Cardiovascular Manifestations of Rheumatologic Diseases

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The prevalence and importance of cardiovascular disease in rheumatologic disorders have increased in the setting of therapeutic advances, resulting in longer life expectancy, a growing understanding of the importance of inflammation and the immune system in the initiation and progression of atherosclerosis, and enhanced disease detection with the use of sophisticated noninvasive cardiac and vascular diagnostic technology. This article will briefly review cardiovascular manifestations of rheumatologic diseases with an emphasis on recent clinical research. Rheumatologic diseases will be discussed individually for ease of reference, although pathophysiology and basis for cardiovascular abnormalities may be common among some of them. When applicable, cardiovascular disease will be categorized as vascular (accelerated atherosclerosis, arterial stiffness, small-vessel disease, aortic disease), myocardial (abnormalities of structure and function), valvular, pericardial, and conduction diseases. Endothelial dysfunction, although reported in some rheumatologic diseases, will not be systematically discussed in view of space limitations and the nonspecific and incompletely characterized nature of this abnormality. Discussion of suggested mechanisms underlying cardiovascular manifestations of rheumatologic diseases is beyond the scope of this review. Rheumatologic diseases with vasculitis as the primary manifestation, such as giant cell arteritis and Takayasu’s arteritis, will not be discussed.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common chronic autoimmune disease associated with systemic inflammation, a female predominance, and a prevalence of ~1% that increases with age.1 The diagnosis is a clinical one, based on the characteristic joint manifestations (Table 1).2 The presence of rheumatoid factor is included in the diagnostic criteria, although antibodies to cyclic citrullinated peptides are more specific for RA.3 Although the precise antigenic stimulus driving the autoimmunity in RA has not been identified, a recent study demonstrated an increased risk of developing RA in smokers in whom citrullinated antigens are expressed on bronchoalveolar immune cells.5 RA is associated with specific human leukocyte antigen (HLA) class II molecules; antigen-activated CD4+ T cells contribute to the initiation of the cascade of cellular and soluble inflammatory mediators that result in the characteristic joint damage.5

Vascular Disease

Atherosclerosis

The excess mortality associated with RA is due largely to cardiovascular disease, particularly ischemic heart disease.6–12 Recent observational studies suggest that the heighten risk is not related primarily to traditional atherosclerosis risk factors8,10,12,13 or to corticosteroid and disease-modifying therapy.7 In view of the importance of chronic inflammation in atherogenesis,14 the presence of RA per se may be of primary importance. Unequivocal evidence of independence of atherosclerosis from traditional risk factors and direct relation to the presence of RA was provided in a case-control study of preclinical atherosclerosis wherein RA patients had a 3-fold increase (44% versus 15%) in carotid atherosclerosis prevalence despite a similar risk profile (Figure).15 In this study, atherosclerosis risk was related to duration of disease and use of anti–tumor necrosis factor (TNF) therapy, a surrogate for disease severity as such therapy was limited to patients with refractory disease at the time of our study. A smaller study likewise detected a relation between carotid atherosclerosis and RA duration as well as more extensive extra-articular disease.16 The presence and amount of coronary calcification are also related to duration of RA.17 In addition, lower levels of circulating endothelial progenitor cells, markers of the capacity for vascular regeneration that are inversely related to cardiovascular risk, are associated with heightened disease activity in RA patients.18 Taken together, these studies suggest that extent and duration of inflammatory burden, as opposed to specific disease aspects, determine premature atherosclerosis in RA. Evidence that therapy with methotrexate19,20 reduces risk of cardiovascular disease further supports the hypothesis that chronic inflammation is primarily responsible for accelerated atherosclerosis in RA. Although use of TNF blockers was associated with more severe and refractory disease in a large observational study in Sweden, RA patients who received such therapy had lower rates of cardiovascular events and death during limited follow-up,21 again suggesting that aggressive antiinflammatory therapy might additionally reduce clinical manifestations of cardiovascular disease.

