

Cardiac involvement in systemic sclerosis

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❖ **S**ystemic sclerosis (SSc) is a systemic disease characterized by microvascular injury and diffuse fibrosis of the skin and internal organs.

- ❖ Among them, **cardiac involvement** (CI) has drawn attention in the last years. CI may be a direct consequence of SSc (**primary** CI) or **secondary** to other organ involvement: concomitant kidney and/or pulmonary vascular/interstitial *disease* ,
- ❖ Right ventricular dilatation or hypertrophy due to pulmonary arterial hypertension (PAH).

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- SSc can affect all structures of the heart. A broad variety of clinical and subclinical manifestations have been related to primary CI in SSc patients, including:
 - **M**ycocarditis, myocardial fibrosis, ventricular systolic and diastolic dysfunction, myocardial ischemia and coronary artery abnormalities,
 - **P**ericarditis and pericardial effusion,
 - **A**rrhythmias, conduction system abnormalities(including brady- and tachyarrhythmias)
 - and rarely, primary Valvular involvement.

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- ➡ Autopsy studies and cardiac MRI studies have shown that subclinical cardiac involvement is extremely common.

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- The prevalence of cardiac involvement differed greatly across the studies, from 7 to 39%, although there was significant heterogeneity in the definitions of cardiac disease.



It is difficult to be estimated accurately for multiple reasons including

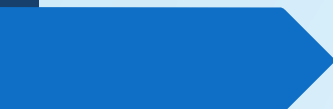
- ▶ the long asymptomatic course of the disease,
- ▶ the variety of clinical manifestations,
- ▶ the diagnostic method,
- ▶ and the definition used to characterize the disease.



➡ Heart involvement

is often asymptomatic and insidious, but when it becomes clinically evident it is a well-recognized poor prognostic factor, responsible for up to 30% of SSc-related mortality.

Clin Exp Rheumatol 2016; 34 (Suppl. 100): S3-S13.



The pathogenesis of primary CI is related to myocardial fibrosis:

- *due to a primary systemic myositic disease , autoimmune myocarditis*
- *repeated focal ischaemic injuries due to microvascular coronary abnormalities*
(dysfunction and/or structural damage of the microvascular bed)
- *Infectious myocarditis*

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- The hallmark of cardiac involvement in SSc is cardiac tissue fibrosis with patchy fibrotic deposits, **equally distributed** throughout left and right ventricular myocardium .

Patchy myocardial fibrosis

It is distinguishable from the fibrosis associated with coronary atherosclerotic disease . Focal fibrosis in a **SSc** patient involving the **mid and epicardial myocardium**, sparing the subendocardium.



Myocardial fibrosis is thought to result from recurrent vasospasm of small vessels

(abnormal vasoreactivity)

and is often associated with **contraction band necrosis**, a histological lesion indicative of myocardial ischemia (MI) followed by reperfusion .

Ischemia–reperfusion injury

As the disease progresses, small perfusion defects can culminate in irreversible tissue damage, myocardial fibrosis and dysfunction.

Likely Sequence of Events in Ischemia/Reperfusion Injury

Aerobic metabolism interrupted

Metabolites accumulate

Oxygen available with reperfusion

Aerobic metabolism resumes with generation of $O_2^{\cdot -}$ and H_2O_2

Antioxidant system overwhelmed

Oxidative cell damage including lipid peroxidation

Cell damage stimulates synthesis of inflammatory cytokines

Synthesis of IL-8 and adhesion molecules

Neutrophils and macrophages attack reperfused tissue

Cytokines act systemically causing remote injury to lungs and other

Possible Interventions

Rapid reperfusion

Inhibitors to prevent accumulation

Free radical defense mechanisms, SOD, radical scavengers, metal chelators

**IL-1 receptor antagonist
IL-1 antibodies
TNF- α soluble receptor
TNF- α antibodies**

Antibodies and inhibitors to adhesion molecules



Aerobic metabolism interrupted



Restoration of blood flow

Aerobic metabolism resumes



Generation of Reactive Oxygen Species (ROS)

hydrogen peroxide (H₂O₂), superoxide anion

Antioxidant mechanisms overwhelmed



Oxidative cell damage

lipid peroxidation

Synthesis of inflammatory cytokines

further inflammation (Neutrophil + macrophage-mediated damage)

Cytokines act systemically

Endothelial dysfunction

Endothelial cell activation is the central immunologic and inflammatory disturbance resulting in the characteristic **widespread vasculopathy**, typical for SSc. It appears that endothelial injury occurs early in the course of the disease as SSc individuals exhibit early signs of vasculopathy such as Raynaud's phenomenon associated with morphological changes in capillaries before or at disease onset.



