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Original Article

Clinical utility of left ventricular strain, wall stress and serum brain natriuretic peptide levels in chronic hemodialysis patients

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ABSTRACT

Background: Left ventricular (LV) global longitudinal strain (GLS) reliably assesses LV systolic function. The precise relation between LV wall stress and serum Brain natriuretic peptide (BNP) concentrations in hemodialysis (HD) patients needs to be clarified. BNP levels are raised in patients with end-stage renal disease (ESRD) and could reflect LV impairment among HD patients.

Aim of this work: This study sought to evaluate the clinical utility of LV-GLS, wall stress and serum BNP levels in chronic HD patients. The correlations between BNP levels with both LV wall stress and LV-GLS were assessed.

Patients and methods: 30 ESRD patients on regular HD {categorized into 15 patients with LV ejection fraction (EF) $\leq$ 50% and 15 patients with LV EF > 50%} and 15-age matched healthy subjects were included. LV function and structure were assessed by conventional echocardiography including LV meridional wall stress (LVMWS), LV mass index (LVMI) and 2-dimensional speckle tracking echocardiography for determination of LV-GLS. Serum BNP levels were evaluated after HD session.

Results: There were significant increase of LVMSW (189.2 ± 81 vs. 72.2 ± 20.6 dynes/cm^2 × 1000, P < 0.0001), higher levels of BNP (1238 ± 1085.5 vs. 71 ± 23.4 pg/ml, P < 0.0001) while LV-GLS was significantly reduced (15.1 ± 3.1 vs. 20.8 ± 1.7%, P < 0.0001) in HD patients compared to controls. Higher values of LVMWS (246.9 ± 67.5 vs. 131.5 ± 43.6 dynes/cm^2 × 1000, P < 0.0001) and BNP (1925.4 ± 1087 vs. 550.5 ± 496.5 pg/ml, P < 0.0005) with further impairment of LV-GLS (13.8 ± 2.5 vs. 16.4 ± 5.4%, P < 0.05) were found in patients with LV EF $\leq$ 50% than those with LV EF > 50%. Serum levels of BNP were positively correlated with LVMI (r = 0.896, P < 0.0001) and LVMWS (r = 0.697, P < 0.0001) but negatively correlated with LV-GLS (r = −0.587, P < 0.0001).

Conclusion: LV-GLS and LVMWS are useful imaging markers for detection of LV dysfunction in HD patients. Serum BNP level is influenced by LV structural abnormalities and suggested to be a crucial hemodynamic biomarker in those patients.

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1. Introduction

Cardiovascular disease (CVD) is a main reason of mortality and morbidity in patients with chronic kidney disease (CKD).[1] Impairment of left ventricular (LV) morphology and functions are correlated with a poor cardiovascular prognosis and frequently identified in CKD patients.[2] In those patients, traditional echocardiography is unable to detect early deterioration of cardiac function.[2]

Ejection fraction (EF) remains preserved in the most of CKD patients inspite of those patients may have high prevalence of CVD and progressive symptoms of heart failure (HF).[3] Moreover, several researches have reported that less than a third of patients with end stage renal disease (ESRD) demonstrated an evidence of LV systolic dysfunction.[4,5] However, this contradiction is related to the complex pathophysiology of CVD in CKD alongside the technical limitations of EF measurement as an additional factor. Standard method for EF measurement entails precise tracing of endocardial border and is operator, volume and load dependent resulting in a limited reproducibility.[6,7]

There is a growing interest in the current literature for other echocardiographic modality to assess of LV function. This is of definite appropriateness to the CKD patients who exhibit progressive

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cardiac remodeling. Global longitudinal strain (GLS) assessed using semi-automated speckle-tracking echocardiography (STE) is a novel technique for detecting and quantifying subtle impairment in LV systolic function.[8,9] GLS reflects the longitudinal contraction of the myocardium and its accuracy has been validated against tagged magnetic resonance imaging (MRI).[10] This method is operator independent, more reproducible than EF, easily measured and integrated to standard echo-Doppler study.[10]

Several reports show that measuring GLS by automated function imaging software is robust, objective, efficient, and reproducible and it can measure LV systolic function promptly.[8,9]

B-type natriuretic peptide (BNP) is synthesized in the ventricular myocardium in response to ventricular stretching and wall stress.[11] Serum BNP levels are associated with the severity of HF and LV function, and considered to be useful markers for diagnosis, management, and prognosis in patients with normal renal function.[11] The prognostic potential of serum BNP concentrations has been investigated in several studies on patients with CKD patients and those on hemodialysis.[12]

