ORIGINAL ARTICLE

Relation of N-Terminal Pro-B-Type Natriuretic Peptide With Diastolic Function in Hypertensive Heart Disease

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BACKGROUND
Elevated natriuretic peptide levels in asymptomatic individuals without heart failure are associated with increased risk of adverse cardiovascular outcomes and may reflect subclinical cardiac dysfunction.

METHODS
In a sample of 313 asymptomatic individuals (51% women, mean age 61 years) with hypertension and diastolic dysfunction, we examined the association of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) with both conventional and advanced echocardiographic measures of systolic and diastolic function, including myocardial strain, using speckle-tracking–based analyses.

RESULTS
In univariate analyses, higher NT-proBNP was associated with greater left ventricular mass index ($P = 0.003$), left atrial volume index ($P = 0.007$), lateral E' velocity ($P < 0.0001$), E/E' ratio ($P < 0.0001$), peak global longitudinal systolic strain ($P = 0.015$), systolic strain rate ($P = 0.021$), and early diastolic strain rate ($P < 0.0001$). In multivariable analyses, NT-proBNP remained associated with measures of diastolic dysfunction, including lateral E' velocity ($P = 0.013$) and the E/E' ratio ($P = 0.008$). However, early diastolic strain rate was the echocardiographic parameter most strongly associated with NT-proBNP ($P = 0.003$).

CONCLUSIONS
In the setting of asymptomatic hypertensive heart disease and preserved ejection fraction, elevation in natriuretic peptide levels is predominantly associated with subclinical diastolic dysfunction.

Keywords: blood pressure; diastolic function; hypertension; imaging; natriuretic peptides; speckle-tracking echocardiography; strain.

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Elevation in circulating natriuretic peptides is known to portend adverse outcomes in the setting of heart failure.[1,2] Community-based studies have demonstrated that incremental elevations in B-type natriuretic peptide (BNP), even below current thresholds used to diagnose heart failure, are also associated with risk for incident heart failure in asymptomatic individuals.[3,4] The physiology underlying this relationship between natriuretic peptides and the eventual development of heart failure in the general population remains unclear. However, it may be related to the cardioprotective effects of natriuretic peptides, such as vasodilation, natriuresis and diuresis, and inhibition of the renin–angiotensin–aldosterone axis. In addition, it may be related to antihypertrophic and antifibrotic properties mediated by activity at the guanylyl cyclase type A receptor and signaling pathways such as calcineurin/nuclear factor of activated T cells (NFAT), the sodium-hydrogen exchanger 1 (NHE-1), and transforming growth factor beta (TGF-β) pathways.[5]

Elevated BNP in apparently healthy individuals may represent an aggregate marker of subclinical abnormalities in cardiac structure and function that can develop during the progression from risk factors to heart failure. Natriuretic peptides have been shown to be associated with left ventricular (LV) hypertrophy and cardiac functional abnormalities in individuals with chronic kidney disease without overt heart failure,[6] as well as LV systolic and diastolic dysfunction in coronary artery disease.[7] Furthermore, prior studies have shown that BNP is increased in the setting of asymptomatic LV systolic dysfunction, defined as the presence of a reduced LV ejection fraction.[8,9] However, the overall prevalence of reduced ejection fraction in the community is low, and the association between BNP and cardiac abnormalities in the setting of preserved ejection fraction is less clear.[10,11]

Conventional approaches to assessing cardiac dysfunction have limited sensitivity. However, the use of advanced

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methods for quantifying myocardial deformation may help to elucidate the relationship between BNP and LV function.[12] Therefore, we examined the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and LV function using a combination of conventional and advanced echocardiographic measures of myocardial performance in a sample of asymptomatic hypertensive individuals with preserved ejection fraction (EF).

