Original Research

Incident Atrial Fibrillation in Systemic Sclerosis: The Predictive Role of B-Type Natriuretic Peptide

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Key words:
Systemic sclerosis, atrial fibrillation, natriuretic peptide, prognosis, outcome, left atrium, diastolic dysfunction.

Introduction: Atrial fibrillation (AF) is common in patients with systemic sclerosis (SSc) and is associated with significant morbidity, mortality, and healthcare expenditures. The aim of this study was to prospectively determine the incidence and the independent predictors of AF in this patient population.

Methods: Forty-nine patients (age 50.15 ± 9.25 years, 87.8% female) and 21 healthy controls, all in sinus rhythm, were studied. Evaluation included blood sampling, B-type natriuretic peptide (BNP) measurement, comprehensive electrocardiography and echocardiography at baseline, and 24h ambulatory Holter monitoring at baseline and every 6 months.

Results: During a mean follow-up of 72 ± 24 months, 18 SSc patients (36.7%) developed AF (SSc-AF group) while 31 remained in sinus rhythm (SSc-SR group); all subjects in the control group (CI group) remained in SR. Baseline differences between SSc-AF, SSc-SR, and CI groups included: a) left ventricular (LV) mass: 84.5 ± 26 vs. 71.8 ± 18.6 vs. 60.5 ± 32.6 g/m^2, respectively ($p=0.017$); b) mitral tissue Doppler imaging E velocity: 14.5 ± 2.8 vs. 17.5 ± 3.4 vs. 20.5 ± 4.4 cm/s ($p<0.001$); c) left atrial (LA) volume: 18.8 ± 7.8 vs. 13.5 ± 5.1 vs. 9.7 ± 5.4 cm^3/m^2 ($p<0.001$); d) LA active emptying volume: 7.6 ± 2.7 vs. 4.7 ± 3.2 vs. 3.3 ± 2.2 cm^3/m^2 ($p<0.001$); and e) logBNP: 1.78 ± 0.47 vs. 1.31 ± 0.54 vs. 0.66 ± 0.38 pg/mL ($p<0.001$). In Cox proportional hazard analysis, BNP was the only independent predictor of incident AF.

Conclusion: Incident AF was high in SSc, especially in the presence of LV diastolic dysfunction with LA mechanical overload and elevated BNP levels. BNP was the only independent predictor of incident AF; therefore, it should be considered for risk stratification in this population.

Manuscript received:
June 10, 2012;
Accepted:
June 19, 2013.

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Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular dysfunction and excessive fibrosis of multiple organs.[1] Cardiac involvement may be isolated and affect the endocardium, myocardium, and pericardium, separately or concomitantly,[2] providing an ideal substrate for tachyarrhythmias dependent on re-entrant circuits. Atrial arrhythmias, such as paroxysmal supraventricular tachycardia, atrial flutter, and atrial fibrillation (AF), are present in 20-32% of SSc patients[3,4] and may be associated with increased cardiovascular morbidity and mortality.[3,5] Population studies have shown that risk factors such as aging, diabetes, hypertension, obesity, elevated natriuretic peptide plasma levels, and cardiovascular disease consistently predispose individuals to AF.[6-8] A recent National Heart Lung and Blood institute workshop drew attention to developing prevention strategies for AF, for which a thorough understanding of the predisposing factors is essential.[9] However, to the best of our knowledge, there are no studies addressing the risk factors predisposing SSc patients to AF. The aim of this

study was to prospectively determine the predictors of incident AF in patients with diffuse SSc.

