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The Heart in Scleroderma

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Abstract

The heart is one of the major organs involved in scleroderma. Cardiac involvement can be manifested by myocardial disease, conduction system abnormalities, arrhythmias, or pericardial disease. Additionally, scleroderma renal crisis and pulmonary hypertension lead to significant cardiac dysfunction secondary to damage in the kidney and lung. This review summarizes the types and mechanism of abnormalities in the heart in scleroderma. The concept of cardiac dysfunction in scleroderma and other rheumatologic conditions has received new interest with the advent of newer non-invasive imaging techniques as well as the interest in detecting subclinical disease. With this increased interest in cardiac manifestations in scleroderma comes the realization that long term studies are needed to better assess the appropriate screening and treatment in this patient population.

Introduction

Just as scleroderma can affect multiple organ systems, the cardiac manifestations of the disease are diverse. Although only relatively recently recognized, the heart is a major organ involved in scleroderma and the presence of cardiac involvement generally portends poorly for the patient. Cardiac involvement can generally be divided into direct myocardial effects and the indirect effect of other organ involvement (ie. Pulmonary hypertension, renal crisis). Direct myocardial disease includes myositis, cardiac failure, cardiac fibrosis, coronary artery disease, conduction system abnormalities, and pericardial disease.

The involvement of the heart in scleroderma was first identified in 1926 by Heine³⁰ followed by Weiss et al, who described 9 cases of SSc with congestive heart failure and it was first postulated that cardiac fibrosis was the etiology⁶⁴. Historically, the cardiac manifestations scleroderma have been confined to a progressive myocardial fibrosis that was observed on autopsy sectioning of the heart^{30,64}. Since these initial observations, it has been established that SSc can involve the myocardium, coronary arteries, pericardium and the conduction system.

Clinical Presentation

Like any presentation of cardiac disease, the symptoms of patients with cardiac involvement in SSc is varied. In patients presenting with signs of left heart failure, pulmonary congestion, and elevated left heart filling pressures, the most common complaints are dyspnea with exertion, paroxysms of nocturnal dyspnea and/or orthopnea and, if chronic in nature, may present with ascites and pedal edema. Patients with pulmonary hypertension and subsequent

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right heart failure usually present with symptoms of indolent, progressive shortness of breath, pedal edema and, ascites, and/or congestive hepatomegaly. When there is right heart failure in the absence of left heart involvement, patients generally do not experience orthopnea or paroxysms of nocturnal dyspnea. In patients with severe pulmonary hypertension, syncope and sudden cardiac death can occur likely as a result of arrhythmias or acute right ventricular failure. Other signs and symptoms of cardiac involvement with SSc may be similar to myocardial ischemia with dyspnea and chest pain. This chest pain may be atypical in nature but the presence of coronary artery disease must always be considered in this patient population. Patients with arrhythmias may experience palpitations due either to bradycardia or tachycardia, or merely a perceived pounding of the heart beat in sinus rhythm, are common^{9,14,15}.

Prevalence and Prognosis of Cardiac Involvement in SSc

The presence of cardiac involvement in SSc is often underestimated due to the occult nature of the signs and symptoms and reports of the prevalence of cardiac disease vary depending on the methods used. Moreover, symptoms of cardiac manifestations are often attributed to non cardiac causes such as pulmonary, musculoskeletal, or esophageal involvement. More recent studies suggest that clinical evidence of myocardial disease may be seen in 20% to 25% of patients with SSc^{14,20-22}. Autopsy studies have observed myocardial fibrosis and pericardial disease to be most prevalent but like any autopsy study this likely represents patients with more advanced disease^{5,6,12,14,43}. Other modalities of study in living patients have been used as well. With thallium scintigraphy the estimated prevalence of clinical cardiac involvement in SSc is much higher^{1,18,29,31,32,34-36}. Other modalities like single photon emission computed tomography (SPECT) thallium imaging have been noted in nearly all SSc patients tested³¹⁻³⁶ but the clinical implications of these defects remain uncertain. In addition to thallium and MRI studies, echocardiography has been used to screen SSc patients for asymptomatic cardiac abnormalities. In a study of 54 patients, 69% were found to have an abnormality by echocardiogram.⁵⁸ the most common of which were elevated right ventricular systolic pressure (RVSP), pericardial effusion, increased RV dimension, and left atrial enlargement. In addition to structural defects, twenty-four-hour ambulatory monitoring has detected arrhythmias and conduction system abnormalities in SSc patients with or without symptoms^{10,11}.

