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Current advances in cardiac magnetic resonance imaging in systemic sclerosis

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Abstract. – Systemic sclerosis (SSc) is a systemic autoimmune disorder characterized by inflammation, fibroproliferative vasculopathy, and progressive fibrosis. Cardiac involvement is common in SSc and may affect the myocardium, pericardium, heart valves, conduction system, as well as coronary arteries. However, it remains asymptomatic for a long time, which leads to delayed diagnosis and poor prognosis. Accurate and early detection of cardiac abnormalities may warrant a better outcome in SSc. Recent advances in cardiac magnetic resonance imaging (CMR) improved the non-invasive evaluation of heart morphology and function. CMR can accurately identify both left and right ventricle dysfunction, which has a significant clinical and prognosis impact on SSc patients. In terms of myocardial structural alterations, CMR has remarkable diagnosis accuracy in identifying the presence and extent of myocardial fibrosis. When it comes to pulmonary arterial hypertension assessment, emerging data endorse the usefulness of CMR for the non-invasive quantification of it. Two-dimensional and time-resolved three-dimensional phase-contrast velocity-encoded CMR has become promising techniques for the assessment of pulmonary artery flow and stiffness measurements. Furthermore, CMR provides valuable prognostic information, both at the time of diagnosis and during follow-up in SSc patients with pulmonary arterial hypertension. The purpose of this review is to provide an overview of the latest findings in advanced cardiovascular imaging in patients with SSc.

Key Words:
Systemic sclerosis, Pulmonary arterial hypertension, Cardiac magnetic resonance imaging, Cardiac fibrosis.

Introduction

Systemic sclerosis (SSc) is a heterogeneous autoimmune connective tissue disease characterized by abnormalities of innate and adaptative immunity, vascular lesions, and fibroblast reactivity, impacting various organs, including the heart[1]. Cardiac involvement in SSc may remain subclinical for a long time; symptoms occur mostly in the later stages of the disease, having an estimated prevalence of 15-35%[2]. Cardiac manifestations in SSc encompass myocardial dysfunction, pericarditis, endocardial and valvular disease, coronary artery disease (CAD), and pulmonary arterial hypertension (PAH)[2-5]. Cardiac dysfunction can occur as a direct result of SSc and secondary to PAH, interstitial pulmonary fibrosis, and renal failure[2,6,7]. SSc promotes atherogenesis, microvascular ischemia, coronary wall hypertrophy, and myocardial fibrosis, which likewise leads to cardiac dysfunction[2,8]. Cardiac SSc is associated with poor prognosis and is responsible for up to 31% of SSc deaths[5].

Being long-time asymptomatic, the real incidence of cardiac manifestations in patients with SSc is quite difficult to be established. In a Danish nationwide cohort study, it has been shown that patients with SSc had a higher prevalence of hypertension, atrial fibrillation, heart failure, myocardial infarction, pericarditis, and PAH than matched controls[9]. Carreira et al[10] conducted a study on EULAR Scleroderma Trials and Research (EUSTAR) database and showed that in patients with early SSc, older age was associated with a higher prevalence of elevated pulmonary artery (PA) systolic pressure (PASP), heart

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blocks, and left ventricular (LV) diastolic dysfunction. Manno et al[11] have also demonstrated that SSc in the elderly increased their risk of PAH and cardiac disease. Other reports have shown that SSc was an important cardiovascular risk factor, independent of hypercholesterolemia, diabetes or hypertension[12].

Current research focuses on the development of accurate diagnosis techniques in order to improve clinical outcomes. Echocardiography is used to assess cardiac function and valvular damage, but its accuracy is questionable due to intra- and inter-observer variability. Cardiac magnetic resonance imaging (CMR) allows a comprehensive evaluation of the cardiac system, which overcomes echocardiography's shortcomings, leading to an earlier diagnosis of silent cardiac abnormalities in SSc[2]. This non-invasive technique is particularly valuable for diagnosing heart impairment in SSc, as it can provide information about morphology, function, and myocardial perfusion, especially when delayed contrast enhancement techniques are used.

This review provides an overview of the latest advances in CMR for diagnosing, assessing, and monitoring cardiovascular disease in SSc patients.

Cardiac Pathological Alterations Due to SSc

The pathogenetic mechanisms of cardiac impairment in SSc include microvascular alterations, vasospasms, fibroblasts activation with excessive collagen production, and autoimmune dysregulations. Similar to Raynaud's phenomenon, arterial spasms can occur in normal coronaries, thus triggering focal myocardial ischemia. Furthermore, excessive diffuse interstitial fibrosis determines distal coronary arterial occlusion[2,6,13], increased myocardial mass, and cardiac wall stiffness[14,16]. Various inflammatory factors that are overproduced in SSc could act as triggers for cardiac alterations (Figure 1). Inflammation and autoimmunity can further facilitate the occlusion of distal microvasculature, which may determine the destruction of parenchymal cells

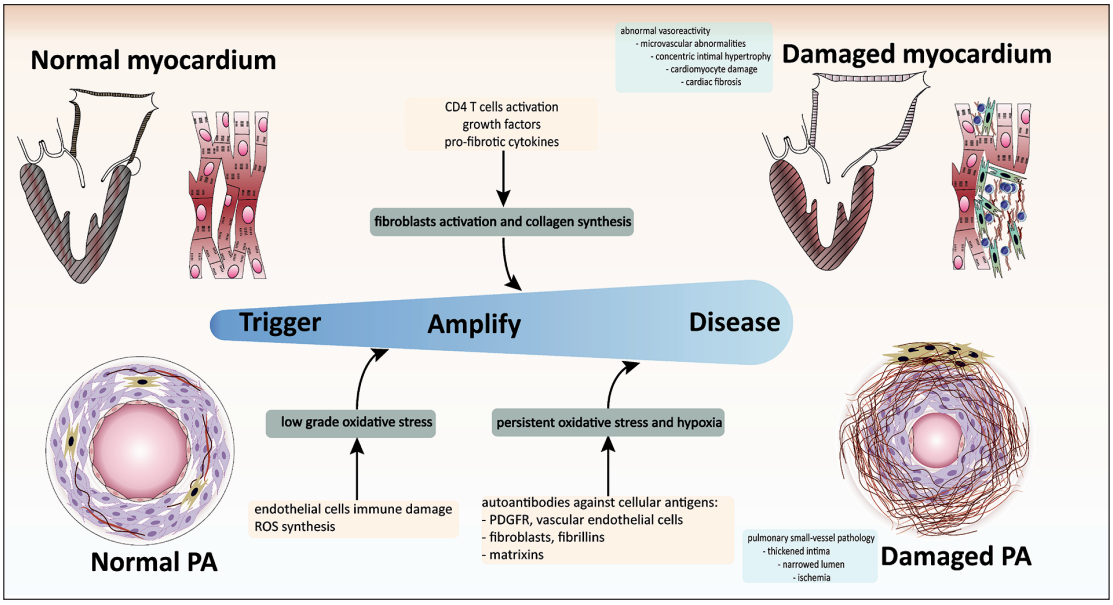

Figure 1. Cardiac pathological alteration due to SSc. Various inflammatory factors that are overproduced in SSc act as triggers for cardiac alterations. These factors determine endothelial dysfunction due to autoimmunity and ROS genesis, resulting in a low-grade inflammatory state that affects both the myocardium and PA. The process amplifies and the changes become irreversible. Low-grade inflammation levels up into a state of persistent oxidative stress and hypoxia due to enhanced synthesis of numerous antibodies against different cellular and tissue structures, such as PDGFR, ECs, fibroblasts, fibrillins, and matrixins. On the other hand, due to inflammatory activation and epitopes exposure, immune cells such as CD4+ cells are being activated, while macrophages start to produce growth factors, interleukins, and pro-fibrotic cytokines resulting in fibroblast activation and collagen synthesis. All of these determine a pathological state of the heart, damaging the myocardium by potentiating abnormal vasoreactivity, microvascular dysfunction, intimal hypertrophy, cardiomyocyte damage, and cardiac fibrosis. Moreover, PA is degrading as well, SSc determining pulmonary small-vessel pathology by thickening the intima, narrowing the lumen, and enhancing ischemia. Abbreviations: CD4, cluster of differentiation 4; PA, pulmonary artery; PDGFR, platelet-derived growth factor receptor; ROS, reactive oxygen species; SSc, systemic sclerosis.

by ischemia. Consequently, fibroblasts activation and recruitment, and differentiation into myofibroblasts, result in the production of collagen, which can ultimately lead to organ fibrosis[13].

Increased levels of lysophosphatidic acid and sphingosine 1-phosphate in SSc suggest their involvement in cardiac fibrosis, vascular and connective tissue disturbances, as well as in alterations of the immune system[13,16]. The microvascular injury seems to play a primary role in the characteristic cardiac impairment, because it enhances endothelial dysfunction and vascular inflammation[17]. Damaged cells determine fibroblasts activation, immune cell recruitment, epithelial-to-mesenchymal trans-differentiation, and collagen overproduction[18]. Inflammatory stress can lead to endothelial disruption with vascular mononuclear infiltration and capillary obliteration. The vascular tone becomes abnormal as a consequence of erratic neuro-endothelial control[19]. These alterations contribute to the development of PAH and electric disturbances. PAH and microvascular dysfunction have a negative impact on morbidity and mortality, accelerating disease progression[20]. Despite recent medical advances in SSc, the 3-year relative mortality remains at 50% and is even higher than in idiopathic PAH[21-23]. As reported in more recent studies, survival rates have increased from 50% at 1 year[24] to up to 80% and 50% after 1 and 3 years, respectively[25].

Endothelial dysfunction is considered to be one of the main causes of vascular impairment due to enhanced expression of adhesion molecules, recruitment of inflammatory cells, and procoagulant environment[26]. Consequently, neointimal proliferation and adventitial fibrosis is triggered, thus causing vascular obliteration[27]. Adaptative mechanisms determine progressive cardiac hypertrophy, which initially overcomes the increased PA pressure and right ventricular (RV) afterload. Both RV systolic and diastolic dysfunctions were shown to be important mortality predictors in SSc, although an association between RV dysfunction and PAH progression has not yet been proved[28]. Moreover, SSc-associated PAH demonstrated the poorest clinical outcome among all connective tissue diseases[29].

