Prognostic value of N-terminal natriuretic peptides in systemic sclerosis: a single centre study

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ABSTRACT

Objective. *Cardiac involvement is an important determinant of prognosis in systemic sclerosis (SSc). The identification of patients with high risk is of great importance. Our aim was to investigate the diagnostic and prognostic value of circulating concentrations of N-terminal fragments of A- and B-type natriuretic peptides (NT-proANP and NT-proBNP) in patients with SSc.*

Methods. *We prospectively studied 144 patients with SSc and followed them up for five years. Blood was collected for natriuretic peptide measurement at the time of the yearly scheduled cardiological check-up. The occurence of clinically significant cardiac disease was measured as the composite of pulmonary arterial hypertension, cardiac revascularisation, development of left ventricular dysfunction or death.*

Results. *Patients diagnosed with heart involvement during the study had significantly higher levels of NT-proANP and NT-proBNP (791.4±379.9 pmol/l vs. 608.0±375.8 pmol/l, p<0.05 and 183.1±162.6 vs. 125.7±117.5 pmol/l, p<0.05, respectively). Receiver-operator-characteristic analysis identified <822.5 pmol/l as the best NT-proANP and <154.5 pmol/l as the best NT-proBNP threshold (sensitivity 56.3%, specificity 79.5%, negative predictive value: 86.4% and sensitivity 50.0%, specificity 76.8%, negative predictive value: 83.7%, respectively). During the follow-up, lower NT-proANP levels were significantly associated with a longer event-free survival (p<0.05), similar but a non-significant trend regarding NT-proBNP levels was also shown (p=0.052)*

Conclusion. *In our cohort, NT-proANP had a supplementary prognostic value for cardiac involvement in systemic sclerosis. In addition, the high negative predictive value of natriuretic peptides supports the more extensive use in identifying SSc patients with high risk of future cardiac involvement.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology that is characterised by vascular dysfunction and excessive collagen production leading to skin and visceral fibrosis. Recent epidemiological studies suggest that besides pulmonary and renal involvement cardiovascular disease is a principal determinant of mortality in SSc (1-5). In contrast to its importance, cardiac disease represent a diagnostic challenge in SSc. The reason for this is the complex nature of cardiac involvements that consist of diverse pathologic processes with overlapping, non-specific symptoms. SSc has been linked to several cardiac abnormalities, including pulmonary arterial hypertension, left ventricular dysfunction due to primary myocardial disease and coronary heart disease that may gain increasing prevalence with the improving care and better life expectancies of the SSc patients (5, 6). Current guidelines recommend regular screening of SSc patients including yearly echocardiography in order to facilitate timely diagnosis and treatment of pulmonary hypertension (7). In addition, there is a need for reliable biomarkers with potential to support diagnosis and define prognosis. Plasma brain natriuretic peptid (BNP) and its more stable precursor, N-terminal proBNP (NT-proBNP) have been extensively studied in the detection of pulmonary hypertension (8, 9). Changes parallel with pulmonary haemodynamics and functional parameters, accordingly can be used as a parameter for follow-up assessement and a potential marker of the response to therapy (10). Furthermore natriuretic peptides are also candidate markers to detect right ventricular dysfunction but also in left systolic or diastolic ventricu-

lar dysfunction, or myocardial ischaemia related to SSc. (11)
However, it is yet unclear, if the determination of natriuretic peptid levels may improve the detection of any cardiac involvement. We aimed to test diagnostic and long term prognostic performance of NT-proANP and NT-proBNP levels supplementing the regular screening of SSc cases.