Methods

Study population

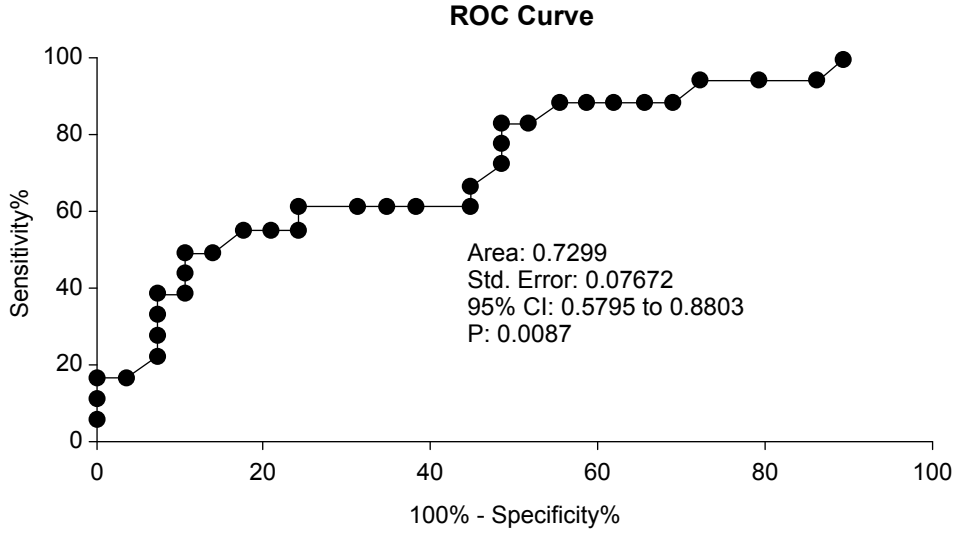
From March 2001 to October 2002, 60 consecutive patients with diffuse SSc in sinus rhythm and 21 healthy control subjects were enrolled in this prospective observational study, conducted in the outpatient rheumatology clinic of the "LAIKO" University Hospital in Athens, Greece. The diagnosis of SSc was based on compatible clinical and laboratory findings, according to the criteria of the American College of Rheumatology.[10,11] Patients with a recent myocardial infarction (prior 3 months), heart failure (New York Heart Association functional class III or IV), with left ventricular ejection fraction <50%, known coronary artery disease, pericarditis, pulmonary hypertension, known valvular heart disease, known hypertrophic cardiomyopathy, prior known episodes of AF or other arrhythmias, previously implanted pacemaker, or chronic renal failure (serum creatinine >2.5 mg/dL) were excluded from the study. Eleven SSc patients in total were excluded from the study based on the above exclusion criteria (Figure 1). Control subjects were healthy individuals with normal resting 12 lead-electrocardiography and cardiac ultrasound.

Clinical assessment

The study population was surveyed for the development of AF every six months with a 24-hour continuous ECG recording (24h Holter). All individuals were instructed to report every case of symptom deterioration or appearance of new symptoms. AF was diagnosed according to current guidelines.[12]

Echocardiography

Baseline echocardiography was performed in all study participants using a Hewlett Packard Sonos 7500, 2.5



BNP	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Likelihood ratio
74.50	44.44	21.53% to 69.24%	89.66	72.65% to 97.81%	4.30
86.00	38.89	17.30% to 64.25%	89.66	72.65% to 97.81%	3.76
104.5	38.89	17.30% to 64.25%	93.10	77.23% to 99.15%	5.64
116.0	33.33	13.34% to 59.01%	93.10	77.23% to 99.15%	4.83
125.5	27.78	9.695% to 53.48%	93.10	77.23% to 99.15%	4.03

Figure 1. Evaluation of the ability of BNP to distinguish SSc patients who developed atrial fibrillation from SSc patients who remained in sinus rhythm with the use of receiver operating characteristic (ROC) analysis. SSc, systemic sclerosis; CI – confidence interval.

MHz ultrasound system (Andover, Massachusetts). From the two-dimensional guided M-mode echocardiogram, right ventricular (RV) diameter, left ventricular (LV) end-systolic and end-diastolic diameter, as well as interventricular septum and posterior wall thickness at end-diastole, were measured.[13,14] LV mass was measured using the formula of Devereux and Reichek.[15] LV stroke volume and cardiac output were determined with pulsed Doppler using the LV outflow method.

Mitral inflow was assessed from the apical 4-chamber view with pulsed wave Doppler. From the mitral inflow profile, the E- and A-wave velocities, E-deceleration time, A-wave duration, and E/A velocity ratio were measured. Doppler tissue imaging was used to measure E' and A' velocities from the lateral mitral and tricuspid annulus. Left atrial (LA) volume was determined using the biplane area-length method:[16]

$$\text{LA volume} = [0.85 \times (LA_{\text{area in four-chamber}}) \times (LA_{\text{area in two-chamber}})] / (LA_{\text{common length}})$$

where common length was defined as the longest line between the posterior LA wall and the mid-portion of the mitral valve. LA maximal volume was measured at the point of mitral valve opening and minimal volume at the point of mitral valve closure. LA volume at the onset of LA systole was considered to be the volume corresponding to the onset of the P wave in the simultaneously recorded electrocardiogram. The LA active emptying volume was defined as the LA volume at onset of LA systole minus the LA minimal volume, and the LA active emptying fraction as the ratio of the LA active emptying volume to the LA volume at onset of LA systole.[17] The LA kinetic energy (kdynes.cm) was obtained from the formula:[18]

$$LA_{\text{kinetic energy}} = 0.5 \times q \times LA_{\text{active emptying volume}} \times A^2$$

where q is blood density = 1.06 gm/cm, and A is transmitral A-velocity.