Although the identity of the initial stimuli remains unclear,

endothelial cell insult is considered the **main driver of**

vascular changes, excess matrix production and

connective tissue accumulation characterizing SSc.





Activated endothelial cells upregulate the expression of adhesion molecules and promote inflammatory cell migration, intimal fibrosis and fibroblast proliferation leading to disruption of the balance between turnover and deposition of extracellular proteins and to the derangement of endothelium homeostasis by inducing the **production of vasoconstriction mediators**—mainly endothelin-1—and by **downregulating the synthesis of vasodilators** such as nitric oxide and prostacyclin .



The earliest, most frequent and characteristic echocardiographic feature of SHD is the **left ventricular diastolic dysfunction**, and multiple symptoms of SSc patients (including decreased exercise capacity, dyspnoea, and decompensation) are strongly related to **LV filling pressure**.

Left ventricular diastolic dysfunction is related to the degree of myocardial fibrosis .



Diffuse fibrosis of right and left ventricles can lead to depressed **myocardial contractility**, which can be undetected for many years.

Left ventricular ejection fraction is not sensitive enough to evaluate subclinical myocardial dysfunction .

However, **tissue Doppler echocardiography** and **cardiac magnetic resonance imaging** are able to detect these defects in myocardial function at asymptomatic stages .



Relying on **LVEF alone** can be misleading, since SSc hearts may have a **restrictive physiology** with relatively intact LVEF, but significant diastolic dysfunction .

Bone Marrow Transplantation (2017) 52, 1495–1503



In daily clinical practice, cardiac evaluation of SSc patients is based on the results from:

- ☐ clinical examination,
- ☐ electrocardiography (ECG)
- ☐ and TTE,
- ☐ and in the presence of palpitations or abnormalities on ECG, 24 h Holter monitoring .

Cardiovascular magnetic resonance (CMR) imaging enables detection of various features including

- inflammatory hyperemia and edema, myocyte necrosis and scar,
- changes in ventricular size and geometry,
- regional and global wall motion abnormalities,
- ventricular kinesic pattern (LV and RV hypokinesia, dyskinesia, dyssynchrony,
- diastolic restriction
- ventricular function
- and identification of accompanying pericardial effusion .



Differentia.... SSc-cardiomyopathy from IHD

The pattern of late gadolinium enhancement (LGE) in myocarditis can generally be distinguished from that in ischemic cardiomyopathy. In myocarditis, LGE preferentially involves the

epicardium and mid myocardium

with sparing of the endocardium. In ischemic cardiomyopathy, LGE reflects the distribution of myocardial infarction, which typically involves the endocardium with variable extension into the mid myocardium and epicardium.



Therapeutic intervention

No specific guidelines

have been established for treatment of cardiac manifestations in SSc.

Early treatment with **calcium channel blockers**, **angiotensin-converting enzyme inhibitors**, and **endothelin receptor antagonists**, can be beneficial for some patients on myocardial perfusion and contractility, as they improve cardiac microcirculation .



phosphodiesterase-5 (PDE5) inhibitors may provide benefit to SSc patients, by modifying coronary microcirculation and alleviating cardiac ischemic injury.

Rheumatol Int (2017) 37:85–95

TABLE I. POSSIBLE TARGETED THERAPEUTIC APPROACHES IN SYSTEMIC SCLEROSIS (INCLUDING AGENTS UNDER EVALUATION)

Immune-inflammatory target	Agent to the target
CD-20	Rituximab
TNF- α	Adalimumab, infliximab, etanercept
CD80/CD86	Abatacept
IL-6	Tocilizumab
IL-2R α	Basiliximab
IL-1	Rilonacept
BLYS	Belimumab
LFS1/ICAM1	Efalizumab
CCR2	MLM-1202
α MSH, IL-10, CCL2	AIMSPRO (HCS)
LPA1	ACT12339
Ig	Immunoglobulin IV
Vascular target	Agent to the target
ETA/ETB receptor	Bosentan, Macitentan
ETA receptor	Ambrisentan, Zibotentan
cGMP agonist	Riociguat
IP receptor agonist	Selexipag



More recently, anti-endothelin-1 (ET) receptor type-1 (ETAR) autoantibodies have been studied in patients with SSc.

