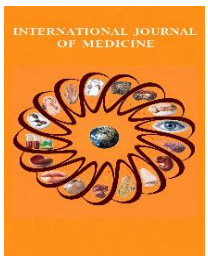

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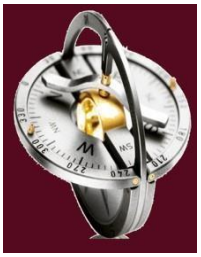

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Original Article

Relations of plasma B-type natriuretic peptides (BNP) to tissue Doppler E/e´, left ventricular systolic functions and BNP predictors in African heart failure subjects: The ABU-BNP survey

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Abstract

Background: To evaluate the relations of B-type natriuretic peptide (BNP) to tissue Doppler (TD) E/e´, left ventricular systolic functions and BNP's predictors as well as determine plasma BNP levels in African heart failure (HF) subjects in comparison to healthy controls as there is paucity of data on these in black African population.

Methods: A cross-sectional analytical study done on 184 subjects: 109 decompensated HF patients at the Ahmadu Bello University Teaching Hospital, Nigeria and 75 healthy controls. Simultaneous BNP assessment and echocardiographic determination of systol ic function and TD E/e´ were done. Pearson's Correlation and Binary Logistic Regression analysis determined BNP's association with parameters. Mann-Whitney U test determined the difference in BNP levels between patients and controls.

Results: Log-transformed (Ln_{10}) BNP inversely correlated with Ln_{10}Ejection fraction (EF) in patients (p=0.005, r = -0.27) and all subjects combined (p<0.001, r = -0.55) with similar trend for Ln_{10}Fractional shortening (FS). BNP significantly (p < 0.001) positively correlated with TD E/e´ in patients (r = 0.46) and all subjects (r = 0.61) respectively. Tissue-Doppler E/e´ > 15 was associated (p=0.01) with higher BNP levels in the unadjusted and adjusted age, sex, body mass index and glomerular filtration rate models of patients with about four times Odd. EF < 40% and FS < 19% as well as EF < 50% and FS < 29% were significantly (p<0.001) associated with higher BNP levels in the unadjusted patient-control model. BNP levels were significantly (p<0.001) higher in patients (median, 412.5 pg/mL) than controls (median, 237.5 pg/mL).

Conclusions: BNP levels can predict systolic dysfunction and independently predict elevated left ventricular filling pressure (LVFP) amidst confounders. BNP levels of Nigerian-Africans are significantly higher in HF patients than controls. BNP and E/e´ provide a better assessment of HF in African HF patients with both systolic and diastolic dysfunctions.

Keywords: Africa, B-type natriuretic peptide, cardiomyopathy, heart failure

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Introduction

B-type natriuretic peptide (BNP) is a biologically active 32-amino acid polypeptide hormone co-secreted with inactive 76 N-terminal (NT) pro BNP from the ventricular cardiomyocytes in response to stretch of the ventricles from elevated left ventricular end-diastolic pressure (LVEDP) and volume overload associated with raised left ventricular filling pressure (LVFP) [1-12]. Both peptides have diuretic, natriuretic and hypotensive effects via inhibition of the renin-angiotensin-aldosterone system [9,13-19]. The strength of the BNP assays is its availability at point of care for rapid diagnosis and it is less influenced by age and renal function, unlike NT-proBNP [5]. It has a single approved cut-point for heart failure (HF) diagnosis with a vast knowledge base validating its usefulness in multiple clinical settings [5]. It is also the gold standard natriuretic peptide for clinical application [17,18].

More so, even though invasively measured LVFP from cardiac catheterization is the gold standard for estimating raised pulmonary venous pressures in dyspneic HF subjects, the feasibility of subjecting all HF patients to this technique may be a limitation [10] in centers where available in sub-Saharan Africa; coupled with the scarcity of such diagnostic facilities, as well as the few expertise in low-middle income countries like Nigeria. The tissue Doppler (TD) imaging is a technique that directly assesses myocardial velocities and has been shown from studies in European countries and the United States to non-invasively estimate LVFP as well as establish HF diagnosis in dyspneic patients [10,11,20,21]. It is however limited with respect to a "gray zone" as well as its low validity in HF with atrial fibrillation (AF), severe mitral stenosis/calcification, mitral valve repair/prosthetic valves, left ventricular assist devices, left bundle branch block and pacemaker induced ventricular rhythm [20].

BNP has been correlated to TD derived LVFP (E/e´) [10,11,20,21] and various structural and functional cardiac abnormalities [1-5,10]. It has also been shown to be affected by several factors inclusive of race, age, sex, obesity and deranged renal function amongst others [5,15,16,22], hence this could preclude its interpretation as a stand-alone test [10]. On account of the strengths and limitations of BNP and TD E/é individually, coupled with the high sensitivity and lower specificity of BNP in view of its documented association with multiple cardiac pathologies [10,20,21,23], it may become imperative to combine them for a more accurate estimation of LVFP in HF subjects.

There is, however, the paucity of published data on the relationship between BNP and TD derived assessment of HF in sub-Saharan Africans [2,22.] Therefore, this study was aimed to evaluate BNP's relationship to echocardiographic TD E/e´, left ventricular (LV) systolic functions and BNP predictors in patients and healthy controls as well as assess plasma BNP levels in a cohort of Nigerian-African HF subjects in comparison with healthy controls.

