Biomarkers of Left Atrial Volume
A Longitudinal Study in Patients With End Stage Renal Disease

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Abstract—Left atrial volume (LAV) has recently emerged as a useful biomarker for risk stratification and risk monitoring in patients with end stage renal disease. We investigated the relationship between cardiac natriuretic peptides (atrial natriuretic peptide [ANP] and brain natriuretic peptide [BNP]) and norepinephrine (NE) with LAV and LAV changes over time in 199 end stage renal disease patients. At baseline, LAV was directly related to BNP (r=0.60), ANP (r=0.59), and NE (r=0.28; $P<0.001$), and these relationships held true in multiple-regression models adjusting for potential confounders ($P\leq0.003$). In the longitudinal study (17±2 months), LAV increased from 9.8±4.6 to 10.9±5.4 mL/m$^{2.7}$ (+11%). In a multiple linear regression model, BNP (β=0.28; P=0.003), ANP (β=0.22; P=0.03), and NE (β=0.27; P=0.003) predicted LAV changes. The area under the receiver operating characteristic curve for predicting LAV changes (>3 mL/m$^{2.7}$ per year) of a risk score on the basis of standard risk factors was 0.72. Plasma BNP (+12%; P=0.004), ANP (+8%; P=0.03), NE (+8%; P=0.05) and midwall fraction shortening (+8%; P=0.05) increased the area under the receiver operating characteristic curve to a significant extent, whereas LV mass did not (+5%; P=0.18). Predictive models, including BNP, ANP, and NE, maintained a satisfactory discriminatory power for LAV and LAV changes also when tested by a bootstrap resampling technique. BNP and ANP are strongly related to LAV in the end stage renal disease patients and predict LAV changes over time in these patients. Because an increased LAV underlies diastolic dysfunction and/or volume overload (ie, potentially modifiable risk factors), the measurement of the plasma concentration of these compounds might be useful for risk stratification and for guiding treatment in dialysis patients. **(*Hypertension*. 2009;54:818-824.)**

Key Words: atrial natriuretic peptide ■ brain natriuretic peptide ■ end stage renal disease ■ left atrial volume ■ norepinephrine

Left atrial volume (LAV), as measured by echocardiography, has emerged recently as a biomarker of potential value for risk stratification[1] and risk monitoring[2] in patients with end stage renal disease (ESRD). Indeed, LAV and LAV changes over time predict death and cardiovascular (CV) outcomes also beyond established echocardiographic markers of high CV risk, like left ventricular (LV) mass (LVM) and LV systolic function.[1,2] Although echocardiography is formally recommended as a fundamental tool for risk stratification in ESRD patients,[3] because of cost and logistic problems, this technique is applied less than needed in many centers. Biomarker research on anatomic and functional alterations of the heart is a growing, promising clinical research area.[4] We have shown previously that atrial natriuretic peptide (ANP), a hormone mainly produced in the atrium, and brain natriuretic peptide (BNP), a hormone secreted by ventricular cardiomyocytes, are reasonably accurate markers of LVM and LV systolic function in ESRD patients.[5,6] The relationship between cardiac natriuretic peptides and LAV and the diagnostic and prognostic values of these peptides for LAV enlargement and for LAV evolution over time have never been tested in well-powered longitudinal studies in an ESRD population. The issue is of importance, because factors predisposing to LAV enlargement in ESRD are in part modifiable by pharmacological and nonpharmacological interventions.

High plasma norepinephrine (NE) is a risk factor for concentric LV hypertrophy (LVH) in ESRD,[7] which is, in turn, a strong determinant of altered diastolic dysfunction.[8] Because, independent of other risk factors, altered LV diastolic function is associated with LAV enlargement,[1] we hypothesized that high plasma NE may contribute to explain the variability in LAV and LAV changes over time in ESRD.

In the present study, we have investigated whether plasma levels of cardiac natriuretic peptides and NE are associated with LAV and whether on longitudinal observation these biomarkers predict LAV progression in a cohort of ESRD patients without clinical evidence of heart failure at baseline.

