Cardiovascular profiles of scleroderma patients with arrhythmias and conduction disorders

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ABSTRACT

Introduction: Arrhythmias and conduction disorders are common among patients with scleroderma. Their early identification is important, since scleroderma patients with arrhythmias have a higher mortality risk compared with scleroderma patients without arrhythmias. The aim of this study was to characterize the cardiovascular profiles of scleroderma patients with different types of arrhythmias and conduction disorders.
Methods: One hundred and ten consecutive patients with a diagnosis of systemic sclerosis according to the ACR criteria were included in the study. Patients underwent a 12-lead ECG and a 24-hour Holter ECG monitoring for arrhythmias and conduction disorders identification. Blood sample testing, echocardiography, spirometry, chest X-ray and, when considered appropriate, high resolution chest CT were also performed. A subgroup of 21 patients underwent NT-pro BNP level measurements. Patients' clinical and para-clinical characteristics were compared according to the presence or absence of arrhythmias and conduction disorders.
Results: The prevalence of arrhythmia and conduction disturbances was 60.9%. Patients with such disorders were older (54.4 ± 13.3 vs. 49.7 ± 10.1 years, p=0.05), had a higher prevalence of pulmonary hypertension (p=0.008), valve disease (p < 0.001), especially mitral and tricuspid regurgitation, chamber enlargement on echocardiography (left atrial and right ventricular, p = 0.012 and 0.005, respectively), as well as, higher NT-pro BNP levels: 265.5 ± 399.7 vs. 163 ± 264.3 pg/ml, p=0.04.
Conclusion: Arrhythmias and conduction disorders are common in patients with scleroderma. Patients with such disorders are older, have a higher prevalence of pulmonary hypertension, more severe mitral and tricuspid regurgitation, left atrial and right ventricular dilation on echocardiography.

Keywords: Scleroderma; Conduction disorders; Cardiac arrhythmias.

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INTRODUCTION

Arrhythmias and conduction disorders are commonly found among patients with scleroderma[1-7]. However, their reported prevalence varies depending on the diagnostic tool used – surface Electrocardiogram (ECG), 24-hour Holter ECG monitoring, electrophysiological study[1, 8], with an abnormal resting ECG being found between 25 - 75% of scleroderma patients[1, 2].

Myocardial causes, especially ventricular arrhythmias, represents the third most common cause of death in patients with scleroderma, after pulmonary fibrosis and pulmonary arterial hypertension, accounting for 6% of the total causes of death[9]. An early diagnosis of arrhythmias is therefore important, patients with scleroderma and arrhythmias having a 2-fold higher risk of death compared with scleroderma patients without arrhythmias[10].

Several studies identified risk markers for mortality in scleroderma patients, including the presence of an abnormal ECG[1, 2], right bundle branch block[6] and clinically significant arrhythmias[10]. However, the cardiovascular profiles of scleroderma patients with various kinds of arrhythmias and conduction disorders have not been described so far. Therefore, the aim of this study was to outline the cardiovascular profiles of scleroderma patients with different types of arrhythmias and conduction disorders.

METHODS

PATIENT POPULATION AND DATA COLLECTION

From October 2011 to December 2014, 113 consecutive patients, males and females, with a diagnostic of systemic sclerosis according to the American College of Rheumatology (ACR)/criteria, were admitted to the Rheumatology Clinic of Cluj-Napoca, Romania. Only patients with the diffuse cutaneous subtype and limited cutaneous subtype were included in the study. Three patients with scleroderma sine scleroderma were excluded from the study and therefore the final population consisted of 110 patients. The research protocol was approved by the Local Ethics Committee.

After giving informed consent, all patients underwent a complete physical examination and blood sample testing. Afterwards, a cardiovascular evaluation was performed for each patient, including a standard 12-lead resting ECG, 24-hour Holter ECG monitoring and transthoracic Doppler echocardiography. Lung evaluation included spirometry and a standard chest X-ray and, in cases where pulmonary fibrosis was suspected based on the patient's history, physical exam and chest X-ray, a high resolution computer tomography (CT).

In order to define their cardiovascular profiles, patients' clinical and para-clinical characteristics were compared according to the presence or absence of arrhythmias and conduction disorders as follows: patients with arrhythmias (either supraventricular or ventricular) and/or conduction disturbances were compared to patients without arrhythmias and/or conduction disorders; patients with ventricular arrhythmias to patients without ventricular arrhythmias; patients with ventricular arrhythmias and high-risk markers (ventricular couplets, non-sustained ventricular tachycardia, right bundle branch block) to patients without these markers; patients with supraventricular arrhythmias to patients without supraventricular arrhythmias; patients with conduction disorders to patients without conduction disorders.

Clinical data were collected from the patients' clinical records. The 12-lead ECG, 24-hour Holter ECG monitoring result and the echocardiographic images were interpreted by a full time cardiologist.

EVALUATION OF PATIENTS

12-lead ECG

The resting ECGs were recorded using an Esaote P8000 electrocardiograph, with an ECG amplifier sensitivity of 10 mm/mV, at a speed of 25 mm/s. The assessed parameters were: rhythm, heart rate, QRS axis, the presence of atrial or ventricular hypertrophy, signs of myocardial ischemia, the PR interval, the duration of the QRS complex, the QT and the QTc interval.

Bradycardia was defined as a heart rate of < 60 bpm, while tachycardia as a heart rate of > 100 bpm.

The presence of left anterior fascicular block was defined as a QRS axis deviation between -30 and – 90 degrees and of left posterior facicular block as a QRS axis deviation between +120 and +180 degrees. Complete right bundle branch block (RBBB) was defined as a QRS duration of >120 ms, with a RSR' pattern in V1--V3 and a wide S wave in lead I, aVL and V5, V6, ± ST depression and T wave inversion in V1-V3. Incomplete RBBB was defined as a QRS duration of 100 – 120 ms, with a rSr' aspect in V1. Left bundle branch block (LBBB) was considered present when the QRS duration exceeded 120 ms and a dominant S wave in V1 was present giving an rS or QS aspect, broad R wave in I, aVL, V5,V6 + ST segment depression in these leads. Incomplete LBBB was defined as a QRS aspect suggestive of LBBB, with a QRS duration of between 100 and 120 ms. Non-specific intraventricular conduction defects were defined as QRS morphology changes incompatible with any of the above mentioned conduction disorders.