Because of the heightened risk of premature atherosclerosis, adherence to primary prevention guidelines is mandatory. Because the prevalence of carotid atherosclerosis in RA is at least as high as in diabetes mellitus,15 which is considered a...
coronary heart disease equivalent and an indication for secondary prevention targets even in the absence of clinical cardiovascular disease, it is attractive to consider application of secondary prevention guidelines to patients with RA. From a practical standpoint, a lower target for low-density lipoprotein cholesterol and aspirin therapy would be the main differences in strategy. Secondary prevention measures should certainly be applied in the setting of established cardiovascular disease. Data are lacking to support widespread screening of RA patients with imaging studies such as carotid ultrasonography or computed tomography to detect coronary calcium. Because a negative screening study does not preclude development of atherosclerosis in the short-term future and because both cardiovascular disease prevention efforts and control of disease activity should be aggressive, the presence or absence of subclinical atherosclerosis would arguably not alter overall management. It has been suggested that anti-TNF therapy be temporarily suspended in the perioperative period in patients undergoing major orthopedic surgery to limit increased risk of infection, and similar considerations are likely to apply to cardiac surgery.

Arterial Stiffness
Arterial stiffness, which can be quantified accurately with the use of noninvasive techniques, is recognized increasingly as an important independent risk factor for adverse cardiovascular outcomes in population-based studies. In view of the development of premature atherosclerosis in RA and of the observation that arterial stiffening is associated with inflammatory markers in the general population, it is not surprising that arterial stiffness is increased in RA, even in the absence of atherosclerosis. Arterial stiffening is related to disease duration, as described for atherosclerosis, and to inflammatory mediators. That arterial stiffening in RA patients is reduced by treatment with anti-TNF therapy or atorvastatin is promising, although these findings are based on small numbers (9 and 29, respectively) of patients followed for short periods of time.

Coronary Arteritis
Although coronary arteritis was detected at autopsy in 20% of 100 patients succumbing to active disease in the era before effective antiinflammatory therapy, at present it is rarely of clinical significance. In fact, the occurrence of rheumatoid vasculitis, in general, has markedly declined in the setting of effective antiinflammatory therapy.

Myocardial Disease
RA is associated with an increased risk of congestive heart failure, but the underlying pathophysiology (ie, systolic versus diastolic dysfunction) is uncertain. Data from the Mayo Clinic indicate that heart failure in RA patients primarily affects those who are positive for rheumatoid factor, may occur before the onset of the arthritis, and is independent of traditional risk factors for cardiovascular disease. Although the prevalence of left ventricular (LV) systolic dysfunction was reported recently to be higher in patients with RA, the extent to which traditional risk factors, including hypertension, diabetes mellitus, and smoking, contributed to this association was not evaluated statistically. In contrast, 4 other case-control studies reported similar LV ejection fractions in RA patients and controls but higher rates of impaired diastolic relaxation based on reductions in transmural ratios of early to late ventricular filling (E/A ratios) in RA. Similar to evidence in atherosclerosis, anti-TNF therapy may protect RA patients from developing heart failure.

Valvular Disease
Clinically significant valvular disease attributable to RA appears to be uncommon. Studies using transthoracic echocardiography have detected no differences in valvular disease between groups of RA patients and controls and no evidence of otherwise unexplained valvular disease. Contrasting, mitral regurgitation was detected in 80% of 30 RA patients undergoing transesophageal echocardiography versus 37% of a control population, although the severity of mitral regurgitation was not reported, and almost 20% of patients were additionally reported to have mitral prolapse, indicative of a select population and/or causes of mitral regurgitation unrelated to RA. Prevalences of aortic and tricuspid regurgitation were not different between RA patients and control subjects undergoing transesophageal echocardiography.
Pericardial Disease
Fibrinous pericarditis may be detected at autopsy in RA patients but is generally not of clinical relevance.34,35 Pericardial effusions may also be seen in echocardiographic studies of RA patients. Although usually clinically silent,32,34,36,46 constrictive pericarditis may develop.35 Case-control studies using echocardiography have variably reported similar41 or increased45 rates of pericardial effusion.