The antibodies are agonistic for endothelin-1 (ET1) and therefore exhibit functional properties, which may contribute to SSc pathogenesis.



Small vessel disease dominates the pathophysiology and clinical manifestations of SSc but there is increasing interest in large-vessel involvement, particularly atherosclerotic cardiovascular disease (CVD).



Impairment of coronary microvascular circulation and cardiac tissue fibrosis are the hallmark of SSc-related myocardial dysfunction.

Macrovascular involvement was thought to have a lesser effect on CVD and overall morbidity. However, recent data and case reports suggest that coronary and cerebral vascular disease might be at least partially responsible for high morbidity and mortality rates associated with cardiac disease among SSc subjects .

Rheumatol Int (2017) 37:85–95

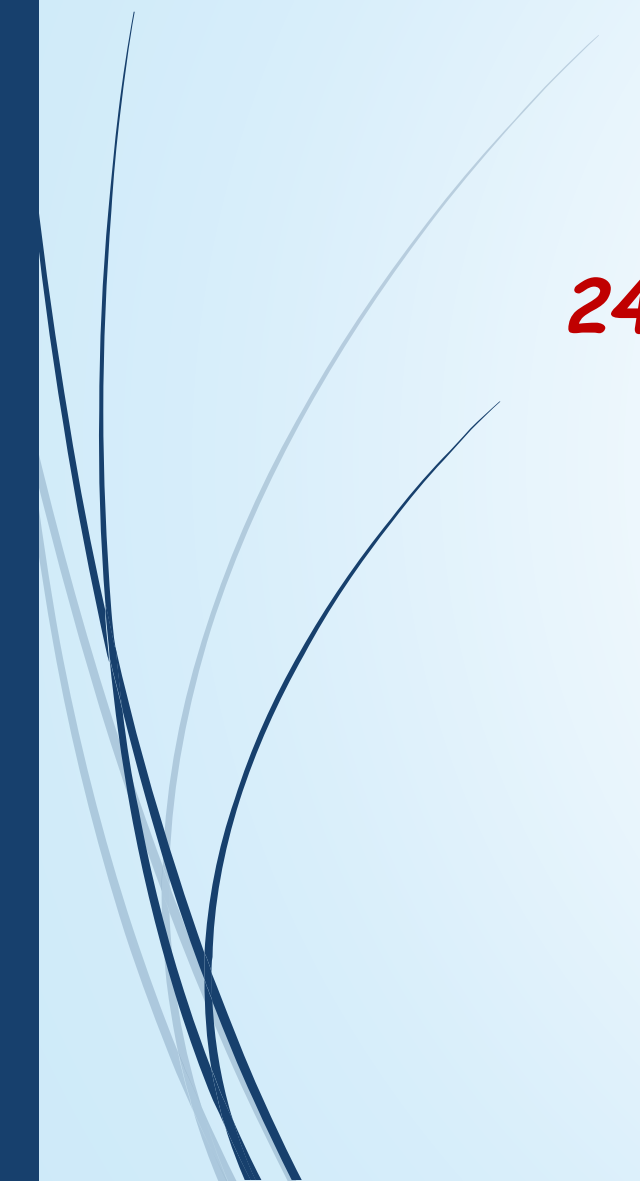


Endothelial dysfunction in SSc patients is not confined to the coronary microcirculation, but also extends to large peripheral conduit arteries.



