

N-terminal pro brain natriuretic peptide: the new cornerstone of cardiovascular assessment in systemic sclerosis

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ABSTRACT

Heart involvement, including primary myocardial involvement, is very common in systemic sclerosis (SSc). When clinically evident, cardiac involvement is recognized to be a very poor prognostic factor. Thus pre-clinical identification is highly encouraged. Echocardiography, including pulsed tissue Doppler echocardiography, is the cornerstone of routine heart assessment as it allows the detection of reduced systolic/ diastolic function, as well as the measurement of pulmonary artery pressure, and the possible detection of valvular or pericardial involvement. Myocardial perfusion may be also assessed by single photon emission computed tomography, and if available, by cardiac magnetic resonance imaging. Since the introduction of routine assay for natriuretic peptides, and their initial application for the diagnosis of acute heart failure, B-type natriuretic peptide assays are now recommended for a wide number of applications and have been introduced as a major tool, in particular in primary care, in worldwide guidelines. Within the context of SSc, recent studies have demonstrated that BNP and NT-proBNP are highly relevant for the diagnosis and the prediction of pulmonary hypertension occurrence. Moreover, NT-proBNP allows the detection of both reduced left ventricular/right ventricular contractility, or pulmonary hypertension, suggesting its potential role as a first line tool in primary care setting for the overall cardiac assessment of SSc in which cardiovascular complications are a burden.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin, internal organs and

small vessels. Cardiac involvement is often clinically occult. However, it is recognized as a very poor prognostic factor, and one of the leading causes of mortality in SSc patients (1). Cardiac involvement may affect the endocardium, myocardium and pericardium, separately or concomitantly. As a consequence, pericardial effusion, auricular and/or ventricular arrhythmias, conduction disease, valvular regurgitation, myocardial ischemia and heart failure have been reported. In addition, pulmonary arterial hypertension, renal and lung involvement can adversely affect cardiac status and may dramatically alter the prognosis of these patients (1, 2).

Prevalence and prognosis of overall cardiac involvement

The prevalence of overall cardiac disease varies among studies according to the methods used for its assessment. Indeed, most past available data are based upon clinical evaluation, ECG and thoracic x-ray. Several lines of evidence suggest that both limited and diffuse cutaneous subtypes can be affected by cardiac involvement (1-3). Nevertheless, an epidemiological Italian study suggested that heart involvement could be more prevalent in the diffuse sub-type (32%) as compared with the limited form (23%) (4). Such an association has been recently confirmed in a recent study that focused on depressed left ventricular ejection fraction (LVEF) and reported data for more than 7,000 patients (5). Data from the Pittsburgh's group also showed that anti-topoisomerase I antibody-positive patients with rapid or intermediate skin thickness progression rate are at considerable early risk for the occurrence of SSc-associated cardiac problems (6). In an international meta-analysis, among 1645 cases, 578 deaths occurred

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over 11,521 person-years of follow-up. In multivariate analyses, adjusted for age and sex, cardiac involvement (defined by major conduction disturbances, ventricular arrhythmia, heart failure or persistent moderate-to-large pericardial effusion detected by echocardiography) increased the risk of mortality (hazard ratio HR=2.8; 95% confidence interval [CI]: 2.1 to 3.8) as well as renal (HR=1.9; 95% CI: 1.4 to 2.5), pulmonary involvement (HR=1.6; 95% CI: 1.3 to 2.2), and anti-topoisomerase I antibodies (HR=1.3; 95% CI: 1.0 to 1.6). Moreover, renal, cardiac, and pulmonary involvements tended to occur concomitantly (7). Such a severity has been recently confirmed in a series of 366 Hungarian patients; 65% of the observed deaths were attributed to cardiopulmonary complications of the disease (8).

A part from cardiac involvement, pulmonary hypertension may also badly affect the prognosis of SSc patients. Indeed, in 2 recent studies (9, 10), the 3-years survival of SSc patients with pulmonary hypertension ranged from 28% to 48% and was significantly reduced when compared to primary pulmonary hypertension or systemic lupus erythematosus associated pulmonary hypertension. As pulmonary hypertension is often associated with both right ventricular (RV) and left ventricular (LV) involvements in SSc, one may wonder if such specific cardiac involvement does not contribute to the observed high-rates mortality (11).