Conclusions
RA results in premature development of atherosclerosis, myocardial infarction, and arterial stiffening. Congestive heart failure is likewise independently related to RA, possibly because of impairment of LV diastolic filling, although large-scale studies with sophisticated assessment of diastolic function are lacking. Effective control of disease activity may be beneficial in ameliorating vascular and myocardial disease. Pericardial disease due to RA is usually of limited clinical significance.

Systemic Lupus Erythematosus
Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with a prevalence of \( \approx 1:2500 \). A marked female predominance exists, even greater than that associated with RA. Black women and men have substantially higher rates of disease and more severe disease manifestations than do whites.1 The diagnosis is based on demonstration of multisystem clinical and laboratory manifestations (Table 2).47 The pathogenesis of SLE is unknown, but its expression is determined by interactions among genetic, environmental, hormonal, and immunologic factors. Valvular disease associated with Libman-Sacks lesions, serositis resulting in pericardial disease, and venous and arterial thromboses associated with the presence of antiphospholipid antibodies are well-established cardiovascular manifestations of SLE. However, premature development of atherosclerosis has emerged as an important cause of morbidity and mortality in patients with SLE as effective treatments for other causes of early mortality, particularly infections and lupus nephritis, have become available.

Vascular Disease
Atherosclerosis
The premature development of atherosclerotic coronary artery disease has been documented in autopsy,48 mortality,49 and population-based observational50,51 studies. Although initial speculation centered on the importance of corticosteroid therapy,48,49 and/or excess traditional risk factors,52–54 the risk of myocardial infarction is, as least in part, independent of traditional risk factors.55 SLE-related factors associated with clinical manifestations of coronary artery disease include older age at diagnosis,51,52 longer duration of SLE,51,52,56 higher damage score (a quantitative measure of cumulative organ damage attributable to SLE or its treatment),56 longer duration of steroid therapy,49,51,52,57 and higher levels of oxidized low-density lipoprotein cholesterol and homocysteine.57 Case-control studies examining preclinical carotid atherosclerosis58 and coronary artery calcification49 clearly indicate that premature atherosclerosis occurs in SLE as a consequence of the disease itself (Figure). Furthermore, imaging studies indicate that the underlying pathophysiology is primarily atherosclerosis rather than in situ thrombosis associated with antiphospholipid antibodies.53,58–60 Features of SLE associated with the presence of subclinical atherosclerosis include older age at diagnosis,58 longer duration of disease,58,61 longer duration of steroid therapy,57 less aggressive immunosuppressive therapy,58 higher damage score,58 and higher homocysteine concentrations.61 Atherosclerosis progresses at twice the rate seen in non-SLE populations; rate of progression is directly related to duration of disease and homocysteine levels.62 Similar considerations regarding preventive and screening strategies as discussed in the RA section apply to patients with SLE.

### Table 2. Diagnostic Criteria for SLE

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
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<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
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<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
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<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of a unusual reaction to sunlight</td>
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<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulcerations, usually painless</td>
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<tr>
<td>Arthritis</td>
<td>Nonscarring arthritis involving ≥2 peripheral joints, characterized by swelling or effusion</td>
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<tr>
<td>Serositis</td>
<td>Pleuritis: convincing history of pleuritic pain, or rub heard by physician, or evidence of pleural effusion</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Pericarditis: documented by ECG, or rub, or evidence of pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria: ≥0.5 g/d, or &gt;3+, if quantification not performed</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>Seizures: in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Anemia with reticulocytosis</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Leukopenia: &lt;4000/mL total on ≥2 occasions</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia: &lt;1500/mL on ≥2 occasions</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia: &lt;100 000/mL in the absence of offending drugs</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Anti-DNA: antibody to native DNA in abnormal titer</td>
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<td></td>
<td>Anti-Sm: presence of antibody to Sm nuclear antigen</td>
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<td></td>
<td>Positive test for antiphospholipid antibody including: (1) abnormal serum IgG or IgM antiphospholipid antibody, (2) positive test for LA, (3) false-positive test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization of fluorescent treponema antibody absorption test for syphilis</td>
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<tr>
<td></td>
<td>Abnormal titer of antinuclear antibody by IF or an equivalent assay at any point in time in the absence of drugs known to be associated with drug-induced lupus syndrome</td>
</tr>
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LA indicates lupus anticoagulant; IF, immunofluorescence.