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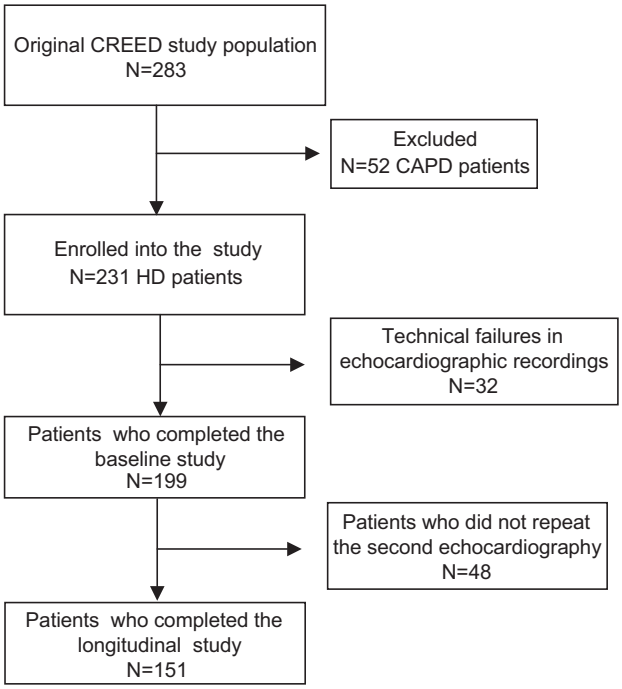

Figure 1. Enrollment scheme of the study. CREED indicates Cardiovascular Risk Extended Evaluation in Dialysis Study patients; CAPD, chronic ambulatory peritoneal dialysis.

Methods

The protocol conformed to the Declaration of Helsinki, and informed consent was obtained from each participant. All of the studies were performed between 8:00 AM and 1:00 PM.

Study Cohort

The original Cardiovascular Risk Extended Evaluation in Dialysis Study cohort was formed by 283 ESRD patients (231 on hemodialysis [HD] and 52 on chronic ambulatory peritoneal dialysis; Figure 1). By protocol, we excluded 52 patients because they were on chronic ambulatory peritoneal dialysis. Among the remaining 231 HD patients, 32 patients were excluded for technical failure in echocardiographic recordings. Hence, 199 HD patients (age: 59±15 years; 111 men and 88 women) were available for the baseline analysis (Table 1). These patients had been on regular dialysis treatment for ≥6 months (median dialysis vintage: 43 months; interquartile range: 20 to 110 months). The enrollment criteria in this cohort were as follows: (1) no history of congestive heart failure (defined as dyspnea in addition to 2 of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest radiograph, requiring hospitalization or extra ultrafiltration); (2) LV ejection fraction >35%; and (3) no intercurrent or terminal illnesses. The average fractional urea clearance in these patients was 1.22±0.27. A total of 109 patients were on treatment with erythropoietin. Seventy-seven patients were being treated with antihypertensive drugs (53 on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II type 1 antagonists, calcium channel blockers, α-blockers, or β-blockers and 24 on double or triple therapy with various combinations of these drugs). All of the patients were being treated thrice weekly with standard bicarbonate dialysis (Na, 138.00 mmol/L; HCO3, 35.00 mmol/L; K, 1.50 mmol/L; Ca, 1.25 mmol/L; and Mg, 0.75 mmol/L) and cuprophane or semisynthetic membranes (dialysis filters surface area: 1.1 to 1.7 m^2).

Patients Who Repeated the Echocardiographic Study

Forty-eight patients of 199 who entered into the study did not repeat the second echocardiography because they died, were transplanted, or for logistic reasons (Figure 1). Thus, 151 ESRD patients underwent a first and a second echocardiography after a mean follow-up of 17±2 months. No patient had severe valvular heart disease, and only a minority had mild-to-moderate valvular heart disease (n=16).

Echocardiography

These studies were performed midweek on a nondialysis day. At the time of the echocardiographic examination, investigators involved in echocardiographic studies were unaware of patients' clinical data. LVM was calculated according to the Devereux formula and indexed to height$^{2.7}$ (LVMI), as proposed by De Simone et al.[9] LAV was calculated by the biplane method of discs[10] at the end of left ventricle systole. LAV data were analyzed as height$^{2.7}$ indexed estimates, because this indexation provides the best prognostic power in dialysis patients.[1] Midwall fractional shortening (mwFS) was calculated according to the method of Shimizu et al,[11] as described in full detail by De Simone et al.[12] Changes in LAV were quantified by subtracting LAV at the second study from that obtained at the baseline study and by factoring this difference for the time interval between the 2 studies. As a normal value for LAV, we considered the 95th percentile of the LAV distribution in a group of 100 subjects without heart disease (ie, 12 mL/$m^{2.7}$).[1]

Blood Pressure and Interdialysis Weight Gain Measurements

Predialysis blood pressure[13] and interdialysis weight gain were calculated as average values of 12 recordings (3 per week) taken by the nurses during the month preceding the echocardiographic study.

