Assessment of heart involvement

C. Ferri¹, M. Emdin², H. Nielsen³, P. Bruhlmann⁴

ABSTRACT
Cardiac involvement frequently occurs in systemic sclerosis (SSc), contributing to the occurrence of symptoms, namely dyspnoea, fatigue, palpitations, and in some instances to the clinical evolution and prognosis of the disease. A thorough baseline screening of heart functioning and appropriate follow-up monitoring is therefore mandatory in all SSc patients. This consists of various simple, non-invasive ambulatory diagnostic procedures (visit, electrocardiogram, chest X-ray, Doppler-bi-dimensional echocardiogram), which provide information on the presence of rhythm and conduction disturbances, cardiac morphology and function, as well as on the possible presence of pulmonary hypertension (PH). When needed, added tests may be carried out, including long-term ambulatory electrocardiographic recording, assessment of cardiopulmonary performance by the six-minute walking test or cardiopulmonary stress test, cardiac catheterization (mandatory to confirm and better estimate PH), cardiac magnetic resonance imaging, and nuclear studies of myocardial function and perfusion.

Introduction
Scleroderma heart involvement (SHI) is classically subdivided into two types: primary SHI and SHI secondary to either lung or kidney involvement. It represents one of the most frequent visceral complications of systemic sclerosis (SSc) and affects the overall prognosis of the disease (1, 2).

Pathology and pathophysiology
The pathological hallmark of SHI is myocardial fibrosis (3-6), which involves both ventricles with a "patchy" distribution and can be distinguished from that occurring in atherosclerotic coronary artery disease by a number of histological features, such as the absence of a link to any single coronary artery and of typical hemosiderin deposits and involvement of the subendocardial layers. In addition, unlike infiltrative disorders of the myocardium, it is not the result of an excess deposition of interstitial material, but merely replaces damaged, necrotic muscle cells. Nevertheless, thickening of the septum and posterior wall and asymmetric septal hypertrophy have been detected in SSc patients (6-9), even in the absence of systemic or pulmonary hypertension. However, it should be stressed that pulmonary hypertension is often subclinical in the patient and may be ignored in autopsy investigations (2). Coronary artery disease in SSc is characterized by small intramyocardial vessel involvement. The prevalence of atherosclerotic coronary artery disease in SSc patients is comparable to that observed in the general population (2). Nevertheless, at autopsy Bulkey et al. (10) detected myocardial infarction in 9/52 SSc patients with normal coronary arteries and found in 7 of them a distinct lesion, i.e. 'contraction band' myocardial necrosis, suggestive of ischemia/reperfusion damage. Subsequently, Follansbee et al. (4) pointed out that this lesion, along with severe fibrosis, is mainly seen in SSc patients with 'primary' SHI. Finally, pericardial disease occurs in a significant percentage of SSc patients, but is often asymptomatic (2, 5, 11, 12).

Cardiac involvement in SSc is likely to result from the general pathogenetic mechanism(s) thought to play a role in the disease (1, 2). A "myocardial Raynaud's phenomenon" involving unaltered small arteries has been hypothesized, but conflicting results have been reported. On the one hand, reversible perfusion defects have been detected in a significant percentage of SSc patients. On the other hand, coronary vasodilator reserve has been found to be markedly reduced in SSc (13-21). One might hypothesize that reversible coronary arteriolar vasospasm plays a role.
**Palpitations**

**Pulmonary artery pressure**

**Class III** Severe limitation of physical activity

**Chest pain**

**Dyspnoea (NYHA scale)**

Diagnostic approach. In addition, in older patients it may be difficult to distinguish from more common causes of heart disease, such as atherosclerosis or hypertension. The manifestations of SHI reflect the following underlying alterations: autonomic neuropathy, myocardial fibrosis, small intramyocardial coronary arteries involvement, and pericardial involvement. Autonomic neuropathy in SSc has been reported by various authors using conventional laboratory tests (22-28). A significantly higher heart rate and lower circadian and spectral indexes of heart rate variability (29) are seen in SSc patients compared with controls. Interestingly, tachycardia, a low circadian heart rate variability, and spectral power values have been reported to predict higher mortality (28). These abnormalities suggest that autonomic cardiac neuropathy may represent an important prognostic feature which should be looked for in any SSc patient.

