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ORIGINAL ARTICLE

Use of serum fibroblast growth factor 23 *vs.* plasma B-type natriuretic peptide levels in assessing the pathophysiology of patients with heart failure

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Recently, fibroblast growth factor 23 (FGF23), a phosphate-regulating hormone, has been linked to the pathophysiology of heart failure (HF), thus encouraging us to examine which hemodynamic abnormalities of HF are linked to either serum FGF23 or plasma B-type natriuretic peptide (BNP) levels. We measured both the serum FGF23 and plasma BNP levels in 154 consecutive prospectively enrolled hospitalized HF patients, with an estimated glomerular filtration rate >40 ml min^{-1} 1.73 m^{-2}, who underwent heart catheterizations and an echocardiogram. The serum FGF23 levels correlated with the diameter of the inferior vena cava and its respiratory changes, whereas the plasma BNP levels did not. Both the plasma BNP and serum FGF23 levels were moderately correlated with the mean pulmonary artery (PA) pressure and pulmonary capillary wedge (PCW) pressure. Interestingly, in patients with an above-median right-atrial (RA) pressure (4 mm Hg), FGF23 levels were correlated with both PA and PCW pressures, but the levels were not correlated in patients with a below-median RA pressure. In contrast, the plasma BNP levels were correlated with both PA and PCW pressures. Finally, serum FGF23 levels, compared with the plasma BNP levels, were more strongly associated with the clinical outcomes in patients with above-median RA pressure. These findings suggested that serum FGF23 levels are predominantly correlated with clinical outcomes, may serve as a biomarker for HF in patients with higher RA pressure, may provide beneficial information for patients with right-sided HF and may represent different clinical information than that provided only by plasma BNP levels.
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INTRODUCTION

Given the diverse mechanisms of heart failure (HF) pathophysiology, correctly assessing the severity of HF, ideally noninvasively, and making an appropriate decision about therapy for HF patients are required in clinical settings. Symptoms of venous congestion are observed in ~60% of patients with acute decompensated HF.[1] Elevation in pressures on the right side of the heart, including central venous pressure (CVP), is associated with decreased renal function[2] and poorer clinical outcomes in patients with HF.[3,4] Renal dysfunction is a strong predictor of clinical outcomes, and recent studies have suggested that in patients with HF, impairment of renal function is associated not only with venous congestion, but also with renal perfusion.[4,5] Venous congestion is strongly related to the outcome of worsening renal function.[2] These findings raise the possibility that elevations in pressures on the right side of the heart, including CVP, influence renal function and that such renal dysfunction might cause neurohormonal abnormalities in association with the subsequent progression of cardiac remodeling, thus potentially creating a vicious cycle.

Recently, fibroblast growth factor 23 (FGF23), a phosphate-regulating hormone, has been linked to both renal and cardiovascular events in HF patients,[6] and may alter cardiovascular function.[7] FGF23 receptors are located in the heart and kidney, and their activation affects both renal and cardiac functions.[8] We have reported that HF progression contributes to elevations in circulating FGF23 levels independently of renal function.[9] However, it has not been clarified whether a relationship exists between circulating FGF23 levels and hemodynamics. Theoretically, the mechanisms of the vicious cycle of HF, including elevated right-atrial (RA) pressure and renal congestion, might elevate circulating FGF23 levels; however, no evidence has been

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found in patients with HF. In this study, we tested the hypothesis that pressures on the right side of the heart are linked to circulating FGF23 levels. In addition, we compared the relationship of hemodynamics on the right side of the heart with plasma BNP levels, which indicate left ventricular end-diastolic pressure.[10]

METHODS

The study population

A total of 154 consecutive patients with HF who were admitted to our department from January to December 2012 were analyzed in this study. The patients all had an estimated glomerular filtration rate (eGFR) >40 ml min^{-1} 1.73 m^{-2} and were scheduled to undergo heart catheterization tests. Previous studies have reported that a robust relationship exists between serum FGF23 levels and GFR, and have suggested that serum FGF23 levels increase marginally when renal function declines below a GFR of 30–40 ml min^{-1}.[11,12] In the present study, we sought to exclude the effects of worsening renal function on serum FGF23 levels to analyze the relationships between serum FGF23 levels and hemodynamic parameters. Therefore, we set the inclusion criteria of an eGFR >40 ml min^{-1} 1.73 m^{-2}. The HF diagnosis was based on the Framingham criteria.[13] We sought to study HF patients with normal renal function and/or relatively early-stage chronic kidney disease (stages 1–2 chronic kidney disease and upper, middle stage 3 chronic kidney disease).[11,12] During the hospitalization, we analyzed blood samples collected during the stable chronic phases of HF, which was defined as New York Heart Association functional class I or II. We also included data on the acute decompensated HF patients in their chronic phases.