METHODS

Study sample

The Valsartan in Diastolic Dysfunction (VALIDD) study was a double-blind randomized trial designed to determine whether blood pressure lowering with the angiotensin receptor blocker (ARB) valsartan plus standard antihypertensive therapy for 38 weeks vs. placebo plus standard therapy improves diastolic function in patients with hypertension and diastolic dysfunction. The primary endpoint was change in early diastolic relaxation velocity of the mitral annulus (E′), a tissue Doppler parameter, between baseline and 38 weeks.[13,14] The trial was conducted in 41 centers across the United States and Canada. Men and women aged ≥45 years with a history of stage 1 or 2 essential hypertension (mean systolic blood pressure [SBP] ≥140 mm Hg or mean diastolic blood pressure [DBP] ≥90 mm Hg) were screened by echocardiography for inclusion in the study if they had no history of hospital admission for heart failure in the past year and had not taken any renin–angiotensin–aldosterone inhibitors in the previous 3 months. Echocardiographic screening in eligible patients included tissue Doppler measurement of lateral E′ with enrollment determined by age-specific E′ thresholds: <10 cm/s for individuals aged 45–54 years, <9 cm/s for individuals aged 55–65 years, and <8 cm/s for individuals aged >65 years. Patients were excluded if they had an LV ejection fraction (LVEF) ≤ 50%; contraindication to angiotensin-converting enzyme inhibitors or ARBs; stage 3 hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg); history of stroke, transient ischemic attack, or myocardial infarction within 6 months of the first visit; a serum creatinine > 221 μmol/l; or uncontrolled diabetes mellitus, defined as a glycosylated hemoglobin >8.5%. Eligible patients were randomized to valsartan (160 mg/day titrated up to 320 mg/day) or matched placebo.

Of the 384 eligible patients who were randomized in the VALIDD trial, 330 had baseline NT-proBNP levels assayed prior to receiving valsartan or placebo. Of these individuals, 313 had echocardiographic images of adequate quality for speckle-tracking–based strain analyses. These individuals comprised the current study sample. Written informed consent was obtained for all patients before any study procedures were performed.

Clinical and echocardiographic assessment

Baseline blood samples were collected for measurement of NT-proBNP and sent to a central laboratory for analysis (Clinical Reference Laboratory, Inc., Lenexa, KS). Analysis was performed using the Elecsys proBNP sandwich immunoassay (Roche Diagnostics, Indianapolis, IN) with a measurable range of 5–35,000 pg/ml. Intraassay and interassay coefficients of variation were 2.7% and 3.2%, respectively, at 175 pg/ml; 2.4% and 2.9% at 355 pg/ml; 1.9% and 2.6% at 1,068 pg/ml; and 1.8% and 2.3% at 4,962 pg/ml.[15] NT-proBNP reference ranges were reported as <125 pg/ml for individuals aged <75 years and <450 pg/mL for individuals aged ≥75 years.[15] Blood pressure and heart rate measurements were performed using automatic cuffs (Omron model HEM-705, Omron, Inc., Song Jiang Lu, China). Clinical histories, including prior diagnoses of atrial fibrillation, coronary artery disease, diabetes mellitus, hyperlipidemia, myocardial infarction, peripheral vascular disease, and/or stroke, were obtained at screening and baseline visits.

All patients had standard echocardiograms at baseline. Echocardiograms were transferred digitally or by videotape to a core laboratory for analysis. LV volumes were derived using the modified biplane Simpsons rule. LVEF was calculated from LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV). LV wall thicknesses, dimensions, mass, and left atrial (LA) volume were also obtained according to guideline recommendations.[16] LV mass and LA volume were additionally indexed to body surface area. Transmitral Doppler was used to obtain early diastolic (E) and late diastolic (A) flow velocities. Spectral pulsed-wave tissue Doppler imaging was used to record E′ and late diastolic relaxation velocity (A′) at both the septal and lateral mitral annuli from the apical four-chamber view. These measures were used to calculate E/E′, mitral deceleration time (DT), and isovolumetric relaxation time (IVRT).

Following review of suitability for strain-based measures, digital echocardiographic images were analyzed using an off-line speckle-tracking software (Velocity Vector Imaging [VVI], Siemens, Inc., Mountain View, CA) that has been previously validated with sonomicrometry and tagged magnetic resonance imaging in animals.[17,18] Manual tracings were performed along the LV endocardial border from the septal mitral annulus to the lateral mitral annulus in apical four-chamber views and from the posterior mitral annulus to the anterior mitral annulus in apical two-chamber views at end-diastole. Images lacking distinct endocardial borders over ≥3 consecutive cardiac cycles were deemed poor quality and excluded from analyses. Software-generated regions of interest along the traced endocardium tracked frame-to-frame pixel movement to yield segmental quantitative strain (%) and strain rate (SR, s⁻¹) data in systole and diastole. Global strain and SR measures were calculated by averaging apical four- and two-chamber segmental data.

