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Diagnostic potential of cardiac natriuretic peptides in dialysis patients

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Background. In the general population, the plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are useful to predict left ventricular hypertrophy (LVH) and LV systolic dysfunction. Whether these cardiac hormones have a similar diagnostic potential in dialysis patients is unknown.

Methods. We studied the diagnostic value of ANP and BNP for alterations in LV mass and function in a cohort of 246 dialysis patients without clinical evidence of heart failure.

Results. Both ANP and BNP were independently related to left ventricular mass ($P < 0.0001$) as well as to ejection fraction ($P < 0.0001$). In an analysis based on a prospectively defined threshold (95th percentile of the normal range), BNP had a significantly higher ($P < 0.01$) sensitivity (88%) than ANP (51%) for the diagnosis of LVH, but the positive predictive value of the two peptides was very similar (92 and 87%, respectively, P = NS). However, the negative predictive value of BNP for excluding LVH was 22% higher than that of ANP (53 vs. 31%, $P = 0.05$). Both natriuretic peptides had a high sensitivity for the detection of LV dysfunction (87 and 94%), but their positive predictive value was low (25 and 15%). Importantly, both ANP and BNP proved to be very useful for excluding this alteration (negative predictive value 97 and 96%, respectively). An analysis based on the "best cut-offs" of each peptide as identified on the basis of the ROC curves augmented the positive and negative prediction values of BNP for the diagnosis of LVH to 95 and 61%, respectively. This approach also raised the BNP-positive prediction value for the identification of LV dysfunction to 31% but did not modify the diagnostic potential of ANP (either for LVH or for LV dysfunction).

Conclusions. Measuring the plasma concentration of cardiac natriuretic hormones, particularly BNP, may be useful for the identification of dialysis patients with LVH or for excluding systolic dysfunction.

The observations that the synthesis of atrial and ventricular natriuretic peptides is enhanced in the presence of alterations in left ventricular (LV) mass and function, and that this phenomenon reliably reflects the severity of left ventricular hypertrophy (LVH) and systolic dysfunction have focused much attention on the potential diagnostic value of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in clinical practice [1–6]. ANP is released by atrial myocytes in response to stretch associated with increased atrial pressure, while ventricular production and release of this peptide are triggered only in the presence of ventricular hypertrophy [7]. BNP is primarily produced by ventricular myocytes [8], and its generation rate is amplified by heart failure or LVH [8–10]. Several studies have examined the utility of natriuretic peptides for the detection of systolic dysfunction or LVH in the general population. Whether or not these observations hold true in patients with end-stage renal diseases has not been studied. The issue is relevant because cardiovascular risk in uremic patients on chronic dialysis treatment is exceedingly high, and LVH and systolic dysfunctions represent the main factors responsible for this great risk [11]. Given the clinical importance

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of properly identifying alterations in cardiac mass and function in uremic patients on chronic dialysis treatment, we prospectively tested the diagnostic potential of ANP and BNP for LVH and LV dysfunction.

METHODS

Protocol

The protocol conformed to the ethical guidelines of our institutions, and informed consent was obtained from each participant. All studies were performed during a nondialysis day between 8 a.m. and 1 p.m.

Patients

Two hundred forty-six patients with end-stage renal disease (137 males and 109 females) who had been on regular dialysis treatment [212 on hemodialysis (HD) and 34 on continuous ambulatory peritoneal dialysis (CAPD)] for at least six months and without clinical evidence of heart failure or hemodynamically significant valvular heart disease were eligible for the study. Heart failure was defined as ejection fraction (EF) of <35% and dyspnea associated with two of the following conditions: raised jugular pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest x-ray, requiring hospitalization or extra ultrafiltration [12]. All participants were in sinus rhythm at the time of the study. These patients represented approximately 70% of the entire dialysis population of the four dialysis units. The prevalence of diabetes mellitus in this cohort was 15% (that is, 37 patients out of 246). Patients excluded from this study had overt heart failure or valvular heart disease, dementia, or terminal diseases or were hospitalized for intercurrent illnesses. No eligible patient refused to participate into the study. One hundred thirty patients were on treatment with erythropoietin. One hundred nine patients were on antihypertensive treatment: 76 on monotherapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 (AT_1) antagonists, calcium channel blockers, α and β blockers, and 33 on double or triple therapy with various combinations of these drugs.

