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REVIEW

Cardiac manifestations in systemic sclerosis

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Abstract

Primary cardiac involvement, which develops as a direct consequence of systemic sclerosis (SSc), may manifest as myocardial damage, fibrosis of the conduction system, pericardial and, less frequently, as valvular disease. In addition, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension and kidney pathology. The prevalence of primary cardiac involvement in SSc is variable and difficult to determine because of the diversity of cardiac manifestations, the presence of subclinical periods, the type of diagnostic tools applied, and the diversity of patient populations. When clinically manifested, cardiac involvement is thought to be an important prognostic factor. Profound microvascular disease is a pathognomonic feature of SSc, as both vasospasm and structural alterations are present. Such alterations are thought to predict macrovascular atherosclerosis over time. There are contradictory reports regarding the prevalence of atherosclerosis in SSc. According to some authors, the prevalence of atherosclerosis of the large epicardial coronary arteries is similar to that of the general population, in contrast with other rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. However, the level of inflammation in SSc is inferior. Thus, the atherosclerotic process may not be as aggressive and not easily detectable in smaller studies. Echocardiography (especially tissue Doppler imaging), single-photon emission computed tomography, magnetic resonance imaging and cardiac computed tomography are sensitive techniques for earlier detection of both structural and functional scleroderma-related cardiac pathologies. Screening for subclinical cardiac involvement *via* modern, sensitive tools provides an opportunity for early diagnosis and treatment, which is of crucial importance for a positive outcome.

Key words: Systemic sclerosis; Cardiac involvement

Core tip: The prevalence of primary cardiac involvement in systemic sclerosis (SSc) is difficult to determine, as it can manifest as myocardial damage, fibrosis of the conduction system, pericardial and valvular disease. When clinically manifested, cardiac involvement is thought to be an important prognostic factor. Echocardiography, magnetic resonance imaging and computed tomography are sensitive techniques for earlier detection of structural and functional SSc-related cardiac pathologies. Screening for subclinical cardiac involvement provides an opportunity for early diagnosis and treatment, which is of crucial importance for a positive outcome.

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INTRODUCTION

Systemic sclerosis (SSc) is a chronic multisystem disease characterized by microangiopathy, fibrosis of the skin and internal organs, and autoimmune disturbances. Two major subsets are recognized, namely, SSc with limited cutaneous involvement (skin thickening is localized to the face, neck and extremities distal to elbows and knees) and

SSc with diffuse cutaneous involvement (skin thickening also involves the extremities proximal to elbows and knees, chest, abdomen and back).

Primary cardiac involvement, which develops as a direct consequence of SSc, may manifest as myocardial involvement, fibrosis of the conduction system, pericardial and, less frequently, as valvular disease. Furthermore, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension (PAH), interstitial lung disease, and kidney pathology[1,2].

PRIMARY CARDIAC INVOLVEMENT IN SSc

The prevalence of the primary cardiac involvement in SSc is difficult to determine due to the numerous possible cardiac manifestations, the applied diagnostic tools and diverse patient populations. Of note, the results of histologic studies, which frequently reveal the presence of myocardial involvement, often disagree with those of the clinical studies, performed with different assessment techniques[3].

Clinical examination and routine non-invasive investigations, such as electrocardiogram and thoracic X-ray, are applied in the everyday cardiac assessment, but their sensitivity is low[1,4,5]. Echocardiography [especially tissue Doppler imaging (TDI)], cardiac computed tomography (CT), single-photon emission CT (SPECT), magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide ventriculography are sensitive techniques for earlier detection of both structural and functional scleroderma-related cardiac pathologies[1]. In the recent years, with the improvement of the prognosis of scleroderma renal crisis (SRC), pulmonary and cardiac involvement are the main causes for disease-associated mortality in SSc. Signs for cardiac involvement have been detected with a prevalence of 15% in a cohort of 953 patients with diffuse cutaneous SSc based on clinical findings, echocardiography, electrocardiography, or Holter monitoring[6]. Asymptomatic decreases in the ejection fraction, asymptomatic pericardial effusion, or asymptomatic arrhythmias were not considered as significant heart manifestations in this study. Disease-associated mortality was found to be 20% in a ten-year follow-up[5,6]. The greatest impact occurred in the first five years (14% mortality rate).

Conventional echocardiography is used for cardiac assessment in most studies. Depressed left ventricle (LV) contractility has been reported in only a few patients, whereas up to 40% present with relaxation abnormalities, valvular regurgitation and possible right ventricular (RV) pathology[3]. A recent analysis of organ involvement in a large cohort of 9165 SSc patients from the European League Against Rheumatism Scleroderma Trials and Research database revealed that diastolic dysfunction was among the most frequent features (17.4%). Palpitations were also a common finding in 23.7% of the cases, whereas conduction blocks were detected in 11% by electrocardiography[7]. In a cohort of 1012 Italian SSc patients, the prevalence of cardiac symptoms of arrhythmia was 35%[3].

LV systolic dysfunction is among the rarest findings in SSc patients. In a large multi-centered study, which included 570 SSc patients, the prevalence of LV systolic dysfunction was found to be 1.4%, whereas LV hypertrophy and LV diastolic dysfunction were observed in 22.6% and 17.7% of patients, respectively[8]. In a recent, large European League Against Rheumatism Scleroderma Trials and Research study (including 7073 consecutive SSc patients with a mean age of 56 ± 14 years) the prevalence of reduced LV ejection fraction was found to be 5.4%[9].