Methods

Study design

It was a comparative cross-sectional analytical study carried out between November 2015 and August 2016 among 184 subjects: 109 HF subjects and 75 healthy controls. Consecutively, the HF subjects whose etiologies were mainly hypertensive HF, peripartum cardiomyopathy and rheumatic valvular heart disease because of the predominance in our environment and other etiologies as they presented were prospectively enrolled from the accident and emergency, medical wards and cardiology clinic of the Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, North-West Nigeria. There were 75 adults randomly selected as controls from apparently clinically healthy and willing patient escorts and staff of the same 599 bedded tertiary facility.

Inclusion and exclusion criteria

Only subjects from the African black population were included. Adult decompensated HF patients >18 years in the New York Heart Association (NYHA) class II, III and IV HF [24] that satisfied the Framingham criteria for HF were included [25]. Subjects who had echocardiography and blood sampling done within 24 hours of enrolment were also included. Exclusion criteria included patients on 3 months history of guideline-directed medical therapy (GDMT) for HF (angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), aldosterone antagonists and β-blockers) as well as diuretics for preceding two weeks. Others excluded were HF from congenital heart disease; renal failure with estimated glomerular filtration rate (eGFR) < 60 mL/min by the Cockroft-Gault equation; [26] subjects with echocardiographic evidence of pericardial disease, severe mitral stenosis/calcification and hypertrophic cardiomyopathy. Concomitant respiratory diseases like chronic obstructive pulmonary disease and bronchial asthma (diagnosis based on patients' medical follow-up records); historical with electrocardiographic (ECG) evidence of atrial fibrillation or myocardial infarction and historical evidence of diabetes mellitus with fasting blood glucose (FBG) > 7 mmol/L were also excluded.

Healthy controls were included if > 18 years of age, non-smoker, non-diabetes (historically with FBG < 7 mmol/L), non-hypertensive (Blood pressure < 140/90 mmHg) and non-pregnant females clinically. Healthy subjects with abnormal echocardiogram, renal, cardiopulmonary and liver disease clinically were also excluded.

The study was approved by the Health Research Ethical Committee (HREC), ABUTH, Zaria, Nigeria with Ref No. ABUTHZ/HREC/K11/2015. It was carried out according to the Helsinki's Declaration and written informed consent was obtained fr om all participants.

Clinical and laboratory methods

Standardized medical history and data collection were by well-structured interviewer-administered questionnaires carried out by the author along with two trained assisting medical doctors. Clinical diagnosis of HF was based on the Framingham criteria which are universally utilized [25] and require the simultaneous presence of at least 2 major or 1 major and 2 minors [24,25]. Anthropometric measurements {weight, height & body mass index calculated in weight (kg)/height^2 (m^2)} and blood pressures were determined in all subjects by standard protocol [27]. Cardiovascular examination was done by two trained medical doctors confirmed by an experienced cardiologist (AO).

Plasma BNP *in-vitro* quantitative assay was done in one batch at the end of the study using the BNP Direct Enzyme-linked Immunosorbent Assay Kit by Elabscience Biotechnology Co. Ltd. with Lot No: AK0016JUL15068 and Catalog No: E-EL-H0598. The ELISA kit used a competitive ELISA assay method. The detection range of this kit was 31.25-2000 pg/mL and the coefficient of variation < 10%. The researcher, two research assistants, supervising consultants and all subjects were blinded to the BNP levels. The partition limit for BNP used in this study was 400 pg/mL [28-31].

The serum electrolyte, urea and creatinine and FBG were assayed using the Chenray 120 automated clinical chemistry auto-analyzer.

Echocardiographic measurement

Echocardiography was performed by an experienced consultant cardiologist (AO) (with over 10 years' experience) blinded to all clinical and BNP data using the SONOSCAPE SSI-18 2-D/3-Dimensional Doppler and color flow machine with tissue Doppler facility and a 3.5-megahertz convex probe. M-mode measurements of left ventricular functions were determined at end-diastole in the parasternal long-axis view; based on the American Society of Echocardiography (ASE) [32] recommendation with the subjects in the left lateral recumbent position. The average of three measurements was taken. The ejection fraction (EF) and fractional shortening (FS) were calculated automatically by the machine using the Teicholz calculation formula. The LVEF was also confirmed by visual estimation on multiple views by the experienced echocardiographer (normal LV systolic function was documented for EF ≥ 50% and LV systolic dysfunction for EF ≤ 50% and FS ≤ 29%) [9]. Systolic function was further classified thus: < 40% as heart failure with reduced ejection fraction (HFrEF); 40 - 49% as heart failure with mid-range ejection fraction (HFmrEF) and > 50% as heart failure with preserved ejection fraction (HFpEF) [24]. M-mode assessment was appropriate as most of the etiologies of HF in our population are due to cardiomyopathy-related or hypertensive causes [9].