The Role of CMR in Assessing Cardiac Abnormalities in SSc

Nowadays, CMR is the gold-standard imaging technique used for cardiac assessment due to its increased spatial resolution, high reproducibility, and excellent interobserver variability[30,31], surpassing echocardiography[32,33]. Therefore, it can properly characterize cardiac function, myocardial structure, being also able to assess important hemodynamic measurements even in patients with SSc[34]. Corroborated data have shown that CMR has an excellent agreement of up to 75% for detecting cardiac abnormalities in patients with SSc[35,36,45,37-44] (Table I).

Myocardial Function

Patients with SSc develop myocarditis and CAD, resulting in both systolic and diastolic dysfunction[15,46]. However, several studies have shown that global systolic function is long-time preserved in most SSc patients, despite extensive myocardial fibrosis[8]. A prospective observational cohort of SSc-associated PAH[47] reported a 5.4% rate of heart failure (HF) with reduced ejection fraction. D'Alto et al[48] showed that LV ejection fraction (LVEF) was impaired only during physical exertion. On the other hand, diastolic dysfunction had a prevalence of up to 60%[49,50]. Maione et al[51] have shown that even though the diastolic function was significantly impaired, a direct relationship with SSc had failed to be identified. However, several studies confirmed the high incidence of diastolic dysfunction in SSc patients and even demonstrated a significant correlation with disease duration[52,53]. Moreover, diastolic impairment was associated with increased serum N-terminal-pro hormone Brain Natriuretic Peptide (NT-proBNP) and asymmetric dimethylarginine levels even in asymptomatic SSc subjects[54,55]. Other clinical features independently associated with diastolic dysfunction in SSc patients include PAH and elevated LV end-diastolic filling pressures[54,55].

The superiority of CMR in the assessment of systolic (Figure 2) and diastolic functions (Figure 3) had been endorsed by several studies. Cardiac function, especially of the RV, is frequently impaired in SSc patients, hence the increased use of CMR[15,56,57]. Hachulla et al[58] found that 29% of SSc patients had LV wall thinning, 23% impaired LVEF, 21% decreased RV ejection fraction (RVEF), 31% segmental LV hypokinesia, 6% biventricular dilations, and only 4% presented RV hypertrophy. Moreover, myocardial motion abnormalities were not correlated with coronary artery distribution. Several studies[58,59] demonstrated that CMR-based myocardial strain and strain rate analysis ensured a proper assessment of RV function compared with speckle-tracking echocardiography. RVEF impairment was not

Table I. Cardiac magnetic resonance imaging studies in patients with systemic sclerosis.

Authors	Year	N.	Purpose	Findings
Ntusi et al[35]	2014	19	To evaluate the role of multiparametric CMR in detecting subclinical myocardial involvement in patients with SSc	- LGE+ with focal fibrosis - 53% - T2M – 13% with myocardial edema) – T1M – ↑ (1007 ± 29, $p < 0.001$) - ECV – ↑ (35.4 ± 4.8, $p < 0.001$), and correlated with disease activity and severity - LV strain ↓ (16.8 ± 1.6, $p < 0.001$) - Diastolic strain ↓ (83 ± 26, $p < 0.001$)
Krumm et al[36]	2017	20	To evaluate morphologic and functional CMR patterns in patients with SSc	- All had LGE patterns - 95% had abnormal RV or LV contractility - 70% had decreased LV or RV function - 45% had moderate pericardial effusion - 35% had minimal pericardial effusion
Mousseaux et al[38]	2018	58	To evaluate the role of CMR and contrast CMR in patients with SSc	- LGE+ – 29.3%, and associated with increased mortality risk ($p = 0.028$) - LVEF ↓ in 18.9% - LVEDV ↑ in 13.7% - RVEDV ↑ in 32.7%
Gargani et al[39]	2018	201	To evaluate the addition of LGE to TTE in patients with SSc.	- T2M – 5% – myocardial edema - LGE+ – 27.9% of cases; and correlated with ventricular arrhythmias ($p < 0.01$);
Lee et al[40]	2018	49	To evaluate the utility of T1M in early SSc and its association with skin score.	- LGE+ in 33% - ECV had 75% Se and 75% Sp for identifying SSc - All 4 T1M parameters were associated with modified Rodnan skin score (ECV = 29.5±4.5%, $p < 0.002$; Partition coefficient (λ) = 0.47 ± 0.05, $p < 0.003$; Pre-T1 = 998 ± 61, $p = 0.033$; Post-T1 = 412±79, $p = 0.048$)
Tipparot et al[41]	2019	30	To ascertain the clinical and laboratory associations with CMR-based myocardial inflammation in SSc patients	- 73.3% had myocardial inflammation in the early-onset of SSc, increase in mRSS being associated with myocardial inflammation
Sugiyama et al[42]	2019	49	To evaluate the association between myocardial abnormalities and LV geometry as assessed by CMR	- LGE+ – 55%; LV structural anormalities were detected in 44% of LGE+ patients and 14% of LGE- patients;
Bratis et al[43]	2019	54	To evaluate myocardial deformation in cardiac asymptomatic SSc using Feature Tracking-CMR	- LVEF ↑(62.6 ± 6%, $p = 0.01$) - LGE+ in 26% - 18% had RV insertion fibrosis - LV-LAS differed in those with insertion fibrosis (-18.0% *vs.* -20.3%, p=0.04). Patients with SSc had lower -RV-LAS ↓ ($p < 0.001$)

Continued

Table I *(Continued)*.

Authors	Year	N.	Purpose	Findings
Poindron et al[44]	2019	72	To determine the prevalence of cardiac involvement by native T1M CMR in patients with SSc	- T1M = 1097.1 ± 33.4, $p < 0.0001$ - T2M = 52.9 ± 3.3, $p = 0.0003$; - LGE+ in 25% of cases
Markousis-Mavrogenis et al[45]	2020	59	To re-evaluate the utility of T1-based indices as indicators of myocardial inflammation in SSc patients	- EGE, LGE, T1M, ECV increased in SSc, but 25% of SSc patients had no CMR evidence of myocardial inflammation representing a bias
Terrier et al[37]	2020	40	To evaluate the role of CMR with intravoxel incoherent motion diffusion-weighted imaging and T1M in assessing myocardial microvascular and interstitium impairment in SSc	- T1M ↑ in SSc - T1M directly correlated with mRSS and forced vital capacity ($p = 0.04$, $p = 0.048$); and inversely correlated with f coefficient ($p = 0.02$), - Higher T1M associated with cardiac events ($p = 0.03$)

Abbreviations: CMR, cardiac magnetic resonance imaging; ECV, extracellular volume fraction; EGE, early gadolinium enhancement; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LV-LAS, left ventricular long-axis strain; mRSS, modified Rodnan skin score; n, number of subjects; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; SSc, systemic sclerosis; T1M, T1 mapping; T2M, T2 mapping.

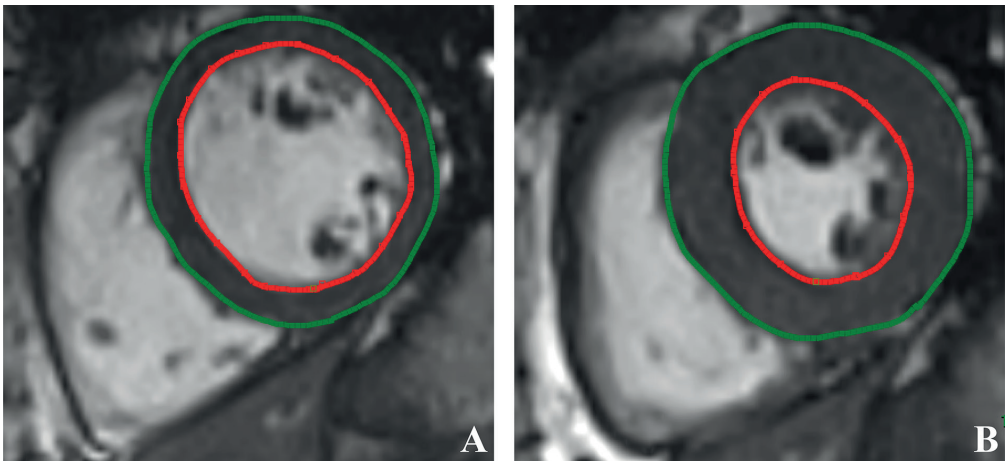

Figure 2. Cardiac magnetic resonance images of a 42-year-old female with systemic sclerosis. Short-axis b-SSFP images determining end-diastolic (green) **(A)** and end-systolic (red) **(B)** for measuring LVEF. LVEF was decreased to 62%. Abbreviations: b-SSFP, balanced steady-state free precision; LVEF, left ventricular ejection fraction.

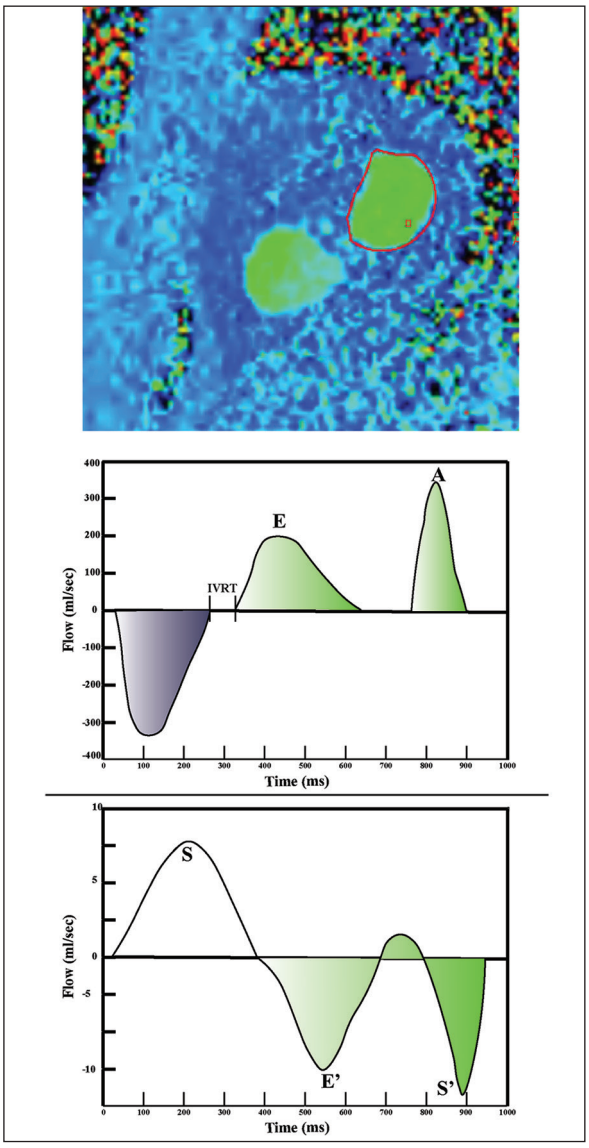

Figure 3. Color-coded displays of the transmitral flow and myocardial longitudinal velocity-encoded phase-contrast (PC) in cardiac magnetic resonance (CMR) images in a patient with systemic sclerosis. PC-CMR segmentation and diastolic parameters extraction from a transmitral flow with a robust delineation of the transmitral flow pattern **(A)**. Transmitral flow imaging assessment of flow-related parameters: mitral early peak filling rate (E, in mL/s), late peak filling rate (A, in mL/s), E/A ratios; mitral isovolumetric relaxation time (IVRT, in ms); mitral E-wave deceleration time (DT, in ms). The negative curve is due to the LV outflow **(B)**. Myocardial tissue imaging assessment of flow-related parameters: systolic mitral myocardial motion (S, in cm/s); myocardial longitudinal early (E') and late (A', in cm/s) peak velocity on the LV lateral wall **(C)**.

statistically associated with PAH[58], but when RVEF decreases, SSc subjects with PAH turn out to be more severely affected[60]. In asymptomatic SSc patients, LVEF remained preserved for a long time, while LV and RV end-diastolic diameters and RVEF were significantly modified[59].