Statistical analyses

Continuous variables were reported as mean ± SD, and categorical variables were reported as percentages unless otherwise noted. Statistically significant differences in baseline clinical and echocardiographic characteristics were reported across tertiles of NT-proBNP levels using an extension of the Wilcoxon rank sum test for trend for continuous variables[19] and χ^2 statistics for categorical variables. NT-proBNP was log-transformed (log NT-proBNP) due to its right-skewed distribution. Pearson coefficient of correlation was used to assess associations between echocardiographic parameters of diastolic function and log

NT-proBNP. Clinical, echocardiographic, and strain measures were related to log NT-proBNP levels using univariate linear regression. Stepwise multivariable linear regression was used to examine the relation of clinical and echocardiographic parameters with log NT-proBNP. All *P* values were two-sided with $P < 0.05$ used to determine statistical significance. All statistical analyses were performed using STATA, version 11.2 (StataCorp., College Station, TX).

RESULTS

Our study sample included patients with a mean age of 61.0 ± 9.2 years, and 51.4% were women. Patients with higher compared to lower NT-proBNP levels were older ($P < 0.0001$), tended to be female ($P = 0.016$), had histories significant for coronary artery disease ($P = 0.005$), had higher pulse pressures ($P < 0.0001$), and had lower estimated glomerular filtration rates (eGFR, $P = 0.009$; Table 1). There was no statistically significant trend in frequency of atrial fibrillation, diabetes mellitus, hyperlipidemia, myocardial infarction, or stroke across NT-proBNP tertiles.

Mean LVEF was in the normal range, defined as 55% or greater,[16] and did not differ across tertiles of NT-proBNP ($P = 0.75$; Table 2). LV mass index (LVMI) and LA volume index (LAVI) were slightly increased in the third tertile relative to the first and second tertiles ($P = 0.034$ and 0.022, respectively). Mean lateral E′ decreased with higher NT-proBNP levels ($P < 0.0001$) and E/E′ ratio increased

Table 1. Clinical Characteristics

Characteristic	NT-proBNP Tertile 1 (N = 105)	NT-proBNP Tertile 2 (N = 104)	NT-proBNP Tertile 3 (N = 104)	*P*-value
NT-proBNP levels, pg/mL				
Median	28.2	67.8	174.9	NA
Interquartile range	17.7-38.1	55.7-82.6	121.3-269.0	NA
Range	5.9-46.1	46.8-95.8	96.6-1252	NA
Age, years	57.5±8.1	59.5±7.8	65.9±9.6	<0.0001
Sex (male), %	60.0	42.3	43.2	0.016
Race, %				
White	77.1	78.9	83.7	0.48
Non-white	22.9	21.1	16.3	
Height, m	1.7±0.1	1.7±0.1	1.7±0.1	0.07
BMI, kg/m²	30.9±6.1	30.0±5.4	29.8±5.7	0.13
Systolic blood pressure, mmHg	145±16	148±16	150±17	0.09
Diastolic blood pressure, mmHg	86±12	86±11	82±12	0.002
Pulse pressure, mmHg	59±13	61±14	69±16	<0.0001
eGFR, mL/min	94.0±28.8	83.8±31.1	84.3±27.1	0.009
History, %				
Atrial fibrillation	1.0	1.0	1.9	0.77
Coronary artery disease	3.8	9.6	17.3	0.005
Diabetes mellitus	8.6	11.5	15.4	0.31
Hyperlipidemia	54.3	50.0	51.0	0.81
Myocardial infarction	1.0	2.9	4.8	0.25
Peripheral vascular disease	0.0	2.9	2.9	0.21
Stroke	1.0	0.0	1.0	0.61
Medications at baseline, %				
Alpha-blockers	2.9	2.9	4.9	0.68
Beta-blockers	38.5	50.5	47.6	0.19
Calcium channel blockers	57.7	54.4	57.3	0.87
Diuretics	76.0	63.1	64.1	0.09
Statins	34.6	29.1	34.0	0.66

Abbreviation: BMI, body mass index.
Values are shown as means ± standard deviations or percentages unless otherwise indicated.

