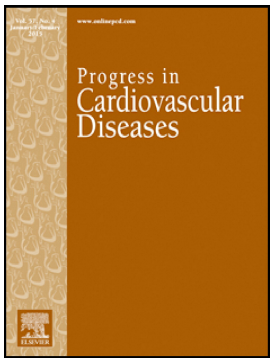

Speckle tracking echocardiography as a new diagnostic tool for an assessment of cardiovascular disease in rheumatic patients.

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Speckle Tracking Echocardiography as a New Diagnostic Tool for an Assessment of Cardiovascular Disease in Rheumatic Patients.

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Highlights

1. The actual prevalence of cardiovascular (CV) involvement in rheumatic disorders is currently underestimated.
2. Rheumatic disorders are burdened by premature mortality mainly due to CV disease (CVD) events and early atherosclerosis occurrence.
3. Speckle tracking echocardiography allows detection of cardiac involvement very precociously.
4. A proper and early detection of subclinical myocardial dysfunction improves patient CV risk stratification.
5. Early assessment of CV involvement may allow tailoring therapy for each patient and rheumatic disorder.

Abstract

Chronic inflammation represents the cornerstone of the raised cardiovascular (CV) risk in patients with inflammatory rheumatic diseases (IRD). Standardized mortality ratios are increased in these patients compared to the general population, which can be explained by premature mortality associated with early atherosclerotic events. Thus, IRD patients need appropriate CV risk management in view of this CV disease (CVD) burden. Currently, optimal CV risk management is still lacking in usual care, and early diagnosis of silent and subclinical CVD involvement is mandatory to improve the long-term prognosis of those patients. Although CV involvement in such patients is highly heterogeneous and may affect various structures of the heart, it can now be diagnosed earlier and promptly treated. CV imaging provides valuable information as a reliable diagnostic tool. Currently, different techniques are employed to evaluate CV risk, including transthoracic or trans-esophageal echocardiography, magnetic resonance imaging, or computed tomography, to investigate valve abnormalities, pericardial disease, and ventricular wall motion defects. All the above methods are reliable in investigating CV involvement, but more recently, Speckle Tracking Echocardiography (STE) has been suggested to be diagnostically more accurate.

In recent years, the role of left ventricular ejection fraction (LVEF) as the gold standard parameter for the evaluation of systolic function has been debated, and many efforts have been focused on the clinical validation of new non-invasive tools for the study of myocardial contractility as well as to characterize the subclinical alterations of the myocardial function. Improvement in the accuracy of STE has resulted in a large amount of research showing the ability of STE to overcome LVEF limitations in the majority of primary and secondary heart diseases.

This review summarizes the additional value that STE measurement can provide in the setting of IRD, with a focus in the different clinical stages.

Abbreviations

2D: two-dimensional, 3D: three-dimensional, ANCA: anti-neutrophil cytoplasmic antibodies, anti-CCP: anti-cyclic citrullinated peptide antibodies, APS: antiphospholipid syndrome, ASp: ankylosing spondylitis, AUC: area under the curve, BD: Behcet's disease, BMI: body mass index, BNP: B-type natriuretic peptide, C-reactive protein: CRP, CAD: coronary artery disease, CDAI: clinical disease activity index, CFR: coronary flow reserve, c-SLE: childhood-onset SLE, CSS: Churg-Strauss syndrome, CV: cardiovascular, CVD: cardiovascular disease, DAS28: disease activity score 28-joints, DE: delayed enhancement, DCM: dilated cardiomyopathy, DLCO: diffusion capacity of lungs for carbon moxide, DMARD: disease-modifying anti-rheumatic drugs, EF: ejection fraction, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, FMF: Familial Mediterranean fever, FVC: forced vital capacity, GAS: as global area strain, GCS: Global Circumferential Strain, GLS: Global Longitudinal Strain, GPA: Granulomatosis with Polyangiitis, GRS: Global Radial Strain, HAQ: Health Assessment Questionnaire, HF: heart failure, HR: heart rate, IHD: ischemic heart disease, IIM: Idiopathic Inflammatory Myopathies, IL: interleukin, IRD: inflammatory rheumatic diseases, j-SLE: juveline SLE, KD: Kawasaki disease, LV: left ventricle, LVH: LV: left ventricle hypertrophy, LVDD: left ventricular diastolic dysfunction, LVEF: left ventricular ejection fraction, MDI: Myositis Damage Index, MI: myocardial infarction, MRI: magnetic resonance imaging, mSASSS: mean Stoke Ankylosing Spondylitis Spine Score, NT: nitrotyrosine, PAH: pulmonary artery hypertension, PsA, psoriatic arthritis, PC: protein carbonyls, PLSS: peak longitudinal systolic strain, PLSSR: peak longitudinal systolic strain rate, PWV: pulse wave velocity, RA: rheumatoid arthritis, RF: rheumatoid factor, RV: right ventricle, sIBM: sporadic inclusion body myositis, SDAI: Simplified Disease Activity Index, SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, sPAP: systolic pulmonary artery pressures, SS: Sjögren's syndrome, SSc: systemic sclerosis, STE: speckle tracking echocardiography, sUA: serum uric acid, TAPSE: Tricuspid Annular Plane Systolic Excursion, TNF: tumor necrosis factor

1. Introduction

The actual prevalence of cardiovascular (CV) involvement in inflammatory rheumatic diseases (IRD) has been underestimated for a long time. However, the availability of advanced and improved therapeutic tools, together with increased patients' life expectancy and better clinical responses to treatments, has led to a closer look to the "behind-the-scene" complications of rheumatic diseases. CV manifestations of rheumatic diseases are increasingly recognized and, in some patients, might also be the initial presentation of the rheumatic disorder [1]. The spectrum of CV disease (CVD) manifestations associated with IRD is considerably broad, since rheumatic disorders can directly affect the myocardium, the cardiac valves, the pericardium, the conduction system, and the vasculature. Fatal CVD outcomes are preceded by a subclinical CVD involvement, which is largely prevalent in patients with systemic conditions and mostly attributed to early development and accelerated progression of atherosclerosis and vascular repair failure. This subclinical stage allows early detection, risk stratification and management in these patients [2] if properly identified. However, in the absence of an appropriate management, accumulating damage culminates in life-threatening complications in the long term. Therefore, assessing and managing the risk of CV manifestations is essential in IRD, and early diagnosis through non-invasive diagnostic tools is highly warranted to prevent accumulating damage. In this review, we aim to thoroughly and comprehensively review the literature focused on the early detection of the cardiac involvement in a wide spectrum of IRD by Speckle Tracking Echocardiography (STE).

2. Cardiac Imaging Biomarkers: an Unmet Need for the Clinical Setting

Traditional CV risk factors cannot fully account for the actual CVD occurrence in IRD and hence, they cannot be used as predictive tools for the clinical setting. As a consequence, new biomarkers are needed in this scenario. Serum and laboratory biomarkers are still of uncertain

value, and imaging biomarkers have been proposed to stratify the risk. Although atherosclerosis measurement, including carotid intimal-medial thickness (cIMT) and vascular function surrogate markers, such as Pulse Wave Velocity (PWV), have been proposed and largely debated, controversial results about their use have been published. More importantly, the cardiac-related imaging biomarkers have been largely neglected, despite their enormous relevance for CVD development. Indeed, the European League Against Rheumatism (EULAR) recommendations for CV risk management state in their research agenda the potential use of other imaging biomarkers and echocardiographic-related ones [3]. Hence, the STE is emerging as a potential tool to cover this unmet need in the clinical setting.

3. STE: a Potential New Tool

The human left ventricle (LV) consists of two muscular helixes that surround the mid-ventricular circumferential layer of muscle fibers. The contraction of these endocardial and epicardial helixes results in a twisting motion that is thought to minimize the transmural stress of the LV muscle. In the healthy myocardium, the LV twist response to stimuli that alter preload, afterload, or contractility has been described and it is deemed to be relatively consistent and predictable [4].

The value of ejection fraction (EF) for the assessment of LV function has been widely discussed during the last years because of intrinsic limitations [5], including late reduction (advanced stage of CVD only), poor reliability in patients with LV hypertrophy (LVH) and volume reduction, inter- and intra-observer variability due to apical foreshortening, difficult endocardial border detection, and others (reviewed in [5]). To potentially overcome these concerns, the two-dimensional STE has been suggested as a useful and cost-effective tool among the most recent non-invasive modalities. STE was introduced to assess the individual myocardial deformation parameters including strain, strain rate and rotation, providing insight into the function of individual myocardial fiber layers [4]. Global Longitudinal Strain

(GLS) has been shown to be more reproducible and more clinically useful than circumferential and radial strains [6, 7]. Typically, strain values are described by negative values, where the more negative values depict the better LV performance. As reference, a value of GLS around -20% (with a standard deviation of ±2%) is suggested as normal range for healthy subjects, and the lower the absolute value of strain is,, the more likely it is to be abnormal [8, 9]. This technique allows assessment of the complexity of LV function in patients with non-ischemic cardiomyopathies and it was validated against cardiac magnetic resonance imaging (MRI) and sonomicrometry in several conditions [10]. Moreover, it has also been proposed to predict mortality in different clinical settings [11]. Indeed, a recent meta-analysis that compared LVEF and GLS in predicting major adverse CV events in patients with different CVD reported that GLS had a superior prognostic value than LVEF to predict all-cause mortality, CVD death, malignant arrhythmias, hospitalization due to heart failure (HF), urgent valve surgery, heart transplantation or acute coronary ischemic events [12].

