Heart Failure Reviews (2019) 24:489–498
https://doi.org/10.1007/s10741-019-09779-0

Pathophysiology and imaging of heart failure in women with autoimmune rheumatic diseases

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Published online: 4 March 2019
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Abstract

Autoimmune rheumatic diseases (ARDs) affect 8% of the population, and approximately 78% of them are women. Cardiovascular disease (CVD) in ARDs encompasses different pathophysiologic processes, such as endothelial dysfunction, myocardial/vascular inflammation and accelerated atherosclerosis with silent clinical presentation, leading to heart failure (HF), usually with preserved ejection fraction. Echocardiography and cardiovascular magnetic resonance (CMR) are the two most commonly used noninvasive imaging modalities for the evaluation of HF in patients with ARDs. Echocardiography currently represents the main diagnostic tool for cardiac imaging in clinical practice. However, the demand for more efficient and prompt diagnostic and therapeutic approach in this specific population necessitates the implementation of modalities capable of providing a more detailed and quantified information from the point of tissue characterization. Furthermore, echocardiography is an operator and acoustic window depended modality, with relatively low reproducibility and unable to perform tissue characterization. CMR is a noninvasive modality without radiation that can give reproducible and operator-independent information about both myocardial function and tissue characterization. By providing quantification of oedema, stress perfusion defects and fibrosis, CMR can diagnose myocardial inflammation, micro–macro-vascular myocardial ischemia and replacement or diffuse fibrosis, respectively. Tissue characterization allows for moving beyond the cardiac function to the assessment of intra- and inter-cellular alterations and promotes the development of personalized cardiac and anti-rheumatic treatment in ARDs with HF. ARDs are mainly female diseases. Cardiac involvement leading in HF is not unusual in ARDs and remains the main cause of death. Noninvasive, nonradiating imaging modalities such as echocardiography and CMR represent the main diagnostic tools. Specifically, echocardiography represents the first diagnostic approach; however, it is CMR that gives information about the pathophysiologic background behind HF in ARDs.

Keywords Heart failure · Echocardiography · Cardiovascular magnetic resonance · Nuclear imaging · Cardiovascular computed tomography · Myocardial perfusion–fibrosis · Coronary artery disease · Vasculitis · Rheumatic cardiovascular disease · Myocarditis

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Introduction

Definition of heart failure

Heart failure (HF) is a syndrome caused by any structural or functional impairment of ventricular filling or blood ejection [1]. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2013 guidelines have classified HF into two categories: (i) HF with reduced (≤ 40%) ejection fraction (HFrEF) or systolic HF and (ii) HF with preserved (≥ 50%) ejection fraction (HFpEF) or diastolic HF, with the diagnosis established by exclusion of all potential noncardiac causes of HF [1]. HFpEF should be differentiated from HFrEF, because etiology, pathophysiology and especially clinical management may be significantly different. Compared to HFrEF, patients with HFpEF are older, usually female with higher prevalence of hypertension and atrial fibrillation and lower prevalence of CAD. During the last two decades, the prevalence of HFpEF has risen from 38 to 54% [2].

Although it is believed that HF is primarily a male disease, due to the higher incidence of CAD in males, most patients with HF are elderly women with preserved EF. There are differences in HF presentation between women and men in epidemio-logy, etiology, pathogenesis, response to treatment and prognosis [3], and the potential mechanisms can be classified into three groups [4]: (a) inherent differences between genders in both disease manifestations and treatment response, (b) different frequency between sexes in disease severity and comorbidities and (c) guidelines are applied in a different way according to sex.

The role of inflammation in HF has been recognized very early, since Braunwald in 1956 identified for first time an increase in C-reactive protein (CRP) during HF [5]. Other investigators have also confirmed that pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), tumour necrosis factor-α (TNF-α) and their receptors are also increased in HF [6, 7]. In HFpEF, high CRP is associated with greater comorbidity. However, CRP was normal in 40% of patients not only supporting the role of systemic inflammation in HFpEF but also emphasizing the need for further biomarkers [8].

Systemic inflammation is the main characteristic of autoimmune rheumatic diseases (ARDs). Great progress has been recently done in the management of musculoskeletal symptoms of ARDs. However, cardiovascular involvement still remains the main cause of death in these patients [9].

Noninvasive imaging modalities are currently the first-line approach to evaluate subclinical and/or clinically overt HF (Table 1). In this review, we aim to discuss the role of various imaging modalities in the assessment of pathophysiologic background of HF in women with ARDs, emphasizing the emerging role of cardiovascular magnetic resonance (CMR).

Heart failure in women with autoimmune rheumatic diseases

ARDs affect 8% of the population, and approximately 78% of patients are women [10]. Gender differences are the result of various factors including sex hormones, microchimerism, genes on X or Y chromosomes, X chromosome inactivation and differing responses to environmental factors [10]. Estrogens may directly increase ARDs in women by elevating autoantibodies and amplifying autoreactive T and B cell responses [11]. Although ARDs affect several organs and tissues, their prognosis is mainly linked to cardiovascular damage. However clinical symptoms of heart involvement are not typical and can be misinterpreted as signs of the underlying systemic disease rather than manifestations of cardiac involvement [11]. Therefore, CVD in ARDs is commonly neglected as the interest of rheumatologists is predominantly attracted by the systemic disease [12]. The chronic effect of systemic inflammation on cardiovascular system results in endothelial dysfunction, myocardial/vascular inflammation and accelerated atherosclerosis all of which contribute to the increased CVD mortality and morbidity, observed in ARDs [13]. Besides the inflammatory burden, the cardiotoxic effects of several anti-rheumatic drugs also contribute to high incidence of CVD in ARDs [14]. Causes of HF in ARDs are presented in Fig. 1.

Female preponderance is observed in rheumatoid arthritis (RA) (9F/1M) [15], systemic lupus erythematosus (SLE) (9F/1M) [16], systemic sclerosis (SSc) (3F/1M) [17], mixed connective tissue diseases (MCTD) (3.3F/1M) [18] and dermatomyositis/polymyositis (2F/1M) [19]. In some types of systemic vasculitides, there is a female preponderance as in Takayasu vasculitis [20], while in others, a male preponderance as in Kawasaki disease [21].

