDL (high-density lipoprotein) ratio, glucose and BNP were independent predictors of endothelial function, and BNP remained an independent predictor ($P = 0.009$) in a binary logistic regression analysis using FBF (forearm blood flow) as a dichotomous variable based on the median value. None of the other plasma biomarkers was independently related to ACH-mediated vasodilatation. In a strategy using several biomarkers to relate to endothelial function, plasma BNP was found to be an independent predictor of endothelial function as assessed by endothelium-dependent vasodilatation in response to ACH.

INTRODUCTION

BNP (B-type natriuretic peptide) possesses complementary functions in regulating BV (blood volume) and vascular smooth muscle tone and is vital to the maintenance of cardiovascular homoeostasis [1]. The physiological actions of BNP include the regulation of vascular tone by activation of the particulate

Key words: acetylcholine, B-type natriuretic peptide, cardiovascular disease, endothelial dysfunction, forearm blood flow, natriuretic peptide.

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitor; ACH, acetylcholine; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CTAD, citrate/theophylline/adenosine/dipyridamole; CVD, cardiovascular disease; FBF, forearm blood flow; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; hs-CRP, high-sensitive C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; MPO, myeloperoxidase; PAI-1, plasminogen-activator inhibitor 1; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ROC, receiver operator characteristic; SBP, systolic blood pressure; sCD40, soluble CD40; TNFα; tumour necrosis factor α; tPA, tissue plasminogen activator.

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isoform of guanyl cyclase after binding to natriuretic peptide receptor A and by direct endothelium-dependent nitric oxide production [2,3]. An inverse relationship between plasma BNP level and endothelial function has been reported in patients with CVD (cardiovascular disease), including patients with heart failure [4–7]. These observations have led to the speculation that BNP can serve as a biomarker of preclinical CVD, including endothelial dysfunction [8]. However, an inverse relationship between plasma natriuretic peptides and endothelial function has not been a consistent finding [5].

To further elucidate the relationship between plasma BNP and endothelial function at an early stage, we have investigated whether BNP is related to resistance vessel endothelial function, assessed by FBF (forearm blood flow) responses to brachial artery infusions of ACH (acetylcholine) [7] in a group of healthy subjects as well as at-risk individuals with cardiovascular risk factors. As endothelial function is also influenced by several other biological pathways such as haemostatic factors and inflammation [9], we have also examined the relationship between endothelial function and a panel of biomarkers of haemostasis and inflammation in our cohort of subjects.

MATERIALS AND METHODS

Study population

Our study subjects were recruited from the control arm of an on-going Wellcome Trust United Kingdom Case Control Collection for Type 2 diabetes study based in Dundee. Consequently, none of the subjects had a diagnosis of diabetes mellitus, but subjects with an IFG (impaired fasting glucose) were included [10]. Subjects varied in terms of cardiovascular risk profile and ranged from zero to multiple conventional risk factors for atherosclerosis. Subjects with a history of atherosclerotic disease (coronary artery disease, cerebrovascular disease and peripheral vascular disease) were excluded. All participants gave their written informed consent to participate in this study which was approved by the Tayside Committee on Medical Ethics. The investigations conformed to the principles outlined in the 2008 Declaration of Helsinki.

A detailed medical history was obtained and cardiovascular risk factors were recorded and included age, smoking history, history of hypertension, hypercholesterolaemia and renal dysfunction. Smoking was defined as current smokers and non-smokers. Current smokers were those who smoked within the previous month. The use of regular medication was also recorded. All subjects underwent physical examination and included measurement of BP (blood pressure), weight and height for determination of BMI (body mass index).

Blood sampling and analysis

Participants attended a temperature-controlled laboratory (24–26 °C) in our research unit after an overnight fast, having refrained from tea, coffee or tobacco for 12 h. All participants had a resting ECG (Eclipse 850; Spacelabs Burdick). BP was measured in the non-dominant arm after at least 30 min of rest. The average of three recordings was used.