Biochemical Measurements

Blood sampling for biochemical measurements was performed before echocardiographic studies. Serum lipids, albumin, calcium, phosphate, and hemoglobin were measured by standard methods in the routine clinical laboratory. The plasma concentration of NE was measured by a commercially available radioimmunoassay kit (Amicyl-Test, Immunologic Laboratories). The upper limit of the normal range of plasma norepinephrine in our laboratory is 3.54 nmol/L. The plasma concentrations of α-human ANP (normal value: <27 pmol/L) and BNP (normal value: <7.8 pmol/L) were measured by commercially available radioimmunoassay kits (Peninsula Laboratory Europe Ltd) after pre-extraction by reverse chromatography (Seppak C-18 cartridges, Waters). Recovery was >80% both for ANP and BNP. There was no cross-reactivity between the 2 assays. The between-assay and within-assay coefficients of variability were 8% and 10% for ANP and 9% and 11% for BNP. The methods used for the determination of serum C-reactive protein and plasma total homocysteine were detailed in a previous study.[14]

Statistical Analysis

Data are expressed as mean±SD (normally distributed data), median, and interquartile range (nonnormally distributed data) or as percentage frequencies. Within-subject comparisons were made by paired t test and χ^2 test, as appropriate. The relationship between paired variables was analyzed by Pearson product moment correlation coefficient. Variables that showed a positively skewed distribution were log transformed before the correlation study.

The independent correlates of baseline LAV and LAV changes were identified by univariate and multiple linear regression analyses. The following variables were considered for multiple linear regression analyses: plasma ANP, plasma BNP, and plasma NE, as well as age, sex, smoking, diabetes mellitus, systolic pressure, LV mass (LVMI), LV systolic function (mwFS), total cholesterol, hemoglobin, albumin, calcium phosphate product, homocysteine, C-reactive protein, CV comorbidities, and interdialysis weight gain. Data are expressed as regression coefficients, SEs of regression coefficients, and standardized regression coefficient (β) and P value. The predictive values of ANP, BNP, and NE for both LAV enlargement at baseline (>12 mL/$m^{2.7}$) and LAV enlargement over time (>3 mL/$m^{2.7}$ per year, which corresponds with the average +1 SD of LAV changes in the whole study cohort) beyond and above that

Table 1. Main Demographic, Somatometric, Clinical, and Biochemical Data in the Study Population

Variables	Original Study Population (n=199)	Patient Who Repeated the Echocardiographic Study (n=151)		*P* (First Visit vs Second Visit)
		First Visit	Second Visit	
Age, y	59±15	57.9±1.2	59.4±15.3	<0.001
Male sex, n (%)	111 (56)	85 (56)	85 (56)	1.0
Smokers, n (%)	78 (39)	53 (35)	53 (35)	1.0
Diabetics, n (%)	26 (13)	17 (11)	17 (11)	1.0
On antihypertensive therapy, n (%)	77 (39)	54 (36)	50 (33)	0.72
Systolic pressure, mm Hg	140±25	139±24	136±27	0.13
Diastolic pressure, mm Hg	77±13	76±13	75±14	0.15
Interdialysis weight gain, %	4.2±1.2	4.3±1.2	4.5±1.7	0.27
Kt/V	1.22±0.27	1.23±0.27	1.33±0.25	<0.001
Cholesterol, mg/dL	206±56	203±55	175±47	<0.001
Hemoglobin, g/L	106±19	105±18	109±16	0.004
Albumin, g/L	42±5	42±5	36±5	<0.001
Calcium*phosphate, $mmol^2/L^2$	4.5±1.2	4.5±1.2	4.3±1.2	0.006
C-reactive protein, mg/L	7.6 (3.4 to 16.3)	7.4 (3.4 to 16.0)	NA	…
Homocysteine, μmol/L	26.5 (19.3 to 42.7)	24.3 (18.2 to 38.3)	NA	…
Norepinephrine, nmol/L	3.13 (1.78 to 5.65)	3.26 (1.71 to 5.73)	NA	…
BNP, pmol/L	22.5 (8.4 to 43.4)	22.3 (8.4 to 37.6)	NA	…
ANP, pmol/L	22.7 (14.9 to 38.8)	22.1 (14.9 to 38.0)	NA	…
LAV, $mL/m^{2.7}$	10.2±5.0	9.8±4.6	10.9±5.4	<0.001
LVMI, $g/m^{2.7}$	61.3±18.7	59.9±17.9	64.0±19.4	<0.001
mwFS, %	14.5±3.3	14.7±3.3	14.4±2.7	0.19
E/A ratio	0.79±0.28	0.80±0.30	0.79±0.28	0.55

Data are expressed as mean±SD, median, and interquartile range or as percentage frequency, as appropriate. The *P* value in the last column refers to the comparison between variables in the first visit and the same set of variables in the second visit. Kt/V denotes fractional urea clearance.

provided by standard risk factors were also investigated by analyzing the area under receiving operating characteristic (ROC) curves. ROC curves were compared by using the standard method.[15] To assess the discriminatory power of prediction models, a bootstrap resampling technique of 200 samples was performed.[16] Statistical analyses were done with standard statistical packages (SPSS for Windows version 9.0.1 and R for Windows version 2.8.1 by R Foundation for Statistical Computing).

