ORIGINAL PAPER

Elevated BNP with normal systolic function in asymptomatic individuals at-risk for heart failure: a marker of diastolic dysfunction and clinical risk

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ABSTRACT

Background B-type natriuretic peptide (BNP) is widely accepted in the evaluation of left ventricular systolic dysfunction and heart failure. However, little is known of the implications of elevated BNP levels in individuals with preserved systolic function (PSF).

Aims To investigate the drivers and clinical implications of elevated BNP levels in asymptomatic individuals with established PSF.

Methods We enrolled 154 individuals who all underwent physical examination, BNP evaluation and Doppler-echocardiographic studies. They were divided into those above and below the median BNP level (50pg/ml).

Results Independent predictors of higher BNP were older age, more severe left ventricular hypertrophy (LVH), reduced E/A ratio and ischaemic heart disease. Survival and multivariable analysis demonstrated more death and/or admission in those above the median BNP (HR: 4.79, p=0.007).

Conclusions Elevated BNP is the strongest, independent predictor of serious adverse cardiovascular outcomes in this population and requires closer clinical follow-up.

INTRODUCTION

B-type natriuretic peptide (BNP) is a member of the family of genetically distinct natriuretic peptides, synthesized and released by cardiomyocytes in response to myocyte stretch due to volume expansion and pressure overload.[1-3] It is predominantly released from ventricular myocytes as NT-BNP (76 amino acid fragment) and BNP (32 amino acid fragment). In addition to natriuretic effects, BNP has been shown to relax vascular smooth muscle and exert anti-proliferative and antifibrotic effects.[4,5]

Increases in plasma BNP concentration have diagnostic and prognostic implications in selected populations. This was shown initially in the presence of heart failure due to left ventricular systolic dysfunction (LVSD) and subsequently in both early stage and asymptomatic LVSD.[6-14] More recently, the diagnostic and prognostic value of BNP has been underlined in a range of settings including the emergency room,[10] in heart failure due to diastolic dysfunction,[11] post-MI [12,13] and in an at-risk renal population.[14] McDonagh and colleagues were among the first to explore the value of BNP screening in the general population, and while they found BNP to be an independent predictor of mortality, such screening programs may be limited by the low screening return and event rates.[15] Recent data from the Framingham Offspring Study support the role of BNP in predicting the risk of death, cardiovascular events, heart failure and stroke, independently of traditional risk factors.[16] Therefore, while BNP is widely accepted in the evaluation of LVSD and heart failure, there are emerging data on its prognostic benefits in the general population.[15-18] However, there has been little analysis of the drivers, and clinical implications of elevated BNP levels in a community population possessing risk factors for heart failure. The aim of this study was to investigate the prevalence, drivers, and clinical implications of elevated BNP levels in asymptomatic individuals with established cardiac risk factors for HF with proven normal systolic function.

METHODS

This was a collaborative study between St Vincents University Hospital Heart Failure Unit and a large General Practice in the South Eastern Area. The study

was approved by the St Vincent's University Hospital Medical Ethics Committee and conforms to the Declaration of Helsinki.

All patients >55 years of age with at least one risk factor for the development of HF were deemed suitable for enrollment: long-standing hypertension, diabetes and coronary artery disease. Patients with a documented history of heart failure, documented left ventricular systolic dysfunction or any individual with documented non-cardiac conditions that could significantly alter BNP levels (e.g. pulmonary hypertension, pulmonary embolism) were excluded.

Database query from an estimated general practice population of 17,000 people identified 816 individuals considered suitable for enrollment. From those identified, approximately a third of the sample were randomly selected using a computer generated protocol and invited to partake in the study (n=254). Those giving informed consent attended the General Practice to give a detailed medical history and undergo physical examination, 12-lead electrocardiography, Chest X-Ray, phlebotomy for BNP level evaluation and urinalysis. These individuals were subsequently referred to the St Vincent's University Hospital Heart Failure Service for Doppler echocardiographic studies.