Tissue doppler assessment

The pulse wave tissue Doppler imaging (TDI) was performed in the apical four-chamber view to acquire mitral annular velocities by pressing on the TDI and pulse wave buttons on the echocardiography machine. The sample volume was positioned at or 1 cm within the septal insertion sites of the mitral leaflets and adjusted within 5-10 mm to cover the longitudinal excursion of the mitral annulus in both systole and diastole [10,19]. Primary measurements were the systolic (S), early diastolic (e´) and late diastolic velocities (a´). The septal mitral annulus early diastolic e´ velocity was used. The LVFP was determined by manually calculating the ratio of mitral inflow E velocity to TD derived e´ velocity (E/e´) [10,11,20,28]. Using the septal E/e´ ratio, a ratio < 8 was regarded as normal LVFP while > 15 was regarded as elevated diastolic LVFP [10,20].

Statistical analysis

Data was validated and analyzed by SPSS version 25-software (IBM). The normality of the distribution of data was checked via the Kolmogorov-Smirnov test. Skewed numerical data was presented as median and interquartile range (IQR) with 25th and 75th percentiles considered. Comparison between patients and controls as well as BNP levels between males and females was by the Mann-Whitney U test. Categorical variables were presented as frequency and percentages with comparisons made via Chi-square (X^2) test. BNP levels were recoded into four classes for the patient group viz: < 100 pg/mL as 1; 100 - 400 pg/mL as 2; > 400 - 500 pg/mL as 3 and > 500 pg/mL as 4. Likewise, same was also recoded into five classes for the control group viz: < 100 pg/mL as 1; 100 - 200 pg/mL as 2; 200 - 300 pg/mL as 3; 300 - 400 pg/mL as 4 and 400 - 500 pg/mL as 5. This was done to determine the frequency of distribution of BNP levels within the patients and healthy controls respectively. LVFP (E/e´) was recoded into three different variables viz: < 8 as 1; 8 - 15 as 2 and > 15 as 3 as well as two different variables viz: < 8.0 as 1 and 8 - 15 as 2. Kruskal-Wallis test with Pairwise comparison was used to determine the BNP levels in patients in relation to the three variable recoded E/e´, while Mann-Whitney U test was used to determine the difference in mean rank of BNP levels in controls in relation to the two variable recoded E/e´. Plasma BNP was log-transformed and

correlated with log-transformed EF and FS, E/e´ as well as age, BMI, GFR and sex using Pearson's correlation analysis in patients as well as all subjects combined. BNP being the dependent variable was recoded thus: < 400 pg/mL as 0 and > 400 pg/mL as 1, while E/e´ was transformed into two variables viz: 8 - 15 as 2 and > 15 as 1 for patient group, control group and all subjects respectively. Similarly, LVEF was recoded thus: < 50% as 1 and > 50% as 2 as well as 40% as 1 and > 40% as 2; LVFS was recoded thus: < 29% as 1 and > 29% as 2 as well as < 19 % as 1 and > 19% as 2. BMI was recoded as 1 if < 25 kg/m^2 and 2 if > 25 kg/m^2 while age was recoded as 1 if < 40 years and 2 if > 40 years. GFR was recoded as 1 if < 90 mls/min and 2 if > 90 mls/min. Binary Logistic Regression analysis was performed to further assess the relationship between dependent variable BNP and recoded LV systolic functions (EF & FS), TD E/e´ as well as recoded age, sex, BMI and GFR in patients as well as all subjects. This was done in the unadjusted model in which recoded candidate variables mentioned above were added individually to a model containing recoded plasma BNP as the dependent variable, with those candidate variables as covariates. Subsequently, this was age, sex, BMI and GFR adjusted in a multivariate manner to determine any further relationships. The level of significance was assumed to be $p \leq 0.05$ at 95% Confidence Interval.

Table 1. Socio-demographic and clinical characteristics of the study population

Parameters	Options	Total (n=184)	Controls (n=75)	Patients (n=109)	P-value
ǂ **Age**	Mean	43.0 ± 13.6	41.7 ± 11.8	43.9 ± 14.6	0.33
	< 30 years	33 (17.9%)	13 (17.3%)	20 (18.3%)	0.25
	30 - 45 years	60 (32.6%)	28 (37.3%)	32 (29.4%)	
	45 - 65 years	75 (40.8%)	31 (41.3%)	44 (40.4%)	
	> 65 years	16 (8.7%)	3 (4.0 %)	13 (11.9%)	
Sex	Male	59 (32.1%)	30 (40.0%)	30 (27.5%)	0.06
	Female	125 (67.9%)	45 (60.0%)	79 (72.5%)	
Tribe	Hausa/Hausa-Fulani	143 (77.7%)	51 (68.0%)	92 (84.4%)	0.007*
	Igbo	8 (4.3%)	6 (8.0%)	2 (1.8%)	
	Yoruba	15 (8.2%)	11 (14.7%)	4 (3.7%)	
	Others	18 (9.8%)	7(9.3%)	11 (10.1%)	
Type of HF	HHF		0.0 (0.0%)	55 (50.5%)	
	PPCF		0.0 (0.0%)	27 (24.8%)	
	RVHD		0.0 (0.0%)	15 (13.8%)	
	DCM		0.0 (0.0%)	12 (11%)	
Duration of HF	<1 Year		0.0 (0.0%)	60 (55%)	
	1-3 Years		0.0 (0.0%)	44 (40.4%)	
	3-5 Years		0.0 (0.0%)	03 (2.8%)	
	>5 Years		0.0 (0.0%)	02 (1.8%)	
NYHA	I		0.0 (0.0%)	0.0 (0.0%)	
	II		0.0 (0.0%)	43 (39.4%)	
	III		0.0 (0.0%)	35 (32.1%)	
	IV		0.0 (0.0%)	31 (28.4%)	
ǂ **SBP (mmHg)**		119.9 ± 20.4	119.8 ± 10.3	120.0 ± 25.9	0.73
ǂ **DBP (mmHg)**		81.9 ± 16.0	77.2 ± 7.5	85.1 ± 19.2	0.001**
ǂ **BMI (Kg/m^2)**		24.3 ± 4.5	25.7 ± 4.0	23.4 ± 4.6	<0.001**