Results

Initial Survey

The original study population included 199 HD patients (Table 1). Plasma ANP and BNP exceed the upper limit of the corresponding normal range in 149 (76%) and in 82 (42%) ESRD patients, respectively. Plasma NE was higher than the normal threshold in 91 patients (46%). On univariate analysis, plasma BNP ($r=0.60$; $P<0.001$), plasma ANP ($r=0.59$; $P<0.001$), and plasma NE ($r=0.28$; $P<0.001$) were all significantly related to LAV (Figure 2). Of note, the association between BNP and ANP with LAV (Figure 2) was coherently stronger than that between the same peptides with LVMI (BNP-LVMI: $r=0.53$, $P<0.001$; ANP-LVMI: $r=0.53$; $P<0.001$) and mwFS (BNP-mwFS: $r=-0.52$, $P<0.001$; ANP-mwFS: $r=-0.42$, $P<0.001$). The relationship between natriuretic peptides and NE with LAV was almost unmodified by multiple data adjustment (Table 2) controlling for Framingham risk factors and factors peculiar to ESRD, homocysteine, C-reactive protein, CV comorbidities, and interdialysis weight gain (a surrogate of volume expansion). Additional adjustment for LVMI and mwFS produced only a moderate reduction in the strength of these associations, which all remained highly significant (BNP-LAV: $\beta=0.39$, $P<0.001$; ANP-LAV: $\beta=0.41$, $P<0.001$; NE-LAV: $\beta=0.20$, $P=0.001$).

Fifty-five patients (28%) of 199 had LAV above the upper limit of the normal range (cutoff: 12 $mL/m^{2.7}$). On ROC curve analysis, both BNP and ANP had higher discriminatory powers for identifying patients with baseline LAV >12 $mL/m^{2.7}$ compared with plasma NE, LVMI, and mwFS (Table 3), and both of these peptides added significant discriminatory powers to a score for LAV enlargement on the basis of standard risk factors (model 1; Table 3), whereas the gains in predictive values provided by LVMI, mwFS, and NE were smaller and not significant ($P\geq0.07$; Table 3). Neither the simultaneous inclusion of LVMI and mwFS into the risk score nor combinations of ANP, BNP, and NE measurements provided significant additional discriminatory power in comparison with that by BNP or ANP considered separately. Bootstrap resampling validation substantially confirmed these results (Table 3).

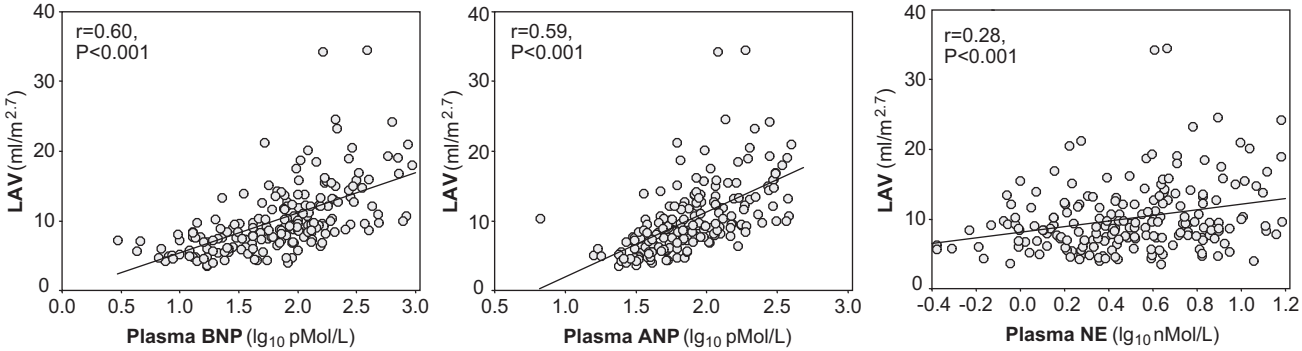

Figure 2. Relationship among plasma BNP, plasma ANP, and plasma NE with baseline LAV. Data are Pearson product moment correlation coefficient and *P* value. Because BNP, ANP, and NE had a positively skewed distribution, these variables were log transformed (lg_{10}) before the correlation study.