The presence of clinical cardiac involvement in SSc is a harbinger of a poor prognosis. Medsger and Masi⁴⁴ showed that clinical cardiac disease in SSc was associated with a 70% mortality at 5 years. Certainly the presence of pulmonary arterial hypertension is a poor prognostic sign and is associated with a higher mortality rate in patients with SSc than idiopathic PAH as shown in the Johns Hopkins Cohort from 2001-2005^{16,23}. In general, higher risk findings in patients with SSc include the presence of clinical heart failure, poor RV function²⁴ pulmonary arterial hypertension, low cardiac index, high right atrial pressure, and documented ventricular arrhythmia. Steen and Follansbee⁶¹ followed 48 patients who had undergone cardiac evaluation and found that thallium perfusion defect scores were the single most powerful predictor of mortality and the subsequent development of clinical cardiac disease in patients with either limited or diffuse scleroderma¹⁴.

Direct Myocardial Involvement: Fibrosis and Myositis

Studies of the cardiac manifestations of SSc have been limited due to a number of reasons. Most histochemical studies involve autopsy specimens and likely do not reflect the cardiac involvement in patients with subclinical disease. Moreover, imaging studies have been limited due to the fact that there were not endomyocardial biopsies to be performed to correlated histopathological fibrosis/hypertrophy/myositis with imaging techniques. In general, myocardial fibrosis is considered to be the hallmark of cardiac involvement in SSc. The fibrosis

tends to be patchy but distributed throughout the myocardium in both ventricles^{6,14,20,39,40,57}. Interestingly, it has been noted that fibrosis in cardiac SSc can be distinguished from the fibrosis present in atherosclerotic coronary artery disease in that SSc the fibrosis may involve the immediate subendocardial layer (which is typically spared in atherosclerosis) and hemosiderin deposits (which are commonly observed in atherosclerotic disease) are not seen in SSc^{6,14,20,22,39,40,57}. In general, the findings of fibrosis are often observed with cardiac hypertrophy. The presence of hypertrophy is nonspecific and may indirectly reflect elevated pulmonary or systemic pressures.

Some patients with SSc have features of polymyositis and reports of SSc patients with coexisting myocardial disease and myositis suggest that there may be an association between myocarditis and peripheral myositis^{7,64}. In another study, patients with an elevated CK at any time had an increased frequency of cardiac dysfunction, congestive heart failure, and cardiac death in comparison with patients with no CK elevation^{14,19}. However, the lack of an elevated CK does not rule out the presence of cardiac inflammation. In our experience, the presence of “low grade” inflammation (evidenced by the lack of elevated plasma troponin or CK-MB levels but with cellular infiltrate on biopsy sample) is often found in many RV biopsies of SSc patients suggesting that cardiac inflammation may be more common than originally appreciated. Moreover, the fibrotic process may be secondary to chronic inflammation of the heart (Champion et al. unpublished observation).

Left Ventricular Systolic and Diastolic Dysfunction

Left ventricular systolic dysfunction is not an uncommon finding in advanced scleroderma, but the timecourse and susceptibility for this is not well understood. Systolic and/or diastolic dysfunction can occur as a result of myocardial fibrosis but the role of ongoing low grade myocarditis in this process is less well characterized. Anecdotally, patients with reduced ejection fraction and normal coronary arteries may benefit from increasing the patient's immunosuppression. It has been observed that patients with scleroderma with reduced ejection fraction and normal LV chamber size may improve their LV function with an increase in their immunosuppression regimen and a concomitant institution of appropriate drugs to treat heart failure (ACE/ARB, beta blockade, aldosterone antagonist; Champion et al, Unpublished observation). Overt congestive heart failure occurs in more advanced disease, but systolic dysfunction is often clinically occult. In four studies using radionuclide ventriculography to evaluate left ventricular ejection fraction (LVEF), only nine of 85 (11%) patients had an abnormal LVEF under resting conditions^{14,18,32-34}. As would be expected, there is a marked difference in symptoms and hemodynamics with exertion and, in one study 46% of patients had a reduced LVEF with exercise while only 15% of this group had reduced function at rest¹⁹.