All HD patients were virtually anuric (24-hour urine volume <200 mL/day), while a minority ($N = 6$) of CAPD patients had a 24-hour diuresis >500 mL/day. HD patients were being treated three times weekly with standard bicarbonate dialysis (Na 138 mmol/L, HCO_3 35 mmol/L, K 1.5 mmol/L, Ca 1.25 mmol/L, Mg 0.75 mmol/L) or by high-flux HD with either cuprophan or semisynthetic membranes (dialysis filters surface area: 1.1 to 1.7 m^2). Patients on CAPD were all on four exchanges per day schedule with standard dialysis bags. Dry weight was targeted in each case to achieve a normotensive edema-free state. Ninety-nine patients were habitual smokers (21 ± 16 cigarettes per day).

Laboratory measurements

Blood sampling was performed between 8 and 10 a.m. during a nondialysis day or with an empty abdomen in CAPD patients. After 20 to 30 minutes of quiet resting in semirecumbent position, samples were taken into chilled ethylenediaminetetraacetic acid (EDTA) vacutainers, placed immediately on ice, and centrifuged within 30 minutes at −4°C, and the plasma was stored at −80°C before assay. The plasma concentrations of α-human ANP and BNP were measured by commercially available radioimmunoassay kits (Peninsula Laboratory Europe Ltd., St. Helens, Merseyside, UK) after pre-extraction by reverse chromatography (Seppak C-18 cartridges; Waters, Mildford, MA, USA). Recovery was >80% for both ANP and BNP. There was no cross-reactivity between the two assays. The between-assay and within-assay coefficients of variability were 8 and 10% for ANP and 9 and 11% for BNP, respectively.

Atrial natriuretic peptide and BNP were also measured in 39 control subjects. These subjects were accurately screened to exclude cardiac or other systemic disease. For the purpose of this study, an elevated value was prospectively defined as greater than the 95th percentile of the normal range (ANP, 27 pmol/L; BNP, 7.8 pmol/L).

Echocardiography

Echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography [13] always within three hours after blood sampling. Left ventricular mass (LVM) was calculated according to the Devereux formula [14] and indexed to height$^{2.7}$ (LVMI) [15]. LVH was defined by a LVMI of over 47 g/$m^{2.7}$ in women or over 50 g/$m^{2.7}$ in men. The height-based indexing of LV mass was specifically chosen to minimize any potential distortion attributable to extracellular volume expansion (surface area indexing being weight sensitive). Systolic dysfunction was defined as an EF <45%.

Statistical analysis

Values are expressed as mean ± SD. The association of each peptide with physiological variables was assessed by simple linear and multiple regression analysis. For regression analysis, we used the natural logarithm (ln) of ANP and BNP to normalize the distribution of their plasma concentrations.

The usefulness of natriuretic peptides to identify LVH (as previously defined) and systolic dysfunction was tested by the analysis of receiver operating characteristic (ROC) curves [16] and their diagnostic value was compared by applying the Wilcoxon rank sum statistics to the areas under the ROC curves [17]. The confidence intervals of sensitivity, specificity, and positive and nega-

Table 1. Demographic, anthropometric, biochemical, and hemodynamic characteristics of the study population