Although CKD is frequently associated with disturbances in CV hemodynamics, the mechanisms responsible for the increase of BNP circulating levels in this condition still remain to be elucidated.[13] Additionally, renal failure per se has also been shown to affect the circulating levels of BNP, a condition not significantly altered by renal replacement therapy.[14]

There is an evidence suggests that circulating BNP levels could reflect the LV end-diastolic wall stress both in patients with systolic and diastolic HF, a correlation maintained even in the presence of significant renal failure.[15] However, little is known about the association of serum BNP levels with LV GLS and LV wall stress in CKD patients on regular hemodialysis.

We aimed to evaluate the clinical utility of LV-GLS, wall stress and serum BNP levels in chronic hemodialysis patients. The correlations between BNP levels with both LV wall stress and LV-GLS were assessed.

2. Patients and methods

2.1. Patients

This cross sectional observational study was conducted on 30 ESRD patients on regular hemodialysis (HD) through arteriovenous fistula (AVF) and 15-age matched healthy subjects. Patients were allocated from the nephrology unit of internal medicine department, Alzahraa university hospital, in the period from November 2016 to May 2017.

Written informed consents were taken from all patients. They were receiving bicarbonate base dialysate using low flux dialyzer with an average blood flow 300–350 ml/min, 3 times/week each session for 4 h duration. All studied patients aged over 18 years of age.

We excluded patients with acute coronary syndrome in the past 6 months, moderate to severe valvular heart disease, chronic atrial fibrillation, congenital heart disease, pregnancy, liver failure, chronic systemic inflammatory conditions, and inadequate echocardiography imaging quality.

2.2. Methods

Demographic and clinical data including comorbidities, medical history, and current cardiovascular medication were obtained by careful review of each patient's medical record

1. **Evaluation of LV wall stress, functions and hypertrophy using transthoracic echocardiography**

Both patients and control persons were evaluated with transthoracic echocardiography (TTE). TTE was done immediately after the dialysis session.

TTE examination was performed using Vivid E9 GE, Vingmed ultrasound, Horten Norway echo machine with (M5Sc) matrix probe (1.5–3.6 MHz). Comprehensive trans-thoracic M-mode, 2Dimensional (2D), and Doppler were done in standard views (parasternal long axis, parasternal short axis, apical four & two chamber and long axis views). Images were obtained at a frame rate of 50 to 70 per second, and saved for off-line analysis (EchoPac 201, General Electric Medical Systems).

The effect of afterload and preload on GLS was evaluated using LV wall stress. LV meridional wall stress (LVMWS) was assessed using validated formula: LVMWS = [0.334 × systolic BP × LV end diastolic diameter]/[LV wall thickness in end diastole × (1 + LV wall thickness in end diastole/LV end diastolic diameter)] dynes/cm^2 × 10,000.[16]

Cardiac chamber measurements were made as suggested by the American Society of Echocardiography, including left atrial (LA) diameter, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), end-diastolic interventricular septum thickness (IVS), end-diastolic LV posterior wall thickness (LVPWd) were measured using two-dimensional (2D), or M-mode images taken from parasternal long axis views of the LV.[17]

From 2D images of the LV obtained from apical four and two-chamber views, LVEF (%) was calculated using biplane disk summation.[18]

LV mass was calculated using the Devereux formula

$$\text{LV mass}\,(\text{g}) = 1.04 \times \left[(\text{LVEDD} + \text{IVS} + \text{LVPWd})^3 - (\text{LVEDD})\right]^3 - 13.6,$$

where 1.04 (g/cm^2) is the specific gravity of the myocardium.

LV mass index (LVMI, gm/m^2) was defined as LV mass divided by body surface area (m^2). Reference upper limits of normal LVMI by linear measurements are 95 gm/m^2 in women and 115 gm/m^2 in men.[18]

Pulmonary artery systolic pressure (sPAP) was estimated by multiplying the square of the peak tricuspid regurgitant flow velocity by four (modified Bernoulli equation) and adding the right atrial pressure as estimated from the change in inferior vena caval diameter with inspiration.

The mitral annular early diastolic velocity (LV.E′) by pulsed wave tissue Doppler was obtained in 6 mitral annular sites (lateral, septal, inferior, anterior, posterior and antroseptal) then averaged to calculate average of early myocardial diastolic wave from these 6 annular sites (Av.E′).

