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Microvascular heart involvement in systemic autoimmune diseases: The purinergic pathway and therapeutic insights from the biology of the diseases

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ABSTRACT

Heart involvement – often asymptomatic – is largely underestimated in patients with systemic autoimmune diseases (SADs). Cardiovascular events are more frequent in patients with SADs compared to the general population, owing to the consequences of inflammation and autoimmunity and to the high prevalence of traditional risk factors. Coronary microvascular disease (CMD) is a form of cardiac involvement that is increasingly recognised yet still largely neglected. CMD, the incapacity of the coronary microvascular tree to dilate when myocardial oxygen demand increases or when there is a microvascular spasm (or subclinical myocarditis), is increasingly reported because of the widespread use of new cardiac imaging tools, even in a subclinical phase. The assessment of myocardial coronary flow reserve (CFR) emerged as the most effective clinical tool to detect microvascular damage. The potential causes of microvascular damage, molecular and cellular inflammation along with a pathological CD39-CD73 axis, need always to be considered because data show that they play a role in the occurrence of acute coronary syndromes, heart failure and arrhythmias, even in the early asymptomatic stage. Data suggest that controlling disease activity by means of methotrexate, biologic drugs, antimalarial medications, statins and aspirin, according to indication, might reduce the cardiovascular risk related to macrovascular and microvascular damage in most patients with SADs, provided that they are used early and timely to control diseases. The need of new biomarkers and a careful assessment of myocardial CFR emerged as the most effective clinical tool to detect microvascular damage.

1. Introduction

Cardiovascular complications are the leading cause of disease-related and overall deaths in patients affected by most systemic autoimmune disorders (SADs) [1]. The development of new therapeutic strategies for the treatment of non-cardiac life-threatening complications has enhanced this trend in the last two decades. The incidence of cardiovascular events is higher in patients with SADs compared to the general population, and this higher risk can only partially be explained by traditional risk factors. Thus SADs – such as diabetes – may be recognised as coronary heart-disease equivalents [2]. The clinical spectrum of heart involvement due to SADs is heterogeneous in terms of the structures involved and their severity. Atherosclerosis of the coronary arteries is the most common and most comprehensively investigated form of cardiac involvement in patients with SADs [3]. Nonetheless there is growing evidence that coronary microvascular disease (CMD) and subtle myocarditis are linked processes, which are still largely under-diagnosed in these patients. Both these conditions may play a key role in acute coronary syndromes, heart failure and arrhythmias. CMD is associated with a higher risk of major

Abbreviations: ADO, Adenosine; CAD, Coronary artery disease; CDUS, Coronary doppler ultrasound; CFR, Coronary flow reserve; CMD, Coronary microvascular disease; CMR, Cardiac magnetic resonance; CPR, C Reactive Protein; DAS, Disease Activity Score; EMB, Endomyocardial biopsy; eNOS, Endothelial Nitric Oxide synthase; hs-CRP, High sensitivity C Reactive Protein; IL1Ra, Interleukin 1 Receptor antagonist; LGE, Late Gadolinium Enhancement; MPRI, Myocardial perfusion reserve index; MTX, Methotrexate; NA, Not Available; NK, Natural Killer; PD, Perfusion Defect; PET, Positron emission tomography; RA, Rheumatoid Arthritis; ROS, Reactive oxygen species; SADs, Systemic autoimmune diseases; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SPECT, Single-photon emission computerised tomography; SSc, Systemic Sclerosis; SSZ, Sulfasalazine; VDAI, Valentini Disease Activity Index

