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B-Type Natriuretic Peptide Is Associated with Indices of Left Ventricular Dysfunction in Healthy Subjects from the General Population: The Akershus Cardiac Examination 1950 Study

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BACKGROUND: Concentrations of B-type natriuretic peptide (BNP) reflect myocardial distension and stress, and are associated with poor prognosis in patients with cardiovascular disease. Accordingly, we hypothesized that concentrations of BNP would be associated with indices of adverse left ventricular (LV) remodeling and early stages of LV systolic and diastolic dysfunction in healthy participants from the general population.

METHODS: We measured BNP in 1757 women and 1677 men free from known coronary heart disease participating in the prospective observational Akershus Cardiac Examination 1950 Study. All study participants underwent extensive cardiovascular phenotyping at baseline, including detailed echocardiography with assessment of indexed LV mass (LVMI), diastolic [tissue Doppler e', E/e' ratio, indexed left atrial volume (LAVI), maximal tricuspid regurgitation velocity (TRVmax), and E/A ratio], and systolic [global longitudinal strain (GLS) and LV ejection fraction (LVEF)] function.

RESULTS: Study participants with the highest BNP concentrations had higher GLS, LVMI, e', E/e' ratio, LAVI, TRVmax, and E/A ratio. In adjusted analyses, both GLS and LVEF exhibited significant nonlinear associations with BNP, with reduced LV systolic function observed in both the low and high concentration range of BNP.

CONCLUSIONS: In healthy participants recruited from the general population, concentrations of BNP exhibit nonlinear associations with LV systolic function, and both low and high concentrations are associated with reduced LV systolic function. This supports the notion that natriuretic peptides are beneficial and elicit cardioprotective effects, and may have important implications for the interpretation of BNP measurements in the general population.

Introduction

Measurement of natriuretic peptides is fundamental in diagnosing heart failure and higher concentrations are strongly associated with risk of incident cardiovascular disease (1, 2). Increasing concentrations of natriuretic peptides are positively associated with left ventricular (LV) mass and inversely associated with LV ejection fraction (LVEF) both in participants from the general population (3) and in patients with heart failure (4). Similar associations have been demonstrated for several indices of LV diastolic dysfunction (5). More recently, novel and increasingly sensitive indices of LV systolic function, such as global longitudinal strain (GLS), have enabled assessment of subtle changes in LV systolic function not detected by LVEF. Large investigations have previously documented associations between LV dilatation (6) and hypertrophy (7, 8), and risk of heart failure, as well as associations between LV systolic dysfunction and cardiovascular morbidity and death, both in patients with established cardiovascular disease (9) and in participants recruited from the general population (10). The associations between natriuretic peptides and indices of LV structure, systolic and diastolic function, in healthy participants from the general population, have yet to be explored.

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Accordingly, using a large cohort of men and women recruited from the general population examined with state-of-the-art echocardiography, we hypothesized that concentrations of B-type natriuretic peptide (BNP) are increased in early stages of LV systolic and diastolic dysfunction and mild LV hypertrophy.

Methods

STUDY OVERVIEW

The Akershus Cardiac Examination (ACE) 1950 Study is a prospective, population-based cohort of 3706 individuals residing in Akershus County, Norway. All community dwellers born in 1950 residing in Akershus County were invited to participate ($n = 5827$), and the baseline examination was conducted from September 2012 to May 2015. The study was conducted at the 2 hospitals of Akershus County, Norway: Akershus University Hospital and Bærum Hospital/Vestre Viken Hospital Trust. The study design has been reported previously (11). The study complies with the Declaration of Helsinki and is approved by the Regional Committees for Medical Research Ethics—South East Norway (REC 2011/1475). All participants provided informed written consent before study commencement.

PARTICIPANTS

Medical history, current medications, and socioeconomic data, including alcohol and tobacco consumption, are based on self-report. Coronary artery disease (CAD) was defined as self-reported history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. Diabetes was defined as self-reported diabetes, the use of antidiabetic medication, or the presence of increased concentrations of hemoglobin A1c (HbA1c) $\geq$6.5% and fasting blood glucose $\geq$126 mg/dL (7.0 mmol/L) on baseline examination. Chronic obstructive pulmonary disease was defined as baseline postbronchodilator spirometry forced expiratory volume (in 1 second) to forced vital capacity ratio below the age-dependent lower limit of normal, or by self-report when spirometry data were missing ($n = 4$). Higher education was defined as education at the level of college, university, or equivalent. Participants with known CAD at baseline ($n = 263$) were excluded from the analyses, as well as participants with missing biomarker data ($n = 9$).

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed using GE Vivid E9 (GE Healthcare) with the M5S probe according to a predefined protocol. Two echocardiography technicians and 4 trained fellows acquired the echocardiograms. Four cardiac cycles were recorded during breath hold at end expiration, from the following views: parasternal long- and short-axis, and apical four-chamber, two-chamber, and long-axis. Standard two-dimensional images with M-mode, tissue velocity imaging, and pulsed and continuous Doppler were recorded, and the images were analyzed with EchoPAC 201 (GE Healthcare).

The echocardiographic assessment included indexed LV mass (LVMI), and diastolic [tissue Doppler e', E/e' ratio, indexed left atrial volume (LAVI), maximal tricuspid regurgitation velocity (TRVmax), and E/A ratio] and systolic (GLS and LVEF) function.

A detailed description regarding echocardiography in the ACE 1950 Study has recently been published (12). LV mass and LA volume were indexed to body surface area according to the Mosteller formula (LVMI and LAVI, respectively) (13). As previously recommended, we used absolute values of GLS in all analyses, i.e., higher absolute values denoting better LV systolic function (14). The reproducibility of GLS has been reported as excellent and superior to that of LVEF, but both indices are suitable for diagnosis and follow-up of LV systolic function (15). Intra- and interobserver variability testing were performed by 2 observers (E.N.A. and B.K.) in 15 randomly selected patients for GLS (Table 1 in the online Data Supplement), with results comparable to those recently reported from a multinational study on strain measurements (16). All echocardiography operators were blinded to the BNP results when performing the analyses.