Of note, cardiac MRI detected heart pathologies in up to 75% (39/52) of cases, including increased intensity signal of the myocardium in T2, thinning of the LV, pericardial effusion, reduced LV and RV ejection fractions, LV diastolic dysfunction and kinetic abnormalities, and myocardial delayed contrast enhancement[10]. Echocardiographic signs of heart abnormalities were also observed in 48% (25/52) of these patients, which underlines the superior sensitivity of the cardiac MRI modality. Cardiac MRI can be used to diagnose both structural and functional pathologies, such as myocardial inflammation and fibrosis (the extent of fibrosis and viable tissue is properly measured after contrast enhancement). The method gives an opportunity for quantitative assessment of myocardial perfusion and the effect of vasodilators[3,10].

TDI also demonstrates an increased proportion of LV abnormalities in SSc patients. In 101 SSc patients, conventional echocardiography detected low LV ejection fraction (< 55%) in 7% (7/100) of patients, which was doubled to 14% (14/100) by use of TDI[11-14].

Appearance of exercise-related changes should also be taken into account. Thus, using radionuclide ventriculography in 19 SSc patients, a reduced LV ejection fraction has been detected in 10.5% (2/19) of patients at rest, while the values were abnormal in 36.8% (7/19) after exercise[15].

Thallium scintigraphy is another sensitive technique that detects perfusion defects in more than 70% of SSc patients with and without clinically manifested myocardial involvement[16].

Some studies have found that scleroderma-related cardiac manifestations occur in both diffuse and limited cutaneous forms of SSc, whereas according to others, the prevalence is greater in the diffuse cutaneous form of the disease. An association between the cardiac involvement and the presence of anti-topoisomerase, anti-U3RNP antibodies, rapidly evolving skin disease, and skeletal myopathy has been implicated[1,17,18].

When clinically manifested, cardiac involvement is thought to be an important prognosis factor[3,19].

Myocardial involvement

The general pathogenetic mechanisms in SSc, including microvascular alterations (vasospastic episodes that are functional in the beginning with subsequent morphological vascular damage), collagen accumulation by activated

Table 1 Features of myocardial involvement in systemic sclerosis distinct from coronary atherosclerotic disease

Characteristic features
Microvascular ischemia
Patchy fibrosis, unrelated to coronary epicardial artery distribution
Involvement of immediate subendocardium, which is spared in atherosclerosis
Contraction band necrosis
Concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries
Hemosiderin deposits are not typically seen; they are evident in the atherosclerotic process

fibroblasts, and complex immune disturbances, are also thought to be involved in the pathogenesis of myocardial heart involvement in SSc[3,20]. The ischemic, fibrotic and inflammatory lesions, which develop as a result of the above-mentioned processes, may also affect the conduction system, the pericardium, and the endocardium.

The consequences of the pathogenetic processes in SSc at the myocardial level result in areas of focal ischemia, recurrent ischemia-reperfusion injury, myocarditis and myocardial fibrosis. Microvascular alterations, but not the traditional atherosclerotic coronary disease, are thought to play a major role in the development of myocardial blood flow disturbances in SSc. Of note, myocardial infarction has been described in SSc patients with unaltered coronary arteries. Vasospasm of the small coronary arteries and arterioles (the so-called myocardial Raynaud's phenomenon) is considered to be involved in the early scleroderma-related ischemic myocardial changes with subsequent ischemia reperfusion injury and the development of structural vascular alterations. The early functional and reversible abnormalities have been demonstrated with thallium-201 SPECT at rest, after exercise and cold stimulation, PET, and cardiac MRI. In addition, an impaired vasodilator reserve has been found in SSc after causing maximum vasodilation with intravenous dipyridamol[1,21].

A "mosaic", "patchy" distribution of myocardial fibrosis is a pathognomonic feature of the disease. In addition, foci of contraction band necrosis are typically found in all parts of the myocardium, including the immediate subendocardial area, which is usually spared in atherosclerotic processes[22,23] (Table 1). At histological examination, distinct differences between myocardial fibrosis due to SSc itself and fibrosis in the context of coronary artery disease have been noted[20]. In scleroderma-related heart involvement, the fibrotic areas do not correlate with pathologic changes of a single coronary artery. Hemosiderin myocardial deposits that are typically seen in atherosclerosis are absent in SSc-related myocardial pathology.

The inflammatory and autoimmune nature of SSc, as well as its possible association with skeletal myopathy, suggests that myocardial inflammation may play a crucial role in SSc heart disease. Myocarditis has been occasionally reported in SSc patients with acute and severe cardiac symptoms[21,24]. Interestingly, in a cohort of 181 SSc patients, a recent-onset heart disease was registered in 7 patients who underwent extensive noninvasive and invasive evaluations, including MRI and endomyocardial biopsy[21]. Strikingly, all SSc patients with newly developed symptoms and signs of cardiac involvement were found to have biopsy-proven myocarditis. Administration of immunosuppressors (corticosteroids, cyclophosphamide, azathioprine) led to significant clinical improvement, normalization of cardiac enzymes, and improvement of MRI findings in nearly all cases.

Of note, a slightly increased thickness of the septum and posterior wall, or asymmetric septal hypertrophy have been found in a significantly higher number of SSc patients, including those without systemic arterial hypertension, as compared with healthy controls. Septal hypertrophy has also been observed secondary to PAH, which is often subclinical[1].

The main clinical consequence of myocardial lesions is diastolic LV dysfunction, and less frequently systolic dysfunction, which both may be asymptomatic. In addition, different forms of atrial and ventricular arrhythmias, as well as symptomatic heart failure, may occur[1,20].