Different manifestations of cardiac involvement by SSc and their prevalence

SSc may be complicated by several distinct cardiac manifestations. Of these, depressed myocardial contractility is supposed to be specific, and the "hallmark" of primary myocardial involvement. However, its existence and prevalence is still a matter of debate, as most studies only investigated LV ejection fraction (LVEF) and reported somewhat low prevalence of reduced LVEF (5, 12-14). One study, which included 570 patients, reported a 1.4% prevalence of LV systolic dysfunction (12). Other authors have reported a low

prevalence of reduced LVEF at rest, though up to 46% of patients had abnormal LV contractility as assessed by LVEF during exercise (15). More recently, the EUSTAR registry provided robust estimates of the prevalence of LV dysfunction and demonstrated an overall of 5.4% prevalence (5).

We have previously reported the observation of reduced LV contractility despite a normal LVEF using radial strain-rate determined by Tissue Doppler Echocardiography (TDE), suggesting that the prevalence of depressed myocardial contractility may be underestimated (16, 17). In a more recent study, we investigated 100 consecutive patients with SSc with matched controls, using conventional echocardiography implemented by pulsed TDE of mitral and tricuspid annular velocity measurements (11). Using this simple and widely available method, we demonstrated that 14% and 15% of SSc patients had respectively reduced LV and RV contractility (11). In addition, both measurements were correlated which may reinforce the existence of a common LV and RV primary myocardial involvement.

The presence of diastolic dysfunction in patients with SSc has been extensively demonstrated (11, 14). However, the distinction of pathologic findings versus age-related changes or other confounding factors may be hard to ascertain. In the largest study, the authors reported the presence of diastolic abnormalities in 101 of 570 patients (17.7%) (12). However, 48 patients (8.4%) had a restrictive mitral flow pattern, which is unequivocally abnormal, while 53 patients (9.3%) had delayed diastolic relaxation, which, in absence of a control group, may not allow formal conclusion (12). In our controlled study, using pulsed TDE, we found that 30/100 patients have definite abnormal LV filling (11). Overall, the prevalence of diastolic dysfunction is increased when compared to age-sex matched controls (11) and may range from 17 to 30% (11, 12).

Primary pulmonary arterial hypertension (PAH) is assumed to be one of the most severe complications of SSc. The more recent studies that focused on PAH and used catheterization for

diagnosis, established a prevalence that ranged from 7.85 to 12% of SSc patients (18-20).

Pericardial effusion has been noted in 33/77 (43%) SSc patients versus 2/45 (4%) controls, but only 11/77 (14%) had a significant effusion, according to a controlled study (14). In our study, 15/100 (15%) patients compared with 1/26 (4%) (NS) controls had pericardial effusion (11). In addition, we demonstrated that SSc patients had a higher prevalence of aortic regurgitation (18%) and a trend towards more prevalent mitral regurgitation; however, valvular regurgitations were associated with age, and most patients had grade I aortic or mitral regurgitation or both, which is a benign finding (11).

Assessment of heart involvement in systemic sclerosis

A few decades ago, radionuclide ventriculography was recommended for heart function assessment. While it has been progressively supplanted by echocardiography, it should be still considered in some patients with poor echogenicity (<5%) and for research purposes. Doppler-echocardiography together with clinical evaluation has been proposed as the candidate methods for routine cardiac assessment (21, 22), as they should possibly detect all forms of cardiac complications by SSc. However, recent studies suggest that these indexes may lack of sensitivity and do not allow a prompt diagnosis at a pre-clinical stage. Indeed, new methods such as magnetic resonance imaging and strain rate imaging have demonstrated to be more sensitive methods than conventional echocardiography. However, the application of these methods for routine assessment does not seem to be encouraged. Pulsed TDE has emerged in recent years as a robust indicator of both LV and RV contractility, as well as LV filling patterns. In the specific context of SSc, we and others have demonstrated that the implementation of conventional echocardiography with mitral and tricuspid annular velocities measurements resulted in a greater detection of cardiac complication (11, 16, 17, 23). The investigation of myocardial perfusion and micro-

circulation may also be considered for some SSc patients. Single photon emission computed tomography (SPECT) has been proposed a few years ago in order to assess myocardial perfusion abnormalities and possibly distinguish reversible ischemia from irreversible lesions. However, SPECT is limited in quantitative studies (1). Cardiac MRI has progressively supplanted SPECT as it allows the identification of small sub-endocardial perfusion defects, but also coronary flow reserve determination, the identification of myocarditis (especially in patients with myositis) and the morphological evaluation of fibrotic myocardium compared to viable tissue (17, 24, 25). In addition, cardiac MRI also appears to be a rapid and noninvasive means of determining subclinical right myocardial involvement (25) and is under development to assess right ventricle in secondary heart involvement related to pulmonary arterial hypertension (26).