The corrected QT (QTc) interval was considered prolonged if > 440 ms for males and > 460 ms for females. Ischemia was defined as the presence of negative T waves, or ST depression of ≥1 mm or the presence of Q waves (as a marker of myocardial infarction) in at least 2 contiguous leads.

The 24-hour Holter ECG monitoring

Recordings were made using a 7-lead BTL CardioPoint H600 device, with a 2000Hz sampling frequency and 16bit digital resolution.

The assessed parameters were: maximum, average and minimum heart rate, average heart rate while awake, average heart rate while asleep, the presence of supraventricular and ventricular arrhythmias, the presence of paroxysmal conduction disorders, QT and QTc interval.

Bradycardia was defined as an average heart rate of < 60 bpm while awake and tachycardia as a heart rate of > 100 bpm while awake or asleep.

All supraventricular and ventricular ectopic beats were recorded. Supraventricular arrhythmia was defined as the presence of > 100 PAC/24 hours and ventricular arrhythmia as the presence of > 1 PVC/hour.

The transthoracic echocardiography

All echocardiographic examinations were performed with an Esaote MyLabTM X-View 50 machine, with a 7.5 - 10 MHz transducer.

The assessed parameters were: chamber size, interventricular septum (IVS) and posterior wall (PW) of the left ventricle (LV) thickness, systolic and diastolic function of the LV, systolic function of the right ventricle (RV), left-sided filling pressures, global and regional motion abnormalities, systolic, mean and diastolic pulmonary aterial pressure (sPAP, mPAP, dPAP), the presence of pericardial effusion, the presence of valve disease (stenosis and regurgitations).

LV hypertrophy was defined as an increased thickness of IVS and PW (>11 mm), LV dilation as an end-diastolic dimension > 60 mm, end systolic dimension > 40 mm, RV dilation as a diameter of the RV > 26 mm in the parasternal long axis view, LV systolic dysfunction as an ejection fraction of < 55%, RV systolic dysfunction as TAPSE < 17 mm.

Pulmonary hypertension was defined as mild when sPAP was 35-49 mmHg, moderate when between 50--69 mmHg and severe if ≥ 70 mmHg. sPAP, mPAP and dPAP were calculated using the simplified Bernoulli ecuation (4 x $vmax^2$), based on the tricuspid regurgitation jet velocity (for sPAP) and on the pulmonary insufficiency jet velocity (for mPAP and dPAP).

Laboratory analyses

Blood sample testing included a complete blood count, ESR, blood urea nitrogen, creatinine, electrolites (Na+, K+, Ca2+, Cl-), glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, uric acid, coagulation parameters (Quick time, INR, activated partial thromboplastin time), GOT, GPT, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, total protein and albumin. Complement levels, C3, C4, circulating immune complexes, IgA, IgG, IgM, rheumatoid factor, antinuclear antibodies and anti-topoisomerase I levels were also measured.

In a subgroup of 21 randomly selected patients, the NT-pro BNP levels (pg/ml) were measured.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, Illinois) version 20. Descriptive statistics were used to summarize patients' characteristics. Normality was assessed for all continuous variables using the Shapiro_Wilk test. When the assumption held, results were expressed as mean ± standard deviation (SD) or otherwise by median ± interquartile range. Categorical variables were presented as counts and proportions (%).

The Chi square test was used to compare different scleroderma characteristics, associated diseases, categorical echocardiographic elements and medical treatment of patients, with and without arrhythmias, and conduction disorders. According to the sample size of the compared patient populations, the t-test for independent samples or Mann-Whitney U test were used to compare the age, duration of clinical manifestation, the skin score, the levels of NT-pro BNP, the LV ejection fraction and the left-sided filling pressures of scleroderma patients with and without arrhythmias and conduction disorders.

Spearman's correlation coefficient was used to assess the relationship between electrocardiographic findings and echocardiographic abnormalities, such as pulmonary hypertension and right ventricular dilation.

Receiver operating characteristic (ROC) curves were used to analyze the accuracy of several ECG parameters in predicting the existence of important echocardiographic abnormalities (pulmonary hypertension, right ventricular dilation).

A p value of < 0.05 was considered statistically significant.

RESULTS

GENERAL CHARACTERISTICS OF THE PATIENTS

The general characteristics of the patients are presented in Table I.

The main features that distinguished patients with diffuse cutaneous scleroderma from patients with limited cutaneous scleroderma were a higher Rodnan skin score (15.35 ± 8.5 vs 6.26 ± 6.28, p<001), a higher number of positive anti Scl70 antibodies tests (80.8% vs. 15.8%, p<0.001) and a higher prevalence of pulmonary fibrosis (65.9% vs. 44.4%, p=0.02). There were no statistically significant differences in what concerns the onset of Raynaud's and non-Raynaud's phenomenon, other significant associated conditions or cardiovascular diseases, echocardiographic and laboratory parameters between the 2 subgroups of patients (Table I).