All participants rested for at least 30 min before venipuncture. Blood was collected through an 18-guage cannula inserted in the anticubital fossa. The tourniquet was removed and blood was allowed to flow freely. Blood (75 ml) was drawn into blood bottles containing citrate [tPA (tissue plasminogen activator)], heparin [E-selectin, ICAM-1 (intercellular adhesion molecule-1) and MPO (myeloperoxidase)], EDTA [sCD40 (soluble CD40), BNP and hs-CRP (high-sensitive C-reactive protein)], CTAD (citrate/theophylline/adenosine/dipyridamole) tubes (BectonDickinson) for PAI-1 (plasminogen-activator inhibitor-1) assay. Serum samples were used for TNFα (tumour necrosis factor α) and ILs (interleukins; IL-6, IL-8 and IL-18). Blood was also collected in vacutainer tubes for measurement of HbA_{1c} (glycated haemoglobin), serum lipids and glucose.

Serum tubes were immediately transferred to a water bath at 37 °C. Citrate, heparin, BNP, EDTA and CTAD tubes were spun at 1500 ***g*** for 15 min at 4 °C. After the first spin, citrate, heparin and EDTA tubes were transferred to an ice bucket and the supernatant aliquoted in 1.5 ml tubes and stored at −80 °C. Serum specimens, EDTA and CTAD were spun for a further 15 min at 1500 ***g*** at 4 °C. The supernatants were stored in small aliquots at −80 °C.

hs-CRP, TNFα, IL-6, IL-8, IL-18, BNP, E-selectin, ICAM-1, sCD40 and MPO were analysed with commercially available kits by the technique of quantitative enzyme immunoassay technique using a specific monoclonal antibody on a microplate. PAI-1 and tPA were measured by quantitative ELISA [11,12]. The inter- and intra-assay coefficients of variability for these assays in our laboratory are as follows: hs-CRP, 16.2 and 8.5 %; TNFα, 7.3 and 3.1 %; IL-6, 6.5 and 6.9 %; IL-8, 5.4 and 6.1 %; IL-18, 5.2 and 5.3 %; BNP, 2 and 14 %; E-selectin, 7.3 and 5.2 %; ICAM-1, 4.4 and 3.6 %); and sCD40, 6.0 % and 4.5 %.

FBF

Subjects underwent cannulation of the non-dominant brachial artery under local anaesthesia with a 27-gauge steel needle (Coopers Needleworks) mounted on to a 16-gauge epidural catheter (Portex). Physiological saline was infused (Graseby 3100 syringe pump) at a constant rate of 1 ml/min in the first 30 min to allow resting blood flow to stabilize. Baseline FBF was measured by means of forearm venous occlusion plethysmography as described previously [13]. When resting flows were

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established, FBF was measured during the last 2 min of 5-min drug infusions. Drugs infused were ACH (50 and 100 nmol/min; Novartis) and sodium nitroprusside (37.8 nmol/min; Mayne Pharma). Each drug infusion period was separated by a washout period (10–30 min) with 0.9 % saline to allow flows to normalize. FBF was expressed as the percentage change in the ratio of infused to the non-infused arm calculated according the method described by Whitney [14]. BP was measured in the non-infused arm before each infusion period and at the conclusion of the study. Forearm vascular resistance was calculated by taking the ratio of MAP (mean arterial pressure) and the FBF value in units of mmHg/ml per 100 ml per min.

All procedures and data analysis were performed by a single researcher to eliminate inter-observer variability.

Statistical analysis

We tested the distribution of continuous variables by visual inspection of the frequency histogram and Shapiro–Wilk test. For non-normally distributed data, a logarithmic transformation was used to achieve a normal distribution. Normally distributed data are presented as means ± S.D., whereas non-normally distributed data are given as medians (interquartile range).

To determine predictors of endothelial function, a univariate and stepwise multivariate linear regression analysis were performed. The variables were chosen based on previous studies and included age, sex, smoking, SBP (systolic blood pressure), statin use, use of ACE-Is (angiotensin-converting-enzyme inhibitors) or ARBs (angiotensin II type 1 receptor blockers), BMI, the total cholesterol/HDL ratio and the plasma biomarkers described. All biomarker measurements (including glucose) were treated as continuous variable. Predictors with a $P < 0.1$ on the univariate analysis were entered into a stepwise multivariate linear regression. The accuracy of the model was determined using the R-value. Assumptions for general linear models were tested including testing of residuals for normal distribution and Durbin–Watson test to detect autocorrelation.