Patients and methods

Consecutive patients with systemic sclerosis diagnosed in the tertiary centre of the University Rheumatology and Clinical Immunology Department were recruited at the time of their regular yearly cardiological check-up from January to November in 2007 into a prospective trial. Diffuse and limited subset of SSc cases were diagnosed by the commonly used criteria (12). All cases complied with the recently updated classification criteria (13). The trial protocol was approved by the Medical Research Council Scientific and Ethical Committee (330/PI/2007) and patients provided informed consent before the study. Each patient underwent a baseline physical examination. Lung involvement was investigated by using chest x-ray, pulmonary function tests, and high resolution computed tomography if interstitial lung disease was suspected. Duration of Raynaud's phenomenon (RP) at the time of the study entry was evaluated by clinical interview, while duration of SSc was determined from the time of the onset of the first SSc-related non-Raynaud symptom. Patients were excluded from further investigations if they had conditions known to affect NP levels or interfere with the compliance to the screening protocol; with severly decreased systolic function (ejection fraction <30% on echocardiography), with significant renal impairment (creatinine >150 μmol/L), with known severe valvular disease or with severe lung fibrosis (forced vital capacity <50%).The details of the screening protocol are published elsewhere (6). Briefly, patients with signs of right ventricular involvement on echocardiography (tricuspid insufficiency diagnosed by flow velocity over 3 m/s, or consistent with 2.5-3m/s in the presence of unexplained dyspnea, signs of right ventricular hypertrophy/dilatation, or right ventricular D sign) and effort related dyspnea with disproportional decrease of CO diffusion capacity (DLCO) compared to the forced vital capacity (FVC/DLCO >1.8) were referred for right heart catheterisation for exclusion pulmonary arterial hypertension. In cases with chest pain, recent deterioration in physical activity, evolving effort dyspnea, those who fulfilled the criteria of the New York Heart Association functional classes III-IV, coronary angiography was performed to exclude coronary artery disease. Follow-up was planned with yearly clinical visits up to five years after inclusion.

Echocardiography

Echocardiography was performed using Aloka ProSound 5500 ultrasound equipment. Ejection fraction was measured by biplane Simpson's method. Systolic pulmonary artery pressure was estimated by using the simplified Bernoulli equation, and calculated from the peak tricuspidal regurgitation velocity ($4v^2$ plus estimated right atrial pressure according to the diameter and collapse index of the inferior vena cava).

Right heart catheterisation

A Swan-Ganz catheter (B. Braun, Melsungen, Germany) was introduced into a main pulmonary artery branch. The diagnosis of pulmonary arterial hypertension is defined at right heart catheterisation (RHC) by a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg with a pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg (14).

Coronary angiography

Angiograms were recorded digitally (Philips Integris, Netherlands) at a speed of 12.5 or 25 frames per second with a 5Fr catheter using a pressure operated pump (ACIST HD101, Eden Prairie, Minesota, USA). Coronary lesions were assessed by visual estimation as well as with quantitative angio-graphy (QCA).

Natriuretic peptide levels

Natriuretic peptide levels were determined from blood samples. Plasma fraction of the blood was separated and the samples were stored at -20°C until analysis. The plasma concentrations of NT-proANP and NT-proBNP were determined with radioimmunoassays utilising antisera directed to $NT\text{-}proANP_{46–79}$ and $NT\text{-}proBNP_{10–29}$, as described previously. (15) The sensitivities of the assays were 60 and 40 pmol/L, respectively (16).

End point definitions

The main outcome parameter of the study was the occurrence of symptomatic heart disease as defined by right heart catheterisation proven PAH, development of left ventricular systolic dysfunction (ejection fraction <50%), non-fatal myocardial infarction (MI) or coronary revascularisation. The primary clinical outcome measure was the composite of the above and all-cause mortality during the period of five years.