PREVALENCE OF ARRHYTHMIAS AND CONDUCTION DISORDERS

Using the 12 lead ECG and the 24-hour Holter ECG

TABLE I. GENERAL CHARACTERISTICS OF THE PATIENTS, ACCORDING TO THE SCLERODERMA SUBTYPE

Patients' characteristic	Diffuse cutaneous scleroderma	Limited cutaneous scleroderma	Total
Number of patients n (%)	47 (42.7)	63 (57.3)	110 (100)
Gender, female n (%)	41 (87.23)	60 (95.23)	101 (91.8)
Average age (years)	50.36 ± 13.79	54.22 ± 10.97	52.57 ± 12.34
Disease characteristics			
Rodnan skin score, average (extreme values)	15.35 (3-35)	6.26 (0-21)	10.56 (0-35)**
Onset of Raynaud's phenomenon (years) (average ± std dev)	8.41 ± 8.87	11.67 ± 8.34	10.11 ± 8.69
Onset of non-Raynaud's phenomenon (years) (average ± std dev)	6.08 ± 6.97	8.00 ± 5.96	7.04 ± 6.5
Auto-antibodies, n (%)			
ANA negative	2 (4.2)	3 (4.7)	5 (4.5)
Anti-Scl70 positive	38 (80.8)	10 (15.8)	48 (43.6)**
Associated conditions: n (%)			
Pulmonary fibrosis	31 (65.9)	28 (44.4)	59 (53.6)*
Abnormal spirometry results			
Obstructive pattern	22 (46.8)	27 (42.8)	49 (44.5)
Restrictive pattern	10 (21.2)	16 (25.3)	26 (23.6)
Diabetes mellitus	1 (2.1)	3 (4.7)	4 (3.6)
Chronic renal failure	3 (6.3)	1 (1.5)	4 (3.6)
Anemia	9 (19.1)	6 (9.5)	15 (13.6)
Thyroid dysfunction	8 (17)	9 (14.2)	17 (14.45)
Cardio-vascular diseases: n (%)			
Arterial hypertension	10 (21.2)	20 (31.7)	30 (27.2)
Ischemic heart disease	6 (12.7)	3 (4.7)	9 (8.1)
Congestive heart failure	2 (4.2)	1 (1.5)	3 (2.7)
Stoke	0 (0)	1 (1.5)	1 (0.9)
Dyslipidemia	18 (38.2)	24 (38)	42 (38.1)
Pulmonary hypertension: n (%)	15 (31.9)	30 (47.6)	45 (40.9)
Mild	10 (21.2)	21 (33.3)	31 (28.1)
Moderate	3 (6.3)	6 (9.5)	9 (8.1)
Severe	2 (4.2)	3 (4.7)	5 (4.5)
Pericardial effusion: n (%)	6 (12.7)	9 (14.2)	15 (13.6)
Mild	3 (6.3)	7 (11.11)	10 (9)
Moderate	2 (4.2)	2 (3.1)	4 (3.6)
Severe	1 (2.1)	0 (0)	1 (0.9)
Left ventricular systolic function			
Abnormal, n (%)	3 (6.3)	4 (6.3)	7 (6.3)
%, Mean ± std dev	61.68 ± 7.69	63.82 ± 7	62.89 ± 7.35
Left ventricular diastolic dysfunction: n (%)	17 (36.1)	30 (47.6)	47 (42.7)
Impaired Relaxation	15 (31.9)	28 (44.4)	43 (39)
Pseudonormal	1 (2.1)	2 (3.1)	3 (2.7)
Restrictive filling	1 (2.1)	0 (0)	1 (0.9)
Right ventricular systolic function: n (%)			
Abnormal	1 (2.1)	3 (4.7)	4 (3.6)
Valve disease (moderate or severe)	21 (44.6)	32 (50.7)	53 (48.1)
Mitral stenosis	0 (0)	2 (3.1)	2 (0.2)
Mitral regurgitation	8 (17)	4 (6.3)	12 (10.9)
Aortic stenosis	2 (4.2)	2 (3.1)	4 (3.6)

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TABLE I. CONTINUATION

Patients' characteristic	Diffuse cutaneous scleroderma	Limited cutaneous scleroderma	Total
Aortic regurgitation	1 (2.1)	3 (4.7)	4 (3.6)
Pulmonary regurgitation	1 (2.1)	2 (3.1)	3 (2.7)
Tricuspid regurgitation	9 (19.1)	19 (30.1)	28 (25.4)
Hypertrophy/Dilation (echocardiography): n (%)			
Left ventricular hypertrophy	7 (14.8)	11 (17.4)	18 (16.3)
Right ventricular dilation	6 (12.7)	3 (4.7)	9 (8.1)
Left atrial dilation	5 (10.6)	6 (9.5)	11 (10)
Right atrial dilation	NA	NA	NA
NT-pro BNP (pg/ml)	265.5 ± 274	185 ± 63.5	207 ± 129
Medication: n (%)			
Beta blockers	3 (6.3)	5 (7.9)	8 (7.2)
ACE inhibitors/ARBs	15 (31.9)	12 (19)	27 (24.5)
Calcium channel blockers	15 (31.9)	17 (26.9)	32 (29)
Digoxin	1 (2.1)	0 (0)	1 (0.9)
Propafenone	3 (6.3)	1 (1.5)	4 (3.6)
Amiodarone	2 (4.2)	0 (0)	2 (1.8)
PAH-specific medication	2 (4.2)	1 (1.5)	3 (2.7)

*p< 0.05; **p<0.01; Arrhythmia was defined as the presence of > 100 PAC/24 hours and/or the presence of > 24 PVC/ 24 hours.
ANA = Antinuclear antibodies; Anti SCL70 = anti topoisomerase I; ACE Inhibitors = Angiotensin converting enzyme inhibitors; ABRs = Angiotensin receptor blockers; PAH = Pulmonary arterial hypertension; NA = not available.

monitoring, a high prevalence of arrhythmias and conduction disorders was found (Table II). All but 4 patients had some sort of supraventricular or ventricular ectopy and/or conduction disorder. Conduction disorders were encountered in 30% of patients (n=33). A number of 35 patients (31.8%) had at least 100 premature atrial contractions/24 hours and 50 patients (45.4%) had at least 1 premature ventricular contraction/hour at the Holter ECG monitoring. There was an important overlap of patients with arrhythmias and conduction disorders, 19% of patients (n=21) having both supraventricular and ventricular arrhythmias and 10% (n=11) of patients having both types of arrhythmias plus some type of conduction disorder.

Taking the cut-off values mentioned above, a total of 67 patients had supraventricular arrhythmia, ventricular arrhythmia or a conduction disorder, the prevalence of arrhythmias and conduction disturbances being 60.9%.

When compared according to the scleroderma subtype, on the 12-lead ECG, patients with the diffuse cutaneous form had a significantly higher prevalence of ventricular arrhythmias compared to patients with the limited cutaneous form. However, on the 24-hour Holter ECG monitoring, there were no significant differences between the 2 groups of scleroderma subtypes in what concerns the prevalence of the different arrhythmias and conduction disorders.

According to the presence or absence of pulmonary hypertension, a significantly higher number of patients from the pulmonary hypertension group had arrhythmias and conduction disorders on the 12-lead ECG (22.2% vs. 7.7%, p=0.035, and 44.4% vs. 20%, p=0.009, respectively (Table 3). During the 24-hour Holter ECG monitoring, patients with pulmonary hypertension had a significantly higher number of premature ventricular contractions (74 ± 327 vs. 4 ± 71, p= 0.01) compared to patients without pulmonary hypertension (Table III).

