

# Atherosclerosis and Other Cardiovascular Manifestations of Rheumatologic Diseases

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## Abstract

Prevalence and importance of cardiovascular diseases have continued to increase as therapeutic advances have led to increasing life expectancy, and better understanding of the role of the immune system in initiation and progression of inflammation and atherosclerosis. Thus, the need for better understanding of the relationship of rheumatologic diseases and cardiovascular disorders is paramount to permit more effective preventive and therapeutic approaches. In our review, we tried whenever applicable, to categorize cardiovascular involvement as atherosclerosis, myocardial, valvular, and pericardial.

**Keywords:** Atherosclerosis; Cardiovascular manifestations; Rheumatologic diseases

**Abbreviations:** aPL: Antiphospholipid Antibody; CHF: Congestive Heart Failure; CVD: Cardiovascular Disease; DMARDs: Disease Modifying Anti-rheumatic Drugs; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus; SSC: Systemic Sclerosis; TNF: Tumor Necrosis Factor

## Introduction

Rheumatologic diseases are chronic inflammatory disorders often autoimmune in etiology with systemic effects. Diagnosis can be difficult due to the myriad of presentations and organ systems that can be involved. Treatment is often aimed at affecting the inflammatory pathways to minimize functional impairment or prevent death. Recognition of cardiac manifestations of rheumatic disease would lead to early diagnosis and initiation of specific treatment. This article will focus on common, established, and clinically relevant cardiovascular manifestations of rheumatologic disorders.

## Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic inflammatory disorder of unknown etiology, the diagnosis of which is largely clinical [1]. None of the clinical, serologic, or radiological criteria involve the cardiovascular system. However, several cardiac manifestations, including coronary atherosclerosis, pericardial, myocardial, and valvular involvement have already been described.

**Atherosclerosis:** Likely one of the most well established cardiac manifestations of (RA) is premature atherosclerosis and ischemic heart disease leading to disproportionate mortality in RA due to Cardiovascular Disease (CVD) [1-4]. Studies have shown greater than two-fold increase in myocardial infarction and worse outcomes compared to controls [5-9]. Also, up to three-fold increase in preclinical atherosclerosis was seen when studied by using carotid artery intimal thickness as a surrogate for atherosclerosis [10]. Even when risk is adjusted to compare to patients with traditional risk factors, such as hyperlipidemia, the rheumatoid arthritis patients have increased incidence of ischemic heart disease [7,11]. It is thought that the inflammation from rheumatoid arthritis is, itself, a contributor to atherosclerosis, plaque formation, and plaque rupture [12]. The increased atherosclerosis has led some authors to suggest that rheumatoid arthritis should be considered as an equivalent risk factor among the traditional heart disease risk factors and has implications for possible immunologic therapies for ischemic heart disease. In a review based on carotid ultrasound as a surrogate of preclinical atherosclerosis studies in (RA) and (SLE) the authors concluded that

in (RA) it is associated with longer and more severe disease, while in (SLE) it is associated with longer disease duration, higher damage, and less immunosuppressive therapy [13].

**Pericardial involvement:** Pericardial effusions are more common in rheumatoid arthritis than the general population [14]. In A recent meta-analysis Corrao et al. [15] reported a pooled odds ratio of 10 when evaluating echocardiographic evidence of cardiac involvement in rheumatoid arthritis without previous cardiac disease [15]. The pericardial effusions seen in rheumatoid arthritis are nearly always asymptomatic and their contribution to morbidity and mortality is unknown. Post-mortem autopsy and various case reports have linked pericarditis to rheumatoid arthritis with some studies suggesting 30% prevalence, although its clinical significance remains unknown [16-18].