Natriuretic peptide in cardiac diseases

Natriuretic peptides (NP) are peptide hormones that are synthesized by the heart, brain and also other organs. Most of these peptides are secreted by heart or vessels in response to pressure and/or volume overload. As a consequence, these peptides may be candidate markers of various pathologic conditions. The atrial natriuretic peptide was the first natriuretic peptide to be reported in 1984. It has been progressively supplanted by the B-type natriuretic peptides, brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide (NT-proBNP). B-type natriuretic peptides are synthesized mainly by ventricular myocytes. Their synthesis and release are controlled at the level of gene expression which can be rapidly upregulated. BNP is first synthesized as preproBNP, which is then cleaved to proBNP and finally to BNP and NT-proBNP. NPs are involved in the long-term regulation of sodium and water balance, blood volume and arterial pressure. They directly dilate veins and thereby decrease central venous pressure, which reduces cardiac output by decreasing ventricular preload. They

also dilate arteries, which decreases systemic vascular resistance and systemic arterial pressure. They affect the kidneys by increasing glomerular filtration rate and increase natriuresis. Taken together, these actions decrease blood volume, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output (27, 28). NPs levels (BNP and NT-proBNP) are now widely used as markers of acute and chronic heart failure in clinical practice and cardiovascular research. They have also been incorporated into cardiovascular guidelines for heart failure diagnosis and management. Elevations can establish the presence of heart failure caused by systolic or diastolic dysfunction with similar accuracy in both settings. They are of major input to risk stratify patients with regard to the need for hospital admission in case of suspicion of cardiac involvement in primary care. NPs levels are also powerful predictors of outcome and mortality in heart failure patients and can guide the therapy. They may also be helpful to screen for asymptomatic left ventricular dysfunction in high-risk patients (29).

In the context of idiopathic PAH, several studies have investigated the performance of natriuretic peptides. NT-proBNP was increased in these patients and its concentration increased with the severity of the patients assessed by the NYHA functional classification. Furthermore, compared to the other variables studied such as hemodynamics and walking test, NT-proBNP had the lowest level of overlap in the stratification of patients. Therefore, NT-proBNP appeared to differ among the different functional classes and correlates with other measures of disease severity (30). The BNP has also been shown to correlate with the functional status and prognosis of iPAH patients and could be a valuable parameter in this respect. BNP levels parallel changes in pulmonary hemodynamics and functional parameters under treatment, including the walking test (31). Furthermore, baseline NT-proBNP has been shown to be an independent predictor of mortality in a heterogeneous group of patients with chronic precapillary PAH

(32). Similar findings were observed for plasma BNP, and in particular, an increase in plasma BNP during follow-up, may have a strong, independent association with increased mortality rates in patients with iPAH (33).

B-type natriuretic peptides in systemic sclerosis

With respect to the various possible cardiac complications of SSc, including primary and secondary heart involvements, and integrating the impact and costs of repeated cardiac echocardiography, other screening methods may be advocated. The use of natriuretic peptides may be considered in this aim. Regarding the burden of pulmonary arterial hypertension, and taking into account that few symptoms are observed until this complication becomes life-threatening; there is an urgent need for early detection and treatment. In a first study, we showed that elevated NT-proBNP concentrations (>90th percentile adjusted for age and sex), measured after wash-out of vasodilators, detected SSc patients with recent elevated systolic pulmonary artery pressure (upper than 40 mmHg) with a sensitivity of 90%, a specificity of 90%, a positive predictive value of 69%, and a negative predictive value of 96%. Furthermore, the NT-proBNP levels correlated with the sPAP ($r=0.44$; $p=0.006$). Therefore, NT-proBNP appeared to be a useful biologic marker to identify early elevated sPAP values in SSc patients without clinical heart failure (34). This was confirmed and extended in a series of 109 SSc patients including 68 with SSc-PAH. It was found that NT-proBNP levels correlated with hemodynamics and prognosis in patients with established PAH (35). Indeed, patients without PAH had a mean NT-proBNP concentration of 139 pg/mL whereas NT-proBNP was 1474 pg/mL in SSc patients with PAH. Baseline NT-proBNP levels correlated positively with mean PAP ($r=0.62$; $p<0.0001$), pulmonary vascular resistance ($r=0.81$; $p<0.0001$), and inversely with walking distance ($r=-0.46$; $p<0.0001$). Among patients with SSc-PAH, 13 patients (19%) were in WHO functional classes II and had mean NT-proBNP levels of