According to the type of arrhythmia and conduction disorders found, we outlined the cardiovascular profiles of the different scleroderma patients.

THE SCLERODERMA PATIENT WITH ARRHYTHMIAS AND CONDUCTION DISORDERS

Several features distinguished scleroderma patients with arrhythmias and conduction disorders from the other scleroderma patients: they were older (p=0.05)

TABLE II. TYPES OF ARRHYTHMIAS, CONDUCTION DISORDERS AND OTHER ABNORMALITIES DIAGNOSED WITH 12 LEAD ECG AND 24 HOUR HOLTER ECG MONITORING

	12 Lead ECG n (%)			24 Hour Holter ECG n (%)		
Findings	Diffuse cutaneous scleroderma (n=47)	Limited cutaneous scleroderma (n=63)	Total (n=110)	Diffuse cutaneous scleroderma (n=47)	Limited cutaneous scleroderma (n=63)	Total (n=110)
Sinus arrhythmias	5 (10.6)	8 (12.6)	13 (11.8)	2 (4.2)	3 (4.7)	5 (4.5)
Sinus bradycardia (HR ≤ 60 bpm)	4 (8.5)	5 (7.9)	9 (8.1)	1 (2.1)	0 (0)	1 (0.9)[a]
Sinus tachycardia (HR ≥ 100 bpm)	1 (2.1)	3 (4.7)	4 (3.6)	1 (2.1)	3 (4.7)	4 (3.6)[b]
Supraventricular arrhythmias	3 (6.3)	7 (11.1)	10 (9)	42 (89.3)	57 (90.4)	99 (90)
Isolated PAC	2 (4.2)	5 (7.9)	7 (6.3)	41 (87.2)	56 (88.8)	97 (88.1)
≤100 / 24 hours	–	–	–	25 (53.1)	37 (58.7)	62 (56.3)
>100 / 24 hours	–	–	–	16 (34)	19 (30.1)	35 (31.8)
Coupled PAC	0 (0)	1 (1.5)	1 (0.9)	24 (51)	32 (50.8)	56 (50.9)
Triplets, Runs of PAC	0 (0)	0 (0)	0 (0)	31 (65.9)	42 (62.6)	73 (66.3)
SVT	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	1 (0.9)
Atrial fibrillation/ atrial flutter/atrial tachycardia	1 (2.1)	2 (3.1)	3 (2.7)	0 (0)	2 (3.1)	2 (1.8)
Ventricular arrhythmias	11 (23.4)	1 (1.5)	12 (10.9)**	33 (70.2)	51 (80.9)	84 (76.3)
Isolated PVC	7 (14.9)	1 (1.5)	8 (7.2)**	31 (65.9)	45 (71.4)	76 (69.1)
≤24/24 hours			–	14 (29.7)	15 (23.8)	29 (26.3)
>24/24 hours			–	17 (36.1)	30 (47.6)	47 (74.6)
Polymorphic/Bigemini/Trigemini	4 (8.5)	0 (0)	4 (3.6)	8 (17)	10 (15.8)	18 (16.3)
Coupled PVC	0 (0)	0 (0)	0 (0)	10 (21.2)	8 (12.6)	18 (16.3)
Non–sustained VT	0 (0)	0 (0)	0 (0)	6 (12.7)	1 (1.5)	7 (6.3)
Sustained VT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
R on T phenomenon	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Idioventricular rhythm	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	1 (0.9)
Conduction disorders	18 (38.2)	16 (25.4)	34 (30.9)	19 (40.4)	16 (25.4)	35 (31.8)
Complete RBBB	4 (8.5)	0 (0)	4 (3.6)	4 (8.5)	0 (0)	4 (3.6)
Incomplete RBBB	5 (10.6)	4 (6.2)	9 (8.1)	5 (10.6)	4 (6.2)	9 (8.1)
Complete LBBB	0 (0)	3 (4.7)	3 (2.7)	0 (0)	3 (4.7)	3 (2.7)
Incomplete LBBB	1 (2.1)	1 (1.5)	2 (1.8)	1 (2.1)	1 (1.5)	2 (1.8)
LAFB	2 (4.2)	5 (7.9)	7 (6.3)	2 (4.2)	5 (7.9)	7 (6.3)
LPFB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Non–specific intraventricular conduction defects	4 (8.5)	1 (1.5)	5 (4.5)	4 (8.5)	1 (1.5)	5 (4.5)
1st degree AV block	1 (2.1)	1 (1.5)	2 (1.8)	1 (2.1)	1 (1.5)	2 (1.8)
2nd degree AV block	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3rd degree AV block	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bifascicular block	1 (2.1)	0 (0)	1 (0)	1 (2.1)	0 (0)	1 (0.9)
Trifasciular block	0 (0)	1 (1.5)	1 (0)	0 (0)	1 (1.5)	1 (0.9)
Alterning bundle branch block	0 (0)	0 (0)	0 (0)	1 (2.1)	0 (0)	1 (0.9)
Hypertrophy	3 (6.3)	6 (9.5)	9 (8.1)			
Left atrial hypetrophy	0 (0)	1 (1.5)	1 (0.9)	0 (0)	1 (1.5)	1 (0.9)
Right atrial hypertrophy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Left ventricular hypertrophy	3 (6.3)	5 (7.9)	8 (7.2)	–	–	–
Right ventricular hypetrophy	0 (0)	0 (0)	0 (0)	–	–	–

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TABLE II. CONTINUATION

Findings	12 Lead ECG n (%)			24 Hour Holter ECG n (%)		
	Diffuse cutaneous scleroderma (n=47)	Limited cutaneous scleroderma (n=63)	Total (n=110)	Diffuse cutaneous scleroderma (n=47)	Limited cutaneous scleroderma (n=63)	Total (n=110)
Ischemia	3 (6.3)	7 (11.1)	10 (9)	4 (8.5)	7 (11.1)	11 (9.9)
↑ QTc interval	1 (2.1)	1 (1.5)	2 (1.8)	7 (14.9)	8 (12.7)	15 (13.6)
Rotation	3 (6.3)	7 (11.1)	10 (9)	–	–	–
Clockwise	1 (2.1)	4 (6.3)	5 (4.5)	–	–	–
Counterclockwise	2 (4.2)	3 (4.7)	5 (4.5)	–	–	–