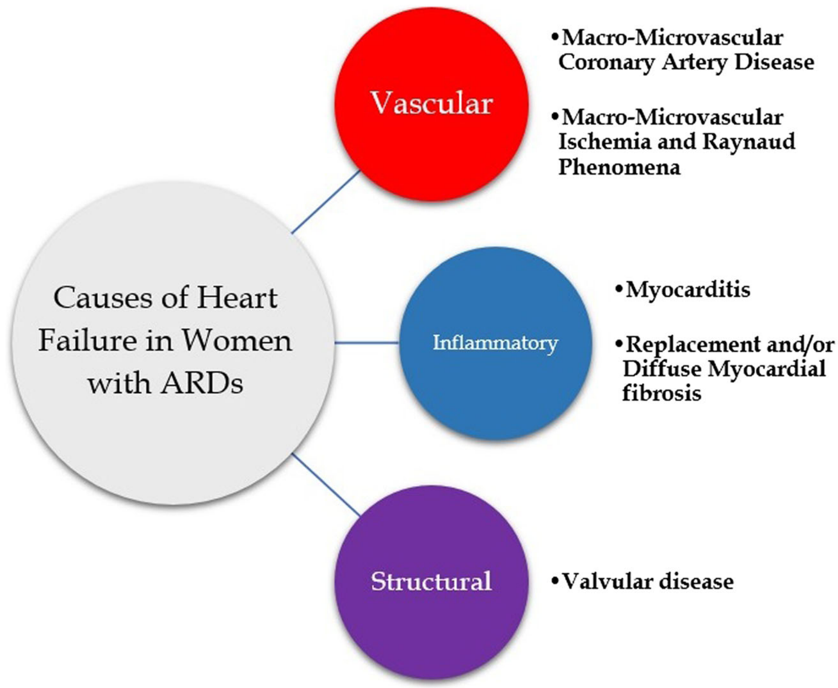
CVD is increased in rheumatoid arthritis (RA) [22], systemic lupus erythematosus (SLE) [23], systemic sclerosis (SSc) [24], inflammatory myopathies (IM) [25], mixed connective tissue diseases (MCTD) [26] and systemic vasculitides [27]. HF in ARDs is the result of various pathophysiologic processes including myopericarditis, atherosclerotic or

Table 1 Pro and contra of various imaging modalities in the evaluation of cardiac involvement in ARDs

Modality	Early disease	Therapy response	Cost	Radiation	Availability	Perfusion	Coronary arteries
CA	–	–	High	High	High	–	Yes
Echo	±	±	Low	No	High	±	No
CMR	+	+	High	No	Low	+++	Yes
CT	±	±	High	High	High	±	Yes
PET	+	+	High	Low	Low	+++	No

CA X-ray coronary artery angiography, *Echo* echocardiogram, *CMR* cardiac magnetic resonance imaging, *CT* computed tomography, *PET* positron emission tomography

Fig. 1 Causes of HF in ARDs



inflammatory coronary artery disease and/or spasm, microvascular disease, valvular heart disease and also the effect of immunosuppressive medication. HF at early stages is typically presented as diastolic dysfunction, a precursor of HF with preserved ejection fraction (HFpEF), which characterizes the whole spectrum of ARDs, irrespective of the underlying pathogenetic mechanisms. HF with HFpEF has been demonstrated in RA [28] and SLE [29], while a recent study in 275 SSc patients documented LV diastolic dysfunction as an independent predictor of mortality in SSc [30]. Taking all together, diastolic dysfunction in ARDs reflects the influence of chronic cumulative inflammatory leading to myocardial fibrosis and reduced contractility [31].

More specifically, CVD in RA occurs a decade earlier than age- and sex-matched controls and RA patients are twice more likely to develop myocardial infarction and HF irrespective of age, past CVD or traditional CV risk factors and shares similarities with diabetes mellitus (DM) [32]. Furthermore, RA increases the risk of nonischemic cardiomyopathy, valvular heart disease and myopericarditis, all of them leading to HF. Additionally, silent diffuse myocardial fibrosis may lead to LV dysfunction and consequent HF [33]. In a recent echocardiographic study, RA was associated with concentric remodeling and abnormal LV geometry [34, 35]. Furthermore, diastolic dysfunction associated with disease duration and IL-6 levels was identified in RA patients using echocardiography [36].

CVD in SLE leading to HF includes myopericarditis, dilated cardiomyopathy, macro–microcoronary artery disease, diastolic dysfunction, vasculitis or valvular disease and represents an important contributor to increased mortality [37, 38].

Cardiac involvement is common in SSc and affects all cardiac structures. SSc has the highest mortality amongst all ARDs, with an estimated 10 year survival of 66–82% [39–42]. After the recent improvements in the treatment of renal crisis and pulmonary hypertension, SSc patients are currently dying mainly due to non-SSc related causes, which account for 50% of all SSc deaths [39–43]. Specifically, CVD accounts for 20–30% of all SSc deaths [43]. Microvascular disease of the myocardium may lead to angina pectoris, acute myocardial infarction or both. Additionally, recurrent vasospasm, together with irreversible structural lesions, may lead to repeated focal ischemia and consequent myocardial fibrosis—the cornerstone of SSc-related heart disease [44]. Furthermore, inflammation presenting either as myocarditis [45] or as acute, diffuse, subendocardial vasculopathy leading to diffuse subendocardial fibrosis [46] may also contribute to increased CVD mortality.

Dermatomyositis (DM) and polymyositis (PM) are common idiopathic inflammatory myopathies that affect mainly women. Heart involvement in DM/PM represents one of the major causes of death in these diseases but the early detection is difficult, as clinically overt cardiac involvement is rare. The most frequently clinical presentation includes HF (associated or not with myocarditis) and conduction abnormalities. Noninvasive approaches using ECG, echocardiography and/or biochemical markers have a place in the diagnosis; however, they suffer lack of sensitivity in identifying patients with subclinical cardiac involvement [47, 48].

Mixed connective tissue disease (MCTD) represents a distinct systemic autoimmune disease, characterized by an overlap of SEL, SSc, PM/DM and RA, in association with antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1snRNP) [49–56]. According to previous studies, one third of MCTD patients had an excellent prognosis; however, continuous treatment with corticosteroids and/or immunosuppressive medication was needed in another one third and a more aggressive disease was observed in the remaining one third [57–59].