Statistical analysis

Continuous variables are presented as means ± SD. Categorical variables are expressed as frequencies and percentages. To correct the logarithmic distribution of the natriuretic factor levels, data were used after logarithmic transformation. Unpaired *t*-tests were used for comparison of normally distributed, continuous variables between groups. Non-normally distributed variables between groups were analysed with the Mann-Whitney test.
The predictive values of natriuretic peptides levels as well as the optimal cut-off points were determined by receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity of the cut-off value for group distinction were determined as follows: sensitivity(%) = true positives/(true positives + false negatives) x100; specificity(%) = true negatives/(true negatives + false positives) x100.
Time-to-event differences between groups were demonstrated with Kaplan-Meier hazard curves and were compared with the Mantel-Cox log rank test. The cumulative event plots according to quartiles of BNP concentration were estimated by the Kaplan-Meier method and compared with use of the log rank test. Cases with prevalent disease at the inclusion were excluded from follow-up analyses to correct the potential bias

they may introduce. Effect of patient characteristics was analysed in Cox proportional hazard models. Univariable and multivariable analyses were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). To control potential confounders in the multivariable models, we included demographic and clinical variables a *p*-value <0.05 in univariable analyses. Multivariable models were analysed using the backward stepwise method. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSSv19.0 software (SPSS Inc. Chicago, Illinois)

Results

150 patients were evaluated for study inclusion. After exclusion of 6 patients (1 patient with grade IV aortic regurgitation, 1 with severely depressed systolic function and, 4 with significant renal impairment) 144 patients were included in the study and followed for the mean follow-up of 4.57±0.9 years. Demographics, treatment and cardiopulmonary characteristics of the included patients are depicted in Table I. Three patients were lost to follow-up (2.1%). We registered 13 deaths. During the study 55 cardiac catheterisation, 19 RHC and 36 coronary angiographies were performed in 28 patients. Pulmonary arterial hypertension was diagnosed in 6 cases, these included 2 cases with known PAH and those 3 where the PAH was diagnosed during the initial check-up. Coronary intervention was performed in 11 cases (4 during the initial work-up, 5 cases during the follow-up period). Five cases had ventricular dysfunction diagnosed.

In case of 8 patients malignancy had been diagnosed (four mammary carcinomas, two lung cancers, colorectal carcinoma, and lymphoid leukaemia in zone case). Natriuretic peptide levels did not differ significantly between patients with malignancies compared to the rest of the cohort.

Levels of NT-proANP and NT-proBNP were significantly higher (791.4±379.9 pmol/l *vs*. 608.0±375.8 pmol/l $p<0.05$ and 183.1±162.6 *vs*. 125.7±117.5 pmol/l $p<0.05$) in patients reaching any of the predefined criteria of significant heart

Table I. Patient characteristics of the 144 systemic sclerosis patients included in the study.