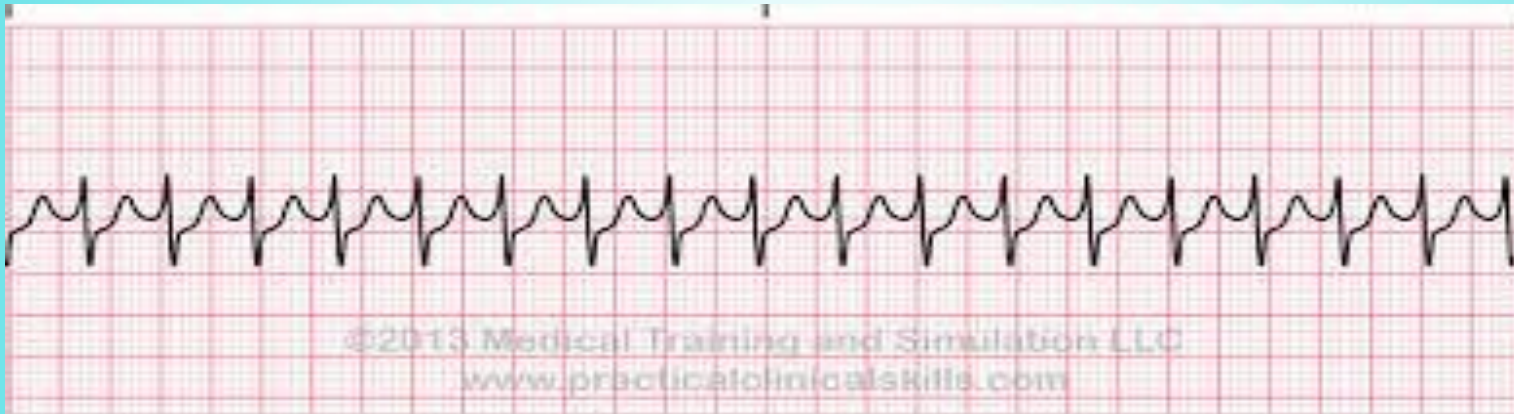


Arrhythmias and **conduction defects** are important and frequent manifestations of cardiac involvement in patients with SSc. These abnormalities may be mild, but can also lead to a fatal outcome. Early recognition of life-threatening ventricular arrhythmias may be crucial in improving the overall prognosis of SSc patients.



24-h Holter ECG monitoring in SSc patients:

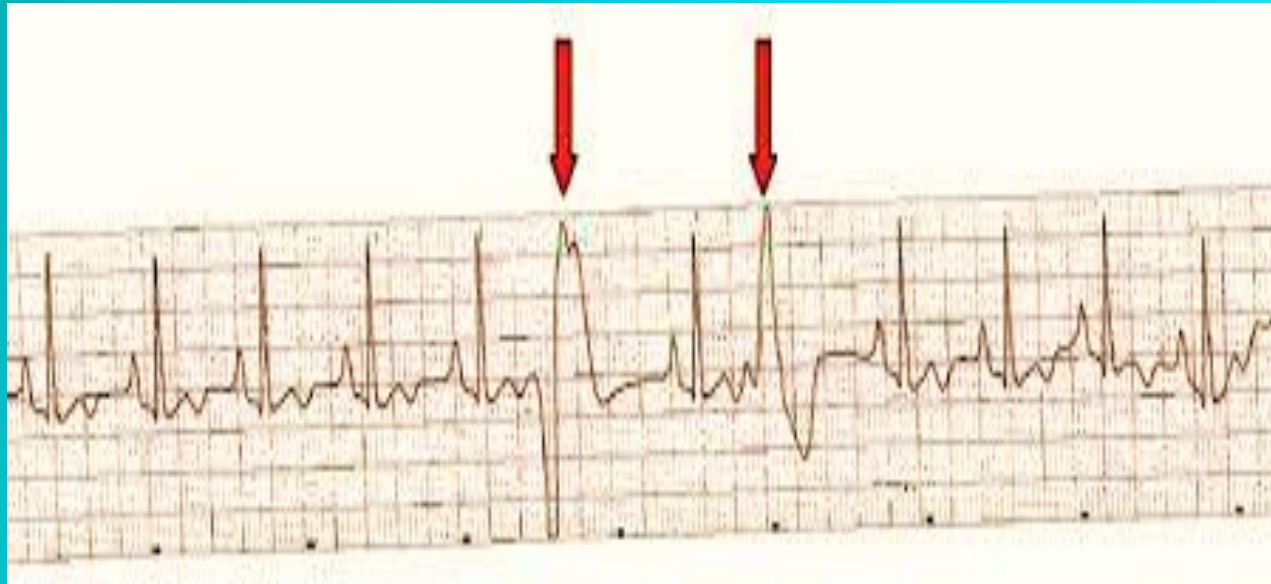
supraventricular tachycardia (SVT)