Therefore, routine RV function assessment is essential in subjects with SSc, being able to identify patients with a subclinical cardiac impairment who may benefit from early therapy and can help determine the risk for PAH development.

Structural Changes of the Myocardial Wall

Structural characterization of the myocardium is one of the main purposes of CMR in patients with SSc. In these patients, decreased myocardial perfusion is caused either by CAD or non-atherosclerotic coronary involvement[61,62]. To date, it has been suggested that nuclear cardiac imaging accurately assesses myocardial damage in early stages[63]. Single positron emission computed tomography (SPECT/CT) with Tc-99m-Sestamibi can identify myocardial perfusion defects in up to 88% of symptomatic patients[64], and Thallium 201 Iobenguane SPECT/CT has proved equally effective[65]. However, these techniques are time-consuming and radiation dependent. CMR overcomes these flaws and is further able to accurately assess myocardial perfusion defects, viability, and flow reserves[8,66,67]. Stress CMR may further improve its diagnostic capacity[66,68]. Late gadolinium enhancement (LGE) is largely used as an imaging marker of myocardial replacement fibrosis. Kobayashi et al[68] demonstrated that even in asymptomatic patients with SSc, steady-state free precession (SSFP) CMR accurately identified microvascular impairment associated with LGE. In addition, Vignaux et al[66] sought to evaluate the effects of calcium channel blockers on myocardial perfusion. The authors showed that CMR had comparable diagnosis efficacy with Tissue Doppler imaging echocardiography in assessing myocardial perfusion.

Patchy myocardial fibrosis not correlated with coronary artery distribution and occlusion was the most common finding in subjects with SSc[5,69]. Fernandez et al[5,69] emphasized in their study that myocardial fibrosis was present in patients with SSc even before symptoms onset and had an important impact on the prognosis of these patients. A histopathological study conducted on 52 subjects with SSc detected several types of lesions: 23 patients with focal tissue abnormalities, ranging from contraction band necrosis to replacement fibrosis, 22 with LV hypertrophy, and 13 with massive RV hypertrophy[70].

Nowadays, CMR is the non-invasive method of choice for evaluating myocardial fibrosis (Figure 4), and it uses LGE for assessing replacement fibrosis[71], and T1-mapping for diffuse interstitial fibrosis[72]. LGE occurs due to inflammation, oedema, and fibrosis since the contrast agent tends to accumulate within the areas where myocardial membranes are disrupted, and the interstitial space is enlarged, ensuing a prolonged wash-out duration[73]. Myocarditis is characterized by focal or diffuse inflammatory oedema with increased longitudinal relaxation times in both early and LGE, as well as in T1-mapping sequences[74]. The new Lake Louise Criteria recommended for the CMR diagnosis of non-ischemic myocardial inflammation uphold the utility of regional increased T2 relaxation time or signal intensity in T2-weighted images, increased T1-weighted images, extracellular volume or LGE. Therefore, to increase diagnosis accuracy, it is recommended to combine CMR markers of both cardiac edema and myocardial inflammatory injury[75].

A study conducted on 35 asymptomatic patients with SSc indicated that 15% had linear LGE with non-ischemic pattern[76]. Rodriguez-Reyna et al[77] identified myocardial fibrosis with microvascular impairment and decreased LVEF in up to 45% of cases. Linear, mid-wall LGE is suggested to be typical for SSc patients[8,58]. Moreover, some data have revealed a prevalence of up to 66% for myocardial fibrosis, mostly focal within the basal and middle LV segments. Nevertheless, the presence of Raynaud's phenomenon for more than 15 years was associated with larger LGE areas. However, no difference in the LGE volume has been reported[8] between patients with diffuse and limited SSc. Interestingly, Nicholson et al[78] showed that LGE was positively correlated with the extent of pulmonary fibrosis and with RVEF impairment. However, the concomitant presence of both LGE and acute inflammatory myocarditis could not be discerned using CMR[79].

Being the method of choice for the detection of diffuse myocardial fibrosis, T1-mapping is also able to evaluate its extent. The modified look-locker inversion-recovery sequence (MOLLI) technique is currently preferred, being able to acquire CMR images within a single breath-hold. Therefore, MOLLI can evaluate myocardial intrinsic T1 relaxation times in combination with tissue signal suppression,

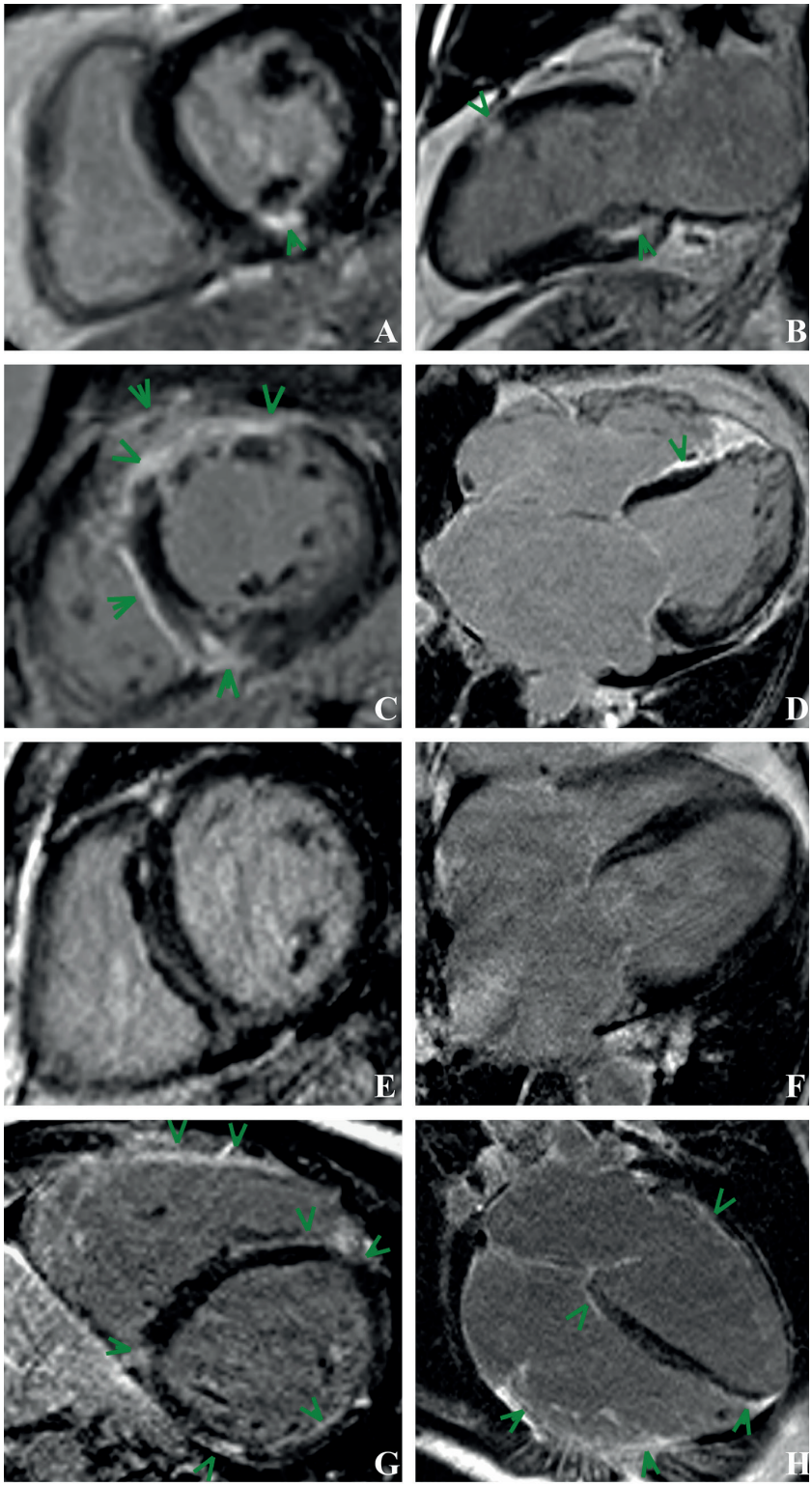

Figure 4. T1-weighted post-contrast short-axis, 2-chamber and 4-chamber CMR patterns in patients with systemic sclerosis: **(A,B)** a patient with focal myocardial LGE of the anterior and inferior walls of the LV; **(C,D)** a patient with sub-epicardial LGE of the interventricular septum and anterior wall of the LV, associated with LGE of the apex of RV; **(E,F)** a patient with mid-myocardial LGE of interventricular septum; **(G,H)** and a patient with mixed LGE of LV (sub-epicardial, mid-myocardial, and transmural) and transmural of the lateral wall of RV. Abbreviations: CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; RV, right ventricle; LV, left ventricle.

thus highlighting the presence of the contrast agent within the fibrotic areas of the myocardium. Furthermore, it is able to create myocardial maps based on the signal intensity of each cardiac voxel[80,81] (Figure 5).