*p< 0.05; **p<0.01; a – average heart rate while awake; b – average heart rate while awake or asleep. HR = Heart rate; PAC = Premature atrial contraction; SVT = Supraventricular tachycardia; PVC = Premature ventricular contraction; VT = Ventricular tachycardia; RBBB = Right bundle branch block; LBBB = Left bundle branch block; LAFB = Left anterior fascicular block; LPFB = Left posterior fascicular block; AV = Atrio-ventricular.

and had a higher prevalence of pulmonary hypertension (p=0.008), valve disease (p < 0.001), especially mitral and tricuspid regurgitation, and chamber enlargement on echocardiography (left atrial and right ventricular, p = 0.012 and 0.005, respectively). These patients also had significantly higher levels of NT-pro -BNP, of 265.5 ± 399.7 pg/ml vs. 163 ± 140.1 pg/ml (p=0.047). There were no statistically significant differences in what concerns the type of scleroderma, the presence of relevant associated diseases, cardiovascular diseases, left ventricular systolic and diastolic function, right ventricular systolic function and cardio-vascular medication used. The characteristics of scleroderma patients with arrhythmias and conduction disorders are presented in Table IV.

THE SCLERODERMA PATIENT WITH SUPRAVENTRICULAR ARRHYTHMIAS

There were more men in this group of patients compared to the "absence of supraventricular arrhythmias" group (17.2% vs. 4%, p=0.019). Patients with these type of arrhythmia were older (p=0.019), had a higher skin score (p=0.04) and a higher prevalence of anaemia (p=0.011).

Their cardiovascular profile was characterized by a higher prevalence of arterial hypertension (p=0.012), pulmonary hypertension (p=0.017), left ventricular diastolic dysfunction (p=0.03), increased left–sided filling pressure (p=0.02), significant valve diseases (p=0.01) especially tricuspid regurgitation (p=0.054) and left atrial dilation (p=0.016). The use of beta--blockers was also significantly higher in this group (p < 0.01).

The characteristics of scleroderma patients with supraventricular arrhythmias are summarized in Table V.

THE SCLERODERMA PATIENT WITH VENTRICULAR ARRHYTHMIAS

The characteristics of scleroderma patients with ventricular arrhythmias are summarized in Table VI. Compared to patients without ventricular arrhythmias, scleroderma patients with ventricular arrhythmias were older (p=0.05). Their cardiovascular profile was characterized by increased left-sided filling pressures (p=0.05), a higher prevalence of significant valve disease (p<0.001) especially tricuspid regurgitation (p=0.02) and right ventricular enlargement (p<0.01), and significantly higher NT-pro BNP levels (p=0.02).

There was no statistically significant difference in what concerns the left ventricular ejection fraction values and associated cardiovascular diseases between these patients and scleroderma patients with no ventricular arrhythmias.

THE SCLERODERMA PATIENT WITH HIGH ARRHYTHMIA RISK MARKERS

There were 21 patients (18 females) who had either ventricular couplets or non-sustained ventricular tachycardia on Holter ECG monitoring, or right bundle branch block. Their average age was 54.4 ± 13.6 years.

Their cardiovascular profile was characterized by a higher prevalence of left ventricular systolic dysfunction (4 patients vs. 3 patients, p<0.01). The prevalence

TABLE III. PREVALENCE AND TYPES OF ARRHYTHMIAS, CONDUCTION DISORDERS AND OTHER ABNORMALITIES DIAGNOSED WITH 12-LEAD ECG AND 24-HOUR HOLTER ECG MONITORING, ACCORDING TO THE PRESENCE OR ABSENCE OF PULMONARY HYPERTENSION

	12–lead ECG		
Finding	Patients with pulmonary Hypertension (n=45)	Patients without pulmonary Hypertension (n=65)	p
Sinus rhythm, n (%)	42 (93.3)	65 (100%)	ns
Average heart rate	77.2 ± 12.5	74.1 ± 11.3	ns
Left ventricular hypertrophy, n (%)	6 (13.3)	3 (4.6)	ns
Ischemia, n (%)	6 (13.3)	3 (4.6)	ns
Arrhythmias, n (%)	10 (22.2)	5 (7.7)	0.035
Conduction disorders, n (%)	20 (44.4)	13 (20)	0.009
QT interval	363 ± 36	365 ± 31	ns
QTc interval	408 ± 27	403 ± 23	ns
	24-hour Holter ECG		
Finding	Patients with pulmonary Hypertension (n=45)	Patients without pulmonary Hypertension (n=65)	p
Maximum heart rate	132 ± 29	134 ± 17	ns
Average heart rate	78 ± 10	76 ± 10	ns
Minimum heart rate	56 ± 9	56 ± 8	ns
Supraventricular arrhythmias			
Total PAC	76 ± 206	17 ± 77	ns
Isolated PAC	63 ± 164	15 ± 66	ns
Couplets	1 ± 5	0 ± 4	ns
Runs	0 ± 1	0 ± 0	0.047
Ventricular arrhythmias			
Total PVC	74 ± 327	4 ± 71	0.01
Isolated PVC	74 ± 319	3 ± 52	0.01
Couplets	0 ± 1	0 ± 0	ns
Number of PVC morphologies	1 ± 1	1 ± 2	ns
QT interval	396 ± 9	395 ± 23	ns
QTc interval	440 ± 19	434 ± 19	ns

PAC = Premature atrial contraction; PVC = Premature ventricular contraction

of significant valve disease was also higher among this subgroup of patients (18 patients vs. 34 patients, p<0.001), especially mitral regurgitation (p=0.03) and tricuspid regurgitation (p<0.01). Right ventricular dilation was also more frequently encountered (6 patients vs. 3 patients, p<0.01).