325 pg/mL. Fifty-three patients (78%) were in WHO classes III and IV and had significantly higher mean NT-proBNP levels of 1677 pg/mL ($p=0.02$). Using a cut-off value of 395 pg/mL, the sensitivity and specificity of NT-proBNP for predicting the presence of SSc-PAH were 56 and 95% respectively. Thus NT-proBNP levels directly relate to the severity of PAH. Some preliminary studies also suggested that NT-proBNP levels could be a useful marker for the response to therapy in patients with SSc-PAH secondary to SSc (36, 37). However, further data are needed to clarify the best strategy and tools to monitor PAH therapy in SSc and guide the therapeutic strategy.

We recently performed a study aiming at the evaluation of predictors of PAH in a prospective cohort of patients with SSc (38). After a planned 36-month follow-up, we evaluated the predictive value of different parameters for the development of precapillary PAH, as demonstrated by cardiac catheterization, in a cohort of 101 SSc patients. We observed that 8 patients developed PAH. Kaplan-Meier analysis identified the following baseline parameters as being predictors of PAH: DLCO/VA ratio $<70\%$ or $<60\%$ ($p<0.01$ for each comparison), elevated plasma NT-proBNP level (>97 th percentile of normal; $p=0.005$), echocardiographically estimated systolic PAP >40 mm Hg ($p=0.08$), and erythrocyte sedimentation rate >28 mm/hour ($p=0.015$). In multivariate analyses, an elevated baseline NT-proBNP level (hazard ratio [HR] 9.97 [95% confidence interval (95% CI) 1.69-62.42]) and a DLCO/VA ratio $<60\%$ (HR 36.66 [95% CI 3.45-387.6]) were predictors of the occurrence of PAH during follow-up. An increased NT-proBNP level together with a decreased DLCO/VA ratio of $<70\%$ was highly predictive of the occurrence of PAH during follow-up (HR 47.20 [95% CI 4.90-450.33]) (38). As a consequence, the use of these markers should result in improved PAH risk stratification and allow earlier initiation of therapy.

Apart from its role in the detection/management of PAH, natriuretic peptides are also candidate markers for the detection of LV/RV dysfunction related

to SSc, and may even represent "THE" marker of overall cardiac involvement by SSc. In this issue, we have recently investigated 69 consecutive patients suffering from SSc using echocardiography, and integrating pulsed TDE measurements, and plasma NT-proBNP (39). Overall, 18 patients had manifestations of cardiac involvement, of whom 7 had depressed left ventricular and 8 depressed right ventricular myocardial contractility, and 8 had elevated systolic pulmonary arterial pressure. In this study, we confirmed that NT-proBNP correlated with pulmonary arterial pressure and inversely correlated with LV contractility. Moreover, we demonstrated that NT-proBNP accurately detected patients with depressed myocardial contractility and overall cardiac involvement (area under the curve 0.905 [0.814-0.996] and 0.935 [0.871-0.996] respectively). Considering SSc patients with normal echocardiography and TDE as controls, and using a 125pg/ml cut-off concentration as recommended by the manufacturer for ambulatory patients, sensitivity and specificity were 92% and 71% in the detection of depressed myocardial contractility, and 94% and 78% for overall cardiac involvement (39). The main observation made in this study was the reliable detection of overall cardiac involvement by measurements of NT-proBNP including depressed LV and RV contractility as well as overall cardiac involvement by the disease. A broad application of these results may have important clinical and economic implications. The 18 patients with overall cardiac involvement represent approximately 25% of our entire population, leaving approximately 75% of patients with an NT-proBNP plasma concentration <125 pg/ml and no cardiac involvement. One might hypothesize that echocardiography and pulsed TDE could be omitted in this latter group of patients, though this hypothesis will need to be tested prospectively. The broad use of NT-proBNP might enable the screening of a larger number of patients presenting with SSc and, perhaps, screening at regular intervals, limiting the referral for more detailed cardiac investigations to those whose

NT-proBNP plasma concentration is >125 pg/ml. Furthermore, the $>90\%$ positive predictive value of a >300 pg/ml NT-proBNP concentration indicates a high likelihood of cardiac complications, and the need for further detailed and exhaustive investigations.