More recently, there has been an increased awareness of non-systolic heart failure (diastolic dysfunction) in scleroderma. Armstrong et al.² and Valentini et al.⁶³ showed echocardiographic findings in scleroderma patients consistent with diastolic dysfunction and this correlated with disease duration, but the prognostic significance of these findings is unknown. Moreover, it was found that patients with scleroderma had impaired LV diastolic relaxation that was worsened with exercise. More recently, using gated myocardial perfusion single photon emission computed tomography scans, Nakajima et al.⁴⁸ found that diastolic dysfunction was found in more than half of patients with scleroderma, even in the absence of myocardial ischemia, and it correlated with the severity of cutaneous disease. This observation has subsequently been confirmed using tissue doppler imaging⁵².

Co-morbid conditions that predispose scleroderma patients to diastolic dysfunction are systemic hypertension, sleep disordered breathing, renal disease, and left ventricular

hypertrophy and/or fibrosis. Echocardiographic signs of diastolic dysfunction are E/A reversal of the mitral inflow pattern and left atrial enlargement. Chronically elevated LV diastolic pressures can lead to increased pulmonary artery pressures via increased pulmonary capillary wedge pressures⁴². Given the fact that diastolic dysfunction may not be clinically present at rest, it is recommended that patients undergo confrontational assessment of diastolic dysfunction by exercise right heart catheterization if clinically suspected.

Right Heart Failure

Right heart failure is most commonly the result of pulmonary hypertension. Pulmonary hypertension is a common manifestation of scleroderma and a poor prognostic sign. It is the ability of the right ventricle (RV) to function under this increased load that determines both the severity of symptoms and survival^{26,41,49,54}. Signs and symptoms of right heart failure by history, echocardiogram, and catheterization are associated with a significantly increased risk of death. In studies addressing hemodynamic variables and survival with PAH, a low cardiac index and high mean right atrial pressure (mRAP) are consistently associated with poorer survival^{41,53}. The mean pulmonary arterial pressure (mPAP) is also a determinant of survival but only when the elevation is extremely severe. Several echocardiography-derived parameters have been reported to correlate with poor outcome particularly with scleroderma^{3,65,66}. Right atrial area index, the diastolic eccentricity index and the presence of a pericardial effusion were all predictors of the combined endpoint of death or transplantation; right atrial area index and pericardial effusion were also independent predictors of mortality. However, although these indices they usually reflect profound RV failure, they are crude at best. With this in mind, novel and practical ways to assess the presence and extent of subclinical RV failure are desperately needed before the stage of overt RV failure⁸. Recently, the use of TAPSE (Tricuspid Annular Plane Systolic Excursion) has been correlated to mortality in patient with SSc and IPAH²⁴. Moreover, the role of pulmonary vascular stiffening and wave reflectance in increasing RV hydraulic load appears to be under-recognized and may be particularly important in PAH-SSc patients in whom there is a significant degree of large artery stiffening in the pulmonary vascular tree⁴².

Coronary Vasculature and Myocardial Perfusion

The prevalence of atherosclerotic coronary artery disease is not increased in SSc^{14,20}. However, in patients with scleroderma and coronary disease, the likelihood of coronary vasospasm is significantly higher than in the general population. It is possible that coronary involvement in scleroderma is not in epicardial vessels, but rests in small arterial segments. Follansbee et al^{14,17,18,20,62} demonstrated normal coronary angiograms in patients with exercise-induced perfusion defects suggesting that abnormal resistance to flow at the level of the microcirculation or myocardial interstitium may account for the observed abnormal perfusion.