THE SCLERODERMA PATIENT WITH CONDUCTION DISORDERS

Thirty-three patients (30%) had some type of conduction disorder. Most were females (n=30), with an average age of 53.1 ± 12.4 years. These patients had a higher prevalence of pulmonary hypertension (p<0.01) and of significant valve disease (p<0.001), namely mitral (p=0.02) and tricuspid regurgitation (p=0.02), and NT-pro BNP values: 452 ± 725 pg/ml vs. 174 ± 98.5 pg/ml, p<0.01.

RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC FINDINGS AND SEVERITY MARKERS OF SCLERODERMA

We found statistically significant but weak associations between several Holter ECG abnormalities and established echocardiographic risk markers of scleroderma. Most importantly, the total number of premature ventricular complexes/24 hours correlated with the sPAP and the right ventricular diameter (p=0.01, r=0.24 and p=0.008, r=0,266, respectively) and the

TABLE IV. CHARACTERISTICS OF SCLERODERMA PATIENTS WITH AND WITHOUT ARRHYTHMIAS (SUPRAVENTRICULAR AND VENTRICULAR) AND CONDUCTION DISORDERS

Patient characteristic	Arrhythmias & Conduction disorders	Absence of Arrhythmias & Conduction disorders	Total
Patient number n (%)	67 (60.9)	43 (39.1)	110 (100)
Gender, female n (%)	59 (88)	42 (97)	101 (91.8)
Mean age (years)	54.4 ± 13.3	49.7 ± 10.1	52.57 ± 12.34*
Disease characteristics			
Disease subtype			
Diffuse cutaneous, n (%)	28 (41.8)	19 (44.2)	47 (42.7)
Limited cutaneous, n (%)	39 (58.2)	24 (55.8)	63 (57.3)
Skin score, mean (range)	10.6 (0-35)	10.3 (0-25)	–
Onset of Raynaud's phenomenon (years) (mean ± std dev)	10.9 ± 9.0	8.94 ± 8.1	–
Onset of non-Raynaud's phenomenon (years) (mean ± std dev)	7.30 ± 7.12	6.72 ± 5.78	–
Auto-antibodies, n (%)			
ANA negative	3 (4.4)	2 (4.6)	5 (4.5)
Anti Scl70 positive	24 (35.9)	22 (51.2)	48 (43.6)
Associated conditions: n (%)			
Pulmonary fibrosis	34 (50.7)	25 (58.1)	59 (53.6)
Abnormal spirometry results			
Obstructive pattern	32 (47.7)	17 (39.5)	49 (44.5)
Restrictive pattern	16 (23.8)	10 (23.2)	26 (23.6)
Diabetes mellitus	3 (4.4)	1 (2.3)	4 (3.6)
Chronic renal failure	3 (4.4)	1 (2.3)	4 (3.6)
Anemia	12 (17.9)	3 (6.9)	15 (13.6)
Thyroid dysfunction	11 (16.4)	6 (13.9)	17 (14.45)
Cardiovascular diseases: n (%)			
Arterial hypertension	21 (31.3)	9 (20.9)	30 (27.2)
Ischemic heart disease	7 (10.4)	2 (4.6)	9 (8.1)
Congestive heart failure	3 (4.4)	0 (0)	3 (2.7)
Stroke	1 (1.5)	0 (0)	1 (0.9)
Dyslipidemia	22 (32.8)	20 (46.5)	42 (38.1)
Pulmonary hypertension: n (%)	34 (50.7)	11 (25.5)	45 (40.9)**
Mild	24 (35.8)	7 (16.2)	31 (28.1)*
Moderate	6 (8.9)	3 (6.9)	9 (8.1)
Severe	4 (5.9)	1 (2.3)	5 (4.5)
Pericardial effusion: n (%)	12 (17.9)	3 (6.9)	15 (13.6)
Mild	8 (11.9)	2 (4.6)	10 (9)
Moderate	3 (4.4)	1 (2.3)	4 (3.6)
Severe	1 (1.5)	0 (0)	1 (0.9)
Left ventricular systolic function			
Abnormal, n (%)	5 (7.4)	2 (4.6)	7 (6.3)
%, Mean ± std dev	61.89 ± 7.79	64.4 ± 6.41	62.89 ± 7.35
Left ventricular diastolic dysfunction: n (%)	30 (44.7)	17 (39.7)	47 (42.7)
Impaired relaxation	26 (38.8)	17 (39.5)	43 (39)
Pseudonormal	3 (4.4)	0 (0)	3 (2.7)
Restrictive filling	1 (1.5)	0 (0)	1 (0.9)

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TABLE IV. CONTINUATION

Patient characteristic	Arrhythmias & Conduction disorders	Absence of Arrhythmias & Conduction disorders	Total
Right ventricular systolic function: n (%)			
Abnormal	2 (2.9)	2 (4.6)	4 (3.6)
Valve disease (moderate or severe)	45 (67.4)	8 (18.6)	53 (48.1)**
Mitral stenosis	2 (3)	0 (0)	2 (1.8)
Mitral regurgitation	11 (16.4)	1 (2.3)	12 (10.9)*
Aortic stenosis	4 (5.9)	0 (0)	4 (3.6)
Aortic regurgitation	3 (4.4)	1 (2.3)	4 (3.6)
Pulmonary regurgitation	2 (3)	1 (2.3)	3 (2.7)
Tricuspid regurgitation	24 (35.8)	4 (4.6)	28 (25.4)**
Hypertrophy / Dilation (echocardiography): n (%)			
Left ventricular hypertrophy	13 (19.4)	5 (11.6)	18 (16.3)
Right ventricular dilation	9 (13.4)	0 (0)	9 (8.1)*
Left atrial dilation	11 (16.4)	0 (0)	11 (10)**
Right atrial dilation	NA	NA	NA
NT-pro BNP (pg/ml)	265.5 ± 399.7	163 ± 140.1	207 ± 129*
Medication: n (%)			
Beta blockers	7 (10.4)	1 (2.3)	8 (7.2)
ACE inhibitors/ARBs	17 (25.3)	10 (23.2)	27 (24.5)
Calcium channel blockers	18 (26.8)	14 (32.5)	32 (29)
Digoxin	1 (1.5)	0 (0)	1 (0.9)
Propafenone	4 (5.9)	0 (0)	4 (3.6)
Amiodarone	2 (3)	0 (0)	2 (1.8)
PAH-specific medication	3 (4.4)	0 (0)	3 (2.7)