Age *years*	60.2 ± 15.3
Males/females	138/108
BMI kg/m^2	24.9 ± 4.4
Duration of dialysis treatment *months*	43(18–99)
Systolic pressure *mm Hg*	133.9 ± 22.4
Diastolic pressure *mm Hg*	75.3 ± 12.3
Heart rate *beats/min*	80.9 ± 10.8
Serum cholesterol *mmol/L*	5.3 ± 1.4
Serum phosphate *mmol/L*	2.0 ± 0.5
Serum calcium *mmol/L*	2.3 ± 0.03
Serum PTHi *pg/mL*	147(60–331)
Kt/V	
HD patients	1.22 ± 0.27
CAPD patients	1.66 ± 0.32
History	
Myocardial infarction	30
Stroke	20
Peripheral vascular disease	31
Drug therapy	
Erythropoietin	130
Antihypertensive drugs	
Monotherapy	
ACE inhibitors	9
Calcium channel blockers	46
β blockers	7
Clonidine or AT_1 antagonist or α blockers	14
Double or triple therapy (combination of ACE inhibitors, Calcium channel blockers, AT_1 antagonist α or β blockers)	33

Data are expressed as mean ± SD or as median (interquartile range), as appropriate. Abbreviations are: BMI, body mass index; PTHi, parathyroid hormone immune reactive; Kt/V, dialysis dose; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; ACE, angiotensin-converting enzyme; AT_1, angiotensin II type 1.

Table 2. Left ventricular (LV) mass and function and natriuretic peptides in dialysis patients and natriuretic peptides in normal subjects

Patients	
LV mass index $g/height^{2.7}$	64.4 ± 19.8
LVEF %	58.1 ± 9.9
ANP *pmol/L*	median 23.7 (15.8–44.9)
BNP *pmol/L*	median 24.4 (10.4–48.2)
Normal subjects	
ANP *pmol/L*	median 4.5 (2.8–14.0)
BNP *pmol/L*	median 2.4 (1.2–4.0)

Data are expressed as mean ± SD or as median (interquartile range), as appropriate. Abbreviations are: EF, ejection fraction; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

tive prediction values were calculated by a standard formula [18]. We tested the value of two thresholds (for each peptide). The first threshold was prospectively defined and coincided with the 95th percentile of the normal range (discussed previously in this article). The second threshold was defined retrospectively on the basis of the analysis of the ROC curves by identifying the value of each peptide giving the best combination of sensitivity and specificity or "best cut-off," that is, the value that maximizes the sum of the sensitivity and specificity [16].

RESULTS

Patient characteristics

The main demographic and clinical characteristics of the patients included in the study are detailed in Table 1. Table 2 reports LV mass, LV function, and natriuretic peptides in the patient population and the natriuretic peptides in the control population. One hundred ninety-four (79%) patients displayed LVH on echocardiography. Systolic dysfunction was present in 31 patients (13%).

Correlation study

The plasma concentrations of the two natriuretic peptides were highly intercorrelated ($r = 0.81$, $P < 0.0001$). There were highly significant linear associations between each peptide and the thickness of the posterior wall (ANP, $r = 0.44$, $P < 0.0001$; BNP, $r = 0.50$, $P < 0.0001$) and of the interventricular septum wall (ANP, $r = 0.42$, $P < 0.0001$; BNP $r = 0.47$, $P < 0.0001$), while the correlations with the LV end-diastolic volume were of small magnitude and borderline significance (ANP, $r = 0.13$, $P = 0.04$; BNP, $r = 0.12$, $P = 0.06$). Notably, both LVMI (Fig. 1) and EF (Fig. 2) were strongly related to ANP and BNP, and these relationships were largely independent of other well established determinants of LVMI in dialysis patients because they also hold true ($P < 0.0001$) in multivariate models, including age, hemoglobin, serum albumin, systolic pressure, Kt/V, treatment modality, and duration of dialysis treatment (Figs. 1 and 2, insets). The correlations between echocardiographic parameters and BNP were slightly but coherently stronger than those of ANP. Natriuretic peptides were also related with the LV end-diastolic volume, but again, these relationships were of relatively small magnitude and some of them of borderline statistical significance.

ROC analysis

The areas under the ROC curves of ANP and BNP were both highly significant ($P < 0.001$; Fig. 3). The areas for BNP detecting abnormal LVMI and EF were slightly larger than those for ANP. This finding suggests that BNP combined higher sensitivity and higher specificity over a range of different cut-off values than ANP.