*The 1982 revised criteria for the classification of SLE57; 4 criteria must be present to qualify for a definite diagnosis.
**Arterial Stiffness**

Similar to RA, arterial stiffness is increased in SLE, even in the absence of atherosclerosis.\textsuperscript{28} Arterial stiffening is related to disease duration and to circulating levels of C-reactive protein and interleukin-6.\textsuperscript{6} Among postmenopausal women with SLE, arterial stiffness is independently related to the organ damage index.\textsuperscript{63} The impact of antinflammatory and immunosuppressive therapy or of statin therapy on arterial stiffening has not been examined in SLE.

**Myocardial Disease**

Abnormalities of LV structure and function have been reported in patients with SLE.\textsuperscript{64–67} However, the extent to which associated conditions, such as significant valvular regurgitation, ischemic heart disease, and renal failure, contribute to these abnormalities has been uncertain. In a case-control study that excluded SLE patients with any of these associated conditions, we detected substantially higher LV mass index in SLE patients that was further elevated by concomitant hypertension.\textsuperscript{68} Arterial stiffness was independently related to LV mass, suggesting that inflammation-related arterial stiffening is the likely mechanism of LV hypertrophy in SLE. LV ejection fractions were higher in SLE patients, likely as a result of the Starling phenomenon (higher end-diastolic and comparable end-systolic dimensions).

Myocarditis is rarely diagnosed clinically or detected at autopsy in SLE patients in the current treatment era.\textsuperscript{48,69,70} It is associated with active disease, including myositis and serositis.\textsuperscript{69} Impaired systolic function and segmental wall motion abnormalities associated with lupus myocarditis are reversible by aggressive immunosuppressive therapy.\textsuperscript{70}

**Valvular Disease**

Although valvular nodules have been described in the majority of patients with SLE at autopsy,\textsuperscript{48,71} clinically significant valvular heart disease is much less common.\textsuperscript{65,72–74} Furthermore, Bulkley and Roberts observed a reduction in the number and size of valvular nodules associated with the introduction of corticosteroid therapy.\textsuperscript{48} Varying prevalences of valvular abnormalities have been reported in the echocardiographic literature, reflecting variable inclusion of nonspecific valvular thickening (separate from the presence of a vegetation or nodule) and valvular regurgitation that may be mild and/or due to other causes. Echocardiographic studies vary with regard to the frequency of vegetations or nodules detected on the mitral (7% to 15%) and aortic (3% to 19%) valves.\textsuperscript{50,72,75,76} Significant (moderate or severe) valvular regurgitation occurs in <20% of relatively unselected patients undergoing Doppler echocardiography.\textsuperscript{50,65,76,77} Independent of the definition of valvular disease, longitudinal echocardiographic studies indicate that abnormalities may persist, resolve, or develop anew over time, independent of disease activity or therapy.\textsuperscript{78} The development of severe valvular regurgitation may be related to high levels of IgG antiphospholipid antibodies.\textsuperscript{77}

A summary of the association of the presence of antiphospholipid antibodies and valvular disease in SLE is also difficult because of differences in definitions of valvular disease (thickening, nodules, presence of regurgitation) and of antiphospholipid antibody positivity. Nevertheless, large transthoracic echocardiographic studies of unselected patients document an association between higher antiphospholipid titers, valvular nodules, and significant regurgitation, particularly involving the mitral valve.\textsuperscript{60,79,80}