ǂMann-Whitney U test for numerical variables. Chi-Square analysis for continuous variables. Categorical variables presented as absolute values and percentages.
*Level of significance at p≤0.01. **Level of significance at p≤0.001.
HF: Heart failure, NYHA: New York Heart Association Classification of HF, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HHF: Hypertensive heart failure, PPCF: Peripartum cardiomyopathy, RVHD: Rheumatic valvular heart disease, DCM: Dilated cardiomyopathy.

Results

The mean age of the study population was 43.0 ± 13.5 (Mean ± SD) years with no significant (p=0.33) difference between patients and controls. There were predominantly females in both groups with no sex differences (p=0.06). Hausa's and Hausa-Fulani tribe predominated significantly (p=0.007) when compared to other tribes. Hypertension was the commonest cause of heart failure (HF)

followed by peripartum cardiac failure (PPCF), rheumatic valvular heart disease (RVHD) and dilated cardiomyopathy (DCM), respectively [Table 1]. There were more subjects in the NYHA II followed by NYHA III and NYHA IV class of HF [Table 1]. The combined representation of the more severe forms of HF (NYHA III and IV), 66 (60.5%) outweighed that of NYHA II. There was no difference (p=0.73) in systolic blood pressure (SBP) between the patients and controls. The mean BMI of patients was significantly (p<0.001) lower than that of controls [Table 1].

The creatinine, fasting blood glucose and packed cell volume (PCV) did not differ significantly (p>0.05) between both groups [Table 2]. However, the glomerular filtration rate was significantly (p<0.001) lower in patients than controls [Table 2]. There were significantly (p<0.001) higher BNP levels {median (IQR), 412.5 (296.5-521.8 pg/mL} in HF patients than controls {median (IQR), 237.5 (200-275) pg/mL}. The left ventricular systolic functions were significantly (p<0.001) higher in controls than patients. The TD E/e´ and left atrial dimensions were significantly (p<0.001) higher in patients than controls [Table 2]. BNP levels were higher in females than males amongst the controls and patients respectively [Table 2].

Table 2. Laboratory, echocardiographic left ventricular systolic function and tissue-doppler derived left ventricular filling pressure parameters between HF patients and normal healthy controls

Parameters	Control	Interquartile range		Patient	Interquartile range		Total	P-value
	(n=75) (z=%)	1st	3rd	(n=109) (x=%)	1st (y=%)	3rd (z=%)	(n=184)	
Packed cell volume (%)	40.00 ± 5.50			39.50 ± 5.00			39.80 ± 5.50	0.08
Urea (mmol/L)	4.20 ± 1.10			4.80 ± 1.40			4.60 ± 1.30	0.004**
Creatinine (µmol/L)	69.00 ±14.40			70.00 ± 19.10			69.40 ±17.30	0.91
Glomerular filtration rate (mls/min)	109.20±17.30			91.10 ± 18.40			98.50 ±20.00	<0.001*
Fasting blood glucose (mmol/L)	5.60 ± 0.90			5.50 ± 1.10			5.50 ± 1.00	0.59
‡**B-type natriuretic peptide (pg/mL)**	237.50	200.0	275.00	412.50	296.25	521.75	298.75	<0.001*
Male	218.75 [a †]			362.00 [c]				0.003** †
Female	250.00 [b]			425.00 [d]				0.05* ¶
‡**Ejection fraction (%)**	67.00	61.00	74.00	34.00	27.00	41.00	43.50	<0.001*
§**LVEF <40%[x]; 40-49%[y]; ≥50%[z]**	75 (100) [z]			74 (67.9) [x]	28(25.0)[y]	6(6.4)[z]		
‡**Fractional shortening (%)**	35.00	30.0	39.0	16.00	12.50	20.00	21.00	<0.001*
‡**Tissue doppler E/e´(LVFP)**	6.60	5.80	8.0	16.50	11.90	21.30	11.30	<0.001*
‡**Tissue Doppler Septal e´ (mm/s)**	0.10	0.09	0.12	0.05	0.04	0.07	0.07	<0.001*
‡**Transmitral E ratio**	0.69	0.58	0.83	0.89	0.69	1.14	0.79	<0.001*
‡**Left atrial dimension (cm)**	3.00	2.66	3.33	4.50	4.05	5.16	3.79	<0.001*

Mean ± SD. ‡Expressed as median and interquartile range (IQR). Difference between parameters of patients and controls by the Mann-Whitney U test. Kruskal-Wallis test for difference in BNP levels between sexes. §Grading of systolic function. [x-z]Percentage distribution of systolic function among patients and controls. [a-b, c-d] Mean ranks in a column without a common superscript letter differs. †Pairwise comparison between a and b significant. ¶ Pairwise comparison between c and d significant.