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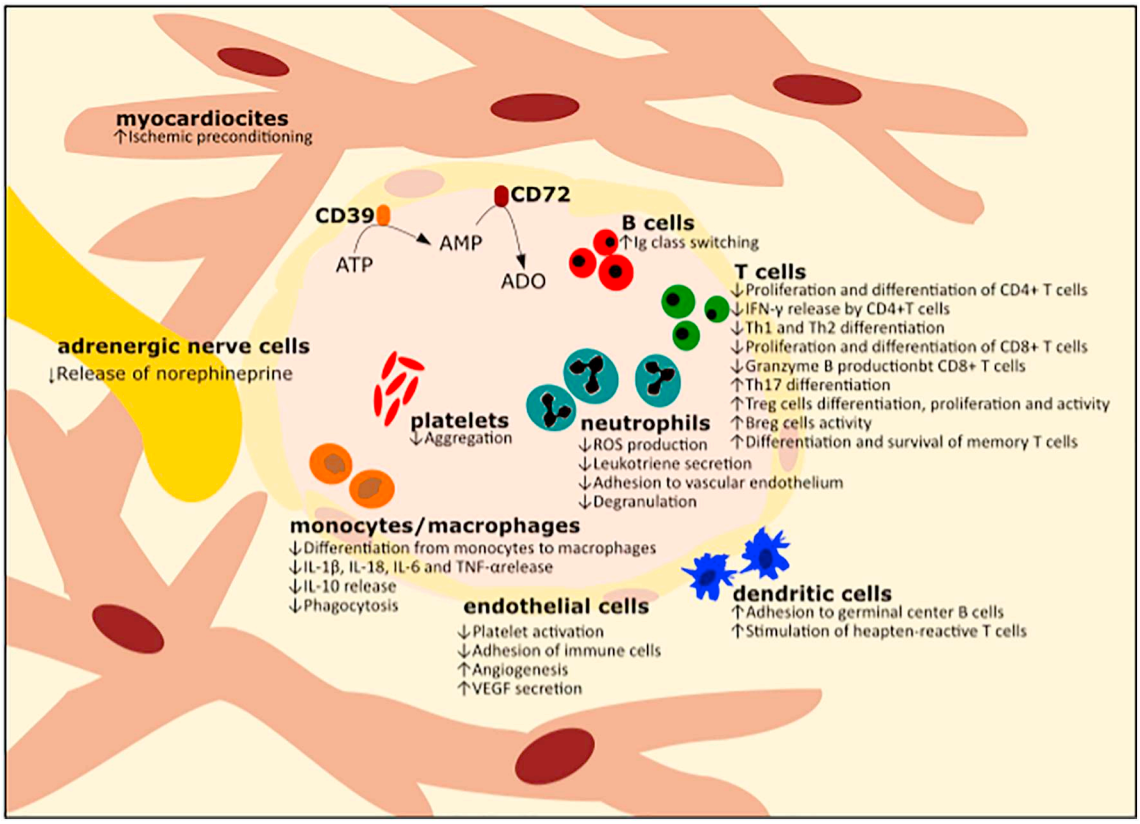

Fig. 1. Biological effects on heart of conversion of extracellular ATP and ADP to adenosine. Even if represented only on endothelial cells most of the target cells express also CD39 and CD73. ATP adenosine triphosphate, AMP adenosine monophosphate, ADA adenosine.

cardiovascular events, even in the absence of atherosclerotic disease. CMD can therefore significantly increase mortality, especially in patients suffering from a systemic disease. The widespread use of new cardiac imaging tools has made it increasingly possible to recognise these forms of heart involvement, even in a subclinical phase, raising new questions about diagnostic flow charts and treatment.

Different biologic mechanisms and risk factors play a role in heart disease associated with SADs. Some of these factors are involved in both atherosclerotic and microvascular driven damage. Traditional cardiovascular risk factors could also be more present in these patients, either because of the direct consequences of the disease, or as a result of adverse effects of medication. The immune-inflammatory state in SADs can both contribute to large epicardial vessel damage, microvascular impairment [4] and variable degrees of myocardial inflammation.

The inflammatory milieu and reactive oxygen species can produce negative functional and structural changes in coronary microcirculation and cardiomyocytes, leading to impaired vasoregulation, contractile dysfunction and arrhythmias [5–7]. Apart from systemic inflammation, CMD shares further risk factors with coronary atherosclerosis, including aging, hypertension, diabetes mellitus, tobacco smoking and dyslipidaemia [8]. However, these factors seem to account for only a part of the overall microvascular damage. The CD39-CD73 axis-pathway appears to be a major player of coronary endothelial dysfunction in all the autoimmune illnesses and CMD is increasingly recognised as the earliest stage of coronary atherosclerosis, responsible for the increased cardiovascular morbidity and mortality.

Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and Systemic Sclerosis (SSc) represent paradigmatic examples of cardiac disease in SADs. Even if these conditions present specific pathophysiological profiles, they are all associated with CMD and accelerated large coronary vessels disease [9].

2. A new common pathogenetic pathway: microvascular disease

CMD has emerged as a mechanism of myocardial ischaemia distinct from obstructive atherosclerosis. Like most autoimmune diseases, CMD is particularly common in women. It is characterised by a limited microvascular vasodilator capacity in small intramural pre-arteriolar coronary arteries due to endothelial and smooth muscle functional and structural changes. Microcirculation cannot be directly visualised in vivo but can be indirectly assessed by means of an evaluation of the coronary flow reserve (CFR).

CMD can occur in patients with or without obstructive coronary atherosclerosis or other myocardial diseases, and it has been associated with an increased risk of major cardiovascular events. The pathogenesis of CMD is still not fully understood, especially in SADs. Different mechanisms may play a role according to the specific inflammatory disease and the overlap with other forms of cardiac disease. Both systemic and local inflammation may contribute to functional and structural changes in endothelial and smooth muscles, leading to an impaired vasodilator response. The high sensitivity C Reactive Protein (hs-CRP) has been recognised as an independent risk marker of microvascular coronary disease, which suggests that there may be an association between systemic inflammation and reduced coronary reserve [10]. In vitro studies suggest a direct role of circulating reactive oxygen species (ROS), monocytes, T cells, B cells, and natural killer cells (NK), but supportive in vivo studies are lacking [5].