Moreover, the possibility of quantifying regional alterations of longitudinal strain (LS) through its polar projection (the so-called bull's-eye map) allows a further evaluation of both the site and the extent of the myocardial damage [13]. Although strain mechanics in other chambers (i.e., right ventricle (RV), left atrium) provide important information, it is a broad topic that cannot be properly addressed in this context and has already been thoroughly discussed elsewhere [14]. Therefore, the aim of this review is to collate the evidence on subclinical myocardial dysfunction in patients with systemic IRD, discussing the additional value in these conditions (summarized in Table 1).

4. STE in IRD

4.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting about 1% of the global population. It is characterized by chronic joint and systemic inflammation and enhanced atherosclerosis. In particular, CVD represents the leading cause of morbidity and mortality, accounting for 40–50% of all deaths. The excess of CV mortality and morbidity could be explained by chronic inflammation, disease duration and activity, immunosuppressive therapy, in addition to traditional CV risk factors [2]. In particular, chronic inflammation, accelerated atherosclerosis and functional abnormalities of the vascular endothelium suggest a subclinical CV involvement beginning rapidly soon after the onset of the disease. Early detection of subclinical cardiac injury and appropriate therapeutic intervention at this stage may potentially limit long term morbidity and mortality in these patients [15].

In an interesting study from Italy [16], 209 RA patients were recruited and prospectively followed-up to assess the prevalence and the prognostic role of subclinical LV systolic dysfunction detected by STE. Nearly half of these patients had a diagnosis of hypertension, and two thirds had dyslipidemia. Low GLS was detected in 51 RA patients and in 3 matched controls, whereas low GCS was found in 42 RA patients and 3 controls. Combined low GLS and GCS were found in 19 RA patients, but not observed among controls. The RA patients who had combined low GLS and GCS at baseline evaluation were older, had more frequent dyslipidemia and LV diastolic dysfunction, higher LV mass and a higher prevalence of LVH. During a median follow-up of 16 months, CV events requiring hospitalization occurred in 14/55 (25%) patients with abnormal strain and in 11/154 (7%) of patients with normal strain measurements at baseline. Multiple Cox regression analyses revealed that abnormal strain was independently associated with CVD-related hospitalization together with LVH.

Løgstrup and colleagues [17] enrolled 66 steroid- and disease-modifying anti-rheumatic drug (DMARD)-naive early RA patients, who were followed-up for 2 years. This total population was dichotomized in two groups: patients with persistently elevated anti-CCP (≥340 kU/L)

antibodies at baseline and during follow-up (high titers) (n = 15), and patients who did not have persistently elevated anti-CCP (≥340 kU/L) antibodies (low/normal titers) (n = 51). Patients with high titers showed a significant worsening in GLS compared to patients with low/normal titers. This remained significant in a multivariate regression model adjusted for age, gender, pulse, treatment and blood pressure. Furthermore, a significant correlation was found between the change in GLS over 2 years and anti-CCP at follow-up. Interestingly, the GCS in the group with low/normal titers improved compared to the group with high titers. These findings indicate that chronically high-level anti-CCP has a negative effect on LV function and deformation. This notion is in line with the observation of increased CVD rates in these patients.

Sitia et al. [15] recruited 22 RA outpatients and 20 controls. LV end-systolic radial strain of basal-lateral, basal- and mid-septal, mid-lateral and apical segments in RA patients were significantly reduced compared to controls. Similarly, they observed a significant impairment of LV longitudinal strain of basal-septal, basal-lateral, mid-septal, mid-lateral and apical segments compared to controls. Among RA patients, patients treated with adalimumab (a TNF inhibitor) had basal-septal and mid-septal longitudinal strain values better than patients under methotrexate treatment. Interestingly, a significant correlation was found only between mid-septal segment radial strain and disease duration and activity.

In a study from Mayo Clinic [18], the authors enrolled 87 patients with RA who underwent STE. A subgroup analysis was performed between 59 RA patients and 59 matched subjects with normal echocardiography and no overt CVD or risk factors. RA patients had significantly worse LV GLS than normal subjects. The difference persisted when normal subjects were compared with the subset of RA patients with normal LV diastolic function. At each LV level (basal, middle and apical), strain values were significantly worse in RA patients than in normal subjects. RA patients also had significantly worse global RV peak

longitudinal systolic strain than normal individuals. A significant association between LV strain and Health Assessment Questionnaire (HAQ) disability index and borderline associations with prior use of corticosteroids and methotrexate were found, while no associations were evidenced between STE features and traditional CV risk factors. Significant associations between acute-phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) were noted when the data were adjusted for age and gender only, but these associations were attenuated following additional adjustment for blood pressure, body mass index (BMI), heart rate (HR) and LV mass index. No significant associations were found between RV strain and disease characteristics. These findings suggest that the strain impairment was more likely caused by their RA, whereas traditional CV risk factors do not predict abnormal STE values in RA.

In a study from Italy [19], 41 patients with very early RA not previously exposed to any medication were enrolled. RA patients exhibited a significant impairment of GLS and GCS compared to healthy controls. Importantly, disease activity was positively correlated to GLS and GCS, and similar associations were retrieved for ESR, CRP and fibrinogen. RA patients were stratified according to disease activity and high disease activity was associated with altered GCS. The disease activity score (DAS28) was found to be the only predictor of GLS and GCS in RA, even after adjusting for potential confounders. Furthermore, multivariate regression analyses showed that only disease-related features were predictors of GLS and GCS in RA [19], hence confirming previous findings. More importantly, these results point to a very early origin of strain impairment in RA.

In a different study, Midtbø and colleagues [20] enrolled a population of 119 RA patients and 46 controls. Among them, 78 RA patients exhibited low, moderate or high disease activity (Simplified Disease Activity Index (SDAI) >3.3), and 41 patients were in remission (SDAI ≤3.3). The active RA group included more patients with hypertension and diabetes than the

remission group, but the total cholesterol levels were lower. The active RA group also included more anti-CCP and rheumatoid factor (RF) positive patients and higher use of DMARD compared with those in remission. GLS was lower in patients with active RA compared to those in remission, in accordance with previous studies. In univariate analyses, having active RA and increasing levels of SDAI, clinical disease activity index (CDAI) and DAS28 scores were all associated with lower GLS. In multivariable analyses, having active RA or increasing levels of disease activity were all associated with lower GLS after adjustment for potential confounders including age, sex, BMI, systolic blood pressure and LVEF. GLS was lowest at the base and increased towards the apex for both groups. Patients in remission had numerically higher longitudinal strain in all segments, but this was only statistically significant for the middle and apical segments of the lateral wall.

In a different study from Greece [21], 46 RA patients were recruited and prospectively followed-up during anakinra (an interleukin (IL)-1b receptor blocker) treatment. At baseline, RA patients had an impaired GLS, GCS, GRS and systolic strain rate compared to controls. Compared to baseline, there was an improvement in GLS, GCS, GRS, systolic and early diastolic strain rate and radial strain after 30 days of anakinra treatment. Conversely, no changes were observed in these parameters in prednisone-treated patients. FMD was related to longitudinal and circumferential diastolic strain rate. Coronary flow reserve (CFR) and nitrotyrosine (NT) were related to longitudinal strain, systolic and diastolic strain rate, circumferential strain and systolic strain rate. These results suggest that the impairment of myocardial deformation in RA patients compared to controls may be a result of the endothelial and coronary microcirculatory dysfunction characterizing these patients. Additionally, interstitial fibrosis caused by cytokine-induced fibroblast activity and collagen deposition in the heart muscle is present in RA and thus may play a part in the abnormal myocardial deformation herein observed. In support of this hypothesis, the authors observed

that nitro-oxidative stress was related to longitudinal systolic and/or diastolic deformation parameters at baseline.

Vizzardi and colleagues [22] recruited 13 patients from Italy undergoing anti-TNF therapy. GLS did not differ before or after anti-TNF treatment in RA patients. Surprisingly, there were no significant differences in any of the segmental strain. Therefore, the authors concluded that LVEF and GLS in RA were neither related to disease activity nor to the use of TNF blockers [22].

In a study from Greece [23], 38 RA patients (20 receiving infliximab and 18 under prednisolone treatment) and 30 healthy controls were recruited. RA patients had lower GLS, GRS and higher GCS compared with controls. Both treatment modalities increased GRS significantly. Pre-treatment GRS was significantly lower in infliximab-treated patients and, after 180 days of treatment, infliximab-treated patients showed a more favorable GRS change than prednisolone-treated patients. Percentage changes of LV twist in infliximab-treated patients were correlated with the percentage changes in LV apical and basal rotation, GLS, LVEF, CRP, and disease activity. A later study from the same group [24] confirmed the effects of infliximab on GLS and GRS (at basal, mid and apical regions). More importantly, this study demonstrated that the infliximab-related LV deformation improvement was related to a concomitant improvement of aortic elasticity, whereas no association was observed in patients under prednisolone treatment.

