Comparison of Brain Natriuretic Peptide (BNP) and NT-proBNP in Screening for Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis

LORENZO CAVAGNA, ROBERTO CAPORALI, CATHERINE KLERSY, STEFANO GHIO, RICCARDO ALBERTINI, LAURA SCELSI, REMIGIO MORATTI, CLAUDIA BONINO, and CARLOMAURIZIO MONTECUCCO

ABSTRACT. ***Objective.*** To compare the performance of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in screening for pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc).

Methods. Between January 2008 and March 2009, outpatients referred to our unit and satisfying LeRoy criteria for SSc were assessed for PAH. Doppler echocardiography, BNP measurement, and NT-proBNP measurement were done concomitantly for a complete clinical, instrumental, and biochemical evaluation. Right-heart catheterization was carried out in cases of suspected PAH [estimated pulmonary arterial pressure (PAP) ≥ 36 mm Hg; diffusion capacity for carbon monoxide (DLCO) ≤ 50% of predicted value; 1-year DLCO decline ≥ 20% in absence of pulmonary fibrosis; unexplained dyspnea].

Results. One hundred thirty-five patients were enrolled (124 women, 11 men; 96 limited SSc, 39 diffuse SSc); precapillary PAH was found in 20 patients (15 limited SSc, 5 diffuse SSc). The estimated PAP correlated with both BNP (R = 0.3; 95% CI 0.14–0.44) and NT-proBNP (R = 0.3, 95% CI 0.14–0.45). BNP [area under the curve (AUC) 0.74, 95% CI 0.59–0.89] was slightly superior to NT-proBNP (AUC 0.63, 95% CI 0.46–0.80) in identification of PAH, with diagnosis cutoff values of 64 pg/ml (sensitivity 60%, specificity 87%) and 239.4 pg/ml (sensitivity 45%, specificity 90%), respectively. BNP (log-transformed, p = 0.032) and creatinine (p = 0.049) were independent predictors of PAH, while NT-proBNP was not (p = 0.50).

Conclusion. In our single-center study, the performance of BNP was slightly superior to that of NT-proBNP in PAH screening of patients with SSc, although normal levels of these markers do not exclude diagnosis. We observed that impaired renal function is associated with an increased risk of PAH in SSc. Further multicenter studies are needed to confirm our results (ClinicalTrials.gov ID NCT00617487). (First Release July 15 2010; J Rheumatol 2010;37:2064–70; doi:10.3899/jrheum.090997)

Key Indexing Terms:
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Pulmonary arterial hypertension (PAH) is one of the most deadly complications of systemic sclerosis (SSc)[1], affecting 7%–12% of patients[2,3,4] and occurring in both limited and diffuse subsets of SSc[5,6]. PAH symptoms at onset are not specific and are frequently ascribed to other features of the disease, such as interstitial lung disease (ILD), with a subsequent diagnostic delay. Because of recent therapeutic developments, the early identification of PAH in SSc is of primary importance[7]. Although the reference technique for PAH diagnosis is right-heart catheterization[8], Doppler echocardiography is preferable as a screening tool[9] because it is not invasive. However, incomplete correspondence between echocardiographic and right-heart catheterization occurs when pulmonary arterial pressures (PAP) are less than 45 mm Hg[8], indicating a grey zone for identification of PAH. Recently, measurement of circulating natriuretic peptides (CNP) has been found effective for the evaluation of patients with suspected PAH; among CNP, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and BNP are the most commonly used markers[10,11,12,13], although in SSc only NT-proBNP has been tested[14,15,16,17]. Because these 2 markers are also used in the evaluation of left-heart failure[18,19], and because in a recent metaanalysis[20], testing for BNP was found to be superior to NT-proBNP in this setting, we aimed to compare the performance of BNP and NT-proBNP in the screening of PAH in a cohort of out-patients with SSc.

From the Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo, Pavia, Italy.

L. Cavagna, MD; R. Caporali, MD; C. Klersy, MD; S. Ghio, MD; R. Albertini, MD; L. Scelsi, MD; R. Moratti, MD; C. Bonino, MD; C. Montecucco, MD, Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo.