Using median FBF as a dichotomous variable, a logistic regression analysis was carried out to determine whether BNP remained an independent predictor of endothelial function. To further examine the incremental effect of BNP on the conventional factors including age, gender, SBP, smoking, the total cholesterol/HDL ratio and glucose, the c-statistic using ROC (receiver operator characteristic) curve analysis was used. A logistic regression model was prepared, and the area under the ROC curve was compared between conventional factors and conventional factors and BNP. The Hosmer–Lemeshow goodness-of-fit test was used to assess the logistic model fit. All probability values are presented as two-tailed, with statistical significance inferred at $P < 0.05$. All statistical analyses were performed using SPSS for Windows version 17.0. ROC curves were tested using Excel spreadsheet.

Table 1 Clinical characteristics of study subjects

Values are expressed as means ± S.D. or medians (interquartile range). Cardiovascular risk factors were hypercholesterolaemia, hypertension, current smoker and impaired fasting glucose. HbA_{1c}, glycated haemoglobin; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HR, heart rate.

Variable	Value
Clinical characteristics	
Age (years)	58.1 ± 4.6
Sex (male)	94.3%
Hypertension	27%
Hypercholesterolaemia	18%
Smoking status (within previous month)	15.7%
HR (beats/min)	59.1 ± 7.3
SBP (mmHg)	136.5 ± 14.4
Diastolic blood pressure (mmHg)	78.0 ± 8.6
BMI (kg/m^2)	28.5 ± 4.2
Total cholesterol/HDL ratio	3.9 ± 1.03
Glucose (mmol/l)	5.40 (1.0)
HbA_{1c} (%)	5.50 (1.0)
Cardiovascular risk factors (n)	
0	21 (30 %)
1	29 (41 %)
2	15 (21 %)
At least 3	5 (7 %)
Medication (%)	
Aspirin	7.1
HMG-CoA reductase inhibitors	18.6
ACE-I/ARB	14.3
Calcium channel blockers	12.9
Bendroflumethiazide	7.1
β-Blockers	5.7

RESULTS

Subject characteristics, biomarkers and vascular function measures

At total of 70 subjects participated in this study. The mean age was 58.1 ± 4.6 years with a predominance of males in our study. Table 1 shows the clinical characteristics of the subjects. Of these, 19 (27 %) subjects reported a history of hypertension and were all on medication [ten (14 %) on ACE-Is or ARBs, nine (12.9 %) on CCBs (calcium channel blockers) and five (7.1 %) on thiazide diuretics]. Then 18 % had a history of hypercholesterolaemia and all were on a statin and five (7.1 %) were on an aspirin (prescribed for primary prevention). Then 34 (48.6 %) had impaired fasting blood glucose.

Serum and plasma levels of the biomarkers of subjects are shown in Table 2. The median plasma BNP level was 26.9 (interquartile range, 18.1–59.3) pg/ml.

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Table 2 Plasma biomarker levels and FBF of the study subjects

Values are medians (interquartile range)

Biomarker	Value
hs-CRP	0.78 (0.35–1.80)
TNFα (pg/ml)	2.15 (1.59–3.49)
IL-6 (pg/ml)	1.28 (0.90–1.79)
IL-8 (pg/ml)	14.4 (8.9–21.7)
IL-18 (pg/ml)	289.5 (203.1–364.1)
PAI-1 (ng/ml)	34.4 (21.1–46.4)
BNP (pg/ml)	26.9 (18.1–59.3)
tPA (ng/ml)	9.1 (6.68–10.88)
ICAM-1 (ng/ml)	242.2 (212.3–286.5)
E-selectin (ng/ml)	47.3 (38.3–58.3)
sCD40 (pg/ml)	72.3 (46.5–112.0)
MPO (ng/ml)	167.8 (81.9-229.2)