In another study from Greece, Ikonomidis and colleagues [25] recruited 60 RA patients with angiographically documented chronic stable coronary artery disease (CAD) (≥70% luminal diameter stenosis) and 20 matched RA patients without evidence of CAD. Elevated IL-1β and protein carbonyls (PC), a marker of oxidative stress, were related with decreasing LV GLS and GCS. Impaired CFR was correlated with reduced GLS, GLS rate, GCS and GCS rate in all patients. In patients with CAD, decreasing LVEF values were associated with

decreasing GLS, GLS rate, GCS and GCS rate, peak twisting, and peak twisting velocity. Three hours after anakinra, there was a significant improvement in STE markers of myocardial deformation and twisting in all patients. Compared to baseline, the percent improvement in LV myocardial deformation, twisting and untwisting markers was greater in CAD than in CAD-free patients. LV function markers remained impaired in patients with CAD compared with controls after anakinra. Conversely, in CAD-free patients, LV myocardial deformation and twisting markers after anakinra became similar to those in controls. In addition, CAD versus CAD-free patients had a 3-fold higher IL-1β level. The higher oxidative stress that may explain the greater impairment of endothelial and coronary microcirculatory function may have contributed to the impaired LV myocardial functional abnormalities of the patients with CAD in the present study.

These data highlight a clear impairment of the cardiac contractile performance in RA, due to, at least in part, the inflammatory status. These findings suggest that an optimal pharmacological control of the disease activity may lead to an improved contractile function in these patients. More importantly, these data point to a prompt occurrence of the subclinical alteration of the myocardial function in the setting of RA, hence allowing for an early stratification.

4.2. Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic and relapsing, inflammatory, immune-mediated disease affecting not only the skin but also the joints [26].

Increased mortality has been reported in PsA patients and CVD was found to be the leading cause of morbidity and mortality among these patients with a 1.3-fold higher rate of CVD-related death among PsA compared to the general population [27].

Shang et al. enrolled 76 patients with PsA (56 patients with psoriasis, 63 with peripheral arthritis and 13 with spondyloarthritis). PsA patients had an impaired apical rotation

compared to controls. Furthermore, authors sub-analyzed patients with PsA without CV risk factors and they found also an impaired apical rotation and LV dysfunction. Patients with impaired apical rotation showed significantly higher DAS28 and ESR than controls, and patients with active disease had a high proportion of abnormal apical rotation. Spearman correlation demonstrated a relationship between disease activity, ESR and impaired apical rotation. However, no correlations were found between GLS, GRS or GCS and disease activity. This study suggests that PsA had a multilayer myocardial involvement and may share a different pathogenic mechanism from ischemic heart disease (IHD) in the early stages.

In a different study, Yilmazer and coworkers [29] evaluated 31 PsA patients and 20 controls.. Ten PsA patients (32.0%) and 4 control subjects (21%) were smokers, 15 PsA patients (48%) and 8 control subjects (42%) had hypertension, and 11 (33.0%) PsA patients and 4 (21.0%) control subjects were obese [29]. PsA patients were found to have markedly lower values of GLS, GCS and GRS. However, there was not any association of STE parameters and disease-related risk factors.

Finally, Lo Gullo and colleagues [19] recruited 35 PsA patients at onset that were not exposed to any medication at the time of sampling. GLS was altered in PsA patients compared to controls. However, although GCS was not significantly different in PsA compared to controls, a positive correlation with the disease activity score (DAS28) was observed. GLS and GCS were impaired in PsA patients with higher disease activity compared to controls, and GLS was found to be a predictor of cIMT in this condition also after adjusting for age, BMI, DAS28, acute-phase reactants (ESR, CRP and fibrinogen), PWV and vitamin D. These results reinforce the relevance of the inflammatory burden in the subclinical impairment of the myocardial functionality in PsA already in the very early stage of these conditions.

Taken together, a series of studies have demonstrated a notable impairment of myocardial functionality in PsA. Although there are some lines of evidence suggesting a connection with the inflammatory burden in this condition, current findings seem to be controversial, probably due to demographical and clinical differences among studies.

4.3. Ankylosing Spondylitis

Ankylosing spondylitis (ASp) is an inflammatory joint disease primarily affecting the sacroiliac joints and the spine [30]. Cardiac involvement in ASp has been known for a long time, in particular alterations of the aortic root geometry and aortic valve dysfunction [31]. ASp is also characterized by an increased risk of premature atherosclerosis [32], which account for the increased CVD occurrence.

Zungur and coworkers [33] enrolled 64 Asp patients; 58 (90.6%) patients received DMARDs, and 6 (9.3%) patients used anti-TNF agents. The 2D STE analysis revealed a preclinical RV impairment, as the parameters in the study were lower in ASp patients compared to matched controls.

Midtbø and collaborators [34] performed conventional and STE analyses in 106 ASp patients. The CV risk factor burden was equally distributed between ASp patients and controls, but more controls were receiving statin therapy. LV systolic myocardial function was assessed by GLS. GLS was significantly lower in ASp compared to controls. When excluding the 21 ASp patients under anti-TNF treatment from the analyses, GLS still remained lower in ASp patients compared to controls. Larger aortic root diameter was only associated with lower GLS in the ASp patients. Furthermore, having ASp remained independently associated with lower GLS after adjusting for confounders. Univariate analyses revealed that, in ASp patients, male sex, larger aortic root diameter and LV mass index emerged as the strongest predictors of lower GLS. In a multivariable analysis, lower GLS was independently associated with larger aortic root diameter after adjusting for

confounders in ASp patients.

In a Chinese study, 104 ASp patients with axial involvement (78.8% with radiological ASp and 21.2% without radiological phenotype) and 50 controls were enrolled. No differences between the two groups were observed regarding traditional CV risk factors. Patients with axial ASp had impaired LV GLS, GCS and GRS. The mean Stoke Ankylosing Spondylitis Spine Score (mSASSS), a marker of disease severity, was strongly associated with strain parameters. Multivariate linear regression analysis adjusting for age, sex and CV risk factors demonstrated that mSASSS was independently associated with GLS. Moreover, the present study further demonstrated, through more advanced 2D STE analysis, that these patients had LV systolic dysfunction despite an apparently normal LVEF measured by conventional echocardiography [35].

Utsun and colleagues [36] recruited a group of 26 ASp patients (22 patients under conventional DMARD treatment and 4 patients under anti-TNF therapy) and 26 healthy controls in their cross-sectional study. All segments showed a significant decrease in left ventricular diastolic/systolic GLS and strain rate in ASp patients compared to the healthy controls. In addition, there was no correlation between the LV STE findings and the disease activity and severity scores [36].

Taken together, these results indicate that LV systolic function assessed by 2D STE, is impaired in ASp patients, regardless of clinical features and the inflammatory burden.

4.4. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a common autoimmune disease, in which many organs and tissues are involved, including the skin, muscles, joints, kidneys, and the CV, hematologic, nervous, and digestive systems. The inflammatory burden and immune dysfunction can result in severe damage to multiple organs due to different pathways, especially the heart and vessels. In fact, a 50-fold increase in IHD, HF, and stroke is reported

compared to the general population [37]. Furthermore, autopsy results have shown that myocardial involvement is present in up to 40–50% of SLE patients. However, only 7–10% of SLE myocardial injury is found during the clinical stage, hence reinforcing the need of non-invasive methods for early detection of impaired myocardial function or subclinical cardiomyopathy during the asymptomatic stage in SLE [38]. In a study from China [38], 34 SLE patients were included. GLS, GCS, GRS as well as global area strain (GAS) were found to be reduced in SLE patients. Also, GCS was found to be correlated with 3D LVEF. The correlation between GLS and 3D LVEF was poorer than those of GCS, GAS, and GRS. Bivariate correlation analyses showed that age, systolic blood pressure, HR, and SLE were all correlated with GAS. Then, a multivariate analysis demonstrated that suffering SLE was an independent predictor of impaired GAS. Gender and HR were also independently associated with GAS after adjustment for confounders. GLS, GAS, and GRS were significantly decreased in patients with severe SLE compared with in patients with inactive/mild SLE. There was a notable correlation between SLE disease activity index (SLEDAI) and the absolute values of GLS, GAS and GRS, but not GCS. In a multivariate regression analysis including HR, GLS, GCS, GAS and GRS, only GLS was independently related to disease activity, measured by SLEDAI.

In a study from China [39], 60 SLE patients were enrolled. Left atrial peak systolic strains were reduced in all seven segments of the SLE group. Global strain, derived as an average of all segments, was reduced in SLE patients compared with the control group. The positive left atrial strain during diastole was reduced in the SLE group compared with that in the control group. Systolic strain rate and early diastolic strain rate were found to be decreased with the LV diastolic dysfunction (LVDD) severity. Multivariate linear analysis revealed that the damage index (SDI) was independently and inversely associated with global strain, systolic strain rate and positive early diastolic strain rate. In conclusion, left atrial functionality was

altered in SLE, demonstrating impairment in conduit function, decrease in storage function and increase in pump function. Meanwhile, the magnitude of this impairment was predictively associated with the severity of LVDD.