Table 2. Echocardiographic Characteristics

Parameter	NT-proBNP Tertile 1 (N = 105)	NT-proBNP Tertile 2 (N = 104)	NT-proBNP Tertile 3 (N = 104)	*P*-value
LV wall thickness, cm	0.89±0.08	0.86±0.10	0.90±0.10	0.57
LVEDD, cm	4.59±0.12	4.56±0.13	4.57±0.13	0.26
Relative wall thickness	0.39±0.04	0.38±0.04	0.40±0.05	0.55
LV mass, g	138.0±18.0	131.7±23.6	140.2±21.6	0.75
LV mass index, g/m^2	69.4±9.4	68.4±10.2	73.2±12.4	0.034
LA volume index, mL/m^2	31.1±4.5	30.4±4.1	32.5±5.0	0.022
LV end-diastolic volume, mL	91.3±13.4	87.3±16.5	88.7±13.2	0.14
LV end-systolic volume, mL	39.4±7.6	38.0±8.8	38.0±7.2	0.20
LVEF, %	57.0±2.9	56.7±3.3	57.2±3.2	0.75
Lateral E' velocity, cm/s	7.74±1.18	7.77±1.08	7.08±1.27	<0.0001
E/E' ratio	9.29±2.37	9.93±2.76	10.67±2.86	0.001
IVRT, msec	104±18	101±18	103±17	0.73
Deceleration time, msec	220±44	211±45	225±51	0.77
Myocardial performance index	0.49±0.12	0.46±0.11	0.47±0.10	0.58
GLSS, %	-14.6±1.9	-14.2±2.1	-14.0±2.2	0.07
GLSSR, s^{-1}	-0.76±0.11	-0.74±0.09	-0.72±0.11	0.022
GLDSR, s^{-1}	0.73±0.12	0.71±0.11	0.68±0.12	0.002

Abbreviations: LVEDD, LV end-diastolic diameter; Deceleration time, E wave deceleration time; GLSS, peak global longitudinal systolic strain; GLSSR, peak global longitudinal systolic strain rate; GLDSR, peak global early diastolic strain rate.

Values are shown as means ± standard deviations.

across tertiles (*P* = 0.001). Mean global longitudinal systolic SR and early longitudinal diastolic SR both decreased across tertiles of NT-proBNP (*P* = 0.022 and 0.002, respectively). We observed lower mean NT-proBNP levels in individuals with higher diastolic strain rates (Figure 1). Pearson correlation coefficients with log NT-proBNP were comparable for diastolic strain rate (−0.220, *P* = 0.0001), lateral E' velocity (−0.219, *P* = 0.0001), and E/E' ratio (−0.239, *P* < 0.0001).

In unadjusted regression models, age (*P* < 0.0001), female sex (*P* = 0.016), DBP (*P* < 0.0001), history of coronary artery disease (*P* < 0.0001), eGFR (*P* = 0.013), and age-specific entry criteria (*P* < 0.0001) showed relations with log-transformed NT-proBNP (Table 3). Among the echocardiographic parameters, LVMI (*P* = 0.003), LAVI (*P* = 0.007), lateral E' (*P* < 0.0001), E/E' ratio (*P* < 0.0001), longitudinal strain (*P* = 0.015), systolic strain rate (*P* = 0.021), and diastolic strain rate (*P* < 0.0001) were significantly associated with log NT-proBNP.

In stepwise multivariable analyses, age (*P* < 0.0001), history of coronary artery disease (*P* = 0.005), lateral E' velocity (*P* = 0.013), E/E' ratio (*P* = 0.008), and diastolic strain rate (*P* = 0.003) remained significantly associated with increased NT-proBNP. Notably, increased diastolic strain rate was the most prominent echocardiographic measure associated with higher log NT-proBNP levels. SBP and DBP were not significantly associated with NT-proBNP in multivariable analyses, adjusting for these echocardiographic traits. In secondary analyses, we observed no effect modification by age or sex on the association between diastolic strain rate and log NT-proBNP (*P* > 0.25).