Address correspondence to Dr. L. Cavagna, Division of Rheumatology, University and IRCCS Foundation Policlinico S. Matteo, P. le Golgi 3, 27100, Pavia, Italy. E-mail: lorenzo.cavagna@unipv.it

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MATERIALS AND METHODS

All patients observed between January 2008 and March 2009 in our outpatient clinic who satisfied the LeRoy criteria for SSc[21] were asked to take part in this longitudinal study. Exclusion criteria included extended ILD, deep venous thrombosis, or pulmonary thromboembolisms; a previous diagnosis of PAH under treatment; pregnancy; significant valvular disease; evidence of either systolic (e.g., left ventricular ejection fraction ≤ 55% at echocardiography) or diastolic dysfunction (e.g., a restrictive mitral inflow pattern at pulsed Doppler or an E/E' value > 15 at tissue Doppler imaging); or a history of atrial fibrillation, myocardial infarction, neoplasia, or severe hepatic diseases. Renal insufficiency by itself was not an exclusion criterion, but dialyzed patients or those with scleroderma renal crisis were not recruited. The study was approved by the local ethics committee and informed consent was obtained in all cases.

Upon enrollment, clinical and demographic characteristics of patients were recorded and the occurrence of renal, cardiac, and pulmonary involvement was assessed. Laboratory tests included a complete blood cell count, erythrocyte sedimentation rate by Westergren, C-reactive protein, and serum creatinine, as well as tests for antinuclear antibodies and anti-extractable nuclear antigen antibodies. Esophageal dysmotility was assessed by barium esophagram and calcinosis by both clinical and radiological evaluation. Lungs were examined by chest radiograph, pulmonary function tests (PFT), and tests for diffusion capacity for carbon monoxide (DLCO). High-resolution computed tomography (HRCT) was done. ILD was established using HRCT[22,23] and its severity was evaluated according to Kazerooni score[24], a well validated system in which each lobe of the lung is scored on a scale of 0–5 for both alveolar and interstitial abnormality, depending on the percentage of each lobe involved and the type of finding observed. We arbitrarily chose 15 as a fibrosis cutoff score for definition of extended ILD. Regarding PFT, forced vital capacity (FVC) was expressed as a percentage of theoretical value, as well as DLCO. Patients with extended ILD or those with increased estimated PAP and an FVC/DLCO ratio lower than 1.4[25] were excluded, to avoid possible cases of ILD-related pulmonary hypertension.

Nailfold capillaroscopy was performed using standard technique[26] and the characterization of cutaneous involvement for both extension[21] and thickening (modified Rodnan skin score) was established[27].

A complete standard 2-D and Doppler echocardiographic examination was performed (Vivid 7, GE Healthcare). Peak systolic PAP was calculated by adding a right atrial pressure value to the systolic transtricuspid pressure gradient. Right atrial pressure was valued at 5 mm Hg when the inferior vena cava (IVC) diameter was < 20 mm and collapsibility ≥ 50%, 10 mm Hg when IVC diameter was < 20 mm and collapsibility < 50%, and 20 mm Hg when IVC diameter was ≥ 20 mm and collapsibility < 50%.

Estimated PAP were regarded as abnormal for values ≥ 36 mm Hg, in keeping with published guidelines[28]. Additional clinical criteria of suspected PAH were DLCO < 50% of predicted value; DLCO decrease > 20% compared to the previous year in the absence of pulmonary fibrosis for patients in followup; and unexplained dyspnea. For all patients meeting these criteria, a CT scan was performed to exclude pulmonary thromboembolisms; right-heart catheterization was then carried out to confirm PAH. According to published guidelines[28], PAH was diagnosed when mean PAP was ≥ 25 mm Hg. Other right-heart catheterization variables were recorded, in particular diastolic and systolic PAP, right atrial pressure (mm Hg), pulmonary capillary wedge pressure (mm Hg), cardiac output (l/min), cardiac index (l/min/m^2), and pulmonary vascular resistance (dyne/s/cm^5). BNP was assayed in EDTA plasma with an automated immunochemistry analyzer (Advia Centaur, Siemens Diagnostic Division, Erlangen, Germany); the analytical method is a 2-site immunochemiluminescent assay using 2 monoclonal antibodies directed against different epitopes of the BNP molecule. The measuring range for BNP was 0–5000 pg/ml. When the results exceeded the upper limit of the analytical range, the samples were automatically diluted and retested. NT-proBNP was assayed with Cobas Core E 411, an immunochemistry analyzer (Roche Diagnostic Division, Basel, Switzerland) equipped with a dedicated reagent kit used according to the manufacturer's instructions. Quality control was ensured by assaying 3 levels of a dedicated control sera in each analytical series and by participation in a national interlaboratory control program 3 times a month (Cardiormo-Check, CNR, Pisa, Italy).