In a different study, Du Toit and coworkers [40] retrospectively reviewed clinical records from 457 SLE patients (28 patients fulfilled inclusion criteria for lupus myocarditis) and 28 healthy controls. At diagnosis, GLS correlated well with other parameters of global and regional LV function. A weaker correlation was observed between GLS and renal function. No other clinical parameters including age, disease activity and duration nor laboratory parameters showed any significant correlation with GLS.

Sun and coworkers [41] enrolled 102 patients with SLE, who were classified into 3 groups according to the severity of pulmonary artery hypertension (PAH) No significant differences were found between patients with the less severe PAH and controls. However, the right atrium maximum and minimum volumes, pre-atrial contraction volume, active EF, and late diastolic strain rate were significantly increased in the patients with the more severe PAH compared with their less severe-counterparts and controls.

In another study from China [42], 102 SLE patients were enrolled. The authors concluded that the 2D STE-derived strain and strain rate imaging could early detect the RV dysfunction, especially in patients with mild PAH. This has an important value in guiding early therapy in clinical settings, improving the prognosis, and increasing the quality of life of SLE patients with PAH.

In a study from Mexico, Medina and colleagues [43] included 38 patients with antiphospholipid syndrome (APS) and 21 healthy controls. The most frequent clinical manifestation of primary APS (pAPS) was deep venous thrombosis. Average GLS was lower in pAPS than in controls. No differences were found between patients with and without obesity or metabolic syndrome, whereas patients with a history of pulmonary embolism had a

more altered GLS at baseline.

In a study from Brazil [44], 35 patients with childhood-onset SLE (c-SLE) and 33 controls were enrolled. Global RV peak longitudinal systolic strain (PLSS) and strain rate (PLSSR) were reduced in c-SLE patients. Similar findings were observed after excluding c-SLE patients with PAH. In c-SLE patients, a positive correlation was observed between RV PLSS and Tricuspid Annular Plane Systolic Excursion (TAPSE), a marker of global RV function. The c-SLE patients revealed higher frequencies of neuropsychiatric manifestations and antiphospholipid antibodies in those with RV PLSS equal or inferior to -23.7%, compared to the ones with RV PLSS greater than -23.7%. Then, a possible link between RV lower PLSS and c-SLE neuropsychiatric manifestations may be related to endothelial cell dysfunction induced by antiphospholipid antibodies. Importantly, multiple thrombotic micro-vasculopathy is responsible for ischemic cardiomyopathy, even in the absence of coronary trunk obstruction. Similarly, cerebral microvascular occlusion attributing to antiphospholipid antibodies is one of the pathophysiological mechanisms implicated in neuropsychiatric manifestations of SLE [45].

From the same group from Brazil, 50 c-SLE patients and 50 controls were enrolled [46]. There was a negative correlation between LV PLSS and disease activity score, as well as the number of traditional CV risk factors. Peak circumferential systolic strain was not different between c-SLE patients and controls. A reasonable explanation is that mid-myocardial layers, which are responsible for LV circumferential mechanisms, are the last to be affected in the progression of myocardial disease. Normal circumferential strain usually maintains a preserved LV pump and guarantees a conserved EF in a subclinical disease stage [47].

Deodoglu et al. [48] evaluated 35 patients with juvenile SLE (j-SLE) and 30 healthy children (control group) from Turkey. There was a significant GLS reduction in the j-SLE group. At all segments, j-SLE patients had significantly lower STE strain measurements than control

patients. Then, the authors divided patients in 2 groups according to the disease activity score. The severe disease group had lower STE strain values than the moderate-disease group. In mid-anterolateral, mid-anteroseptal, and basal anterolateral segments, j-SLE patients had significantly lower values than patients without anti-phospholipid antibodies. Importantly, azathioprine use, an immunosuppressive agent, was related to better strain values at the basal inferior LV segment. On the other hand, patients using mophetil micophenolate had lower cardiac strain values at the basal inferior and inferoseptal segments.

4.5. Systemic Sclerosis

Systemic sclerosis (SSc) is a chronic, multi-system disease characterized by extensive fibrosis and vascular damage which can result in severe dysfunction of almost any internal organ. Cardiac manifestations are common in SSc, with an estimated clinical prevalence of 15–35% and when clinically evident, are often associated with mortality [49]. Cardiac involvement is one of the leading causes of disease-related deaths (accountable for 20–26% of total mortality), mainly due to HF and arrhythmias [50]. Thus, monitoring of myocardial involvement represents an important aspect of the disease management.

In a study from Germany, Spethmann and coworkers enrolled 22 SSc patients. The LV global longitudinal 2D peak systolic strain was significantly lower in the SSc group compared with controls.

In another study from Turkey, Tigen and colleagues [52] enrolled 53 SSc patients and 26 healthy controls. SSc patients had significantly lower LV GLS, GRS, GCS and twist compared to controls. There was only a weak correlation between LV GLS and modified Rodnann skin thickness score in SSc patients. Importantly, SSc patients with fragmented QRS in DII, DIII, and aVF (n=30) leads exhibited an impaired GLS and delay in time to peak longitudinal strain in inferior LV segments, compared to those with normal QRS.

In a study from Italy [53], 90 SSc and 55 age- and gender-matched healthy adult non-athletes were enrolled. SSc patients showed a significant impairment of right atrial function and right atrial enlargement, measured by 2D STE at rest and during exercise compared to controls. These findings were more evident in SSc patients with pulmonary fibrosis and in patients with high systolic pulmonary artery pressures (sPAP) during exercise. In a multivariate analysis performed in the SSc patients, right atrial lateral strain was significantly associated with sPAP during effort, right atrial area, left ventricle stroke volume and inferior vena cava diameter. The findings of this study suggest that a high proportion of SSc patients exhibit right atrial dysfunction even without clinically manifest PAH. Moreover, impaired right atrial function occurred mostly in patients with pulmonary fibrosis or elevated sPAP during exercise, was independently associated with prognostic factors and may therefore be useful for risk stratification.

In a different study from Italy [54], 45 SSc patients and 20 healthy subjects were enrolled. ST echocardiography was used to assess longitudinal function in the two groups during exercise, revealing a reduced GLS and GLS rate at peak exercise in SSc patients compared to controls. Patients with GLS$\leq$18% at peak exercise showed a worse diastolic function at rest, with higher E/E', larger left atrial volumes, higher sPAP and a reduced physical capacity. Furthermore, significant correlations between stress GLS and the change in sPAP and physical capacity were found.

In a study from Turkey [55], 80 SSc patients were included (11 patients with PAH diagnosis). Patients with PAH were older and had a higher age at diagnosis than those PAH-free. PLSS values from the apical segment of the RV free wall were significantly lower in the PAH group at baseline compared with the non-PAH group. PLSS at the basal, mid, and apical segments of the RV free wall were significantly correlated with mean sPAP. Moreover, PLSS at the apical segment of the RV lateral wall was an independent predictor of PAH and

significantly discriminated SSc patients with PAH from patients without PAH. In fact, a PLSS value of −14.48% in the apical segment of the RV lateral wall yielded a 62% sensitivity to predict PAH and a 100% specificity to rule out PAH.

In a single-center pilot study from Germany, Spethmann [56] included 19 PAH-free SSc patients with preserved LVEF. STE was performed at baseline and after two years. The LV GLS at follow-up was still in normal range, but significantly reduced compared to baseline examination. Since cardiac involvement is common, these results may be explained by a progression of subclinical myocardial fibrosis.

Agoston and coworkers [57] evaluated 42 SSc patients without clinical evidence of cardiac involvement and 42 controls [57]. Left atrial strain values were significantly different between patients and controls, hence suggesting that this method may be a sensitive tool to assess impairment of LV mechanics, which is detectable in absence of changes in left atrial size and volume, and may represent an early sign of cardiac involvement in SSc.

Yiu and colleagues [58] enrolled 102 consecutive SSc patients and 36 healthy individuals. A total of 51 patients were free of pulmonary fibrosis and PAH, 32 patients had pulmonary fibrosis but no PAH and 19 patients had both pulmonary fibrosis and PAH. RV free wall strain was significantly impaired in SSc patients compared with controls. Furthermore, patients with pulmonary fibrosis and PAH had the most impaired RV free wall strain compared with patients with pulmonary fibrosis and no PAH, and patients free of pulmonary fibrosis and PAH. Importantly, RV free wall strain was significantly impaired also in SSc patients with no pulmonary fibrosis and no PH compared with controls. Univariate linear regression analyses revealed that age, forced vital capacity (%FVC), diffusing capacity for carbon monoxide (%DLCO), pulmonary fibrosis score, evidence of pulmonary fibrosis, LVEF and sPAP were significantly associated with impaired RV free wall strain. In the multivariate analysis, evidence of pulmonary fibrosis, LVEF and sPAP were independently

associated with impaired RV free wall strain.