Active LA contribution was defined as the ratio of the LA active emptying volume to LV stroke volume. All echocardiographic variables were determined from the average of three consecutive cardiac cycles and were corrected for body surface area where appropriate.

Electrocardiography

12-Lead surface ECG

A baseline 12-lead digital ECG was recorded in the supine resting position using a computer-based ECG system (CardioControl NV, the Netherlands). The 12 ECG leads were recorded simultaneously at a sampling rate of 1200 Hz for 5 minutes. From each lead, the average complex was calculated by the modular ECG analysis system (MEANS). Individual average complexes were stored digitally. The mean heart rate (HR) was calculated. The averaged stored ECGs were displayed on a high resolution computer screen. Each averaged complex in each lead was separately magnified at a magnification of 160 mm/s and 60 mm/mV. The onset and offset of the P wave were defined as the intersections between the P wave pattern and the isoelectric line and were marked with a cursor. If the baseline noise was >10 μV and/or the peak to isoelectric line P wave amplitude was <15 μV, the lead was excluded from the analysis. Two independent investigators measured the P waves without access to other information. The measurements of the two observers were averaged. The following indices were derived from measurement of each ECG:[19] 1) maximum P-wave duration in any of the measurable leads (P_{max}); 2) minimum P-wave duration in any of the measurable leads (P_{min}); 3) P-wave dispersion (P_{dis}), defined as the difference between P_{max} and P_{min}; and 4) presence of interatrial block (IAB) when maximum P-wave duration exceeded 110 ms.[20]

Holter monitoring

Twenty-four-hour ambulatory ECG Holter recordings were performed at baseline and every six months, using a portable three-channel recorder (processed by a Synescope Holter, version 3.1 ELA Medical, France). To be considered eligible for the study, each recording had to have a duration of ≥20 hours. Holter analysis was based on the ACC/AHA Guidelines for Ambulatory Electrocardiography.[21] Each ECG Holter recording was analyzed by two physicians in a blind process and the diagnosis of AF was established upon agreement.

B-type natriuretic peptide

Blood samples were collected by venipuncture performed at the time of the index visit. B-type natriuretic peptide (BNP) was measured using the Triage CardioProfilER panel method (fluorescence immunoassay; Biosite, Inc., San Diego, California).[22]

Statistical analysis

Normally distributed data were expressed as means

Table 1. Baseline demographic and clinical characteristics of the study population.

Variable	Cl Group (n=21)	SSc-SR Group (n=31)	SSc-AF Group (n=18)	p-value
Female, n (%)	18 (85.7)	27 (87.1)	16 (88.9)	0.957
Age, years (±SD)	48.4±11.7	49.9±10.2	51.3±9.6	0.692
Body surface area, m^2 (±SD)	1.53±0.79	1.68±0.37	1.64±0.19	0.574
Body mass index, kg/m^{-2} (±SD)	26.0±4.2	25.0±4.4	23.5±4.4	0.206
Mean arterial pressure, mmHg (±SD)	88.1±11.3	88.5±7.4	92.4±15.8	0.412
History of hypertension, n (%)	0 (0)	3 (9.7)	3 (16.7)	0.612
History of diabetes mellitus, n (%)	0 (0)	1 (3.2)	0 (0)	0.442
Disease duration, years (±SD)	0 (0)	8.17±7.87	11.74±9.98	0.209
Current smoker, n (%)	8 (38.1)	4 (12.9)	1 (5.6)	0.018
ACE inhibitors, n (%)	0 (0)	3 (9.7)	2 (11.1)	0.873
Beta-blockers, n (%)	0 (0)	2 (6.5)	0 (0)	0.272
Calcium channel blockers, n (%)	0 (0)	18 (58.1)	11 (61.1)	0.834
Prednisone, n (%)	0 (0)	16 (51.6)	9 (50)	0.913

ACE – angiotensin converting enzyme; AF – atrial fibrillation; Cl – control; SD – standard deviation; SR – sinus rhythm; SSc – systemic sclerosis.

