Cardiovascular complications of systemic sclerosis: What to look for

ABSTRACT

Systemic sclerosis, an autoimmune disease characterized by fibrosis of the skin and various internal organs, is associated with cardiovascular abnormalities including pulmonary hypertension, atherosclerosis, right and left ventricular dysfunction, arrhythmias, conduction defects, pericardial disease, and valvular heart disease. Clinicians caring for patients with this disease should regularly screen for cardiac symptoms, and patients with abnormal findings should be managed in conjunction with a cardiologist to optimally modify cardiovascular risks.

KEY POINTS

Pulmonary hypertension is common in systemic sclerosis and carries a poor prognosis. Patients with systemic sclerosis should be screened regularly with echocardiography, followed, when necessary, by right heart catheterization to detect it early.

Myocardial infarction and stroke are more common in patients with systemic sclerosis, and preventive measures are the same as for the general population.

Right ventricular dysfunction secondary to pulmonary hypertension is common in systemic sclerosis; left ventricular dysfunction is less so. Routine echocardiography should include assessment of right and left ventricular function.

Electrocardiography should be performed periodically, and urgently when indicated, to look for potentially dangerous arrhythmias.

AUTOIMMUNE RHEUMATIC DISEASES increase the risk of cardiovascular disease. In rheumatoid arthritis and systemic lupus erythematosus, the risk is driven primarily by the inflammatory milieu, leading to accelerated coronary and cerebrovascular atherosclerosis independent of traditional atherosclerotic risk factors.1–3 The extent of cardiovascular involvement in other rheumatologic diseases has been less well characterized but is an area of growing interest.

In this review, we focus on the cardiovascular complications of systemic sclerosis and review recommendations for monitoring these patients in clinical practice.

SYSTEMIC SCLEROSIS, AN AUTOIMMUNE RHEUMATIC DISEASE

Systemic sclerosis is an autoimmune rheumatic disease characterized by excessive extracellular matrix deposition leading to diffuse fibrosis, endothelial dysfunction, and microvascular injury. It is most common in North America, Southern Europe, and Australia,4,5 and it affects women more than men in ratios ranging from 3:1 to 14:1.6 The mean age at diagnosis is around 50.

The disease can affect the lungs (interstitial lung disease and pulmonary hypertension), the heart, the kidneys, and the gastrointestinal tract.

Systemic sclerosis has 2 main subtypes: limited cutaneous systemic sclerosis (formerly called CREST syndrome) and diffuse cutaneous systemic sclerosis. The limited cutaneous subtype is characterized by tightening of the skin of the distal extremities (below the elbows and knees) and face, while diffuse cutaneous systemic sclerosis can manifest as more exten-
sive skin tightening also involving proximal extremities and the trunk. Both subtypes can have an effect on the cardiovascular system.

Some cardiovascular risk factors such as dyslipidemia, diabetes mellitus, and high body mass index are less common in patients with systemic sclerosis than in patients with rheumatoid arthritis, while the rates of arterial hypertension, smoking, chronic obstructive pulmonary disease, osteoporosis, and neoplasms are similar between the 2 groups.7

HEART INVOLVEMENT HAS SERIOUS CONSEQUENCES

Overt cardiac involvement in systemic sclerosis is associated with a mortality rate of up to 70% over 5 years,8,9 and about one-fourth of deaths in patients with systemic sclerosis are from cardiac causes.10,11 Studies in Europe10,12 showed that many patients with systemic sclerosis have cardiac involvement detectable by magnetic resonance imaging even if they do not have clinical disease. Pulmonary arterial hypertension (PAH) is a complication of both subtypes of systemic sclerosis and portends a higher risk of death.8

Thus, it is critical for clinicians to understand the potential comorbid conditions associated with systemic sclerosis, particularly the cardiovascular ones, and to work closely with cardiologists to help optimize the evaluation and management.
Microvascular disease in systemic sclerosis is primarily driven by endothelial cell activation and injury, leading to overexpression of adhesion molecules, recruitment of immune cells, intimal fibrosis, and fibroblast proliferation (Figure 1). Abnormal vasoreactivity, a consequence of an imbalance between endothelium-derived vasoconstrictors and vasodilators, defective angiogenesis, and endothelial injury, leads to tissue ischemia and vascular endothelial growth factor expression, which initiates injury and fibrosis in the myocardium and in other organs. Fibrosis involves the myocardium, pericardium, and conduction system.