Systemic sclerosis (n=144)	
Age (years)	56.4 ± 11.1
lSSc:dSSc	101:43
Gender (male:female)	14:130
Body Mass Index	26.3 ± 9.0
Disease duration (years)	10.9 ± 8.7
SSc Disease Activity Index	2.4 ± 1.9
Medsger Severity Scale	6.4 ± 2.8
Anti-centromere antibody (n)	31 (21.5%)
Anti Scl-70 antibody (n)	54 (37.5%)
Biochemical data:	
Blood sedimentation (mm/h)	22.9 ± 17.9
hsCRP (mg/l) (norm.: <5mg/l)	11.0 ± 15.9
haemoglobin (g/l) (norm.:120-170g/l)	126.7 ± 13.4
lactate-dehydrogenase (U/l) (norm.:<450 U/l)	336.9 ± 97.7
creatinine (μmol/l) (norm.: 44-80 μmol/l)	80.3 ± 17.8
NT-proANP pmol/l[1]	648.8 ± 383.1
NT-proBNP pmol/l[1]	138.4 ± 130.46
Clinical manifestations, case history: (n)	
Six-minute walk test (m)	363.3 ± 62.6
Raynaud's phenomenon	139 (96.5%)
Subcutaneous calcinosis	17 (11.8%)
Teleangiectasia	61 (42.4%)
Pigmentation disorder	47 (32.6%)
Myositis	5 (3.5%)
Modified Rodnan skin score	4.4 ± 5.0
Abnormal Shirmer's test	56 (37.8%)
Pericarditis	6 (4.2%)
Renal involvement	1
Esophageal stricture	44 (29.7%)
Major cardiovascular risk factors (n)	
Hypertension	63 (43.8%)
Smoking	21 (14.6%)
Hypercholesterinaemia	8 (5.6%)
Obesity (BMI >25)	70 (48.6%)
Treatment history: (n)	
Ca-channel blockers	97 (67.4%)
ACE inhibitors	55 (38.2%)
Spironolactone	44 (30.6%)
Pentoxyphilline	131 (91.0%)
Cyclophosphamide[2]	37 (25.7%)
Low dose corticosteroid[2]	47 (32.6%)
H_2 blocker and/or proton-pump inhibitor	115 (80.0%)
Echocardiography:	
Ejection fraction (%)	62.1 ± 7.1
Calculated RV systolic pressure (mmHg)	31.3 ± 6.8
Diastolic dysfunction [3](n)	92 (62.2%)
Pulmonary status:	
Pleuritis (in case history)	5 (3.4%)
Pulmonary fibrosis (X Ray, diffuse)	8 (5.4%)
Pulmonary fibrosis (HRCT)	79 (53.4%)
Pulmonary fibrosis (HRCT diffuse)	20 (13.5%)
Forced vital capacity (FVC)	95.9 ± 19.3
CO diffusion capacity (DLCO)	64.9 ± 17.6
DLCO calculated to alveolar volume (DLCO/VA)	79.1 ± 17.2
FVC/DLCO	1.7 ± 0.7

[1]Natriuretic factor levels were entered into the analysis after logarithmic transformation. [2]Cyclophosphamide treatment was encoded when at least 12 months, with an average dose of 1000 mg/month, was recorded in the patient's medical history. Steroid intake was marked when low or medium dose corticosteroid treatment was recorded in the patient's medical history for at least 12 months. [3]Left ventricular diastolic function was measured by peak early (E) and late (A) velocities of the transmitral flow. lSSc: limited cutaneous systemic sclerosis, dSSc: diffuse cutaneous systemic sclerosis, hsCRP: high-sensitivity C-reactive protein, ACE: angiotensin converting enzyme, RV: right ventricle, HRCT: high resolution computer tomography, FVC: forced vital capacity, DLCO: diffusing capacity for carbon monoxide, DLCO/VA: carbon monoxide diffusing capacity adjusted for alveolar volume.