BLOOD SAMPLING PROCEDURES AND BIOCHEMICAL ASSAYS

Fasting venous blood samples were collected on study visit, centrifuged at room temperature, and frozen at −80 °C. Analyses of hemoglobin, white blood count, C-reactive protein (CRP), glucose, HbA1c, cholesterol [total, high-density lipoprotein (HDL)], triglycerides, and creatinine were performed immediately by routine hospital laboratory clinical chemistry. For CRP, concentrations above or equal to 3 mg/L were used to denote the presence of low-grade systemic inflammation. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation (17). BNP was measured in previously never-thawed EDTA plasma samples in May 2017 with the ARCHITECT BNP assay. Limit of detection for this assay is reported to be 10 ng/L (18) and concentrations below the limit of detection were assigned a value of 5.0 ng/L. The upper reference limit of the assay is 100 ng/L at a coefficient of variation of $\leq$12% as reported in the package insert from Abbott Diagnostics (19). Data on coefficients of variation in the very low concentration range provided by Abbott Research & Development are presented in Supplemental Fig. 1, with a coefficient of variation of

Table 1. Baseline characteristics according to sex specific quartiles of BNP.

				Quartiles of BNP							
		Total cohort		Quartile 1		Quartile 2		Quartile 3		Quartile 4	
			Women	<10.9 ng/L		11.0 to 19.0 ng/L		19.1 to 33.6 ng/L		≥33.7 ng/L	
			Men	<10.0 ng/L		10.0 to 14.5 ng/L		14.6 to 26.6 ng/L		≥26.7 ng/L	
	n	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Value	*P* for trend
Study site Akershus University Hospital, *n* (%)	3434	2270 (66.1%)	1009	624 (61.8%)	713	478 (67.0%)[a]	856	586 (68.5%)[b]	856	582 (68.0%)[b]	0.008
Demographics											
Male sex, *n* (%)	3434	1677 (48.8%)	1009	566 (56.1%)	713	277 (38.8%)[c]	856	415 (48.5%)[b]	856	419 (48.9%)[b]	<0.001
Age, years	3434	63.9 (63.4 to 64.4)	1009	63.8 (63.4 to 64.4)	713	63.9 (63.4 to 64.4)	856	63.9 (63.4 to 64.4)	856	63.9 (63.4 to 64.5)[b]	0.044
Higher education, *n* (%)	3424	1613 (47.1%)	1002	459 (45.8%)	713	327 (45.9%)	854	422 (49.4%)	855	405 (47.4%)	0.40
Current smoker, *n* (%)	3407	484 (14.2%)	1003	160 (16.0%)	706	105 (14.9%)	847	109 (12.9%)	851	110 (12.9%)	0.16
Alcohol consumption, units/2 weeks	3434	6.0 (2.0 to 11.0)	1009	6.0 (2.0 to 10.0)	713	5.0 (1.0 to 10.0)	856	6.0 (2.0 to 12.0)	856	6.0 (2.0 to 12.0)[a]	0.05
Clinical measurements											
Body mass index, kg/m^2	3434	26.6 (24.1 to 29.4)	1009	26.8 (24.5 to 29.8)	713	26.6 (24.1 to 29.2)	856	26.4 (23.8 to 29.1)[b]	856	26.5 (23.7 to 29.5)[a]	0.036
Heart rate, beats/min	3433	62.0 (56.0 to 69.0)	1009	65.0 (60.0 to 72.0)	713	62.0 (57.0 to 69.0)[c]	855	61.0 (55.0 to 68.0)[c]	856	59.0 (54.0 to 67.0)[c]	<0.001
Systolic blood pressure, mmHg	3432	137.0 (125.0 to 149.0)	1009	134.0 (124.0 to 146.0)	713	136.0 (125.0 to 147.0)	855	137.0 (125.0 to 150.0)[b]	855	140.0 (126.0 to 155.0)[c]	<0.001
Diastolic blood pressure, mmHg	3432	77.0 (70.0 to 84.0)	1009	77.0 (71.0 to 84.0)	713	76.0 (70.0 to 83.0)	855	76.0 (70.0 to 83.0)	855	78.0 (70.0 to 85.0)	0.011
History of											
Chronic obstructive pulmonary disease, *n* (%)	3404	239 (7.0%)	999	67 (6.7%)	708	53 (7.5%)	849	54 (6.4%)	848	65 (7.7%)	0.68
Diabetes mellitus, *n* (%)	3433	267 (7.8%)	1009	106 (10.5%)	712	56 (7.9%)	856	57 (6.7%)[b]	856	48 (5.6%)[c]	<0.001
Current medication											
Diuretics, *n* (%)	3434	98 (2.9%)	1009	20 (2.0%)	713	21 (2.9%)	856	25 (2.9%)	856	32 (3.7%)[a]	0.15
β blockers, *n* (%)	3434	316 (9.2%)	1009	43 (4.3%)	713	51 (7.2%)[a]	856	71 (8.3%)[c]	856	151 (17.6%)[c]	<0.001
Calcium antagonists, *n* (%)	3434	256 (7.5%)	1009	72 (7.1%)	713	55 (7.7%)	856	62 (7.2%)	856	67 (7.8%)	0.93

Continued

Table 1. (continued)