Pericardial Involvement

Pericardial involvement occurs in up to 70% of SSc patients, being mostly represented by mild pericardial effusion[82], frequently asymptomatic[83]. Cardiac tamponade is a rare complication in subjects with SSc who develop significant PAH. Although echocardiography is non-invasive and widely available, the occurrences of SSc-related pericarditis in echocardiographic studies vary widely. When differentiating between pericardial fibrosis and calcification, echocardiography is lacking[84].

CMR (Figure 6) and cardiac computed tomography are able to overcome the limitations of echocardiography and can be used to assess pericardial effusions, especially in localized forms. Nevertheless, the severity of pericardial effusion is often overestimated by these techniques. However, CMR cannot discriminate between chronic pericardial thickening and calcifications. Therefore, CMR diagnosis of constrictive pericarditis requires the evaluation of systemic venous hypertension, ascites, hepatomegaly and pleural effusion. However, it can be quite useful in differentiating between constrictive pericarditis and restrictive cardiomyopathy[85,86], and also for the evaluation of other associated cardiac abnormalities[87].

Cardiac Valve Involvement

Echocardiography-based studies have identified an increased incidence of valvular heart diseases in SSc, mainly of the mitral valve[70,88]. There is controversy regarding the association between SSc and valvular impairment since pathological studies have failed to establish a causal link between them[89,90]. However, recent data suggests that tricuspid regurgitation occurs in up to 40%, aortic and mitral valves are thickened in 20% and 4% of cases, respectively[90,91], while valvular vegetations have also been reported. Others have found that mitral valve thickening is the most frequent valvular disease[88].

CMR is useful for estimating valvular hemodynamic impact since it can accurately measure ventricular masses and volumes[87]. The assessment of valvular regurgitation by CMR involves tracking the decreased signal that extends from the valve into the upward chamber, recording the regurgitant flow duration with respect to the cardiac cycle. Velocity-encoded CMR is a valuable tool for blood flow evaluation, particularly because it allows simultaneous assessment of multiple valvular diseases, unlike classic CMR that relies on stroke volume discrepancies[85,87].

CMR Assessment of PAH

PAH is frequently associated with SSc, leading to poor prognosis and increasing all-cause mortality in these patients. PAH is characterized by increased PASP and pulmonary vascular resistance (PVR). Right heart catheterization (RHC)

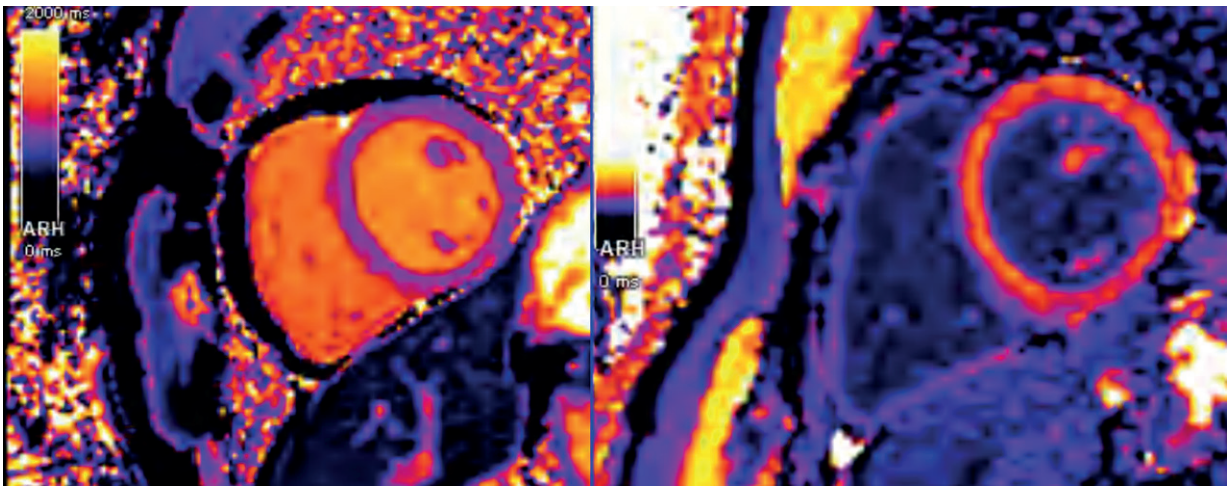

Figure 5. A 33-year-old female cu systemic sclerosis. Native Short-Axis Mid-Ventricular T1 Map shows normal native T1 values in septal wall (976 msec) and borderline increased T1 value in the lateral walls (1029 msec).

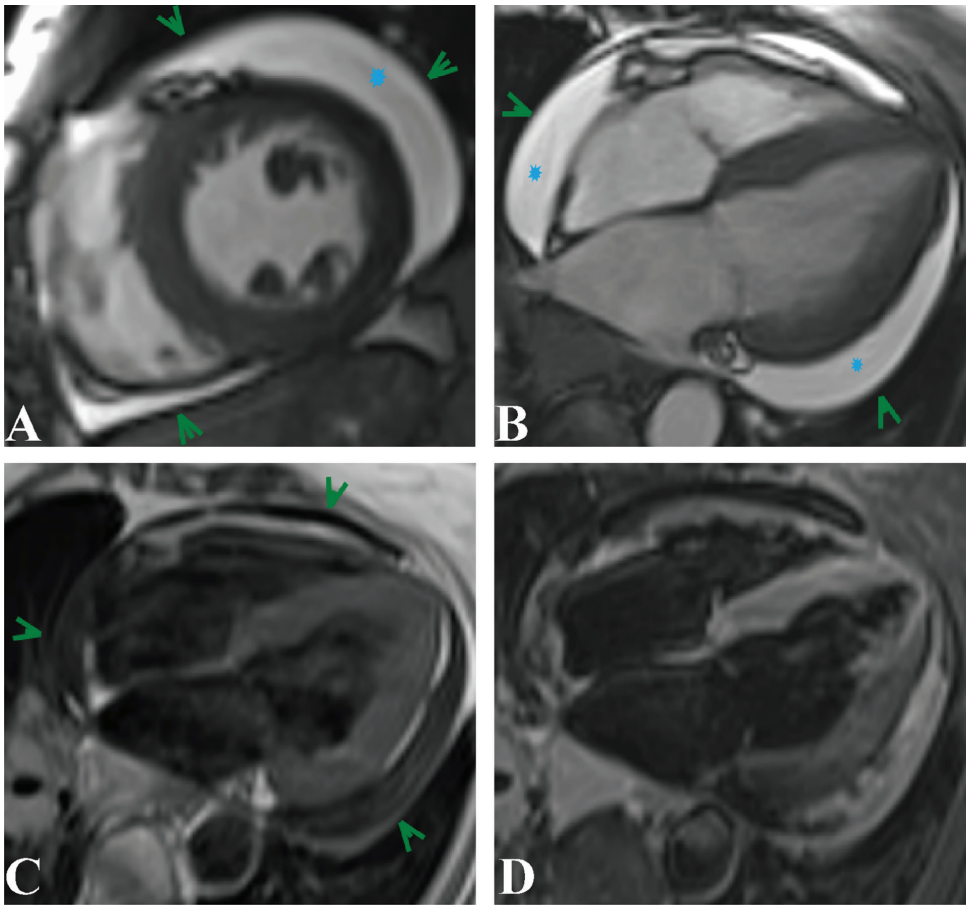

Figure 6. Cardiac magnetic resonance of a 32-year-old patient with systemic sclerosis with circumferential pericardial effusion visible from short-axis **(A)** and long-axis images **(B)** of balanced SSFP (*bleu arrowheads*); T2-weighted short-tau inversion-recovery spin-echo **(C)**; T1-weighted spin-echo **(D)**. The pericardial effusion has an inhomogeneous spread, especially on T2-weighted short-tau inversion-recovery spin-echo CMR. Abbreviations: b-SSFP, balanced steady-state free precision; CMR, cardiac magnetic resonance imaging.

is the gold standard assessment tool for PAH. However, its repeated use is often prohibitive due to its invasive nature. Nowadays, a resting value of mean PA pressure ≥ 20 mmHg determined by RHC is the threshold used for confirming PAH[92,93]. According to WHO, the most frequent types of pulmonary hypertension in patients with SSc are PAH (group 1), pulmonary venous hypertension (PVH) due to left heart disease (group 2), and pulmonary hypertension due to lung disease or hypoxemia (group 3)[94].

A recent French study reported an incidence of PAH up to 0.61 cases per 100 patient-years in patients with SSc[95]. Moreover, echocardiography-based studies estimated a prevalence of PAH ranging between 13% to 35%[95,96]. RHC studies described a prevalence of 7.85% to 12% in patients with SSc and interstitial lung disease[25,83,97], and of 5% and 8% in the absence of lung disease[97,98]. Another noteworthy aspect revealed by these studies was that 13% to 19% of SSc patients suspected of PAH were invasively diagnosed with PVH due to left heart disease. Patients with limited cutaneous SSc displayed the highest risk of developing PAH, regardless of LV impairment. Furthermore, Denton et al[99] revealed that PAH occurred after an average period of 10 to 15 years in these patients. Echocardiography has been successfully used as a screening test, especially in the follow-up of patients with SSc, but its accuracy is sometimes questionable. Despite its shortcomings, echocardiography still remains a reliable non-invasive method for diagnosing PAH and assessing its progression[100]. Mukerjee et al[101] have shown that a 45 mmHg threshold for the RV-right atrium gradient was able to identify PAH. However, a cut-off value for excluding PAH was not yet established.

Current research aims to increase the diagnostic accuracy of non-invasive techniques for PAH assessment. CMR has proved to be the most efficient non-invasive diagnostic tool for comprehensive evaluation of PAH. Its main strength is represented by the ability to assess RV dynamics and pulmonary circulation, as well as other structural abnormalities in three-dimensional projections. Velocity-encoded CMR allows pulmonary flow assessment and early diagnosis of PAH[102]. Phase-contrast CMR (PC-CMR) can provide valuable information regarding various time velocities, along with PA minimum and maximum areas. The quantification of pulmonary flow profile within the main PA had shown significantly reduced peak flow velocities in PAH, being inversely correlated with the mean PASP and PVR[103,104]. Bogren et al[105] showed that PA distensibility was lower in PAH patients when compared to healthy subjects (8% *versus* 23%). Moreover, PA stiffness parameters were associated with increased mortality and seem to be useful predictors of exertion capacity in these patients[106]. Furthermore, CMR can identify the earliest changes that occur within the pulmonary circulation (Figure 7), even before RV impairment starts to develop.