Measurements of biomarkers

We placed the patients' blood samples into tubes with ethylenediaminetetraacetate, and then separated and froze the serum in plastic tubes at -80 °C until analysis. We measured the FGF23 levels by using a chemiluminescence enzyme immunoassay (Kyowa Medex, Tokyo, Japan), as described previously.[14] The eGFR was calculated according to the published equation for Japanese persons: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times (0.739$ for females).[15]

Echocardiography

We measured the left ventricular (LV) dimensions and heart-wall thicknesses according to the American Society of Echocardiography Guidelines.[16] We also recorded the presence/absence of respiratory changes in the inferior vena cava and the diameter of the inferior vena cava.[16]

Right- and left-heart catheterization

We performed right- and left-heart catheterizations on the study participants and prospectively collected clinical data. We performed a standard right-heart catheterization via either the internal jugular vein or the femoral vein by using a Swan–Ganz catheter (Goodman, Tokyo, Japan). The cardiac output was calculated by the direct Fick method, using the oxygen consumption, which was measured by gas analysis with an Aeromonitor AE-300S (Minato Medical Science, Osaka, Japan). A standard left-heart catheterization was performed via either the radial artery or femoral artery by using an angled pigtail catheter (Terumo, Tokyo, Japan).

Using the right- and left-heart catheterization data, we obtained the cardiac hemodynamic parameters for the right and left sides of the hearts, including the RA pressure, pulmonary artery (PA) pressure, pulmonary capillary wedge (PCW) pressure and cardiac index (CI), all of which are essential hemodynamic markers for HF.

Clinical outcomes

We followed up the 154 patients for 180–500 days (minimum period to maximum period, average period, 338 ± 113 days), and observed the incidence of cardiovascular death and hospitalization from HF. An independent physician determined whether cardiovascular conditions were the cause of death and made the decisions regarding the causes of the hospitalizations of the patients.

Ethics

Written informed consent was obtained from all subjects. This study was approved by National Cerebral and Cardiovascular Center Institutional Ethics

Table 1 Clinical characteristics

Characteristics		*(n = 154)*
Demographic data		
Age	(years)	65 (48–72)
Female	(*n*, %)	79, 51
Medical history		
Hypertension	(*n*, %)	78, 51
Hyperlipidemia	(*n*, %)	68, 44
Diabetes mellitus	(*n*, %)	36, 24
Stroke	(*n*, %)	15, 10
Atrial fibrillation	(*n*, %)	41, 27
Etiology of heart failure		
Cardiomyopathy	*n*, %	65, 42
Valvular heart disease	*n*, %	69, 45
Hypertensive heart disease	*n*, %	10, 6
Ischemic heart disease	*n*, %	4, 3
Others	*n*, %	6, 4
Physical findings		
Blood pressure	(mm Hg)	
Systolic		114 (103–126)
Diastolic		65 (57–72)
Heart rate	(bpm)	68 (59–76)
Body mass index	(kg m^{-2})	23 (20–26)
Medications		
β-blockers	(*n*, %)	77, 50
ACE inhibitors or ARBs	(*n*, %)	81, 53
Loop diuretics	(*n*, %)	58, 38
Statins	(*n*, %)	49, 32
Laboratory data		
Total bilirubin	(mg dl^{-1})	0.7 (0.5–0.9)
Albumin	(g dl^{-1})	4.3 (4.1–4.5)
AST	(U l^{-1})	22 (19–27)
ALT	(U l^{-1})	18 (13–27)
Sodium	(mg dl^{-1})	141 (139–142)
Calcium	(mg dl^{-1})	9.4 (9.1–9.7)
P_i	(mg dl^{-1})	3.6 (3.3–4.0)
Parathyroid hormone	(pg dl^{-1})	52 (41–70)
eGFR	(ml min^{-1} 1.73 m^{-2})	70.7 (58.6–80.7)
Creatinine	(mg dl^{-1})	0.8 (0.6–0.9)
BUN	(mg dl^{-1})	16 (14–20)
UA	(mg dl^{-1})	5.6 (4.6–7.1)
Hb	(g dl^{-1})	13.3 (12.2–14.4)
Erythropoietin	(mIU^{-1} ml)	19 (13–24)
Troponin T	(ng ml^{-1})	0.012 (0.008–0.020)
TNF α	(pg ml^{-1})	1.1 (0.5–1.7)
IL-6	(pg ml^{-1})	1.8 (1.0–3.0)
BNP	(pg ml^{-1})	99 (49–232)
FGF23	(pg ml^{-1})	38.8 (31.0–48.2)

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, asparatate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; IL-6, interleukin-6; Others, myocarditis, aortitis syndrome and corrected transposition of the great arteries; TNF, tumor necrosis factor; UA, uric acid. Data are expressed as percentages and median values (25th–75th percentiles).