BNP levels were measured using the Triage Meter point-of-care assay (Biosite, Ca).[19,20] Doppler echocardiographic analyses were performed using 2.5 and 3.5-MHz transducers (Hewlett-Packard Sonos 5500). Preserved left ventricular systolic function was defined as a LVEF ≥ 45% [21] Left ventricular hypertrophy (LVH) was assessed as a mean value of interventricular wall thickness and posterior wall thickness assessed at end-diastole. Values were subsequently graded as Grade 1 (mean value <11mm); Grade 2 (mean value 11-15.9mm); Grade 3 (mean value 16.0 to 19.9mm) and Grade 4 (mean value ≥ 20mm). Parameters of left ventricular diastolic function were made using standard methods and included: peak velocities of both the early (E) and atrial (A) diastolic filling and the derived E/A ratio; E-wave deceleration time (DT); isovolumetric relaxation time (IVRT). For individuals in atrial fibrillation, five Doppler complexes were sampled for measurements of E-wave deceleration time and IVRT at an average ventricular rate of >90 beats/min. Premature or aberrant ventricular complexes were ignored and modal values were accepted as being representative of diastolic filling.

Operators and physicians interpreting echocardiography were blinded to BNP score. Individuals identified at this stage with LVSD (LVEF <45%)[21] and those with left ventricular chamber enlargement and normal ejection fraction were excluded from further analysis leaving a population with preserved systolic function (PSF).

The population was divided into two groups, those above and below the median BNP value for the total cohort. These two groups were termed 'Elevated BNP' (EB Group) and 'Controls' (C Group).

All participants were subsequently reviewed at the general practice, at a mean of 10 months following the initial analysis with regard to the primary endpoints of death and/or unplanned hospital admission for cardiovascular causes. The secondary endpoints evaluated were new diagnoses of heart failure and/or new cardiac diagnoses/events not requiring hospitalisation.

STATISTICAL ANALYSIS

Comparisons between EB and C Groups were conducted using independent sample t-tests for continuous variables and Mann-Whitney test for non-normal distributions (two-sided, α = 0.05). Chi-squared analysis was used for discrete variables. Since the BNP values are positively skewed, the univariate and multivariable analysis to determine predictors of higher BNP was carried out using log-transformed BNP values. Data are presented as the mean value ± the standard deviation (SD) for continuous variables and absolute or relative frequencies for discrete variables. Univariate and multivariable analyses were conducted using binary (or binomial) logistic regression using death and/or unplanned hospital admission as the outcome variable. The multivariable model included theoretically reasonable variables and those with univariate p-values of ≤ 0.25. The likelihood ratio test was conducted to identify independent variables with low explanatory power. In addition, the Hosmer and Leme show goodness of fit indices were compared to assess the fit of each specification of the multiple regression model. The Kaplan-Meier product limit method of survival analysis was used to generate and adjust survival curves (death and/or unplanned cardiovascular hospital admission) using the EB Group variable. People lost to follow-up or known to be still alive were censored. The Mantel-Haenszel log-rank test was used to test the equality of the survivor functions. Multivariable analysis incorporating both continuous and discrete predictors of survival was