Longitudinal Study

Patients who repeated echocardiography (n=151) did not differ from those of the original cohort (n=199; Table 1). LAV increased from 9.8±4.6 to 10.9±5.4 mL/m$^{2.7}$ (+11%; $P<0.001$). Individual changes in LAV were inversely related to baseline LAV ($r=-0.17$; $P=0.04$), implying that regression to the mean may be a confounder for the interpretation of the evolution of LAV over time. To allow for this relationship, we adjusted LAV changes for corresponding baseline values and used this estimate as an outcome measure in the data analysis. Significant differences between the first and the second echocardiographic studies were also observed in serum cholesterol, fractional urea clearance, hemoglobin, albumin, and calcium phosphate product (Table 1). The rate of increase in LAV was higher in patients with concentric LVH (1.20±2.70 mL/m$^{2.7}$ per year) than in those without (0.52±2.07 mL/m$^{2.7}$ per year). Plasma BNP ($r=0.23$; $P=0.004$), ANP ($r=0.17$; $P=0.04$), NE ($r=0.25$; $P=0.002$), homocysteine ($r=0.19$; $P=0.02$), mwFS ($r=-0.20$; $P=0.01$), and interdialysis weight gain ($r=0.16$; $P=0.05$) were all related to LAV changes. Multiple linear regression analysis indicated that the association among plasma BNP ($\beta=0.28$; $P=0.003$), ANP ($\beta=0.22$; $P=0.03$), and NE ($\beta=0.27$; $P=0.003$) with LAV changes (Table 4) was independent of other risk factors.

The predictive values of BNP, ANP, and NE for changes in LAV were further investigated by ROC curve analysis. Patients were divided into 2 groups, below and above our prespecified definition of progressive LAV enlargement over time (ie, an LAV increase exceeding the average change +1S D [3 mL/m$^{2.7}$ per year]). This analysis showed that BNP had a higher discriminatory power (area under the curve: 0.75) as compared with that of ANP, NE, LVMI, and mwFS (Table 3). The area under the ROC curve of a risk score on the basis of Framingham risk factors, CV comorbidities, hemoglobin, albumin, calcium phosphate product, C-reactive protein, homocysteine, and interdialysis weight gain was 0.72. Plasma BNP (+12%; $P=0.004$), ANP (+8%; $P=0.03$), NE (+8%; $P=0.05$), and mwFS (+8%; $P=0.05$) increased to a significant extent the area under the ROC curve, whereas LVMI did not (+5%; $P=0.18$; Table 3). Neither the simultaneous inclusion of LVMI and mwFS nor combinations of ANP, BNP, and NE provided significant additional discriminatory information in comparison with the risk score and BNP.

The discriminatory power of the model including BNP and NE (area under ROC curve: 87%) was marginally superior to that including the 2 cardiac natriuretic peptides (area under ROC curve: 84%) or to that including ANP and NE (area under ROC curve: 84%). Natriuretic peptides and NE maintained an adequate discriminatory power for identifying LAV enlargement also when tested by a bootstrap resampling technique (Table 3).

Discussion

In a cohort of ESRD patients without clinical evidence of heart failure, cardiac natriuretic peptides and NE emerged as independent correlates of LAV and predicted LAV enlargement over time independent of Framingham risk factors, factors peculiar to ESRD, and other risk factors. Notably, both in the initial survey and in the longitudinal analysis, the predictive power for LAV enlargement of these biomarkers was higher than that provided by LV mass and function.

Left Atrium in ESRD Patients

LA enlargement, as measured by echocardiography, is a common finding in the dialysis population.[1] LV systolic and diastolic dysfunctions,[1,17] valvular heart disease,[18] extracellular volume expansion,[19–21] LVH,[1] and hypertension[1] are all regarded as likely mechanisms leading to LA remodeling in this population. LAV enlargement predicts mortality over and above LVH and LV dysfunction and other risk factors in ESRD,[1] and LAV monitoring provides prognostic information beyond that of these major echocardiographic markers of high CV risk.[2] These observations, which are germane to findings in population-based studies,[22] mildly hypertensive individuals,[23] and in patients with heart disease,[24] coherently establish LAV as a relevant prognostic factor in ESRD and expand the information that can be obtained by standard echocardiography. Notwithstanding the fact this technique is formally recommended by practice guidelines[3] as an important tool for risk stratification in chronic kidney disease, because of cost and logistic reasons it is applied less than needed in many dialysis centers. To surrogate information by echocardiography, several studies investigated the diagnostic and prognostic values for major clinical events of biomarkers