**Heart failure:** There is an increased risk of developing heart failure with rheumatoid arthritis compared to the general population [19,20]. Patients without history of cardiovascular disease have an increased incidence of diastolic dysfunction [21,22]. Whether those patients eventually develop systolic dysfunction remains unknown and needs further study. The risk of heart failure is disproportionate despite adjusting for the traditional risk factors [23,24]. It has been proposed that increased Tumor Necrosis Factor (TNF) is a possible cause of heart failure in rheumatoid arthritis, and anti-TNF agents have been used as treatment for advanced heart failure in patients showing elevated TNF levels [19]. The apparent paradoxical finding is some studies that showed an increase in plaque development in patients who received TNF antagonists, may be due to that it possibly represented a surrogate marker for disease severity as more of these patients had a higher number of diagnostic criteria for (RA) [13].

## Valvular involvement

Initial studies did not find significant differences in valvular function between the general population and rheumatoid arthritis patients as reported by Roman and Salmon [2,22,25,26]. In contrast

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to these earlier reports, Roldan et al. [27] and Carrao et al. [15] meta-analysis found with TEE and TTE, respectively, to frequently have rheumatoid arthritis-associated valvular heart disease most commonly affecting the mitral valve, aortic valve, and aortic root. The changes are associated with nodules and valve thickening that cannot be explained by another etiology [27]. It is important to note that the valvular heart disease described is subclinical and the valve nodules seen in RA-associated valvular heart disease are distinct from Libman-Sacks vegetations commonly associated with systemic lupus erythematosus and antiphospholipid antibody syndrome. Further studies to evaluate the long-term progression of RA-associated valvular heart disease have not been performed.

## Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an inflammatory autoimmune disorder affecting multiple organ systems. Cardiac manifestations, such as pericarditis, are even included in the diagnostic criteria for SLE among other clinical and serological criteria [28]. The following will focus on specific cardiac manifestations of SLE including atherosclerosis, Libman-Sacks, thrombosis, and pericarditis.

### Atherosclerosis

As in rheumatoid arthritis, patients with systemic lupus erythematosus also have an increased risk of atherosclerosis [29-35]. The highest risk group is young females with 2-fold increase in atherosclerosis above the general population [29,35-37]. While traditional CVD risk factors do contribute to CAD in SLE [34], the rate of CVD/atherosclerosis is not solely explained by traditional risk factors according to Framingham risk scores. This implies SLE itself contributes to atherosclerosis [32,38]. Earlier studies attributed the increased risk of atherosclerosis to the high doses of prednisone that patients received to control their symptoms [25,36], but more recent studies have been mixed for implicating steroids as the culprit for causing atherosclerosis [29]. The pathogenesis is largely unknown, but theories suggest that SLE causes endothelial injury associated with immune complexes, complement activation, antiphospholipid, and/or antiendothelial antibodies [30].

### Valvular

SLE is associated with valvular vegetations known as Libman-Sacks that are usually univalvular, small, and left-sided [25]. The frequency of vegetations, as quoted by Roman and Salmon is 7-15% for the mitral valve, and 3-19% for the aortic valve [2]. The lesions may be clinically silent [39] or present similar to infectious endocarditis with fever, arthritis, new murmur, and splinter hemorrhages [40]. To distinguish Libman-Sacks from infectious endocarditis, the use of white blood cell count, C-reactive protein, antiphospholipid antibody (aPL), and blood cultures are helpful [40]. If aPL is positive, there is a 3-fold increased risk of Libman-Sacks endocarditis [41]. On echocardiography the vegetations may be indistinguishable from infective endocarditis [40]. Studies are conflicting on the association between presence of Libman Sacks and disease duration, severity, and treatment [42-44]. There is not much literature addressing the treatment of Libman-Sacks endocarditis, but Lee et al. [40] recommends aggressive control of SLE. Any patient that has a thromboembolic event with Libman Sacks endocarditis should be on lifelong anticoagulation [45].