Myocardial Raynaud's phenomenon (RP) has been postulated in scleroderma, but the available findings suggest that it is different from peripheral RP. Peripheral RP appears to involve significant anatomic narrowing of the vessels^{59,60}. In contrast, SSc patients with myocardial ischemia demonstrate only infrequent luminal narrowing of the small arteries in the heart^{59,60}. A number of studies have examined the effect of cold pressor provocation on myocardial function and perfusion in SSc patients to assess the presence of possible cold-induced coronary vasospasm but the results of these studies have been mixed and the clinical and prognostic significance, if any, require further investigation^{13,60}.

Pericardial Disease

Pericardial abnormalities in scleroderma have noted fibrinous pericarditis, fibrous pericarditis, pericardial adhesions, and pericardial effusions at the time of autopsy¹³. However, clinically symptomatic pericardial disease (5%-16%) is much less frequent than autopsy-demonstrated pericardial involvement (33%-72%)^{4,12,17,18,25,50,55,56,58}. Asymptomatic pericardial effusions commonly occur in scleroderma²⁷. Moreover, there also have been large effusions causing tamponade and can even occur prior to skin thickening and the diagnosis of scleroderma^{28,38}. Pericardial effusions are also frequently associated with pulmonary hypertension and may be the presenting feature of pulmonary hypertension in scleroderma⁶⁰. Large pericardial effusions can lead to pericardial tamponade and are a marker for poor outcome. If an inflammatory component is thought to be the cause of the effusion, immunosuppression therapy can markedly reduce the volume of the effusion. Moreover, if clinical heart failure is present, the effusion can be reduced with diuresis. However, if the pericardial effusion is present in the setting of significant pulmonary hypertension, it has been the experience at Johns Hopkins that attempts at percutaneous drainage should be avoided as this is associated with an increased risk of hemodynamic compromise and death (AR Hemnes, unpublished observation).

Conduction System Disease

Conduction defects and arrhythmias are seen frequently in scleroderma patients and are thought to be a result of fibrosis or ischemia of the conduction system⁶⁰. While Zakopoulos et al.⁶⁸ found that there was no difference in the cumulative 24-hour heart rate and blood pressure when comparing scleroderma patients with control subjects, while Wranicz et al.⁶⁷ found that scleroderma patients had a higher mean heart rate. Depending on the underlying cardiac involvement, increased numbers and frequency of ventricular ectopic beats, as well as episodes of ventricular tachycardia, can be seen in scleroderma^{45,47}. Paradiso et al.⁵¹, using signal averaged electrocardiography, found that 46% of the scleroderma patients (vs 8% of control subjects) had late ventricular potentials (LVPs) and Morelli et al.⁴⁶ also found an increase in LVPs in scleroderma patients (20%) who frequently had a septal infarct pattern on their electrocardiogram.

Cardiac involvement with a cardiomyopathy and ventricular arrhythmias is cause for great concern in scleroderma given the increased likelihood for sudden death. Electrophysiologic studies are recommended in this patient population and AICD implantation is recommended in patients with inducible ventricular tachycardia or reduced LVEF.

Valvular Disease

Prior studies using echocardiography as well as studies on autopsy samples have suggested a relatively minor valvular involvement in SSc¹³. Nodular thickening of the mitral valve was shown in 38% of their autopsy subjects with SSc¹². Shortening of the chordae tendinae of the mitral valve has been noted as well as mitral and tricuspid valve vegetations some autopsy samples^{12,50,55,56}. Nodular thickening of the mitral and aortic valves with regurgitation and mitral valve prolapse have also been noted^{27,37,58}.

Conclusions

In summary, while the influence of scleroderma on cardiac function has been known for nearly a century, only recently have we begun to gain a new understanding of the prevalence and prognosis in this patient population. Through new and more refined imaging modalities as well as more frequent use of invasive hemodynamics we will be able to better assess patients for subclinical disease and gain new insight as to the long term prognosis in patients with SSc.

Moreover, early detection will allow us to improve quality of life and longevity in patients with cardiac involvement in scleroderma.

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