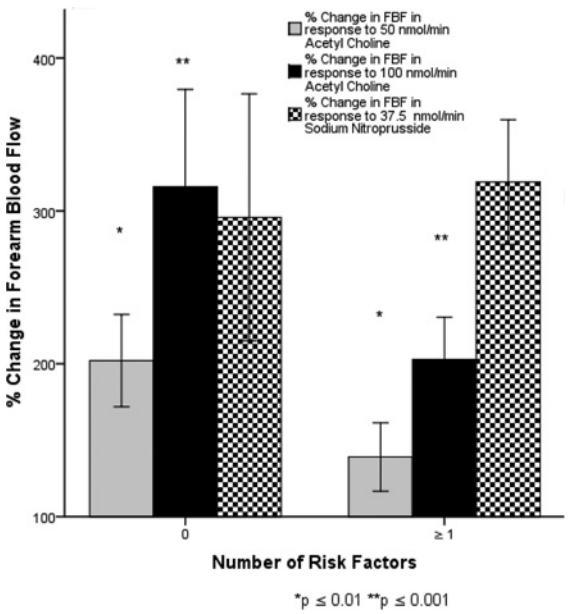

Figure 1 FBF response in subjects without and with conventional risk factors for coronary artery disease

The mean hs-CRP in the present study was 0.78 and ranged from 0.1 to 4.5, reflecting volunteers with a spectrum of cardiovascular risk profile.

FBF responses to ACH at 50 and 100 nmol/min were significantly lower in at-risk subjects when compared with healthy subjects at both doses ($P \leqslant 0.01$) (Figure 1). There was no difference endothelial independent vasodilatation between healthy subjects and at-risk subjects with cardiovascular risk factors.

Univariate and multivariate linear regression analysis

In the univariate model, age, BMI, SBP, the total cholesterol/HDL ratio, glucose, log BNP and log MPO

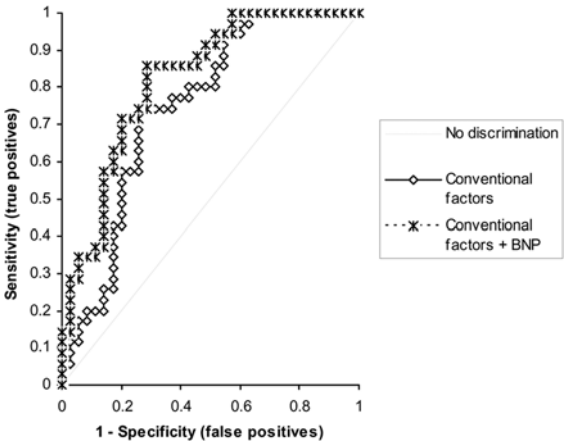

Figure 2 ROC curve for conventional risk factors with and without BNP for predicting FBF

reached the pre-specified $P < 0.1$ criteria to be entered into the model. In the multivariate analysis only age, the total cholesterol/HDL ratio, glucose and log BNP were independent predictors of FBF. The overall R value of the model was 0.63 ($P = 0.049$) with BNP and 0.60 ($P = 0.03$) without BNP. There were no co-linearity ($r > 0.9$) between the predictors and the residuals were normally distributed.

BNP (log-transformed) remained an independent predictor ($P = 0.009$) in a binary logistic regression analysis using FBF as a dichotomous variable based on the median value together with age ($P = 0.031$) and the total cholesterol/HDL ratio ($P = 0.028$), although glucose was non-significant in this model.

The area under the ROC curve for conventional risk (age, SBP, glucose and the total cholesterol/HDL ratio) factors was 0.75 [95 % CI (confidence interval), 0.63–0.87; ($P < 0.001$] and 0.82 (95 % CI, 0.72–0.92; $P < 0.001$) for conventional risk factors and BNP (Figure 2). The difference between the two ROC curves was, however, not statistically significant. In our study, BNP was not associated with forearm vascular resistance.

DISCUSSION

Our study has two main findings. First, in a cohort of individuals without overt coronary artery disease, plasma BNP together with the established cardiovascular risk factors of age, glucose and the total cholesterol/HDL ratio correlated inversely with endothelial function as assessed by the invasive ACH-induced forearm vasodilation technique. Secondly, none of the biomarkers related to haemostasis and inflammation was found to be related to endothelial function.