*Level of significance at p≤0.01. **Level of significance at p≤0.001.

HF: Heart failure, E/é: Early mitral inflow velocity to tissue Doppler early mitral é velocity, IQR: Interquartile range, LVFP: left ventricular filling pressure, mm/s: millimeters per second, cm: centimeters.

Additionally, two thirds of HF subjects had HFrEF followed by HFmrEF and only few subjects had HFpEF [Table 2]. Almost half, 50 (45.7%) had BNP levels within the “gray zone” (100 - 400 pg/mL) with 28 (25.7%) subjects between 400 - 500 pg/mL. There were 31(28.4%) HF subjects with BNP levels > 500 pg/mL, however, none had BNP levels < 100 pg/mL (Data not shown). No control subjects had BNP levels < 100 pg/mL as well as > 500 pg/mL. Almost all fell within the “gray zone” (100 - 400 pg/mL). Further sub-analysis showed that more than half, 44 (58.7%) of the controls had BNP levels between 200 - 300 pg/mL followed by 27 (29.3%) with levels between 100 - 200 pg/mL and 7 (9.3%) with levels between 300 - 400 pg/mL. Only 2 (2.7%) had BNP levels > 400 pg/mL (Data not shown).

There were few HF subjects with E/e´ within normal (< 8) with a median BNP level of 300 pg/mL [Table 3]. Likewise, 40 (36.7%) HF subjects had their median E/e´ within the "gray zone" (8 - 15) with a median BNP level of 356.3 pg/mL. The highest median BNP level (475.0 pg/mL) was found in HF subjects with elevated LVFP (> 15) which constituted more than half of the subjects [Table 3]. The Kruskal-Wallis test showed a significant (p<0.001) difference between the three classes of LVFP (E/e´). The Pairwise comparison showed the difference (p<0.001) existed between the mean ranks of HF subjects with E/e´ within the normal zone and the “gray zone” as well as elevated LVFP respectively as well as those within the “gray zone” and elevated LVFP [Table 3]. The mean ranks of BNP levels differed

significantly (p<0.001) between the three classes of LVFP using the Kruskal-Wallis test. The actual difference existed in BNP levels of HF subjects with normal E/e´ and elevated E/e´ as well as those within the "gray zone" and elevated E/e´ (p<0.001, respectively) [Table 3].

Table 3. BNP levels in relation to tissue Doppler derived left ventricular filling pressure in heart failure patients and healthy controls

Variables	LVFP (E/é)	Proportion	Median E/é	LVFP Min – Max	p-value	Median BNP	BNP levels Min – Max	P-value
Patients (n=109)	† < 8	6.0 (5.5%)	7.3[a]	5.4 - 7.8	< 0.001**†	300.0[da]	162.5 - 537.5	< 0.001*₸
	† 8 – 15	40.0 (36.7%)	11.7[b]	9.2 - 14.8	< 0.001**j	356.3[ea]	137.5 - 1212.5	0.50
	† >15	63.0 (57.8%)	20.2[c]	15.1 - 51.3	< 0.001**t	475.0[f]	187.5 - 1625.0	< 0.001*¶
	Total	109.0 (100%)	16.5	5.4 - 51.3		418.5	137.5 - 1625.0	
Controls (n=75)	ǂ < 8	59.0 (78.7%)	6.2	4.3 - 8.0[b]	< 0.56	237.5	118.5 - 475[c]	0.18
	ǂ 8 – 15	16.0 (21.3%)	10.2	8.3 - 12.5[b]		250.0	187.5 - 425[c]	
	> 15	0.0 (0.0%)	0.0	0.0 - 0.0		0.0	0.0 - 0.0	
	Total		6.6	4.3 - 12.5		237.5	118.5 - 475	

Data expressed as median and minimum and maximum levels. †Kruskal-Wallis analysis with the pairwise comparison. ǂMann-Whitney U test for controls. [a-c, d-f]Mean ranks in a column without a common superscript letter differs. † j t Pairwise comparison between a and c, a and b as well as b and c significant respectively. ₸ ¶Pairwise comparison between d and f as well as e and f significant respectively. †Pairwise comparison between g and h significant.[a-a, b-b, c-c]Mean ranks in a column without a common superscript letter do not differ.
LVFP: Left ventricular filling pressure, E/é: Early mitral inflow velocity to tissue Doppler early e' velocity, Min: Minimum, Max: Maximum, BNP: B-type natriuretic peptide.

The control group had no subjects with elevated E/e´ and 19 (21.3%) subjects had E/e´ within the "gray zone". Most of the controls had normal E/e´ [Table 3]. There was also no significant (p=0.56) difference in LVFP amongst the controls within normal and the "gray zone" using the Mann-Whitney U test. Similarly, no significant (p=0.18) difference existed in mean ranks of BNP levels in controls who had their E/é within normal and those within the "gray zone" [Table 3].
Log-transformed plasma BNP was negatively correlated to log-transformed LVEF (p=0.005) and FS (p=0.004) in the HF subjects using Pearson's Correlation analysis. It also showed a negative correlation to LVEF (r=-0.55, p<0.001) and a similar correlation to LVFS in all the subjects [Table 4]. On the contrary, BNP showed significant (p<0.001) positive correlation to E/e´ in the HF subjects as well as all the subjects combined [Table 4].