Table 3 shows the sensitivity, specificity, and positive and negative predictive value of an elevated value of each peptide as prospectively defined (>95th percentile of the normal range; **Methods** section) for the identification of LVH and systolic dysfunction. BNP had a significantly higher sensitivity ($P < 0.0001$) than ANP for the diagnosis of LVH, but the positive predictive value of the two peptides was very similar (P = NS, 92 and 87%, respectively). However, the negative predictive value of BNP for excluding LVH was 22% higher than that of ANP ($P = 0.05$). Both natriuretic peptides had a high sensitivity for the detection of LV dysfunction (87 and 94%), but their positive predictive value was low (25 and

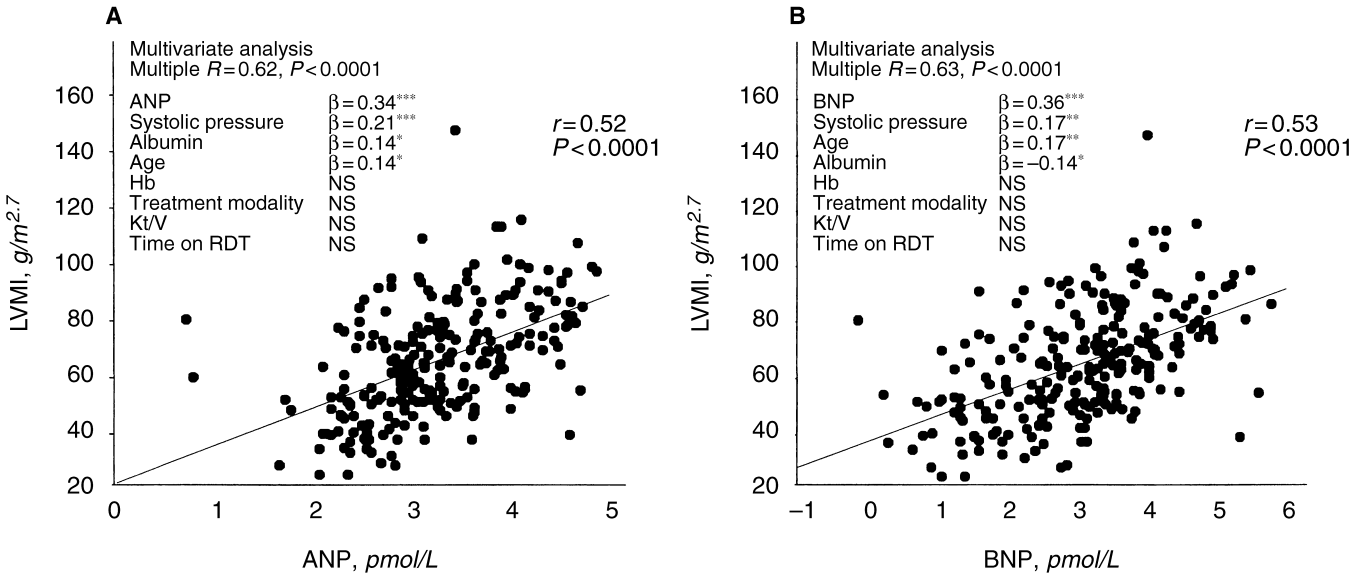

Fig. 1. Relationship between atrial natriuretic peptide (ANP; *A*) and brain natriuretic peptide (BNP; *B*) with left ventricular mass indexed to height (LVMI). Data are expressed as the Pearson product moment correlation coefficient and the relative *P* value. The corresponding multivariable models are reported in the insets. ***$P < 0.0001$; **$P < 0.01$; *$P < 0.05$.

15%). Importantly, both ANP and BNP proved to be very useful for excluding this alteration (negative predictive value 97 and 96%, respectively). Table 4 shows the analysis based on the "best cut-offs" of each peptide as identified by the analysis of the ROC curves. This analysis augmented the positive prediction value of BNP for the diagnosis of LVH to 95% in comparison with the prospective analysis. This increase was paralleled by a nonsignificant gain in negative prediction power that attained the 61%. By the same token, this approach raised the BNP-positive prediction value for the identification of LV dysfunction to 31%, and this increase was again of borderline statistical significance ($P = 0.05$). This type of analysis did not modify the diagnostic potential of ANP (either for LVH or for LV dysfunction).