Emerging data suggest a pivotal role of purinergic signalling deregulation in microvascular and inflammatory diseases through the CD39 and CD73 pathway leading to accumulation of adenosine, with specific references to heart patho-physiology [11]. CD39 is an ectoenzyme that hydrolyzes ATP and ADP to AMP providing the substrate for generation of adenosine on the cell surface by CD73. CD39 and CD73 are both expressed on cell surface of endothelial cell, circulating

platelets, myocardiocytes, nerve cells and part of leukocytes including T cells, B cells, monocytes, macrophages, neutrophils, dendritic cells and NK cells. This pathway is indeed involved in both endothelial and immune dysfunction so it can be proposed as a link between microvascular disease and direct inflammation of the myocardium (myocarditis). In normal conditions, ATP is almost exclusively present inside the cells but it can be released by cell lysis or by non-lytic mechanisms involving vesicles trafficking and specific nucleotide permeable channels. Because most of the adenosine producing cells also express adenosine receptors, this molecule can act as autocrine modulator. CD39 and CD73 con be up-regulated by hypoxia, oxidative stress and presence of pro-inflammatory mediators including TGF-β, type I IFN, IL-6 and IL-1. The extracellular concentration of adenosine depends ultimately on the balance between CD39 and CD73 activity, cellular reuptake by specific transporters and release from cells. All conditions of metabolic stress including ischaemia and immune activation can increase extracellular concentrations of adenosine. ATP and ADP exert biological effects that are typically opposite to adenosine-mediated activities (Fig. 1). Moreover, ATP and ADP are competitive inhibitors of CD73 by binding to the active site of enzyme without being hydrolyzed [12]. The conversion of ATP and ADP to adenosine can definitely induce an anti-inflammatory and immunosuppressive milieu and exert an anti-thrombotic activity [13]. Murine models also suggest a specific cardio-protective role of CD39 and CD73. They both can attenuate infarct size through ischemic pre-conditioning and C39 can also reduce the noradrenaline release from cardiac sympathetic nerve terminals in response to ischemia preventing major arrhythmias [14,15]. As reported below, deregulation of CD39 and CD73 expression has been described in rheumatoid arthritis, systemic lupus erythematosus and in systemic sclerosis, thus leading to less adenosine in the tissues, more inflammation, more endothelial damage.

Most of the in vivo data about the relationship between CMD and inflammation (in the heart), are derived from studies of viral infections. A biopsy-proven inflammatory infiltrate in patients with viral myocarditis is associated with a reduced CFR [16]. Moreover – as detailed below – many of the studies recognising CMR findings in myocarditis, demonstrated a reduced CFR thus suggesting that one way to analyse CMD is to assess the CFR.

2.1. Assessment of coronary microvascular dysfunction

Currently, direct visualisation of the coronary microcirculation in vivo is not technically feasible. A reduction of CFR – i.e. the ratio between myocardial blood flow during near maximal coronary vasodilatation to baseline – is the most reliable marker of microvascular coronary impairment. CFR can be assessed by non-invasive testing, such as nuclear medicine imaging, coronary doppler ultrasound (CDUS) or cardiac magnetic resonance imaging (CMR), comparing myocardial blood flow at rest and under pharmacologic stress conditions induced by infusion of adenosine, dobutamine or dypiridamole. Moreover the presence of perfusion abnormalities on a CMR or radioisotope scan without a segmental coronary distribution or in the absence of coronary macrovascular disease is a reason to suspect the presence of CMD or inflammatory myocardial disease. Compared to the other techniques, CMR has better reproducibility and the possibility of a tissue characterisation that can be informative even without a pharmacologic stress test. Moreover, T2-weightened imaging can identify tissue œdema suggestive of concomitant myocarditis. Late gadolinium enhancement can detect areas of myocardial fibrosis or necrosis that – in the absence of a coronary artery distribution – can be driven by an inflammatory or microvascular disease. Finally, CMR can also directly estimate the CFR through the myocardial perfusion reserve index (MPRI) that measures the ratio of myocardial blood flow at hyperaemia in response to vasodilator stress and rest [17].

3. Systemic lupus erythematosus

Cardiovascular complications are the main causes of mortality in patients with SLE and the leading cause of death after the first five years from the onset of the disorder [18]. After the first phase of the disease the influence of lupus activation on mortality is lower and the cumulative adverse effect of therapy on the heart is more pronounced. The prevalence of acute myocardial infarction or angina is between 6 and 10% and the risk of coronary heart disease is increased five- to six-fold in SLE patients compared to the general population [19]. In fact SLE patients are exposed to the highest cardiovascular risk among all patients with SADs.

Subclinical coronary artery disease is largely underestimated. More than half of the patients with SLE show a generalised atherosclerotic disease on autopsy, regardless of the specific cause of death, and electron-beam CT scans detect coronary-artery calcifications in about 31% of SLE patients without a known history of coronary disease. This SLE complication occurs more frequently at a younger age compared to healthy controls [20].