Myocardial involvement in systemic sclerosis is thought to be due mainly to abnormal vasoreactivity and microvascular abnormalities such as transient coronary artery spasm leading to repeated focal ischemia. Abnormal vasoreactivity has been demonstrated during cardiac catheterization: while mean coronary sinus blood flow in systemic sclerosis patients was normal at rest, vasodilator reserve was significantly reduced in patients with diffuse cutaneous systemic sclerosis after maximal vasodilation with dipyridamole. Additionally, endomyocardial biopsy showed fibrosis and concentric intimal hypertrophy with normal epicardial coronary arteries.

More research into other mechanisms of cardiovascular disease in systemic sclerosis is needed to allow for better preventive care for these patients.

Pulmonary arterial hypertension defined
PAH is defined as the combination of all of the following:
• Mean pulmonary artery pressure > 20 mm Hg at rest
• Normal pulmonary capillary wedge pressure (≤ 15 mm Hg)
• Pulmonary vascular resistance ≥ 3 Wood units on right heart catheterization.

Other causes of pulmonary hypertension such as interstitial lung disease, chronic pulmonary thromboembolic disease, and left heart disease must be excluded.

Remodeling in the pulmonary arteries
The events that lead to PAH in systemic sclerosis remain unclear but are believed to involve initial inflammation or endothelial injury that leads to a dysequilibrium between proliferative mediators and antiproliferative vasodilators. This dysequilibrium, along with endothelial dysfunction, causes an obliterator vasculopathy in the pulmonary artery branches and arterioles. Sympathetic overactivity, hypoxemia, and ischemia-reperfusion injury additionally promote vascular proliferation, fibrosis, and remodeling, leading to increased pulmonary vascular resistance, PAH, and increased right ventricular pressures.

The subtype of systemic sclerosis is an important factor in the development and progression of PAH. PAH appears to be the major cause of death in limited cutaneous systemic sclerosis, while interstitial lung disease is the major cause of death in diffuse cutaneous systemic sclerosis.

Pulmonary arterial hypertension is a late complication of systemic sclerosis
Data from the South Australian Scleroderma Registry revealed that PAH tends to be a
late complication of systemic sclerosis, occurring around 20 years after disease onset. In this study of 608 patients, no patient with diffuse cutaneous systemic sclerosis developed PAH.

Systemic sclerosis-related PAH initially follows an indolent course with few symptoms until right ventricular function deteriorates. Early in the disease, patients may experience nonspecific symptoms of fatigue, lightheadedness, and dyspnea on exertion. As it progresses, they tend to have worsening dyspnea and may experience exertional syncope, palpitations, and chest pain.

Physical findings may suggest elevated right ventricular pressure and right ventricular failure; these include a loud P2, a prominent jugular a wave, a tricuspid regurgitant murmur, jugular venous distention, and lower-extremity edema.27

Screening for pulmonary arterial hypertension in systemic sclerosis

Significant signs and symptoms usually occur late in the disease; thus, it is important to appropriately screen patients who are at risk so that they can begin aggressive treatment.

Doppler echocardiography is recommended by European and American guidelines to screen for PAH in patients who have systemic sclerosis, and most agree that screening is appropriate even if the patient has no symptoms. European consensus documents recommend that transthoracic echocardiography be done annually for the first 5 years of disease and be continued every year in patients at high risk, ie, those with anticientromere antibodies, anti-Th/To antibodies, or interstitial lung disease. Patients not at high risk of developing pulmonary hypertension should also have regular transthoracic echocardiography, though the exact timing is not defined. While American societies have not issued corresponding recommendations, many experts follow the European recommendations.