Combined analysis of the two natriuretic peptides

The sensitivity, specificity positive, and negative prediction value of the combined diagnostic value of the two peptides is shown in Tables 3 and 4. This analysis, based on either the prospectively identified threshold (>95th percentile in healthy subjects) or the "best cut-off" (**Methods** section), did not materially improve either the detection of LVH or that of LV dysfunction based on separate analysis of the two peptides.

DISCUSSION

The measurement of the plasma concentration of cardiac natriuretic peptides, particularly BNP, in uremic patients on chronic dialysis proved to be useful for the diagnosis of LVH and for excluding the presence of LV dysfunction.

Left ventricular hypertrophy and LV dysfunction are currently considered the strongest predictors of cardiovascular and total mortality in the dialysis population [11, 19]. LVH is a notoriously pervasive complication in end-stage renal disease with a prevalence rate ranging from 60 to 80%. LV systolic dysfunction is relatively much less frequent, with its prevalence being approximately 15% [19]. Our study again further confirms in a large dialysis population the high prevalence of these alterations. If these alterations are to be a target for intervention, simple and reliable methods specifically validated in the dialysis population are needed. Echocardiography is undoubtedly of proven value, and most agree that serial echocardiographic studies in patients entering renal replacement therapy is a better system to identify and treat alterations in LV mass and function in these patients. However, hospital-based echocardiographic services are often stretched, and for this reason, in daily clinical practice, this technique is applied much less often than desirable. The situation is probably similar to that of general practice [20]. Echocardiography apart, there are no simple and validated methods to clinically diagnose these abnormalities in dialysis patients. Echocardiogram, which is a widely available method, in the general population has a sensitivity that may reach at most 40% [21], and its use in dialysis patients poses additional problems because of the effect of dialysis on the QRS complex [22], that is, the main criterion for the diagnosis of LVH by echocardiogram. Thus,