The high incidence of coronary atherosclerosis and CMD in SLE patients can be linked to standard and disease-related risk factors. SLE patients are subject to more cardiovascular risk factors than the general population, such as sedentary lifestyle, obesity, dyslipidaemia, insulin resistance and early menopause, but since the CV risk is higher compared to the population of the same age [21] a relevant contribution of disease-related mechanisms is suggested.

Inflammatory cytokines and autoantibodies directed against oxidised-LDL, Apo-A1 and phospholipids [22,23] can promote atherogenesis. The presence of lupus nephropathy is an additional disease-specific risk factor, especially if associated with proteinuria.

Because accelerated atherosclerosis and CMD correlate with disease activity and severity [24], an adequate immunosuppressive therapy could reduce cardiovascular risk. Corticosteroids may potentially have a double-edged effect: they reduce disease activity, but on the other hand they worsen traditional risk factors such as dyslipidaemia, hypertension, obesity and insulin resistance. Antimalarial drugs may have specific additional benefits due to their antiaggregant, anti-hyperglycaemic and cholesterol-lowering properties, especially in patients taking steroids and with anti-phospholipid antibodies [25]. Antimalarial drugs, in addition to improve lipid metabolism and their well-known immunomodulatory effect [26], also inhibit IL1-beta, as well as IL6 and TNF-alfa biological synthesis by stimulated monocytes-macrophages [27]. Statins have favourable effects on endothelial dysfunction [28,29] and atherogenesis and even reduce RA activity, through several possible biologic mechanisms [30] thus mitigating the cardiovascular risk [3]. This appears to be mediated in particular by the increase of endothelial Nitric Oxide synthase (eNOS), by the inhibition of IL6 synthesis in stimulated vascular smooth muscle -mononuclear cell cultures [31] and of IL1-beta in monocytes of patients with CAD [32].

In the absence of a long-term prospective trial, a primary prophylaxis with aspirin and antimalarials could be considered for all SLE patients especially in the presence of other classic risk factors [33]. Statins can be similarly useful, not only for their lipid-lowering properties in dyslipidemic patients, but potentially in all lupus patients for their atheroprotective effects and their potential beneficial role on microvascular function and positive regulation of CD39 and CD73 ectoenzymes. Experimental data suggest in fact that mice null for CD39−/− and CD73 −/− are prone to develop antiphospholipid induced prothrombotic events, whereas hyperexpression of CD39/CD73 activity protects against thrombosis [34]. There is a real need for prospective studies in this regard [33].

3.1. Microvascular damage in SLE: imaging

Atherosclerotic heart disease is the most common form of SAD-related cardiopathy but half of SLE patients without signs or symptoms of

Table 1
CMR in SLE patients without symptomatic heart disease.

	Patients (n)	Age (y)	Female (n)	Disease duration (y)	SLEDAI	LGE (n)	Segmental LGE (n)	Stress induced PD	Myocardial Oedema
Seneviratne MG 2015 [37]	41	39 ± 12	33 (75%)	11 (0.5–34)	4 (0 − 12)	15 (37%)	1 (3%)	NA	Similar T2 œdema ratio regardless of the extent of LGE (no control group)
Ntusi NA 2015 [38]	29	42 ± 9	28 (97%)	9 ± 12	9 (1–16)	10 (43%)	0	NA	Higher T2 œdema ratio compared to controls
Zhang Y 2014 [39]	24	54 ± 9	19 (76%)	NA	0.71 ± 0.8	0	0	NA	Higher T2 values on T2 mapping sequence compared to controls
Puntmann VO 2013 [40]	33	40 ± 9	14 (79%)	7.4	0 (0–3)	20 (61%)	0	No Dobutamine Induced PD	Similar T2 œdema ratio compared to controls
Kobayashi H 2010 [41]	16	41.5 ± 16.1	12 (75%)	7.1 ± 5.1	4.9 ± 2.9	6 (33%)	0	Dobutamine Induced PD in 7 patients (44%)	NA

SLEDAI Systemic Lupus Erythematosus Disease Activity Index, LGE Late Gadolinium Enhancement, PD Perfusion Defects, NA Not Available.

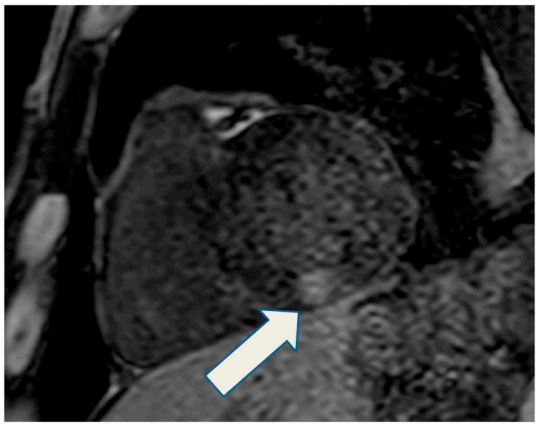

Fig. 2. Cardiac magnetic resonance findings in new-diagnosed SLE patients without symptoms of heart involvement and normal coronary angiogram. Evidence of a transmural area of delayed enhancement in the inferior wall of the left ventricle (arrow).