Cusmà and colleagues [59] enrolled 29 SSc patients from Italy. LV GLS and GCS were lower in patients than in controls, whereas GRS was comparable between groups. In addition, in patients with Scl-70 antibodies, a significant correlation between serum levels of Scl-70 antibodies and both GLS and GCS were found. Follow-up was available for 26 (89%) patients and 22 (73%) healthy subjects. Patients with CV events during follow-up showed a greater impairment of GCS and higher values of Scl-70 antibodies serum levels compared with their CV-free counterparts.

Yiu et al [60] recruited 104 SSc patients (51 patients with localized SSc and 53 patients with diffuse SSc); both GLS and GCS were significantly impaired in SSc compared to controls. Of note, patients with diffuse SSc showed worse values for both parameters compared to patients with limited SSc. In SSc patients, GLS and GCS correlated with the peak VO2. Additionally, SSc patients with abnormal Holter electrocardiography exhibited impaired GLS and GCS, and each strain measure was independently associated with abnormal Holter findings [60].

4.6. Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is a rare systematic disease, which is characterized by pulmonary and systemic small-vessel necrotizing vasculitis, vascular and/or extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils, occurring in individuals with asthma and allergic rhinitis or nasal polyposis [61].

Heart involvement, attributed to eosinophilic infiltrates and, to a smaller extent, to necrotizing small vessel vasculitis, represents the major cause of death in CSS patients and both systolic and diastolic LV dysfunction have been described [62].

In a study from Poland, Miszalki-Jamka and collaborators [63] recruited 22 CSS patients who underwent STE analysis. Peak systolic GLS, GCS and GRS were lower in CSS patients with

respect to controls. However, these parameters in CSS patients with preserved/normal LV systolic function did not differ from those of controls [63]. Blood eosinophilia was positively correlated with global peak-systolic strain and strain rate both for longitudinal and circumferential analysis, respectively. Furthermore, a negative correlation was found between blood eosinophilia and LVEF, as well as global longitudinal and circumferential early diastolic strain rate. Importantly, in CSS, LV systolic dysfunction strongly correlated with longitudinal and circumferential systolic components, but not radial or rotational ones, thus indicating that impaired LV systolic function may result predominantly from an altered contraction of the inner and middle, but not outer, myocardial fiber layers [63].

4.7. Granulomatosis with Polyangiitis

Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a granulomatous disorder associated with vasculitis involving the small and medium-sized blood vessels. It mostly common affects the upper and lower respiratory tracts and the kidneys, but almost any organ can be involved [64]. GPA is associated with a cytoplasmic pattern of antineutrophil cytoplasmic antibodies (c-ANCA), with a specificity against proteinase-3.

Cardiac involvement in GPA is rare, and different manifestations are described such as pericarditis, valvular lesions, coronary arteritis, myocarditis and cardiac rhythm disorders [65]. Cardiac involvement in GPA has been reported to range between 6 and 44%, with coronary arteritis and pericarditis reported in the 50% of all cases of heart involvement in GPA [65, 66]. Moreover, the GPA patients were found to have a 3.6-fold increased risk of acute myocardial infarction (MI) occurring 5 years after GPA onset [67].

In a study from Poland, Miszalski-Jamka [68] evaluated STE parameters in 22 GPA patients. Regional LV wall motion abnormalities were found in 7 (32%), while abnormal global STE

was detected in 16 (73%) subjects. GLS, GCS and GRS peak-systolic deformational parameters were impaired in 11 (50%), 9 (41%), and 3 (14%) patients, respectively. Patients with abnormal and normal STE derived global systolic function had higher cumulative disease extent index and vasculitis damage index. No differences were found in disease duration, markers of inflammation and ANCA titers, or comorbidities (obesity, hypertension, diabetes) [68].

As in CSS patients, also in GPA the systolic GLS and strain rate is most commonly affected, suggesting the predominant involvement of the LV inner and mid myocardial fiber layers in this group of patients [68].

4.8. Behcet's Disease

Behcet's disease (BD) is an inflammatory disorder of unknown aetiology, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. It is now well known that BD is a multisystem disorder that may affect any organ in different combinations [69] The heart and the CV system can also be involved including pericarditis, myocarditis, endocarditis, endomyocardial fibrosis, conduction system disturbances, coronary arteritis, acute MI, and dilated cardiomyopathy, in a clinical setting defined as Cardio-BD [70].

In a study from Turkey [69], Yagmur and colleagues recruited 32 BD patients and 27 matched controls who underwent cardiac evaluation. No differences were observed between patients and controls in traditional CV risk factors and conventional echocardiography features. Regional and GLS was significantly lower in BD patients when compared with the healthy controls, but regional and GCS values were not different. However, further correlations between strain imaging findings and clinical features or therapies were not observed in this study [69].

In another study from Korea [71], 81 BD patients and 145 healthy controls were enrolled.

GLS was significantly reduced in BD patients. In this study, patients were divided in 3 groups according to diseases activity (minimal, controlled and active disease). In STE analysis, patients of all three groups consistently displayed GLS reduction compared to controls. However, there were no significant differences in GLS according to BD activity.

In another study, Demirelli and coworkers [72] included 30 consecutive BD patients and 25 controls. BD patients had significantly lower LV GLS and strain rate measurements than controls. Although LV basal rotation (LVR) values were similar in both groups, LVR apical and LV torsion were significantly higher in patients. LVR apical was found to have a good positive correlation with LV GLS ($r=0.440$, $p<0.001$). Moreover, a weaker but significant positive correlation between LV torsion and LV GLS was observed ($r=0.290$, $p<0.05$).

4.9. Kawasaki Vasculitis

Kawasaki disease (KD) is an acute, multisystem vasculitis well acknowledged as one of the most common causes of acquired heart diseases in children. It is a self-limiting vasculitis that primarily involves coronary arteries. In KD, coronary artery involvement is the largest contributor to morbidity and mortality. Coronary artery aneurysms may develop during the subacute phase in 20% of untreated patients. Coronary artery lesions are reported in 8.5% in the acute phase, and in 2.9% as CV sequelae. On the other hand, myocarditis is rarely reported (0.16%) [34]. Moreover, myocarditis is the most common KD extracoronary cardiac abnormality, which can cause LV dysfunction. Because of the serious cardiac complications of KD, early diagnosis and treatment are extremely important.

In a study from Turkey [73], 15 KD patients underwent STE analysis and were followed-up upon therapy. The LV GLS, GLS rate, GCS and GCS rate values obtained at baseline were significantly lower in patients compared to controls. After treatment, GLS and strain rate values were found to be significantly improved compared to baseline. However, GCS

remained significantly lower than healthy controls. There were no significant differences in RV GLS and GLS rate even before therapy. There was a significant positive correlation between hemoglobin level and LV GLS.

In another study from Korea [74], 50 KD patients were included. Basal GLS and mid-longitudinal strain were lower in KD than in control subjects during the acute phase of the disease, and associated with serum albumin level and LV mass index. Moreover, patients with coronary artery lesions exhibited low GRS compared with controls, despite similar LVEF.

Dedeoglu and coworkers [75] enrolled 35 KD patients. There were no significant differences in strain values between KD patients with and without coronary aneurysms in LV segments. Patients' strain values at the basal inferoseptal, basal anterolateral, apical septal, and apical inferior segments were lower compared to controls. KD patients with pyuria, a laboratory finding supportive of KD diagnosis, had lower LV strain at the mid anterior, mid anteroseptal, apical anterior, and apical inferior segments and GLS than their pyuria-free counterparts.

In a recent study, Kato and colleagues [76] recruited 52 KD patients who underwent STE. Interestingly, there were no associations between B-type natriuretic propeptide (NT-proBNP) levels and GLS values.

In another study, Yu and collaborators [77] recruited 25 adolescents with history of KD (14 with aneurism). Patients with coronary aneurisms had significantly lower 3D LV systolic GLS and twist gradient with respect to controls, but similar LVEF. Within the whole patient cohort, multiple linear regression analysis revealed a significant association between the persistence of coronary arterial aneurysms and 3D LV GLS also after adjusting for age, sex, presence of perfusion abnormalities, LV twist gradient, systolic dyssynchrony index, and LVEF. The authors concluded that impairment of LV mechanics occurs in KD, and it is more

severe in patients with coronary complications [77]

4.10. Gout

Gout is a common metabolic condition characterized by chronic hyperuricemia. In gout, uric acid accumulates as monosodium urate in tissues, including joints, thus prompting an inflammatory response which leads to the development of an inflammatory arthritis [33]. The severity of gout can be divided into four stages, including asymptomatic hyperuricemia, acute gout attack, intercritical gout, and chronic tophaceous gout. A number of studies have reported elevated serum uric acid (sUA) as a risk factor of CAD, atrial fibrillation, CV-related death [78] and it has been associated with poor outcomes in patients with HF, with or without gout diagnosis. Elevated sUA is also associated with LVH in patients without underlying CVD [32] and it has been also related to diastolic dysfunction in HF patients [31]. Furthermore, hyperuricemia has been found to accelerate the CVD occurrence due to LV remodeling [30].

In a study from Taiwan, 173 gout patients (classified according to disease stages) underwent a comprehensive Doppler-echocardiography examination. Patients with tophaceous gout exhibited the worst LV GLS values. Multiple regression analysis revealed that gout severity had an independent negative impact on strain parameters after adjusting for confounders [79].