Echocardiography, BNP, and NT-proBNP determinations were performed concomitantly; blood samples for BNP and NT-proBNP testing were rapidly collected and processed in all cases. Patients enrolled were not treated with iloprost/calcium channel blockers for at least 1 week before the screening; this drug treatment was due to Raynaud's phenomenon.

Statistical analysis. The data were expressed as a median and interquartile range (IQR), mean and SD, or counts and percentage. Correlations of estimated PAP with BNP and NT-proBNP were evaluated by Spearman rho coefficient. In addition, dependence of BNP and NT-proBNP on age, creatinine levels, and hemodynamic measures was assessed through linear regression models. For that, BNP and NT-proBNP were log-transformed. Patients were then categorized according to PAH. Association between PAH diagnosis and categorical variables (sex, limited or diffuse SSc, anticentromere antibodies, Scl-70, ulcers, scleroderma pattern, ILD) was assessed using Fisher's exact test. For continuous variables (age, age at disease onset, disease duration, BNP, NT-proBNP, skin score, Kazerooni score, DLCO, FVC, creatinine), the Mann-Whitney U test was used. Multivariable logistic models were then fitted, including either BNP or NT-proBNP, while adjusting for other factors potentially associated with PAH (with $p < 0.2$ at univariable analysis). To informally compare the performance of both markers, bootstrapped validation was performed to compute the models' discrimination (c statistic), and calibration (shrinkage coefficient) was computed. The closer these estimates were to 1, the better the model performance. Moreover, the area under the receiver-operating characteristic (ROC) curve was computed and compared for each marker, and the optimal cutoff values of both BNP and NT-proBNP for PAH diagnosis were established. Stata 10.1 (Stata Corp., College Station, TX, USA) was used for computation. A 2-sided p value < 0.05 was considered statistically significant; 95% CI were computed.

RESULTS

A total of 158 patients were evaluated and 135 were enrolled in the study [124 women and 11 men, 96 with limited cutaneous SSc (lcSSc) and 39 diffuse cutaneous SSc (dcSSc)]. Exclusion was due to extended ILD (e.g., Kazerooni score > 15; 8 patients), systolic (4 patients) or diastolic (6 patients) left ventricular dysfunction, myocardial infarction (3 patients), valvular heart disease (4 patients), well established PAH under treatment (2 patients), atrial fibrillation (4 patients), and neoplasia (2 patients). Six patients had 2 or more concomitant exclusion criteria. Doppler echocardiography data are summarized in Table 1. Abnormal Doppler echocardiographic PAP was found in 23 (17%) patients, while other criteria for suspected PAH were not met.

Table 1. Main Doppler echocardiography data.

Characteristic	
LV EDV, ml	75.4 ± 18.2
Interventricular septum thickness, mm	8.4 ± 1.4
LV EF, %	61 ± 4
E/A ratio	1.2 ± 0.4
Mitral regurgitation (none/trivial)	62/38
Estimated systolic PAP, mm Hg	26.5 ± 9.5

LV: left ventricle; EDV: end diastolic volume; EF: ejection fraction; PAP: pulmonary arterial pressure.