Table 2 Hemodynamics data

		(n = 154)
Central hemodynamics		
Mean RA pressure	(mm Hg)	4 (2–5)
Mean PA pressure	(mm Hg)	17 (14–22)
Mean PCW pressure	(mm Hg)	10 (7–14)
LV end-diastolic pressure	(mm Hg)	12 (8–19)
Flow and resistance data		
Cardiac index	(l min^{-1} m^{-2})	2.5 (2.1–3.0)
SVRI	(Wood units per m^2)	13.3 (10.4–16.8)
PVRI	(Wood units per m^2)	1.1 (0.7–1.7)

Abbreviations: PA, pulmonary artery; PCW, pulmonary capillary wedge; PVRI, peripheral vascular resistance index; RA, right atrial; SVRI, systemic vascular resistance index.
Data are expressed as median values (25th–75th percentiles).

Committee and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The normally distributed data are expressed as the median and interquartile range (IQR), or mean ± s.d. Pearson's correlation coefficient analysis and a univariate linear regression analysis were used to assess the relationships between FGF23 and the other variables. For the combined end-point analysis and the survival rate, log-rank tests and Kaplan–Meier survival analyses were performed, respectively. The relative risk of cardiovascular events was estimated using the Cox proportional hazard regression model. All of the tests were two-tailed, and $P<0.05$ was considered to be significant. These analyses were performed with the JMP software for Windows (version 8.0.2, SAS, Cary, NC, USA).

RESULTS

A total of 154 HF patients (75 men and 79 women, median patient age 65 years (IQR, 48–72 years)) were prospectively enrolled in this study and their characteristics are shown in Table 1. All of the patients were

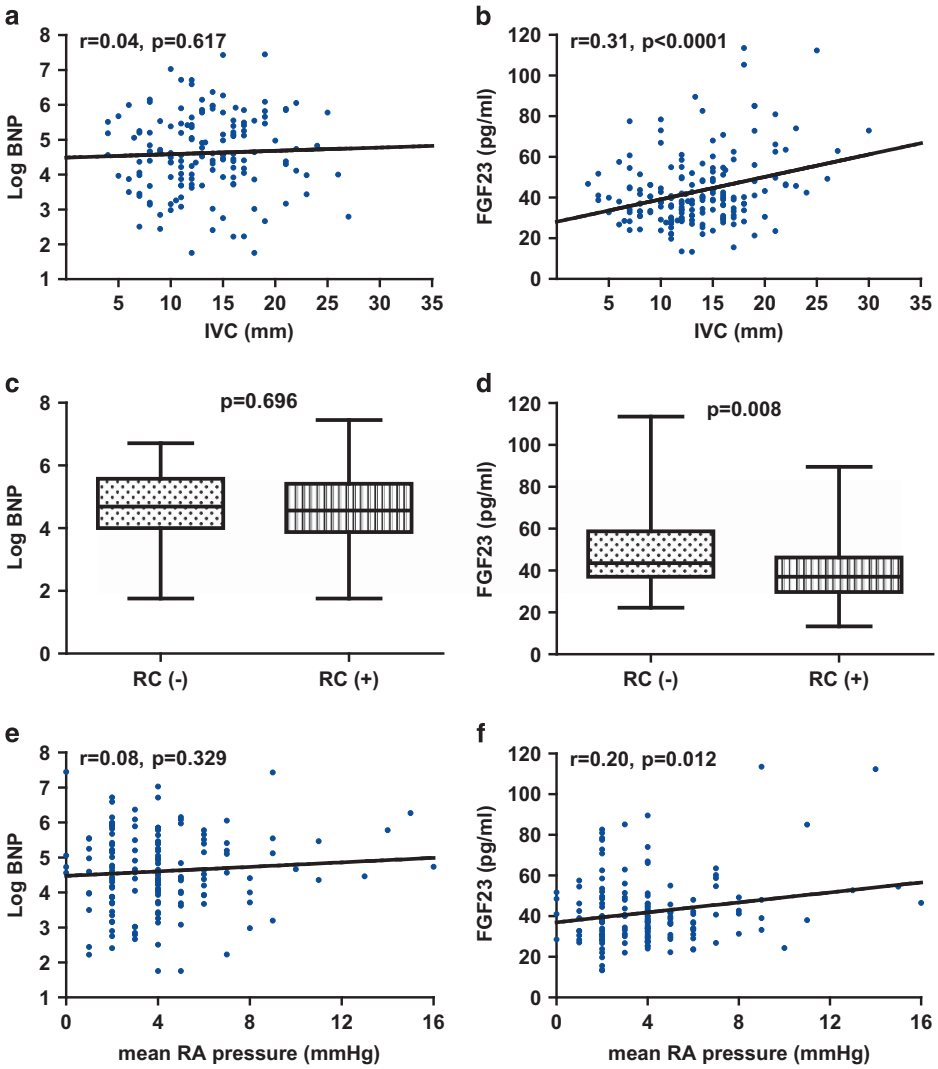

Figure 1 The association of the plasma BNP levels (left panels) and serum FGF23 levels (right panels) with the HF parameters obtained from the heart-catheterization echocardiograms. The serum FGF23 levels were well correlated with the IVC values (**b**), the RC (**d**) and RA (**f**) pressure values, but the plasma BNP levels were not (**a**, **c**, **e**). BNP, B-type natriuretic peptide; FGF23, fibroblast growth factor 23; HF, heart failure; IVC, inferior vena cava; RA, right atrial; RC, respiratory changes.