Table 2. Multiple Regression Models of Baseline LAV

Model	Units of Measure	b±SE	β (P)
BNP-based model			
BNP	lg_{10} pmol/L	5.50±0.67	0.56 (<0.001)
CV comorbidities	0=no; 1=yes	1.71±0.67	0.17 (0.01)
Hemoglobin	g/L	−0.02±0.02	−0.07 (0.28)
Homocysteine	lg_{10} μmol/L	1.00±1.20	0.05 (0.41)
C-reactive protein	lg_{10} mg/L	−0.56±0.73	−0.05 (0.44)
Albumin	g/L	0.05±0.07	0.05 (0.49)
Age	y	0.02±0.02	0.05 (0.50)
Cholesterol	mg/dL	0.003±0.006	−0.04 (0.57)
Sex	0=F; 1=M	−0.12±0.71	−0.01 (0.87)
Interdialysis weight gain	kg	−0.05±0.40	−0.008 (0.90)
Systolic pressure	mm Hg	−0.001±0.01	−0.007 (0.91)
Calcium phosphate product	$mmol^2/L^2$	−0.03±0.26	−0.007 (0.91)
Diabetes mellitus	0=no; 1=yes	−0.04±0.93	−0.003 (0.97)
Smoking	0=no; 1=yes	−0.02±0.69	0.002 (0.97)
Constant: −1.477			
ANP-based model			
ANP	lg_{10} pmol/L	8.89±1.09	0.57 (<0.001)
CV comorbidities	0=no; 1=yes	1.79±0.67	0.18 (0.008)
C-reactive protein	lg_{10} mg/L	−0.84±0.73	−0.07 (0.25)
Hemoglobin	g/L	−0.01±0.02	−0.05 (0.42)
Albumin	g/L	0.06±0.07	0.06 (0.44)
Homocysteine	lg_{10} μmol/L	0.79±1.21	0.04 (0.51)
Sex	0=F; 1=M	−0.40±0.72	−0.04 (0.58)
Age	y	0.007±0.02	0.02 (0.76)
Systolic pressure	mm Hg	0.0003±0.01	0.02 (0.80)
Interdialysis weight gain	kg	0.09±0.40	0.01 (0.83)
Calcium phosphate product	$mmol^2/L^2$	−0.05±0.26	−0.02 (0.84)
Smoking	0=no; 1=yes	0.03±0.70	0.003 (0.96)
Cholesterol	mg/dL	0.00004±0.006	0.00 (1.00)
Diabetes mellitus	0=no; 1=yes	0.004±0.93	0.00 (1.00)
Constant: −9.452			
NE-based model			
NE	lg_{10} nmol/L	1.89±0.62	0.31 (0.003)
CV comorbidities	0=no; 1=yes	−0.62±0.44	0.24 (0.002)
Systolic pressure	mm Hg	0.007±0.009	0.15 (0.04)
Albumin	g/L	−0.06±0.04	−0.15 (0.05)
Homocysteine	lg_{10} μmol/L	1.61±0.78	0.07 (0.33)
Hemoglobin	g/L	−0.004±0.01	−0.12 (0.10)
Smoking	0=no; 1=yes	0.43±0.47	0.11 (0.14)
Interdialysis weight gain	kg	0.41±0.28	−0.09 (0.24)
Sex	0=F; 1=M	−0.19±0.48	−0.04 (0.59)
C-reactive protein	lg_{10} mg/L	0.17±0.48	−0.04 (0.62)
Calcium phosphate product	$mmol^2/L^2$	0.14±0.17	−0.03 (0.66)
Diabetes mellitus	0=no; 1=yes	0.036±0.70	0.03 (0.66)
Cholesterol	mg/dL	0.002±0.004	−0.02 (0.75)
Age	y	−0.01±0.01	−0.01 (0.85)
Constant: 13.194			

Data are expressed as regression coefficients (b), SE of the regression coefficient, standardized regression coefficients (β), and P values. F indicates female; M, male.