LV diastolic function was evaluated by obtaining the ratio of LV E wave of mitral flow by pulsed Doppler/Av.E′ (E/Av.E′).

2. **2D Speckle tracking echocardiography was used to assess LV-GLS.** The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views. Speckles were tracked frame by-frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created. GLS was calculated as the mean strain of 17 segments. A cut off at -16.5% has been shown to provide important risk stratification and prognostic value.[19] Therefore, in our study we defined impaired GLS as >−16.5% (a less negative value reflects a more impaired GLS).

HD Patients (whom were compared to 15-age matched healthy volunteers as control group) were classified according to LV EF into 2 groups:

Group I: including HD patients with LVEF > 50%

Group II: including HD patients with LVEF ≤ 50%

3. **Laboratory investigations**: six ml of venous blood were collected and divided into 4 ml In serum separator tube, allowed to stand in room temperature for 30 min and then centrifuged at 3000 rpm for 20 min; serum was used for measurement of urea, creatinine, cholesterol, triglycerides, calcium and phosphorus (COBAS® INTEGRA 400 plus Autoanalyzer, Roche – Germany), parathormone hormone (PTH) (E-COBAS, Roche – Germany), the estimated glomerular filtration rate (eGFR) was calculated using EPI.CKD eGFR calculator. The remaining serum was stored at −20 °C until measurement of BNP by ELIZA assay.

The remaining 2 ml were placed in a vacutainer tube containing disodium EDTA for complete blood count (done on sysmex Kx-21N, Japan).

2.3. Measurement of serum BNP

Serum levels of Human Brain Natriuretic Peptide (BNP) were measured by quantitative sandwich Enzyme Linked Immunosorbent Assay (ELISA) using Human brain natriuretic peptide (BNP) ELISA kit (Bioassay, England/China, Cat# E1287Hu) according to the manufacturer instructions. The detection range of the kit is 5–2000 ng/ml. Each sample was run in duplicate and compared with a standard curve. The mean concentration was determined for each sample.

2.4. Statistical analysis

Results were analysed using the SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as percentages, means and standard deviations (SD). The parameters with normal distribution were expressed as the mean 1 SD. Univariate analysis for group comparisons were performed using the Student's *t*-test and one-way ANOVA. The associations between variables were assessed by Pearson and Spearman's r correlation analysis. $P < 0.05$ was accepted as statistically significant.

3. Results

3.1. Baseline demographic clinical data and serum BNP

The demographics of the patients and controls are provided in Table 1. No statistically significant difference was found between both groups regarding age ($P > 0.05$). Participants were predominantly female; 53.3% of the patients group and 80% of the control group. The patients group had a high prevalence of hypertension (63.3%), hypercholesterolemia (56.7%) and diabetes mellitus (20%). We noted that in HD patients, chronic hypertension represents the most common cause of ESRD (50%) followed by diabetes mellitus (16.7%).

The median duration of HD before the study was 74.8 ± 35.6 months. There were statistically significant higher serum levels of BNP in HD patients group compared to the healthy group ($P < 0.0001$).

Conventional, TDI echocardiographic and GLS parameters have been analysed. Table 2 summarizes the results of the LV dimensions, LV mass, LA, sPAP, and LV systolic and diastolic functions. There was significant increase in LV internal diastolic and systolic dimensions and volumes in HD patients compared to control group. LVMI was increased significantly in HD patients ($P < 0.0001$). sPAP and LA diameter were significantly higher in HD patients compared to the controls ($P < 0.0001$ *for both*).

Echocardiographic study showed significant impairment of the cardiac functions of HD patients compared to healthy controls (Table 2).

Table 1
Clinical and laboratory data of HD population.

Demographic Data	HD patients (n = 30)	Control (n = 15)	*P*-value
Age in years	51.2 ± 10.2	48.9 ± 6.6	NS
Sex:			
• Male	14 (46.7%)	3 (20%)	
• Female	16 (53.3%)	12 (80%)	
Risk factors:			
• HTN	19 (63.3%)		
• Hyperlipidemia	17 (56.7%)		
• DM	6 (20%)		
Causes of CKD (no& %):			
• HTN	15 (50%)		
• DM	5 (16.7%)		
• Analgesic	1 (3.3%)		
• UTI	1 (3.3%)		
• FMF	1 (3.3%)		
• SLE	1 (3.3%)		
• Unknown	6 (20%)		
Duration of dialysis (months)	74.8 ± 35.6		
Blood pressure:			
• SBP (mmHg)	130 ± 16.6	111.3 ± 8.3	<0.0001
• DBP (mmHg)	79 ± 8	70 ± 8.5	<0.005
BNP (ng/ ml)	1238 ± 1085.5	71 ± 23.4	<0.0001
S. creatinine (mg/dL)	10.1 ± 2.4	0.9 ± 0.2	<0.0001
eGFR ((mL/min/1.73 m^2)	12.5 ± 3	–	