in New York Heart Association functional class I or II. The HF etiologies were cardiomyopathy (42%), valvular heart disease (45%), hypertensive heart disease (6%), ischemic heart disease (3%) and other (4%). The median eGFR value, plasma BNP levels and serum FGF23 levels were 70.7 ml min^{-1} 1.73 m^{-2} (IQR, 58.6–80.7 ml min^{-1} 1.73 m^{-2}), 99 pg ml^{-1} (IQR, 49–232 pg ml^{-1}) and 38.8 pg ml^{-1} (IQR, 31.0–48.2 pg ml^{-1}), respectively.

Table 2 shows the cardiac hemodynamic data that were obtained during the right- and left-heart catheterizations. Figure 1 shows the relationships between the plasma BNP and serum FGF23 levels and the hemodynamic parameters evaluated by the right-heart catheterizations and echocardiogram. The serum FGF23 levels were moderately correlated with the inferior vena cava parameters and RA pressure values, but the plasma BNP levels were not. Figure 2 shows the relationship between the plasma BNP and serum FGF23 levels and the hemodynamic parameters determined by the right- and left-heart catheterizations in the patient groups with below- and above-/equal-median RA pressures. The plasma BNP levels were well correlated with all parameters (CI, mean PA pressure and mean PCW pressure) in both the below- and above-/equal-median RA pressure groups (Figures 2a,c and e). The serum FGF23 levels in both the below- and above-/equal-median RA pressure groups were correlated with the CI