Myocardial fibrosis causes both systolic and/or diastolic left ventricular dysfunction. Clinically overt heart failure is uncommon in SSc patients, except when there is severe systemic hypertension, often associated with scleroderma renal crisis (2,11,12). Different degrees of right heart failure, including cor pulmonale, may be linked to pulmonary arterial hypertension. On the contrary, an abnormally reduced left ventricular ejection fraction, that is more pronounced during exercise, may be detected in a significant percentage of SSc patients (13, 30-32). Similarly, impaired left ventricular filling is frequently found onDoppler echocardiography (9, 33-35). Left-sided diastolic dysfunction, as shown by an inversion of the E/A ratio, is more pronounced in patients with predisposing conditions such as systemic or pulmonary hypertension. A high prevalence of right-sided diastolic abnormalities, as expressed by the tricuspid E/A ratio inversion, has been reported in SSc patients unrelated to the SSc subset, and was independently correlated with both pulmonary hypertension and left ventricular diastolic dysfunction (36).

Conduction system defects, as evaluated by resting EKG, are detectable in about 25% of SSc patients (37-39); in particular, PR interval prolongation, left anterior fascicular block, and intraventricular conduction defects were the most common findings. On the whole, the prevalence of conduction disturbances on 24-hour ambulatory EKG (Holter) monitoring is significantly higher than on resting EKG (38, 39). Finally, this prevalence increases during the follow-up (37). Moreover, a high prevalence (70%) of conduction system abnormalities was observed in a subgroup of unselected patients undergoing intra-cardiac electrophysiologic study.

Arrhythmias frequently occur in the SSc patient and can be responsible for sudden death (2, 38, 39). Their prevalence is significantly higher on 24-hour ambulatory EKG monitoring with respect to rest EKG. Supraventricular tachycardia is the most frequent finding, while ventricular arrhythmias, including monomorphic or coupled extrasystoles and runs of ventricular tachycardia are

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**Table I.** Prevalence of different manifestations of scleroderma heart involvement.

<table>
<thead>
<tr>
<th>Autopsy studies</th>
<th>Clinical studies</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>% range</td>
<td>% range</td>
<td></td>
</tr>
<tr>
<td>Pericardial disease</td>
<td>33-72</td>
<td>11-41</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17*</td>
<td>71-100*</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>30-81</td>
<td>90**</td>
</tr>
<tr>
<td>Impaired LVEF rest vs exercise</td>
<td>15-46</td>
<td>40</td>
</tr>
<tr>
<td>Impaired LV filling</td>
<td>41-44</td>
<td>2, 32, 33, 34, 35</td>
</tr>
<tr>
<td>Impaired RV filling</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Conduction system disturbances</td>
<td>40**</td>
<td>18-28</td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
<td>5-59</td>
<td>2, 11, 37, 38</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>8-70</td>
<td>2, 11, 37, 38, 39</td>
</tr>
<tr>
<td>Cardiac autonomic neuropathy</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Valvular involvement</td>
<td>12-38</td>
<td>22, 23, 24, 25, 26, 27, 28, 29</td>
</tr>
<tr>
<td>Whole heart involvement*</td>
<td>35</td>
<td>1, 2, 12, 30, 41, 44</td>
</tr>
</tbody>
</table>

*Symptomatic scleroderma heart involvement; *coronary arterioles; **sinus node fibrosis; *percentage of 201-Thallium myocardial perfusion defects; **ultrasonic videodensitometric analysis.