Table 3. ROC Curve Analyses of Natriuretic Peptides, NE, LVMI, and mwFS for LAV Enlargement and Additional Discriminatory Power of These Variables Above and Beyond That Provided by Standard Risk Factors (Basic Model)

	AUC for LAV >12 $mL/m^{2.7}$		AUCs for LAV Changes >3 $mL/m^{2.7}$ per y	
Variables	Original Set	Bootstrap Validation	Original Set	Bootstrap Validation
ANP	0.82	0.83	0.68	0.70
BNP	0.83	0.82	0.75	0.75
NE	0.65	0.72	0.70	0.72
BNP+NE	0.81	0.86	0.73	0.72
BNP+ANP	0.82	0.78	0.75	0.67
ANP+NE	0.81	0.82	0.72	0.63
LVMI	0.77	0.77	0.61	0.59
mwFS	0.75	0.73	0.71	0.71
LVMI+mwFS	0.79	0.79	0.71	0.71
Prediction models				
Model 1*	0.73	0.76	0.72	0.60
Model 1+ANP	0.86	0.85	0.80	0.78
Model 1+BNP	0.85	0.83	0.84	0.78
Model 1+NE	0.80	0.79	0.80	0.81
Model 1+BNP+NE	0.86	0.87	0.87	0.86
Model 1+BNP+ANP	0.87	0.89	0.84	0.82
Model 1+ANP+NE	0.87	0.89	0.84	0.80
Model 1+LVMI	0.80	0.79	0.77	0.64
Model 1+mwFS	0.81	0.81	0.80	0.63
Model 1+LVMI+mwFS	0.83	0.83	0.81	0.64

LAV enlargement at baseline was defined as an LAV exceeding the upper limit of the normal range (>12 $mL/m^{2.7}$) in a series of 100 individuals without CV disease studied at our institution. LAV enlargement progression over time was defined as an increase exceeding the average change +1 SD (3 $mL/m^{2.7}$ per year).

*Model 1 includes: age, sex, smoking, diabetes mellitus, cholesterol, CV comorbidities, hemoglobin, albumin, calcium phosphate product, C-reactive protein, homocysteine, and interdialysis weight gain.

of LVM and function.[25] The relationship between LAV and ANP was studied in detail in a recent population-based survey.[26] However, until now there was virtually no information on cardiac natriuretic peptides as biomarkers of LAV and as predictors of LAV enlargement over time in the ESRD population.

Cardiac Natriuretic Peptides and NE as Biomarkers of LAV in ESRD Patients

Under physiological conditions, the atria represent the most rich source of circulating ANP, whereas BNP synthesis in this cardiac chamber is relatively small.[27] In the presence of volume overload, LVH, and/or LV dysfunction (ie, in pathophysiological situations that commonly occur in ESRD), the synthesis of BNP in the left atrium increases substantially and matches that of ANP.[28,29] Because of the lack of renal clearance, these peptides accumulate in ESRD. However, it was also shown that, in ESRD, plasma levels of ANP and BNP mainly depend on alterations in LV mass and function

Table 4. Multiple Regression Models for LAV Changes (Adjusted for LAV at Baseline)

Model	Units of Measure	b±SE	β (*P*)
BNP-based model			
BNP	lg_{10} pmol/L	1.32±0.43	0.28 (0.003)
Homocysteine	lg_{10} μmol/L	1.68±0.78	0.20 (0.03)
Interdialysis weight gain	kg	0.60±0.27	0.20 (0.03)
CV comorbidities	0=no; 1=yes	−0.71±0.44	−0.15 (0.11)
Calcium phosphate product	$mmol^2/L^2$	0.20±0.17	0.10 (0.24)
Cholesterol	mg/dL	0.0004±0.004	0.07 (0.44)
Albumin	g/L	−0.02±0.04	−0.05 (0.62)
Diabetes mellitus	0=no; 1=yes	−0.28±0.68	−0.04 (0.68)
Systolic pressure	mm Hg	−0.002±0.009	−0.02 (0.80)
Sex	0=F; 1=M	0.12±0.46	0.03 (0.80)
Age	y	−0.003±0.01	−0.02 (0.82)
C-reactive protein	lg_{10} mg/L	0.09±0.48	0.02 (0.84)
Hemoglobin	g/L	0.0009±0.01	0.007 (0.94)
Smoking	0=no; 1=yes	−0.02±0.47	−0.004 (0.96)
Constant: −5.055			
ANP-based model			
ANP	lg_{10} pmol/L	1.60±0.71	0.22 (0.03)
Interdialysis weight gain	kg	0.60±0.28	0.20 (0.03)
Homocysteine	lg_{10} μmol/L	1.60±0.80	0.19 (0.05)
CV comorbidities	0=no; 1=yes	−0.69±0.45	−0.14 (0.12)
Calcium phosphate product	$mmol^2/L^2$	0.19±0.17	0.10 (0.25)
Cholesterol	mg/dL	0.004±0.004	0.09 (0.35)
Albumin	g/L	−0.03±0.04	−0.07 (0.52)
Diabetes mellitus	0=no; 1=yes	−0.29±0.70	−0.04 (0.68)
Age	y	−0.005±0.01	−0.04 (0.71)
Sex	0=F; 1=M	0.09±0.47	0.02 (0.85)
Hemoglobin	g/L	0.001±0.01	0.01 (0.91)
Systolic pressure	mm Hg	0.0003±0.009	0.003 (0.97)
C-reactive protein	lg_{10} mg/L	0.02±0.49	0.003 (0.97)
Smoking	0=no; 1=yes	0.01±0.47	0.002 (0.98)
Constant: −5.462			
NE-based model			
NE	lg_{10} nmol/L	1.89±0.62	0.27 (0.003)
Homocysteine	lg_{10} μmol/L	1.61±0.78	0.19 (0.04)
Interdialysis weight gain	kg	0.41±0.28	0.14 (0.15)
Albumin	g/L	−0.06±0.04	−0.13 (0.15)
CV comorbidities	0=no; 1=yes	−0.62±0.44	−0.13 (0.16)
Age	y	−0.01±0.01	−0.10 (0.31)
Smoking	0=no; 1=yes	0.43±0.47	0.09 (0.36)
Calcium phosphate product	$mmol^2/L^2$	0.14±0.17	0.07 (0.40)
Systolic pressure	mm Hg	0.007±0.009	0.08 (0.40)
Cholesterol	mg/dL	0.002±0.004	0.04 (0.66)
Sex	0=F; 1=M	−0.19±0.48	−0.04 (0.69)
Hemoglobin	g/L	−0.004±0.01	−0.03 (0.71)
C-reactive protein	lg_{10} mg/L	0.17±0.48	0.03 (0.72)
Diabetes mellitus	0=no; 1=yes	0.036±0.70	0.005 (0.96)
Constant: −1.743			