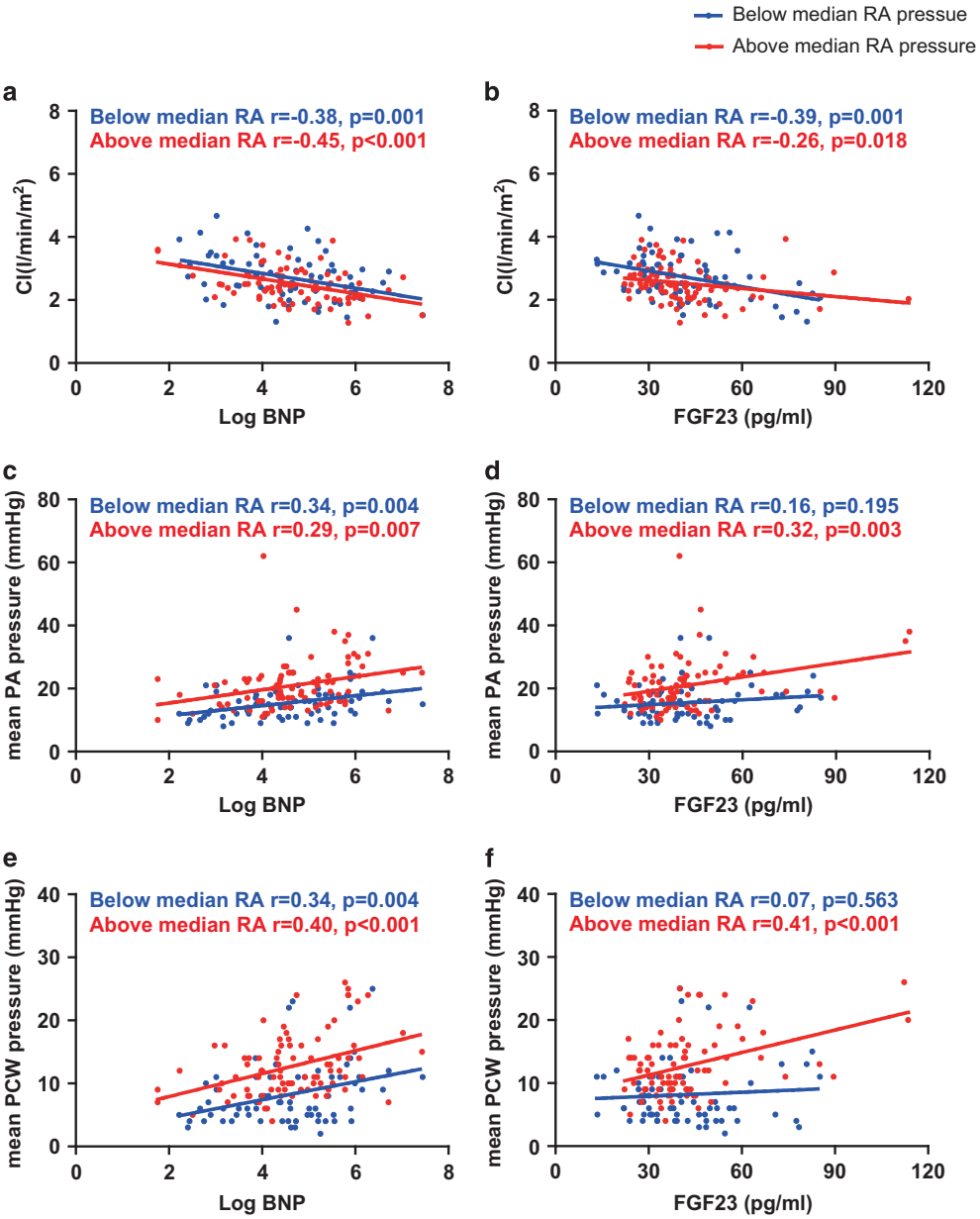

Figure 2 The association of the plasma BNP and serum FGF23 levels in the below- and above-/equal-median RA pressure groups and the hemodynamic parameters obtained by heart catheterizations and echocardiograms. The plasma BNP levels were well correlated with all of these parameters in both the below- and above-/equal-median RA pressure groups (**a**, **c**, **e**). The serum FGF23 levels in both below- and above-/equal-median RA pressure groups correlated with the CI (**b**). The levels in the above-/equal-median RA pressure group were correlated with PA pressure (**d**) and PCW pressure (**f**), whereas those in the below-median RA pressure group were not (**d**, **f**). BNP, B-type natriuretic peptide; CI, cardiac index; FGF23, fibroblast growth factor 23; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrial.

(Figure 2b). The serum FGF23 levels in the above-/equal-median RA pressure group were correlated with both the mean PA pressure and the PCW pressure. In contrast, the serum FGF23 levels were not correlated with the mean PA and PCW pressures in the patient group with below-median RA pressures. Furthermore, the serum FGF23 levels were associated with the levels of serum sodium and blood urea nitrogen, and eGFR, indexes of right-sided HF, whereas the plasma BNP levels were not (Table 3).

We also investigated the relationships between plasma BNP and serum FGF23 levels and the clinical outcomes. Figure 3 shows the Kaplan–Meier cardiovascular event-free curves according to the plasma BNP levels (Figure 3a), serum FGF23 levels (Figure 3b), and the combination of serum FGF23 and plasma BNP levels (Figure 3c) above/equal and below the medians of 99.2 and 38.8 pg ml^{-1}, respectively. These figures reveal that the serum FGF23 and BNP levels were associated with the incidence of cardiovascular death and/or hospitalization owing to HF, and that the strongest association was present between the combination of the above-/equal-serum FGF23 levels and -plasma BNP levels and the clinical outcomes.

The multivariate analysis of the right-heart catheterization data revealed stronger relationships between the serum FGF23 levels and the mean RA pressure and PA pressure, than those observed for the plasma BNP levels (Table 4). Table 5 shows that plasma BNP levels were associated with the mean PA pressure independently of the mean RA pressure. In contrast, serum FGF23 levels were not associated with the mean PA pressure after accounting for mean RA pressure.

The multivariate Cox regression analysis revealed that serum FGF23 levels, but not plasma BNP levels, were independent predictors of clinical outcomes (Table 6).

DISCUSSION

This study produced the following major findings: (1) the statistical association of pulmonary hypertension with serum FGF23 levels in the HF patients was found only in HF patients with above-median RA pressures, not in those with below-median RA pressure, and (2) serum FGF23 levels were associated with the cardiovascular outcomes as well as plasma BNP levels, thus suggesting equivalent predictability for clinical outcomes as BNP levels.[17]

The pathophysiological reasons for the production of BNP and FGF23 *in vivo* are markedly different. Ventricular stress and excess neurohormonal factors are major factors stimulating cardiac BNP production.[10,18,19] Owing to differences in left and right ventricular sizes, more marked elevations of plasma BNP levels are often observed in left-sided HF rather than right-sided HF. BNP is an established biomarker for HF patients. However, it has occasionally been observed that plasma BNP levels vary in hospitalized patients, and BNP can also be affected by other HF-associated factors,[20] which suggests that

Table 3 Relationship between either FGF23 levels or log (BNP) levels and laboratory data

		FGF23		*Log BNP*	
		r^2	P-*value*	r^2	P-*value*
Laboratory data					
Total bilirubin	(mg dl^{-1})	0.065	0.0008	<0.0001	0.8220
AST	(U l^{-1})	0.031	0.0185	0.004	0.3989
ALT	(U l^{-1})	0.002	0.5495	0.054	0.0020
Sodium	(mg dl^{-1})	0.029	0.0231	0.002	0.5096
BUN	(mg dl^{-1})	0.117	<0.0001	0.016	0.0951
eGFR	(ml min^{-1} 1.73 m^{-2})	0.099	<0.0001	0.065	0.0006
UA	(mg dl^{-1})	0.188	<0.0001	0.027	0.0340

Abbreviations: ALT, alanine aminotransferase; AST, asparatate aminotransferase; BNP, B-type natriuretic peptide; BUN, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; UA, uric acid.