DISCUSSION

In a sample of asymptomatic individuals with hypertension and diastolic dysfunction, we observed significant associations of NT-proBNP with age, coronary artery disease, and conventional echocardiographic measures of diastolic dysfunction. Systolic function as measured by myocardial strain parameters was also reduced in relation to NT-proBNP levels. However, diastolic dysfunction was more prominently associated with NT-proBNP than systolic dysfunction. Furthermore, we observed that among echocardiographic measures studied, reduction in early longitudinal diastolic strain rate demonstrated the strongest association with increased NT-proBNP.

Population-based investigations have reported age-related increases in BNP levels in individuals without cardiovascular, renal or pulmonary disease or diabetes as well as normal LV systolic and diastolic function.[20,21] Several explanations have been offered for this association, including a higher prevalence of subclinical cardiac dysfunction in the elderly,[22] decreased clearance of natriuretic peptides in elderly patients without underlying renal dysfunction,[23] and less effective nonrenal clearance mechanisms such as platelet-associated clearance receptors.[24] Additionally, animal studies suggest an age-related increase in expression of genes coding for natriuretic peptides.[25]
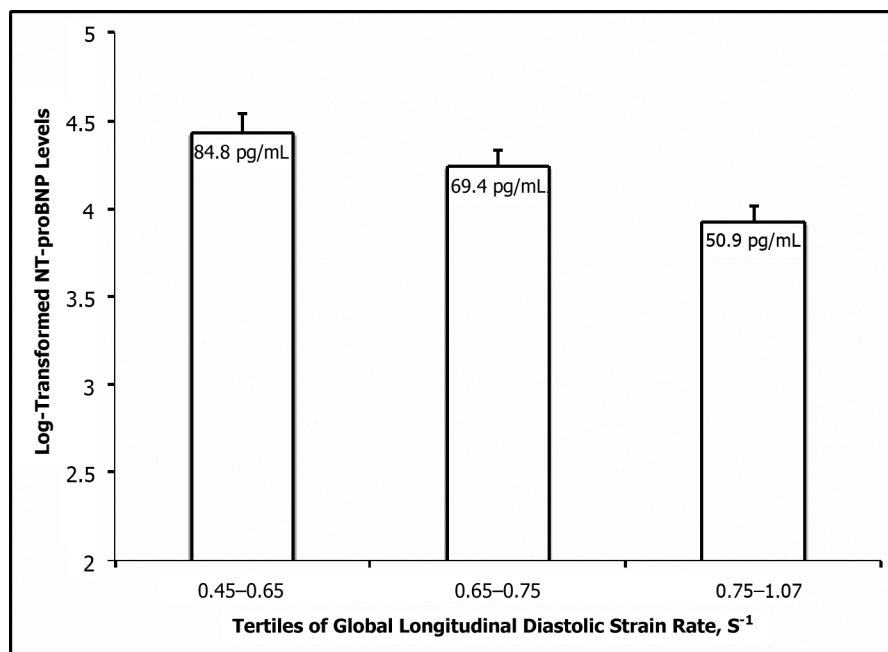
Figure 1. Mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels across tertiles of peak global longitudinal early diastolic strain rate. Mean (± standard error of the mean) of NT-proBNP levels are shown across tertiles of peak global longitudinal early diastolic strain rate ($P_{trend} = 0.001$). NT-proBNP levels tend to be higher as diastolic strain rates decrease.