Values in table were presented as a number (n) with the percentage in square brackets, the mean ± standard deviation (SD). HTN = hypertension, DM = diabetes mellitus, UTI = urinary tract infection, FMF=, familial mediterranean fever, SLE = systemic lupus erythematosis, BNP = brain natriuretic peptide.S. = serum, eGFR = estimated glomerular filtration rate.

Table 2
Echocardiographic parameters in HD patients and control groups.

Echocardiographic parameters	HD patients n = 30	Control n = 15	P value
LVEDD (mm)	53.1 ± 10.1	44.3 ± 4.4	<0.0005
LVESD (mm)	37.4 ± 9	27.5 ± 3	<0.0001
IVS (mm)	9.3 ± 2	9.1 ± 1.7	NS
LVPWd (mm)	8.9 ± 1.5	7.4 ± 1.1	<0.0005
LVMI (gm/m^2)	115.3 ± 53	64.6 ± 14.8	<0.0001
LVEF-MM (%)	56.5 ± 9.5	67.1 ± 4.1	<0.0001
LV FS (%)	28.8 ± 7.2	37.2 ± 4.1	<0.0001
LVEDV4 (ml)	116.8 ± 46.7	81.3 ± 33.6	<0.01
LVESV4 (ml)	57.1 ± 27.3	31.4 ± 14.3	<0.001
LVEDV2 (ml)	104.8 ± 41.8	73.3 ± 22.9	<0.005
LVESV2 (ml)	50.6 ± 28.3	27.5 ± 8.7	<0.0005
LVEF-biplane (%)	52.4 ± 8.8	62.2 ± 3.1	<0.0001
sPAP (mmHg)	43.4 ± 1.5	25.7 ± 4.9	<0.0001
E/A	1.1 ± 0.5	1.5 ± 0.4	<0.005
LV E/av.E′	19.2 ± 7.2	7.8 ± 1.2	<0.0001
LA (mm)	41.9 ± 7.3	30.8 ± 2.5	<0.0001
LV-GLS (%)	15.1 ± 3.1	20.8 ± 1.7	<0.0001
LVMWS (dynes/cm^2 × 1000)	189.2 ± 81	72.2 ± 20.6	<0.0001

*Values in table were presented as mean ± standard deviation (SD). HD = hemodialysis, LVEDD: left ventricular end diastolic dimension, LVESD: LV end systolic dimension, IVS: LV inter ventricular septum, LVPWd: LV posterior wall, LVM: LV mass, LVMI: LV mass index, LVEF-MM: LV ejection fraction by M-mode, LVEDV: LV end diastolic volume, LVESV: LV end systolic volume, 4: four chamber view, 2: two chamber view, sPAP: pulmonary arterial systolic pressure, E/A: ratio of early diastolic flow to late diastolic flow across the mitral valve, LV E/av.E′: early diastolic wave velocity/average of early myocardial diastolic wave velocity at 6 mitral annulus sites, LA: left atrium, LV-GLS: LV – global longitudinal strain, LVMSW: LV meridional wall stress.

Systolic dysfunction was evident in patients with ESRD by decreased EF (either measured by M-mode or modified Simpson's method) ($P < 0.0001$ *for both*) and fractional of shortening (FS) ($P < 0.0001$) in conventional echocardiography while severe grade of diastolic dysfunction in HD patients group was evident by the high E/Av.E′ ratio ($P < 0.0001$) compared to healthy controls.

LV-GLS was significantly lower in HD patients when compared with the controls ($P < 0.0001$) which denotes systolic dysfunction (Table 2: note: the more negative value of GLS, the better LV systolic function is). Also, Table 2 showed significant increase in LVMSW in HD patients compared to the healthy group ($P < 0.0001$).