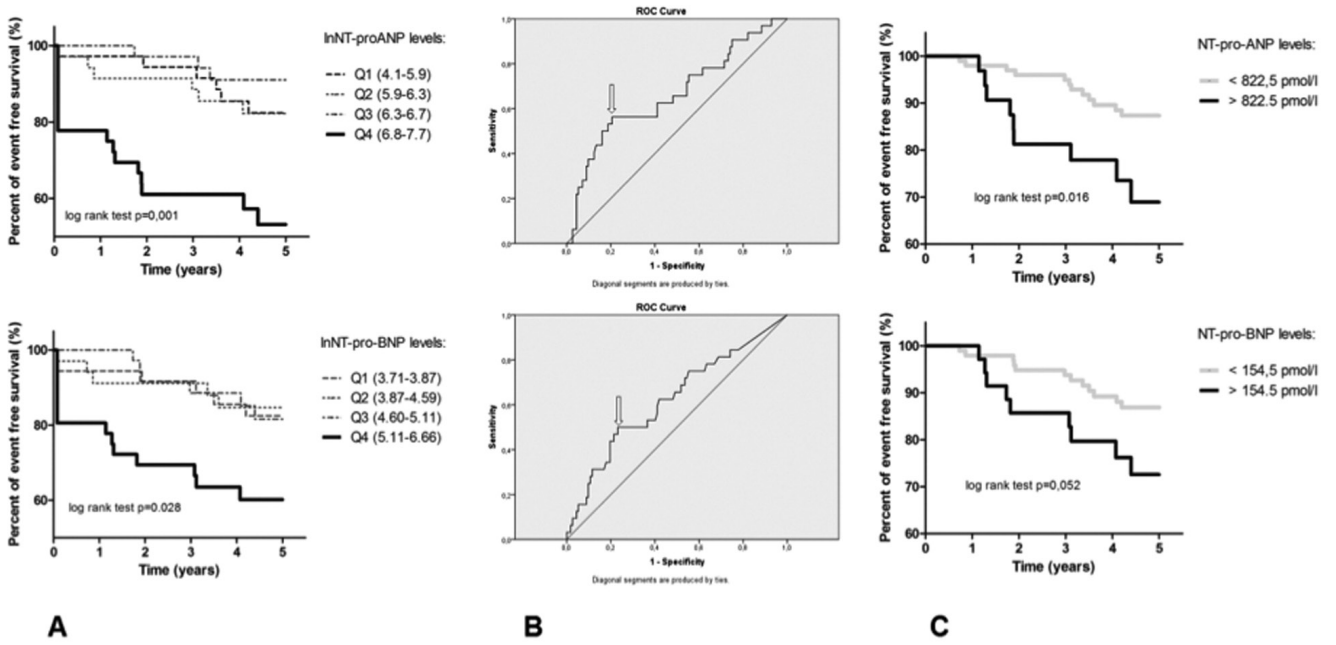

Fig. 1. Prognostic values of natriuretic peptid levels for the 5-year event-free survival.
Column A shows Kaplan-Meier survival curves for 4 groups based on quartiles of distribution of ln natriuretic peptides. Differences in 5-year event-free survival with log rank test for trend in the level of lnNT-proANP and lnNT-proBNP were statistically significant. Q: quartile.
Column B presents the Receiver-operator characteristic (ROC) curve analyses of the predictive values of natriuretic factor levels in determining the composite endpoints. The optimal cut-off value with 56.3% sensitivity and 79.5% specificity was 822.5 pmol/l NT-proANP (arrow), and with 50.0% sensitivity and 76.8% specificity was 154.5 pmol/l NT-proBNP (arrow). Diagonal segments are produced by ties.
Column C demonstrates the prognostic values of NT-proANP and NT-proBNP measurements in systemic sclerosis. Kaplan-Meier curves of event-free survival of patients who did not reach end-point during the initial visit separated significantly if patients were divided according to the ROC definied cut-off of NT-pro-ANP level.

disease during the study. Analysis of the Kaplan-Meier event-free survival curves showed a significant trend for better outcome in patients within the lower quartiles of baseline NT-proANP and NT-proBNP concentrations. (Fig. 1A)

An optimal NT-proANP cut-off value of 822.5 pmol/l was suggested with a sensitivity of 56.3%, specificity of 79.5%, negative predictive value of 86.4% and NT-proBNP cut-off value of 154.5 pmol/l with a sensitivity of 50.0%, specificity of 76.8%, negative predictive value of 83.7%. (Fig. 1B) An area under the curve (AUC) of 0.663±0.058 (Asymptotic significance (AS): p=0.005; 95% Asymptotic Confidence Interval (CI): 0.549–0.777) was slightly superior in case of the NT-proANP levels to NT-proBNP (AUC: 0.624±0.059, p=0.015, CI: 0.509–0.738).