heart involvement, present CMR abnormalities suggestive of CMD. The broad heterogeneity of clinical phenotype and disease activity may explain the different prevalence of CMR findings among the studies. Moreover, Doppler echocardiography, single-photon emission computerised tomography (SPECT) scans and Positron Emission Tomography (PET) scans can all show a reduction of CFR in SLE patients [5]. SPECT imaging reveals a high prevalence of perfusion defects in SLE patients, often with no suspected or documented coronary artery disease. Persistent or reversible perfusion abnormalities can be detected in up to 88% of patients [35], of which up to two thirds may be negative on coronary angiograms, suggesting the presence of a CMD. These data agree with the reduction of myocardial coronary flow reserve CFR on MRI studies in about 44% of SLE patients with angina and a normal angiogram [36]. In SLE, cardiac MRI studies suggest a large prevalence of subclinical myocardial inflammation and microvascular dysfunction even in patients with low disease activity [37–41] (Table 1) (Fig. 2). This subtle myocarditis may contribute to the high incidence of heart failure in SLE patients through microvascular disease. The risk of heart failure in SLE patients – almost five times higher compared to the general population – seems indeed to be only partially attributable to the macrovascular coronary disease [42].

4. Rheumatoid arthritis

The cardiologic implications of RA have been neglected for a long time, even though cardiovascular events are by far the leading cause of death in RA patients [43,44]. The risk of acute coronary syndromes and heart failure is doubled in RA compared to the general population, and these complications tend to occur about a decade earlier than in matched controls [45]. Traditional CV risk factors seem to have the same prevalence in RA and non-RA patients, and thus do not fully explain the increased CV burden [46]. More than two thirds of RA patients that are asymptomatic for heart disease can present with coronary plaque in CT angiography indicating a large prevalence of subclinical coronary disease [47]. Furthermore, among hypertensive patients, RA emerged as one of the five leading comorbidities [48].

About one in two RA patients without symptomatic heart disease exhibit signs of microvascular impairment or subtle myocarditis on imaging. RA patients have a CFR reduction as assessed by transthoracic doppler echocardiography and PET [5]. RA therapies may modify the endothelial dysfunction, and therefore the cardiovascular risk. As recently stated, more benefits were seen in patients treated with Methotrexate (MTX) than in patients receiving MTX plus anti-TNFalfa, thus suggesting a better efficacy of MTX [49]. Therefore, disease activity should be controlled optimally in order to lower CVD risk in all patients with RA [50]. The major effect of some inflammatory molecules (not all) was demonstrated by a single injection of Interleukin 1 Receptor Antagonist (IL1Ra) in disease modifying anti rheumatic drugs (DMARDs) treated patients, showing a clearcut improvement after 3 h in coronary endothelial function in those patients already having coronary artery disease (CAD) [51]. According to this study IL1 appears to be of paramount importance in patients with already active vascular damage. Even though there is at present insufficient clinical evidence to justify a recommendation for a systematic use of antimalarials, statins and aspirin as primary prevention in patients with RA without traditional cardiovascular risk factors, considering the high subclinical prevalence of coronary microvascular and macrovascular disease, statins and antimalarials prescription might be considered as the primary prophylaxis in all RA patients which are at cardiovascular risk, regardless of the serum lipid profile. A further key to understand the pathogenesis and the appropriate therapy, appears to be the CD39-CD73 axis. In fact CD39 expression was shown to be increased on TRegs of RA synovial fluids. These TRegs did not produce cytokines and suppressed T effector functions and synthesis of TNF-alfa, IFN-gamma, IL-17F [52]. Of key importance MTX as well as sulfasalazine (SSZ) increase extracellular adenosine, and it is crucial that the expression of CD39, the ectoenzyme that catalyses the dephosphorylation of ATP and ADP to AMP (which is critical for extracellular adenosine production), had been shown to be a biomarker for MTX efficacy in patients with RA [53]. Importantly an high expression of CD39 on hematopoietic cells or endothelial cells dampen thrombosis in mice [54].

4.1. Microvascular damage in RA: imaging

Few studies have focused CMD in patients with rheumatoid arthritis without signs or symptoms of overt cardiac disease. Up to half of RA patients without a history of heart disease may show areas of

Table 2
CMR in RA patients without symptomatic heart disease.