Treatment

The administration of vasodilators, such as calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors, has demonstrated beneficial effects on myocardial perfusion and limiting further progression of life-threatening complications[3]. Improved myocardial perfusion and function in SSc patients with microvascular coronary pathology has been observed after treatment with nifedipine, nicardipine, or bosentan, using sensitive tests for evaluation such as cardiac MRI, TDI, and radionuclide ventriculography[1,25-27]. Improved myocardial perfusion in scleroderma myocardial disease has also been found after treatment with ACE inhibitors[28]. It has been hypothesized that there is a concomitant presence of ischaemic lesions accessible to reperfusion after vasospasm of small coronary vessels and irreversible lesions, such as morphological vessel pathology or myocardial fibrosis[1]. Thus, administration of vasodilators may influence the reversible component of myocardial ischaemia.

A significantly lower number of SSc patients with reduced LV ejection fraction were found to have been previously treated with calcium channel blockers[9]. These observations suggest that calcium channel blockers may protect against microvascular complications. Currently, dihydropyridine calcium channel blockers are the most well-studied and validated option for clinically apparent myocardial disease in SSc, and may be considered also for protective therapy. They have minimal negative inotropic effects and are generally well-tolerated, with reflex tachycardia and lower extremity edema being the most frequent side effects. Thus, they are recommended for regular administration in SSc-related myocardial disease unless contraindicated. In cases with concomitant PAH, they should be used with caution as they may lead to se-

vere systemic hypotension[1].

Atherosclerosis

Accelerated atherosclerosis with increased cardiovascular morbidity and mortality is a well-known complication of many systemic inflammatory diseases that cannot be explained by the traditional cardiovascular risk factors. The hyperactivation of the immune system and systemic inflammation lead to premature atherosclerosis and earlier occurrence of its clinical manifestations. Thus, ischemic heart disease secondary to coronary atherosclerosis is the first cause of cardiovascular mortality in rheumatoid arthritis patients. Late mortality in systemic lupus erythematosus patients is mainly related to atherosclerotic disease, while in early phases, intercurrent infections are the leading cause[29].

There are contradictory reports regarding the prevalence of atherosclerosis in SSc[30]. According to some authors the prevalence of atherosclerosis of the large epicardial coronary arteries is similar to that of general population[31]. In an autopsy study comparing 58 SSc cases to 58 controls, a significantly higher prevalence of ischaemic heart disease was found in the SSc patients[32]. The frequency of epicardial vessel coronary atherosclerosis was similar (48% *vs* 43%), but atherosclerotic lesions of the small coronary arteries or arterioles occurred in 17% of SSc patients, compared with only 2% of controls. A study by Khurma *et al*[33] comprised of 17 SSc patients and 17 healthy subjects that assessed the presence of coronary calcification by coronary CT, showed that signs of coronary atherosclerosis were present in 56.2% of SSc patients and in only 18.8% of age-, sex-, and race-matched controls.

Ho *et al*[34] performed carotid duplex scanning and measurement of ankle brachial blood pressure index in 54 SSc patients and 43 control subjects that did not differ regarding cardiovascular risk factors. Their results showed that 64% of SSc patients had carotid artery disease compared with only 35% of the controls. In addition, SSc patients had a significantly higher prevalence (17%) of peripheral arterial disease. The results led to the conclusion that macrovascular disease is more common in SSc patient population. In addition, the mean intima media thickness, which is an indicator for the presence of atherosclerotic disease, has been shown to be either increased in SSc patients[35] or unchanged[36] as compared with healthy individuals.

The development of accelerated atherosclerosis in SSc is though to be influenced by viral agents, immune reactions, anti-endothelial antibodies, or ischemia-reperfusion injury. Increased levels of C-reactive protein, homocysteine, von Willebrand factor, and vascular adhesion molecules, which are associated with the atherosclerotic process, as well as elevated and normal levels of lipids, have been reported in SSc[29,37].

In a systematic review and meta-analysis of the literature, Au *et al*[38] concluded that SSc patients are at an increased risk for atherosclerotic disease as compared with healthy subjects. Microvascular disease is a pathognomonic feature of SSc as both vasospasm and structural alterations are present. Such alterations are thought to predict macrovascular atherosclerosis over time. However, the level of inflammation in SSc is lower than in rheumatoid arthritis and systemic lupus erythematosus. Thus, the atherosclerotic process may not be as aggressive and not easily detectable in small-number studies[37].

Arrhythmias and conduction defects

Arrhythmias and conduction abnormalities are thought to be a result from conduction system fibrosis[39,40] and myocardial fibrosis[41]. Atrial and ventricular tachyarrhythmias result from myocardial fibrosis, whereas conduction defects and bradyarrhythmias are a consequence of conduction system fibrosis[1].

Conduction system involvement is uncommon overall, rarely correlates with myocardial involvement, and is not usually clinically manifested[39,40]. However, autopsy findings show that when fibrosis of the conduction tissues occurs, it most commonly affects the sinoatrial node[39,40]. The most common clinical symptoms are dyspnea, palpitations, syncope. Of note, sudden death may also occur[38].

At rest, normal electrocardiography has been recorded in over 50% of SSc patients, with an increase of arrhythmia rate noted during exercise[41]. In 50 SSc patients, the most frequent abnormalities on the resting electrocardiogram were left anterior fascicular block (16%) and first-degree atrio-ventricular heart block (8%). The overall percentage of the abnormal findings was 32%. Of note, left bundle branch block and right bundle branch block with left anterior fascicular block were associated with abnormal left ventricular function, whereas isolated right bundle branch block or left anterior fascicular block were found in patients with normal left ventricular function[41]. Twenty four-hour ambulatory continuous tape-recorded electrocardiograms demonstrated serious pathologic findings in a greater number of patients (62%): including supraventricular tachycardias (32%), conduction disturbances (14%), coupled ventricular extrasystoles (20%), and ventricular tachycardia (10%)[42]. This same methodology also revealed conduction disturbances (such as sinus node dysfunction and first-degree heart block) and arrhythmias (*e.g.*, supraventricular tachycardia, atrial fibrillation, premature contractions from atrial or junctional origin, ventricular tachycardia, multifocal ventricular premature contractions) in 56.5% (26/46) of SSc patients[43].