3.2. Patients' classification according to LV systolic function

Patients were categorized into two groups according to the LV systolic function measured by modified Simpson's method with EF cut-off point of 50%. Patients in reduced LV systolic function (Group I) (n = 15; of whom 8 were females, EF $\leq$ 50%) with mean age 51.8 ± 10 years. Patients with preserved LV systolic function (Group II) (n = 15; of whom 8 were females, EF > 50%) whom mean age was 50.7 ± 10.7 years.

There were no significant differences between the two dialysis groups (group I and group II) with respect to conventional clinical measurements as age, diabetes mellitus, and hypertension.

Table 3 showed that, in this study, there were no significant differences in most of laboratory data between both groups. Patients with LV systolic impairment (group I) were more likely to have lower serum calcium levels compared with those with preserved LV systolic function (group II). No differences in the level of serum creatinine, parathormone hormone, phosphate and total cholesterol between both groups.

Notably, serum levels of BNP in patients with LV systolic dysfunction (group I) were significantly elevated compared to patients with preserved LV systolic function (group II) ($P < 0.0005$) (Table 3).

Conventional, TDI echocardiographic and GLS parameters have been summarized in Table 4. Group I patients had increased LV internal dimensions in diastole, LV end diastolic volumes, and LA diameter compared to patients in group II. LVMI and sPAP were significantly higher in Group I patients ($P < 0.0001$ and < 0.05; respectively) than group II.

Furthermore, both groups had reversed E/A ratio, and high E/Av.E′ values, indicating the presence of increased LV filling pressure, compatible with LV diastolic dysfunction. E/Av.E′ values were statistically higher in Group I patients when compared with patients in Group II ($P < 0.01$).

LV-GLS was significantly reduced in group I than in Group II (Table 4) (Fig. 1). Significant increase in LVMWS was noted in group I patients compared to the group II ($P < 0.0001$).

On the other hand, we compared patients in group II with healthy controls. There was no significant difference between both groups regarding age. We found statistical significant higher levels of serum BNP in group II patients (P < 0.005) compared to controls.

Table 3
Laboratory data of HD groups (group I and Group II).

Laboratory parameters	G1 (n = 15)	G2 (n = 15)	P value
HB (g/dl)	10.3 ± 1.6	9.7 ± -0.9	NS
WBCs (cell/mm^3)	8.1 ± 7.3	6.6 ± 2.7	NS
Platelets (cell/mm^3)	181.3 ± 57.3	220 ± 73.8	NS
BUN (mg/dL)	143.6 ± 39.6	165.3 ± 32.3	NS
S. creatinine (mg/dL)	10 ± 2.5	10.1 ± 2.3	NS
S. Ca (mg/dL)	8.9 ± 0.4	8.3 ± 0.7	<0.01
eGFR (mL/min/1.73 m^2)	12.9 ± 3.2	12 ± 2.9	NS
S.Ph (mg/dL)	5.9 ± 2	5.4 ± 1.7	NS
PTH (pg/mL)	800.3 ± 581.4	436.8 ± 408.5	NS
Cholesterol (mg/dL)	141.1 ± 40.6	169.6 ± 52.4	NS
Triglycerides (mg/dL)	132 ± 53.3	155 ± 83.4	NS
BNP (ng/ ml)	1925.4 ± 1087	550.5 ± 496.5	<0.0005

Values in table were presented as a number (n) with the percentage in square brackets, the mean ± standard deviation (SD). S = serum, BUN = blood urea nitrogen, Ca = calcium, Ph = phosphorous, PTH = parathormone hormone, BNP = brain natriuretic peptide, eGFR = estimated glomerular filtration rate.

Table 4
Comparison of echocardiographic data of HD patients groups (Group I and Group II).

Echocardiographic Parameters	G1 (n = 15)	G2 (n = 15)	P value
LVEDD (mm)	59.4 ± 7.4	46.7 ± 8.4	<0.0001
LVESD (mm)	44.2 ± 5.7	30.7 ± 6	<0.0001
IVS (mm)	10.9 ± 1.8	8.5 ± 1.4	<0.0005
LVPWd (mm)	10 ± 1.6	8.5 ± 1.14	<0.01
LVEDV4 (ml)	143.4 ± 43.1	90.2 ± 33.9	<0.01
LVESV4 (ml)	76.9 ± 20.5	37.3 ± 16.7	<0.0001
LVEDV2 (ml)	132.1 ± 36.7	77.5 ± 25.9	<0.0001
LVESV2 (ml)	70.1 ± 26.4	31 ± 12	<0.0001
LVMI (gm/m^2)	1523 ± 39.5	78.6 ± 37	<0.0001
LA (mm)	45.3 ± 5.1	38.6 ± 7.8	<0.01
PAP (mmHg)	48.7 ± 12.2	38.2 ± 16	<0.05
LVEF-biplane (%)	45 ± 5.6	59.8 ± 3.7	<0.0001
LVEF-MM (%)	49.3 ± 5.8	63.7 ± 6.2	<0.001
LV FS (%)	23.3 ± 3.2	34.3 ± 5.6	<0.0001
LV E/av.E′	22.5 ± 7.4	15.9 ± 5.4	<0.01
LV-GLS (%)	13.8 ± 2.5	16.4 ± 5.4	<0.05
LVMWS (dynes/cm^2 × 1000)	246.9 ± 67.5	131.5 ± 43.6	<0.0001