Chong et al. [4] first reported an inverse correlation between FMD (flow-mediated dilatation) and BNP levels in patients with heart failure. Elevated levels of BNP predict abnormal coronary endothelial function [6] and

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the burden of coronary atherosclerosis determined by electron-beam CT (computed tomography) [15]. The findings of the current study add to evidence that BNP may serve as a plasma biomarker of endothelial dysfunction.

However, it should be noted that the findings of the present study differ from the results of some previous studies. In the Framingham study, BNP was related to FMD, another measure of endothelial function [16] [and a positive rather than an inverse relationship was reported between plasma N-terminal pro-ANP (atrial natriuretic peptide) and FMD] [5]. An analysis of the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study showed that BNP was not related to endothelial function assessed both by FMD and by the intra-brachial ACH infusion method [17]. The reason for discrepancy between these findings and our study is not clear. One possibility is that, in the Framingham study, the plasma natriuretic peptides were measured on an average of 2.9 years before the vascular measures. There were also measurement-related problems in the Framingham study with undetectable BNP levels reported in 25–40 % of the subjects. The PIVUS study was a study of Caucasians aged 70 years. This striking difference in age between study samples may explain the difference in findings.

In our present study, we did not find any relationship between endothelial function and plasma biomarkers of inflammation. Although there have been studies that have reported an inverse relationship between endothelial function and inflammatory markers, including hs-CRP [18–20], this is not a universal finding [21,22]. The manner in which endothelial function is assessed may be important. Lind et al. [23] recently reported that ACH-induced vasodilatation in the forearm, but not FMD, was inversely related to hs-CRP levels and E-selectin independently of traditional risk factors in elderly subjects. Thus inflammation evaluated by hs-CRP levels could have different influences on endothelium-dependent vasodilatation in resistance vessels evaluated by ACH stimulation as opposed to conductance vessels evaluated by FMD in the brachial artery.

What are the potential mechanisms linking endothelial dysfunction and a raised BNP? One possible explanation is that endothelial dysfunction tracks arterial stiffness, a measure of the viscoelastic properties of arteries and hence afterload [24]. We previously showed in patients with diabetes that BNP increases as the augmentation index increases [25], although it is recognized that the augmentation index may be influenced by factors other than arterial stiffness, such as HR (heart rate), height and ejection duration [26]. Nevertheless, our previous study would suggest that stiff arteries/arterioles could increase afterload and subtly increase intra-cardiac pressure and thus BNP. BNP levels were, however, not related to endothelial-independent vasodilatation. Another possible explanation is that endothelial dysfunction may be a sign of early atherosclerosis in a wide variety of blood vessels, including the coronary vessels. In turn, coronary atherosclerosis could produce myocardial ischaemia. In fact, myocardial tissue that is injured in any way, such as by ischaemia, appears to express and release more BNP than non-injured or non-ischaemic myocardial tissue, irrespective of haemodynamic considerations [27,28]. Thus endothelial dysfunction could imply subtle but asymptomatic myocardial ischaemia that is identifiable by a subtly elevated NP level. In fact, we recently showed that subtle elevations in BNP are indicative of silent myocardial ischaemia in Type 2 diabetics [28].

Although BNP was an independent predictor of endothelial function, it does not seem to have incremental value over the traditional risk factors (age, BMI, BP and glucose) as assessed by the area under the ROC curve in our study.

Limitations

We have carried out an observational study and thus the design of our study does not allow conclusions on possible causal relationships observed and further studies are warranted.

Conclusions

In a strategy using several biomarkers to relate to endothelial function assessed by the invasive ACH-induced forearm vasodilatation technique, plasma BNP was found to be an independent predictor of endothelial function.

AUTHOR CONTRIBUTION

Maheshwar Pauriah, Allan Struthers and Chim Lang conceived and designed the study, acquired, analysed and interpreted the data, wrote the paper and revised the paper critically for intellectual content and final approval; Faisel Khan, Tiong Lim, Douglas Elder and Valerie Godfrey analysed and interpreted the data, and revised the paper critically for intellectual contect and final approval; Gwen Kennedy, Jill Belch and Nuala Booth aquired, analysed and interpreted the data, and revised the paper critically for intellectual contect and final approval.

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