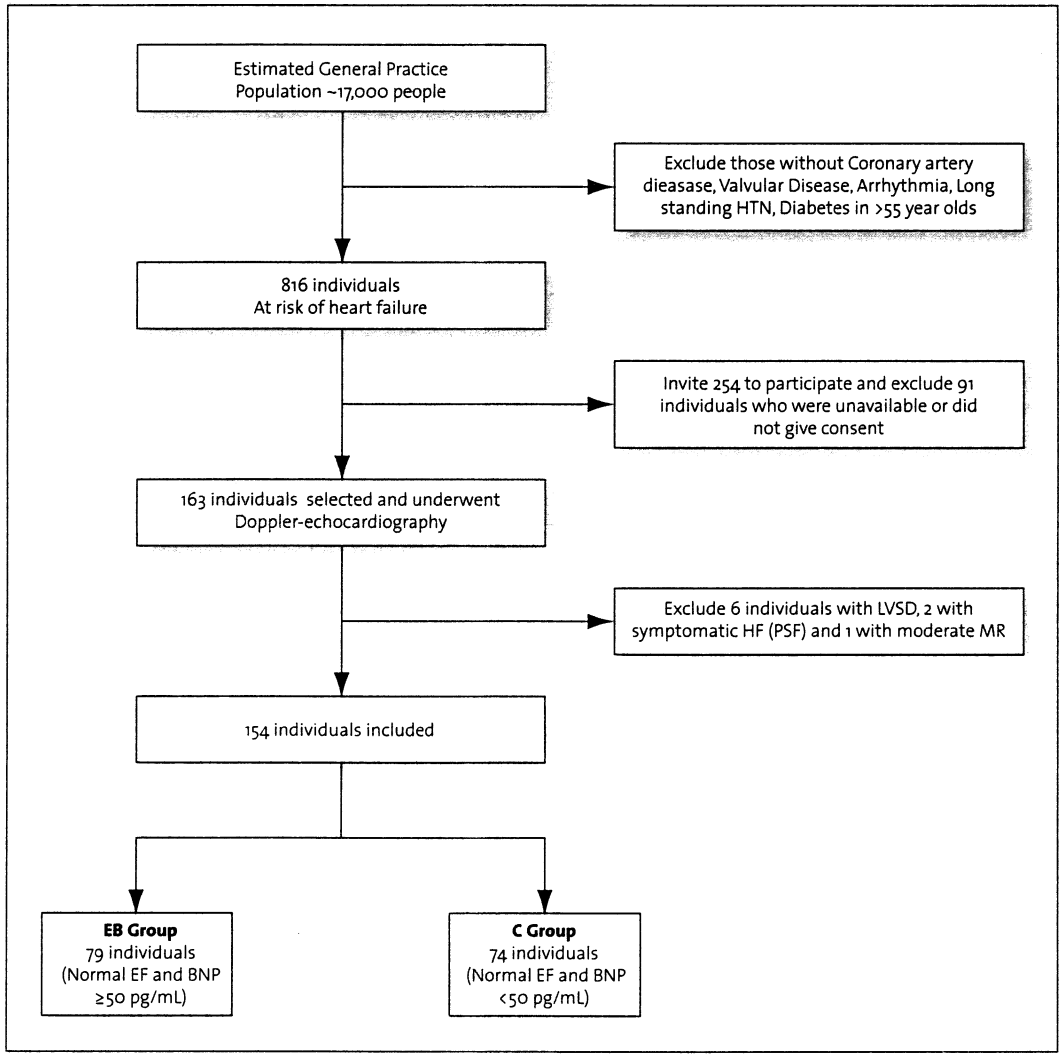

Figure 1— SCHEME OF INDIVIDUAL SCREENING AND INCLUSION

conducted using Cox Proportional Hazards regression statistical model. Receiver Operated Characteristic (ROC) analysis was carried out on different cutoff levels of BNP for the prediction of primary endpoints. The adequacy of these curves is assessed by comparing the Area Underneath the Curve (AUC) statistics (Area, P Value and 95% Confidence interval) and the sensitivity and specificity of selected BNP cutoffs were calculated. All analyses were carried out using SPSS Vs. 11 statistical software.

RESULTS

The study schedule is outlined schematically in Figure 1. A total of six individuals were found to have LVSD (population rate 3.6% of which 1 (0.6%) had a BNP <50 pg/ml) and along with a further three individuals (two with mild symptomatic heart failure and a third with moderate mitral regurgitation) were excluded leaving a study population of 154 (age 67.4 ± 9.7 years, 57% male, 40% history of ischaemic heart disease, 62% history of long-standing hypertension, 7% history of valvular heart disease, 10% cardiac arrhythmia and 20% diabetes mellitus). Participants were followed-up for an average of 282 ± 149 days.

The median BNP for the study population was 50pg/ml and the cohort was divided into those above and below this value. There were 79 patients (51.2%) with BNP levels above the median value (EB Group) and 75 patients (48.2%) with BNP levels below the median value (C Group). The demographic characteristics of the population are presented in Table 1. Univariate analysis demonstrated that in addition to higher BNP, individuals in the EB group were older with a more

frequent history of arrhythmia. The only difference in medications noted between the groups was in usage of digoxin, albeit in small numbers of individuals.

Doppler-echocardiographic analyses of both groups are presented in Table 2. They demonstrate longer DT and IVRT, reduced E/A ratio and higher LVH score consistent with more marked diastolic dysfunction and evidence of hypertensive heart disease in the EB Group. The differences in E:A ratio and LVH score were independent of age.