Values in table were presented as a number (n) with the percentage in square brackets, the mean ± standard deviation (SD). LVEDD: left ventricular end diastolic dimension, LVESD: LV end systolic dimension, IVS: LV inter ventricular septum, LVPWd: LV posterior wall, LVM: LV mass, LVMI: LV mass index, LVEF-MM: LV ejection fraction by M-mode, LVEDV: LV end diastolic volume, LVESV: LV end systolic volume, 4: four chamber view, 2: two chamber view, sPAP: pulmonary arterial systolic pressure, E/A: ratio of early diastolic flow to late diastolic flow across the mitral valve, LV E/av.E′: early diastolic wave velocity/average of early myocardial diastolic wave velocity at 6 mitral annulus sites, LA: left atrium, LV-GLS: LV – global longitudinal strain, LVMSW: LV meridional wall stress.

Regarding echocardiographic indices, group II patients had significantly increased LA diameter (P < 0.005), LVPWd (<0.05), E/A ratio (P < 0.005), sPAP (P < 0.01), E/Av.E′ (P < 0.0001), LVMWS (P < 0.0001) with significant impairment of LV-GLS (P < 0.0001). However, we could not find any significant difference between both groups in LV dimensions, volumes or EF by both M-mode and biplane.

By comparing group I HD patients with LV systolic dysfunction to healthy participants, we found no significant difference between both groups regarding age. We found statistical significant higher levels of serum BNP in group II patients (P < 0.0001) compared to controls.

As expected, group II HD patients with LV systolic dysfunction had significantly increased LA diameter (P < 0.0001), IVS (P < 0.01), LVPWd (<0.0001), LV dimensions, volumes and LV EF (by M-mode and bi-plane) (P < 0.0001). Group II HD patients had significant higher levels of sPAP (P < 0.0001), LVMWS (P < 0.0001), more impairment of LV diastolic function defined by E/Av.E′ (P < 0.0001), and significantly reduced LV systolic function detected by LV-GLS (P < 0.0001).

3.3. Correlation of serum BNP concentrations with renal functions and different echocardiographic indices

No correlation was found between serum BNP levels and renal functions either serum creatinine or eGFR in HD patients.

We found significant positive correlation between serum BNP concentrations with LV Av.E/E′ (r = 0.512, P < 0.01), LVMI (r = 0.869, P < 0.0001) and LVMWS (r = 0.697, P < 0.0001) whilst BNP serum levels correlated negatively with LV EF-biplane (r = −0.642, P < 0.001) and LV-GLS (r = −0.587, P < 0.0001) (Fig. 2).

4. Discussion

Chronic kidney disease (CKD) is a worldwide growing disease associated with an increased risk of cardiovascular morbidity and mortality.[20]