± SD. A log transform was used for skewed data. Intergroup differences in continuous data were examined using one-way analysis of variance, followed by the Scheffe test. The chi-squared test was used for comparisons of categorical data. The association between the time to AF development and variables exhibiting baseline differences between SSc patients that developed AF and SSc patients that remained in sinus rhythm was explored using Cox proportional hazard analysis. Receiver operating characteristic (ROC) analysis was performed to characterize the ability to distinguish SSc patients who developed AF from those who remained in sinus rhythm. P values <0.05 were considered statistically significant. The Statgraphics Centurion XVI (1982-2010 StatPoint Technologies, Inc.) and the Prism 5.04 (1992-2010 GraphPad Software, Inc.) packages were used for data analysis.

Results

Incident AF

During a mean follow-up period of 72 ± 24 months (range 6-96), 18 SSc patients (36.7%) developed AF (paroxysmal, n=16, permanent, n=2; SSc-AF group), while 31 (63.3%) SSc patients remained in sinus rhythm (SSc-SR group). The mean duration from baseline assessment to incident AF was 54.36 ± 36.68 months. All subjects in the control group (Cl group) remained in sinus rhythm. There was no thromboembolic complication during the follow-up period in any patient, while patients with AF received either propafenone or amiodarone treatment as an antiarrhythmic and oral anticoagulants where needed.

Baseline characteristics

Demographic and clinical characteristics (Table 1)

No significant differences were observed between the three groups with regard to sex distribution, age, body surface area, body mass index, or mean arterial pressure. Similarly, no significant differences were observed between the SSc-SR and the SSc-AF group with regard to disease duration, history of hypertension, $CHADS_2$ and CHA_2DS_2VASc scores, or drug treatment.

Ventricular function (Table 2)

LV end-systolic diameter, intraventricular septal thickness, posterior wall thickness, fractional shortening and ejection fraction did not differ between the three groups. In contrast, LV mass was higher in the SSc-AF group, whereas LV end-diastolic diameter was higher in the Cl-group. No differences were observed in the transmitral E-wave velocity or mitral deceleration time. In contrast, the transmitral A-wave velocity was higher, whereas the E/A was lower in the SSc-SR and SSc-AF groups. The mitral tissue Doppler imaging $(TDI)_E$ velocity was lower in the SSc-AF than in the SSc-SR group and was lower in the latter

Table 2. Echocardiographic/Doppler evaluation of ventricular function.

	Cl Group (n=21)	SSc-SR Group (n=31)	SSc-AF Group (n=18)	P value
Left ventricle:				
End-diastolic diameter, mm (±SD)	47.2 ± 4.1	44.3 ± 4.3*	43.7 ± 3.8*	0.017
End-systolic diameter, mm (±SD)	28.2 ± 3.8	25.6 ± 4.4	25.6 ± 4.8	0.084
Intraventricular septum, mm (±SD)	8.6 ± 1.1	8.4 ± 1.1	8.8 ± 1.2	0.430
Posterior wall, mm (±SD)	7.8 ± 0.87	7.9 ± 1.2	8.4 ± 1.4	0.274
LV mass, g/m^2 (±SD)	60.5 ± 32.6	71.8 ± 18.6	84.5 ± 26*	0.017
Fractional shortening, % (±SD)	0.40 ± 0.05	0.42 ± 0.07	0.42 ± 0.07	0.613
E-wave, m/s (±SD)	0.80 ± 0.16	0.80 ± 0.19	0.86 ± 0.13	0.414
A-wave, m/s (±SD)	0.60 ± 0.14	0.78 ± 0.22*	0.88 ± 0.22*	<0.001
E/A ratio, (±SD)	1.40 ± 0.46	1.1 ± 0.46*	1.03 ± 0.26*	0.011
Mitral deceleration time, ms (±SD)	200.7 ± 42.2	189.1 ± 37.1	209.2 ± 55.4	0.289
Mitral TDI_E, cm/s (±SD)	20.5 ± 4.4	17.5 ± 3.4*	14.5 ± 2.8*†	<0.001
Mitral TDI_A, cm/s (±SD)	13.8 ± 3	17.7 ± 4.3*	16.4 ± 5.1	0.007
Mitral TDI_S, cm/s (±SD)	13.3 ± 2.5	13 ± 1.9	11.9 ± 2	0.082
Right ventricle:				
Diameter, mm (±SD)	33.5 ± 4.6	29.9 ± 4.2*	31.7 ± 4.4	0.033
Tricuspid TDI_E, cm/s (±SD)	14.3 ± 3.1	15.7 ± 3.1	16.6 ± 5.5	0.240
Tricuspid TDI_A, cm/s (±SD)	22,1 ± 5.3	19.8 ± 3.8	14.3 ± 4.5*†	<0.001
Tricuspid TDI_S, cm/s (±SD)	16.2 ± 2.7	16 ± 2.5	15 ± 4.2	0.463

*p<0.05 vs. Cl Group. †p<0.05 vs. SR Group.
AF – atrial fibrillation; Cl – control; LV – left ventricular; SD – standard deviation; SR – sinus rhythm; SSc – systemic sclerosis; TDI – tissue Doppler imaging.