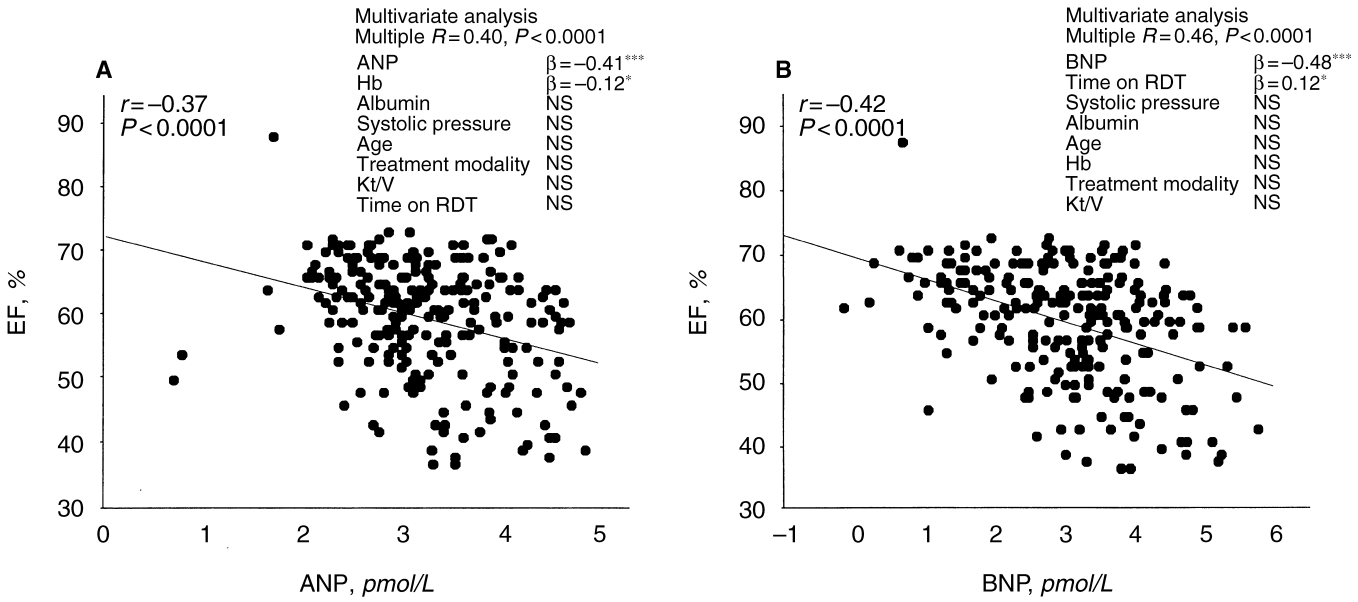

Fig. 2. Relationship between ANP and BNP with ejection fraction (EF). Data are expressed as the Pearson product moment correlation coefficient and the relative *P* value. The corresponding multivariable models are reported in the insets. ***$P < 0.0001$; **$P < 0.01$; *$P < 0.05$.

the opportunity for intervention on LVH and systolic dysfunction is in part limited by the availability of simple, easily accessible diagnostic tools.

The possibility of using cardiac natriuretic peptides for the diagnosis of LVH and systolic dysfunction was prompted by investigations in early 1990s [1–6], which showed that the measurement of these hormones, particularly BNP [6], has a substantial potential for predicting anatomical and functional alterations of the left ventricle. More recently, both ANP (particularly aminoterminal ANP) and BNP have been used in primary care to diagnose left ventricular dysfunction [4, 23–27]. With the exception of the study by McClure et al [25], there is a consensus that the measurement of cardiac peptides is clinically useful and could be a cost-effective method of screening for left-ventricular systolic dysfunction in the general population, especially if its use was targeted to individuals at high risk [24].

Cardiac natriuretic peptide levels are very frequently raised in dialysis patients. The high plasma concentration of ANP and BNP in end-stage renal disease is multifactorial and depends on extracellular volume expansion, concomitant heart disease [28, 29], and abolished renal clearance [30, 31]. ANP in these patients is strictly related to cardiac filling pressure or to atrial volume [32–35], and although to a different rate, the plasma concentration of both cardiac peptides declines after ultrafiltration dialysis treatment [36]. The measurement of ANP was used to enhance the identification of the "dry weight." However, cardiac function represents a major confounder for the interpretation of prevailing ANP and BNP plasma concentration in chronic renal failure, and it is now well recognized [37] and further confirmed [38] that it is unlikely that cardiac natriuretic peptides are of use in this respect.

Left ventricular hypertrophy is a potentially important cause of raised natriuretic peptides in dialysis patients because there is strong evidence that the myocardial synthesis of ANP and BNP is markedly enhanced in both animal models [7] as well hypertensive subjects with raised LVM [6]. The relationship between ANP and BNP and cardiac mass, geometry, and function in dialysis patients has received only very scanty attention [38, 39]. Nitta et al reported that BNP may be a possible indicator of reduced ventricular function in HD patients [39]. More recently Franz, Woloszczuk, and Horl in a detailed study of ANP, pro-ANP, and two aminoterminal pro-ANP fragments noted that both this cardiac hormone and the parent prohormone were substantially higher in patients with cardiac dysfunction (congestive heart failure or LV dysfunction, significant valvular heart disease) [38]. In neither of these studies reported the formal diagnostic value (that is, the prediction power for alterations in LV mass and function) of the cardiac peptides. However, the high pretest probability of these heart alterations in the dialysis population suggests that ANP and BNP might be helpful for their identification. The issue is important in that LVH and left ventricular dysfunction are modifiable risk factors in dialysis patients [40].