We analysed the dataset to determine the predictors of a higher BNP levels using log transformed values. Univariate results, presented in Table 3, suggest that the influencing variables are age, DT, E/A ratio, LVH and histories of ischaemia, hypertension and arrhythmia. However, multivariable analysis identified only four independent predictors of elevated BNP levels in the following order of decreasing significance: age ($p<0.0001$), LVH ($p<0.0001$), E/A ratio ($p=0.026$) and ischaemic heart disease ($p=0.046$).

During an average follow-up of 282 ± 149 days, 16.5% of individuals in the EB Group had reached the primary endpoints which comprised of four deaths (two cancer, one sudden death, one fall with neck fracture), nine emergency CV admissions (six arrhythmias, one preserved systolic function heart failure, one MI, one worsening angina). In contrast, 4% of the C Group had reached the primary endpoints comprising of one death (peri-operative for valvular heart disease) and two emergency cardiovascular admissions (unstable angina). Analysis of survival curves using death and/or unplanned cardiovascular readmission showed a significantly poorer outcome for people in the EB Group ($p=0.004$, Figure 2).

Univariate analysis using death and/or unplanned cardiovascular readmission as outcome measures is presented in Table 5. Multivariable analysis demonstrated that the only independent predictors of outcome were the categorical EB Group variable ($p=0.032$; HR: 4.0, 95% CI 1.12- 14.25) and ischaemic heart disease ($p=0.046$; HR: 2.9, 95% CI 1.08-8.70).

Secondary endpoints in the EB group were five diagnoses of PSF heart failure (four outpatient diagnoses and one during an emergency admission for heart failure), and three reported cardiovascular events not requiring hospitalization (two reported symptomatic episode of atrial fibrillation and one reported incidence of angina). In the C group there were two new diagnoses of PSF heart failure and one episode of syncope not requiring hospitalization. In total, 24.1% of the individuals in the EB group had events in the follow-up period compared to the 8.0% in the C group ($p=0.0004$).

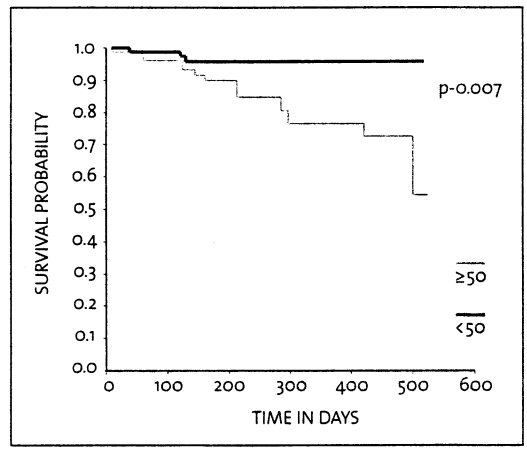

Figure 2— Kaplan Meier event-free (death and/or unplanned hosptialisation) survival curves of people with elevated BNP levels and normal systolic function (EB Group, normal EF and elevated BNP ≥50pg/ml, n=79) and Controls (C Group, normal EF low BNP <50pg/ml, n=75).

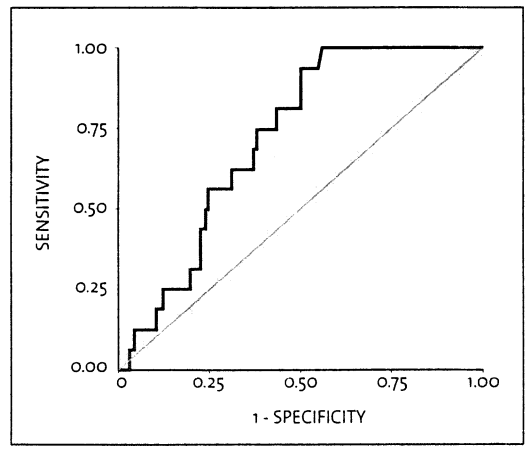

Figure 3— Receiver Operated Characteristic (ROC) curve using different BNP cutoff levels for the prediction of (primary endpoints) death and/or unplanned readmission. Sensitivities and specificities of selected cutoff levels are presented in Table 6.