Premature atrial contractions



multiform ventricular premature beats



first-degree atrioventricular block



Third-degree atrioventricular block

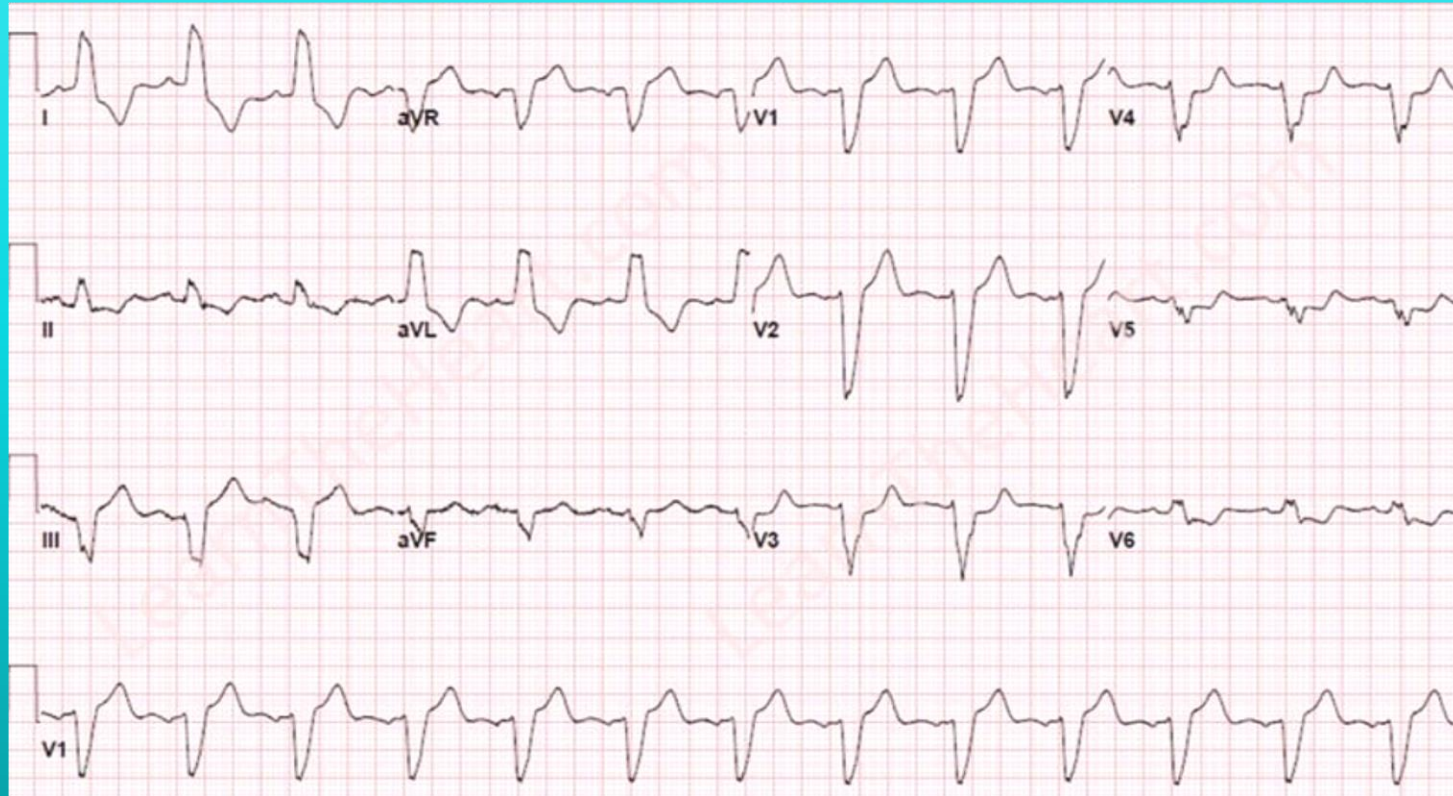




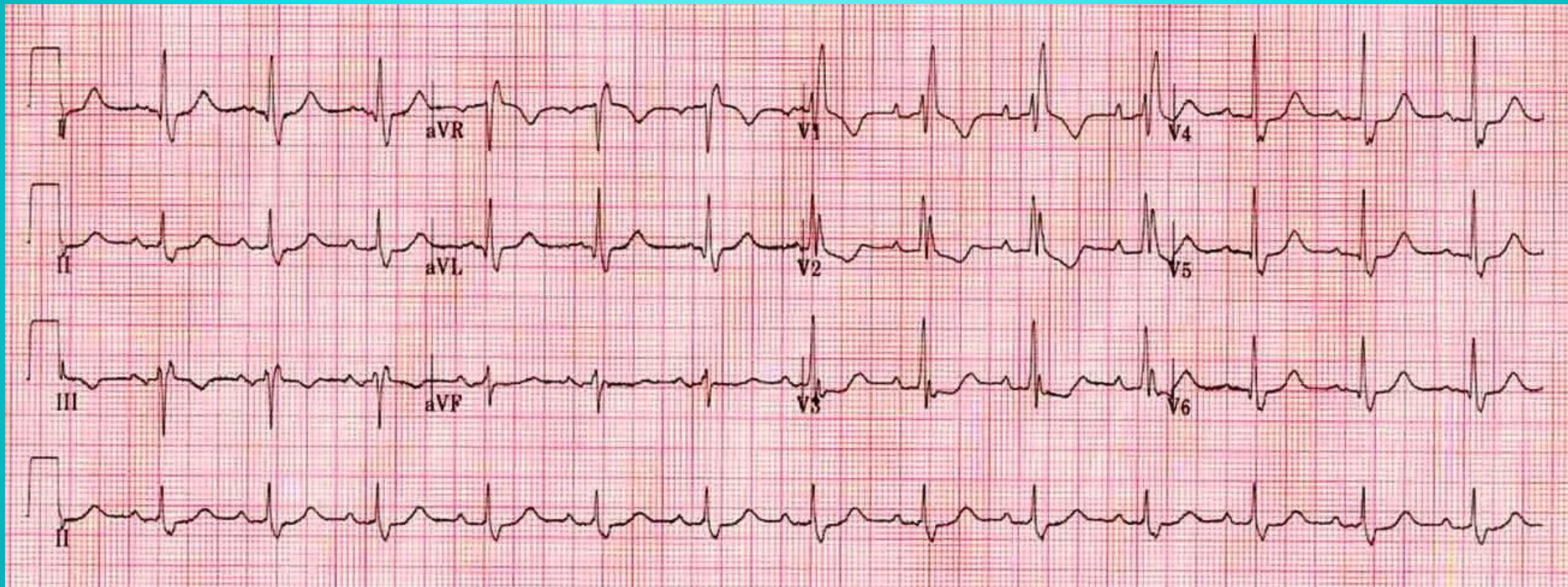
Conduction abnormalities