Analysis of the outcome of patients after exclusion of those with known cardiac disease or diagnosed at the initial work-up of the study (prevalent cases), revealed that cases with higher NT-pro-ANP levels over the ROC defined cut-off had significantly worse event-free survival. Similar strong trend in the level of NT-proBNP was observed, however this latter differences did not reach the level of statistical significance (p=0.052). (Fig. 1C)

Univariate analysis found significant correlation in 7 characteristics: elevated NT-proANP (OR: 4.17 [2.06–8.41], p<0.001), elevated NT-proBNP (OR: 2.83 [1.41–5.67], p<0.01), diffuse cutaneous subset of SSc (OR: 2.16 [1.03-4.55], p<0.05), renal involvement (OR: 8.39 [1.11–63.24], p<0.05), carbon-monoxide diffusion capacity (DLCO) (OR: 0.97 [0.95–0.99], p<0.01), and DLCO/VA (OR: 0.96 [0.94-0.99], p<0.01), and ratio of the forced vital capacity and the DLCO (FVC/DLCO) (OR: 0.97 [0.95–0.99], p<0.01). In the multivariable model elevated NT-pro-ANP level (OR: 4.062 [1.89–8.73] p<0.001) and the ratio of FVC/DLCO (OR: 0.97 [0.95–0.99] p<0.01) were independent significant predictors.

Discussion

The main finding of our study is that natriuretic peptide levels beside their diagnostic value also have an important prognostic value in patients with systemic sclerosis.

Natriuretic peptides (NP) have emerged as important candidates for the development of diagnostic tools in cardiovascular disease. Plasma natriuretic peptide levels are consequence of production and secretion by cardiac myocytes in response to increased myocyte stretch. NPs exert multiple physiological properties, such as vasodilation, natriuresis, growth suppression and inhibition of the sympathetic nervous as well as the renin-angiotensin-aldosterone system. The gene expression of ANP and BNP is almost exclusively restricted to cardiac myocytes, the production and secretion is increased when the heart is loaded. ANP is largely stored in atrial secretory granules providing a rapid release of the peptide upon stimulus (17). BNP may also be involved in the pathogenesis of cardiac hypertrophy and fibrosis as it acts as a local antifibrotic factor in the heart (18).

Due to their diagnostic and prognostic relevance natriuretic peptide levels

became important diagnostic tools in numerous cardiac diseases including cardiac failure and pulmonary hypertension. A number of immunoassays became available, however, there are several analytical differences including assay specificity and calibration. Therefore, the measured concentrations may vary between assays (19). In addition, the available assays measure one analyte at time, although the ANP and BNP systems are differently regulated, and combined information from both systems might have potential for higher clinical sensitivity (20).

Natriuretic peptides play a key role in the complex multiorgan and cellular adaptation in heart failure (HF), regardless of the initial injury (21). The plasma concentration of NT-proBNP is typically increased in patients with asymptomatic or symptomatic left ventricular systolic dysfunction (22). BNP has been shown to be useful in distinguishing between congestive heart failure and chronic obstructive pulmonary disease (23-25). Multiple studies have examined the threshold concentration that excludes HF for the commonly used natriuretic peptides, NT-proBNP and NT-proANP (26-28). For patients presenting with acute onset the optimal exclusion cut-off points are 300 pg/ml for NT-proBNP, 120 pmol/l for NT-proANP. This cut-off point for NT-proANP shown to be non-inferior to the threshold for NT-proBNP (28). Furthermore plasma natriuretic peptide concentrations are also valuable predictors of outcome (29).

In SSc meticulous and detailed cardiac investigations are warranted in search of valvular or primary myocardial involvement (30). Left ventricular systolic dysfunction is not common in this disease, but severely depressed LVEF is of major concern (31, 32). Left ventricular diastolic dysfunction is much more frequent; however, the rate of occurrence is highly dependent on the methodology used. In our study we used only the analysis of the transmitral flow pattern (E/A), while the additional use of tissue Doppler echocardiography (TDI) offers a more sensitive assessment of the left ventricular systolic and diastolic function (30). Nevertheless there are still limiting data on the prognostic significance of diastolic dysfunction.