	Patients (n)	Age (y)	Female (n)	Disease duration (y)	DAS28-CPR	LGE (n)	Segmental LGE (n)	Stress induced PD	Myocardial Oedema
Ntusi NA 2015 [55]	55	54 ± 11	39 (71%)	9 (5–13)	3,4 ± 1,4	27 (49%)	0	Reduced MPRI compared to controls	Higher T2 œdema ratio compared to controls
Bradham W 2018 [56]	59	53 (40–59)	45 (76%)	10 (5–15)	3.16 (2.03–4.05)	2 (3%)	0	NA	NA

DAS Disease Activity Score, CPR C Reactive Protein, LGE Late Gadolinium Enhancement, PD Perfusion Defects, NA Not Available, MPRI Myocardial Perfusion Reserve Index.

myocardial fibrosis without a segmental pattern on CMR, even though the latest study did not show clearcut evidences [55,56]. A similar proportion of asymptomatic subjects with stress-induced ischaemia present a normal angiogram [57], suggesting an impaired myocardial CFR and a microangiopathic coronary disease. Furthermore, CMR studies indicate a high prevalence of subclinical myocarditis in RA patients, which may be involved in the pathogenesis of microangiopathic disease and in doubling the risk of heart failure [1] and atrial fibrillation compared to the general population (Table 2). More prospective studies are needed.

We may conclude that prevention should be a key factor in lessening the overall CV risk that RA patients may be exposed to [58]. Research agenda should define whether patients carrying high levels of CD39-TRegs are those at lower CV and CMD and whether MTX, along with antimalarials and statins, in responders can really down-modulate CMD.

5. Systemic sclerosis

Scleroderma heart disease accounts for 14% of scleroderma-related mortality, largely caused by arrhythmias, and it only follows pulmonary complications as a cause of death [59].

The influence of macrovascular coronary disease in SSc has been widely discussed [60]. Even if an increased risk of coronary heart disease in SSc patients can be assumed, this phenomenon seems to be somewhat different from other conditions with a more inflammatory pathogenesis, such as RA and SLE [61].

Microvascular disease is the core of scleroderma pathogenesis in every part of the body affected, including the heart. Autopsy studies identified cardiac abnormalities in almost all patients with SSc, which can be linked either to primary involvement in heart disease or secondary involvement resulting from pulmonary or renal complication of the disease. Nevertheless, only 15 to 35% of SSc patients are symptomatic for heart involvement, and the clinical onset of symptoms occurs after a long phase of silent disease progression. Endothelial dysfunction and myocardial subclinical inflammation are considered the earliest and mutual alterations. An abnormal vasomotor response to cold stress with a confirmed cardiac Raynaud's phenomenon is a hallmark of the scleroderma microangiopathic disease compared to other SADs. It contributes to heart damage through an ischaemia-reperfusion injury, which leads to progressive parenchymal fibrosis in primary heart involvement [62].

The histopathologic pattern of heart involvement is characterised by patchy distribution, involvement of the immediate subendocardium, mononuclear cell infiltration, contraction-band necrosis and concentric intimal hypertrophy, and it is clearly distinct from large-vessel coronary disease [63]. Structural heart changes are associated with myocardial diastolic dysfunction and with arrhythmias of varying severity degrees, ranging from subclinical ECG alteration to sudden cardiac death. Heart biopsies of symptomatic patients reveal inflammation in 96,3% of patients and fibrosis in 100% of patients. The degree of these alterations correlates with the risk of major cardiovascular complications [64]. How can we explain the persistent inflammation and the fibrotic manifestations? Again the purinergic pathway can lead us closer to the point. In SSc the purinergic cascade can be involved in a very complex way [65]. First, extracellular generation of Adenosine (ADO) by ecto-nucleotidases promotes dermal fibrosis [66] and mice with high levels of adenosine in the tissue of mice lacking adenosine deaminase are led to pulmonary fibrosis by engaging both A2a and A2b [67]. Second, hyper-expression of CD39 in monocytes, down-modulate thrombosis [68]. Third, ADO through the receptor A2AR suppresses thrombospondin-1 in microvascular endothelial cells, and thrombospondin-1 suppresses angiogenesis in vitro in microvascular endothelial cells [69] and favours dermal fibrosis [70]. All these data suggest that ADO in SSc might favour fibrosis but it likely exerts angiogenic effects, besides being a potent anti-inflammatory and regulatory molecule. It is very likely that targeting fibrosis on one side and exerting anti inflammatory and pro-angiogenesis effects should be the way to look forwards. How can we deal pharmacologically with this complex setting? Statins may have an anti-inflammatory action and restore endothelial function, thus improving Raynaud's phenomenon and digital ulcers [71]. Importantly ADO is required for ERK1/2 activation by statins, which results in Akt and eNOS phosphorylation [72]. Because of their good safety profile they can be considered for the treatment of patients with systemic sclerosis regardless of serum lipids and other cardiovascular risk factors [3].

Experimental data have shown that CD39 -TRegs cultivated with IL-1 and IL-6 down-regulate CD39 and Foxp3 function, and that following the injection of rhIL-2 or the IL-6R inhibitor tocilizumab in vivo, there is a much stronger protective ability of CD39-TRegs function and less pathogenic conversion than the Tregs from the groups that did not receive rhIL-2 or the IL-6R inhibitor [73]. These experimental data suggest that tocilizumab might be the molecule targeting the CD39 pathway, that appears to be so critical in SSc (as well as in RA).