Supraventricular arrhythmias are considered to be more common in SSc patients, occurring in approximately two thirds of the cases, and much more frequent than ventricular tachyarrhythmias[43]. Ferri *et al*[44] also registered arrhythmias and conductions defects in a substantially higher proportion of SSc patients using 24-h Holter monitoring. In 53 SSc patients [34 with diffuse scleroderma and 19 with Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Telangiectasia syndrome (CREST)], rhythm and conduction abnormalities (*e.g.*,

conduction defects, supraventricular or ventricular arrhythmias and ST-T changes) were found in only 42% (22/53) on resting electrocardiogram. Using Holter monitoring, the number of detected conduction abnormalities increased from 10 to 16 patients, and transient ST-T changes increased from 2 to 18 patients. In addition, 48 patients had ventricular arrhythmias, with multiform ventricular premature beats in 21 (40%), pairs of runs of ventricular tachycardia in 15 (28%), and one or more runs of ventricular tachycardia in 7 (13%) cases. Furthermore, echocardiographic examination revealed asymmetric septal hypertrophy (10/53), impaired ventricular function (9/53), congestive cardiomyopathy (2/53), mitral prolapse (4/53), and pericardial effusion (3/53). Of note, multiform and/or repetitive ventricular premature beats occurred more frequently in patients with echocardiographic abnormalities, but were also present in patients who had normal findings on echocardiographic examination. It should be underlined, that the cardiac abnormalities did not correlate with the clinical variant of SSc (CREST syndrome or diffuse scleroderma), nor with other signs and symptoms of the disease.

Holter monitoring is therefore recommended in patients with symptoms of palpitations, lightheadedness, dizziness, or syncope, irrespective of the normal resting electrocardiogram. Exercise treadmill electrocardiogram may be helpful to identify exertional type arrhythmias. In all cases, a correlation with echocardiographic findings should be sought. Treatment protocols should follow the general guidelines in cardiology for management of the different forms of arrhythmias[1].

Pericardial involvement

Pericardial abnormalities in SSc may manifest as fibrinous or fibrous pericarditis, pericardial adhesions, or pericardial effusion, and rarely as pericardial tamponade or constrictive pericarditis. Pericardial pathology is clinically apparent in over 5%-16% of the cases[45]. The prevalence may be greater in SSc with limited cutaneous involvement (30%) *vs* patients with diffuse cutaneous form of the disease (16%)[46]. At echocardiography, pericardial effusion can be detected in up to 41% of patients[46], and in a larger proportion of cases (33%-72%) at autopsy[45].

Pericardial involvement in SSc is usually clinically silent and benign. In the majority of cases, the presence of small pericardial effusion does not produce clinical symptoms and does not possess prognostic significance[46]. Large hemodynamically significant pericardial effusions associated with heart failure may carry a poor prognosis and cause renal failure, probably due to the cortical renal hypoperfusion in the context of the large pericardial effusions and the administration of diuretics. Cardiac tamponade is rare and has a poor outcome. It should be emphasized that a small amount of rapidly accumulating pericardial fluid may cause tamponade because of the relative incapacity of the fibrotic pericardium for distension. Thus, close monitoring of SSc patients with acute pericarditis is recommended until complete resolution of the symptoms, especially in the cases with coexisting myocardial involvement[46]. Exudative pericarditis is easily diagnosed *via* echocardiography, which may be ordered after the findings on electrocardiogram (ST-T changes, low voltage) and chest X-ray (enlarged heart with a globular shape)[46].

Pericardial effusions usually occur after the manifestations of other clinical features of SSc. Of note, large pericardial effusions, including those with development of tamponade, have been described prior to skin thickening and the establishment of the SSc diagnosis[7,45,47,48]. Thus, SSc should be included in the diagnostic algorithm for the pericardial effusion of unknown origin. Pericardial effusions may also develop secondary to PAH or in the context of renal failure[45].

Constrictive pericarditis presents as a right-sided heart failure with symptoms of shortness of breath, fatigue, anorexia, and wasting. Clinical manifestations may be in the context of both constrictive pericarditis and restriction due to myocardial fibrosis. Echocardiography, invasive measurement of LV and RV hemodynamic parameters, cardiac MRI and CT, may facilitate the differentiation. Diastolic septal bounce with increased respiratory variation in mitral inflow, discordance of peak left and right ventricular pressure at maximal inspiration, and enhanced and/or thickened pericardium on cardiac MRI, support the diagnosis of constrictive pericarditis. Of note, B-type natriuretic peptide (BNP) [and its cleavage product N-terminal pro BNP (NT-proBNP)], which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch, and is increased in myocardial involvement, is normal or close to normal in constrictive pericarditis. Treatment includes diuretics, sodium and fluid restriction, and in selected cases, in the absence of contraindications (simultaneous presence of constrictive and restrictive pathologies and comorbidities), and pericardial stripping[1].

The pathogenesis of pericardial effusion in SSc is thought to differ from rheumatoid arthritis and systemic lupus erythematosus. This notion is based on the findings that the pericardial fluid is noninflammatory by nature; auto-antibodies, immune complexes and complement depletion are absent. In addition, a general lack of response to corticosteroid treatment in scleroderma pericardial disease has been noted[48]. At histological examination, nonspecific fibrotic pericardial thickening with adhesions and perivascular inflammatory cell infiltration have been found[45].