In another study from China [80], 40 patients with isolated hyperuricemia were enrolled. The 3D STE parameters reflecting LV function, including stroke volume, GLS and GCS, were significantly decreased in hyperuricemia. Furthermore, GCS was significantly correlated with the sUA levels even after adjusting for confounding factors (age, BMI, and serum creatinine) [80].

In another study from Shangai, Fang and coworkers recruited 164 patients with hyperuricemia and/or hypertension. GCS was significantly decreased in patients with

hypertension and hyperuricemia compared to controls, but the difference was not significant for patients with hyperuricemia or hypertension alone. Moreover, the sUA levels were significantly correlated with the absolute value of GLS and LV mass index in hypertensive and non-hypertensive hyperuricemia patients [81]

4.11. Sarcoidosis

Sarcoidosis is a multi-system disorder of unclear etiology characterized by the presence of non-caseating granulomas, which are comprised of macrophages, epithelioid and mononuclear cells, including CD4+ T cells with a few CD8+ T cells in the peripheral zone. Lung and intra-thoracic lymph nodes are the most commonly affected organs, although any organ can be affected [82]. Cardiac involvement has been demonstrated in the 20–50% of sarcoidosis patients with an autopsy series [83].

In a pilot study from Japan [84], 23 patients with cardiac sarcoidosis (CS) and 16 matched controls with dilated cardiomyopathy (DCM) were enrolled. GCS and GLS in patients with CS and DCM were similar, but GRS in CS patients was lower than in DCM individuals. GRS was the best predictor for differentiating CS from DCM (70% sensitivity and 88% specificity). These findings suggest the non-uniformity of the cardiomyocyte damage in CS [84]. Sarcoid infiltration often occurs in the middle or epicardial portion of the LV wall in the early stage [85], thus those findings may be reflected by such phenomenon in CS patients with relatively mild LV dysfunction.

In a pilot study from Greece, Aggeli and colleagues [86], recruited 76 patients with biopsy-proven, treatment-naïve, newly diagnosed sarcoidosis and 29 healthy individuals who underwent echocardiographic evaluation. Patients with sarcoidosis presented with lower GLS, while twist appeared to be increased compared to the control group. Given that

sarcoidosis affects mostly the basal segments [83], this could in turn explain the elevated twist angles, also shown in this study.

In a more recent study from the same group [87], 117 patients with extracardiac sarcoidosis were enrolled and compared to 45 age-and sex-matched controls. In this study, strain values were significantly lower in patients with sarcoidosis and especially in those who experienced an adverse event. Univariate Cox regression analyses identified LVEF, LV systolic diameter, and GLS as the variables which were more strongly associated with adverse outcomes.

In a study from France, 35 sarcoidosis patients and 35 controls underwent STE analysis. LV 4-chamber GLS was significantly lower in sarcoidosis compared to normal values and reduced in comparison with controls. The same GLS reduction in sarcoidosis patients was observed with LV 2-chamber and 3-chamber longitudinal strain. Although LV GLS was significantly reduced in sarcoidosis, no significant differences in LV GCS were observed between sarcoidosis and controls. LV 4-chamber longitudinal strain, LV 3-chamber longitudinal strain, LV 2-chamber longitudinal strain and LV GLS were significantly associated with new onset arrhythmia occurrence, CS development and cardiac device implantation [88].

In a prospective study from the Netherlands [89], 100 patients and 100 age- and gender-matched controls were enrolled and LV GLS was measured by STE analysis. The primary endpoint was a composite of all-cause mortality, HF hospitalization, device implantation, new arrhythmias, or development of CS on advanced cardiac imaging modalities. LV GLS was significantly impaired in sarcoidosis patients compared with controls. Overall, 27 patients (27%) reached the endpoint during a median follow-up of 35 months. On Cox proportional hazards model analysis, abnormal 24h Holter findings, larger LV end-diastolic diameters, and more impaired LV GLS were significantly associated with the endpoint. However, only LV GLS remained independently associated in multivariate analysis.

Tigen and colleagues [90] recruited 40 sarcoidosis patients and 20 age- and sex-matched controls. LV GLS, GCS, GRS, twist, untwist, and RV GLS were significantly lower in patients with sarcoidosis than in controls. These data suggest an early subclinical cardiac involvement in sarcoidosis, probably due to direct atrial involvement or secondary to prolonged exposure to elevated LV filling pressures.

Orii and collaborators [91] retrospectively analyzed the clinical records from 45 patients with biopsy-proven extracardiac sarcoidosis and 40 age-matched healthy control subjects were recruited as the control group. Myocardial damage was detected by delayed enhancement (DE) magnetic resonance imaging. A total of 13 patients exhibited DE in MRI studies. Patients with DE had lower GLS than their DE-free counterparts and control subjects. GRS and GLS allowed the distinction between normal and fibrotic segments (sensitivity: 58% and 67%, specificity: 52% and 60%, and AUC: 0.55 and 0.62, respectively). Peak GCS yielded a sensitivity of 92% and a specificity of 91% to identify DE. The AUC ROC curve of GCS for the identification of DE was significantly higher than those of GRS and GLS. In conclusion, GCS showed a better diagnostic ability than GRS and GLS to detect DE in sarcoidosis patients.

4.12. Sjögren Syndrome

Sjögren's syndrome (SS) is a common chronic autoimmune disease with a global prevalence of 0.5–1% that is characterized by lymphocytic infiltration and progressive injury to the exocrine glands. In general, the main lesions affect the salivary and lacrimal glands, and lead to dry eyes and mouth [92]. The disease spectrum ranges from sicca syndrome to systemic involvement (extra-glandular manifestations), and may be complicated by the development of lymphoma. There are often also systemic features due to cutaneous, respiratory, renal, hepatic, neurological and vascular involvement [93]. This syndrome may present as a

primary disease (pSS) or be associated with other autoimmune diseases (secondary SS). SS patients are known to have a high CVD risk [94].

In a study from Italy [95], 22 SS outpatients with no clinical history or signs of CVD underwent STE. The conventional echocardiography parameters did not differ between patients and controls. However, STE features were significantly different between the two groups, with GLS in the apical 4-chamber view and GRS deformation in short axis view being significantly lower in pSS patients. Moreover, there were no associations between STE findings and RF, anti-Ro and anti-La antibodies, inflammatory markers or subclinical atherosclerosis [95].

In a more recent study from the same group [96], 49 SS outpatients and 49 healthy volunteers were enrolled. GLS deformation in the apical 4-chamber view was found to be significantly lower in pSS patients, hence confirming previous results.

4.13. Polymyositis and Dermatomiositis

Idiopathic Inflammatory Myopathies (IIM) are rare immune-mediated chronic inflammatory diseases characterized by symmetric and progressive weakness of the proximal muscles. Among them, polymyositis and dermatomyositis are characterized by chronic inflammation, fibrosis, and damage and destruction of the muscle fibers. Inflammatory infiltrates surrounding vessels are preferentially found in patients with dermatomyositis, whereas cell infiltrates predominately surround muscle fibers in patients with polymyositis and sporadic inclusion body myositis (sIBM), and might indicate an autoimmune reaction directed against muscle fibers in these myositis subsets [97].

A number of studies confirmed that CV involvement (including active myocarditis, mononuclear infiltration, focal fibrosis, vasculitis, intima proliferation and media sclerosis of the vessels) is common and it represents an important unfavorable prognostic factor in IIM

[98-100]. Due to the very heterogeneous presentations of the disease, in a recent meta-analysis the authors concluded that the incidence of cardiac involvement in IIM can range between 9% and 72% [98].

In a study from China [101], 60 patients with polymyositis and dermatomyositis and 30 controls were enrolled. IIM patients had a significantly diminished LV GLS and RV GLS compared to controls. Moreover, patients with established disease (longer than one year) had significantly reduced LV GLS and RV GLS than patients with a disease duration less than one year. The LV GLS, RV GLS and E/E′ ratio correlated with the disease course of IIM as well as with the organ damage score. Importantly, BNP levels were significantly associated with LV GLS, RV GLS and Myositis Damage Index (MDI) score. In multivariate analyses of the pooled data of all IIM patients, where MDI was excluded due to missing observations, Interstitial Lung Disease was independently associated with worse RV GLS, whereas disease duration was an independent predictor of worse LV GLS, and both disease duration and hypertension were associated with the E/E′ ratio. These results demonstrated a correlation between diminished biventricular strain and disease duration and severity, thus indicating that cardiac abnormalities in IIM patients might be connected to its clinical heterogeneity.

In a study from Italy [102], 28 IIM patients and 28 matched controls were enrolled. LV GLS was significantly lower in patients compared to controls. IIM patients had a 5-fold increased risk of impaired LV GLS. LV GLS in IIM patients was lower in basal and mid-segments of the anterior, anterior-septal, and lateral wall. Additionally, RV GLS was significantly lower in patients compared to controls. According to an univariate analysis, GLS was not directly associated with any clinical features, comorbidities or treatments in IIM.