			Quartiles of BNP							
		Total cohort		Quartile 1		Quartile 2		Quartile 3		Quartile 4	
ACE-I/ARB, *n* (%)	3434	860 (25.0%)	1009	274 (27.2%)	713	164 (23.0%)	856	187 (21.8%)[b]	856	235 (27.5%)	0.010
Statins, *n* (%)	3434	736 (21.4%)	1009	248 (24.6%)	713	144 (20.2%)[a]	856	173 (20.2%)[a]	856	171 (20.0%)[a]	0.042
Clinical chemistry											
CRP ≥3 mg/L	3434	732 (21.3%)	1009	213 (21.1%)	713	154 (21.6%)	856	182 (21.3%)	856	183 (21.4%)	1.00
Glucose, mg/dL[d]	3426	5.3 (4.9 to 5.7)	1005	5.4 (5.0 to 5.8)	712	5.3 (4.9 to 5.7)[b]	855	5.2 (4.9 to 5.7)[c]	854	5.2 (4.9 to 5.7)[c]	<0.001
HbA1c, %	3420	5.7 (5.5 to 5.9)	1003	5.7 (5.5 to 6.0)	710	5.7 (5.5 to 5.9)[b]	853	5.7 (5.5 to 5.9)[c]	854	5.6 (5.4 to 5.9)[c]	<0.001
Total cholesterol, mg/dL[d]	3432	5.5 (4.8 to 6.2)	1008	5.5 (4.8 to 6.2)	713	5.6 (4.9 to 6.2)	856	5.5 (4.8 to 6.2)	855	5.4 (4.7 to 6.1)[a]	0.017
HDL cholesterol, mg/dL[d]	3431	1.5 (1.2 to 1.8)	1007	1.4 (1.1 to 1.7)	713	1.5 (1.3 to 1.9)[c]	856	1.5 (1.2 to 1.9)[c]	855	1.6 (1.3 to 1.9)[c]	<0.001
Triglycerides, mg/dL[d]	3431	1.2 (0.8 to 1.6)	1008	1.3 (0.9 to 1.8)	713	1.1 (0.9 to 1.6)[b]	856	1.1 (0.8 to 1.7)[c]	854	1.1 (0.8 to 1.5)[c]	<0.001
eGFR, mL/min/1.73 m^2	3418	85.0 (75.3 to 92.6)	1005	85.1 (75.8 to 92.5)	710	85.1 (75.4 to 92.9)	853	84.8 (75.5 to 92.3)	850	85.4 (74.2 to 92.7)	0.88
Echocardiography											
Global longitudinal strain, %	2389	20.3 (18.6 to 21.8)	687	19.8 (18.2 to 21.3)	518	20.3 (18.8 to 21.8)[c]	620	20.6 (18.9 to 22.0)[c]	564	20.6 (18.8 to 22.2)[c]	<0.001
Left ventricular ejection fraction, %	3247	55.8 (52.3 to 59.4)	949	55.3 (52.1 to 58.9)	678	55.9 (52.7 to 59.9)[b]	812	56.3 (52.8 to 60.0)[c]	808	55.4 (52.0 to 59.1)	<0.001
Left ventricular mass index, g/m^2	3369	73.4 (63.7 to 85.9)	984	71.3 (62.7 to 83.1)	699	73.0 (63.4 to 83.6)	842	74.5 (64.2 to 87.2)[b]	844	75.4 (64.8 to 89.9)[c]	<0.001
E′, cm/s	3369	7.5 (6.5 to 8.5)	994	7.3 (6.4 to 8.2)	695	7.5 (6.4 to 8.5)[b]	843	7.7 (6.7 to 8.7)[c]	837	7.7 (6.7 to 8.7)[c]	<0.001
E/e′ ratio	3307	8.6 (7.2 to 10.2)	978	8.4 (7.1 to 9.9)	681	8.6 (7.3 to 10.1)[a]	829	8.6 (7.2 to 10.1)[a]	819	8.9 (7.4 to 10.5)[c]	<0.001
Left atrial volume index, mL/m^2	3237	25.7 (21.6 to 30.7)	948	23.3 (19.7 to 27.4)	672	24.9 (21.4 to 29.8)[c]	808	26.3 (22.5 to 30.6)[c]	809	29.1 (24.3 to 34.7)[c]	<0.001
Maximal tricuspid regurgitation velocity, m/s	2665	2.2 (2.1 to 2.4)	729	2.2 (2.0 to 2.3)	551	2.2 (2.1 to 2.4)[a]	701	2.2 (2.1 to 2.4)	684	2.3 (2.1 to 2.4)[c]	<0.001
E/A ratio	3312	1.0 (0.9 to 1.2)	986	0.9 (0.8 to 1.1)	692	1.0 (0.9 to 1.2)[c]	835	1.0 (0.9 to 1.2)[c]	799	1.1 (0.9 to 1.3)[c]	<0.001

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$ compared to quartile 1.
[d] To convert glucose concentrations from mg/dL to mmol/L, multiply by 0.05556. To convert triglyceride concentrations from mg/dL to mmol/L, multiply by 0.01129. To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.
ACE-I, angiotensin-converting-enzyme inhibitors. ARB, angiotensin II receptor blockers. BNP, B-type natriuretic peptide. CRP, C-reactive protein. eGFR, estimated glomerular filtration rate. GLS, global longitudinal strain. HDL, high-density lipoprotein. LAVI, indexed left atrial volume. LVEF, left ventricular ejection fraction. LVMI, indexed left ventricular mass. TRVmax, maximal tricuspid regurgitation velocity.

10% observed at approximately 8 ng/L. For the current investigation, coefficients of variation derived from control material from Abbott Diagnostics were 2.9% in the high concentration range (3392 ng/L), 6.2% in the medium concentration range (454 ng/L), and 7.7% in the low concentration range (85.3 ng/L).