Worrisome features on echocardiography in asymptomatic patients should be followed up with right heart catheterization to assess mean right ventricular pressure. These include:

- Estimated right ventricular systolic pressure $\geq 40$ mm Hg
- Tricuspid regurgitant jet velocity $> 2.8$ m/s
- Right atrial enlargement $> 53$ mm
- Right ventricular enlargement (mid-cavity dimension $> 35$ mm).32

Although echocardiography is the most common form of screening, it gives only an estimate of right ventricular systolic pressure, which is imprecise. Other noninvasive markers are helpful and necessary to appropriately screen this population.

**Diffusion capacity.** The Itinerair study found that a diffusing capacity for carbon monoxide (Dlco) of 60% or higher has a high specificity in excluding PAH.

**Uric acid** has been found to be elevated in patients with systemic sclerosis-related PAH, and levels inversely correlate with 6-minute walking distance.34

**Other predictors.** N-terminal pro-B-type natriuretic peptide (NT-proBNP), left atrial volume, and the right ventricular myocardial performance index have also been shown to be independent predictors of PAH in patients with systemic sclerosis.35

**An algorithm.** The DETECT study enrolled patients at increased risk who had had systemic sclerosis longer than 3 years and a Dlco less than 60%. The investigators developed a 2-step algorithm to determine which patients should be referred for right heart catheterization to try to detect PAH earlier while minimizing the number of missed diagnoses and optimizing the use of invasive diagnostic right heart catheterization.

The first step was to assess serum values of anticientromere antibodies, NT-proBNP, and urate, and clinical features (telangiectasias), forced vital capacity, and electrocardiographic changes of right axis deviation to derive a prediction score. The second step was to assess surface echocardiographic features of the right atrial area and tricuspid regurgitation velocity.

This approach led to right heart catheterization in 62% of patients and was associated with a false-negative rate of 4%. Importantly, of the patients with PAH, 1 in 5 had no symptoms, and 33% had tricuspid regurgitation velocity less than 2.8 m/s. No single measurement performed well in isolation in this study.37

Thus, we recommend that, in addition...
to routine surface echocardiography, a multimodal approach be used that includes laboratory testing, clinical features, and electrocardiographic findings when screening this high-risk patient population.

**ATHEROSCLEROTIC DISEASES**

Although macrovascular disease has not typically been regarded as a significant systemic feature in systemic sclerosis, myocardial infarction and stroke are more common in patients with systemic sclerosis than in controls.\(^{38,39}\)

**Coronary artery disease in systemic sclerosis**

Man et al\(^{38}\) reported that the incidence of myocardial infarction in patients with systemic sclerosis was 4.4 per 1,000 persons per year, and the incidence of stroke was 4.8 per 1,000 persons per year, compared with 2.5 per 1,000 persons per year for both myocardial infarction and stroke in healthy controls matched for age, sex, and time of entry.

The Australian Scleroderma Cohort Study\(^{39}\) found a 3-fold higher prevalence of coronary artery disease in systemic sclerosis patients than in controls after factoring in traditional risk factors.

Aviña-Zubieta et al,\(^{40}\) in a cohort of 1,239 systemic sclerosis patients, estimated a hazard ratio (HR) of 3.49 for myocardial infarction and 2.35 for stroke compared with age- and sex-matched controls. Not all of these events were related to macrovascular atherosclerosis—vasospasm and microvascular ischemia may have played significant roles in the etiology of clinical manifestations.

Studies of coronary atherosclerosis in systemic sclerosis are limited. An autopsy study\(^{41}\) of 58 patients with systemic sclerosis and 58 controls matched for age, sex, and ethnicity found that the prevalence of atherosclerosis of small coronary arteries and arterioles was significantly higher in systemic sclerosis patients than in controls (17% vs 2%, \(P < .01\)). However, the prevalence of medium-vessel coronary atherosclerosis was similar (48% vs 43%).

Why patients with systemic sclerosis develop atherosclerosis has not yet been determined. Traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, and obesity are typically no more prevalent in systemic sclerosis patients than in controls,\(^{38,42}\) and thus do not explain the increased risk of atherosclerotic cardiovascular disease. There is some evidence that novel markers of atherosclerotic risk such as homocysteine,\(^{43}\) lipoprotein[a],\(^{44}\) and oxidized low-density lipoprotein\(^{45}\) are more prevalent in systemic sclerosis, but these results have not been substantiated in more extensive studies.