Eighteen of these 23 patients were affected by lcSSc and 5 by dcSSc. ILD was observed in 55 patients (41%), 20 were anti-Scl70- and 19 anticentromere-positive; 11 of these patients had increased PAP (8% of the total, 20% of patients with ILD). Of note among the 8 patients initially excluded because of extended ILD, 4 had a slight increase of estimated PAP; however, there was evidence of an FVC/DLCO ratio < 1.4. No signs of pulmonary thromboembolisms were reported by CT scans in patients with suspected PAH. Seventeen patients had creatinine levels > 1.2 mg/dl (higher value 1.7 mg/dl); 9 of them had abnormal PAP. Esophageal dysmotility was observed in 42 patients, 6 with abnormal PAP; cutaneous calcinosis was observed in 23 patients (all with lcSSc), and 5 of them had increased PAP. No cases of scleroderma renal crisis (both classic and normotensive) or myositis were observed. Precapillary PAH was excluded by right-heart catheterization in 3 patients with lcSSc, without ILD, increased creatinine levels, esophageal dysmotility, or cutaneous calcinosis; precapillary PAH was confirmed in the remaining 20 patients (15%; Table 2); of these, 6 were in New York Heart Association (NYHA) functional class III-IV, 8 in class II, and 6 in class I.

Both BNP (Spearman R = 0.30, 95% CI 0.14–0.44, p < 0.001) and NT-proBNP (Spearman R = 0.30, 95% CI 0.14–0.45, p < 0.001) were significantly, although weakly, associated with PAP levels (Figure 1). A weak, although significant, association was also shown with age (Spearman R = 0.50, 95% CI 0.36–0.61, and Spearman R = 0.45, 95% CI 0.30–0.57, respectively; both p < 0.001) and creatinine levels (Spearman R = 0.16, 95% CI –0.01 to 0.32, p = 0.06 and Spearman R = 0.26, 95% CI 0.09–0.41, p = 0.003, respectively).

Upon univariable analysis, patients with PAH were older (p = 0.019), had reduced DLCO (p < 0.001) and FVC (p = 0.025), and higher creatinine (p = 0.003) with respect to patients without PAH (Table 3); NT-proBNP was higher, but not significantly (p = 0.06), while BNP was significantly higher (p < 0.001) in patients with PAH. The other demographics and general findings were similar between the 2 groups.

Upon multivariable analysis, BNP (on a log scale) maintained independent predictive ability for PAH (OR 2.10, 95% CI 1.07–4.14, p = 0.032), when adjusted for age (p = 0.53), DLCO (p = 0.09), and creatinine levels (p = 0.049). This was not the case for NT-proBNP (on a log scale), which lost its predictive ability (OR 1.16, 95% CI 0.75–1.78, p = 0.50) when adjusted for age (p = 0.95), DLCO (p = 0.027), and creatinine levels (p = 0.034). Upon bootstrap validation, the c statistic and the shrinkage coefficient were 0.73 and 0.80, respectively, for the BNP model and 0.72 and 0.84 for the NT-proBNP model. Finally, the area under the ROC curve was larger (although not significantly, p = 0.19) for BNP (0.74, 95% CI 0.59–0.89) than for NT-proBNP (0.63, 95% CI 0.46–0.80), denoting a greater ability to diagnose PAH (Figure 2). The identified optimal BNP cutoff value of 64 pg/ml showed a sensitivity of 60% (95% CI 36.1–80.9) and a specificity of 87% (95% CI 79.4–92.5) for recognition of PAH, while the identified optimal NT-proBNP cutoff of 239.4 pg/ml showed a sensitivity of 45% (95% CI 23.1–68.5) and a specificity of 90% (95% CI 83.5–95.1). The negative predictive values were 93% (95% CI 86–97%) and 90% (95% CI 83–95%) for BNP and NT-proBNP, respectively, for a prevalence of PAH of 15%. Evaluating hemodynamic data, both BNP and NT-proBNP were significantly associated with mean PAP, diastolic PAP, and pulmonary vascular resistance, while pulmonary capillary wedge pressure, right atrial pressure, cardiac output, and cardiac index were not (Table 4).