In this study, to our knowledge the largest performed thus far, the plasma concentrations of ANP and BNP were strongly interrelated, a finding in line with previous data by Buckley et al [31]. Notably, we found that both natriuretic peptides were correlated to a high degree

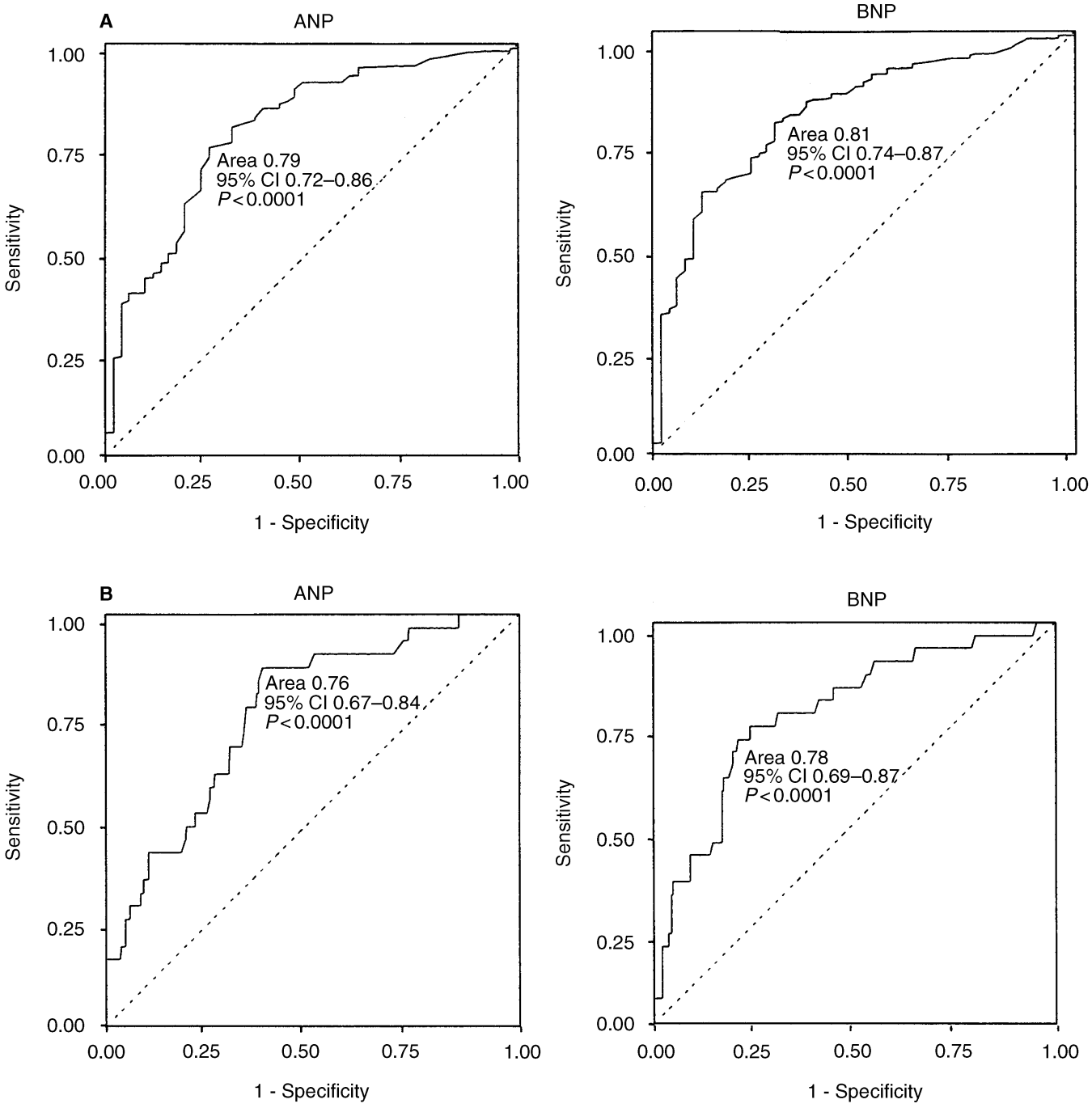

Fig. 3. Receiver operating characteristic (ROC) curves for natriuretic peptide concentrations in predicting abnormal LV mass and EF (Methods section). (*A*) Left ventricular hypertrophy; (*B*) left ventricular dysfunction.