When evaluating patients with PAH, both cardiac output and RV stroke volume (RVSV) should always be measured[107]. Overbeek et al[108] described the "pump function graph" by assessing the relationship between mean RV pressure and RVSV in patients with SSc and PAH when compared with patients with idiopathic PAH. They showed that RVSV was considerably lower in patients with SSc-related PAH for any given mean RV pressure than in those with idiopathic PAH, inferring that contractility was more severely impaired than in the former category. As PAH is known to correlate with RVSV and exertion capacity, these findings can explain the poorer exercise capacity in patients with SSc-related PAH, hence their increased morbidity and mortality. Bredfelt et al[109] showed that left atrial enlargement detected by CMR along with PAH determined the worst clinical outcome in this category of patients. In a comparative study, Rajaram et al[110] demonstrated that CMR and echocardiography are equally accurate in terms of assessing PAH and predicting mortality, whereas cardiac computed tomography proved to be inferior.

Recently, it has been shown that CMR accurately predicted PAH by determining the ventricular mass index (VMI), the latter being a ratio between the LV and RV masses[111]. Hence, in patients with SSc, a VMI under 0.7 was associated with a 91% survival at 2 years, while a value of over 0.7 predicted a lower survival rate. Furthermore, the superiority of CMR-based VMI over echocardiography in patients with SSc has been recently demonstrated by several studies[111,112]. It was also significantly associated with PASP[113-115]. Future studies should aim to evaluate the ability of VMI in discriminating the presence of PAH in patients with SSc and overt dyspnea.

Emerging developments in the field of advanced cardiovascular imaging endorse the increasing accuracy of CMR in assessing PAH.

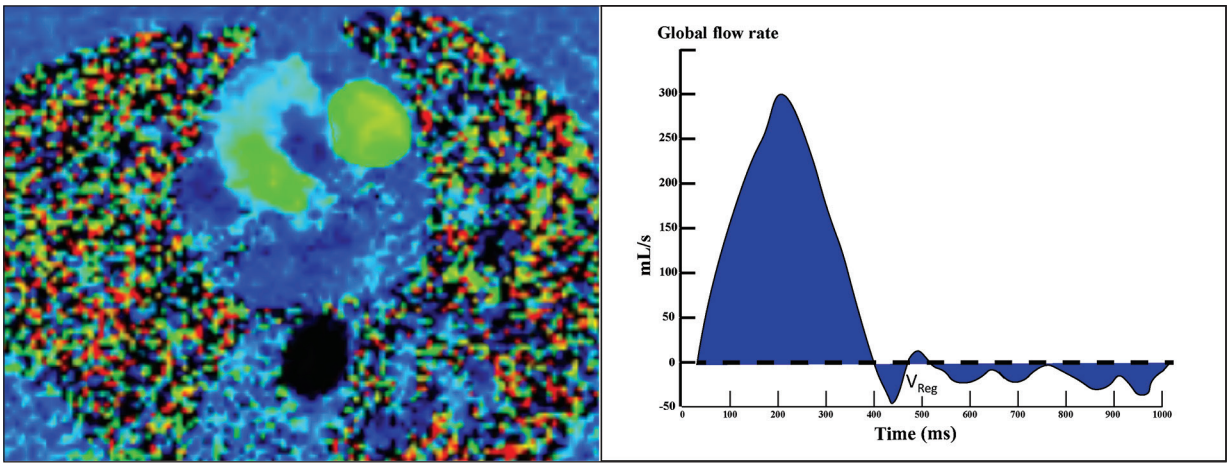

Figure 7. Phase-contrast CMR of a 49-year-old patient with systemic sclerosis representing the pulmonary artery **(A)** and specific characteristics regarding forward and backward flow characteristics **(B)**. *Abbreviations:* CMR, cardiac magnetic resonance imaging.

Two-dimensional PC-CMR (2D PC-CMR) can evaluate various types of velocities throughout the entire bloodstream by applying velocity-encoded gradients. Time-resolved three-directional velocity encoding PC-CMR (4D-flow CMR) provides comprehensive information regarding the flow patterns within a vessel[116]. PC-CMR imaging holds particular utility for non-invasive evaluation of PAH, as it allows for the accurate assessment of numerous flow parameters such as RVSV, regurgitant volume, regurgitant fraction, and forward blood flow. Furthermore, PC-CMR enables analysis of several measures of PA stiffness, such as pulsatility, compliance, capacitance, distensibility, elastic modulus, and the pressure-independent stiffness index beta[117].

In a study conducted by our research team, we showed that in healthy individuals, 2D PC-CMR was able to identify age-related changes in PA forward and backward flow, and also in stiffness parameters[118]. In patients with chronic obstructive pulmonary disease, PA stiffness parameters determined by 2D PC-CMR had increased diagnostic accuracy and provided important prognostic information[119].

A rising trend in cardiovascular research is the development of computational models based on multiparametric non-invasive indexes that could significantly increase diagnostic accuracy in PAH. In a study based on 2D PC-CMR, Johns et al[120] showed that a multiparametric model that comprises measurements of interventricular septal angle, VMI, and black-blood slow flow score could help identify patients suspected of PAH with a sensitivity of 93% and a specificity of 79%. 4D-flow CMR enables the complete spatial evaluation of PA and provides comprehensive data regarding the blood flow and wall shear stress. In a study conducted by Reiter et al[121] 4D-Flow CMR was shown to be useful in predicting PAH. In addition, they detected the presence of specific vortexes within the PA. Furthermore, Schafer et al[122] sought to characterize flow patterns and helicity and vorticity parameters in patients with PAH when compared to healthy individuals. PAH patients demonstrated lower helicity and vorticity, while helicity was inversely correlated with ventricular-vascular coupling and mean PASP, and directly associated with RVEF, cardiac output and PA relative area change (PA RAC). Another study that compared 4D-flow CMR patterns between subjects with clinically overt PAH, subclinical PAH, and normal subjects showed that the presence of vortices was significantly correlated with clinically overt PAH[121]. Moreover, 4D-flow CMR could also be used for a non-invasive estimate of PVR. In the study of Kheyfets et al[123], the combined use of PA RAC, peak systolic vorticity, and cardiac output allowed for an accurate assessment of PVR in patients with PAH. These promising results suggest that PC-CMR could become a useful tool for the non-invasive assessment of patients with SSc and suspected PAH. Further studies are needed to evaluate the diagnostic accuracy of these novel CMR techniques in patients with SSc.

Clinical Approaches of CMR in Patients with SSc and PAH

Since PAH is a common and redundant complication of SSc, the development of early diagnostic tools and specific therapeutic strategies should be an utmost priority for researchers[21,28]. In the attempt of improving prognosis in these patients, recent studies have sought to identify predictors of PAH development. Allanore et al[124] showed that a low diffusing capacity of carbon monoxide (DLCO)/alveolar volume ratio and high levels of NT-proBNP can accurately predict the development of PAH, while Williams et al[125] established a direct relationship between elevated NT-proBNP levels and PAH severity. Furthermore, a DLCO/forced vital capacity ratio of over 1.4 was also shown to predict PAH[126]. To date, the most important predictors of developing PAH include advanced age at disease onset, Raynaud's phenomena, elevated PVR, decreased or progressive decline in DLCO/alveolar volume, and a DLCO/forced vital capacity over 1.4[124-128]. Recently, several studies have demonstrated that elevated CMR-based RVSV and decreased myocardial mass are associated with improvement in symptoms and increased 6-minutes walking test distances[129-131]. Moreover, an increase in RV end-diastolic volume and/or reduction in RVSV have been shown to strongly predict a poor prognosis[103]. A CMR study that evaluated the short-term effects of Bosentan on myocardial perfusion and function in SSc patients reported a significant improvement in terms of perfusion index and systolic and diastolic strain rates[132].

Despite the aforementioned results, the use of CMR is just at the beginning since its general reliability is not yet supported by strong evidence[98]. Furthermore, there is currently no conclusive data that CMR can reliably predict long-term outcomes in patients with PAH. Moreover, the discovery of novel layers in the complex pathophys-

iology of PAH could ensure the identification of novel prognostic factors, thus helping define new correlations between hemodynamic parameters and exercise function or life quality. Future strategies of the research on the relevance of CMR for patients with SSc should include extensive use of fibrosis markers to create computational models based on hemodynamic parameters and clinical outcomel[33].

Conclusions

In summary, SSc can affect all structures of the heart, leading to poor prognosis in these patients. The development of early diagnosis and assessment methods is crucial for improving patients' outcomes. CMR offers promising results in terms of assessing cardiac morphology and functions, as well as in characterizing the myocardial wall. Another noteworthy trend in the field of CMR research is the development of advanced methods for the non-invasive assessment of PAH.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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References

1) Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. Expert Rev Clin Immunol 2019; 15: 753-764.
2) Lambova S. Cardiac manifestations in systemic sclerosis. World J Cardiol 2014; 6: 993-1005.
3) Meune C, Vignaux O, Kahan A, Allanore Y. Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. Arch Cardiovasc Dis 2010; 103: 46-52.
4) Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, Riemekasten G, Airò P, Joven B, Vettori S, Cozzi F, Ullman S, Czirják L, Tikly M, Müller-Ladner U, Caramaschi P, Distler O, Iannone F, Ananieva LP, Hesselstrand R, Becvar R, Gabrielli A, Damjanov N, Salvador MJ, Riccieri V, Mihai C, Szücs G, Walker UA, Hunzelmann N, Martinovic D, Smith V, Müller CS, Montecucco CM, Opris D, Ingegnoli F, Vlachoyiannopoulos PG, Stamenkovic B, Rosato E, Heitmann S, Distler JHW, Zenone T, Seidel M, Vacca A, Langhe E, Novak S, Cutolo M, Mouthon L, Henes J, Chizzolini C, Mühlen CAV, Solanki K, Rednic S, Stamp L, Anic B, Santamaria VO, De Santis M, Yavuz S, Sifuentes-Giraldo WA, Chatelus E, Stork J, Laar JV, Loyo E, García de la Peña Lefebvre P, Eyerich K, Cosentino V, Alegre-Sancho JJ, Kowal-Bielecka O, Rey G, Matucci-Cerinic M, Allanore Y; EUSTAR group. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017; 76: 1897-1905.
5) Ioannidis JPA, Vlachoyiannopoulos PG, Haidich A-B, Medsger TA, Lucas M, Michet CJ, Kuwana M, Yasuoka H, van den Hoogen F, te Boome L, van Laar JM, Verbeet NL, Matucci-Cerinic M, Georgountzos A, Moutsopoulos HM. Mortality in systemic sclerosis: An international meta-analysis of individual patient data. Am J Med 2005; 118: 2-10.
6) Varga J. Scleroderma and Smads: dysfunctional Smad family dynamics culminating in fibrosis. Arthritis Rheum 2002; 46: 1703-1713.
7) Dinser R, Frerix M, Meier FMP, Klingel K, Rolf A. Endocardial and myocardial involvement in systemic sclerosis – is there a relevant inflammatory component? Joint Bone Spine 2013; 80: 320-323.
8) Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Kampolis C, Gialafos EJ, Moyssakis I, Moutsopoulos HM. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced magnetic resonance imaging study. Arthritis Rheum 2007; 56: 3827-3836.
9) Butt SA, Jeppesen JL, Torp-Pedersen C, Sam F, Gislason GH, Jacobsen S, Andersson C. Cardiovascular manifestations of systemic sclerosis: a Danish nationwide cohort study. J Am Heart Assoc 2019; 8: e013405.
10) Carreira PE, Carmona L, Joven BE, Loza E, Andréu JL, Riemekasten G, Vettori S, Balbir-Gurman A, Airò P, Walker U, Damjanov N, Matucci-Cerinic M, Ananieva LP, Rednic S, Czirják L, Distler O, Farge D, Hesselstrand R, Corrado A, Caramaschi P, Tikly M, Allanore Y. Differences associated with age at onset in early systemic sclerosis patients: a report from the EULAR Scleroderma Trials and Research Group (EUSTAR) database. Scand J Rheumatol 2019; 48: 42-51.
11) Manno RL, Wigley FM, Gelber AC, Hummers LK. Late-age onset systemic sclerosis. J Rheumatol 2011; 38: 1317-1325.
12) Oreska S, Tomcik M. Atherosclerosis and cardiovascular risk in systemic sclerosis. Syst Scler. InTech; 2017. 10.5772/67495.
13) Pattanaik D, Postlethwaite AE. A role for lysophosphatidic acid and sphingosine 1-phosphate in the pathogenesis of systemic sclerosis. Discov Med 2010; 10: 161-167.
14) Hirooka K, Naito J, Koretsune Y, Irino H, Abe H, Ichikawa M, Yasuoka Y, Yamamoto H, Hashimo-

to K, Chin W, Kusuoka H, Inoue M, Hori M. Analysis of transmural trends in myocardial integrated backscatter in patients with progressive systemic sclerosis. J Am Soc Echocardiogr 2003; 16: 340-346.

15) Meune C, Allanore Y, Devaux JY, Dessault O, Duboc D, Weber S, Kahan A. High prevalence of right ventricular systolic dysfunction in early systemic sclerosis. J Rheumatol 2004; 31: 1941-1945.

16) Postlethwaite, Pattanaik D, Brown M. Vascular involvement in systemic sclerosis (scleroderma). J Inflamm Res 2011; 4: 105-125

17) Cannarile F, Valentini V, Mirabelli G, Alunno A, Terenzi R, Luccioli F, Gerli R, Bartoloni E. Cardiovascular disease in systemic sclerosis. Ann Transl Med 2015; 3: 8.

18) Wei J, Bhattacharyya S, Tourtellotte WG, Varga J. Fibrosis in systemic sclerosis: emerging concepts and implications for targeted therapy. Autoimmun Rev 2011; 10: 267-275.

19) Deswal A, Follansbee WP. Cardiac involvement in scleroderma. Rheum Dis Clin North Am 1996; 22: 841-860.

20) Ngian G-S, Sahhar J, Wicks IP, Van Doornum S. Cardiovascular disease in systemic sclerosis - an emerging association? Arthritis Res Ther 2011; 13: 237.

21) Launay D, Sitbon O, Hachulla E, Mouthon L, Gressin V, Rottat L, Clerson P, Cordier J-F, Simonneau G, Humbert M. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Ann Rheum Dis 2013; 72: 1940-1946.

22) Launay D, Sitbon O, Le Pavec J, Savale L, Tcherakian C, Yaici A, Achouh L, Parent F, Jais X, Simonneau G, Humbert M. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatology 2010; 49: 490-500.

23) Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, Housten T, Champion HC, Lechtzin N, Wigley FM, Girgis RE, Hassoun PM. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. Am J Respir Crit Care Med 2010; 182: 252-260.

24) Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest 2003; 123: 344-350.

25) Mukerjee D. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003; 62: 1088-1093.

26) Le Pavec J, Humbert M, Mouthon L, Hassoun PM. Systemic sclerosis-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2010; 181: 1285-1293.

27) Schachna L, Wigley FM. Targeting mediators of vascular injury in scleroderma. Curr Opin Rheumatol 2002; 14: 686-693.

28) Vonk Noordegraaf A, Naeije R. Right ventricular function in scleroderma-related pulmonary hypertension. Rheumatology 2008; 47: v42-v43.

29) Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-Harris T, Hummers L, Krishnan JA, Wigley F, Hassoun PM. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum 2006; 54: 3043-3050.

30) Valbuena-López S, Hinojar R, Puntmann VO. Cardiovascular magnetic resonance in cardiology practice: a concise guide to image acquisition and clinical interpretation. Rev Española Cardiol 2016; 69: 202-210.

31) Schalla S, Nagel E, Lehmkuhl H, Klein C, Bornstedt A, Schnackenburg B, Schneider U, Fleck E. Comparison of magnetic resonance real-time imaging of left ventricular function with conventional magnetic resonance imaging and echocardiography. Am J Cardiol 2001; 87: 95-99.

32) Erley J, Genovese D, Tapaskar N, Alvi N, Rashedi N, Besser SA, Kawaji K, Goyal N, Kelle S, Lang RM, Mor-Avi V, Patel AR. Echocardiography and cardiovascular magnetic resonance based evaluation of myocardial strain and relationship with late gadolinium enhancement. J Cardiovasc Magn Reson 2019; 21: 46.

33) van Wijngaarden SE, Ben Said-Bouyeri S, Ninaber MK, Huizinga TWJ, Schalij MJ, Bax JJ, Delgado V, de Vries-Bouwstra JK, Marsan NA. Progression of left ventricular myocardial dysfunction in systemic sclerosis: a speckle-tracking strain echocardiography study. J Rheumatol 2019; 46: 405-415.

34) Cojan Minzat BO, Cionca C, Mihalcea I, Lupu S, Agoston-Coldea L. Clinical utility of echocardiography and magnetic resonance imaging for detecting cardiac complications in systemic sclerosis. A case report. Med Ultrason 2015; 17: 262-265.

35) Ntusi NA, Piechnik SK, Francis JM, Ferreira VM, Rai AB, Matthews PM, Robson MD, Moon J, Wordsworth PB, Neubauer S, Karamitsos TD. Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis – a clinical study using myocardial T1-mapping and extracellular volume quantification. J Cardiovasc Magn Reson 2014; 16: 21.

36) Krumm P, Mueller KAL, Klingel K, Kramer U, Horger MS, Zitzelsberger T, Kandolf R, Gawaz M, Nikolaou K, Klumpp BD, Henes JC. Cardiovascular magnetic resonance patterns of biopsy proven cardiac involvement in systemic sclerosis. J Cardiovasc Magn Reson 2017; 18: 70.

37) Mousseaux E, Agoston-Coldea L, Marjanovic Z, Stanciu R, Deligny C, Perdrix L, Boutouyrie P, Azarine A, Soulat G, Farge D. Left ventricle replacement fibrosis detected by CMR associated with cardiovascular events in systemic sclerosis patients. J Am Coll Cardiol 2018; 71: 703-705.

38) Gargani L, Todiere G, Guiducci S, Bruni C, Pingitore A, De Marchi D, Bellando Randone S, Aquaro GD, Bazzichi L, Mosca M, Lombardi M, Pepe A, Matucci-Cerinic M, Picano E. Early detection of cardiac involvement in systemic sclerosis. JACC Cardiovasc Imaging 2019; 12: 927-928.

39) Lee DC, Hinchcliff ME, Sarnari R, Stark MM, Lee J, Koloms K, Hoffmann A, Carns M, Thakrar A, Aren K, Varga J, Aquino A, Carr JC, Benefield BC, Shah SJ. Diffuse cardiac fibrosis quantification in early systemic sclerosis by magnetic resonance imaging and correlation with skin fibrosis. J Scleroderma Relat Disord 2018; 3: 159-169.

40) Tipparot T, Foocharoen C, Mahakkanukrauh A, Suwannaroj S, Nanagara R, Pussadhamma B, Chaosuwannakit N. Clinical and laboratory predictions of myocardial inflammation as detected by cardiac magnetic resonance imaging in patients with systemic sclerosis: a pilot study. Int J Rheum Dis 2019; 22: 2125-2133.

41) Sugiyama K, Kobayashi H, Kobayashi Y, Yokoe I, Takei M, Kitamura N. Association of cardiac magnetic resonance-detected myocardial abnormalities with disease characteristics and brain natriuretic peptide levels in systemic sclerosis without cardiac symptoms. Int J Rheum Dis 2019; 22: 1016-1022.

42) Bratis K, Lindholm A, Hesselstrand R, Arheden H, Karabela G, Stavropoulos E, Katsifis G, Kolovou G, Kitas GD, Sfikakis PP, Koutsogeorgopoulou L, Mavrogeni S, Ostenfeld E. CMR feature tracking in cardiac asymptomatic systemic sclerosis: clinical implications. PLoS One 2019; 14: e0221021.

43) Poindron V, Chatelus E, Canuet M, Gottenberg J-E, Arnaud L, Gangi A, Gavand P-E, Guffroy A, Korganow AS, Germain P, Sibilia J, El Ghannudi S, Martin T. T1 mapping cardiac magnetic resonance imaging frequently detects subclinical diffuse myocardial fibrosis in systemic sclerosis patients. Semin Arthritis Rheum 2020; 50: 128-134.

44) Markousis-Mavrogenis G, Koutsogeorgopoulou L, Katsifis G, Dimitroulas T, Kolovou G, Kitas GD, Sfikakis PP, Mavrogeni SI. The double-edged sword of t1-mapping in systemic sclerosis--a comparison with infectious myocarditis using cardiovascular magnetic resonance. Diagnostics 2020; 10: 335.