- ❖ Conduction system alterations are present in about 20% of patients.

left bundle branch block



Right bundle branch block

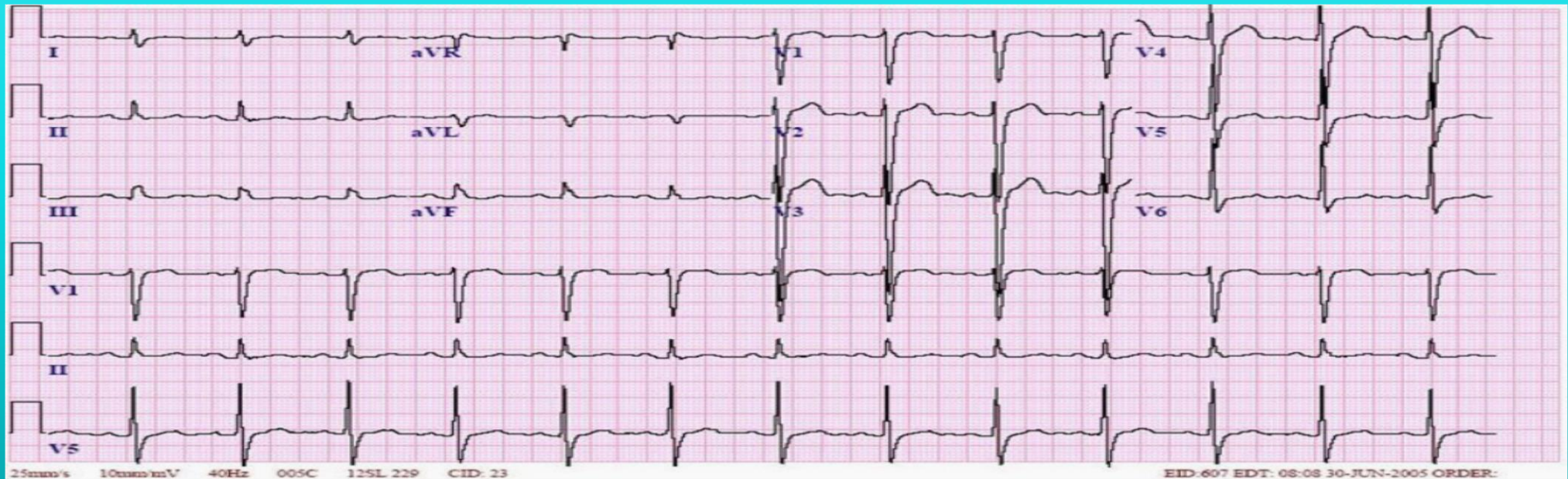




➡ **Right bundle** branch block has been recently described to be an independent predictor of mortality in this group.