with several echocardiographic parameters, including LV mass, the thickness of the left ventricular walls, and the EF. The link with LVMI and EF was particularly strong, so that both peptides had a high positive prediction power (>85%) for LVH coupled to substantial negative prediction power for LV systolic dysfunction (>95%). In general, BNP was a better predictor than ANP, particularly in the analysis based on the "best cut-off." Given the high intercorrelation of the two peptides, there was no gain in diagnostic power when they were used in a combined way. Thus, our data indicate that the measurement of ANP or, probably better, BNP has diagnostic potential for alterations in LV mass and function in dialysis patients. The fact that BNP measurement is stable in routine tubes containing EDTA and stored at room temperature for at least six hours makes the

Table 3. Percent and 95% CI using the threshold of >95th percentile of the normal range

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
	% (95% CI)			
LVH				
Abnormal ANP	51(44–58)	83(73–83)	92(87–97)	31(23–39)
Abnormal BNP	88(83–93)	50(36–64)	87(82–92)	53(39–67)
LV dysfunction				
Abnormal ANP	87(75–99)	62(56–68)	25(17–33)	97(94–100)
Abnormal BNP	94(86–100)	22(16–28)	15(10–20)	96(91–100)
LVH				
Abnormal ANP or BNP	89(85–93)	50(36–64)	87(82–92)	54(40–68)
LV dysfunction				
Abnormal ANP or BNP	93(86–100)	21(16–28)	15(10–20)	96(90–100)

Table 4. Percent and 95% CI using the threshold of best cut-off values

	Best cut-off *pmol/L*	Sensitivity	Specificity	Positive predictive value	Negative predictive value
		% (95% CI)			
LVH					
Abnormal ANP	18.8	75(69–81)	75(63–87)	92(88–96)	44(34–54)
Abnormal BNP	23.4	62(55–69)	88(79–97)	95(91–99)	61(52–70)
LV dysfunction					
Abnormal ANP	27.1	87(75–99)	62(56–68)	25(17–33)	97(94–100)
Abnormal BNP	38.9	74(59–89)	76(70–82)	31(20–42)	95(92–99)
LVH					
Abnormal ANP or BNP		80(74–86)	75(63–87)	92(88–96)	50(39–61)
LV dysfunction					
Abnormal ANP or BNP		87(75–99)	61(54–68)	24(16–32)	96(93–99)

The best cut-off threshold values are defined as those values which maximize the sum of the sensitivity and specificity (see Methods).

measurement of this substance feasible in daily clinical practice [41]. Given the high negative prediction power for systolic dysfunction (96% in the prospective study), the measurement of BNP could be reliably applied to exclude this alteration in dialysis patients. Although the positive prediction power of this peptide for LVH is high (87% in the prospective study), the negative prediction power is rather unsatisfactory (51%), thus limiting its usefulness for excluding this abnormality.

Our study has limitations. We focused on patients without overt heart failure because we believed that in overt heart failure echocardiography is almost always performed to confirm the clinical diagnosis and to incorporate anatomic and hemodynamic information into the clinical decision process. Thus, the diagnostic value of these peptides for overt heart failure, although likely, cannot be extrapolated from our data. The second limitation derives from the fact that we did echocardiographic studies and plasma sampling during the dialysis interval rather than before or after dialysis. While this approach is probably ideal on a physiological standpoint (the volume status approximates the individual steady state in between dialyses), it demands an additional outpatient appointment during a nondialysis day. Predialysis sampling tends to shift upwardly the diagnostic thresholds of these peptides, and it remains to be seen whether this affects the diagnostic power of ANP and BNP. Nonetheless, it is common practice in many dialysis centers to periodically re-examine patients in the dialysis interval, and this may be a good occasion for ANP or BNP testing. Finally, although we analyzed data both on the basis of prospectively preset thresholds and on retrospectively defined "best cut offs," the diagnostic potential of BNP was maximized by the second, retrospective, approach. Thus, these retrospective thresholds, which are specific for patients on dialysis, remain to be prospectively tested in other dialysis centers to prove the external validity of our findings.

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