4.14. Familiar Mediterranean Fever

Familial Mediterranean fever (FMF) is an autosomal recessive disease manifested by recurrent attacks of peritonitis, pleuritis, pericarditis, synovitis/arthritis, fever, and arthritis

and characterized by clinical, histological, and laboratory evidence for localized and systemic inflammation [67]. Although the disease course in FMF involves exacerbations and attack-free periods, the presence of localized and systemic inflammation has been shown in attack-free periods as well [66].

Among the organic manifestations, several CV abnormalities are connected to FMF, including a higher incidence of pericarditis, predisposition to vasculitis, rheumatic carditis, and myocardial infarction [103, 104].

In a study from Turkey, Kalkan and coworkers [65] recruited a total of 23 FMF patients and 22 healthy controls. LV strain values in middle segment of the septum, middle, and basal segments of the lateral wall, middle, and basal segments of the anterior wall were significantly lower in patients than controls. Moreover, the mean systolic strain value was significantly lower in FMF patients than in controls.

Ceylan and collaborators [64] enrolled 45 FMF patients and 45 controls in a cross-sectional study. GLS (basal anterolateral, mid-anterolateral, and apical interventricular septum) values were significantly lower in the patient group than in controls. The GCS did not significantly differ between groups. The LV endocardium was the most affected region by hypoperfusion, fibrosis, and ischemic changes. An increased pro-inflammatory response, the accumulation of amyloid and drugs as well as the intensification of the longitudinal muscle fibers in the subendocardial region may account for these ischemic changes and thus, the lower GLS found in this group of patients.

5. **Conclusion**

IRD are definitely burdened by increased CV risk, and there is a compelling body of evidence supporting a notable, early impairment of myocardial function in these conditions, mostly linked to the inflammatory burden and independently of traditional CV risk factors.

As a result, there is an unmet need in estimating and reporting the cardiac involvement in a standardized and uniform manner so far.

The STE is able to detect and measure the subclinical myocardial dysfunction, and growing evidence can help to define accepted cut-offs and ranges of 'normal' values, in order to improve patient stratification. Moreover, this imaging approach can also support the longitudinal evaluation of the subclinical cardiac involvement, including the response to therapy. Also, the availability of a measurable index of functional deterioration could contribute to facilitate the decision-making process in the clinical scenario. As a consequence, patients may benefit from a more meticulous screening of CVD risk assessment and more specific CV prevention strategies. In conclusion, the STE evaluation in IRD should be considered as a valid tool to detect the subclinical myocardial dysfunction and thus improve patient stratification and risk management over time.

Table 1: Study Description and patient demographic and clinical characteristics

Disease	Mean Duration	Study [ref] (year)	Numbers	M/F	Mean Age	LV-GLS% (p value)	LV-GCS% (p value)	LV-GRS% (p value)
Rheumatoid Arthritis								
	7.14± 5.57	Ayyildiz [23] (2015)	P:38		52.1 ± 11.1	-16.5 ± 2.9	-23.6 ± 3.5	37.6 ± 1.5
			C:20		50.7 ± 3.4	-20.0 ± 2.8	-22.4 ± 2.5	40.7 ± 4.8
						<0.01	0.04	<0.01
	14±10	Cioffi [16] (2017)	P:209	115/94	58 ± 11	-18.4±3.4	-23.6±6.9	-
			H: 52	18/34	59 ±16	-19.9±2.6	-24.7±4.5	
						0.005	0.31	
	10.0±6.1	Fine [18] (2014)	P:59	14/45	55.7±12.1	−15.7±3.2	−17.9±4.7	-
			C:59	14/45	54.5±12.2	−18.1±2.4	−20.7±2.4	
						<0.001	<0.001	
		Ikonomidis [21] (2009)	P: 46	15/31	56 (16)	-18.5 (4.0)	-17.5 (4.5)	43.8 (16.0)
			C:23	5/23	56 (12)	-22.50 (2.16)	-21.9 (2.6)	52.9 (11.5)
						0.002	0.002	0.026
	12 (5–23.5)	Ikonomidis [25] (2014)	P:60	20/40	59.5±18	−14.0±4.3	−14.9±4.2	
			C:30	12/18	57.1±19	−22.1±1.9	−21.7±4.1	
	0.53±0.5	Lo Gullo [19] (2018)	P:41	9/32	46 (32 – 62)	-18.13±1.36	-20.15±1.34	-
			C: 58	23/35	45 (24 – 66)	-23.25±1.80	-24.50±0.70	
						<0.001	<0.001	
		Løgstrup [17] (2017)	P: 66	24/42	57.8 ± 11.9	−17.4 ± 3.5	−21.1 ± 4.1	
	16.8 (2.1)	Midtbø [20] (2017)	P: 78Active	18/60	60.7 (11.7)	−18.9 (3.1)		
			C:46	19/27	52.7 (8.9)	−19.7 (3.3)		
						0.40		
		Sitia [15] (2012)	P:22	12/12	46±12	Reduced in RA		Reduced in RA
			C:20	10/10	50±11			
	11.4±4.9	Vizzardi[22] (2015)	P:13	7/6	51±13	-17.08		
Psoriatic Arthritis								
		Shang [28]	P: 33	15/ 18	43.9 ± 12.8	20.0 ± 3.4	21.3 ± 5.1	34.5 ± 20.0

		(2014)	C :24	11/13	46.6 ± 8.9	21.7 ± 2.5	33.6 ± 4.8	37.7 ± 18.4
						0.048	<0.001	0.562
	5 (3-10)	Yilmazer [29] (2016)	P: 31	10/21	41.3±11	-17.1±2.8	-14.3 ±3	29.3±10
			C: 19	9/10	41±8	-19.3±2	-20.3 ±4.8	46.5±17
						0.005	<0.001	<0.001
	0.78±0.64	Lo Gullo [19] (2018)	P:35	9/26	45 (23 – 59)	-21.57±2.59	-24.97±2.50	
			C: 58	23/35	45 (24 – 66)	-23.25±1.80	-24.50±0.70	
						0.020	1.000	
Ankylosing Spondylitis								
		Zungur [33] (2018)	P: 64	53/11	55.7±9.2	-	-	-
			C: 70	55/15	54.9±8.5			
	22±11	Midtbø [34] (2018)	P: 106	63/53	48.0±12.2	-17.5±2.5	-	-
			C:106	63/53	51.1±11.5	-18.4±2.3		
						0.03		
Axial Spondyloarthritis		Chen [35] (2015)	P: 104	72/32	45.5 (13.3)	-18.1 (2.4)	-17.2 (2.2)	37.1 (8.6)
			C: 50	29/21	43.8 (10.8)	-20.1 (2.5)	-20.3 (2.9)	43.2 (10.9)
						<0.01	<0.01	<0.01
		Ustun [36] (2015)	P:26	22/4	43.7 ± 11.8	17 ± 1.2	-	-.
			C:26	21/5	42.5 ± 9.5	19.5 ± 1		
						<0.001		
Systemic Lupus Erythematosus								
		Huang [38] (2014)	P: 34	4/30	31.2±8.1	-18.2±2.9	-18.4±3.1	51.4±10.2
			C: 34	5/29	34.0±10.1	-21.4±2.5	-20.6± 2.5	61.9±10.0
						<0.001	0.002	<0.001
C-SLE		Leal [44] (2015)	P :35	7/28	14.75 (7.88–19.37)	-19.64±3.12	-	-
			C: 33	9/24	14.88 (7.2–17.67)	-22.56±2.67		
						0.0004		
C-SLE		Leal [46] (2016)	P: 50	9/41	14.74 (4.38–19.37)	−20.3(−11.0 to−26.0)	−23.67 ± 3.46	33.09 ± 8.6 <
			P: 50	12/38	14.82 (4.90–19.87)	−22.0 (−17.8 to−30.4)	−24.6 (2.86)	44.36 ± 8.72
						<0.0001	0.43	0.0001
		Dai [39] (2016)	P: 60	12/48	36.3±7.6	26.2±9.5	-	-
			C: 60	10/50	35.8±8.1	32.5±9.8		
						<0.01		
j-SLE	4.75±2.8	Dedeoglu [48] (2016)	P: 35		12.3± 3.55	–20.8 ± 5.1	-	-
			C:30		12.3± 3.55	–24.0 ± 3.1		