STATISTICAL METHODS

Baseline data are reported as absolute numbers (proportion) or median (interquartile range) unless otherwise stated. Continuous variables were analyzed with the Mann–Whitney *U*-test, and categorical variables were analyzed with the Fisher exact test. Concentrations of BNP were transformed by the natural logarithm prior to regression analyses due to a right-skewed distribution. Correlations were assessed by Spearman rank correlation. Linear regression analyses were used to assess determinants of continuous BNP concentrations, and the associations between echocardiographic variables and BNP concentrations. Nonlinear associations were assessed by quadratic effects in the linear regression models, as well as restricted cubic splines with knots placed at the 10th, 50th, and 90th sample percentiles. All models were incrementally adjusted for sex, age, study site, and a priori selected variables influencing cardiovascular risk (BMI, eGFR, total, and HDL cholesterol, CRP, education, heart rate, systolic blood pressure, diabetes mellitus, smoking status, and alcohol consumption). Additional adjustments were made for current medication influencing cardiac function and structure [i.e., β blockers, angiotensin-converting-enzyme inhibitors (ACE-I)/angiotensin II receptor blockers (ARB), and statins]. We performed interaction analyses by sex and obesity (BMI ≥30) due to their established impact on BNP concentrations (20, 21). Additional sensitivity analyses were performed by (1) replacing eGFR with creatinine concentrations and BMI with height and body weight and (2) excluding participants with LVEF ≤40% or significant LV hypertrophy (≥95 g/m^2 for women and ≥115 g/m^2 for men). Statistical significance was assumed at $P < 0.05$. The analyses were performed with STATA 16 (StataCorp LP).

Results

BASELINE CHARACTERISTICS

Of the 3706 participants from the ACE 1950 Study baseline examination, 1757 women and 1677 men were included in the following analyses (Fig. 1). Characteristics of participants excluded due to history of CAD [$n = 263$ (7.1%)], or missing biomarker data [$n = 9$ (0.2%)] are summarized in Supplemental Table 2.

Concentrations of BNP were measurable in 72.3% of study participants, with a median concentration of 17.2 (interquartile range 5.0 to 30.3) ng/L, total range 5.0 to 478.7 ng/L. Distribution of BNP according to sex is shown in Fig. 2. Concentrations of BNP were positively associated with systolic blood pressure (B coefficient 0.006, 95% CI 0.005 to 0.008), β-blocker therapy (B 0.61, 95% CI 0.51 to 0.72), and HDL cholesterol (B 0.24, 95% CI 0.17 to 0.32), and negatively associated with male sex (B −0.27, 95% CI −0.34 to −0.21), heart rate (B −0.02, 95% CI −0.02 to −0.01), history of diabetes mellitus (B −0.15, 95% CI −0.26 to 0.04), statin therapy (B −0.16, 95% CI −0.23 to 0.08), and total cholesterol (B −0.09, 95% CI −0.12 to 0.06; Supplemental Table 3).

Study participants in the upper sex specific quartile of BNP were less frequently men, and had higher blood pressure and lower BMI and heart rate. They had less prevalent diabetes mellitus, and were more frequently prescribed β blockers, ACE-I/ARBs and statins. GLS, LVMI, e', E/e', LAVI, TRVmax, and E/A were higher in this group (Table 1).

ASSOCIATIONS BETWEEN BNP AND ECHOCARDIOGRAPHIC INDICES

BNP concentrations correlated with absolute values of GLS ($r = 0.15$; $P < 0.001$), LVMI ($r = 0.06$; $P < 0.001$), e' ($r = 0.11$; $P < 0.001$), E/e' ($r = 0.10$; $P < 0.001$), LAVI ($r = 0.29$; $P < 0.001$), and E/A ($r = 0.23$; $P < 0.001$), but not with LVEF ($r = 0.02$; $P = 0.17$). Figure 3 illustrates the adjusted associations of BNP with the different echocardiographic indices. For GLS, the linear and nonlinear associations were fairly comparable, and the strongest nonlinear associations were observed for LVEF. For the remaining echocardiographic indices, the linear models most correctly described the associations with BNP (Table 2).

Men had significantly stronger linear associations of BNP with LVMI (B 2.18, 95% CI 1.20 to 3.15 vs B 0.79, 95% CI −0.11 to 1.68; $P_{interaction} = 0.01$), E/e' (B 0.49, 95% CI 0.36 to 0.62 vs B 0.05, 95% CI −0.09 to 0.20; $P_{nteraction} = 0.01$) and LAVI (B 2.90, 95% CI 2.51 to 3.29 vs B 1.76, 95% CI 1.39 to 2.13; $P_{interaction} < 0.001$), and obese participants had stronger nonlinear associations of BNP with GLS (B −0.33, 95% CI −0.62 to −0.04 vs B −0.06, 95% CI −0.18 to 0.07; $P_{interaction} = 0.012$) and weaker linear associations of BNP with E/A (B 0.06, 95% CI 0.04 to 0.08 vs B 0.07, 95% CI 0.06 to 0.09; $P_{interaction} = 0.023$). No other significant interactions were observed for these 2 prespecified groups (Supplemental Table 4).

In the sensitivity analyses, substituting serum creatinine, height, and body weight for eGFR and BMI did