*p< 0.05; **p<0.01; Arrhythmia was defined as the presence of > 100 PAC/24 hours and/or the presence of >24 PVC/ 24 hours.
ANA = Antinuclear antibodies; Anti SCL70 = Anti topoisomerase I; ACE Inhibitors = Angiotensin converting enzyme inhibitors; ABRs = Angiotensin receptor blockers; PAH = Pulmonary arterial hypertension; NA = not available.

number of ventricular couplets on Holter ECG correlated with the right ventricular diameter (p=0.003, r=0.298). A number of ≥ 119 premature ventricular complexes/24 hours was associated with the presence of a dilated right ventricle on echocardiography, with a sensitivity of 77% and a specificity of 76% (area under the curve = 0.807). Also, the presence of ≥ 3.5 morphologies of premature ventricular contractions/24 hours had a sensitivity of 44% and a specificity of 90% in predicting the presence of a dilated right ventricle on echocardiography (area under the curve = 0.711).

DISCUSSION

The present study describes the cardiovascular profiles of scleroderma patients with arrhythmia and conduction disorders. Based on the nature of the arrhythmias (supraventricular, ventricular, high risk ventricular) and conduction disturbances identified with the 12-lead ECG and 24-hour Holter ECG monitoring, patients were compared to scleroderma patients without these findings. Several clinical and echocardiographic features distinguished these patients from the other scleroderma patients, which merit to be commented upon.

There was a high prevalence of arrhythmias and conduction disturbances in the present population, of 60.9%, a prevalence comparable to the one reported in other studies[1-5,7]. Using the same diagnostic tools, Roberts et al[1] found a very similar prevalence of conduction defects and arrhythmias, of 32% using the ECG and of 62% using the Holter ECG. However, several points need to be made. First, there is no unanimous-

TABLE V. CHARACTERISTICS OF SCLERODERMA PATIENTS WITH AND WITHOUT SUPRAVENTRICULAR ARRHYTHMIAS

Patient characteristic	Supraventricular arrhythmias	Absence of Supraventricular arrhythmias
Patient number n (%)	35 (31.8)	75 (68.2)
Gender, female n (%)	29 (82.8)	72 (96)*
Mean age (years)	57.0 ± 13.1	50.4 ± 11.4*
Disease characteristics		
Skin score, mean (range)	14 (0-35)	9 (0-25)*
Associated conditions: n (%)		
Anemia	9 (25.7)	6 (8)*
Cardiovascular diseases: n (%)		
Arterial hypertension	15 (42.8)	15 (20)*
Pulmonary hypertension: n (%)	20 (57.1)	25 (33.3)*
Left ventricular diastolic dysfunction	20 (57.1)	27 (36)*
E/Em	7.84 ± 4.04	6.11 ± 1.89*
Valve disease (moderate or severe)	23 (65.7)	30 (40)*
Chamber dilation (echocardiography): n (%)		
Left atrial dilation	7 (20)	4 (5.3)*
Medication: n (%)		
Beta blockers	6 (17.1)	2 (2.6)**

*p< 0.05; **p<0.01; Supraventricular arrhythmia was defined as the presence of > 100 PAC/24 hours at Holter ECG monitoring.
E = E wave of the transmitral flow on Doppler echocardiography; Em = Myocardial E wave on tissue Doppler echocardiography; std dev = standard deviation

ly accepted low threshold for defining the presence of supraventricular and ventricular arrhythmias, since a low number of premature atrial and ventricular contractions can be found in the healthy population as well[11,12]. In one study performed on healthy military individuals[13], using the 12-lead ECG, the prevalence of PVC was 0.8% (between 0.2% in individuals younger than 20 years and 2.2% in individuals older than 50 years). However, in contrast to individuals with structurally normal hearts, in whom the presence of a low number of PVC is considered benign[14,15], in the presence of structural heart disease, the prognostic significance of PVC is different[16]. The majority of patients with scleroderma have subclinical cardiac disease[17], represented mainly by myocardial fibrosis[18] as a result of repeated ischemic episodes involving the small coronary arteries[19]. Therefore, we chose a low cut-off value for defining the presence of ventricular arrhythmia, of one PVC/hour.

Regarding supraventricular arrhythmias, 90% of patients had at least one isolated PAC on Holter ECG monitoring. Given the frequent occurrence of isolated PAC in normal individuals, the cut-off value for defining the presence of supraventricular arrhythmia was 100 PAC/24 hours, as in other studies[20]. Using this threshold, we identified 35 patients (31.8%) with supraventricular arrhythmias.

It should be mentioned, however, that only 6 patients (5.5%) required class I or III antiarrhythmic medication and that no patient fulfilled, at the time of enrolment in the study, the current recommendations for ICD or pacemaker implantation.

There were no statistically significant differences between the 2 groups of scleroderma patients regarding the prevalence and type of arrhythmias found using the 24 hour Holter ECG monitoring, nor between the prevalence and type of the different conduction disorders found using the 12 lead ECG and the 24 hour Holter ECG monitoring. Similar findings have been reported before. For instance, in their study, Ferri et al[7] found that the prevalence and severity of ventricular arrhythmias did not correlate with the clinical variants of scleroderma.

Among patients with arrhythmias and conduction disorders, there was a higher prevalence of pulmonary hypertension and right ventricular dilation, findings that have previously been reported. Based on data analysis form the EULAR and EUSTAR databases, among

TABLE VI. CHARACTERISTICS OF SCLERODERMA PATIENTS WITH AND WITHOUT VENTRICULAR ARRHYTHMIAS

Patient characteristic	Ventricular arrhythmias	Absence of ventricular arrhythmias
Patient number n (%)	50 (45.4)	60 (54.6)
Gender, female n (%)	46 (92)	55 (91.6)
Mean age (years)	55.1 ± 11.9	50.4 ± 12.3*
Left ventricular diastolic dysfunction: n (%)	21 (42)	26 (43.3)
E/Em, n ± std dev	7.2 ± 3.5	6.1 ± 1.9*
Valve disease (moderate or severe)	33 (66)	20 (33.3)**
Tricuspid regurgitation	18 (36)	10 (16)*
Chamber dilation (echocardiography): n (%)		
Right ventricular dilation	8 (16)	1 (1.6)**
NT-pro BNP (pg/ml)	277 ± 644	163 ± 90.5*

The presence of ventricular arrhythmia was defined as > 24 PVC/ 24 hours at Holter ECG monitoring. E = E wave of the transmitral flow on Doppler echocardiography; Em = Myocardial E wave on tissue Doppler echocardiography; std dev = standard deviation.

scleroderma patients who died of arrhythmias, 47% had a history of PAH[9]. Elevated pulmonary arterial pressure can trigger ventricular arrhythmias[21]. As a consequence of an increased pulmonary vascular resistance, there is an increase in right ventricular afterload, leading to right ventricular hypertrophy and dilatation, which contributes to the initiation of ventricular tachyarrhythmias.