Treatment

Treatment may include nonsteroidal anti-inflammatory drugs with close monitoring of renal function. Corticosteroids are considered to be of limited benefit in SSc-related pericardial disease[45], but steroid-responsive cases also occur[49], and corticosteroids may be life-saving in cases with associated myocarditis[45]. Immunosuppressors may be indicated if profound inflammation is evident. Diuretics are considered in cases of heart failure but

should be used with caution due to the risk for development of renal failure[45]. Pericardiocentesis is indicated in cases of life-threatening tamponade[1].

SSc-related endocarditis

Valvular vegetations are considered to be rare manifestations in SSc. However, such lesions were found in 5 out of 28 autopsied SSc cases, including lesions of the mitral and tricuspid valve (alone or in combination), along with involvement of the chordae tendineae[50], or the aortic valve[51]. Nodular thickening of the mitral and aortic valves with regurgitation and mitral valve prolapse has also been noted[45,52]. The clinical significance of such changes in SSc patients is unknown. Of note, endocarditis may occur in association with severe myocardial damage[53].

Interestingly, embolisms in the brain and foot in SSc in the presence of mitral vegetation were found on echocardiography, and infective endocarditis was excluded on the basis of serial negative blood cultures and the absence of fever or known rheumatic valvular disease[53].

SECONDARY CARDIAC COMPLICATIONS IN SSc

PAH

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation with subsequent increased pulmonary vascular resistance and right heart failure[54]. The prevalence of PAH in SSc is about 10%-12%[55], varying between 4.9% and 26.7% depending on the applied diagnostic tools[56]. PAH in SSc may be associated with pulmonary fibrosis, or may develop due to vascular narrowing or occlusion in cases with or without minimal pulmonary fibrosis. Pulmonary fibrosis is found in more than one third of SSc patients with either the diffuse or limited form of the disease. Post-mortem examinations revealed alveolar, interstitial, peribronchial and pleural fibrosis. PAH in the context of pulmonary fibrosis is usually of moderate degree and is characterized with relatively slow progression that develops as a result of the gradually increasing resistance of the pulmonary vasculature[57,58]. PAH in SSc patients with minimal or no pulmonary fibrosis is a severe complication, and is a consequence of narrowing or occlusion of small pulmonary arteries caused by smooth muscle hypertrophy, intimal hyperplasia, vascular inflammation, and thrombosis *in situ*. Dyspnea from normal exercise tolerance to oxygen dependency progresses over 6-12 mo, with a mean survival of two years, whereas PAH in the context of lung fibrosis progresses more slowly, over two to ten years[54,57,59,60].

Of note, isolated PAH, in the absence of pulmonary fibrosis, is more frequent in the limited cutaneous form of SSc (45%) than in the form with diffuse cutaneous involvement (26%)[61]. Histological evidence for PAH at autopsy is also more frequent (over 65%-80% of cases). These data suggest a substantial prevalence of mild and moderate forms of PAH in SSc[54,62]. PAH is considered to be one of the most important factors contributing to the increased morbidity and mortality in SSc[63]. The high incidence and prevalence of PAH in SSc, its poor prognosis, and the efficacy of the new evidence-based treatment that improves survival, stimulated the recommendation of an obligatory regular screening of pulmonary arterial pressure (PAP) in SSc patients.

Clinical signs of PAH include dyspnea on exertion, fatigue, chest pain, dizziness, palpitations, and edema at the lower extremities. Upon physical examination, an accentuated pulmonary component of the second heart sound, gallop, and pansystolic murmur of tricuspid regurgitation may be found, as well as features of right heart failure in advanced cases[56]. The chest X-ray and electrocardiogram may reveal signs suggestive of PAH, mainly in the later stages, such as an enlarged pulmonary artery, attenuation of peripheral pulmonary vascular markings (at the chest X-ray), and peaked *P* wave $\geqslant$ 2.5 mm in leads Ⅱ, Ⅲ and aVF[54,56]. If PAH is suspected, a transthoracic Doppler echocardiography is recommended[54,56]. At echocardiography, PAH is defined as mean PAP > 25 mmHg at rest, > 30 mmHg during exercise, or systolic pulmonary pressure > 40 mmHg. Clues to diagnosis can be an elevated tricuspid regurgitation velocity (TRV) jet above 2.8 m/s, or a dilated right ventricle or atrium[64]. The decreasing carbon monoxide diffusing capacity (DLco) is a marker of pulmonary vascular disease and is standardly used in the diagnostic approach when PAH is suspected. Of note, it is associated with poor prognosis. CT and MRI may also be used to assess right ventricular mass, volume, and function. At MRI, the ratio of septal curvature, right ventricular ejection fraction, and right ventricular volume may be evaluated[54].

All patients that are suspected of having PAH after noninvasive evaluation should undergo right heart catheterization (RHC) prior to therapy initiation. This method is the gold standard for diagnosing PAH, and allows for the measurement of the transpulmonary gradient (PAP mean wedge), which was found to be significantly elevated only in PAH patients, but not in patients whose pulmonary hypertension was due to increased cardiac output, left heart myocardial or valvular disease[54,65]. A more reliable diagnostic parameter for PAH is pulmonary vascular resistance (PVR), which reflects the influence of transpulmonary gradient and cardiac output and is only elevated if the vascular obstruction occurs within the precapillary pulmonary circulation. However, PVR can also be elevated in patients with valve disease or left ventricular heart disease[56]. Consequently, PAH is a diagnosis of exclusion. In the absence of lung disease, thromboembolism, left ventricular or valve pathology, the diagnosis of PAH requires both a mean PAP greater than 25 mmHg and a PVR greater than 3 Wood units with a pulmonary capillary wedge pressure < 15 mmHg (for exclusion of left heart disease)[54,65]. In addition, BNP and NT-proBNP are promising screening parameters in SSc-related PAH, as increased levels correlate with disease severity