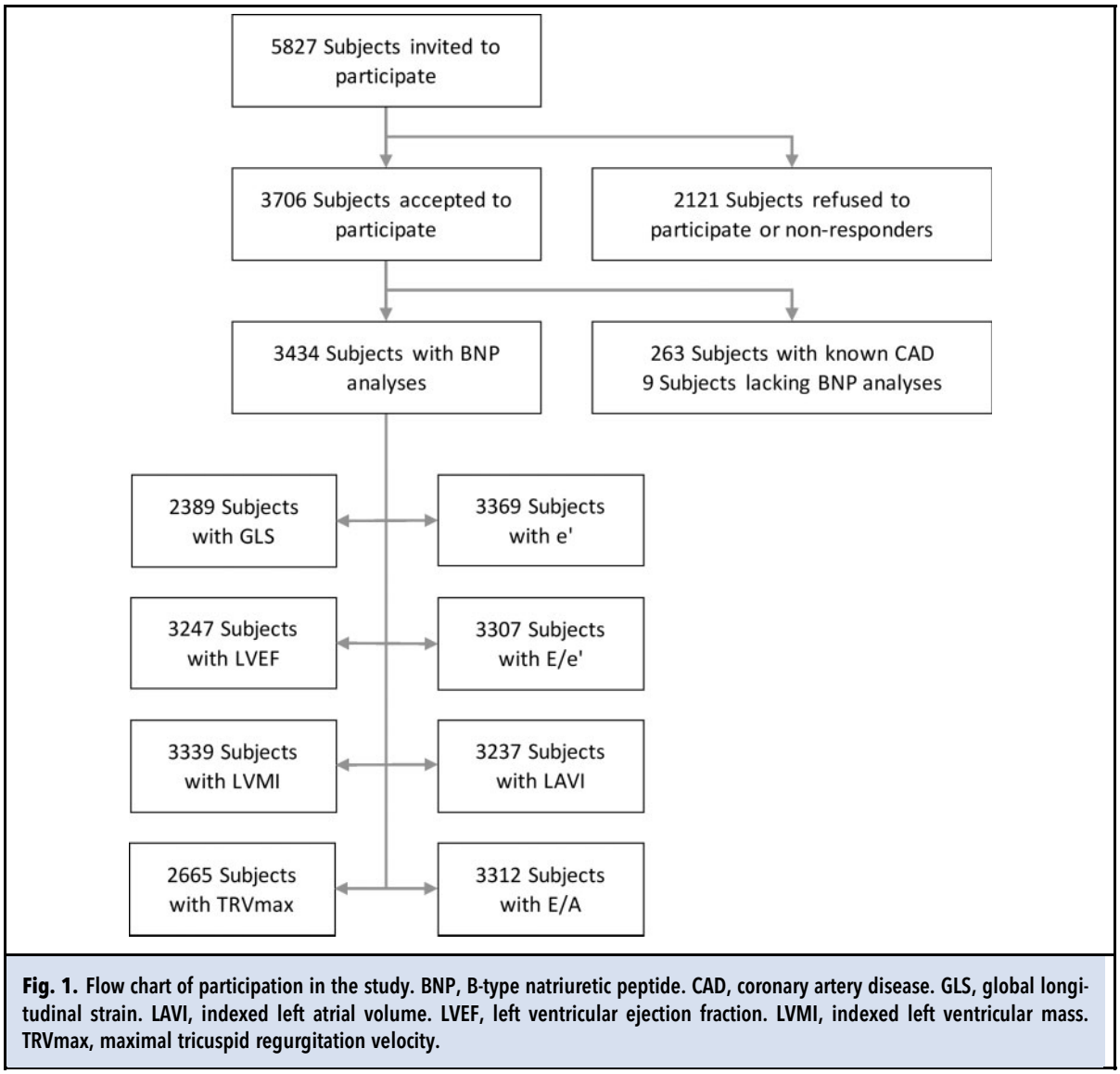

Fig. 1. Flow chart of participation in the study. BNP, B-type natriuretic peptide. CAD, coronary artery disease. GLS, global longitudinal strain. LAVI, indexed left atrial volume. LVEF, left ventricular ejection fraction. LVMI, indexed left ventricular mass. TRVmax, maximal tricuspid regurgitation velocity.

not alter the associations of BNP with echocardiographic indices (Supplemental Fig. 2; Supplemental Table 5). Excluding participants with LVEF $\leq$40% ($n = 25$), significant LV hypertrophy ($\geq$95 g/m^2 for women and $\geq$115 g/m^2 for men; $n = 257$), or both ($n = 6$) attenuated the nonlinear association of BNP with GLS, as well as enhanced a nonlinear association of BNP with LVMI (Supplemental Fig. 3; Supplemental Table 6).

Discussion

The principal finding of the current study is that, in a large cohort of healthy participants recruited from the general population, higher concentrations of BNP are independently associated with favorable LV systolic function, expressed as higher absolute values of GLS. A similar trend was observed for LVEF, but both associations exhibited significant nonlinear effects, with the most favorable systolic function observed in the BNP range of 25–30 ng/L. With regard to LV diastolic function, concentrations of BNP were linearly associated with e' and E/A. A more exponential association was observed between concentrations of BNP and E/e' and LAVI, with an apparent break point at 20 ng/L.

Measurement of natriuretic peptides is currently the preferred biochemical investigations in diagnosing chronic and acute heart failure. Measurement of GLS by echocardiography is considered the most sensitive investigation of LV systolic function (9), but has so far not replaced estimation of LVEF in routine practice.