Data are expressed as regression coefficients (b), SE of the regression coefficient, standardized regression coefficients (β), and *P* values. F indicates female; M, male.

rather than on reduced renal clearance.[5] As to the relative prognostic value of these peptides, BNP may be a more accurate marker of increased intracavitary pressure and LV dysfunction[30] than ANP, because the induction of BNP mRNA is faster[31] and more responsive to stretch[32] than that of ANP. Accordingly, we found that BNP displayed a stronger association with LAV changes over time than ANP. In particular, the additional predictive value for progressive LAV enlargement of BNP above established risk factors was higher (+12%) than that provided by ANP (+8%). Notably, this additional prognostic information by BNP was also superior to that of echocardiographic parameters of LV mass (+5%) and function (+8%). Our study did not include direct measurements of a fundamental determinant of LAV (ie, extracellular volume). Observations on the basis of a very large dialysis population have shown recently that interdialysis weight gain, a surrogate of volume expansion, predicts death and CV events in ESRD.[33] We found that this surrogate predicts progression in LAV enlargement, thus implicating volume expansion in progressive LAV enlargement and associated alterations in LV mass and function in ESRD.

NE is a marker of sympathetic activity and a risk factor for CV events in ESRD patients.[34] This neurotransmitter promotes myocardial cell hypertrophy in vitro,[35] and it was shown that ESRD patients with high NE have a high risk of concentric LVH.[7] We found that LAV changes were more pronounced in patients with concentric LVH than in those without, suggesting that high NE is a critical element in the chain of events leading to LAV enlargement via concentric LVH and diastolic dysfunction.

An important question addressed in our study was whether a strategy based on single biomarkers is preferable to one based on multiple biomarkers for predicting the evolution of LAV over time. We found that the simultaneous measurements of BNP and NE were marginally superior (*P* value not significant) to the ANP-BNP combination and that both combinations were better than isolated measurements of the same compounds. BNP and ANP are strongly interrelated and, therefore, provide overlapping predictive information. The small gain in predictive power by the BNP-NE combination may depend on the fact that these biomarkers reflect partially nonoverlapping pathophysiological pathways leading to LAV enlargement. Whether the additional information provided by the multiple biomarkers strategy translates into better clinical outcomes is an important clinical question that remains to be investigated in future clinical trials.

Our study has limitations. First, although the bootstrap procedure is a powerful technique to internally validate prediction models,[16] our findings need to be externally validated in other cohorts of ESRD patients. Second, the use of a single measurement of biomarkers predicting LAV changes may have generated "regression dilution bias."[36] However, this bias generally leads to an underestimation, rather than to an overestimation, of the true relationship between a predictor and a given outcome variable.

Perspectives

Plasma BNP and ANP are strongly related to LAV in the ESRD patients and predict LAV changes over time in these

patients. Because an increased LAV underlies diastolic dysfunction and/or volume overload (ie, potentially modifiable risk factors), the measurement of the plasma concentration of these compounds might be useful for risk stratification and for guiding treatment in dialysis patients.

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Disclosures

None.

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