**Peripheral artery disease**

It remains unclear whether peripheral artery disease is more prevalent in systemic sclerosis patients than in controls.

Individual studies have shown mixed results in comparing carotid artery stenosis between systemic sclerosis patients and controls using carotid duplex ultrasonography,\(^{46}\) the ankle-brachial index,\(^{46-48}\) carotid intima-media thickness,\(^{49-54}\) and brachial flow-mediated dilation.\(^{51,53,55-58}\) A meta-analysis found that the carotid intima and media are significantly thicker in systemic sclerosis patients than in controls,\(^{59}\) and the magnitude of difference is similar to that in other groups at increased cardiovascular risk, such as those with rheumatoid arthritis, diabetes, and familial hypercholesterolemia.\(^{60-63}\)

A meta-analysis of brachial artery findings showed significantly lower flow-mediated dilation in systemic sclerosis patients than in controls.\(^{64}\)

Overall, given the inconsistency of study results, systemic sclerosis patients should be screened and managed as in other patients with peripheral artery disease, but the clinician should be aware that there may be a higher risk of peripheral artery disease in these patients.

**RIGHT AND LEFT VENTRICULAR DYSFUNCTION**

Many patients with systemic sclerosis have right ventricular dysfunction as a consequence of PAH.\(^{65}\) It is important to detect diastolic dysfunction in this population, as it may be an even stronger predictor of death than pulmonary hypertension on right heart catheterization (HR 3.7 vs 2.0).\(^{66}\)

Fewer patients have left ventricular dysfunction. In a multicenter study of 570 systemic sclerosis patients, only 1.4% had left ventricular systolic dysfunction on echocar-
diography, though 22.6% had left ventricular hypertrophy and 17.7% had left ventricular diastolic dysfunction. In the European League Against Rheumatism (EULAR) database, the prevalence of reduced left ventricular ejection fraction was 5.4%.

Though traditional echocardiographic screening suggests the prevalence of left ventricular dysfunction in systemic sclerosis patients is low, cardiac magnetic resonance imaging (MRI) may be more sensitive than echocardiography for detecting subclinical myocardial involvement. Cardiac MRI has been shown to detect evidence of myocardial pathology (increased T2 signal, left ventricular thinning, pericardial effusion, reduced left ventricular and right ventricular ejection fraction, left ventricular diastolic dysfunction, and delayed myocardial contrast enhancement) in up to 75% of systemic sclerosis cases studied.

Patients with systemic sclerosis should already be undergoing echocardiography every year to screen for PAH, and screening should also include tissue Doppler imaging to detect various forms of left and right ventricular systolic and diastolic dysfunction that may not be clinically apparent.

Though cardiac MRI can provide useful additional information, it is not currently recommended for routine screening in patients with systemic sclerosis.

### Arrhythmias and Conduction Defects

Patients with systemic sclerosis are prone to arrhythmias due to both conduction system fibrosis and myocardial damage.

Arrhythmias accounted for 6% of the deaths in the EULAR Scleroderma Trials and Research (EUSTAR) database.

In the Genetics Versus Environment in Scleroderma Outcome Study (GENISOS), 250 patients who had had systemic sclerosis for at least 3 years were studied during a period of approximately 6 years, during which there were 52 deaths, 29 of which were directly attributable to systemic sclerosis. Multivariable Cox modeling showed that 7 variables predicted mortality:

- Body mass index < 18.5 kg/m²
- Age ≥ 65
- Forced vital capacity < 50% predicted
- Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mm Hg
- Pulmonary fibrosis
- Positive anticentromere antibodies
- Cardiac arrhythmias.

The hazard ratio for death in patients with arrhythmias in this model was 2.18 (95% CI 1.05–4.50, P = .035). Thus, finding arrhythmias in systemic sclerosis patients can provide important prognostic information.