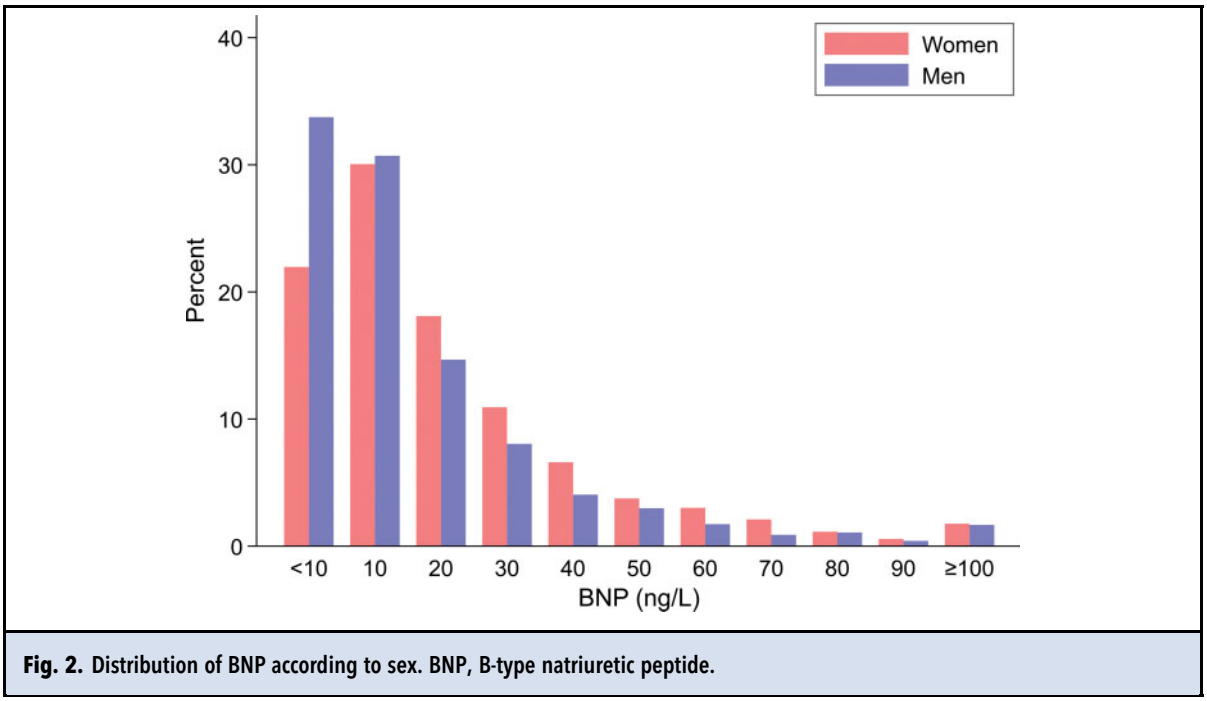

Fig. 2. Distribution of BNP according to sex. BNP, B-type natriuretic peptide.

Evidence is growing for the use of these tools in predicting unfavorable outcomes such as heart failure, acute myocardial infarction, and cardiovascular death (1, 10). To our knowledge, our study is the first to document significant associations between these sensitive biochemical and imaging biomarkers in a healthy population-based cohort.

ASSOCIATION OF NATRIURETIC PEPTIDES WITH LV SYSTOLIC FUNCTION

Two important echocardiographic estimates of LV systolic function were assessed in the current study, GLS and LVEF. The reference standard in assessing LV systolic function is cardiac magnetic resonance imaging (22), but LVEF by echocardiography is still the primary modality in the clinical evaluation of patients with suspected heart failure, and LVEF is the criterion that separates patients in heart failure with reduced and preserved EF (23). Concentrations of natriuretic peptides are inversely associated with LVEF in patients with established heart failure (4) and in patients that have undergone acute myocardial infarction (24). In the Framingham Study, concentrations of BNP were associated with increased probability of LV systolic dysfunction (25). In the current study, we report independent associations of BNP with GLS, the most sensitive index of LV systolic function currently available. The positive association of higher BNP with favorable LV systolic function is intriguing and merits further discussion. Contrary to the established inverse association between natriuretic peptides and LV systolic function in both participants with established cardiovascular disease and in participants recruited from the general population, we demonstrate positive associations between higher BNP and favorable LV systolic function, as assessed by GLS. BNP is a hormone with cardioprotective properties, mediated by vasodilatation, natriuresis, and inhibition of the the renin–angiotensin–aldosterone system. In patients with heart failure, concentrations of natriuretic peptides increase in response to cardiac overload and reflect degree of congestion. In participants from the Atherosclerosis Risk in Communities Study, a single polymorphism in the promoter region of the BNP gene was associated with increased concentrations of NT-proBNP, and subsequently reduced blood pressure, hypertension, and mortality (26). Concentrations of natriuretic peptides are also positively associated with beneficial indices of cardiovascular health, such as non-smoking, regular physical activity, healthy diet, and well-regulated blood pressure and cholesterol (27). Our study lends further support to the notion that in healthy participants, increased concentrations of natriuretic peptides are beneficial and, in the absence of a high-risk cardiovascular phenotype, are associated with favorable LV systolic function. With increasing concentrations of BNP, the association with GLS leveled out and started to decline and this trend toward an inverse U-shaped relationship was even stronger for LVEF. The association of low concentrations of BNP with lower LV systolic function is in accordance with current understanding of