Aspirin is commonly prescribed in SSc patients with digital ulcers, even though there are no reputable studies to determine if antiplatelet therapy is actually helpful. Despite the activated endothelium of scleroderma patient promoting thrombosis, there are no recommendations to use aspirin in those SSc patients not suffering from digital ulcers.

5.1. Microvascular damage in SSc: imaging

CMR studies reveal that up to 60% of scleroderma patients may have areas of patchy delayed enhancement, indicating fibrosis or inflammation [74–78] (Table 3). A reduction of CFR – which is the first detectable abnormality in coronary microcirculation – can be found even at an early stage in at least one half of patients [79]. A small percentage of symptomatic patients with biopsy-proven myocarditis may not even show areas of altered signal intensity on CMR (Fig. 3). Vasoactive and immunosuppressive therapies may partly reverse myocardial alterations. Vasodilator therapy with calcium antagonists, ACE inhibitors or endothelin receptor antagonists [80] may reverse part of the ischaemic lesions on MRI or perfusion scintigraphy. From this it may be concluded that hypoperfused areas may be ascribed both to reversible vasoconstriction or irreversible fibrosis. In addition, the administration of immunosuppressors can lead to clinical improvement, normalisation of cardiac enzymes and partial regression of MRI findings

Table 3
CMR in SSc patients without symptomatic heart disease.

	Patients (n)	Age (y)	Female (n)	Disease duration (y)	VDAI	LGE (n)	Segmental LGE (n)	Stress induced PD	Myocardial Oedema
Mavrogeni SI 2015 [74]	46	41 ± 5	42 (91%)	15.0 ± 0.5	NA	0	0	Reduced MPRI compared to controls	T2 œdema ratio > 2 in 2 patients (4%)
Galea N 2015 [75]	30	35	20 (67%)	NA	NA	7 (23%)	NA	NA	Increased signal intensity on T2–weighted sequences in 3 patients (10%)
Ntusi NA 2015 [76]	17	55 ± 9	16 (94%)	13 (7–16)	4 (2–5)	10 (59%)	0	NA	Similar T2 œdema ratio compared to controls
Hachulla AL 2009 [77]	52	56 ± 11	8 (15%)	11.2	NA	11 (21%)	0	NA	Increased signal intensity on T2–weighted sequences in 6 patients (12%)
Naßenstein K 2008 [788]	34	54.7 ± 13.7	30 (88%)	8.4 ± 7.4	NA	5 (34%)	0	NA	No patient with increased signal intensity on T2–weighted sequences

VDAI Valentini Disease Activity Index, LGE Late Gadolinium Enhancement, PD Perfusion Defects, MPRI Myocardial Perfusion Reserve Index, NA Not Available.

in patients with acute onset of severe cardiac symptoms and biopsy-proven myocarditis [81] (Fig. 4).

6. Conclusions

Heart involvement is underestimated in patients with SADs. This should lead rheumatologists to assume that a coexistent heart disease is very likely present in every single active RA, SLE or SSc patient, and thus a full cardiovascular risk profile should be obtained at baseline along with all the data needed to manage the rheumatologic illness [2,48]. This justifies an aggressive strategy in the management of traditional risk factors, reduction of inflammation and disease activity in all patients but, above all, a reduction of the coronary risk [82]. A full understanding of the purinergic CD39-CD73 and Adenosine pathway, with effects on inflammation and vascular damage, appears to be a key point. This is reflected by the prescription of antimalarials and statins. Statins could be considered more in patients with SADs in view of their good safety profile and positive effects on endothelial function and immunomodulation. A recent survey among rheumatoid patients clearly showed that statin use still falls short of the recommendations reflected in this paper [83,84]. In addition, there is a paucity of reliable scientific evidence justifying the extensive prescription of antiplatelet medication to all patients with SADs. In conclusion, the evidence-based data suggest that the joints and heart of patients with SADs should be carefully assessed, evaluated and treated simultaneously. Accordingly, in clinical situations in which any of the symptoms discussed here are observed, microvascular damage should be suspected along with a classical coronary disease. These cases (i.e. conduction system defects, atrial arrhythmias, ventricular arrhythmias, angina, valvular heart disease, congestive heart failure, cerebrovascular disease) should lead to a comprehensive cardiac and CFR assessment, the microvascular assessment, by way of CMR (or PET).