While resting electrocardiography in patients with systemic sclerosis most commonly shows sinus rhythm, 24-hour electrocardiographic monitoring has revealed nonsustained supraventricular and ventricular arrhythmias in a significant percentage. Although difficult to quantify in routine practice, parameters controlled by the autonomic nervous system including heart rate variability and heart rate turbulence have been shown to be impaired in systemic sclerosis, and these measures are associated with an increased risk of malignant arrhythmias and sudden cardiac death.

### Conduction Abnormalities

Conduction abnormalities occur in one-fifth to one-third of patients with systemic sclerosis. The most common abnormal conduction finding is left bundle branch block, followed by first-degree atrioventricular block. High-degree atrioventricular block is uncommon, though a few case reports of complete heart block thought to be related to systemic sclerosis have been published. An autopsy study showed that the conduction system is relatively spared from myocardial changes seen in systemic sclerosis patients, and thus it is speculated that the conduction disturbances are a consequence of damaged myocardium rather than damage to conduction tissue.

Given the array of electrophysiologic abnormalities that systemic sclerosis patients can have, it is critical to monitor all patients with routine (annual or biannual) electrocardiography; to take possible arrhythmia-related symptoms seriously; and to evaluate them with further workup such as Holter monitoring for 24 hours or even longer, event monitoring, exercise testing, or tilt-table testing.
**PERICARDIAL DISEASE**

Pericardial disease is clinically apparent in 5% to 16% of patients with systemic sclerosis; patients with limited cutaneous systemic sclerosis have more pericardial disease than those with diffuse cutaneous systemic sclerosis (30% vs 16%). Forty-one percent of systemic sclerosis patients have been shown to have pericardial effusion by echocardiography, but the effusions are typically small and rarely cause tamponade, though tamponade is associated with a poor prognosis.

Large pericardial effusions can develop before skin thickening and diagnosis of systemic sclerosis. Thus, systemic sclerosis should be considered in patients with pericardial effusions of unknown etiology.

In a small study, the pericardial fluid in systemic sclerosis was typically exudative, with lactate dehydrogenase greater than 200 U/L, a fluid-serum lactate dehydrogenase ratio greater than 0.6, and a fluid-serum total protein ratio greater than 0.5.

Pericardial effusion can be a sign of impending scleroderma renal crisis, and thus renal function should be carefully monitored in systemic sclerosis patients with pericardial effusion. Constrictive pericarditis and restrictive cardiomyopathy can rarely occur in systemic sclerosis and may more commonly present with symptoms.

Pericardial disease in systemic sclerosis should be treated in a standard fashion with nonsteroidal anti-inflammatory drugs. Corticosteroids are generally of limited benefit and should be avoided, especially in the setting of scleroderma renal crisis.

**VALVULAR HEART DISEASE**

Based on limited studies, the prevalence of significant valvular heart disease in systemic sclerosis does not seem to be higher than that in the general population. While patients with systemic sclerosis and CREST syndrome (calcinosi, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) have been shown to have a higher frequency of mitral valve prolapse and mild mitral regurgitation; these abnormalities do not often progress in severity, and thus their clinical significance is limited.

**RECOMMENDATIONS FOR CARE OF SYSTEMIC SCLEROSIS PATIENTS**

It is important for physicians caring for patients with systemic sclerosis to be aware of its most common cardiac manifestations, including left and right ventricular systolic and diastolic dysfunction, pulmonary hypertension, conduction abnormalities, arrhythmias, and cardiomyopathy.

**Look for volume overload**

On clinical examination, assess for clinical markers of volume overload such as distended neck veins, peripheral edema, or an abnormal blood pressure response to the Valsalva maneuver. These findings should prompt measurement of NT-proBNP, and may warrant prescription of a diuretic.

**Electrocardiography to investigate arrhythmias**

Electrocardiography should be done if patients describe symptoms of palpitations, and should also include continuous rhythm monitoring with Holter or event monitoring, depending on the frequency of symptoms. Otherwise, patients should routinely undergo electrocardiography once or twice a year.

Q waves are common in systemic sclerosis patients (especially those with diffuse cutaneous systemic sclerosis), notably in the precordial leads, and can occur without coronary artery disease. Symptoms such as presyncope should be further investigated with Holter monitoring and tilt-table testing.