ESC Heart Failure 2017; 4: 365–370

Intra ventricular conduction disturbances





Intra ventricular conduction disturbances in SSc are clinically relevant, as they have been associated with the future development of AV block and other rhythm disturbances .

Rheumatology 2017;56:882-895



In addition **QTc prolongation**, which can lead to life-threatening tachyarrhythmias, has also been reported.

Septal infarction pattern

ECG abnormality associated with SSc, related to abnormal perfusion in the septum and anteroseptal wall in the absence of extramural coronary artery disease.



**Despite the very frequent occurrence of ventricular arrhythmias,
sudden cardiac death is not very common in SSc.**

Rheumatology 2014;53:1172-1177



Pathophysiological alterations

The majority of conduction defects appear to be a consequence of **damaged myocardium** rather than specific damage to the proximal portion of the **specialized conduction tissue**. The conduction tissue of the heart was relatively spared from injury by the SSc disease process when compared with the changes seen within the contracting myocardium.



Cardiac diagnostic workup in patients with SSc for investigations of electrical disturbances

Clinical manifestation:

- Fatigue
- Palpitations
- Syncope, fall
- Dizziness



Electrical assessment:

➤ **Routine:**

- CV risk factor assessment
- Standard 12-lead ECG
- 24-h Holter monitoring

➤ **Second level:**

- Exercise testing
- Upright tilt-table testing
- Invasive electrophysiological studies



Heart assessment



Routine:

- ▶ Doppler echocardiography
- ▶ Tissue Doppler echocardiography
- ▶ Natriuretic peptides



Second level:

- ▶ Coronary angiography
- ▶ Right heart catheterization
- ▶ Cardiac MRI

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- *Implantable cardioverter defibrillators (ICDs)*,
 - which monitor the cardiac rhythm and can deliver competing pacing stimuli and low- and high-energy shocks, have been used effectively in selected patients to prevent malignant ventricular arrhythmias. There is no specific recommendation in SSc patients.



Catheter ablation therapy :

It should be considered as first-line therapy in patients with recurrent re-entrant tachycardia or atrial flutter, in patients with symptomatic, sustained, monomorphic ventricular tachycardia resistant or intolerant to pharmacological treatment and in patients with recurrent symptomatic atrial fibrillation despite antiarrhythmic drugs.

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- *Pacemaker implantation: is the treatment of choice for complete heart block and other serious bradyarrhythmias.*



Pericardial involvement

Symptomatic pericarditis occurs in 7 to 20 percent of patients with SSc, but pathologic evidence of pericardial involvement is observed in 70 to 80 percent at autopsy.

Pericardial effusions may be small or large and can develop rapidly.



Pericardial involvement is thought to be immune-mediated, although concomitant infection may play a role in some cases. While some patients may manifest with the typical signs and symptoms of pericarditis (fever, pleuritic chest pain) or a hemodynamically significant effusion (dyspnea, fatigue, hypotension), *many are incidentally found to have pericardial involvement.*

Cardiac tamponade and constrictive pericarditis are possible, but rare, complications.



The treatment approach to pericardial involvement :

- ❑ Dependent on symptoms. When a patient with pericardial involvement is asymptomatic, treatment is essentially that of the underlying systemic disease. Patients with a hemodynamically significant pericardial effusion should have the fluid drained (eg, pericardiocentesis or pericardiotomy). Most patients with symptoms of acute pericarditis: colchicine .



Case presentation



A 55 year - old woman with a 9 - year medical history of SSc developed exertional dyspnea **NYHA** Functional class III and palpitation for 1- 2 weeks.

Tracing back her past medical history , one year ago she underwent coronary angiography and right heart catheterization which revealed normal epicardial coronary arteries and normal pulmonary artery pressure. Also ,prior trans-thoracic echocardiography showed that normal left and right ventricular systolic function .



On admission , she was afebrile , pulse was 115 beats per minute and blood

pressure was 104/74 mmHg . Auscultation did not reveal any cardiac murmur or rub .

The electrocardiogram (ECG) on presentation demonstrated sinus tachycardia without significant ST-T wave changes .

Blood tests revealed elevated Pro-Brain natriuretic peptide (Pro-BNP),normal ESR and CRP.