DISCUSSION

Testing for BNP and NT-proBNP has been done for numerous indications, including evaluation of left-heart failure[18,19] and PAH[10,11,12,13]. These hormones originate from a 108-amino acid precursor, which is progressively cleaved by circulating endoproteases to form an active fragment, the 32-residue carboxyl-terminal BNP, and an inactive fragment, the 76-residue NT-proBNP[29]; BNP is then rapidly metabolized in the blood, making rapid processing of samples necessary for its determination, while NT-proBNP levels are more stable over time[29]. Further, although data confirm a close correlation and a satisfactory agreement between BNP and NT-proBNP, frequent discrepancies are observed in individual patients, demonstrating that the 2 markers are not completely clinically equivalent[30]. In a

Table 2. Hemodynamic data by right-heart catheterization in patients with SSc who have confirmed PAH.

	mPAP, mm Hg	sPAP, mm Hg	dPAP, mm Hg	CI, l/min/m^2	CO, l/min	RAP, mm Hg	Ppcw, mm Hg	PVR, dyne/s/cm^5
Mean	32.2	43.1	25	2.9	4.9	5.3	8.3	410.3
SD	8.8	12.9	7.6	0.47	0.8	3	2.4	223.8
Median	28	37.5	22	2.87	5	5.5	9	323
IQR	26.7–34.5	36.7–43.2	20–26.7	2.6–3.1	4–5.5	3–7.2	6–10	286–408

SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; sPAP: systolic PAP; dPAP: diastolic PAP; CI: cardiac index; CO: cardiac output; RAP: right atrial pressure; Ppcw: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; IQR: interquartile range.

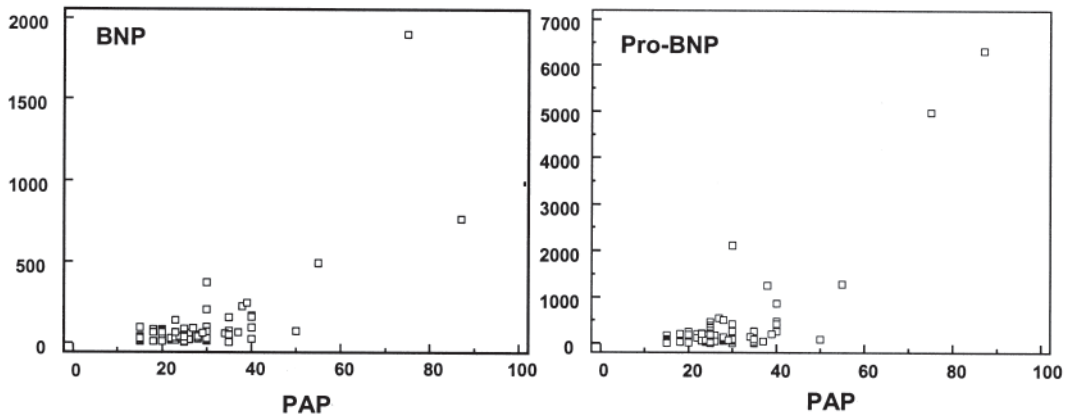

Figure 1. Correlations of estimated pulmonary arterial pressure (PAP; mm Hg) with brain natriuretic peptide (BNP; pg/ml) and N-terminal probrain natriuretic peptide (NT-proBNP; pg/ml).

Table 3. Characteristics of patients.