Table 4. Correlation between log-transformed plasma BNP (Ln_{10}BNP) and log-transformed (Ln_{10}) echocardiographic left ventricular systolic function, tissue-doppler derived left ventricular filling pressure and other parameters

Parameters	Total (n=184)		Control (n=75)		Patients (n=109)	
Ln_{10}BNP	**r**	**P-value**	**r**	**P-value**	**R**	**P-value**
Ln_{10}Ejection fraction (%)	- 0.55	< 0.001***	0.09	0.46	-0.27	0.005*
Ln_{10} Fractional shortening (%)	- 0.55	< 0.001***	0.10	0.38	-0.27	0.004*
Ln_{10} Tissue Doppler E/e´ (LVFP)	0.61	< 0.001***	-0.14	0.22	0.46	< 0.001**
Age (Years)	0.26	< 0.001**	0.09	0.42	0.35	< 0.001**
Sex	0.24	0.001**	0.33	0.003**	0.23	0.01*
Ln_{10}Body mass index (Kg/m^2)	- 0.28	< 0.001	0.03	0.77	-0.17	0.08
Ln_{10}Glomerular filtration rate (mls/min)	- 0.36	< 0.001***	-0.04	0.76	-0.23	0.02*
Ln_{10}Duration of heart failure					-0.47	< 0.001**

Pearson's Correlation Analysis.
*Level of significance at p≤0.05. **Level of significance at p≤0.01. *** Level of significance at p≤0.001.
Ln_{10}: Log-transformed variable, r: Correlation coefficient, E/e´: Early mitral inflow velocity to tissue Doppler early e´ velocity, LVFP: Left ventricular filling pressure.

Furthermore, BNP was significantly (p<0.001) positively correlated to age in the patients and all subjects (p=0.01) as well as BMI (p=0.01) in all subjects. Female sex was positively related to BNP in both controls (p=0.003) and patients (p=0.01) as well as all subjects combined (p=0.001). The estimated GFR was significantly (p<0.001) negatively correlated to BNP levels in all subjects as well as the patient group only (p=0.02) with similar findings in relation to the log-transformed duration of HF [Table 4].

Further assessment of the relationship between BNP and echocardiographic LV systolic, TD derived LVFP and other parameters were determined by the Binary Logistic Regression analysis in the unadjusted model [Table 5]. Elevated plasma BNP (> 400 pg/mL) was not associated with LVEF < 40% (p>0.05) as well as LVFS < 19% (p=0.35) in the unadjusted patient group. However, this was significant (p<0.001) in all subjects with 6 times Odd of systolic dysfunction being associated with higher BNP levels. A higher partition limit of systolic ejection fraction (EF < 50%) and LVFS (< 29%) also showed no significant (p>0.05) association with elevated BNP levels in the unadjusted patient group [Table 5]. However, this was significant (p<0.001) with much higher Odds in all subjects combined [Table 5]. In addition, TD E/e´ showed significant (p=0.003 and p<0.001) relationship to elevated BNP levels in the unadjusted patient group as well as all subjects respectively [Table 5]. Other parameters associated with elevated BNP levels were increasing age (p=0.01 and p=0.04) and female sex (p=0.002 and p=0.002) in both patients and all subjects respectively. Lower BMI (< 25kg) and lower GFR (< 90 mls/min) were only significant (p=0.01) in the combined patient-control model with no statistical significance (p>0.05) in the patient group only [Table 5].

Table 5. Association of plasma BNP with echocardiographic LV systolic, tissue doppler derived LV filling pressure and other parameters in the unadjusted model of the patient group as well as combined patient and control group

Parameters Unadjusted model	Dependent variable BNP Patient (n=109)			Dependent variable BNP Total (n=184)		
	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI
†Ejection fraction (<50%)	0.51	1.69	0.36 - 7.93	< 0.001***	14.96	5.98 - 37.43
Ejection fraction (<40%)	0.35	1.47	0.66 - 3.29	< 0.001***	6.24	3.10 - 12.19
†Fractional shortening (<29%)	0.35	0.92	0.86 - 0.99	< 0.001***	11.79	4.42 - 31.14
Fractional shortening (<19%)	0.82	0.81	0.13 - 5.04	< 0.001	6.24	3.10 - 12.19
‡†Estimated LVFP (E/é)	0.003**	3.58	1.56 - 8.23	< 0.001***	3.57	1.61 - 7.94
Body mass index-BMI (<25 Kg/m²)	0.94	0.97	0.43 - 2.16	0.02*	2.12	1.12 - 4.01
Age (>40 Years)	0.01*	0.38	0.17 - 0.82	0.04*	0.51	0.27 - 0.96
Sex (Female)	0.002**	0.35	0.12 - 0.85	0.002**	0.31	0.15 - 0.66
Glomerular filtration rate (<90 mls/min)	0.26	1.50	0.72 - 3.32	0.01*	2.38	1.27 - 4.48

Binary Logistic Regression Analysis. Data presented as Odds Ratio with 95% Confidence Interval (CI).
*Level of significance at p ≤ 0.05. **Level of significance at p ≤ 0.01. ***Level of significance at p ≤ 0.001.
‡n=103 for the patient group. †n=122 for both patients and control groups combined.