45) Terrier B, Dechartres A, Gouya H, Ben Arfi M, Bérézne A, Régent A, Dunogué B, London J, Cohen P, Guillevin L, Le Jeunne C, Legmann P, Vignaux O, Mouthon L. Cardiac intravoxel incoherent motion diffusion-weighted magnetic resonance imaging with T1 mapping to assess myocardial perfusion and fibrosis in systemic sclerosis: association with cardiac events from a prospective cohort study. Arthritis Rheumatol 2020; 72:1571-1580.

46) Sahin ST, Yilmaz N, Cengiz B, Yurdakul S, Cagatay Y, Kaya E, Aytekin S, Yavuz S. Subclinical biventricular systolic dysfunction in patients with systemic sclerosis. Eur J Rheumatol 2019; 6: 89-93.

47) Lammi MR, Saketkoo LA, Gordon JK, Lauto P, Fagan K, Steen VD. Clinical characteristics and survival of systemic sclerosis patients with pulmonary hypertension and elevated wedge pressure: observations from the PHAROS cohort. Respirology 2017; 22: 1386-1392.

48) D'Alto M, Romeo E, Argiento P, Mattera Iacono A, Vettori S, Riccardi A, Allanore Y, D'Andrea A, Rea G, Bossone E, Valentini G, Naeije R, Golino P. Hemodynamic changes after acute fluid loading in patients with systemic sclerosis without pulmonary hypertension. Pulm Circ 2019; 9: 204589401881608.

49) Hinchcliff M, Desai CS, Varga J, Shah SJ. Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. Clin Exp Rheumatol 2012; 30(2 Suppl 71): S30-S37.

50) Lee SW, Choi EY, Jung SY, Choi ST, Lee SK, Park YB. E/E' ratio is more sensitive than E/A ratio for detection of left ventricular diastolic dysfunction in patients with systemic sclerosis. Clin Exp Rheumatol 2010; 28(2 Suppl 58): S12-S17.

51) Maione S, Cuomo G, Giunta A, Tanturridehoratio L, Lamontagna G, Manguso F, Alagia I, Valentini G. Echocardiographic alterations in systemic sclerosis: a longitudinal study. Semin Arthritis Rheum 2005; 34: 721-727.

52) Valentini G, Vitale DF, Giunta A, Maione S, Gerundo G, Arnese M, Tirri E, Pelaggi N, Giacummo A, Tirri G, Condorelli M. Diastolic abnormalities in systemic sclerosis: evidence for associated defective cardiac functional reserve. Ann Rheum Dis 1996; 55: 455-460.

53) Roque MC de F, Sampaio-Barros PD, Arruda AL, Gomes SB, Becker D, Andrade JL de, Rodrigues ACT. Evaluation of left ventricular diastolic function by echocardiography with tissue doppler in systemic sclerosis. Arq Bras Cardiol 2017; 109: 410-415.

54) Chighizola C, Meroni PL, Schreiber BE, Coghlan JG, Denton CP, Ong VH. Role of N-terminal probrain natriuretic peptide in detecting clinically significant cardiac involvement in systemic sclerosis patients. Clin Exp Rheumatol 2012; 30(2 Suppl 71): S81-S85.

55) Dimitroulas T, Giannakoulas G, Papadopoulou K, Karvounis H, Dimitroula H, Koliakos G, Karamitsos T, Parcharidou D, Settas L. Early detection of cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography: relationship with neurohormonal activation and endothelial dysfunction. J Rheumatol 2010; 37: 993-999.

56) Giunta A. Right ventricular diastolic abnormalities in systemic sclerosis. Relation to left ventricular involvement and pulmonary hypertension. Ann Rheum Dis 2000; 59: 94-98.

57) Bewley AP, Cooper JP, Levell NJ, Walker JM, Dowd PM. Systemic sclerosis associated with right ventricular cardiomyopathy. Br J Dermatol 1996; 134: 1141-1143.

58) Hachulla AL, Launay D, Gaxotte V, de Groote P, Lamblin N, Devos P, Hatron P-Y, Beregi J-P, Ha-

chulla E. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. Ann Rheum Dis 2009; 68: 1878-1884.

59) Bezante GP, Rollando D, Sessarego M, Panico N, Setti M, Filaci G, Molinari G, Balbi M, Cutolo M, Barsotti A, Indiveri F, Ghio M. Cardiac magnetic resonance imaging detects subclinical right ventricular impairment in systemic sclerosis. J Rheumatol 2007; 34: 2431-2437.

60) Hesselstrand R, Scheja A, Wuttge D, Arheden H, Ugander M. Enlarged right-sided dimensions and fibrosis of the right ventricular insertion point on cardiovascular magnetic resonance imaging is seen early in patients with pulmonary arterial hypertension associated with connective tissue disease. Scand J Rheumatol 2011; 40: 133-138.

61) Alexander EL. Reversible cold-induced abnormalities in myocardial perfusion and function in systemic sclerosis. Ann Intern Med 1986; 105: 661-668.

62) Follansbee WP, Curtiss EI, Medsger TA, Owens GR, Steen VD, Rodnan GP. Myocardial function and perfusion in the CREST syndrome variant of progressive systemic sclerosis. Am J Med 1984; 77: 489-496.

63) Nakajima K, Matsuo S, Hasegawa M, Kinuya S, Takehara K. Identification of myocardial damage in systemic sclerosis: a nuclear cardiology approach. Int J Rheumatol 2010; 2010: 496509.

64) Nakajima K. Normal values for nuclear cardiology: Japanese databases for myocardial perfusion, fatty acid and sympathetic imaging and left ventricular function. Ann Nucl Med 2010; 24: 125-135.

65) Lin CC, Ding HJ, Chen YW, Wang JJ, Ho ST, Kao A. Usefulness of technetium-99 m sestamibi myocardial perfusion SPECT in detection of cardiovascular involvement in patients with systemic lupus erythematosus or systemic sclerosis. Int J Cardiol 2003; 92: 157-161.

66) Vignaux O. Evaluation of the effect of nifedipine upon myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue Doppler echocardiography in systemic sclerosis. Ann Rheum Dis 2005; 64: 1268-1273.

67) Allanore Y, Meune C, Kahan A. Outcome measures for heart involvement in systemic sclerosis. Rheumatology 2008; 47: v51-v53.

68) Kobayashi H, Yokoe I, Hirano M, Nakamura T, Nakajima Y, Fontaine KR, Giles JT, Kobayashi Y. Cardiac magnetic resonance imaging with pharmacological stress perfusion and delayed enhancement in asymptomatic patients with systemic sclerosis. J Rheumatol 2009; 36: 106-112.

69) Fernandes F, Ramires FJA, Arteaga E, Ianni BM, Bonfá ESDO, Mady C. Cardiac remodeling in patients with systemic sclerosis with no signs or symptoms of heart failure: an endomyocardial biopsy study. J Card Fail 2003; 9: 311-317.

70) Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM. Myocardial lesions of progressive systemic sclerosis. A cause of cardiac dysfunction. Circulation 1976; 53: 483-490.

71) Mewton N, Liu CY, Croisille P, Bluemke D, Lima JAC. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011; 57: 891-903.

72) Iles LM, Ellims AH, Llewellyn H, Hare JL, Kaye DM, McLean CA, Taylor AJ. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. Eur Hear J Cardiovasc Imaging 2015; 16: 14-22.

73) Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. J Mol Cell Cardiol 2016; 90: 84-93.

74) Dziadzio M, Giovagnoni A, Pomponio G, Recanatini A, della Costanza OP, Manzin A, Casagrande W, Gabrielli A. Acute myocarditis associated with adenoviral infection in a patient with scleroderma. Clin Rheumatol 2003; 22: 487-490.

75) Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation. J Am Coll Cardiol 2018; 72: 3158-3176.

76) Nassenstein K, Breuckmann F, Huger M, Ladd SC, Schlosser T, Kreuter A, Barkhausen J. Detection of myocardial fibrosis in systemic sclerosis by contrast-enhanced magnetic resonance imaging. Rofo 2008; 180: 1054-1060.

77) Rodriguez-Reyna TS, Morelos-Guzman M, Hernandez-Reyes P, Montero-Duarte K, Martinez-Reyes C, Reyes-Utrera C, Vazquez-La Madrid J, Morales-Blanhir J, Nunez-Alvarez C, Cabiedes-Contreras J. Assessment of myocardial fibrosis and microvascular damage in systemic sclerosis by magnetic resonance imaging and coronary angiotomography. Rheumatology 2015; 54: 647-654.

78) Nicholson PJ, Hegarty C, Jackson M, Keane D, Fitzgerald O, Bresnihan B, Veale D, Dodd JD. Pulmonary fibrosis in systemic sclerosis. J Thorac Imaging 2012; 27: 44-50.

79) Mavrogeni SI, Buch M, Markousis-Mavrogenis G, Dumitru B, Pugliese NR, Gargani L. The perpetual sword of Damocles: cardiac involvement in systemic sclerosis and the role of non-invasive imaging modalities in medical decision making. Eur J Rheumatol 2020; 7: 203-211.

80) Jellis CL, Kwon DH. Myocardial T1 mapping: modalities and clinical applications. Cardiovasc Diagn Ther 2014; 4: 126–137

81) Burt JR, Zimmerman SL, Kamel IR, Halushka M, Bluemke DA. Myocardial T1 mapping: techniques and potential applications. RadioGraphics 2014; 34: 377-395.

82) Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, Bullo A, Cazzato M, Tirri E, Storino F, Giuggioli D, Cuomo G, Rosada M, Bombardieri S, Todesco S, Tirri G. Systemic sclerosis. Medicine (Baltimore) 2002; 81: 139-153.

83) Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. Best Pract Res Clin Rheumatol 2010; 24: 387-400.

84) Dunne JV, Chou JP, Viswanathan M, Wilcox P, Huang SH. Cardiac tamponade and large pericardial effusions in systemic sclerosis. Clin Rheumatol 2011; 30: 433-438.

85) Maksimović R, Seferović PM, Ristić AD, Vujisić-Tešić B, Simeunović DS, Radovanović G, Matucci-Cerinic M, Maisch B. Cardiac imaging in rheumatic diseases. Rheumatology 2006; 45: iv26-iv31.

86) Masui T, Finck S, Higgins CB. Constrictive pericarditis and restrictive cardiomyopathy: evaluation with MR imaging. Radiology 1992; 182: 369-373.