Table 2 Therapies for systemic sclerosis-related pulmonary arterial hypertension[64-82]

Therapeutic approach	Dosage/comments
Prostanoids	
Epoprostenol: a prostacyclin with a very short half-life of 6 min; unstable at pH values below 10.5, requires intravenous administration[54,68]	Starting dose is 1-2 ng/kg per minute, gradually increased up to 25-40 ng/kg per minute
Treprostinil: an epoprostenol analogue with a half-life of 4.5 h, given as a continuous subcutaneous or intravenous infusion in patients with PAH from functional class Ⅱ, Ⅲ and Ⅳ[54,69]	10-20 ng/kg per minute
Iloprost: a chemically stable prostacyclin analogue with a longer half-life (20–25 min), given as a continuous intravenous infusion for 6-8 h[70]	0.5-3.0 ng/kg per minute
Beraprost: the first oral prostacyclin analogue with vasodilative and antiplatelet action and a half-life of approximately 1 h, indicated in primary and secondary PAH[72,73]	20 μg qid, may be increased by 20 μg/wk. The maximum allowed dose was 120 μg qid with a mean of 80 μg qid
Prostaglandins for inhalation	
Iloprost: inhalation has a pulmonary vasodilative potency similar to prostacyclin with longer effects (30-90 *vs* 15 min); effective in patients with severe PAH functional class Ⅲ and Ⅳ[71]	2.5 or 5.0 mg six or nine times/d; median inhaled dose, 30 μg/d
Endothelin receptor antagonists	
Bosentan: the first drug from this group that was approved for treatment of PAH associated with systemic rheumatic diseases in the United States, Canada, Switzerland and European Union; indicated for PAH functional classes Ⅱ, Ⅲ and Ⅳ[74,75]	62.5 mg bid for 4 wk before titration up to 125-250 mg bid
Sitaxsentan: highly selective endothelin receptor antagonist with a long duration of action; high specificity for type A over type B receptors (6500:1) leads to blockade of the vasoconstrictory effect of endothelin-1 and maintainence of the vasodilative and clearance function of type B receptors[76]	50-100 mg/d
Ambrisentan: antagonist selective for type A over type B endothelin receptors (4000:1)[77]	2.5-10 mg
PDE inhibitors	
(PDE degrades cGMP, which mediates the effect of nitric oxide-a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle)	
Sildenafil: a specific inhibitor of the PDE-5 isoform present in large amounts in the lung[78]	20 mg 3 tid
Vardenafil: a PDE-5 inhibitor[80]	20 mg 3 tid
Tadalafil: a specific inhibitor of PDE-5 with a longer half-life (17.5 *vs* 3.8 h for sildenafil)[79]	20 mg 3 tid
Combination therapy	
(oral with inhaled and intravenous drugs)	
Sildenafil with intravenous epoprostenol Sildenafil and bosentan[81]	
Others	
Sodium consumption needs to be restricted to 2400 mg/d in patients with right ventricular failure; digoxin and diuretics when indicated	Saturation < 90% at rest or with exercise; Titration to an international normalized ratio of 1.5-2.5
Surgical options: atrial septostomy, single and double lung transplantation and combined heart and lung transplantation are ultimate therapeutic options in patients with end-stage disease[54]	
Routine immunization against influenza and pneumococcal pneumonia	
Oxygen therapy	
Anticoagulation therapy: (warfarin) in advanced stages with continuous intravenous therapy and in the absence of contraindications	
Although inflammation plays a significant role in the development and the progression of PAH, immunosuppression is not a common treatment, as systemic sclerosis-PAH is usually quite refractory to immunosuppressive drugs[82]. However, immunosuppressive treatment has led to improvements in some cases of PAH in other connective tissue diseases (*e.g.*, systemic lupus erythematosus, primary Sjögren syndrome)	

PDE: Phosphodiesterase; PAH: Pulmonary arterial hypertension.

and predict survival[54,64,65].

Treatment

The general therapeutic algorithm in SSc-PAH is summarized in Table 2. During RHC, vasodilator testing is performed in order to predict the therapeutic response. The response is defined as a reduction ⩾ 10 mmHg to a mean PAP ⩽ 40 mmHg, without a decrease in cardiac output[54]. It includes administration of inhaled nitric oxide, intravenous epoprostenol or intravenous adenosine. It has been found that responders are more likely to have a sustained beneficial response to oral calcium channel blockers (long-acting nifedipine, diltiazem and amlodipine) than non-responders[54,83-85]. Verapamil should be avoided because of its potential for negative inotropic effects. High doses of calcium-channel blockers may improve survival in patients with primary PAH who respond with reductions in pulmonary arterial pressure and vascular resistance[86].

SSc-associated PAH historically had a poor prognosis with a one-year survival rate of 45%[55,87]. Survival, though still poor, has significantly increased with modern therapies such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, which can improve pulmonary hemodynamics and functional capacity in patients with PAH in the context of connective tissue diseases. A six-year follow-up (2001-2006) of 315 patients with SSc-related PAH from the United Kingdom National registry has demonstrated one-, two- and three-year survival rates of 78%, 58% and 47%, respectively[55,88,89].