### Pericarditis

The rate of pericarditis ranges from 5% to 62% [46-48]. Analysis of the pericardial fluid shows an exudative inflammatory fluid with leukocytosis with neutrophils >90% [48]. If asymptomatic no treatment

is recommended. If symptomatic and uncomplicated then NSAIDs are used [47,48]. On rare occasion, <1%, patients may develop pericardial tamponade, that requires drainage and corticosteroids [47,48].

### Thrombosis

SLE patients have an increased risk of arterial and venous thrombosis. Al-homood et al. [49] reported thrombosis prevalence greater than 10% and Zoller et al. [50] reporting 10-26% increased risk. Cervera et al. [51] showed that thrombosis is the second most common cause of mortality in lupus patients (26%) with cerebral thrombosis most common [51]. The pathogenesis of increased thrombosis is unknown, but it is suspected that the inflammation affects the coagulation cascade, circulating immune complexes contribute to thrombosis, and/or cytotoxic antibodies [52]. Well-identified risk factors include antiphospholipid antibody, anticardiolipin antibody, lupus nephritis with nephrotic range proteinuria, and traditional risk factors such as smoking [52].

### Systemic Sclerosis

Systemic Sclerosis (SSc), also known as scleroderma, is a chronic inflammatory systemic disorder affecting multiple organs, notably the skin, lungs, kidneys, GI tract, and the heart. As treatments for scleroderma advanced, especially for renal disease, survival increased and mortality became mostly due to cardiopulmonary events [53-55]. The presence of clinical cardiac manifestations is associated with a poor prognosis [55-58]. One study demonstrated 87% mortality at 7 years once clinical cardiac disease was present [58]. The cardiac manifestations include myocardial fibrosis, arrhythmias, and pericardial disease.

### Myocardial fibrosis

Myocardial fibrosis is a well-known manifestation of SSc that has been described in several autopsy studies [59-62]. It is thought that there may be a "myocardial Raynaud's phenomenon" with vasospasm during cold or exertion contributing to myocardial fibrosis [60] which is further supported by studies showing improvement in perfusion with nifedipine and nicardipine [63,64]. However, no mortality benefit has been shown and the improvements were only short-term [65]. It is suspected, but not directly studied, that myocardial fibrosis contributes to left ventricular systolic and diastolic dysfunction in SSc [59]. Atherosclerotic disease is not increased in SSc, and it is thought that atherosclerosis does not contribute to CHF in these patients [58,59].

### Arrhythmias

Both supraventricular and life-threatening ventricular arrhythmias are seen in SSc [60,61,65-67]. The etiology is unknown but it is suspected that myocardial fibrosis leads to conduction abnormalities rather than directing causing conduction system disease [60]. The presence of these arrhythmias is high enough that many suggest screening for arrhythmias; with a 24-hour holter [59,66]; even in asymptomatic SSc patients. There is no evidence showing decreased mortality from ventricular arrhythmia with use of antiarrhythmic drugs in SSc. Bernardo et al. presented a 9 patient case series of SSc patients with ventricular tachycardia and suggested that patients unresponsive to anti-arrhythmics or with contraindications to anti-arrhythmics may benefit from ICD placement [68].

### Pericardial disease

Pericardial disease in SSc patients presents as either a chronic pericardial effusion (usually asymptomatic) or less commonly, as acute pericarditis [62,65,69]. Most cases of pericardial involvement are asymptomatic and tamponade has not been reported [65].