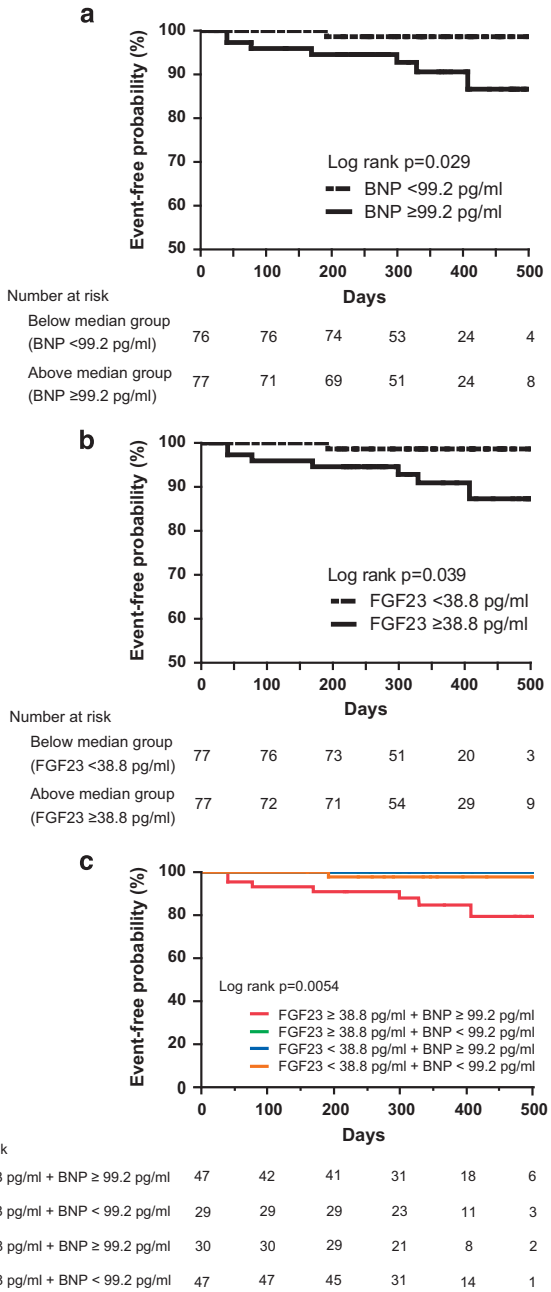

Figure 3 Kaplan–Meier analyses of cardiovascular events, that is, rehospitalization and cardiovascular death, in the above-/equal- and below-median BNP levels (**a**) and FGF23 levels (**b**), and the combination of BNP and FGF23 levels (**c**). The serum FGF23 levels predicted the incidence of cardiovascular death and/or hospitalization owing to HF, and the plasma BNP levels predicted these same clinical outcomes. The most potent predictor of cardiovascular outcomes was the combination of BNP and FGF23 levels in (**c**). BNP, B-type natriuretic peptide; FGF23, fibroblast growth factor 23; HF, heart failure.

Table 4 Multivariate analysis of right-heart catheterization data

	Model 1			*Model 2*		
	Regression coefficient	*95% CI*	P-*value*	*Regression coefficient*	*95% CI*	P-*value*
Mean RA pressure, mm Hg						
FGF23 (pg ml^{-1})	0.0334	0.007, 0.060	0.0129	0.0367	0.009, 0.065	0.0106
BNP (pg ml^{-1})	−0.00003	−0.002, 0.002	0.9775	0.00005	−0.002, 0.002	0.9595
Mean PA pressure, mm Hg						
FGF23 (pg ml^{-1})	0.096	0.026, 0.165	0.0073	0.0958	0.023, 0.169	0.0107
BNP (pg ml^{-1})	0.005	−0.0002, 0.009	0.0604	0.0045	−0.0003, 0.009	0.0641
Mean PCW pressure, mm Hg						
FGF23 (pg ml^{-1})	0.0649	0.015, 0.115	0.0110	0.0682	0.015, 0.121	0.0120
BNP (pg ml^{-1})	0.0049	0.002, 0.008	0.0048	0.0050	0.002, 0.008	0.0048

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrial.
Model 1 was unadjusted. Model 2 was adjusted for age, sex and eGFR.

Table 5 Multivariate analysis of mean PA pressure

	Multivariate analysis		
Variables	*Regression coefficient, mm Hg*	*95% CI*	P-*value*
Model 1			
FGF23 (pg ml^{-1})	0.054	−0.010, 0.118	0.0977
Mean RA pressure	1.342	0.972, 1.712	<0.0001
Model 2			
BNP (pg ml^{-1})	0.005	0.001, 0.009	0.0221
Mean RA pressure	1.394	1.033, 1.754	<0.0001

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PA, pulmonary artery; RA, right atrial
In the multivariate model, eGFR was adjusted.