Table 3. Relations of NT-proBNP with Clinical and Echocardiographic Parameters

Variable	Unadjusted		Multivariable-Adjusted*		
	Coefficient (SE)	P value	Coefficient (SE)	P value	Partial R²
Age, years	0.043 (0.006)	<0.0001	0.042 (0.007)	<0.0001	0.114
GLDSR, s⁻¹	-1.900 (0.479)	<0.0001	-1.488 (0.500)	0.003	0.034
E/E' ratio	0.087 (0.021)	<0.0001	0.067 (0.025)	0.008	0.030
History of coronary artery disease	0.725 (0.182)	<0.0001	0.522 (0.179)	0.004	0.028
Lateral E' velocity, cm/s	-0.180 (0.045)	<0.0001	0.175 (0.070)	0.013	0.027
Female sex	0.270 (0.112)	0.016	—	—	—
Non-white race	-0.275 (0.140)	0.051	—	—	—
BMI, kg/m²	-0.019 (0.010)	0.052	—	—	—
Systolic blood pressure, mmHg	0.006 (0.003)	0.07	—	—	—
Diastolic blood pressure, mmHg	-0.016 (0.005)	0.001	—	—	—
eGFR, mL/min	-0.005 (0.002)	0.013	—	—	—
LV mass index, g/m²	0.015 (0.005)	0.003	—	—	—
LA volume index, mL/m²	0.033 (0.012)	0.007	—	—	—
LV end-diastolic volume, mL	-0.005 (0.004)	0.16	—	—	—
LV ejection fraction, %	0.016 (0.018)	0.39	—	—	—
IVRT, msec	0.801 (3.309)	0.81	—	—	—
Deceleration time, msec	0.586 (1.224)	0.63	—	—	—
GLSS, %	0.066 (0.027)	0.015	—	—	—
GLSSR, s⁻¹	1.292 (0.555)	0.021	—	—	—

*Stepwise multivariable regression model included all covariates shown, in addition to age-specific entry criteria ($P = 0.29$ in the multivariable model).

Previous studies of asymptomatic individuals have consistently reported increased natriuretic peptide levels in relation to abnormalities in LV structure, including alterations in LV dimensions, volumes, and mass. However, studies of the association between natriuretic peptide levels and measures of LV function, assessed using conventional echocardiographic methods, have been mixed.[9,26,27] Consistent with the results from prior studies, we observed an unadjusted association between NT-proBNP and increased LV mass. However, this association became nonsignificant in multivariable models. As mean values of LV mass and wall thickness in our sample were within normal ranges, individuals included in the present analyses may represent patients at an earlier stage of cardiac dysfunction in the progression from hypertensive heart disease to heart failure.[13,28,29] We observed associations of elevated NT-proBNP with both systolic and diastolic dysfunction, particularly as reflected by sensitive strain-based measures of myocardial performance. While previous studies of the association of natriuretic peptides with myocardial strain have focused on patients with a history of or concomitant symptoms consistent with heart failure,[10,12] our analysis extends these findings to individuals with subclinical disease, suggesting a possible role for natriuretic peptide levels in identifying the presence of subclinical cardiac dysfunction among hypertensive individuals without a history of heart failure.

While the cross-sectional design of the present study precludes an ability to draw conclusions about causality, our findings are consistent with those of previous studies regarding the role of LV diastolic wall stress on natriuretic peptide levels[9] and suggest that impaired myocardial relaxation in early diastole may also contribute to peptide elevations in hypertensive individuals with preserved ejection fraction. Conventional echocardiographic measures of diastolic function, such as IVRT and deceleration time, are abnormally elevated across all tertiles[30] as expected per VALIDD inclusion criteria. However, these measures were not associated with NT-proBNP in the present study. E′ velocity and E/E′ ratio were associated with NT-proBNP levels, but peak early diastolic strain rate displayed the strongest association with peptide levels. Thus, increases in natriuretic peptides may represent an aggregate marker of increased LV filling pressures and intrinsic myocardial dysfunction. Additionally, the stronger association between parameters of diastolic function and NT-proBNP levels suggests that subclinical diastolic dysfunction in individuals with hypertension may be among the major contributors to peptide elevations within the normal range. The association of systolic function, as measured by strain parameters, with natriuretic peptides may be more prominent with progressive dysfunction or perhaps may reflect the mechanical coupling of systole and diastole.