Table 3. Left atrial function.

Variable	Cl Group (n=21)	SSc-SR Group (n=31)	SSc-AF Group (n=18)	P value
Echocardiography:				
LA maximal volume index, cm^3/m^2 (±SD)	16.8 ± 9.3	24.1 ± 7.3*	29.3 ± 8.4*	<0.001
LA volume index at onset of atrial systole, (cm^3/m^2) (±SD)	9.7 ± 5.4	13.5 ± 5.1	18.8 ± 7.8*†	0.01
LA minimal volume index, (cm^3/m^2) (±SD)	6.4 ± 3.6	8.8 ± 3.8	11.1 ± 6.9*	<0.001
LA active emptying volume index, cm^3/m^2 (±SD)	3.3 ± 2.2	4.7 ± 3.2	7.6 ± 2.7*†	<0.001
LA active emptying fraction, % (±SD)	0.28 ± 0.16	0.33 ± 0.17	0.43 ± 0.13*	0.01
LA kinetic energy, kdynes.cm (±SD)	1.6 ± 1,1	3.2 ± 2.9	5.6 ± 4*†	<0.001
Active LA contribution (±SD)	0.11 ± 0.08	0.15 ± 0.11	0.26 ± 0.1*†	<0.001
Electrocardiography:				
P maximal, ms (±SD)	118.4 ± 4.9	123.8 ± 9.4*	126 ± 7.9*	0.009
P minimal, ms (±SD)	82 ± 6.6	81.1 ± 10.5	79.9 ± 10.6	0.788
P dispersion, ms (±SD)	35.2 ± 8.2	42.7 ± 8.4*	46.1 ± 10.3*	<0.001

*p<0.05 vs. Cl Group. †p<0.05 vs. SR Group.
AF – atrial fibrillation; Cl – control; LA – left atrial; SD – standard deviation; SR – sinus rhythm; SSc – systemic sclerosis.

than in controls. The mitral TDI_A was higher in the SSc-SR group than in controls, whereas the mitral TDI_S did not differ significantly between the three groups. The RV diameter was lower in the SR than in the Cl group. Finally, the tricuspid TDI_A was lower in the SSc-AF than in the SSc-SR group and was lower in the latter than in controls.

Left atrial function (Table 3)

The LA maximal volume was higher in the SSc-SR and SSc-AF groups than in controls, whereas the LA volume at the onset of atrial systole, LA active emptying volume, LA kinetic energy, and the active LA contribution were higher in the SSc-AF than in the

SSc-SR group and greater in the latter than in controls. The LA minimal volume and LA active emptying fraction were higher in the SSc-AF group. Although maximal P wave and P dispersion were higher in the SSc-SR and SSc-AF groups than in controls, no difference was shown in minimum P wave or the presence of interatrial block.

BNP plasma levels.

The BNP plasma levels were significantly higher in the SSc-AF than in the SSc-SR group and greater in the latter than in controls (logBNP 1.78 ± 0.47 vs. 1.31 ± 0.54 vs. 0.66 ± 0.38 pg/mL, respectively; $p<0.001$).

Predictors of AF

The association between the time to AF and variables exhibiting baseline differences between the SSc-AF and SSc-SR groups was examined with Cox proportional hazard regression analysis (Table 4). BNP emerged as the only significant predictor of incident AF. At a cutoff level of 104.5 pg/mL the development of AF was predicted with a sensitivity of 39% and a specificity of 93% (Figure 1).

Discussion

The findings of this study indicate that: a) approximately one third of patients with diffuse SSc may develop AF within a mean follow-up of 6 years, b) AF usually develops in those SSc patients with LV diastolic dysfunction associated with LA mechanical overload and elevated BNP levels, and c) BNP is the only independent predictor of incident AF in this patient population.