Characteristics	All SSc	SSc without PAH	SSc with PAH	p
Patients, n	135	115	20	
Sex (M/F)	11/124	10/105	1/19	1.000
SSc limited/diffuse	96/39	80/33	15/5	0.794
Age, yrs, at onset, median (IQR)	52 (43–59)	51 (42–58)	53.5 (48–65.5)	0.192
Age, yrs, enrollment, median (IQR)	61 (55–59)	60 (53–68)	67.5 (62–74)	0.019
Disease duration, yrs, at enrollment, median (IQR)	6 (2–15)	6 (3–15)	6 (3–15.5)	0.571
ACA + (%)	28 (49)	57 (49)	10 (50)	1.000
Anti-Scl70 + (%)	28 (21)	24 (21)	4 (20)	1.000
Skin score, median (IQR)	5.5 (4–12)	5 (4–12)	6 (2–18)	0.664
Acral ulcers (%)	33 (24)	30 (26)	3 (15)	0.402
Calcinosis (%)	23 (17)	18 (16)	5 (25)	0.335
Esophageal dysmotility (%)	42 (31)	36 (31)	6 (30)	1.000
ILD (%)	55 (41)	44 (38)	11 (55)	0.221
Kazerooni score in ILD patients, median (IQR)	4 (1–7)	3.5 (1–7.25)	4 (1–6)	0.726
BNP, pg/ml, median (IQR)	30 (18–61)	30 (18–49)	74.5 (29–196.5)	< 0.001
NT-proBNP, pg/ml, median (IQR)	86 (40–188)	84 (39–181)	189 (44–665)	0.061
Creatininemia, mg/dl median (IQR)	0.9 (0.8–1)	0.89 (0.8–1)	1.15 (0.9–1.3)	0.003
DLCO theoretical %, median (IQR)	75 (63–84)	77 (66–85)	58 (50–64)	< 0.001
FVC theoretical %, median (IQR)	101 (87–117)	102 (89–118)	86 (75–109)	0.025

IQR: interquartile range; ILD: interstitial lung disease; ACA: anticentromere antibodies; SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity.

recent metaanalysis, Ewald, *et al*[20] showed that BNP was better than NT-proBNP in the diagnosis of heart failure and in screening of left ventricular systolic dysfunction; although both these markers are currently used in screening for PAH, in this setting no comparison studies between BNP and NT-proBNP are available. To date in SSc there are no data evaluating BNP as a PAH screening tool, with studies addressing only NT-proBNP[14,15,16,17]. Thus, to our knowledge, our study is the first performed on a cohort of patients with SSc in which BNP is assessed and in which circulating natriuretic peptides are compared as a screening tool for PAH.

We found that prevalence of PAH was not different from that described by Mukerjee, *et al*[2] in a similarly selected and screened cohort of patients with SSc. We also confirmed that PAH is not rare in patients with dcSSc and ILD, as suggested[6]. Indeed, on the basis of selection criteria (not including patients with extended ILD or with increased estimated PAP and an FVC/DLCO ratio < 1.4), the cases of ILD-related pulmonary hypertension were theoretically excluded from our study population. Further, we evaluated BNP and NT-proBNP on a continuous scale, although some authors described the need for different age-related and sex-related

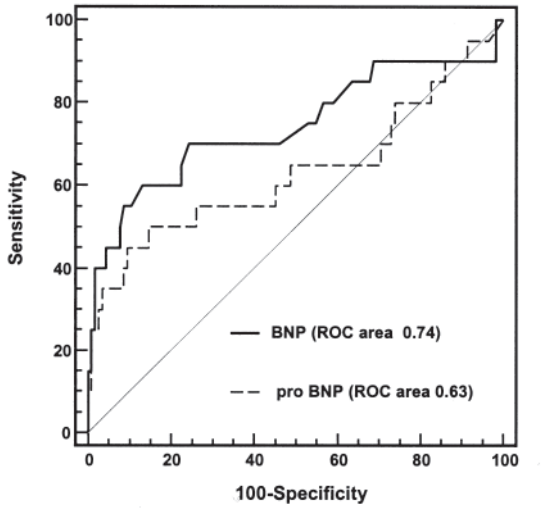

Figure 2. Receiver-operating characteristic (ROC) curve for brain natriuretic peptide (BNP; pg/ml) and for N-terminal probrain natriuretic peptide (NT-proBNP; pg/ml) in diagnosis of pulmonary arterial hypertension.

Table 4. Association between hemodynamic data and natriuretic peptides. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were log-transformed.