						0.001		
		Du Toit [40] (2017)	P: 28	2/26	28.32 ± 11.35	−10.9 (−13.7 to −7.8)		
			C: 28	2/26	28.48 ± 11.33	−22.1 (−23.5 to −20.8)		
						<0.001		
		Luo [42] (2018)	P: 102	11/91	43.2±9.3	Reduced compared to controls		
			C: 30	3/27	42.1±10.5			
		Sun [41] (2018)	P: 102	11/91	43.2±9.3			
			C: 30	3/27	42.1±10.50			
Systemic Sclerosis								
		Spethmann [51] (2012)	P: 22	5/17	57.1±13.3	-19.0±2.4	-20.4±5.2	38.7±21.3
			C: 22	5/17	57.4±14.0	-21.1±2.5	-21.0±7.6	48.3±21.8
						0.008	0.893	0.138
	7.4 ± 5.8	Tigen [52] (2014)	P: 53	6/47	49.1±11.5 (nQRS)	−21.6 ± 2.1(nQRS)	−18.8 ± 4.9	37.9 ± 17.5
			C: 26	4/22	42.8 ± 11.7	−25.8 ± 2.7	−25.2 ± 3.3	47.7 ± 7.0
						<0.001	<0.001	0.022
	12.1 ± 10.3	D'Andrea [53] (2016)	P: 90	22/68	52.4 ± 15.2	-	-	-
			C: 55	15/40	50.6 ± 12.4			
		Cadeddu [54] (2015)	P:45	9/36	60.4 ± 10.3	-18.15 ± 2.15		
			C:20	4/16	60.8 ± 10.8	-15.74 ± 3.57		
						<0.005		
	11.1 ± 8.3	Hekimsoy [55] (2018)	P : 8o	11/69	51 ± 12	-	-	-
	60 ± 4.5	Spethmann [56] (2014)	P:19	6/13	55.2 ± 10.8	−22.0 ± 2.3	-	-
		Agoston [57] (2014)	P:42	2/40	50 ± 14	-	-	-
			C: 42	2/40	49 ± 13			
		Yiu [60] (2016)	P: 102	32/70	51 (S.D. 12)			
			C: 36	9/27	54 (s.d. 14)			
		Cusmà-Piccione [59] (2013)	P: 29	1/ 28	65±4	−13.1±4.8	−15.3±6.2	35.5±8.1
			C: 30	7/23	64±2	−22.6±4.1	−20.4±5.6	38.5±9.3
	5.1±2.3	Yiu [60] (2011)	P: 104	24/80	54 ± 12	-18.2±1.8	-18.2±2.3	37.0±13.9
			C: 37	10/27	54 ± 10	-21.3±1.7	-21.3±2.1	40.3±12.4
						<0.01	<0.01	0.18
Churg- Strauss								

		Miszalski-Jamka[63] (2012)	P: 22	8/14	43.2±9.5	−16.9±5.3	−18.4±4.7	37.0±12.7
			C: 22	8/14	age-sex matched	−19.7±2.8	−21.2±3.6	52.0±17.1
						0.03	0.04	0.002
Granulomatosis with poliangioitis								
	6.6±5.7	Miszalski-Jamka[68] (2012)	P: 22	11/11	46.8±12.3	−17.98±2.34	−18.42±4.11	38.78±10.12
			C: 22	11/11	age-sex matched	−19.74±2.74	−21.58±3.90	50.09±15.55
						0.03	0.01	0.007
Behcet Syndrome								
		Yagmur [69] (2011)	P: 32	19/13	35.47±8.96	-18.0±2.3	-22.0±1.6	-
			C: 27	19/8	36.44±8.29	-20.5±1.8	-22.2±2.3	
						<0.0001	0.63	
		Sun [71] (2018)	P: 81	22/59	51±11	-17.1±2.9	-	-
			C: 145	40/105	51±12	-20.8±2.2		
						<0.001		
	8.8±5.9	Demirelli [72] (2014)	P: 30	10/20	28.4±7.0	20.1±1.74	-	-
			C: 25	9/16	27.7±4.9	22.2±1.53		
						0.001		
Kawasaki Disease								
		Azak [73] (2018)	P: 15	11/4	4.5 ± 3.1	-18.9 ± 3.5	20.3± 3.4	-
			C: 15	9/6	5.7 ± 2.8	23.7 ± 3.2	26.3 ± 4.5	
						0.001	0.001	
		Yu [74] (2010)	P: 50	24/26	2.20 ± 1.97	-19.2± 3.5	18.0±3.5	51.8± 16.8
			C : 35	17/18	2.64 ± 1.63	22.2 ± 3.1	20.3 ± 3.3	54.2 ± 16.0
						<0.001	<0.01	0.01
		Dedeoglu [105] (2017)	P: 35	22/13	2.13±1.28	−23.1 ± 3.5	-	-
			C: 30	20/10	2.06 ±1.52	24.0 ± 3.1		
						<0.05		
		Kato [76] (2018)	P: 52	31/21	0.25-11	−19.8±3.4	-35.0±4.7	56.7±21.4
		Yu [77] (2014)	P:14 group I	10/4	1.5±0.47	43.7±7.3	-	-
			C :14	10/4	1.66±0.51	50.4±6.6		
						0.02		
Gout - Hyperuricemia								

		Pan [79] (2014)	P:50stage III	45/5	61.0±14.15	-20.2±3.06	-	-
			C: 35	26/9	53.5±15.64	-21.79±2.27		
						0.002		
		Zhang [80] (2018)	P: 40	38/2	38.74 ± 9.9	− 31.30 ± 5.0	−35.65±2.5	
			C: 15	11/4	33.89 ± 7.8	− 20.51 ± 4.0	− 23.20 ± 4.0	
						0.019	0.0001	
		Fang [81] (2016)	P: 44	23/21	60.3 ± 6.8	−18.04 ± 2.32	−20.53±2.79	
			C: 40	20/20	60.3 ± 6.8	−21.23 ± 2.23	−22.23 ± 2.63	
						<0.05	<0.05	
Sarcoidosis								
		Tsuji [84] (2013)	P : 23	12/11	64 ± 12	12.2 ± 4.3	23.8 ± 7.3	18.5 ± 8.4
			C: 16	11/5	59 ± 11	11.8 ± 2.6	21.0 ± 5.8	28.5 ± 8.3
						0.94	0.83	0.0007
		Aggeli [86] (2013)	P: 67	26/41	46.0 ± 2.6	14.41±3.01	-	-
			C: 29	11/18	45.2 ± 1.9	22.93 ± 2.28		
						<0.005		
		Felekos [87] (2018)	P: 117	43/74	46.3	-14.4 ± 3	-	-
			C: 45	13/22	45 ± 8	-20.9 ± 2.3		
						0.02		
		Schouver [88] (2016)	P: 35	13/22	47.5 ± 16.3	-17.2 ± 3.10	-21.3 ± 1.50	-
			C: 35	13/22	47.9 ± 14.8	-21.3 ± 1.50	-19.9 ± 4.30	
						<0.001	0.12	
		Joyce [89] (2015)	P: 100	48/52	55±13	–17.3±2.5		
			C: 100	48/52	55±13	–20.0±1.6		
						<0.001		
		Tigen [90] (2015)	P: 40	6/34	46.4±10.5	-21.9±3.3	-21.1±3.6	45.0 ± 11.0
			C: 20	17/3	41.9±12.4	-25.7±3.0	-25.4±3.1	49.7 ± 5.9
						<0.001	<0.001	0.015
		Orii [91] (2015)	P: 13 MRI+	5/8	64±9	-19±3	-22±8	43±19
			C: 10		age matched	-23±3	-30±4	45±9
						0.03	0.04	0.95
		Kul [106] (2014)	P: 34 No Cs	9/25	45 (9.1)	-17.6 (-1.9)	-19(-2.7)	-
			C: 26	8/18	44.3 ± 9	-20.8 (-1.9)	-22.7 (-3.1)	
						<0.001	<0.001	
Sjögren Syndrome								
	46.1±8.24	Atzeni [95]	P: 22	6/16	60.14 ± 7.81	15.28[12.30–16.20]	26.00 [24.26 – 31.90]	

		(2014)	C: 22	6/16	59.25 ± 2.08	19.80 [19.30 – 20.40]	31.50 [28.30 – 34.50]	
						<0.0001	0.02	
	77.1±34.7	Atzeni [96] (2017)	P: 49	7/42	57.5 ± 6.90	15.28 [12.3–16.2]		
			C: 49	9/40	59.6 ± 2.08	19.8 [19.3–20.40]		
						<0.001		
Polymyositis - Dermatoyositis								
	23.5 (8.5–60)	Zhong [101] (2018)	P: 60	16/44	51.1 ± 12.6	− 20.3 ± 2.5		
			C: 30	7/21	51.0 ± 14.1	− 23.4 ± 1.7		
						<0.001		
		Guerra [102] (2017)	P: 28	6/22	61.3 ± 13.1	–18.7 ± 4.2		
			C: 28	6/22	63.6 ±15.6	–21.2 ± 2.1		
						0.006		
Antiphospholipid Syndrome								
		Medina [43] (2018)	P: 38	6/32	46.7±10.2	− 18.68		
			C: 21	4/17	42±7.2	− 20.7		
						0.015		
Familiar Mediateranean Fever								
	9.4±6.5	Kalkan [65] (2010)	P:23	10/13	32.3±9.4	−21.1±2.2		
			C:22	10/12	32.5±7	−23.8±2.2		
						<0.001		
	4.6±2.4	Ceylan [64] (2015)	P:45	21/24	11.3±3.7	-14.44±4.77	-16.18±3.12	14.80±6.29
			C:45	24/21	11.2±3.4	-17.40±1.79	-17.03±2.51	17.53±4.63
						<0.001	0.157	0.022

C: controls, F: female, LV GCS: left ventricular global circumferential strain, LV GLS: left ventricular global longitudinal strain, LV GRS: left ventricular global radial strain, M: male, P: patients, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus

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