AF in SSc

These findings are in accordance with previous reports demonstrating transient AF, flutter or paroxysmal supraventricular tachycardia in 20–32% of SSc patients.[3,4] Although it has been demonstrated that "AF begets AF", the presence of a pre-existent pathological substrate is required for its manifestation.[23] Atrial fibrosis, a common feature of clinical AF and a hallmark of arrhythmogenic structural remodeling, is directly related to the degree of LA dilation that accompanies LV diastolic dysfunction.[24,25] Specifically, in patients with LV diastolic dysfunction, LA myocyte hypertrophy, LA areas of fibrosis, elevated LA pressure, and LA dilation constitute the basis for the occurrence of AF and have been associated with a poor prognosis.[26-28]

Left ventricular diastolic dysfunction in SSc

LV diastolic dysfunction, a common finding in SSc, may be due to direct myocardial effects (myositis, cardiac fibrosis, coronary artery disease, and pericardial disease) and/or the indirect effect of other organ involvement (i.e. hypertension resulting from renal involvement).[29,30] Since patients with renal dysfunction were not included in this study, LV diastolic dysfunction in SSc patients who developed AF was most likely due to direct myocardial involvement. Thus, it is reasonable to assume that the LA dilation that preceded the development of AF in SSc was secondary to LV diastolic dysfunction.[30,31] The possibility, however, of direct LA myocardial involvement due to the disease process cannot be excluded.[32]

Table 4. Cox proportional hazards analysis with time to appearance of atrial fibrillation as the dependent variable.

		Estimated regression model			Likelihood ratio test		
Parameter	Estimate	Standard error	Lower 95.0% conf. limit	Upper 95.0% conf. limit	Chi-square	Df	p-value
LA kinetic energy	0.117464	0.0626172	-0.00526394	0.240192	1.47539	1	0.2245
LA contribution to LV stroke volume	0.0155212	0.0259063	-0.0352544	0.0662968	0.127209	1	0.7213
BNP	0.0070701	0.00211084	0.00293293	0.0112073	4.10397	1	0.0428
Mitral deceleration time	-0.00231727	0.00310379	-0.00840059	0.00376605	0.221649	1	0.6378
Tricuspid TDI_E	-0.0193066	0.047762	-0.112919	0.0743054	0.0559785	1	0.8130
LA volume at onset of atrial systole	-0.0483732	0.0385796	-0.123988	0.0272416	0.502571	1	0.4784
LA active emptying volume	0.0252163	0.110038	-0.190455	0.240888	0.0230271	1	0.8794

Log likelihood = -79.4198.
LA – left atrial; LV – left ventricular; BNP – brain natriuretic peptide; TDI – tissue Doppler imaging.

BNP, AF and SSc

B-type natriuretic peptide production is stimulated by stretch receptors and reflects LV end-diastolic wall stress;[33-35] elevated levels have been reported in AF patients.[36,37] In a population-based study, a single determination of elevated BNP was found to be predictive of the future development of AF.[38] Furthermore, a recent community-based study in the elderly showed that elevated NT-proBNP is a marker of substantial risk for AF, to a degree not shown for any other known risk factor.[8] These findings are in full accordance with the findings of this study, which showed that approximately 40% of the SSc patients with BNP plasma levels ≥105 pg/mL will develop AF, whereas this arrhythmia is highly unlikely in SSc patients with lower BNP levels (specificity of 93%). Importantly, elevated BNP in SSc patients who develop AF reflect the presence of more severe LV diastolic dysfunction.[39] It is highly unlikely that pulmonary arterial hypertension leading to RV dysfunction contributed significantly to BNP elevation in the SSc-AF group, since no differences were detected between the SSc-AF and the SSc-SR group regarding RV diameter, tricuspid TDI_E, or tricuspid TDI_S.[40,41]

Clinical implications

AF is highly prevalent among SSc patients and its onset is associated with increased morbidity and mortality.[3,42,52] Therefore, early identification of patients at risk for developing AF is important, since it may allow AF prevention and/or early targeted intervention. There have been no clinical trials on the primary prevention of AF in SSc. Experimental data indicate that activation of the renin–angiotensin system and inflammation contribute to the initiation and auto-perpetuation of AF.[24] Accordingly, upstream therapy for the prevention of AF has included non-antiarrhythmic drugs, such as angiotensin-converting enzyme inhibitors[43] and statins,[44] with encouraging results. Thus, careful extrapolation of these treatment modalities to the individual patient with SSc seems rational. It is not known whether the treatment target should be normalization of the BNP plasma levels, as the findings of the relevant randomized controlled trials in heart failure patients have been inconsistent.[45,46] However, the weight of the available evidence suggests that a BNP-guided approach might be effective in young patients.[47]

Study limitations

The use of BNP as a tool for the prediction of AF in SSc is limited by factors that may influence its concentration.[48] Advanced age, low hemoglobin values, low body mass index and renal failure increase BNP levels.[49] Moreover, pulmonary arterial hypertension (PAH) increases BNP levels in proportion to the extent of right ventricular dysfunction. However, the prevalence of PAH in SSc patients is as low as 10-12%,[50] varying from 4.9% to 26.7% in different reports.[51] Thus, elevated BNP levels point to non-PAH-related cardiac involvement associated with the increased incidence of AF in the vast majority of SSc patients. Finally, it should be noted that the number of patients enrolled in our study was rather small, and only speculations about the pathophysiological mechanism can be made. Although rheumatic disorders like systemic sclerosis are inflammatory diseases, and inflammation has been associated with atrial remodeling, we did not have the opportunity to provide data regarding inflammatory markers in this setting.