Patients with arrhythmias and conduction disorders from the present studies were also older, a fact which is not surprising, since the prevalence of ventricular arrhythmias increases with age[11,22,23].

In our study, a significantly higher prevalence of moderate and severe valve disease (especially mitral and tricuspid regurgitation), left atrial and right ventricular dilation on echocardiography was found among patients with arrhythmias and conduction disturbances. The prevalence of echocardiographic abnormalities is high in scleroderma patients. Smith et al[24] reported a prevalence of 69%, the most common being high right ventricular systolic pressure, right ventricular dilation, left atrial enlargement and the presence of pericardial effusion. Ferri et al[7] also found that ventricular arrhythmias were more likely to be present in patients with echocardiographic abnormalities. However, the abnormalities found on echocardiography (asymmetric septal hypertrophy, impaired ventricular function, congestive cardiomyopathy, mitral prolapse and pericardial effusion) were mostly different than the ones from the present study.

Another important finding was that scleroderma patients with ventricular arrhythmias also had significantly higher NT-pro BNP levels. Currently little is known about the relationship between NT-pro BNP levels and ventricular arrhythmias in patients with scleroderma. However, in other populations of patients, there is evidence linking increased levels of NT-pro BNP and the occurrence of ventricular arrhythmias, both in patients with a severely reduced LV ejection fraction[25], and a normal ejection fraction[26]. Given the scarcity of data in patients with scleroderma, this possible association needs further investigation.

Among the 50 patients with ventricular arrhythmias, 21 (42%) had markers of high cardiovascular risk, namely complex ventricular arrhythmias[10,16,27,28] and right bundle branch block[6]. These patients had a higher prevalence of left ventricular systolic dysfunction. As recognized before, the association of a reduced systolic function of the LV and the presence of complex ventricular arrhythmias caries a poor prognosis[27,29]. Right ventricular dilation, also more frequently encountered among these patients, leads to right heart failure, which represents one of the most important causes of death in scleroderma patients[9].

In the present study, scleroderma patients with supraventricular arrhythmias were significantly older compared to scleroderma patients without supraventricular arrhythmias. A higher prevalence of supraventricular arrhythmias in the elderly, especially atrial fibrillation and atrial flutter has been reported before[30-32]. The higher prevalence of arterial hypertension, left ventricular diastolic dysfunction, increased left-sided fil-

ling pressure and left atrial dilation among this subgroup of scleroderma patients is not surprising, since one of the most frequent causes of supraventricular arrhythmias is arterial hypertension, the underlying mechanism being diastolic dysfunction, with subsequent increased left–sided filling pressures and left atrial enlargement[33]. Pulmonary arterial hypertension is another important cause of supraventricular arrhythmias[21], which can explain its higher prevalence found in this subgroup of patients. The higher levels of NT-pro BNP found in these patients did not reach statistical significance ($p > 0.5$).

Among the 33 patients (30%) with conduction disorders, 4 patients (13.3%) had RBBB. Pulmonary hypertension and significant valve disease were also more frequently encountered compared to the other scleroderma patients. Both pulmonary hypertension and RBBB are predictors of mortality among scleroderma patients[6, 9]. NT-pro BNP values were significantly higher in this group of patients, but given the low number of patients with conduction disorders in which NT-pro BNP levels were measured (n=5), these results should be interpreted with caution.

The present study also demonstrated a positive correlation between electrocardiographic abnormalities (the total number of isolated and coupled premature ventricular complexes/24 hours) and echocardiographic abnormalities, more exactly the diameter of the right ventricle. Right ventricular dysfunction is an established risk marker for adverse cardiovascular events in patients with scleroderma[9]. Therefore, simple Holter ECG findings suggesting its presence would be useful in clinical practice. We found that a number of ≥ 119 premature ventricular complexes/24 hours has an acceptable sensitivity and specificity for detecting the presence of a dilated right ventricle and that the presence of multiple morphologies of premature ventricular contractions (≥3.5) has a low sensitivity but good specificity for detecting the presence of right ventricular dilation. However, due to the small-sample size of the population included in the study, these findings should be prospectively tested on larger populations of patients.

LIMITS OF THE STUDY

The most significant limitation of the present study is the absence of a clear cut-off value, which separates patients with supraventricular and ventricular arrhythmia from healthy individuals. The cut-off value of 100 PAC/24 hours and 1 PVC/hour at the Holter ECG monitoring chosen in this study influenced the way patients were defined as having an arrhythmia or not. Based on these definitions, patients were categorized into arrhythmia positive and arrhythmias free, which markedly influences the detected prevalence of arrhythmias among scleroderma patients and consecutively the described cardiovascular profiles.

The small subgroup of patients in which NT-pro BNP levels were measured is another important limitation which might have influenced the results, by sometimes not identifying or overestimating the possible correlation between the NT-pro BNP levels and the presence of ventricular arrhythmias and conduction disorders.

CONCLUSION

Arrhythmias and conduction disorders are common in patients with scleroderma. Their prevalence and types do not differ significantly according to the scleroderma subtype (diffuse cutaneous and limited cutaneous). Patients with such disorders are older, have a higher prevalence of pulmonary hypertension, more severe mitral and tricuspid regurgitation, left atrial and right ventricular dilation on echocardiography and increased levels of NT-pro BNP. Since the prevalence of arrhythmias and conduction disorders is high in scleroderma patients, all patients with symptoms and signs suggesting their presence (palpitations, syncope, chest pain, dyspnea, fatigue, peripheral edema) should have a thorough cardiovascular examination.

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