The utility of BNP as a predictor of primary endpoints (death and/or emergency hospital admission) was evaluated using receiver operating characteristic (ROC) curves (Figure 3). The area underneath the curve (AUC) statistics (Area 0.720, Std Error 0.49, P Value 0.002 and 95% Confidence interval 0.624 to 0.817) demonstrate that BNP is a highly significant predictor of the primary endpoints, although its overall performance as a clinical screen is somewhat limited by compromise between sensitivity and specificity. Accordingly, the sensitivity and specificity of a range of selected BNP cut-off values is presented in Table 6.

Table 1
DEMOGRAPHIC CHARACTERISTICS OF THE EB GROUP (N=79) AND THE C GROUP (N=75)

Variable	Total	C Group (BNP<50pg/ml)	EB Group (BNP>=50pg/mL)	P
Population	154	75	79	
Age (Years)	67.4±9.7	64.4±10.0	71.1±8.29	0.00001
Gender: Male:Female	88:66	47:29	41:37	0.206
BMI (Kg/m²)	27±4	28±4	27±4	0.127
LVEF (%)	63±9	64±9	62±9	0.157
BNP (pg/ml)	99±178	23±14	171±226	N/A
Ischaemic Heart disease (Y:N)	61:93	24:51	37:42	0.060
Valvular Heart Disease (Y:N)	11:143	3:72	8:71	0.211*
Diabetes (Y:N)	31:123	17:58	14:65	0.444
Hypertension (Y:N)	95:59	51:24	44:35	0.116
Arrythmia (Y:N)	15:139	2:73	13:66	0.005*
HR (BPM)	69.8±12.9	68.5±11.3	71.0±14.2	0.248
SBP (mmHg)	150±22	147±19	152±24	0.162
DBP(mmHg)	84±12	85±11	84±13	0.621
Pulse Pressure (mmHg)	44±10	43±9	45±10	0.135
Creatinine (µmol/L)	90.5±30.6	89.5±26.6	91.6±34.3	0.685
ACE Inhibitor (Y:N)	50:104	22:53	28:51	0.418
AII Antagonist (Y:N)	14:140	6:69	8:71	0.646
Beta Blocker (Y:N)	72:82	32:43	40:39	0.322
Calcium Antagonists (Y:N)	31:123	18:57	13:66	0.243
Nitrate (Y:N)	28:126	13:62	15:64	0.790
Alpha Blocker (Y:N)	1:153	0:75	1:78	N/A
Diuretic (Y:N)	50:104	28:47	22:57	0.209
Antiplatelet (Y:N)	70:84	34:41	36:43	0.977
Statin (Y:N)	38:116	22:53	16:63	0.191
Anti-arrythmic (Y:N)	1:153	0:75	1:78	N/A
Warfarin (Y:N)	11:143	4:71	7:72	0.535*
Digoxin (Y:N)	10:144	2:73	8:71	0.099*

**Fishers Exact Test used. (Y:N)=Yes:No*

Table 2
DOPPLER ECHOCARDIOGRAPHIC CHARACTERISTICS OF THE EB GROUP (N=79) AND THE C GROUP (N=75)

VARIABLE	TOTAL	C GROUP (BNP<50pg/ml)	EB GROUP (BNP>=50pg/mL)	P
DT	263.01±57.04	244.81±52.45	280.29±56.13	0.00008
IVRT	92.02±39.29	84.65±35.43	99.10±41.68	0.020
E/A Ratio	1.00±0.46	1.19±0.44	0.83±0.42	0.000001
LVH Score	1.71±0.59	1.45±0.60	1.95±0.48	<0.000001

Table 3
UNIVARIATE PREDICTORS OF HIGHER BNP LEVELS FOR THE ENTIRE STUDY COHORT AT BASELINE (N=154)