Importantly, when adjusted for age, sex, BMI and GFR in the multivariate Binary Logistic Regression analysis, the LV systolic functions were not significantly associated with elevated BNP levels in the patient group as well as all subjects combined. However, TD E/e´ was significantly (p=0.01) associated with elevated BNP levels in both patients and all subjects respectively with about a four times Odd ratio [Table 6]. Other parameters were no longer significantly (p>0.05) associated with elevated BNP levels following the adjustment, except female sex in both patient groups (p=0.02) as well as all subjects (p=0.01) [Table 6].

Table 6. Association of plasma BNP with echocardiographic LV systolic, tissue Doppler-derived LV filling pressure and other parameters in the adjusted model of the patient group as well as combined patients and control group

Parameters Unadjusted model	Dependent variable BNP Patient (n=109)			Dependent variable BNP Total (n=184)		
	P-value	Odds ratio	95% CI	P-value	Odds ratio	95% CI
Ejection Fraction (<50%)	0.99	NS	NS	1.00	NS	NS
Ejection Fraction (<40%)	0.75	0.69	0.07 - 6.59	0.77	0.71	0.08 - 6.74
Fractional shortening (<29%)	0.99	NS	NS	1.00	NS	NS
Fractional shortening (<19%)	0.65	1.69	0.18-16.07	0.61	1.79	0.19 - 16.88
‡†Estimated LVFP (E/é)	0.01*	3.55	1.31 - 9.62	0.01*	3.82	1.42 - 10.27
Body mass index-BMI (<25 Kg/m²)	0.92	0.95	0.36 - 2.53	0.78	0.88	0.36 - 2.18
Age (>40 Years)	0.30	0.59	0.23 - 1.60	0.25	0.58	0.23 - 1.47
Sex (Female)	0.02*	0.30	0.11 - 0.81	0.01*	0.28	0.11 - 0.73
Glomerular filtration rate (<90 mls/min)	0.84	0.91	0.35 - 2.33	0.76	0.87	0.35 - 2.13

Multivariate Binary Logistic Regression Analysis. Data presented as Odds Ratio with 95% Confidence Interval (CI).
*Level of significance at p≤0.05.
‡n=103 for the patient group. †n=122 for both patients and the control group. Adjusted for body mass index, age, sex and glomerular filtration rate, NS: Non-significant.

Discussion

This study is unique as it is the first to report on BNP in relation to tissue Doppler in HF in sub-Saharan Africa as studies in this direction are lacking in the black African population. BNP showed weak to moderate correlation to TD E/e´ in patients and all subjects respectively similar to previous studies [34-36]. The weak correlation demonstrated by Dokainish et al was with pulmonary capillary wedge pressure in critical care patients with indwelling pulmonary artery catheters [36]. The weak to moderate correlation observed in this study despite significantly higher BNP levels in the HF subjects with elevated filling pressures may be attributed to an acute rise in pressure as most of the subjects were in the NYHA III and IV HF indicative of advanced and more severe forms of HF. It has been reported that such weak correlations occur if pressures rise acutely or LVFP is only mildly elevated [37]. Some other reports showed that in acute decompensated HF where baseline BNP and NT-proBNP levels are markedly elevated, the correlation between peptide levels and filling pressure is weaker especially in advanced HF or unselected intensive care patients [34,37].

Consistent with previous reports [10,21], HF patients with normal LVFP had the lowest BNP levels while those with elevated filling pressure had the highest BNP levels. This was further supported by the TD E/e´ which was higher in patients than controls as well as the positive correlation of BNP to E/e´. This means that with worsening HF and reduction in compliance from diastolic dysfunction consequently resulting in elevated LVFP's, the ventricular myocytes respond to pressure/volume overload and wall stress by releasing more BNP [33]. This also relates to the state of neurohormonal over-drive, renin-angiotensin-aldosterone and cytokine system activation in patients with chronic HF irrespective of the presence of LV systolic dysfunction [33].

Furthermore, more than a third of the HF patients had their E/e´ ratio within the “gray zone” hence the assessment of diastolic dysfunction may not be complete without other parameters viz-a-viz: the left atrial volume indexed to body surface area (BSA); of which if < 32mL/m^2 rules out raised left atrial pressure as well as pulmonary venous flow assessment; in which if the systolic wave is greater than the diastolic wave, a normal LVFP is implied [10,20]. However, these were not assessed in this study. Hence, in this case, a rapid assay of BNP can, therefore, detect diastolic dysfunction [33]. More so, the association between BNP and E/e´ was stronger in subjects (OR=2.15) within the "gray zone" of the patient group (Data not shown). Some experts reported that it's been suggested that a BNP level of >200 pg/mL was required to confirm HFpEF in patients with E/e´ in the “gray zone [10,33]. Furthermore, the unadjusted Logistic Regression Analysis showed a significant relationship of BNP with E/e´ with high Odds in the patient group.