**Table II.** Core set variables for SHI.

Dyspnea (NYHA scale)*

Palpitations*

Chest pain*

Dizziness*; pre-syncope*; syncope*;

Heart rate*; conduction defects*; arrhythmias*;

Edema/venous congestion**

Pericardial effusion*; **

Ejection fraction (EF)*; peak E/peak A ratio*; pulmonary artery pressure**

*History; **Physical examination; *EKG; **Echocardiography with echo-Doppler study.

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in early disease and structural alterations occur subsequently.

**Clinical manifestations**

SHI may be clinically silent, but more often it is either entirely overlooked or not correctly diagnosed due to its insidious nature, the frequent coexistence of lung involvement, and/or an inadequate diagnostic approach. In addition, in older patients it may be difficult to distinguish from more common causes of heart disease, such as atherosclerosis or hypertension. The manifestations of SHI reflect the following underlying alterations: autonomic neuropathy, myocardial fibrosis, small intramyocardial coronary arteries involvement, and pericardial involvement. Autonomic neuropathy in SSc has been reported by various authors using conventional laboratory tests (22-28). A significantly higher heart rate and lower circadian and spectral indexes of heart rate variability (29) are seen in SSc patients compared with controls. Interestingly, tachycardia, a low circadian heart rate variability, and spectral power values have been reported to predict higher mortality (28). These abnormalities suggest that autonomic cardiac neuropathy may represent an important prognostic feature which should be looked for in any SSc patient.

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**Table III.** New York Heart Association classification of dyspnea.

<table>
<thead>
<tr>
<th>Class</th>
<th>No limitation of physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Current physical activity does not induce dyspnea, fatigue or palpitations</td>
</tr>
<tr>
<td>II</td>
<td>Mild limitation of physical activity</td>
</tr>
<tr>
<td>III</td>
<td>Severe limitation of physical activity</td>
</tr>
<tr>
<td>IV</td>
<td>Impossibility of performing physical activity without symptoms; symptoms at rest Dyspnea is present at rest, worsened by even mild effort</td>
</tr>
</tbody>
</table>

Dyspnea is present at rest, worsened by even mild effort

No symptoms at rest. Current physical activity does induce dyspnea and fatigue

No symptoms at rest. Physical activity lower than usual does induce dyspnea and fatigue

Imp possibility of performing physical activity without symptoms; symptoms at rest Dyspnea is present at rest, worsened by even mild effort

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less common. Kostis et al. (39) reported ventricular arrhythmias in 67% of 183 SSc patients evaluated by 24-hour EKG monitoring and found a significant correlation with an increased risk of sudden death and with mortality. The worst prognosis in severe cardiac arrhythmias is significantly more frequent in those patients with both skeletal and cardiac muscle involvement (40). There is general agreement that the presence of cardiac arrhythmias is correlated with the severity of heart involvement and, in general, with a worse prognosis (2,11,37-40).

SHI has been reported to be less severe in anticientromere antibody positive patients and in limited cutaneous disease with respect to diffuse cutaneous disease (41,42), which is the subset characterized by the worst prognosis (43,44). Conversely, right heart involvement secondary to pulmonary arterial hypertension (independent of pulmonary fibrosis) is more frequently observed in limited SSc (45). Conflicting results have been reported concerning the prevalence of cardiac arrhythmias and conduction defects in different cutaneous subsets (2,11,38,45-48). Such discrepancies may depend on different systems used to distinguish subsets of patients (43,44).

Pericardial disease is symptomatic in a low percentage of patients and may herald the development of a scleroderma renal crisis.

Table I shows the frequency of the above mentioned disease manifestations as determined by clinical or autopsy studies.

**Candidate variables**

**Symptoms and signs**

Fatigue and dyspnea on exertion or at rest are the most common symptoms of SHI, but they can depend on other disease manifestations (lung fibrosis with or without pulmonary hypertension, anemia, and/or musculoskeletal involvement).