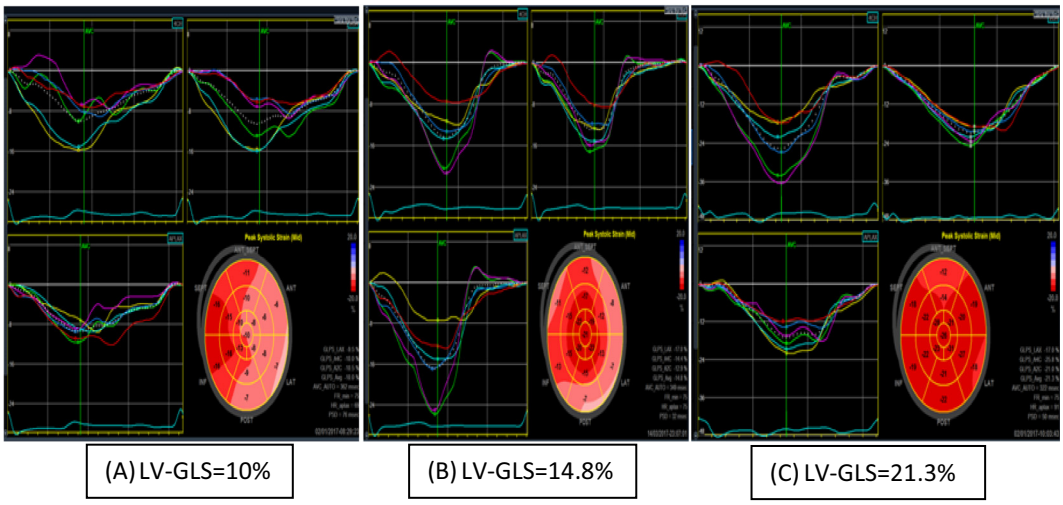

Fig. 1. Ball's eye for 17-segments of LV-GLS in (A) group I patient, (B) group II patient, and (C) control volunteer.

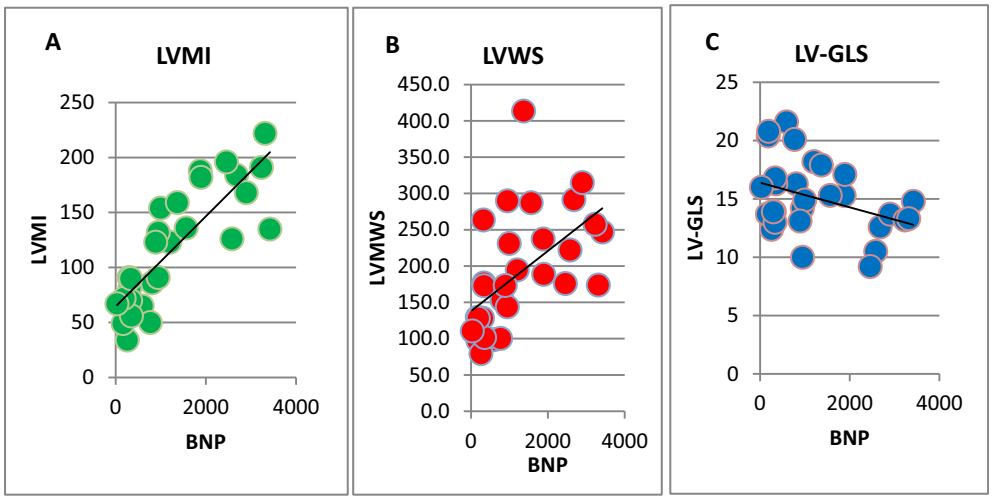

Fig. 2. Correlations of BNP serum concentrations and (A) LVMI, (B) LVMWS and (C) LV-GLS. BNP correlated positively with LVMI (r = 0.869, P < 0.0001) and LVMWS (r = 0.697, P < 0.0001). Serum BNP levels showed negative correlation with LV-GLS (r = −0.587, P < 0.0001). BNP = brain natriuretic peptide, LVMI = left ventricular mass index, LVMWS = LV meridional wall stress, LV-GLS = left ventricular global longitudinal strain.

CKD is associated with structural and functional LV remodeling as a consequence of pressure and volume over- load and nonhemodynamic factors.[21] Pressure overload is the result of chronic hypertension and vascular stiffness, whereas anemia, arteriovenous fistulas, and sodium and water retention lead to volume overload. To keep LV wall stress close to normal, the LV responds to pressure and volume overload with hypertrophy and dilatation.[22]. As LVH progresses, the interstitial space also increases with accumulation of collagen (interstitial or replacement fibrosis) potentially causing a reduction in contractility. In addition, LVH increases the myocardial oxygen demand, which causes myocardial hypoperfusion, cardiomyocyte loss, and further interstitial fibrosis.[23] Furthermore, non-hemodynamic factors are associated with CKD such as inappropriate renin-angiotensin-aldosterone system activation, oxidative stress, inflammation, and stimulation of prohypertrophic and profibrogenic factors also contribute to LV remodeling.[23] These structural changes cause impaired LV contractility, which can be detected with LV-GLS in addition to LV wall stress. Besides, it has been shown that LV GLS is a more sensitive marker of LV systolic dysfunction than LV ejection fraction.[24]

In the current study, mean LV EF in HD patients was >50% (either by using M-mode or biplane methods) despite of significant increase of LV dimensions and volumes. However, mean LV-GLS among those patients was significantly reduced suggesting that the LV contractility is significantly reduced probably because of ongoing LV remodeling that was evidenced by increased LVMWS, LVMI and severe grade of LV diastolic dysfunction detected by LV E/Av.E′ ratio.