Conclusions

The incidence of AF is high in SSc, with one third of patients developing AF during a mean follow-up of 6 years. AF occurs predominately in SSc patients with LV diastolic dysfunction associated with LA mechanical overload and elevated BNP plasma levels. Conversely, the incidence of AF is extremely low in SSc patients with low BNP levels. Finally, among many parameters examined, BNP was the only independent predictor of incident AF in this patient population. Although there are no data on the primary prevention of AF in SSc, aggressive medical treatment aiming at restoration of LV diastolic function and normalization of BNP levels seems a rational approach that needs further study.

References

1. Varga JA, Trojanowska M. Fibrosis in systemic sclerosis. Rheum Dis Clin North Am. 2008; 34: 115-143; vii.
2. Allanore Y, Meune C, Kahan A. Systemic sclerosis and cardiac dysfunction: evolving concepts and diagnostic methodologies. Curr Opin Rheumatol. 2008; 20: 697-702.
3. Seferović PM, Ristić AD, Maksimović R, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. Rheumatology (Oxford). 2006; 45 Suppl 4: iv39-42.
4. Roberts NK, Cabeen WR Jr, Moss J, Clements PJ, Furst DE.

The prevalence of conduction defects and cardiac arrhythmias in progressive systemic sclerosis. Ann Intern Med. 1981; 94: 38-40.
5. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. Cardiol Clin. 2009; 27: 13-24, vii.
6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994; 271: 840-844.
7. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998; 82: 2N-9N.
8. Patton KK, Ellinor PT, Heckbert SR, et al. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. Circulation. 2009; 120: 1768-1774.
9. Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation. 2009; 119: 606-618.
10. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980; 23: 581-590.
11. Lonzetti LS, Joyal F, Raynauld JP, et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. Arthritis Rheum. 2001; 44: 735-736.
12. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006; 114: e257-354.
13. Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels. Technique, image orientation, structure identification, and validation. Mayo Clin Proc. 1978; 53: 271-303.
14. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986; 57: 450-458.
15. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977; 55: 613-618.
16. Ren JF, Kotler MN, DePace NL, et al. Two-dimensional echocardiographic determination of left atrial emptying volume: a noninvasive index in quantifying the degree of nonrheumatic mitral regurgitation. J Am Coll Cardiol. 1983; 2: 729-736.
17. Triposkiadis F, Harbas C, Sitafidis G, et al. Echocardiographic assessment of left atrial ejection force and kinetic energy in chronic heart failure. Int J Cardiovasc Imaging. 2008; 24: 15-22.
18. Stefanadis C, Dernellis J, Lambrou S, Toutouzas P. Left atrial energy in normal subjects, in patients with symptomatic mitral stenosis, and in patients with advanced heart failure. Am J Cardiol. 1998; 82: 1220-1223.
19. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol. 2001; 6: 159-165.
20. Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. Am Heart J. 2001; 142: 823-827.
21. Crawford MH, Bernstein SJ, Deedwania PC, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol. 1999; 34: 912-948.
22. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006; 92: 843-849.
23. Chimenti C, Russo MA, Carpi A, Frustaci A. Histological substrate of human atrial fibrillation. Biomed Pharmacother. 2010; 64: 177-183.
24. Pellman J, Lyon RC, Sheikh F. Extracellular matrix remodeling in atrial fibrosis: mechanisms and implications in atrial fibrillation. J Mol Cell Cardiol. 2010; 48: 461-467.
25. Knackstedt C, Gramley F, Schimpf T, et al. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. Cardiovasc Pathol. 2008; 17: 318-324.
26. Agha SA, Kalogeropoulos AP, Shih J, et al. Echocardiography and risk prediction in advanced heart failure: incremental value over clinical markers. J Card Fail. 2009; 15: 586-592.
27. Triposkiadis F, Harbas C, Kelepeshis G, et al. Left atrial remodeling in patients younger than 70 years with diastolic and systolic heart failure. J Am Soc Echocardiogr. 2007; 20: 177-185.
28. Giamouzis G, Sui X, Love TE, Butler J, Young JB, Ahmed A. A propensity-matched study of the association of cardiothoracic ratio with morbidity and mortality in chronic heart failure. Am J Cardiol. 2008; 101: 343-347.
29. Aguglia G, Sgreccia A, Bernardo ML, et al. Left ventricular diastolic function in systemic sclerosis. J Rheumatol. 2001; 28: 1563-1567.
30. Dimitroula H, Damvopoulou E, Giannakoulas G, et al. Effects of renin-angiotensin system inhibition on left atrial function of hypertensive patients: an echocardiographic tissue deformation imaging study. Am J Hypertens. 2010; 23: 556-561.
31. Dimitroulas T, Giannakoulas G, Papadopoulou K, et al. Early detection of cardiac involvement in systemic sclerosis assessed by tissue-Doppler echocardiography: relationship with neurohormonal activation and endothelial dysfunction. J Rheumatol. 2010; 37: 993-999.
32. Triposkiadis F, Pitsavos C, Boudoulas H, Trikas A, Toutouzas P. Left atrial myopathy in idiopathic dilated cardiomyopathy. Am Heart J. 1994; 128: 308-315.
33. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med. 1998; 339: 321-328.
34. Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol. 2006; 47: 742-748.
35. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical impli-