In SSc patients coronary artery disease (CAD) may mimic, and may appear in combination with PAH. Reduced physical capacity and exertional dyspnoea shows a considerable overlap between PAH and CAD. We previously found that CAD represents an important problem in differential diagnosis and that revascularisation results in improvement of symptoms (6). As a potential cause of myocardial dysfunction we included CAD in our current study. Dimitroulas and coworkers showed that elevated NP levels may imply primary heart involvement evidenced by systolic or diastolic dysfunction and/or SSc PAH (33). Allanore *et al*. demonstrated that NT-proBNP accurately detects patients with depressed myocardial contractility and overall cardiac involvement (AUC: 0.905 and 0.935). SSc patients with normal echocardiography and TDI as controls, and using a 125 pg/ml cut-off concentration, sensitivity and specificity were 92% and 71% in the detection of depressed myocardial contractility, and 94% and 78% for overall cardiac involvement (11). Our results are in line with these observations and extended them with the notion that patients with higher NP levels have worse prognosis even if cases with prevalent left ventricular dysfunction, coronary artery disease and PAH are disregarded.

Pulmonary arterial hypertension is a life-threatening disease that can rapidly progress to severe right heart failure. Righ ventricular (RV) failure is the main cause of death in PAH, and BNP and NT-proBNP levels reflect the severity of RV dysfunction (14). The REVEAL registy (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management), demonstrated that SSc associated PAH patients had the poorest 1 year survival compared to idiopathic- and other connective tissue disease associated PAH subgroups (34). Among SSc patients active screening for detection of PAH is recommended to ensure earlier diagnosis, treatment and better prognosis (7, 35). In a prospective trial of 135 patients, Cavagna *et al*. found that the performance of BNP was slightly superior in screening patients with systemic sclerosis to diagnose PAH than measurement of NT-proBNP (36). However as NT-proBNP is a more stable peptide and the measurement of this cleavage product gained widespread acceptance (37). Multiple lines of evidence support that plasma NT-proBNP level is elevated in SSc-PAH, and the values correlate to echocardiographic signs of pulmonary hypertension, *i.e*. velocity of tricuspidal regurgitation (9, 33, 36, 38). The elevated plasma level may be useful in selecting patients for right-heart catheterisation (39). The recently published prospective, international, multicentre, DETECT (DETECTion of PAH in systemic sclerosis) study that aimed to establish evidence-based detection for PAH in SSc with selection of the best discriminatory variables confirmed these findings and included NT-proBNP measurement in the proposed algorithm (40). Potential of NT-proBNP that may exceed that of yearly echocardiography in a 4 year follow-up study where investigating the survival rate in systemic sclerosis patients with PAH (39). Furthermore, NT-proBNP levels correlated significantly with mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) measured by right heart catheterisation in scleroderma patients with PAH (41). Elevated baseline and change in NT-proBNP levels may help identifying SSc-PAH patients with particularly adverse prognosis who may have benefit from the introduction or modification of advanced therapies (9).

In contrast to the role of NT-proBNP, data regarding diagnostic and prognostic value of NT-pro ANP are scarce. Kazzam *et al*. assessed elevated ANP in patients with SSc. Reduced LV compliance, probably due to increased fibrosis may cause changes in atrial pressure sufficient to stimulate ANP production without systolic dysfunction as a prerequisite (42). In the clinical praxis ANP has been progressively supplanted by the B-type natriuretic peptides. In our study NT-proANP was superior to NT-proBNP in prediction of prognosis that may support more extensive use of this marker.

The major limitations of our study are due to its restricted size and the single centre design. Consequently our study was not adequately powered to assess the different forms of cardiac involvement individually. Furthermore, the low number of patients was also the more putative reason for the marginal sigfificance found regarding the NP levels. Therefore further validation is required in a larger SSc population to support the routine use of NT-proANP.

In conclusion, our study extended the earlier observations regarding the non-specific nature of natriuretic peptid levels. They are useful in selecting SSc patient requiring more detailed cardio-pulmonary work-up and more rigorous follow-up. NT-proANP might also be an additional prognostic marker for cardiac involvement.

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