Table 6 Multivariate Cox regression analysis for 500 days' cardiac events

Above-median value vs. below-median value	*HR*	*95% CI*	P-*value*
Model 1			
FGF23 (pg ml^{-1})	1.05	1.02–1.08	0.001
BNP (pg ml^{-1})	1.00	0.99–1.00	0.934
Model 2			
FGF23 (pg ml^{-1})	1.06	1.03–1.10	<0.001
BNP (pg ml^{-1})	1.00	0.99–1.00	0.903

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; HR, hazard ratio.
Model 1 was unadjusted. Model 2 was adjusted for age, sex and eGFR.

knowing the plasma BNP levels is not sufficient to understand the severity and pathophysiology of HF, given the diverse pathophysiological mechanisms underlying left- and right-sided HF.

In contrast, FGF23, which is produced in the bones in response to changes in serum phosphate levels,[21] affects cardiac function;[7] FGF23 increases phosphate efflux from the kidney and consequently reduces serum phosphate levels and causes cardiac hypertrophy.[22] Therefore, renal dysfunction caused by kidney congestion may decrease the efflux of phosphate to the urine and increase serum phosphate levels. Indeed, serum phosphate levels have been reported to increase in patients with HF,[8] and to contribute to the increased mortality and morbidity in these patients. In response to the renal congestion caused by elevated CVPs, serum phosphate levels may increase, which may in turn increase serum FGF23 levels. If this scenario were true, elevations in CVP and/or RA pressures might plausibly increase FGF23 levels, thus indicating that serum FGF23 levels may serve as a biomarker of HF, particularly, right-sided HF. Indeed, eGFR and plasma sodium levels, which may be the result of renal congestion or edema, are closely related to serum FGF23 levels (Table 3). RA pressure, which is the index of preload in the heart, was closely related to serum FGF23 levels, but not to plasma BNP levels. Table 4 shows the relatively stronger relationships of serum FGF23 levels with RA pressure and PA pressure. Interestingly, Table 5 shows that serum FGF23 levels were not associated with the mean PA pressure after accounting for RA pressure. Statistically, this result indicated that serum FGF23 levels were indirectly associated with PA pressure, suggesting that its levels were associated with PA pressures under the conditions of high RA pressures. In contrast, such findings were not observed in the relationship between serum BNP levels and PA pressure (Table 5). Furthermore, we showed that HF progression increased the production of FGF23 independent of renal dysfunction in the previous report, although we have not clarified how HF increases FGF23 levels.[9] Together, these findings raise the possibility that serum FGF23 levels may serve as a biomarker representing the conditions of both higher RA pressures and pulmonary hypertension, rather than lower RA pressure, even in a setting of pulmonary hypertension owing to elevations in LV end-diastolic pressure.

However, it was puzzling that the increases in serum FGF23 levels were positively correlated with a reduced CI, but not with increased CI, given that the increased preload following the FGF23 levels should have increased the CI. Indeed, the increased preload did not enhance the CI in the HF, but instead decreased it. Ross[23] has shown that when the preload reserve is fully utilized, the LV function easily moves to an apparent descending limb of the Frank–Starling curve and is followed by a decrease in CI. Another possible explanation for the connection between serum FGF23 levels and decreased CI is that FGF23 itself may worsen LV performance. Indeed, FGF23 has been reported to cause

cardiac hypertrophy and remodeling in animal models.[22] In this sense, FGF23 is an index of both left- and right-sided cardiac dysfunction. FGF23 levels may increase in response to the increased preload and the increased FGF23 may worsen ventricular function.

In contrast to the patterns of the FGF23 levels, the BNP levels corresponded to CI; the increase in the plasma BNP level was linked to a decrease in the CI. A low CI further increased both the PCW pressure and PA pressure, but did not affect RA pressure, because the majority of the plasma BNP was attributable to LV and because the BNP level is an index of stress in the LV.[10]

If the BNP level predominantly reflects the LV dysfunction and if FGF23 levels are associated with the LV dysfunction, and further indicate increases in the LV preload and RV dysfunction, then serum FGF23 levels may be a more sensitive indicator of the pathophysiology of HF than plasma BNP levels. This hypothesis seems to be supported by the results in Table 6, which shows that serum FGF23 may be a superior biomarker to the plasma BNP. At a minimum, we suggest that FGF23 levels reflected elements of the pathophysiology of HF that are not reflected by the plasma BNP levels in these patients, thus indicating that the serum FGF23 levels may be an independent and unique gauge of the pathophysiology of HF, and may be a predictor of the clinical outcomes of HF patients independently of BNP.

Limitations

Our study has some limitations. First, because this study was a single-center study, the number of patients was limited, particularly, those subjects with acute decompensated HF. Second, there was a selection bias in the patients who underwent right- and left-heart catheterizations; therefore, we analyzed a limited number of patients. We believe that our hypothesis should be evaluated in future multicenter trials. Clinically, RA pressure has often been investigated, not the CVP; thus, we performed our investigation using the RA pressure, not the CVP.