Inflammation and fibrinoid necrosis of blood vessel wall are the typical characteristics of systemic vasculitides (SVs). They can be either primary or secondary, due to underlying SLE or RA. The classification of SV according to Chapel Hill Consensus Conference [60] depends on the predominant type of vessels affected. They can involve the aorta and its major branches, as in giant cell arteritis (GCA) and Takayasu arteritis (TA); medium-sized vessels, as in polyarteritis nodosa (PAN) and Kawasaki disease (KD); and small-sized vessels (arterioles, capillaries and venules), as in *granulomatosis with polyangiitis* (GPA), formerly known as Wegener granulomatosis, microscopic polyangiitis (MPA), *eosinophilic granulomatosis with* polyangiitis (EGPA)—traditionally termed Churg–Strauss syndrome and in mixed cryoglobulinemic vasculitis (MCV), amongst several other syndromes. GPA, MPA and EGPA share a common pathology with necrotizing granulomatous lesions without immune deposits, are characterized by anti-neutrophil cytoplasmic antibodies (ANCA) and grouped as ANCA-associated SVs [61]. HF in SVs includes valvular heart disease, myocarditis and microvascular coronary artery disease [61].

Noninvasive imaging modalities for the assessment of HF

Echocardiography and CMR are the two most commonly used noninvasive imaging modalities for the evaluation of HF in ARDs. However, cardiovascular computed tomography (CCT) and nuclear modalities (SPECT, PET) can also play a role in the assessment of great/peripheral vessels/coronary arteries and perfusion–viability evaluation, respectively [9].

Echocardiography is the first-line diagnostic tool in clinical practice (Fig. 1). Being bedside, widely available and cost effective has significantly contributed to the flexibility and independency of clinical decision making in cardiology [9] (Fig. 2). However, it is based on the assumption of ellipsoid shape of LV and therefore its application in HF may be problematic [9]. It has roughly classified HF as diastolic with preserved left ventricular ejection fraction (LVEF) and systolic and systolic HF with impaired LVEF. However, the necessity to be more efficient in the treatment of HF in ARDs demands information about tissue characterization. In this context, echocardiography can only give rough information about the existence of cardiac abnormalities, but it is unable to provide further assessment of the underlying pathophysiology such as oedema, perfusion defects and fibrosis, usually occurring in ARDs. Furthermore, it is operator and acoustic window depended modality [9]. Specifically in obese women and in those with increased breast size, or breast implants, the acoustic window can be severely distorted [9].

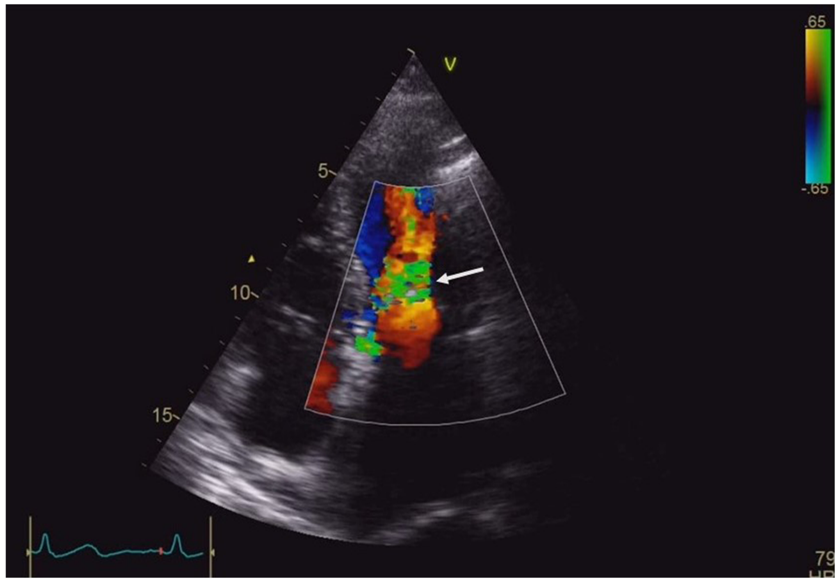
CCT can assess both stenotic and aneurysmatic lesions and can assess treatment follow-up in great and peripheral arteries. Additionally, it can evaluate coronary artery calcifications and serve as a tool to rule out significant coronary artery disease. However, it uses radiation and the contrast agents used for CCT imaging have a nephrotoxic effect [9].

Nuclear modalities include SPECT and PET. SPECT is widely available, but it uses radioactive tracers and has low spatial resolution, unable to detect small subendo- or subepicardial ischemic or fibrotic lesions, commonly found in ARDs. Compared with SPECT, PET has lower radiation, fewer artefacts, improved spatial resolution and better diagnostic performance. Due to its capacity to provide quantification of rest–peak stress left ventricular systolic function and coronary flow reserve, PET is superior to other modalities for the detection of multivessel coronary artery disease. Hybrid PET–CT scanners allow concurrent evaluation of myocardial perfusion and anatomic assessment of the epicardial coronary arteries offering great potential for better risk stratification and treatment. However, further studies are needed to validate the prognostic value and cost effectiveness of PET [9, 62].

CMR, a noninvasive modality without radiation, can give detailed, reproducible and operator-independent information about both myocardial function and tissue characterization. It is the gold standard for ventricular function evaluation and by providing quantification of oedema, stress perfusion defects and fibrosis can noninvasively diagnose myocardial inflammation, micro- and macro-vascular myocardial ischemia and replacement or diffuse fibrosis, respectively. Various patterns of replacement fibrosis in ARDs with HF are presented in Figs. 3, 4, 5 and 6. Finally, stress CMR is of special value in ARDs with HF, since most of patients are women unable to perform adequate exercise, due to musculoskeletal disease. Additionally, it can detect myocardial Raynaud phenomena, commonly found in ARDs and specifically in mixed connective tissue diseases and systemic sclerosis [9].