cations. J Am Coll Cardiol. 2009; 54: 1747-1762.
36. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol. 2005; 45: 82-86.
37. Rossi A, Enriquez-Sarano M, Burnett JC Jr, Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. J Am Coll Cardiol. 2000; 35: 1256-1262.
38. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 2004; 350: 655-663.
39. Dimitroulas T, Giannakoulas G, Karvounis H, Dimitroula H, Settas L. N-terminal pro-brain natriuretic peptide in systemic sclerosis related pulmonary arterial hypertension under bosentan treatment. Rheumatol Int. 2009; 29: 347-348.
40. Moustapha A, Lim M, Saikia S, Kaushik V, Kang SH, Barasch E. Interrogation of the tricuspid annulus by Doppler tissue imaging in patients with chronic pulmonary hypertension: implications for the assessment of right-ventricular systolic and diastolic function. Cardiology. 2001; 95: 101-104.
41. Giannakoulas G, Parcharidou D, Efthimiadis G, Karvounis H, Styliadis I, Parcharidis G. Right ventricular dysfunction in chronic heart failure. Am J Cardiol. 2008; 101: 1070.
42. Ringborg A, Nieuwlaat R, Lindgren P, et al. Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on atrial fibrillation. Europace. 2008; 10: 403-411.
43. Schneider MP, Hua TA, Böhm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. J Am Coll Cardiol. 2010; 55: 2299-2307.
44. Abuissa H, O'Keefe JH, Bybee KA. Statins as antiarrhythmics: a systematic review part I: effects on risk of atrial fibrillation. Clin Cardiol. 2009; 32: 544-548.
45. Adams KF Jr, Felker GM, Fraij G, Patterson JH, O'Connor CM. Biomarker guided therapy for heart failure: focus on natriuretic peptides. Heart Fail Rev. 2010; 15: 351-370.
46. Giamouzis G, Giannakoulas G, Tsarpalis K, et al. Natriuretic peptide-guided levosimendan therapy for heart failure: a promising new approach. Int J Cardiol. 2008; 128: 91-93; author reply 94-96.
47. O'Donoghue M, Braunwald E. Natriuretic peptides in heart failure: should therapy be guided by BNP levels? Nat Rev Cardiol. 2010; 7: 13-20.
48. Dimitroulas T, Giannakoulas G, Karvounis H, Settas L. Limitations of the findings regarding the relationship between N-terminal pro-brain natriuretic peptide and systemic sclerosis-related pulmonary arterial hypertension: comment on the article by Allanore et al. Arthritis Rheum. 2008; 58: 2215-2216; author reply 2216.
49. Knudsen CW, Clopton P, Westheim A, et al. Predictors of elevated B-type natriuretic peptide concentrations in dyspneic patients without heart failure: an analysis from the breathing not properly multinational study. Ann Emerg Med. 2005; 45: 573-580.
50. 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: 151-157.
51. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J. 2007; 37: 485-494.
52. Plastiras SC, Toumanidis ST. Systemic sclerosis: the heart of the matter. Hellenic J Cardiol. 2012; 53: 287-300.