Wang et al.,[25] demonstrated the reliability of GLS in detecting subclinical systolic dysfunction in patients with LVH and preserved EF in HD patients. They concluded that myocardial function was impaired not only in longitudinal direction but also in circumferential direction despite preserved LVEF.

Liu et al.,[26] demonstrated that despite preserved LV systolic function revealed by conventional echocardiographic parameters and TDI, worsening renal function is associated with a reduction of systolic function as reflected by the decline of LV-GLS, circumferential strain and strain rate.

Our results revealed that HD patients (either with preserved or reduced LV EF) had marked elevation of serum levels of BNP

compared to control group. Elevated serum BNP concentrations closely correlated with significant elevation of LVMI and LVMWS and LV E/Av. E' (marker of diastolic dysfunction) in addition to significant decline of LV-GLS and LV EF in both patients groups. However, BNP levels were not found to be correlated with renal functions (neither serum creatinine nor eGFR).

In agreement to our results, Sanjuan et al.,[27] observed significant rise in the BNP concentration in patients on chronic dialysis. Renal insufficiency by itself does not appear to explain the serum BNP levels. General consensus exists that BNP is related to the stretching of myocardial fibers following volume overload.[28] However, since BNP levels remain elevated after significant fluid loss after each dialysis session in both HD patients, other factors must also be involved.[27] Bavbek et al.,[29] and Sanjuan et al.,[27] found that there was a good correlation between BNP and LVMI, with LVMI being the most significant factor indicating the BNP increase. Sanjuan et al.,[27] concluded that in asymptomatic patients, marked increases in BNP levels may reflect very early stages of pathological processes that precede the development of apparent cardiac signs (such as measurable LVH) in patients on extrarenal dialysis. Only echocardiographic parameters of cardiac dysfunction should be used as diagnostic criteria.

Discordant to our results, the study by Cataliotti et al.,[30] stated that BNP concentrations in HD patients without cardiovascular anomalies, hypertensive cardiopathy or ventricular dysfunction did not differ from those obtained from healthy subjects without cardiovascular or renal pathology. Similar results were found by Akiba et al.,[31] who did not find differences in BNP levels between asymptomatic patients with and without renal insufficiency; consequently, renal insufficiency by itself does not appear to explain the increased serum BNP levels.

BNP is released from ventricular myocytes in response to LV wall stress and is a marker of cardiac distress.[32] Serum levels of BNP increase with reduction LV function and BNP levels correlate negatively with left ventricular ejection fraction both in nonrenal and HD patients.[33] BNP also reflects diastolic dysfunction.[32]

Charfeddine et al.,[34] concluded that in patients with ESRD, the longitudinal and radial systolic functions are reduced although the LVEF may remain within normal limits. This could be explained by the preservation of the circumferential functions. 2D-STE has the potential to detect the severity of uraemic cardiomyopathy in the early stages of the disease and might provide useful information for the risk stratification in ESRD patients with preserved LVEF.

In agreement to our results, Niizuma et al.,[35] found that BNP concentrations increased progressively with the grade of LV end diastolic wall stress (EDWS) in both the normal and CKD groups. In the ESRD group, there were no significant differences between the low and middle EDWS groups. However, patients with ESRD and high EDWS showed the highest serum BNP concentrations. Also, they concluded that the group defined in terms of renal dysfunction and the levels of log EDWS were both independent determinants of BNP concentrations.

Several limitations should be considered in interpreting our results. First, the study population was relatively small. Second, only serum BNP concentrations were considered in our study that had been measured only after dialysis session. We suggest to measure BNP concentrations before and after dialysis then the change of BNP concentrations is better to be used.

5. Conclusions

The results suggested that LV-GLS and LVMWS in addition to degree of LV E/Av.E′ ratio could be useful imaging markers for detection of LV dysfunction (either systolic or diastolic) in HD patients. Serum BNP levels are influenced by LV structural and functional abnormalities rather than renal functions that would be crucial hemodynamic biomarker in those high risk patients.

6. Disclosure

None.

7. Conflict of interest

The authors declare that there are no conflict of interest.

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