Take-home messages

- Cardiovascular complications are the leading cause of disease-related and overall deaths in patients affected by most SADs.
- A critical role of the CD39-CD73 and Adenosine in conditioning the endothelial dysfunction arose as a possible targets for therapy in SLE, RA and SSc.
- Macrovascular (and microvascular) coronary disease in SADs are very frequent, often asymptomatic and largely underestimated due to the systemic immune response and to the presence of traditional risk factors.
- Methotrexate, some biologic drugs, antimalarials, statins and aspirin, if used timeously to achieve remission, may reduce cardiovascular risk in most of patients with SADs.
- CMR, along with imaging studies assessing the CFR (PET), can be

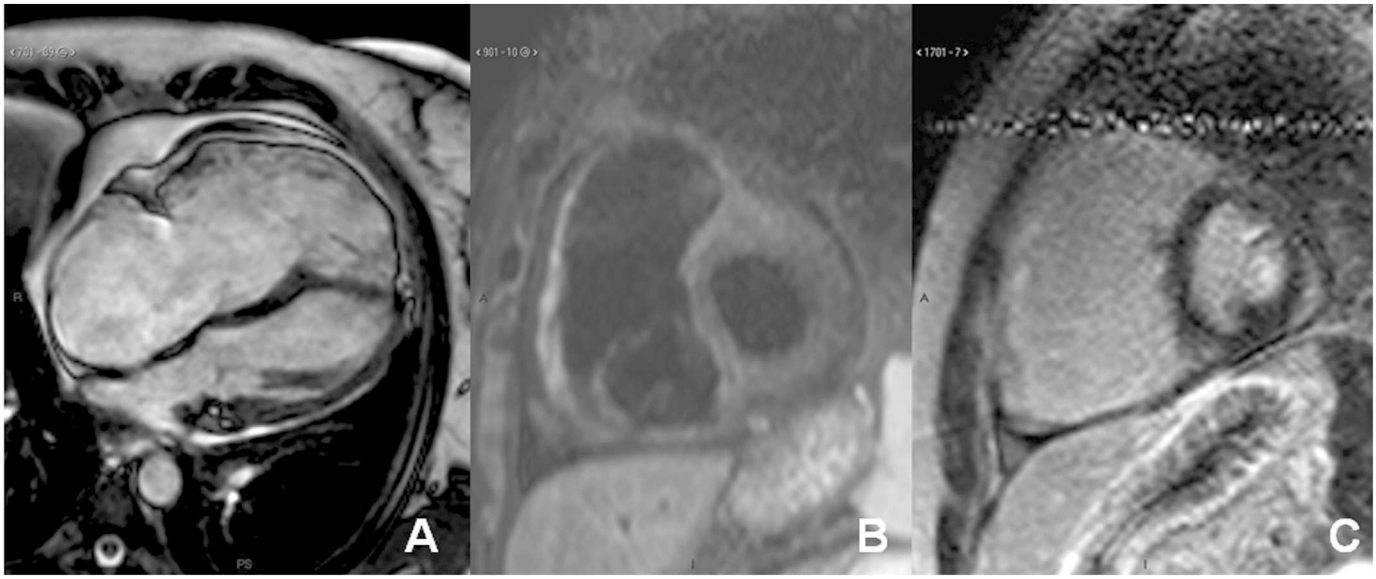

Fig. 3. MRI images of a systemic sclerosis patient with an endomyocardial biopsy (EMB), proven inflammatory and fibrotic myocarditis. Patient presents an enlargement of four heart chambers (A) without T2 hyperintensity (B) and delayed enhancement (C) in T1-weighted images.

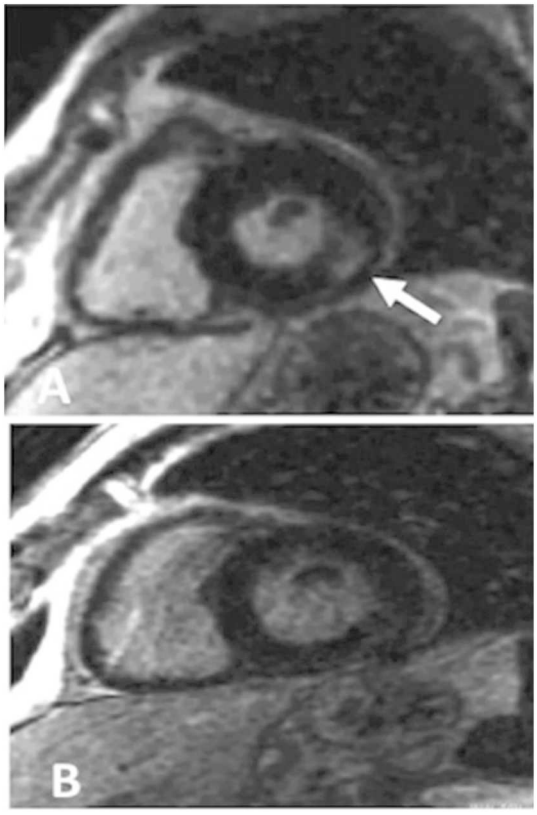

Fig. 4. Cardiac magnetic resonance findings before and after immunosuppressive therapy in SSc patients with myocarditis. Evidence of delayed enhancement in the posterolateral segment (A, arrow), which disappears after immunosuppression (B). Inversion recovery fast gradient recalled-echo post-gadolinium sequences (A and B).

adopted as a tool to evaluate the microvascular damage that is increasingly being recognised as a significant pathogenetic event.

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