Variable	R^2	F	β (Unstandardised)	P	CI-Lwr	CI-Upr
Age	0.172	31.602	0.415 (0.057)	<0.00001	0.037	0.076
Gender: Male=1	0.002	0.278	-0.043 (-0.115)	0.599	-0.546	0.316
BMI	0.008	1.136	-0.088 (-0.027)	0.288	-0.077	-0.023
EF%	0.006	0.855	-0.075 (-0.011)	0.357	-0.035	0.013
DT	0.063	10.256	0.251 (0.006)	0.002	0.002	0.009
IVRT	0.011	1.710	0.106 (0.004)	0.193	-0.002	0.009
E/A Ratio	0.076	12.565	-0.276 (-0.792)	0.001	-1.234	-0.351
LVH	0.242	48.403	0.491 (1.099)	<0.00001	0.787	1.411
Ischaemia	0.053	8.467	0.230 (0.621)	0.004	0.199	1.043
Diabetes	0.009	1.330	-0.093 (-0.307)	0.251	-0.833	0.219
Hypertension	0.031	4.873	-0.176 (-0.479)	0.029	-0.908	-0.050
Arrhythmia	0.047	7.457	0.216 (0.964)	0.007	0.267	1.662
Creatinine	0.011	1.686	0.106 (0.005)	0.196	-0.002	0.012

Table 4
FINAL MULTIVARIABLE MODEL OF PREDICTORS OF HIGHER BNP LEVELS FOR THE ENTIRE STUDY COHORT (N=154)

Variable	R^2	F	β (Unstandardised)	P	CI-Lwr	CI-Upr
Age	0.391	23.908 P<0.00001	0.309 (0.042)	0.000006	0.024	0.060
LVH			0.389 (0.870)	<0.000001	0.575	1.165
E/A Ratio			-0.149 (-0.427)	0.026	-0.803	-0.052
Ischaemic			0.132 (0.356)	0.046	0.006	0.707

Table 5
UNIVARIATE PREDICTORS OF PRIMARY END-POINT

VARIABLE	MODEL $\chi 2$	-2LL	P	HR	CI-LWR	CI-UPR
Age	0.099	143.02	0.753	0.992	0.943	1.044
Male Gender	0.469	142.44	0.496	1.423	0.516	3.929
BMI	0.461	132.02	0.497	1.040	0.928	1.167
EF	0.072	143.04	0.789	0.993	0.943	1.046
EB vs C group	7.274	135.37	0.015	4.790	1.363	16.838
DT	0.002	143.12	0.966	1.000	0.992	1.008
IVRT	2.12	140.69	0.151	0.992	0.980	1.003
E/A	0.477	142.68	0.491	1.389	0.547	3.524
LVH	3.920	139.07	0.048	2.294	1.009	5.215
DD	0.309	142.81	0.579	1.307	0.508	3.364
Hx of Ischaemia	6.601	136.76	0.016	3.665	1.269	10.583
Hx of Diabetes	0.986	142.22	0.326	1.698	0.590	4.891
Hx of Hypertension	3.25	140.05	0.081	0.414	0.154	1.114
Hx of Arrhythmia	0.016	143.10	0.899	1.101	0.248	4.897
Creatinine	1.111	131.64	0.288	0.992	0.978	1.007

Table 6
SENSITIVITY AND SPECIFICITY VALUES OF DEFINED BNP THRESHOLDS FOR THE PREDICTION OF PRIMARY ENDPOINTS (DEATH AND/OR EMERGENCY HOSPITAL ADMISSION)

BNP LEVEL THRESHOLDS	SENSITIVITY (%)	SPECIFICITY (%)
BNP: ≥25 pg/ml	100	31
BNP: ≥50 pg/ml	81	52
BNP: ≥75 pg/ml	63	68
BNP: ≥100 pg/ml	44	77
BNP: ≥125 pg/ml	25	82

DISCUSSION

These data indicate that there is a high prevalence of elevated BNP levels in asymptomatic individuals with preserved systolic function possessing risk factors for heart failure. In this cohort, elevated BNP levels are associated with older age, LVH, diastolic abnormalities and ischaemic heart disease. Furthermore, a clinically important proportion of these individuals had serious adverse event within one year of follow-up. An elevated BNP level was the strongest independent predictor of serious adverse outcome in this population.