Table 3 Criteria for definition of hypertensive scleroderma renal crisis

In the presence of limited or diffuse cutaneous scleroderma renal crisis:
A new onset of blood pressure > 150/85 mmHg obtained at least twice over a 24 h period. This blood pressure is defined as significant hypertension by the New York Heart Association
A documented decrease in renal function as defined by a decrement of at least 30% in the calculated glomerular filtration rate. When possible, initial results should be confirmed by a repeat serum creatinine concentration and recalculation of the glomerular filtration rate
To corroborate further the occurrence of acute renal crisis, it would be desirable to have any of the following (if available):
Microangiopathic hemolytic anemia on blood smear
Retinopathy typical of acute hypertensive crisis
New onset of urinary red blood cells (excluding other causes)
Flash pulmonary edema
Oliguria or anuria
Renal biopsy showing characteristic changes
Renal biopsy showing an alternative cause excludes the case from classification as scleroderma renal crisis

Early diagnosis of SSc-PAH and early subsequent intervention are essential for delaying disease progression. Early detection of PAH, when patients have few or no symptoms (*i.e.*, functional class Ⅰ and Ⅱ), is challenging. Available data broadly support annual screening of all SSc patients with and without symptoms. Patients with SSc who are at high risk for development of PAH are those with DLco < 60% predicted or who have declining DLco (*e.g.*, 20% decrease over a one-year period). Doppler echocardiography conducted at rest is considered to be the method of choice for PAH screening. For patients with TRV > 3.4 m/s (corresponding to a systolic PAP > 50 mmHg) or with a TRV between 2.9 and 3.4 m/s (corresponding to a systolic PAP between 34 and 49 mmHg) in the presence of other signs suggestive of PAH, non-invasive workup is recommended, including biomarkers, high-resolution CT and decision for confirmation of PAH *via* RHC[90,91]. In the recently performed DETECT study aimed to define recommendations for earlier detection of SSc-related PAH, six variables were determined to guide to the echocardiography, including forced vital capacity/DLco (% predicted), presence of current/past telangiectasias, serum anticentromere antibodies, serum NT-proBNP, serum urate and right-axis deviation on electrocardiogram. TRV and right atrium area are evaluated in order to define the necessity of RHC for confirmation of PAH. It has been postulated that using TRV alone would fail to diagnose 20% of PAH patients when using a PAH suspicion threshold of ≥ 2.5 m/s, 36% when using a threshold of > 2.8 m/s, and 63% when using a threshold of > 3.4 m/s[92].

Cardiac symptoms in severe scleroderma-related kidney involvement

A severe systemic hypertension due to SRC may trigger the development of systolic dysfunction and congestive heart failure[4]. SRC occurs in over 10% of SSc patients, in 10%-25% in the subgroup of SSc patients with diffuse cutaneous involvement, and in only 1%-2% of those with a limited form of the disease[1,93]. Most patients have a profound elevation of blood pressure at the onset of SRC; 90% have a pressure > 150/90 mmHg, and 30% have a diastolic pressure > 120 mmHg. Of note, an increase of 20 mmHg in blood pressure values may be significant for a particular patient even though the values may still be in the normal range, and this also may represent a renal crisis. Only 10% of SRC are clinically associated with normal values of blood pressure. SRC is the most important renal complication in SSc based on vasculopathy, fibrosis and autoimmunity with a central role of the renin-angiotensin axis, as demonstrated by the striking clinical efficacy of ACE inhibitors[1]. The diagnosis of hypertensive SRC is established on the basis of recently developed criteria (Table 3)[94]. Factors for predicting the development of SRC include diffuse cutaneous involvement, rapid progression of skin involvement, disease symptoms for less than four years, presence of anti-RNA polymerase Ⅲ antibody, new anemia, new cardiac events (pericardial effusion, congestive heart failure), and antecedent high-dose corticosteroids. Of note, previous blood pressure elevations, stable, mildly elevated serum creatinine, abnormal urine analysis, anti-topoisomerase and anticentromere antibodies, or pathologic findings in renal blood vessels are not predictive for the development of SRC[1]. The clinical features include headache, breathlessness, dizziness, syncope. All SSc patients should be encouraged to check their blood pressure if such clinical symptoms are present. It is recommended that the SSc patients with predictive factors for the development of SRC should monitor their blood pressure twice weekly[1].

Hypertension that occurs prior to the onset of SSc is usually essential, while those that develop after the onset of the disease could be either essential hypertension or, more likely, SSc-related[95]. ACE inhibition is the cornerstone for the treatment of hypertension in SRC. ACE inhibitors should immediately be started once the diagnosis is established, or the dose increased if the patient is already taking them. ACE inhibitor resistance is a frequent finding in SSc patients. In such cases, the dose must be gradually increased to a maximum level. Early reduction or discontinuation of ACE inhibitors should be avoided. Denton *et al*[96] recommend doubling the dose every 24 h, though deterioration of renal function may continue in this period. Frequently, it takes several days for blood pressure to fall to normal. In cases of insufficient blood pressure decrease, the authors recommend adding angiotensin receptor blockers, calcium channel blockers, doxazosin or clonidine[96]. Beta blockers are contraindicated in

SRC due to their effect on peripheral circulation. Parenteral antihypertensives are not generally recommended, although nitrate infusion is sometimes indicated for the management of pulmonary edema[1]. The aim of the antihypertensive treatment is to achieve pre-SRC values of blood pressure. The mean decrease per 24 h should be over 20 mmHg for the systolic and 10 mmHg for the diastolic blood pressure. Prolonged periods of hypotension should be avoided[96]. If renal replacement is required, hemofiltration and hemodialysis are used depending on the hemodynamic stability and availability of the center. More than half of the patients who have undergone dialysis were able to discontinue it in 3-18 mo. Over 20% of the cases require chronic dialysis and 20% had an early death[1].

SRC has been a leading cause for increased mortality in SSc, though survival has dramatically improved with the use of ACE inhibitors. Patients with SRC who received ACE inhibitors had an impressive one-year survival of 76% and a five-year survival of 65%, compared with 15% one-year survival and 10% five-year survival of patients not receiving ACE inhibitors, despite other aggressive antihypertensive treatment[97,98]. The use of ACE inhibitors should continue indefinitely because recurrences occur years after the initial event when ACE inhibitors are discontinued[1]. Prophylactic use of ACE inhibitors prior to SRC does not prevent its development[1,99].