Data	BNP		NT-proBNP	
	R	p	R	p
mPAP, mm Hg	0.72	0.002	0.61	< 0.001
dPAP, mm Hg	0.67	0.002	0.59	< 0.001
sPAP, mm Hg	0.61	0.002	0.59	< 0.001
CI, l/min/m^2	0.24	0.267	0.35	0.142
CO, l/min	0.30	0.196	0.28	0.298
RAP, mm Hg	0.14	0.513	0.17	0.413
Ppcw, mm Hg	0.25	0.450	0.16	0.535
PVR, dyne s/cm^5	0.61	0.016	0.61	< 0.001

mPAP: mean pulmonary arterial pressure; dPAP: diastolic PAP; sPAP: systolic PAP; CI: cardiac index; CO: cardiac output; RAP: right atrial pressure; Ppcw: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

cutpoints[31,32]. To date, there appears to be no clear advantage to using age-specific or sex-specific cutoffs for these markers[20]. Our results showed that both BNP and NT-proBNP correlated linearly with estimated PAP. Accounting for univariable results, we observed a close association between BNP levels and PAH, while NT-proBNP values were not statistically associated with the final diagnosis of PAH, although a trend toward the association was found. The ROC curve also confirmed that the performance of BNP is better than that of NT-proBNP in the diagnosis of PAH in this setting. Moreover, in multivariable analysis we observed that among the CNP, only BNP could be regarded as an independent predictor of PAH. It is interesting that in PAH confirmed by right-heart catheterization, BNP and NT-proBNP levels were not always increased; this may be because some patients had mild PAH, being in NYHA functional class I. Similar results were obtained when NT-proBNP was used to screen for PAH in subjects who were positive for human immunodeficiency virus (HIV)[33]. In that study, normal NT-proBNP values were observed in patients who were HIV-positive and who had PAH; their echocardiograms showed a nondilated right ventricle with normal systolic function.

It will be interesting to follow these patients in order to evaluate clinical development, to understand the prognostic value of basal and periodic BNP monitoring; to date we are unaware of the progression of patients with SSc with similar characteristics[34]. Renal dysfunction is associated with a worse hemodynamic profile and prognosis in patients with PAH; this finding reflects both impaired renal perfusion related to diminished right-heart function and decreased renal responsiveness to CNP[35,36], which links the kidney to cardiac function. To our knowledge, this is the first study to also observe that serum creatinine is an independent predictor of PAH in SSc. Pertinent data is generally lacking, whether the impaired renal function is an exclusion criterion[16,37] or is not taken into account[2,3,15,38]. To date, the available data have not highlighted a relationship between creatinine levels and occurrence of PAH[39] or development during followup[17] in patients with SSc. According to our results, it is possible to suggest that in a disease with a frail hemodynamic balance such as SSc, mild renal dysfunction may lead to fluid retention, which could add further stress to the right ventricle, thus increasing the risk of PAH.

We are aware of our study's limitations; e.g., right-heart catheterization and Doppler echocardiography were not performed concomitantly, with a delay between the screening test and the diagnostic confirmation of PAH ranging from 21 to 45 days. Although this may indicate a selection bias, none of the patients deteriorated in their functional state during this period, suggesting disease stability over time. Moreover, this was a single-center study with a limited number of patients enrolled, and thus potentially associated with the risk of selection bias. The last limitation is the arbitrary cutoff we chose for definition of extended ILD; however, we observed that the patients excluded for this reason and with increased PAP had an FVC/DLCO ratio < 1.4, suggesting ILD-related pulmonary hypertension[25]. We suggest that although arbitrary, this cutoff was functional for our purpose.

Despite these problems, our study is of interest because it is the first to use BNP in patients with SSc, with direct comparison of this marker with NT-proBNP; our data confirm that despite the similarities, BNP and NT-proBNP are not completely equivalent. In particular, in our BNP population, performance seems to be slightly better than that of NT-proBNP in the screening of patients with SSc for PAH, according to multivariable analysis and area under ROC curve results. Our results were not enough to state that BNP is superior to NT-proBNP in screening for PAH, considering

the limitations of our study. As well, normal CNP levels are not sufficient for exclusion of PAH in this setting. Further, a complete evaluation of patients with SSc is mandatory for early identification of PAH; among the risk factors for PAH, renal dysfunction may also be important. Despite these encouraging results, other concerns about BNP primarily arise from its short half-life[29]. Rapid processing of the samples is not always possible and this may be seen as a negative aspect of the marker, potentially limiting its usefulness in certain situations. Further multicenter studies involving a larger number of patients are needed to confirm our preliminary results and to assess the prognostic value of CNP in this setting.

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