Conclusion

Heart involvement is frequent in SSc but often clinically occult. Once symptomatic, it is of poor prognosis and can lead to life-threatening. Several distinct cardiac manifestations can occur including mainly RV and LV dysfunction (through primary or secondary involvements). PAH is a major source of end-stage heart failure. The clinical symptoms together with Doppler Echocardiography are the first line tool to evaluate heart involvement in primary care setting. However, several lines of evidence have raised the major input of B-type natriuretic peptides in this context. Given the simplicity and wide availability of BNP and NT-proBNP assays, we recommend its use for the detection of any cardiac involvement in SSc patients, and believe that it might become the test of first choice to risk stratify and follow the cardiac status of patients with SSc. In a research agenda, further data are required to validate the use of a peptide assay before echocardiography in a general practice setting, to determine their prognostic value and their potential role for monitoring therapies, especially in the setting of PAH.

References

- KAHAN A, ALLANORE Y: Primary myocardial involvement in systemic sclerosis. *Rheumatology* (Oxford) 2006; 45 (Suppl. 4): iv14-iv17.
- KARASSA FB, IOANNIDIS JP: Mortality in systemic sclerosis. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S85-93.
- MEUNE C, ALLANORE Y, VIGNAUX O *et al.*: Predominant primitive right ventricular involvement in systemic sclerosis. *Clin Exp Rheumatol* 2007; 25: 658.
- FERRI C, VALENTINI G, COZZI F *et al.*: Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine* (Baltimore) 2002; 81: 139-53.
- ALLANORE Y, MEUNE C, VONK MC *et al.*: Prevalence and factors associated with left ventricular dysfunction in the EULAR