CMR is the ideal technique for tissue characterization, due to excellent spatial resolution. The signal intensity of CMR images is based on the magnetic properties of hydrogen nuclei in the patient's body. The two most commonly evaluated parameters are longitudinal relaxation time (T1) and transverse relaxation time (T2). T2 imaging can offer qualitative or semi-quantitative information about myocardial oedema using the ratio of myocardial vs skeletal signal intensity. Recently, a true quantitative approach of myocardial oedema using T2 and native (pre-contrast) T1 mapping has been proposed. T1 imaging can be also used for perfusion evaluation (first-pass assessment) or for fibrosis assessment using images taken

Fig. 2 Four chamber 2D echocardiographic image of a patient with juvenile rheumatoid arthritis and mitral stenosis



15 min post gadolinium injection (late enhanced imaging: LGE). The unique additional clinical utility of CMR compared to echocardiography is the use of LGE for the detection of replacement fibrosis, due to myocardial infarction (MI), myocarditis or cardiomyopathies. LGE is based on the differences of signal intensity between scarred and normal myocardium to generate image contrast. This technique, although of great utility for detecting replacement myocardial fibrosis, is incapable of visualising diffuse myocardial fibrosis. To overcome this limitation, another CMR imaging technique called T1 mapping (native/pre-contrast and post contrast) has been developed and enables identification of myocardial fibrosis, also otherwise undetectable by currently used circulating biomarkers. The use of T1/T2 mapping indices has demonstrated that patients with ARDs have higher T1 and T2 mapping values (more diffuse fibrosis and myocardial oedema) compared to controls, with most significant differences between patients and controls in native T1 and T2 mapping values, which are independent of the presence of LGE [63]. Furthermore, the application of native T1, T2 mapping techniques and extracellular volume fraction (ECV) allowed the quantification of myocardial oedema and diffuse fibrosis, respectively. Native T1 and T2 mapping are highly sensitive to myocardial water content and superior to the currently used T2-weighted short-tau imaging in detecting myocardial oedema [64]. ECV measurements can also be used as a surrogate measurement of diffuse fibrosis, as they have been shown to correlate well with histological indices of myocardial fibrosis in various clinical contexts [65]. There are no specific values of these indices for each ARD. There are normal values for

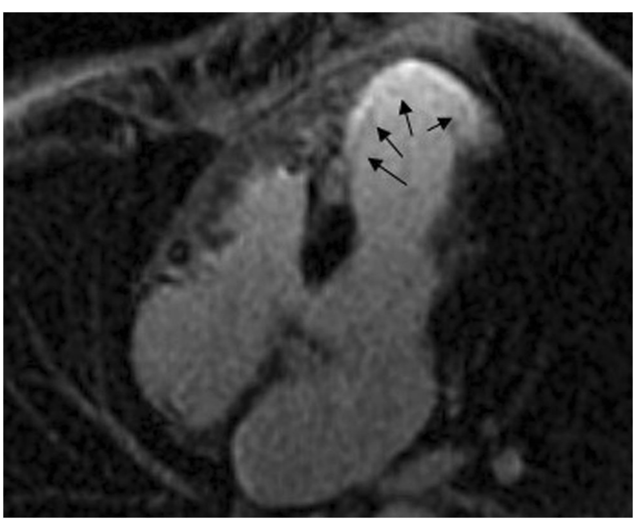


Fig. 3 Apical myocardial infarction in a patient with SLE

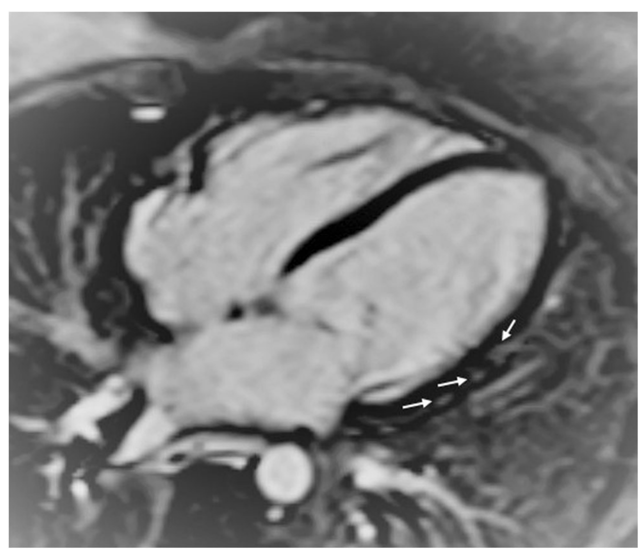


Fig. 4 Lateral wall subepicardial LGE, due to myocarditis, in a patient with SSc

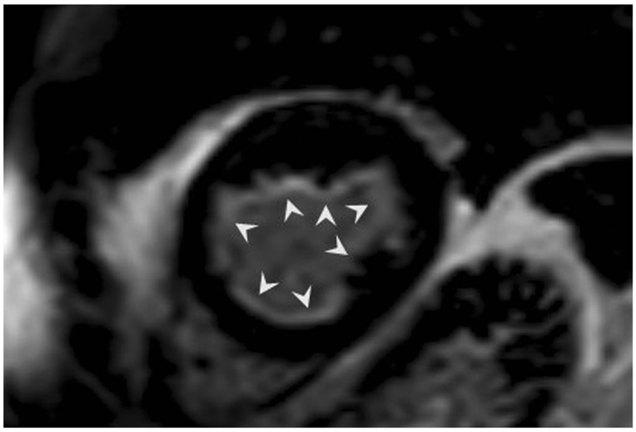


Fig. 5 Diffuse subendocardial fibrosis in a patient with CSS

each index, proposed by the international literature. However, every CMR department must create its own normal values and the diagnosis should be performed based on the clinical background of each disease [66]. Tissue characterization allows for moving beyond of functional capacity of the heart to the assessment of intra- and inter-cellular cardiac alterations promoting the development of personalized treatment. However, CMR is far more expensive than echocardiography, more time consuming and demands high expertise [9].