EVALUATION OF SSc PATIENTS WITH CARDIAC INVOLVEMENT

Laboratory investigations

Screening for biologic markers of possible cardiac dysfunction may be beneficial. One such laboratory marker is BNP, which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch. Annual measurement of BNP is thought to be beneficial, as plasma concentrations correlate with the risk of death and cardiovascular events. BNP originates from the precursor protein pre-proBNP, which is first cleaved to proBNP, and then to active BNP and NT-proBNP. Both BNP and NT-proBNP can be measured in clinical practice, but the advantages of the latter are its longer half-life and increased stability. Of note, their levels vary according to gender and age. These markers are used for the screening of overall cardiovascular pathology in SSc, including PAH. There is not sufficient evidence that one natriuretic peptide is superior to another in this regard. The upper normal limits are 125 pg/mL for NT-proBNP and 60 pg/mL for BNP[1,13,100,101]. Levels may be elevated in primary scleroderma-related myocardial involvement, as well as in pulmonary or systemic hypertension and in conventional concomitant cardiac diseases, such as acute and chronic coronary artery disease, left and right ventricular systolic and diastolic dysfunction, valvular heart disease, atrial arrhythmias, and heart failure[1,13].

It should be emphasized that NT-proBNP is not cleared by natriuretic peptide clearance receptors and is primarily excreted by the kidney. Thus, renal dysfunction is more likely to cause its elevation with less effect on BNP level. Of note, a number of noncardiac conditions may increase the level of natriuretic peptides, such as older age, female gender, weight loss, renal insufficiency, sepsis, pulmonary embolism, anemia, cirrhosis, corticosteroid administration, hyperthyroidism, malignancies, or central nervous system injury. On the other hand, factors such as obesity, constrictive pericarditis, pulmonary edema, and some cardiac medications (ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, spironolactone) are associated with normal or decreased natriuretic peptide levels[1].

Other laboratory markers that have been investigated together with NT-pro-BNP to evaluate a subclinical cardiac involvement in SSc and have shown significantly higher levels as compared with controls, are ischaemia modified albumin, high-sensitivity C-reactive protein, and Erythrocyte Sedimentation Rate. No significant differences have been detected for ischemia modified albumin and NT-pro-BNP levels between the limited and diffuse cutaneous forms of SSc. Ischaemia modified albumin is thought to appear in different conditions of local or generalized hypoxia and thus is not a specific cardiac marker[101].

Troponin has not been found to be elevated in SSc despite myocyte loss and myocardial fibrosis. Thus, when elevated troponin is present, myopericarditis or non-scleroderma cardiovascular disease, such as coronary syndrome or pulmonary embolism, should be suspected[1,101].

Instrumental investigations

A resting electrocardiogram is not sufficient to diagnose rhythm and conduction disturbances in SSc. Thus, when clinical signs like palpitations or syncopes are present, 24-h Holter monitoring is indicated. Holter monitoring has demonstrated good sensitivity to detect arrhythmias and conduction abnormalities in a significantly higher percentage of patients as compared with the resting electrocardiography[44], and should be included in the diagnostic algorithm of SSc patients with symptoms of palpitations, syncope, or dyspnea with unknown origin. New devices of Holter electrocardiographs may collect data for up to 14 d. In patients with less frequent symptoms, long-term Holter assessment (usually for a 30-d period) may be necessary. Of note, there are implantable monitors, which can detect arrhythmias indefinitely and may be also used in difficult cases[1]. Exercise treadmill electrocardiogram may be helpful to identify the exertional type of arrhythmia[1].

A transthoracic echocardiography should be included in the routine diagnostic screening of SSc patients[1,44]. Of note, normal electrocardiographic findings were associated with normal left ventricular function at rest[40]. Echocardiography allows measurement of atrial and ventricular dimensions, volumes (including ejection fraction), diagnosing of systolic and diastolic dysfunction, pericardial, valvular disease, and pulmonary hypertension[1]. TDI

is a modern echographic method that allows the accurate measurement of regional and global LV and RV function, and the inclusion of this technique has improved the accuracy and reproducibility of standard echocardiography[11].

Nuclear imaging, such as thallium-201 SPECT and PET scanning, are sensitive tools for detection of microvascular abnormalities in SSc-related myocardial disease. Detection of subendocardial ischemia by nuclear imaging is limited and inferior as compared with cardiac MRI[1]. Cardiac MRI with or without contrast enhancement is a modern imaging modality that detects both structural and functional cardiac abnormalities in SSc patients with significantly superior sensitivity as compared with echocardiography (75% *vs* 48% detection rate in a cohort of 53 SSc patients)[10]. Cardiac MRI gives an opportunity for quantitative assessment of myocardial perfusion and the effect of vasodilators[3]. Chest CT may be used for combined assessment of lung and cardiac involvement in SSc. Cardiac CT and MRI are valuable techniques for detection of pericardial thickness and inflammation[1].

Cardiac catheterization is indicated in SSc for diagnosis of PAH, constrictive pericarditis, cardiac tamponade and epicardial coronary artery disease, for performing endomyocardial biopsy in cases of suspected infiltrative cardiac disease[1].

CONCLUSION

Cardiac involvement in SSc may present with various manifestations and is an indicator of a poor prognosis. The rheumatologists should be acquainted with the different forms of primary and secondary cardiac involvement in SSc and the necessity for screening for the detection of subclinical cases *via* modern sensitive tools, as early diagnosis and treatment are crucial for a positive outcome.

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