## Spondyloarthritis

The spondyloarthritis are a group of rheumatologic disorders consisting of ankylosing spondylitis, psoriatic arthritis, reactive arthritis, spondylitis, enteropathic arthritis, and undifferentiated spondyloarthritis. Extra-articular manifestations, including cardiac, have been documented, but the amount of literature is sparse though growing. One recent study from Brazil evaluated almost 1500 patients with spondyloarthritis and found that the frequency of extra-articular manifestations, including cardiac manifestations, ranged from 0.9 to 3% [70]. Of this group, the main disorders associated with extraarticular manifestations were ankylosing spondylitis and psoriatic arthritis, and the prevalence of cardiac manifestations was 2% and 0.7%, respectively [70]. For the rest of the spondyloarthritis cardiac manifestations were less prevalent at 0.1% [70]. There is growing evidence that ankylosing spondylitis and psoriatic arthritis have increased risk of atherosclerosis [71-76]. The literature for premature atherosclerosis and spondyloarthritis is not nearly as vast as that for RA or SLE, but the proposed mechanism is similar. It is thought that the chronic inflammatory state from spondyloarthritis leads to premature atherosclerosis [71-76]. Specifically for psoriatic arthritis, studies have found increased carotid artery intima-media thickness, a surrogate for atherosclerosis, which correlated to disease duration and activity [72]. Specifically for ankylosing spondylitis, the meta-analysis by Mathieu et al. showed that ankylosing spondylitis worsens the traditional cardiovascular risk factors including decreased HDL [73]. In addition to worsening the cardiovascular risk factors, it has been suggested that the increased cardiovascular risk from ankylosing spondylitis could not solely be attributed to traditional risk factors when evaluated against matched controls [74]. This rather suggests that an independent risk factor such as chronic inflammatory state contributes to atherosclerosis in ankylosing spondylitis [74]. The only other clinically significant cardiac manifestation is aortic regurgitation, first described by Bulkley and Roberts in 1973 in 8 patients [77]. Early studies had shown prevalence ranging from 1-10% [78-81], with recent studies describing an incidence up to 26% [73]. In summary, cardiac disease in spondyloarthritis may be present but more studies are needed to elucidate its clinical significance.

## Conclusion

Rheumatologic diseases have various cardiac manifestations, which may increase morbidity and mortality. In these patients, cardiac disease varies from atherosclerosis, heart failure, valvular dysfunction, conduction defects, to pericardial disease. Treatment is targeted at the specific cardiac disorder in addition to treating the associated rheumatologic condition. Regarding atherosclerosis, most studies recommend controlling disease activity in the hope of controlling atherosclerosis progression, but this is based on limited and conflicting data. Rheumatologic disease severity and duration does not always correlate with the presence or degree of atherosclerosis. There is recent evidence that Disease Modifying Anti-Rheumatic Drugs (DMARDs) especially methotrexate may reduce atherosclerosis progression in rheumatoid arthritis [82-85]. The effect of DMARDs on atherosclerosis in other rheumatologic disorders, such as SLE, is unknown. Disease modifying agents are not always beneficial, as discussed above with anti-TNF agents in heart failure. Treatment of heart failure in patients with rheumatologic disease is the same as treating heart failure without rheumatologic disorder. In systemic sclerosis, nifedipine and nifedipine have shown short-term benefit for myocardial perfusion [63,64], but the long-term effects have not been studied. Arrhythmias in systemic sclerosis patients are treated with anti-arrhythmic drugs although no mortality benefit has been realized. Recent evidence

suggests that placement of ICD may improve mortality [68]. One difference when treating valvular disease in rheumatologic disorders is in patients with Libman-Sacks endocarditis, life-long anticoagulation is required if a thrombotic event has occurred [45]. SLE duration and activity may contribute to developing Libman-Sacks vegetations [43] but no studies have evaluated whether SLE treatment slows progression of these vegetations or not. Pericardial disease is more common in active flares of rheumatologic disorders. However, it is treated the same regardless of the presence of rheumatologic disorder. Thus, NSAIDs are adequate for most patients, and corticosteroids are used for unresponsive cases. Pericardiocentesis is indicated in large effusions and/or tamponade.

In summary, while there is a growing data looking at cardiac involvement in rheumatologic disorders, it is obvious that more research is needed regarding specific targeted therapy and how best to reduce associated cardiovascular risk. The need for better understanding of the relationship between rheumatic diseases and cardiovascular disorders is paramount to permit more effective preventive and therapeutic approaches.

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