Recently, CMR detected subclinical myocardial disease in RA [67]. Myocarditis, already identified in autopsy series [63], has been now detected in vivo using CMR in RA patients [67]. Interestingly, LVEF, cardiac output and stroke volume are modestly lower in RA compared to controls [68]. Recent studies, using T1 mapping, documented frequent subclinical CVD in RA, including both focal and

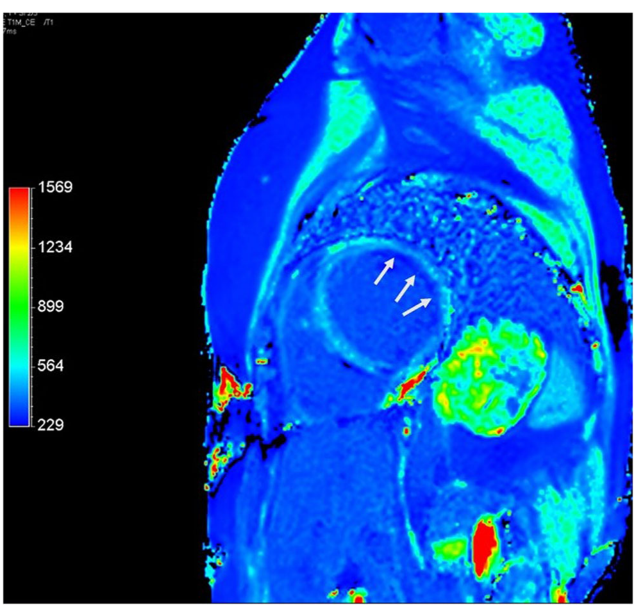


Fig. 6 T1 mapping showing subendocardial fibrosis in antero-lateral wall in a patient with SSc

diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and RA disease activity [69]. However, other CMR studies supported that cardiac structure and function were not significantly altered in RA and the amount of fibrosis was similar or lower in RA patients with low to moderate disease activity, compared to matched controls [70].

Cardiac lesions in SLE with HF are independent from disease duration/activity and may have an atypical presentation with normal echocardiographic findings [71]. CMR can assess occult cardiac lesions including vasculitis, myocarditis and myocardial infarction in SLE with atypical signs and normal echocardiographic findings and prompt the modification in both anti-rheumatic and cardiac treatment and/or closer follow-up for secondary prevention [72].

Other studies using T2 and T1 mapping detected subclinical CVD [68] and response to anti-inflammatory treatment [73], respectively. Furthermore, T2 mapping was increased in SLE patients, due to subclinical myocardial oedema, supporting that even in SLE with inactive disease and normal cardiac function, low-grade myocardial inflammation can be detected using novel quantitative CMR techniques [74].

CMR is currently considered as the strongest player in the diagnostic arena of cardiovascular imaging in SSc, due to its capability to perform excellent biventricular function, tissue characterization and reliable discrimination between myocardial inflammation and fibrosis. Additionally, it has better reproducibility, compared to both 2D and 3D echocardiography, specifically in patients with poor acoustic window, severe lung disease and dilated ventricles, as it is the majority of SSc [75].

CMR identified myocardial lesions in cardiac asymptomatic MCTD patients such as myocardial infarction, inflammation, diffuse subendocardial perfusion defects and fibrosis that need further cardiac investigation and/or treatment [76]. Furthermore, myocardial perfusion rate index (MPRI) was reduced in MCTD patients with Raynaud phenomenon promoting the development of HF [77].

CMR can reliably detect both cardiac and vascular inflammation in SVs. In large vessel vasculitis, CMR can detect vascular and myocardial inflammation, missed by echocardiography [78]. Finally, in ANCA-associated vasculitides, CMR demonstrated increased ECV, T1 and T2 mapping values, independently of the LGE presence [79].

Extensive comparative analyses between CMR and contemporary evaluation of endomyocardial biopsies (EMB) including histology, immunohistology as well as morphometry and quantification by digital image analysis are not present as in inflammatory cardiomyopathy [80, 81] for autoimmune rheumatic diseases, yet. Future analyses are warranted to evaluate the diagnostic yield and especially the therapeutic implications of this synergistic approach.

Conclusions

HF, specifically HFpEF, is common in women with ARDs and should be detected and treated early before clinically overt symptoms/signs will be developed. Therefore, close noninvasive evaluation using echocardiography and CMR is recommended. Echocardiography can give early information about "something is abnormal in the myocardium". However, it is CMR that can precisely assess the etiologic background of HF in ARDs and guide further risk stratification and both anti-rheumatic and cardiac treatment [82].

Algorithm for cardiac evaluation of ARD patients with cardiac involvement

At the moment, there is no internationally accepted algorithm about how to assess cardiac involvement in ARDs. According to the experience from our Cardio-Rheumatology Clinic, we propose the following algorithm.

1. Detailed history and examination including clinical and laboratory evaluation
2. Echocardiographic evaluation
3. Baseline CMR, because cardiac involvement may be silent and precede the diagnosis of ARD.
4. Arrhythmia evaluation using 24 h Holter recording
5. Coronary intervention if CMR shows evidence of myocardial ischemia and/or start of cardiac medication. Potential modification of rheumatic treatment if there is evidence of acute myocardial involvement