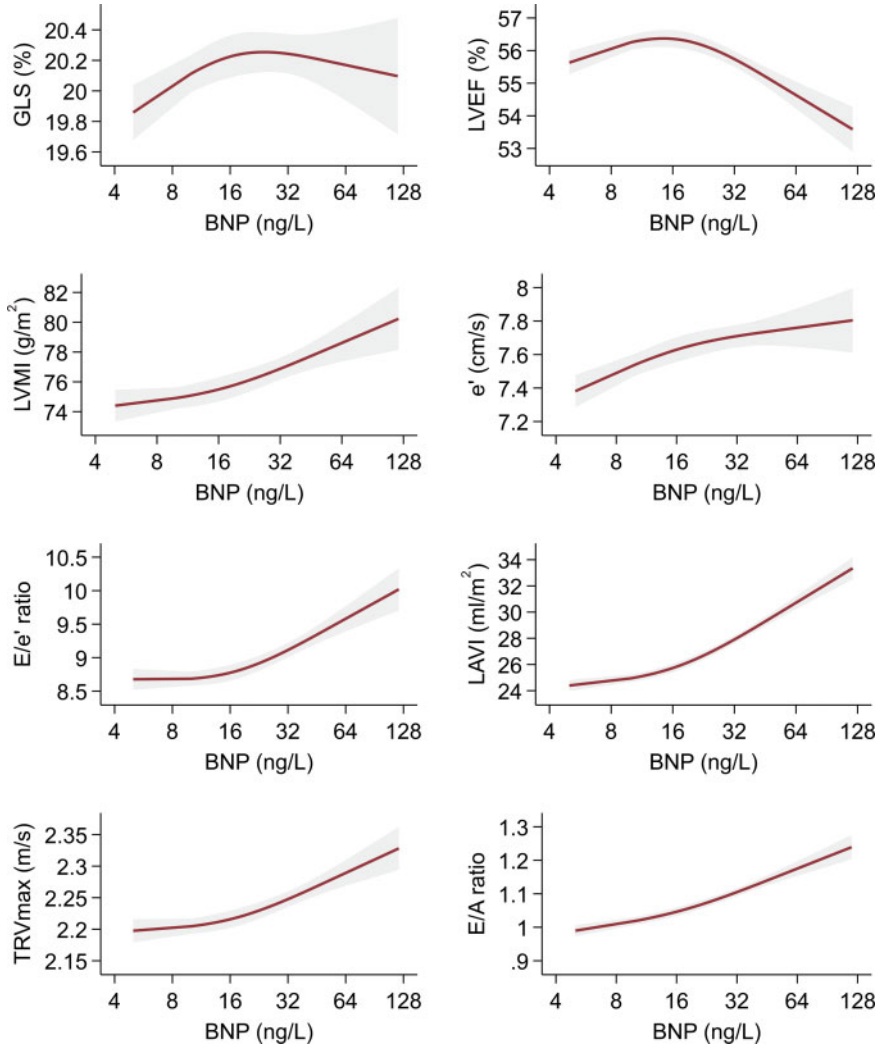

Fig. 3. Associations of BNP with indices of left ventricular structure and function. Adjusted for sex, age, study site, systolic blood pressure, heart rate, BMI, eGFR, total and HDL cholesterol, CRP, higher education, β blockers, ACE-I/ARB, statin therapy, diabetes mellitus, current smoking, and alcohol consumption. Restricted cubic splines with knots placed at the 10th, 50th, and 90th sample percentiles, shading representing 95% CI. BNP, B-type natriuretic peptide. GLS, global longitudinal strain. LAVI, indexed left atrial volume. LVEF, left ventricular ejection fraction. LVMI, indexed left ventricular mass. TRVmax, maximal tricuspid regurgitation velocity.

natriuretic peptide deficiency, a phenomenon linking relative lack of natriuretic peptides with incident hypertension and diabetes mellitus, and increased cardiovascular risk (28) and mortality (29). Pertaining to this notion, obese participants exhibit lower concentrations of BNP (30), and obesity as measured by BMI is associated with impaired LVEF and GLS (31). The nonlinear relationship of BNP with GLS was stronger for obese participants in the current study, suggesting an impact of obesity on the association of BNP with GLS independently of BMI.

ASSOCIATION OF NATRIURETIC PEPTIDES WITH LV STRUCTURE

Quantification of LV mass is a fundamental part of the basic echocardiographic assessment, primarily used to determine the presence of LV hypertrophy. LV mass is strongly associated with incident cardiovascular disease (32), and attenuation of LV hypertrophy is associated with reduced cardiovascular risk (33, 34). Several large-scale population-based studies have previously demonstrated associations of NT-proBNP with LV mass (35, 36). In the current study, we demonstrate similar independent associations between concentrations of BNP

Table 2. Associations between concentrations of BNP and echocardiographic indices.

		B (95% CI)				
	BNP	Model 1	Model 2	Model 3	$P_{linearity}$	$P_{nonlinearity}$
GLS	Linear	0.40 (0.29 to 0.51)	0.30 (0.19 to 0.41)	0.15 (0.04 to 0.27)	0.009	0.023
	Quadratic	−0.16 (−0.28 to −0.04)	−0.16 (−0.27 to −0.04)	−0.13 (−0.25 to −0.02)		
LVEF	Linear	−0.02 (−0.24 to 0.19)	−0.17 (−0.38 to 0.04)	−0.28 (−0.50 to −0.06)	0.013	<0.001
	Quadratic	−0.85 (−1.06 to −0.64)	−0.78 (−0.98 to −0.57)	−0.70 (−0.90 to −0.49)		
LVMI	Linear	1.65 (0.98 to 2.32)	2.29 (1.66 to 2.92)	1.49 (0.83 to 2.15)	<0.001	0.018
	Quadratic	0.71 (0.04 to 1.38)	0.55 (−0.08 to 1.17)	0.76 (0.13 to 1.39)		
e′	Linear	0.17 (0.12 to 0.23)	0.18 (0.12 to 0.24)	0.16 (0.10 to 0.22)	<0.001	0.31
	Quadratic	−0.07 (−0.12 to −0.01)	−0.07 (−0.13 to −0.01)	−0.03 (−0.09 to 0.03)		
E/e′	Linear	0.38 (0.28 to 0.47)	0.30 (0.21 to 0.40)	0.30 (0.20 to 0.39)	<0.001	0.001
	Quadratic	0.20 (0.10 to 0.29)	0.23 (0.13 to 0.33)	0.15 (0.06 to 0.25)		
LAVI	Linear	2.67 (2.40 to 2.93)	2.87 (2.62 to 3.13)	2.36 (2.09 to 2.63)	<0.001	<0.001
	Quadratic	0.86 (0.59 to 1.12)	0.77 (0.52 to 1.03)	0.96 (0.71 to 1.22)		
TRVmax	Linear	0.03 (0.02 to 0.04)	0.04 (0.02 to 0.05)	0.03 (0.02 to 0.04)	<0.001	0.017
	Quadratic	0.02 (0.01 to 0.03)	0.02 (0.01 to 0.03)	0.01 (0 to 0.02)		
E/A ratio	Linear	0.08 (0.07 to 0.09)	0.09 (0.08 to 0.10)	0.07 (0.06 to 0.08)	<0.001	0.09
	Quadratic	0.01 (0 to 0.02)	0.01 (0 to 0.02)	0.01 (0 to 0.03)		