The trans-thoracic echocardiography including tissue - Doppler imaging revealed severely impaired left ventricular systolic function [**left ventricular ejection fraction (LVEF) of 20%**] with marked regional wall motion abnormalities including severely hypokinetic LV apex , inferior , inferoseptal and anteroseptal walls . Left ventricular wall thickness and dimension were within normal levels .



Other findings were mild pericardial effusion and mild to moderate right ventricular enlargement with moderate right ventricular systolic dysfunction.



We diagnosed her as **acute myocarditis** and she was treated with conventional medical treatment for ventricular dysfunction in line with current guidelines on heart failure ,and immunomodulatory therapy .

She treated with loop diuretic ,angiotensin receptor blockade ,beta -adrenergic blockade and aldosterone receptor antagonist .



Intravenous immunoglobulin (IVIg) was given as
immunomodulatory therapy.

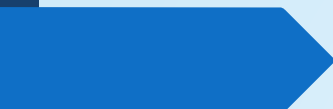


Repeat trans-thoracic echocardiogram 4 weeks after the start of treatment showed an improvement of left ventricular systolic function with an **ejection fraction of 35%** .

This improvement continued over the next few weeks .

A cardiac **MRI 3 months after the start of treatment**

(3 cycles of monthly IVIG) showed evidence of localized myocardial inflammation (edema) in the inferoseptal segments , normal LV size with mildly reduced systolic function and normal RV size with mild to moderately reduced systolic function .



After 6 months (receiving a total of 6 courses of high dose IVIG), we observed complete recovery of ventricular contractile function.

Echocardiogram 6 months post - initiation of treatment showed complete recovery of left ventricular systolic function (LVEF 55%).

In addition , right ventricular systolic function was normal , tricuspid annular plane systolic excursion (TAPSE) = 25 mm , Doppler tissue imaging septal velocity , pulsed wave (DTI s') = 17 cm/s .



At 9 month follow up , left ventricular systolic function was normal (LVEF 55%). It was our first experience to treat acute myocarditis in a scleroderma patient with high dose IVIG with good response .



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- **Myocarditis** is an inflammatory disease of the myocardium .
 - **Inflammatory cardiomyopathy** is defined as myocarditis accompanied by cardiac dysfunction.



Diagnosis

Endomyocardial biopsy (EMB) is the gold standard .

Using current histological, immunological, immunohistochemical and molecular tools, it provides differentiation between **infectious and non-infectious myocarditis.**

European Heart Journal (2017) 38, 2649–2662



Autoimmune myocarditis should be managed by immunosuppressive treatment, while heart failure, arrhythmia, and conduction disturbances should be treated according to current guidelines.

European Heart Journal (2017) 38, 2649–2662



➡ Intravenous immune globulin

- ❖ Intravenous immune globulin (IVIg) has antiviral and immunomodulatory effects.
- ❖ has no major side effects
- ❖ IVIG may be used in both viral and autoimmune forms.



CASE 2

- ❖ RV dilatation independent from pulmonary hypertension
 - ❖ RV involvement as a primary RV cardiomyopathy
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- A 41-year-old female with a 8-year history of dcSSc .
 - Palpitations along with lightheadedness and dizziness.
 - She was found to have typical atrial flutter with rapid ventricular response.

Past history :

Her echocardiogram **1 year ago** showed:

normal left ventricular diameter and wall thickness, left ventricular ejection fraction 55%,

normal RV size and systolic function,

right atrial (RA) dilation,

mild to mod... tricuspid regurgitation

and PAP:30-35 mmHg.

Right heart catheterization showed Normal PA pressure.



Her echocardiogram showed:

normal left ventricular diameter and wall thickness,

left ventricular ejection fraction 50%,

mild RV dilation, mildly reduced RV systolic function,

right atrial (RA) dilation,

mod...tricuspid regurgitation

and PAP:33 mmHg.



Cardiac MRI revealed:

RA and RV dilation as well as RV systolic dysfunction.

There was RV interstitial fibrosis and edema .

Normal LV size;LV EF:48%

In light of these findings, we considered the patient's symptoms to be related to SSc-associated RV cardiomyopathy from RV fibrosis.

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- A case of SSc induced RV cardiomyopathy in a patient with normal PA pressures .
 - Preferential RV fibrosis on cardiac MRI and consequent RV dysfunction in a patient with scleroderma. Therefore, RV dysfunction in scleroderma patients may not always be a consequence of pulmonary hypertension.