Chest pain rarely reflects angina pectoris and myocardial infarction; it is more frequently associated with pericarditis, esophageal reflux, and/or musculoskeletal chest wall disorders.

Palpitations are likely due either to sinus tachycardia, or to other conduction and/or rhythm disturbances.

Dizziness and, less frequently, syncope or sudden death are other clinical manifestations likely to be related to either autonomic cardiac neuropathy or conduction system disorders.

Heart rate, arrhythmias, murmurs indicative of valvular incompetence, and signs of right ventricular and pulmonary vascular bed overload (jugular venous congestion, tender hepatomegaly, and peripheral edema) must be looked for at the physical examination. Finally, congestive heart failure, even if rare, must always be kept in mind as a possibility (49).

**Electrocardiographic, radiological and echocardiographic examination**

The baseline standard 12-lead EKG can detect tachycardia at rest (i.e., heart rate >85 bpm), which indicates vagal withdrawal and sympathetic shift, atrial and right/left ventricular overload, conduction and/or rhythm disturbances, and pericardial involvement. Chest radiology assessment can detect atrial, left or right ventricular enlargement, altered pulmonary vascular flow

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**Routine cardiac assessment in SSc**

**1) Symptoms**

- Dyspnea
- Chest pain
- Palpitations
- Dyspnea on day/pace

**2) Physical Examination**

- Arthralgia
- Tachynea
- Tachycardia
- ECG

**3) Chest X-ray**

- Cardiac size
- Signs of pulmonary hypertension

**4) Electrophysiologic Test**

- Heart rate
- PQ time
- Right ventricular involvement
- QT dispersion
- Articular/paradoxical enhancement

**5) Doppler Echocardiography**

- LA, RV, LV dimensions
- PAP

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Fig. 1. Multi-step work-up in the assessment of heart involvement.
distribution and pericardial abnormalities. Echo-Doppler studies investigate left ventricular systolic and diastolic dysfunction, the presence of pericardial effusion and can be used to estimate systolic pulmonary artery pressure (50). Right heart catheterization for PHT and left and right heart catheterization for left-sided cardiac involvement are the most definitive studies at present. A simple bicycle/treadmill effort stress test can quantify physical tolerance and cardiac performance, provide information on symptoms (mainly dyspnoea, and muscle fatigue, graded by the Borg scale), heart rate and blood pressure competence (by a comparison of these parameters at baseline, during stress, and recovery), and finally on the occurrence of transient myocardial ischemia triggered by stress (51).

Rationale for excluding other variables
Other variables have been excluded essentially because they are not available in most centers, but also in some instances because they have not yet been standardized.

Clinical practice guidelines
Turning from clinical investigation to clinical practice, one can however hypothesize a multi-step process (Fig. 1). The first step should consist in the assessment of the above listed core set variables. Such an evaluation should preferably be carried out by a specific cardiologist and should be repeated every 12 months, even in the asymptomatic patient. Depending on the symptom, sign or instrumental finding detected, the clinician should then examine the patient to exactly define the nature of the cardiac pathology.

Discussion
Identification of core set variables
Table II lists the core set variables that the subcommittee members suggest be examined in any patient enrolled in a clinical investigational study in order to define the presence of cardiac involvement. The variables listed are both reliable and easily detectable and can be used by the clinician specifically to define the involvement of the heart in the SSc patient.

Rationale for the selection of the variables
The variables listed in Table II concern the presence of cardiac involvement in the SSc patient. Despite the lack of specificity, dyspnea and fatigue suggest cardiac and/or lung involvement and, together with other findings, are highly indicative. In addition, the grading of dyspnea according to currently accepted New York Heart Association guidelines, may provide relevant clinical and prognostic information in SSc patients, as is the case in most heart diseases (Table III) (49). The inclusion of other variables, such as those measured by EKG and Echo-Doppler, will reduce to a minimum the percentage of SSc patients with asymptomatic cardiac who are missed.

References
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