Model 1, unadjusted. Model 2, adjusted for sex, age, and study site. Model 3, adjusted for model 2, systolic blood pressure, heart rate, BMI, eGFR, total and HDL cholesterol, CRP, higher education, β blockers, ACE-I/ARB, statin therapy, diabetes mellitus, current smoking, and alcohol consumption. *P* for linearity and nonlinearity in model 3. ACE-I, angiotensin-converting-enzyme inhibitors. ARB, angiotensin II receptor blockers. BMI, body mass index. BNP, B-type natriuretic peptide. CRP, C-reactive protein. eGFR, estimated glomerular filtration rate. GLS, global longitudinal strain. HDL, high-density lipoprotein. LAVI, indexed left atrial volume. LVEF, left ventricular ejection fraction. LVMI, indexed left ventricular mass. TRVmax, maximal tricuspid regurgitation velocity.

and LVMI. Considering that natriuretic peptides are synthesized intracellularly in ventricular cardiomyocytes, this finding is not entirely unexpected and in accordance with the associations of BNP with subclinical LV hypertrophy demonstrated in previous population cohorts (37). In sensitivity analyses excluding participants with significant LV hypertrophy, the linear association of BNP with LVMI was attenuated, leaving an inverse U-shaped association. Two mechanisms are most likely responsible for this shift. First, participants with grossly pathological LV hypertrophy exhibit high concentrations of BNP, fueling linear associations when included in the analyses. Second, due to the inherently higher concentrations of BNP in women, the proportion of women will naturally be higher in the upper range of BNP when participants with significant LV hypertrophy are excluded. Women have lower LV mass, and negative associations between BNP and LVMI should accordingly be expected in the upper BNP range. The discrepancy between higher LV mass and lower BNP concentrations additionally explains the stronger associations of BNP with LVMI in men.

ASSOCIATION OF NATRIURETIC PEPTIDES WITH LV DIASTOLIC FUNCTION

In contemporary cardiology, natriuretic peptides are utilized to determine the presence of systemic congestion due to LV systolic dysfunction, and are strongly correlated with declining LVEF (4). Increasing concentrations of natriuretic peptides additionally correlate with several indices of LV diastolic function, in both participants with reduced and preserved LVEF (38). In smaller cohorts recruited from the general population, increasing concentrations of natriuretic peptides are associated with increased risk of LV diastolic dysfunction (37, 39). Our study adds to this understanding by demonstrating independent associations with impaired LV diastolic relaxation (e'), and acute (E/e', TRVmax, E/A) and chronic (LAVI) increases in LV filling pressure. Contrary to the models for LV systolic function, the

associations of BNP with E/e', LAVI, TRVmax, and E/A were more linear in nature, with an exponential increase at BNP values surpassing 20 ng/L, probably due to low-grade increases in LV diastolic filling pressures and myocardial distension. The associations with E/e' and LAVI were also more pronounced in men, possibly due to attenuated natriuretic peptide release compared to women.

NATRIURETIC PEPTIDES IN CARDIOVASCULAR SCREENING

Measurement of natriuretic peptides is fundamental in making the diagnosis of chronic heart failure, and concentrations of BNP <35 ng/L (or NT-proBNP <125 ng/L) exclude chronic heart failure with a negative predictive value close to 100% in the nonacute setting (23). In the current study, we observed a favorable association between concentrations of BNP with LV systolic function, but with strong trends toward inverse U-shaped relationships for both GLS and LVEF. The vertex of these associations was reached around 25–30 ng/L, corresponding well with the established diagnostic limits for excluding chronic heart failure. With regard to risk prediction, the association between natriuretic peptides and risk of cardiovascular outcomes also appear nonlinear, with a steep increase in risk when concentrations approach the cutoffs recommended in current guidelines (1). In healthy patients free from cardiovascular risk factors and overt cardiac dysfunction, concentrations of natriuretic peptides are apparently not associated with cardiovascular risk (40). Conversely, in ambulatory patients with risk factors for heart failure, increased concentrations of BNP >50 ng/L identify participants who especially benefit from preventive medical interventions (2). Such a threshold effect may largely explain of the principal findings of the current study. As long as the concentrations of natriuretic peptides remain within the normal reference interval, the release and physiological effects are undoubtedly beneficial and participants with attenuated natriuretic peptide release are at risk of impaired LV systolic function. With increasing concentrations of natriuretic peptides surpassing the high reference limit, the associations with LV systolic function invert. In this setting, increasing concentrations of natriuretic peptides is a pathophysiological compensatory mechanism to incipient cardiac dysfunction, ultimately associated with increased cardiovascular risk.

STRENGTHS AND LIMITATIONS

Several strengths and limitations of the current study merit mentioning. A major strength of the study is the use of some of the most sensitive biomarker assays currently available, in addition to an extensive and highly sensitive echocardiographic evaluation of LV structure, diastolic, and systolic function. We have used data from a large community-based cohort with broad phenotypical characterization, as well as thorough registration of socioeconomic status and medical history. Nonresponse bias must, however, be taken into account, as we have no information on participants who actively refused to participate or were otherwise inaccessible for study inclusion. As of yet, we do not have follow-up data for the study cohort, barring us from investigating the associations between biomarkers, echocardiography, and incident cardiovascular disease. Finally, external validity to other age strata is limited, as all participants of the study were born in 1950.

Conclusions

In healthy participants recruited from the general population, concentrations of BNP exhibit a nonlinear association with LV systolic function, and both low and high concentrations are associated with impaired LV systolic function. This supports the notion that natriuretic peptides are beneficial and elicit cardioprotective effects, and may have important implications for the interpretation of BNP measurements in the general population.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations BNP, B-type natriuretic peptide; LV, left ventricular; LVMI, left ventricular mass index; LAVI, indexed left atrial volume; TRVmax, maximal tricuspid regurgitation velocity; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; ACE, Akershus Cardiac Examination; CAD, coronary artery disease; HbA1c, glycated hemoglobin; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; BMI, body mass index; ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers.

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