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References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 128:1810–1815
2. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE (2008) Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 101: 1016–1022
3. Petrie M, Dawson N, Murdoch D, Davie A, McMurray J (1999) Failure of women's hearts. Circulation. 99:2334–2341
4. Rumsfeld J, Masoudi F (2004) Sex differences: implications for heart failure care. Eur Heart J 25:101–103
5. Elster SK, Braunwald E, Wood HF (1956) A study of C-reactive protein in the serum of patients with congestive heart failure. Am Heart J 51:533–541
6. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL (2001) Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation 103:2055–2059
7. Levine B, Kalman J, Mayer L, Fillit HM, Packer M (1990) Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 323:236–241
8. DuBrock HM, AbouEzzeddine OF, Redfield MM (2018) High-sensitivity C-reactive protein in heart failure with preserved ejection fraction. PLoS One 13(8):e0201836
9. Mavrogeni SI, Kitas GD, Dimitroulas T, Sfikakis PP, Seo P, Gabriel S, Patel AR, Gargani L, Bombardieri S, Matucci-Cerinic M, Lombardi M, Pepe A, Aletras AH, Kolovou G, Miszalski T, van Riel P, Semb A, Gonzalez-Gay MA, Dessein P, Karpouzas G, Puntmann V, Nagel E, Bratis K, Karabela G, Stavropoulos E, Katsifis G, Koutsogeorgopoulou L, van Rossum A, Rademakers F, Pohost G, Lima JA (2016) Cardiovascular magnetic resonance in rheumatology: current status and recommendations for use. Int J Cardiol 217:135–148
10. Zandman-Goddard G, Peeva E, Shoenfeld Y (2007) Gender and autoimmunity. Autoimmun Rev 6:366–372
11. Fairweather D, Frisancho-Kiss S, Rose NR (2008) Sex differences in autoimmune disease from a pathologic perspective. Am J Pathol 173:600–609
12. Mavrogeni S, Dimitroulas T, Gabriel S, Sfikakis PP, Pohost GM, Kitas GD (2014) Why currently used diagnostic techniques for heart failure in rheumatoid arthritis are not enough: the challenge of cardiovascular magnetic resonance imaging. Rev Cardiovasc Med 15(4):320–331
13. Nurmohamed MT, Heslinga M, Kitas GD (2015) Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheumatol 11(12): 693–704
14. Gasparyan AY, Ayvazyan L, Cocco G, Kitas GD (2012) Adverse cardiovascular effects of antirheumatic drugs: implications for clinical practice and research. Curr Pharm Des 18(11):1543–1555
15. Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL (2011) Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995–2007 versus 1985–1994: a population-based study. J Rheumatol 38:983–989
16. Ramagopalan SV, Goldacre R, Skingsley A, Conlon C, Goldacre MJ (2013) Associations between selected immune-mediated diseases and tuberculosis: record-linkage studies. BMC Med 11:97
17. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA Jr (1997) Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963–1982. Arthritis Rheum 40(3):441–445
18. Gaubitz M (2006) Epidemiology of connective tissue disorders. Rheumatology 45:iii3–iii4
19. Carlos de Souza FE, Levy-Neto M, Katsuyuki Shinjo S (2011) Prevalence of clinical and laboratory manifestations and comorbidities in polymyositis according to gender. Rev Bras Reumatol 51(5)
20. Lim AY, Lee GY, Jang SY, Gwag HB, Choi SH, Jeon ES, Cha HS, Sung K, Kim YW, Kim SM, Choe YH, Kim DK (2015) Gender differences in clinical and angiographic findings of patients with Takayasu arteritis. Clin Exp Rheumatol 33(2 Suppl 89):S-132–S-137
21. Chang RK (2002) Epidemiologic characteristics of children hospitalized for Kawasaki disease in California. Pediatr Infect Dis J 21(12):1150–1155
22. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV et al (2005) The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 52:412–420