- Scleroderma Trial and Research group (EUS-TAR) database of systemic sclerosis patients. *Ann Rheum Dis* 2009 Mar 10. [Epub ahead of print].
6. PERERA A, FERTIG N, LUCAS M *et al.*: Clinical subsets, skin thickness progression rate, and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. *Arthritis Rheum* 2007; 56: 2740-6.
 7. IOANNIDIS JP, VLACHOYIANNPOULOS PG, HAIDICH AB *et al.*: Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005; 118: 2-10.
 8. CZIRJÁK L, KUMÁNOVICS G, VARJÚ C *et al.*: Survival and causes of death in 366 Hungarian patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 59-63.
 9. CONDLIFFE R, KIELY DG, PEACOCK AJ *et al.*: Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009; 179: 151-7.
 10. FISHER MR, MATHAI SC, CHAMPION SC *et al.*: Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006; 54: 3043-50.
 11. MEUNE C, AVOUAC J, WAHBI K *et al.*: Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: A controlled study of 100 consecutive patients. *Arthritis Rheum* 2008; 58: 1803-9.
 12. DE GROOTE P, GRESSIN V, HACHULLA E *et al.*: Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 31-6.
 13. HANDA R, GUPTA K, MALHOTRA A *et al.*: Cardiac involvement in limited systemic sclerosis: non-invasive assessment in asymptomatic patients. *Clin Rheumatol* 1999; 18: 136-9.
 14. MAIONE S, CUOMO G, GIUNTA A *et al.*: Echocardiographic alterations in systemic sclerosis: a longitudinal study. *Semin Arthritis Rheum* 2005; 34: 721-7.
 15. FOLLANSBEE WP, CURTISS EI, MEDSGER TA JR *et al.*: Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. *N Engl J Med* 1984; 310: 142-8.
 16. MEUNE C, ALLANORE Y, PASCAL O *et al.*: Myocardial contractility is early affected in systemic sclerosis: a tissue Doppler echocardiography study. *Eur J Echocardiography* 2005; 6: 351-7.
 17. ALLANORE Y, MEUNE C, VIGNAUX O, WEBER S, LEGMANN P, KAHAN A: Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and Tissue-Doppler echography study. *J Rheumatol* 2006; 33: 2464-9.
 18. MUKERJEE D, ST GEORGE D, COLEIRO B *et al.*: Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003; 62: 1088-93.
 19. HACHULLA E, GRESSIN V, GUILLEVIN L *et al.*: Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005; 52: 3792-800.
 20. VONK MC, BROERS B, HEIJDRÁ YF *et al.*: Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. *Ann Rheum Dis* 2009; 68: 961-5.
 21. FERRI C, EMDIN M, NIELSEN H, BRUHL-MANN P: Assessment of heart involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S24-8.
 22. VALENTINI G, MATUCCI CERINIC M: Disease-specific quality indicators, guidelines and outcome measures in scleroderma. *Clin Exp Rheumatol* 2007; 25 (Suppl. 47): 159-62.
 23. D'ANDREA A, STISI S, BELLISIMO S *et al.*: Early impairment of myocardial function in systemic sclerosis: non-invasive assessment by Doppler myocardial and strain rate imaging. *Eur J Echocardiogr* 2005; 6: 407-18.
 24. TZELEPIS GE, KELEKIS NL, PLASTIRAS SC *et al.*: Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. *Arthritis Rheum* 2007; 56: 3827-36.
 25. BEZANTE GP, ROLLANDO D, SESSAREGO M *et al.*: Cardiac magnetic resonance imaging detects subclinical right ventricular impairment in systemic sclerosis. *J Rheumatol* 2007; 34: 2431-7.
 26. MCCANN GP, GAN CT, BEEK AM, NIESSEN HW, VONK NOORDEGRAAF A, VAN ROSSUM AC: Extent of MRI delayed enhancement of myocardial mass is related to right ventricular dysfunction in pulmonary artery hypertension. *AJR Am J Roentgenol* 2007; 188: 349-55.
 27. DANIELS LB, MAISEL AS: Natriuretic peptides. *J Am Coll Cardiol* 2007; 50: 2357-68.
 28. MARTINEZ-RUMAYOR A, RICHARDS AM, BURNETT JC, JANUZZI JL JR: Biology of the natriuretic peptides. *Am J Cardiol* 2008; 101: 3-8.
 29. MAISEL A, MUELLER C, ADAMS K JR *et al.*: State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail* 2008; 10: 824-39.
 30. SOUZA R, JARDIM C, JULIO CESAR FERNANDES C, SILVEIRA LAPA M, RABELO R, HUMBERT M: NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension. *Respir Med* 2007; 101: 69-75.
 31. LEUCHTE HH, HOLZAPFEL M, BAUMGARTNER RA, NEUROHR C, VOGESER M, BEHR J: Characterization of brain natriuretic peptide in long-term follow-up of pulmonary arterial hypertension. *Chest* 2005; 128: 2368-74.
 32. ANDREASSEN AK, WERGELAND R, SIMONSEN S, GEIRAN O, GUEVARA C, UELAND T: N-terminal pro-B-type natriuretic peptide as an indicator of disease severity in a heterogeneous group of patients with chronic precapillary pulmonary hypertension. *Am J Cardiol* 2006; 98: 525-9.
 33. NAGAYA N, NISHIKIMI T, UEMATSU M *et al.*: Plasma Brain Natriuretic Peptide as a Prognostic Indicator in Patients With Primary Pulmonary Hypertension. *Circulation* 2000; 102: 865-70.
 34. ALLANORE Y, BORDERIE D, MEUNE C *et al.*: NT-pro-B-type brain natriuretic peptide as a diagnostic marker of early pulmonary arterial hypertension and effects of calcium channel blockers in systemic sclerosis. *Arthritis Rheum* 2003; 48: 3503-8.
 35. WILLIAMS MH, AKRAM R, SMITH CJ *et al.*: Role of N-terminal brain natriuretic peptide (NT-proBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 1485-94.
 36. SIMEONI S, LIPPI G, PUCCETTI A *et al.*: N-terminal pro-BNP in scleroderma patients on bosentan therapy for PAH. *Rheumatol Int* 2008; 28: 657-60.
 37. DIMITROULAS T, GIANNAKOULAS G, KARVOUNIS H *et al.*: N-terminal probrain natriuretic peptide as a biochemical marker in the evaluation of bosentan treatment in systemic-sclerosis-related pulmonary arterial hypertension. *Clin Rheumatol* 2008; 27: 655-8.
 38. ALLANORE Y, BORDERIE D, AVOUAC J *et al.*: High NT-pro brain natriuretic peptide and low carbon monoxide lung diffusion capacity are independent predictors of the occurrence of pre-capillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum* 2008; 58: 284-91.
 39. ALLANORE Y, WAHBI K, BORDERIE D, WEBER S, KAHAN A, MEUNE C: N-terminal brain natriuretic peptide in systemic sclerosis: a new cornerstone of cardiovascular assessment? *Ann Rheum Dis* 2008 Dec 3. [Epub ahead of print].