**Assess, modify traditional risk factors**

Subclinical atherosclerosis as detected by carotid intima-media thickness is as common in systemic sclerosis as in rheumatoid arthritis. However, traditional risk indices such as SCORE (Systematic Coronary Risk Evaluation), QRISK2, and the American College of Cardiology/American Heart Association indices may underestimate risk in patients who have systemic sclerosis.

Strict hypertension control should be the goal for all systemic sclerosis patients. Though there are no specific guidelines on which antihypertensive medications are preferred, calcium channel blockers or angiotensin II receptor blockers, which are typically used to treat systemic sclerosis-related Raynaud phe-
A risk of arrhythmias may prompt a conversation about an implantable cardiac defibrillator

nomenon, may be appropriate.

**Statins** reduce vascular complications and are generally well tolerated in patients with systemic sclerosis.91,92

**Aspirin is not recommended for routine primary prevention** in view of data suggesting that its benefits in diabetic patients are counterbalanced by increased bleeding risk.93

**Echocardiography to detect pulmonary arterial hypertension**

At this time, guidelines for monitoring for cardiovascular manifestations in systemic sclerosis patients are limited. The only well-defined ones are European consensus guidelines, which suggest annual transthoracic echocardiography for the first 5 years after systemic sclerosis is diagnosed and continued annual screening in patients at risk of developing PAH.31

We support this strategy, with annual screening for the first 5 years followed by surveillance echocardiography every 2 to 3 years unless there is a high risk of PAH. Specific attention should be paid to right ventricular diastolic function, right atrial volume, and right ventricular myocardial performance index.

Emerging data suggest that the addition of global longitudinal strain of ventricles to routine echocardiography can help detect subclinical cardiac risk.94 Although further study is needed into the predictive value of global longitudinal strain, it is a low-cost and noninvasive addition to standard echocardiography that can help guide risk stratification, and thus we recommend that it be part of the echocardiographic examination for all systemic sclerosis patients.

**Pulmonary function testing.** In addition to screening for PAH with echocardiography, we recommend obtaining baseline pulmonary function tests, including DLCO, at the time systemic sclerosis is diagnosed, with repeat testing annually.

**Magnetic resonance imaging**

While echocardiography is the gold standard for monitoring systemic sclerosis patients, cardiovascular MRI may have a role in identifying those at higher risk of dangerous arrhythmias such as ventricular tachycardia and ventricular fibrillation. In addition to assessing ventricular function, MRI can detect myocardial inflammation, ischemia, and fibrosis that may predispose a patient to develop ventricular tachycardia or fibrillation.95 Variables such as T1/T2 mapping, extracellular volume fraction, T2 signal ratio, and early vs late gadolinium enhancement can help identify patients who had past ventricular tachycardia or fibrillation.96

Finding an increased risk of arrhythmias may prompt a conversation between the patient and the physician about the need for an implantable cardiac defibrillator.

If cardiac MRI is available and is reimbursed by the patient’s insurance carrier, physicians should strongly consider obtaining at least one baseline scan in systemic sclerosis patients to identify those at risk of highly fatal arrhythmias.

**Teamwork is needed**

Systemic sclerosis has not traditionally been associated with cardiovascular disease to the extent of other rheumatic conditions, but the cardiovascular system can be affected in various ways that can ultimately lead to an early death. These manifestations may be asymptomatic for long periods, and overt clinical disease portends a poorer prognosis.

Primary care physicians managing these patients should be aware of the cardiovascular complications of systemic sclerosis and should implement appropriate screening tests in conjunction with rheumatologists and cardiologists. It is also essential for general and subspecialty cardiologists to understand the broad spectrum of organ system involvement that can affect systemic sclerosis patients and to tailor their investigation and management recommendations accordingly. By designing a multidisciplinary approach to the treatment of systemic sclerosis patients, physicians can help to optimize cardiovascular risk modification in this vulnerable population.

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ADDRESS: Preethi Mani, MD, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; mani@ccf.org; pmani87@gmail.com

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