23. Schoenfeld SR, Kasturi S, Costenbader KH (2013) The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Semin Arthritis Rheum 43:77–95
24. Mavrogeni S, Karabela G, Koutsogeorgopoulou L, Stavropoulos E, Katsifis G, Plastiras SC, Kitas GD, Panopoulos S, Pentazos G, Tzatzaki E, Markousis-Mavrogenis G, Kolovou G, Sfikakis PP (2016) Pseudo-infarction pattern in diffuse systemic sclerosis. Evaluation using cardiovascular magnetic resonance. Int J Cardiol 214:465–468
25. Mavrogeni S, Sfikakis PP, Dimitroulas T, Kolovou G, Kitas GD (2014) Cardiac and muscular involvement in idiopathic inflammatory myopathies: noninvasive diagnostic assessment and the role of cardiovascular and skeletal magnetic resonance imaging. Inflamm Allergy Drug Targets 13(3):206–216
26. Mavrogeni S, Sfikakis PP, Dimitroulas T, Koutsogeorgopoulou L, Karabela G, Katsifis G, Stavropoulos E, Gialafos E, Spiliotis G, Kolovou G, Kitas GD (2015) Imaging patterns of cardiovascular involvement in mixed connective tissue disease evaluated by cardiovascular magnetic resonance. Inflamm Allergy Drug Targets. 14(2):111–116
27. Mavrogeni S, Markousis-Mavrogenis G, Kolovou G (2014) Cardiovascular magnetic resonance for evaluation of heart involvement in ANCA-associated vasculitis. A luxury or a valuable diagnostic tool? Inflamm Allergy Drug Targets. 13:305–311
28. Biskup M, Biskup W, Majdan M, Targońska-Stępniak B (2018) Cardiovascular system changes in rheumatoid arthritis patients with continued low disease activity. Rheumatol Int 38(7):1207–1215
29. Wislowska M, Dereń D, Kochmański M, Sypuła S, Rozbicka J (2009) Systolic and diastolic heart function in SLE patients. Rheumatol Int 29:1469–1476
30. Tennøe AH, Murbræch K, Andreassen JC, Fretheim H, Garen T, Gude E, Andreassen A, Aakhus S, Molberg Ø, Hoffmann-Vold AM (2018) Left ventricular diastolic dysfunction predicts mortality in patients with systemic sclerosis. J Am Coll Cardiol 72(15):1804–1813
31. Yndestad A, Damås JK, Øie E, Ueland T, Gullestad L, Aukrust P (2007) Role of inflammation in the progression of heart failure. Curr Cardiol Rep 9:236–241
32. Mavrogeni S, Karabela G, Stavropoulos E, Gialafos E, Sfendouraki E, Kyrou L, Kolovou G (2013) Imaging patterns of heart failure in rheumatoid arthritis evaluated by cardiovascular magnetic resonance. Int J Cardiol 168(4):4333–4335
33. Mavrogeni S, Bratis K, Sfendouraki E, Papadopoulou E, Kolovou G (2013) Myopericarditis, as the first sign of rheumatoid arthritis relapse, evaluated by cardiac magnetic resonance. Inflamm Allergy Drug Targets 12(3):206–211
34. Chung CP, Giles JT, Petri M, Szklo M, Post W, Blumenthal RS, Gelber AC, Ouyang P, Jenny NS, Bathon JM (2012) Prevalence of traditional modifiable cardiovascular risk factors in patients with rheumatoid arthritis: comparison with control subjects from the multi-ethnic study of atherosclerosis. Semin Arthritis Rheum 41(4):535–544
35. Sherer Y, Shoenfeld Y (2006) Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol 2(2):99–106
36. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, Stampfer MJ et al (2003) Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 107(9):1303–1307
37. Mavrogeni S, Karabela G, Stavropoulos E, Plastiras S, Spiliotis G, Gialafos E, Kolovou G, Sfikakis PP, Kitas GD (2014) Heart failure imaging patterns in systemic lupus erythematosus. Evaluation using cardiovascular magnetic resonance. Int J Cardiol 176(2):559–561
38. Mavrogeni S, Sfikakis PP, Gialafos E, Bratis K, Karabela G, Stavropoulos E, Spiliotis G, Sfendouraki E, Panopoulos S, Bournia V, Kolovou G, Kitas GD (2014) Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases. Arthritis Care Res (Hoboken) 66:104–112
39. Poudel DR, Derk CT (2018) Mortality and survival in systemic sclerosis: a review of recent literature. Curr Opin Rheumatol 30(6):588–593
40. Poudel DR, Jayakumar D, Danve A, Sehra ST, Derk CT (2018) Determinants of mortality in systemic sclerosis: a focused review. Rheumatol Int 38(10):1847–1858
41. 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, OprisD IF, Vlachoyiannopoulos PG, Stamenkovic B, Rosato E, Heitmann S, JHW D, Zenone T, Seidel M, Vacca A, Langhe E, Novak S, Cutolo M, Mouthon L, Henes J, Chizzolini C, CAV M, 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 (2017) Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 76(11):1897–1905
42. Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, Gonzalez-Juanatey C, Gonzalez-Gay MA (2008) Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine (Baltimore) 87:272–280
43. Mok MY, Lau CS (2010) The burden and measurement of cardiovascular disease in SSc. Nat Rev Rheumatol 6:430–434
44. Dimitroulas T, Giannakoulas G, Karvounis H, Garyfallos A, Settas L, Kitas GD (2014) Micro- and macrovascular treatment targets in scleroderma heart disease. Curr Pharm Des 20(4):536–544
45. Pêgo GM, Ramalho AR, Costa S, Silva F, Donato P, Franco F (2017) Autoimmune myocarditis in systemic sclerosis: an unusual form of scleroderma heart disease presentation. ESC Heart Fail 4(3):365–370
46. Mavrogeni S, Markousis-Mavrogenis G, Kolovou G (2011) Diffuse, subendocardial vasculitis identified by cardiovascular magnetic resonance. Use of images to learn pathophysiology. J Vasc 2(2):106
47. Mavrogeni S, Douskou M, Manoussakis MN (2011) Contrast-enhanced CMR imaging reveals myocardial involvement in idiopathic inflammatory myopathy without cardiac manifestations. JACC Cardiovasc Imaging 4(12):1324–1325
48. Huber AT, Bravetti M, Lamy J, Bacoyannis T, Roux C, de Cesare A, Rigolet A, Benveniste O, Allenbach Y, Kerneis M, Cluzel P, Kachenoura N, Redheuil A (2018) Non-invasive differentiation of idiopathic inflammatory myopathy with cardiac involvement from acute viral myocarditis using cardiovascular magnetic resonance imaging T1 and T2 mapping. J Cardiovasc Magn Reson 20(1):11
49. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR (1972) Mixed connective tissue disease: an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 52:148–159
50. Sharp GC (1987) Diagnostic criteria for classification of MCTD. In: Kasukawa R, Sharp GC (eds) Mixed connective tissue diseases and anti-nuclear antibodies. Elsevier, Amsterdam, pp 23–32
51. Kasukawa R, Too T, Miyawaki S et al (1987) Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC (eds) Mixed connective tissue diseases and anti-nuclear antibodies. Elsevier, Amsterdam, pp 41–47
52. Alarcon-Segovia D, Villareal M (1987) Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R,