Several possible biological mechanisms may be responsible for the observed relation between subclinical myocardial dysfunction and elevated natriuretic peptide levels in the setting of hypertension. In particular, natriuretic peptides may be markers of the pathologic processes associated with hypertension, such as increased interstitial fibrosis and/or abnormalities in myocardial calcium homeostasis.[31,32] Alternatively, BNP may be directly involved in underlying changes in cardiac mechanics. BNP stimulates its downstream effects through a cyclic guanosine monophosphate-dependent (cGMP) signaling cascade after binding natriuretic peptide receptor A (NPR-A).[33] Altered cGMP levels from natriuretic peptide activity offers one viable mechanism, although data from current literature are conflicting. *In vivo* studies in experimentally hypertensive canines suggest titin-based cardiomyocyte stiffness decreases in the setting of increased cGMP activity following BNP supplementation after administration of a phosphodiesterase-5A inhibitor, thus improving LV diastolic distensibility.[34] *In vitro* studies of rabbit ventricular cardiomyocytes suggest that increased cGMP levels reduce cardiomyocyte shortening as well as the rate of relaxation.[35] The effect of BNP on ventricular contractility and distensibility may also be concentration dependent.[36]

Alternatively, BNP levels may mediate cardioprotective responses to hypertension, as shown by investigation of the association between common variants at the natriuretic peptide precursor A and natriuretic peptide precursor B with increased natriuretic peptides levels that also demonstrated lower SBP and DBP and a 15% reduction in odds of hypertension.[37] Individuals with lower circulating concentrations of natriuretic peptides exhibited elevated blood pressures and risk for hypertension. Similarly, increased cardiac rat proBNP expression via single injection of a myocardium-tropic adeno-associated virus serotype 9 vector in spontaneously hypertensive rats improved blood pressure and conventional measures of cardiac structure and function, including LV wall thickness, LV mass, and ejection fraction.[38] These results lend further support for a cardioprotective effect of natriuretic peptides in cardiac dysfunction and remodeling related to early hypertension. Elevated NT-proBNP levels in individuals with hypertensive heart disease may be indicative of a compensatory mechanism. However, persistent increases of NT-proBNP to thresholds diagnostic of heart failure may reflect desensitization of the NPR-A, possibly via a calcineurin-mediated pathway.[39] In this setting, the cardioprotective effect of natriuretic peptides may not be a long-term phenomenon.

Our overall findings suggest that among individuals with hypertension, incremental elevations in natriuretic peptide levels may indicate the presence of subclinical cardiac dysfunction, particularly diastolic dysfunction that may manifest as a reduction in early diastolic strain rate. The extent to which elevated natriuretic peptides in this specific setting portends the eventual development of heart failure warrants further investigation. Additional studies are also needed to clarify the mechanisms by which natriuretic peptides may be associated with cardiac dysfunction, even at a very early stage in the progression from risk factors to heart failure.

Limitations

Several limitations of this study deserve consideration. Patients in VALIDD were generally young, only mildly hypertensive, and without LV hypertrophy or heart failure, which may limit the generalizability of our findings to other populations. Silent ischemia cannot be ruled out in this cohort given the statistically significant trend in coronary artery disease among the tertiles. The number of medications taken by study participants at time of entry into VALIDD

and dosing was not reported. Right ventricular systolic pressure was not measured due to inadequate tricuspid regurgitant jet velocity profiles in a majority of individuals. Strain analyses were conducted on images converted and digitized from videotape-based cassette, resulting in lower frame rates (approximately 30 frames per second) and increased probability of peak strain and strain rate values falling between image frames. However, any resulting reduction in measurement precision would have biased our results to the null. Additionally, previous comparison of peak strain rate and time to peak strain rate between video and digital images to test the effect of frame rate suggest a good correlation between the formats and support use of videotape-based images when digital images are unavailable.[40] Long-term clinical outcomes were not collected in VALIDD, precluding any analyses of the predictive value of NT-proBNP and/or myocardial function parameters in this sample.

Conclusions

In a sample of asymptomatic individuals with hypertensive heart disease, we observed that impairment in diastolic, more so than systolic, myocardial function was prominently associated with increased NT-proBNP. Thus, elevations of NT-proBNP levels, even within the normal range, may indicate subclinical cardiac dysfunction despite a preserved EF. Further research is needed to investigate the biological mechanisms underlying the relation of increased natriuretic peptides with abnormalities in diastolic function and its possible implications for prognostication and stratification with respect to risk for future HF.

DISCLOSURE

The authors declared no conflict of interest.

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