On a further note, BNP showed an inverse correlation to LVEF and LVFS. This suggests that BNP levels are higher in HFrEF and lower in patients with higher systolic functions, similar to previous reports [1-5,9,12,13,17]. It may also add to support the evidence from existing data that the rise in BNP levels is worse in HFrEF (especially as more than two-thirds of the patients had HFrEF) than HF with mid-range ejection fraction (HFmrEF) and or HF with preserved ejection fraction (HFpEF); possibly reflecting an association with greater pathology in patients presenting with HFrEF. This relationship was significant ($p<0.001$) in the unadjusted Binary Logistic model with high Odds for LV systolic dysfunction. This signifies the ability of BNP to predict systolic dysfunction when distinguishing HF patients from an apparently healthy population.

However, it was observed that following multivariate age, sex, BMI and GFR adjusted BNP levels; there was no longer a significant association of elevated BNP to systolic dysfunction except TD E/e´. This may be attributed to the selection criteria inclusive of heterogeneity of the population studied viz-a-viz: patients with abnormal and normal EF, combined LV systolic and diastolic dysfunction, patient and healthy control models, a variety of diagnosis, the greater proportion with worsening HF as well as the younger age group studied [10]. It is imperative to deduce from this study that TD E/e´ is an independent predictor of elevated BNP levels as it was significantly associated with BNP in both unadjusted and adjusted Binary Logistic Regression models similar to other studies [11,34-39].

Similar to previous global reports in the white population, BNP levels were higher in HF patients than controls [1-3] which is consistent with findings on the equivalent biomarker (NT-proBNP) in Nigeria [9,40]. This confirms previous reports showing that the failing heart triggers the release of BNP and NT-proBNP in response to ventricular myocardial changes. The high levels found in this study were most likely cardiac in origin because of the significantly ($p<0.001$) higher levels in relation to healthy controls. More so, diseases that may have elevated the value such as COPD, asthma, severe renal failure, AF and diabetes were excluded abinitio [4,5,15,16,22].

Consistent with previous reports, the BNP levels were higher in females than males [1-9,22]. Females have been shown to have higher BNP levels than males attributed to the stimulatory effect of estrogen on atria natriuretic peptide (ANP) and BNP productio n as opposed to the suppressive androgenic effect [5,22,41]. Several studies have shown that physiological factors like race, age, sex, obesity and renal derangement affect peptide levels which were confirmed by this study in a black African population [20,33,41-43]. This study showed that BNP was higher with increasing age. Age-related changes such as decreased myocardial function, increased ventricular stiffness, myocardial fibrosis and decreased natriuretic peptide clearance associated with advancing age has been established [33]. The weak correlation and lower Odds of age > 40 years being associated with elevated BNP levels may be attributed to the younger age group

studied (fourth decade) contrary to the elderly age group in industrialized nations in which similar studies were done. The elderly group which is the group expected to show great changes with BNP were represented by very few subjects.

Similar to previous reports, BNP levels were higher with lower body mass index (BMI) and vice-versa. Obesity has been shown to be associated with lower BNP levels as the natriuretic peptide clearance receptors (NPR-C) are more expressed in adipose tissues, resulting in increased receptor-mediated clearance of BNP and consequently lower levels [30,33]. Hyperinsulinemia has also been linked to lower natriuretic peptide levels in obesity and BNP has been documented to induce lipolysis and may underlie the cachexia in patients with advanced HF [30]. This may further explain the difference in BMI between the HF patients and controls.

Similar to the study by McCullough et al [5], there was a weak inverse correlation of BNP to estimated GFR in the patients. I t has been reported that BNP and NT-proBNP levels can be elevated in the setting of renal dysfunction due to volume overload, even though NT-proBNP has been found to be more associated with higher inverse correlation values ($r \geq 6$) [5,10-11]. However, the relationship was no longer significant in both unadjusted and adjusted regression models; possibly due to the exclusion of subjects with severe renal dysfunction.

Additionally, BNP was inversely correlated to HF duration, signifying that the longer the chronicity of HF, the lower the BNP levels. This is expected, as it has been documented that some patients with end-stage HF have very low BNP levels probably because of the effect of exhaustion; the ventricles fail to synthesize and release the peptide [31].

Limitations

There are more recent innovations of echocardiographic techniques, for instance, the speckle tracking spectral Doppler as well as the invasive method of LVFP assessment which were not available in the center of study. However, TD derived markers of raised LVFP have been well validated and utilized universally [10,11,20,21,33-39,47]. The ACE/ESC recommended Simpson's echocardiographic method for determining LVEF was not used, however, the M-mode assessment was appropriate as most of the etiologies of HF in our population are due to cardiomyopathy-related or hypertensive causes [9].

Conclusion and Recommendations

This study shows that BNP levels can predict systolic dysfunction and independently predict elevated LVFP amidst confounders. BNP levels of Nigerian-Africans are significantly higher in HF patients than controls. BNP and TD E/é provide a better assessment of HF in African HF patients with both systolic and diastolic dysfunctions.

It is therefore recommended that in third world countries Nigeria inclusive, BNP assay kits and point of care systems should be made readily available in the laboratories and emergencies for rapid HF diagnosis. BNP should be combined with echocardiographic TD imaging for better assessment of HF in Nigerian-Africans especially in subjects within the "gray zone" of LVFP.

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Conflict of interest

The authors declare that they have no competing interests with regards to authorship and/or publication of this paper.

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