Sharp GC (eds) Mixed connective tissue diseases and anti-nuclear antibodies. Elsevier, Amsterdam, pp 33–40
53. Cappelli S, Bellando Randone S, Martinović D, Tamas MM, Pasalić K, Allanore Y, Mosca M, Talarico R, Opris D, Kiss CG, Tausche AK, Cardarelli S, Riccieri V, Koneva O, Cuomo G, Becker MO, Sulli A, Guiducci S, Radić M, Bombardieri S, Aringer M, Cozzi F, Valesini G, Ananyeva L, Valentini G, Riemekasten G, Cutolo M, Ionescu R, Czirják L, Damjanov N, Rednic S, Matucci Cerinic M (2012) "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. Semin Arthritis Rheum 41:589–598
54. Habets WJ, de Rooij DJ, Salden MH et al (1983) Antibodies against distinct nuclear matrix proteins are characteristic for mixed connective tissue disease. Clin Exp Immunol 54:265–276
55. Mosca M (2014) Mixed connective tissue diseases: new aspects of clinical picture, prognosis and pathogenesis. Isr Med Assoc J 16(11):725–726
56. Nimelstein SH, Brody ST, McShane D, Holman HR (1980) Mixed connective tissue disease: a subsequent evaluation of the original 25 patients. Medicine 59:239–248
57. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC (1999) Long-term outcome in mixed connective tissue disease. Arthritis Rheum 42:899–909
58. Hajas A, Szodoray P, Nakken B, Gaal J, Zöld E, Laczik R, Demeter N, Nagy G, Szekanecz Z, Zeher M, Szegedi G, Bodolay E (2013) Clinical course prognosis, and causes of death in mixed connective tissue diseases. J Rheumatol 40:1134–1142
59. Tani C, Carli L, Vagnani S, Talarico R, Baldini C, Mosca M, Bombardieri S (2014) The diagnosis and classification of mixed connective tissue disease. J Autoimmun 48-49:46–49
60. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA (2013) 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65(1):1–11
61. Mavrogeni S, Markousis-Mavrogenis G, Kolovou G (2014) Cardiovascular magnetic resonance for evaluation of heart involvement in ANCA-associated vasculitis. A luxury or a valuable diagnostic tool? Inflamm Allergy Drug Targets 13:305–311
62. Di Carli MF, Murthy VL (2011) Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. Radiographics. 31(5):1239–1254
63. Mavrogeni S, Markousis-Mavrogenis G, Koutsogeorgopoulou L, Kolovou G (2017) Cardiovascular magnetic resonance imaging: clinical implications in the evaluation of connective tissue diseases. J Inflamm Res 10:55–61
64. Mavrogeni S, Apostolou D, Argyriou P, Velitsista S, Papa L, Efentakis S, Vernardos E, Kanoupaki M, Kanoupakis G, Manginas A (2017) T1 and T2 mapping in cardiology: "mapping the obscure object of desire". Cardiology. 138(4):207–217
65. Greulich S, Mayr A, Kitterer D, Latus J, Henes J, Vecchio F, Kaesemann P, Patrascu A, Greiser A, Groeninger S, Romeo F, Braun N, Alscher MD, Sechtem U, Mahrholdt H (2017) Advanced myocardial tissue characterisation by a multi-component CMR protocol in patients with rheumatoid arthritis. Eur Radiol 27(11):4639–4649
66. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson RB, Ugander M, van Heeswijk RB, Friedrich MG (2018) Correction to: Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 20(1):9
67. Kobayashi H, Kobayashi Y, Yokoe I, Akashi Y, Takei M, Giles JT (2017) Magnetic resonance imaging-detected myocardial inflammation and fibrosis in rheumatoid arthritis: associations with disease characteristics and N-terminal pro-brain natriuretic peptide levels. Arthritis Care Res 69(9):1304–1311
68. Kobayashi Y, Jon T, Giles JT, Hirano M, Yokoe I, Nakajima Y, Bathon JM, Lima JAC, H. (2010) Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. Arthritis Res Ther 12(5):R171
69. Ntusi NAB, Piechnik SK, Francis JM, Ferreira VM, Matthews PM, Robson MD, Wordsworth PB, Neubauer S, Karamitsos TD (2015) Diffuse myocardial fibrosis and inflammation in rheumatoid arthritis: insights from CMR T1 mapping. JACC Cardiovasc Imaging 8(5):526–536
70. Bradham W, Ormseth MJ, Elumogo C, Palanisamy S, Liu CY, Lawson MA, Soslow JH, Kawel-Boehm N, Bluemke DA, Stein CM (2018) Absence of fibrosis and inflammation by cardiac magnetic resonance imaging in rheumatoid arthritis patients with low to moderate disease activity. J Rheumatol 45(8):1078–1084
71. Mavrogeni S, Koutsogeorgopoulou L, Markousis-Mavrogenis G, Bounas A, Tektonidou M, Lliossis SC, Daoussis D, Plastiras S, Karabela G, Stavropoulos E, Katsifis G, Vartela V, Kolovou G (2018) Cardiovascular magnetic resonance detects silent heart disease missed by echocardiography in systemic lupus erythematosus. Lupus 27(4):564–571
72. Puntmann VO, D'Cruz D, Smith Z, Pastor A, Choong P, Voigt T, Carr-White G, Sangle S, Schaeffter T, Nagel E (2013) Native myocardial T1mapping by cardiovascular magnetic resonance imaging in subclinical cardiomyopathy in patients with systemic lupus erythematosus. Circ Cardiovasc Imaging 6(2):295–301
73. Hinojar R, Foote L, Sangle S, Marber M, Mayr M, Carr-White G, D'Cruz D, Nagel E, Puntmann VO (2016) Native T1 and T2 mapping by CMR in lupus myocarditis: disease recognition and response to treatment. Int J Cardiol 222:717–726
74. Zhang Y, Corona-Villalobos CP, Kiani AN, Eng J, Kamel IR, Zimmerman SL, Petri M (2015) Myocardial T2 mapping by cardiovascular magnetic resonance reveals subclinical myocardial inflammation in patients with systemic lupus erythematosus. Int J Cardiovasc Imaging 31(2):389–397
75. Mavrogeni SI, Schwitter J, Gargani L, Pepe A, Monti L, Allanore Y, Matucci-Cerinic M (2017) Cardiovascular magnetic resonance in systemic sclerosis: "pearls and pitfalls". Semin Arthritis Rheum 47(1):79–85
76. Mavrogeni S, Sfikakis PP, Dimitroulas T, Koutsogeorgopoulou L, Karabela G, Katsifis G, Stavropoulos E, Gialafos E, Spiliotis G, Kolovou G, Kitas GD (2015) Imaging patterns of cardiovascular involvement in mixed connective tissue disease evaluated by cardiovascular magnetic resonance. Inflamm Allergy Drug Targets 14(2):111–116
77. Mavrogeni S, Bratis K, Koutsogeorgopoulou L, Karabela G, Savropoulos E, Katsifis G, Raftakis J, Markousis-Mavrogenis G, Kolovou G (2017) Myocardial perfusion in peripheral Raynaud's phenomenon. Evaluation using stress cardiovascular magnetic resonance. Int J Cardiol 228:444–448
78. Mavrogeni S, Dimitroulas T, Chatziioannou SN, Kitas G (2013) The role of multimodality imaging in the evaluation of Takayasu arteritis. Semin Arthritis Rheum 42(4):401–412
79. Greulich S, Mayr A, Kitterer D, Latus J, Henes J, Steubing H, Kaesemann P, Patrascu A, Greiser A, Groeninger S, Braun N, Alscher MD, Sechtem U, Mahrholdt H (2017) T1 and T2 mapping for evaluation of myocardial involvement in patients with ANCA-associated vasculitides. J Cardiovasc Magn Reson 19(1):6

80. Noutsias M, Seeberg B, Schultheiss HP, Kühl U (1999) Expression of cell adhesion molecules in dilated cardiomyopathy: evidence for endothelial activation in inflammatory cardiomyopathy. Circulation 99(16):2124–2131
81. Gutberlet M, Spors B, Thoma T, Bertram H, Denecke T, Felix R, Noutsias M, Schultheiss HP, Kühl U (2008) Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 246(2):401–409
82. Mavrogeni SI, Sfikakis PP, Dimitroulas T, Koutsogeorgopoulou L, Katsifis G, Markousis-Mavrogenis G, Kolovou G, Kitas GD (2018) Can cardiovascular magnetic resonance prompt early cardiovascular/rheumatic treatment in autoimmune rheumatic diseases? Current practice and future perspectives. Rheumatol Int 38: 949–958