Data from the Framingham Offspring Study have shown that elevated BNP is strongly associated with adverse outcome in the general population.[16] This observation suggests that BNP testing may be of benefit as a screening tool for occult structural and functional abnormalities of the heart, in particular, the left ventricle. [16,17,22,23]

The Doppler-echocardiographic data from this study support this concept by demonstrating a close relationship between BNP and both LVH and parameters of diastolic dysfunction. Individuals in the EB Group had a significant increase in DT and IVRT and decrease in E/A ratio in comparison with the C Group. Additionally, the E/A ratio was found to be an independent predictor of elevated BNP levels in multivariable analysis. Moreover, the entire incident cases of heart failure during follow-up in the EB Group (6.25% rate) were associated with preserved systolic function.

Other studies have shown that BNP can identify individuals with asymptomatic LVSD [24,25] although they provide no information on subsequent cardiovascular events. The data by Wang et al [16] demonstrate a high correlation between BNP levels and outcome in a community population, but give few Doppler-echocardiographic data. Our study further develops these observations by identifying a high prevalence of diastolic abnormalities, strongly associated with elevated BNP levels, which is in turn associated with a high risk of subsequent cardiac events.

The clinical implication of identifying these at-risk individuals remains unclear. However, it likely includes the need to manage more intensively the risk factors of individuals with elevated BNP levels, paying particular attention to LVH, the strongest modifiable driver of BNP in the EB Group. This relates not solely to hypertension management, including 24-hour control of blood pressure, but also potentially to vascular compliance and myocardial fibrosis. Interestingly a lower rate of defined history of hypertension was observed in the EB Group compared to controls. However, there were no differences in blood pressures at baseline between the groups or in antihypertensive medications taken. It has been shown that BNP has anti-fibrotic properties [5] and may therefore be produced in response to an early fibrotic process. Such a process could explain the subtle abnormalities in diastolic function observed in the EB Group. In this regard, it is also of note that BNP can reduce the expression of aldosterone synthase, an enzyme involved in the production of aldosterone, a hormone closely linked to fibrosis.[27,28] Furthermore, it is of note that the most common clinical events observed in this study were arrhythmia and diastolic heart failure, both of which can be potentially explained by an accelerated fibrotic process.

There are a number of limitations to this study which warrant further comment. Firstly, although representative of a large, asymptomatic, at-risk population, these are preliminary data in a relatively small sample. The ability of BNP to reliably predict outcome in this particular population or to add

value over conventional and newer risk stratification methods must be examined in larger studies.

Secondly, more work is needed to define optimal BNP cut-off levels depending on screening objectives,[17,22] population assessed,[22,29] and BNP assay used.[30] It is interesting to note that McDonagh et al demonstrated that a truly "normal" community population will have BNP values below 20 pg/ml,[15] Wang et al identified values above 20 pg/ml for males and 23 pg/ml for females as conferring substantial risk [16] and the present work demonstrates 100% sensitivity for subsequent serious clinical events using a cut-off of 25pg/ml. Although asymptomatic, the present study population is more selected and has a higher prevalence of cardiovascular disease than the general community populations described in the aforementioned studies and may, therefore warrant a higher screening threshold. Therefore, the BNP cut-off of 50pg/ml in this setting may offer a reasonable compromise between sensitivity and specificity in predicting subsequent serious clinical events.

Thirdly, a cut-off of LVEF <45% may have allowed for inclusion of patients with established ischaemic heart disease and mild but important degrees of LVSD. Furthermore, the error of measurement of echocardiography may also have resulted in the inclusion of some patients with LVSD.

Finally, although the observation of diastolic abnormalities and increased risk among individuals in the EB Group is made in this study, we have not clarified in detail any causative mechanism. Clearly this population requires further evaluation to identify these mechanisms of increased risk and other means of reducing this risk apart from aggressive risk factor management.

CONCLUSIONS

Elevated BNP levels in the setting of preserved systolic function in asymptomatic, at-risk individuals is associated with older age, ischaemic heart disease, more severe LVH and abnormalities of diastolic function. Elevated BNP is the strongest, independent predictor of serious adverse outcome in this population. More work is required to clarify whether BNP testing may be a suitable screening tool for echocardiography and to establish its value as means of risk stratifying community populations with cardiovascular risk factors for intensive therapy and close clinical follow-up.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the dedication and hard work of Tracey Reynolds in the organisation of this study.

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