CONCLUSIONS

Serum FGF23 levels, compared with plasma BNP levels, are predominantly correlated with pressures on the right side of the heart. These findings suggest that serum FGF23 levels can predict the pathophysiology and clinical outcomes of the HF patients independently of plasma BNP levels, mainly in patients with right-sided HF.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno K, Tanaka K, Kasanuki H, Takano T, ATTEND Investigators. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. *Am Heart J* 2010; **159**: 949–955.e1.
2 Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; **53**: 589–596.
3 Gardner RS, Henderson G, McDonagh TA. The prognostic use of right heart catheterization data in patients with advanced heart failure: how relevant are invasive procedures in the risk stratification of advanced heart failure in the era of neurohormones? *J Heart Lung Transplant* 2005; **24**: 303–309.
4 Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; **53**: 582–588.
5 Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, Hillege HL. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. *Eur J Heart Fail* 2007; **9**: 872–878.
6 Wohlfahrt P, Melenovsky V, Kotrc M, Benes J, Jabor A, Franekova J, Lemaire S, Kautzner J, Jarolim P. Association of fibroblast growth factor-23 levels and angiotensin-converting enzyme inhibition in chronic systolic heart failure. *JACC Heart Fail* 2015; **3**: 829–839.
7 Seiler S, Cremers B, Rebling NM, Hornof F, Jeken J, Kersting S, Steimle C, Ege P, Fehrenz M, Rogacev KS, Scheller B, Bohm M, Fliser D, Heine GH. The phosphatonin fibroblast growth factor 23 links calcium-phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. *Eur Heart J* 2011; **32**: 2688–2696.
8 Plischke M, Neuhold S, Adlbrecht C, Bielesz B, Shayganfar S, Bieglmayer C, Szekeres T, Hörl WH, Strunk G, Vavken P, Pacher R, Hülsmann M. Inorganic phosphate and FGF-23 predict outcome in stable systolic heart failure. *Eur J Clin Invest* 2012; **42**: 649–656.
9 Imazu M, Takahama H, Asanuma H, Funada A, Sugano Y, Ohara T, Hasegawa T, Asakura M, Kanzaki H, Anzai T, Kitakaze M. Pathophysiological impact of serum fibroblast growth factor 23 in patients with nonischemic cardiac disease and early chronic kidney disease. *Am J Physiol Heart Circ Physiol* 2014; **307**: H1504–H1511.
10 Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, Goto Y, Nonogi H. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol* 2006; **47**: 742–748.
11 Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. *J Am Soc Nephrol* 2010; **21**: 1427–1435.
12 Kestenbaum B. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 520–528.
13 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285**: 1441–1446.
14 Shimizu Y, Fukumoto S, Fujita T. Evaluation of a new automated chemiluminescence immunoassay for FGF23. *J Bone Miner Metab* 2012; **30**: 217–221.
15 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
16 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.
17 Hasegawa T, Asakura M, Eguchi K, Asanuma H, Ohara T, Kanzaki H, Hashimura K, Tomoike H, Kim J, Kitakaze M. Plasma B-type natriuretic peptide is a useful tool for assessing coronary heart disease risk in a Japanese general population. *Hypertens Res* 2015; **38**: 74–79.

18 Harada M, Itoh H, Nakagawa O, Ogawa Y, Miyamoto Y, Kuwahara K, Ogawa E, Igaki T, Yamashita J, Masuda I, Yoshimasa T, Tanaka I, Saito Y, Nakao K. Significance of ventricular myocytes and nonmyocytes interaction during cardiocyte hypertrophy: evidence for endothelin-1 as a paracrine hypertrophic factor from cardiac nonmyocytes. *Circulation* 1997; **96**: 3737–3744.
19 Kuwahara K, Saito Y, Harada M, Ishikawa M, Ogawa E, Miyamoto Y, Hamanaka I, Kamitani S, Kajiyama N, Takahashi N, Nakagawa O, Masuda I, Nakao K. Involvement of cardiotrophin-1 in cardiac myocyte-nonmyocyte interactions during hypertrophy of rat cardiac myocytes *in vitro*. *Circulation* 1999; **100**: 1116–1124.
20 Desai AS. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are not useful in heart failure management: the art of medicine remains long. *Circulation* 2013; **127**: 509–516.
21 Riminucci M, Collins MT, Fedarko NS, Cherman N, Corsi A, White KE, Waguespack S, Gupta A, Hannon T, Econs MJ, Bianco P, Gehron Robey P. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. *J Clin Invest* 2003; **112**: 683–692.
22 Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro OM, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121**: 4393–4408.
23 Ross J Jr. Mechanisms of cardiac contraction. What roles for preload, afterload and inotropic state in heart failure? *Eur Heart J* 1983; **4**(Suppl A): 19–28.