87) Pennel D. Clinical indications for cardiovascular magnetic resonance (CMR): consensus panel report? Eur Heart J 2004; 25: 1940-1965.

88) D'Angelo WA, Fries JF, Masi. AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). Am J Med 1969; 46: 428-440.

89) Croisille P. Comment je fais la différence en IRM entre une cardiomyopathie restrictive et une péricardite constrictive en présence d'une adiastolie ? J Radiol 2010; 91: 630-638.

90) Knockaert DC. Cardiac involvement in systemic inflammatory diseases. Eur Heart J 2007; 28: 1797-1804.

91) Kazzam E, Waldenström A, Landelius J, Hällgren R, Arvidsson A, Caidahl K. Non-invasive assessment of left ventricular diastolic function in patients with systemic sclerosis. J Intern Med 1990; 228: 183-192.

92) Michalska-Kasiczak M, Bielecka-Dabrowa A, von Haehling S, Anker SD, Rysz J, Banach M. Biomarkers, myocardial fibrosis and co-morbidities in heart failure with preserved ejection fraction: an overview. Arch Med Sci 2018; 14: 890-909.

93) Hoeper MM, Humbert M. The new haemodynamic definition of pulmonary hypertension: evidence prevails, finally! Eur Respir J 2019; 53: 1900038.

94) Rose-Jones L, Mclaughlin V. Pulmonary hypertension: types and treatments. Curr Cardiol Rev 2014; 11: 73-79.

95) Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, Mouthon L, Hatron PY, Jego P, Allanore Y, Tiev KP, Agard C, Cosnes A, Cirstea D, Constans J, Farge D, Viallard JF, Harle JR, Patat F, Imbert B, Kahan A, Cabane J, Clerson P, Guillevin L, Humbert M; Itinér AIR-Sclérodermie Study Group. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009; 60: 1831-1839.

96) MacGregor AJ. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology 2001; 40: 453-459.

97) Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, Kahan A, Cabane J, Francès C, Launay D, Mouthon L, Allanore Y, Tiev KP, Clerson P, Groote P de, Humbert M. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005; 52: 3792-3800.

98) Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, Tiev K, Cappelli S, Diot E, Vacca A, Cracowski JL, Sibilia J, Kahan A, Matucci-Cerinic M, Allanore Y. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010; 37: 2290-2298.

99) Denton CP, Pope JE, Peter H-H, Gabrielli A, Boonstra A, van den Hoogen FHJ, Riemekasten G, De Vita S, Morganti A, Dolberg M, Berkani O, Guillevin L. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheum Dis 2007; 67: 1222-1228.

100) Hsu VM, Moreyra AE, Wilson AC, Shinnar M, Shindler DM, Wilson JE, Desai A, Seibold JR. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. J Rheumatol 2008; 35: 458-465.

101) Mukerjee D. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology 2004; 43: 461-466.

102) Dimitroulas T, Mavrogeni S, Kitas GD. Imaging modalities for the diagnosis of pulmonary hypertension in systemic sclerosis. Nat Rev Rheumatol 2012; 8: 203-213.

103) Swift AJ, Wild JM, Nagle SK, Roldán-Alzate A, François CJ, Fain S, Johnson K, Capener D, van Beek EJR, Kiely DG, Wang K, Schiebler ML. Quantitative magnetic resonance imaging of pulmonary hypertension. J Thorac Imaging 2014; 29: 68-79.

104) Kondo C, Caputo GR, Masui T, Foster E, O'Sullivan M, Stulbarg MS, Golden J, Catterjee K, Higgins CB. Pulmonary hypertension: pulmonary flow quantification and flow profile analysis with velocity-encoded cine MR imaging. Radiology 1992; 183: 751-758.

105) Bogren HG, Klipstein RH, Mohiaddin RH, Firmin DN, Underwood SR, Rees RSO, Longmore DB. Pulmonary artery distensibility and blood flow patterns: a magnetic resonance study of normal subjects and of patients with pulmonary arterial hypertension. Am Heart J 1989; 118: 990-999.

106) Kang K-W, Chang H-J, Kim Y-J, Choi B-W, Lee HS, Yang W-I, Shim C-Y, Ha J, Chung N. Cardiac magnetic resonance imaging-derived pulmonary artery distensibility index correlates with pulmonary artery stiffness and predicts functional capacity in patients with pulmonary arterial hypertension. Circ J 2011; 75: 2244-2251.

107) Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: what can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol 2012; 110: S25-S31.

108) Overbeek MJ, Lankhaar J-W, Westerhof N, Voskuyl AE, Boonstra A, Bronzwaer JGF, Marques KMJ, Smit EF, Dijkmans BAC, Vonk-Noordegraaf A. Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. Eur Respir J 2008; 31: 1160-1166.

109) Bredfelt A, Rådegran G, Hesselstrand R, Arheden H, Ostenfeld E. Increased right atrial volume measured with cardiac magnetic resonance is associated with worse clinical outcome in patients with pre-capillary pulmonary hypertension. ESC Hear Fail 2018; 5: 864-875.

110) Rajaram S, Swift AJ, Capener D, Elliot CA, Condliffe R, Davies C, Hill C, Hurdman J, Kidling R, Akil M, Wild JM, Kiely DG. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. J Rheumatol 2012; 39: 1265-1274.

111) Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004; 147: 218-223.

112) Hagger D, Condliffe R, Woodhouse N, Elliot CA, Armstrong IJ, Davies C, Hill C, Akil M, Wild JM, Kiely DG. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. Rheumatology 2009; 48: 1137-1142.

113) Saba TS, Foster J, Cockburn M, Cowan M, Peacock AJ. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. Eur Respir J 2002; 20: 1519-1524.

114) Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot CA, Wild JM, Kiely DG. Diagnostic accuracy of cardiovascular magnetic resonance imaging of right ventricular morphology and function in the assessment of suspected pulmonary hypertension results from the ASPIRE registry. J Cardiovasc Magn Reson 2012; 14: 40.

115) Roeleveld RJ, Marcus JT, Boonstra A, Postmus PE, Marques KM, Bronzwaer JGF, Vonk-Noordegraaf A. A comparison of noninvasive MRI-based methods of estimating pulmonary artery pressure in pulmonary hypertension. J Magn Reson Imaging 2005; 22: 67-72.

116) Reiter U, Reiter G, Fuchsjäger M. MR phase-contrast imaging in pulmonary hypertension. Br J Radiol 2016; 89: 20150995.

117) Sanz J, Kariisa M, Dellegrottaglie S, Prat-González S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC Cardiovasc Imaging 2009; 2: 286-295.

118) Horvat D, Zlibut A, Orzan RI, Cionca C, Muresan ID, Mocan T, Revnic R, Agoston-Coldea L. Aging influences pulmonary artery flow and stiffness in healthy individuals: non-invasive assessment using cardiac MRI. Clin Radiol 2021; 76: 161.e19-161.e28.

119) Agoston-Coldea L, Lupu S, Mocan T. Pulmonary artery stiffness by cardiac magnetic resonance imaging predicts major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. Sci Rep 2018; 8: 14447.

120) Johns CS, Kiely DG, Rajaram S, Hill C, Thomas S, Karunasaagarar K, Garg P, Hamilton N, Solanki R, Capener DA, Elliot C, Sabroe I, Charalamopopoulos A, Condliffe R, Wild JM, Swift AJ. Diagnosis of pulmonary hypertension with cardiac MRI: derivation and validation of regression models. Radiology 2019; 290: 61-68.

121) Reiter G, Reiter U, Kovacs G, Kainz B, Schmidt K, Maier R, Olschewski H, Rienmueller R. Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. Circ Cardiovasc Imaging 2008; 1: 23-30.

122) Schäfer M, Barker AJ, Kheyfets V, Stenmark KR, Crapo J, Yeager ME, Truong U, Buckner JK, Fenster BE, Hunter KS. Helicity and vorticity of pulmonary arterial flow in patients with pulmonary hypertension: quantitative analysis of flow formations. J Am Heart Assoc 2017; 6: e007010.

123) Kheyfets VO, Schafer M, Podgorski CA, Schroeder JD, Browning J, Hertzberg J, Buckner JK, Hunter KS, Shandas R, Fenster BE. 4D magnetic resonance flow imaging for estimating pulmonary vascular resistance in pulmonary hypertension. J Magn Reson Imaging 2016; 44: 914-922.

124) Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, Mouthon L, Guillevin L, Meyer O, Ekindjian OG, Weber S, Kahan A. High N-terminal pro–brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008; 58: 284-291.

125) Williams MH, Handler CE, Akram R, Smith CJ, Das C, Smee J, Nair D, Denton CP, Black CM, Coghlan JG. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006; 27: 1485-1494.

126) Robertson L. Pulmonary arterial hypertension in systemic sclerosis: diagnostic pathway and therapeutic approach. Ann Rheum Dis 2005; 64: 804-807.

127) Hinchcliff M, Fischer A, Schiopu E, Steen VD. Pulmonary hypertension assessment and rec-

ognition of outcomes in scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol 2011; 38: 2172-2179.

128) Bae S, Saggar R, Bolster MB, Chung L, Csuka ME, Derk C, Domsic R, Fischer A, Frech T, Goldberg A, Hinchcliff M, Hsu V, Hummers L, Schiopu E, Mayes MD, McLaughlin V, Molitor J, Naz N, Furst DE, Maranian P, Steen V, Khanna D. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. Ann Rheum Dis 2012; 71: 1335-1342.

129) Michelakis ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D, Wang SH, Modry D, Archer SL. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. Circulation 2003; 108: 2066-2069.

130) Roeleveld RJ, Vonk-Noordegraaf A, Marcus JT, Bronzwaer JGF, Marques KMJ, Postmus PE, Boonstra A. Effects of epoprostenol on right ventricular hypertrophy and dilatation in pulmonary hypertension. Chest 2004; 125: 572-579.

131) van Wolferen SA, Boonstra A, Marcus JT, Marques KMJ, Bronzwaer JGF, Postmus PE, Vonk-Noordegraaf A. Right ventricular reverse remodelling after sildenafil in pulmonary arterial hypertension. Heart 2006; 92: 1860-1861.

132) Allanore Y, Meune C, Vignaux O, Weber S, Legmann P, Kahan A. Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and tissue-Doppler echography study. J Rheumatol 2006; 33: 2464-2469.

133) Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol 2008; 52: 1683-1692.