Formal guidelines for antibiotic prophylaxis in the setting of valvular nodules do not exist. The presence of significant regurgitation, even in the absence of nodules, may heighten the risk of bacterial endocarditis, particularly in the setting of jet lesions, and warrants antibiotic prophylaxis. Indications for surgical intervention for valvular heart disease do not differ from those applied in the general population. The major added risks involve anticoagulation concerns and thrombotic complications if antiphospholipid antibody syndrome coexists. In addition, wound healing may be impaired and infec tion risk may be increased in the setting of long-term and/or perioperative stress doses of corticosteroid therapy. An unresolved issue concerns causal relations between valvular and cerebrovascular disease and hence the indications for valve replacement in the absence of other explanations for cerebrovascular complications.\textsuperscript{81}

**Pericardial Disease**

Pericardial disease, as a manifestation of serositis, is a diagnostic feature of SLE and its most common clinical cardiovascular manifestation. Clinical features of pericarditis with or without pericardial effusion occur in 20% to 50% of patients in relatively large series.\textsuperscript{64,65,72,76,79,82} Pericardial effusions occur most commonly in the setting of active disease (flares).\textsuperscript{64,65,76} but may be asymptomatic.\textsuperscript{65} The effusions are usually small, although moderate to large pericardial effusions were detected in 5 of 70 patients (7%) in 1 series.\textsuperscript{65} Interestingly, mild pericardial effusions associated with lupus pericarditis are usually not associated with typical electrocardiographic changes.\textsuperscript{65,72,81} None of the relatively large series of echocardiographic studies has reported major complications (cardiac tamponade or constrictive pericarditis) of lupus pericarditis in the absence of renal failure. Treatment of symptomatic pericarditis and pericardial effusions includes high-dose aspirin, nonsteroidal antiinflammatory drugs, or corticosteroid therapy, particularly if prednisone is required for management of other manifestations of active disease. In rare instances of tamponade or constrictive pericarditis, treatment is not specific to SLE.

**Conclusions**

Like RA, SLE results in premature development of atherosclerosis, myocardial infarction, and arterial stiffening. LV hypertrophy develops in SLE unrelated to traditional stimuli to hypertrophy and may be due to inflammation-related arterial stiffening. Pericardial disease is common, and clinically significant valvular disease due to SLE develops in a minority of patients.

**Systemic Sclerosis**

Systemic sclerosis is a systemic, autoimmune disorder characterized by tissue fibrosis due to excess accumulation of collagen and other extracellular matrix proteins. Its cause is unknown, but its pathophysiology involves microvascular abnormalities, secondary ischemia, and fibroblast overreac-
tivity. The disease is rare (prevalence of \( \approx 2 \) in 10,000) and occurs predominantly in women. The frequency and serological and clinical features of the disease vary in different races. The diagnosis is based on the presence of proximal scleroderma, defined as symmetrical thickening, tightening, and induration of the skin of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joints; the face, neck, and trunk may also be involved. Diagnostic criteria are also met if 2 of the following 3 minor manifestations are present: sclerodactyly (skin changes limited to the fingers); digital pitting scars or loss of substance of the finger pad; and basilar pulmonary fibrosis. Systemic sclerosis may be further subdivided into limited cutaneous disease, including CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), and diffuse cutaneous disease, in which organ involvement (kidneys, lungs, heart) may be seen. Visceral involvement, particularly heart, substantially increases mortality. The most specific autoantibodies found in patients with systemic sclerosis are antinuclear antibodies with a nucleolar staining pattern, anticentromeric antibodies (for CREST syndrome), and antitopoisomerase antibodies. Recent data indicate that stimulatory autoantibodies to platelet-derived growth factor and antitopoisomerase antibodies. Recent data indicate that stimulatory autoantibodies to platelet-derived growth factor receptor may be both highly specific and sensitive for systemic sclerosis as well as potentially causally related to the fibrotic phenotype of the disease.

**Myocardial and Coronary Vascular Disease**

Myocardial disease in systemic sclerosis may be multifactorial: related to associated pulmonary or renal involvement or to hypertension. However, of note is an autopsy study that suggested the existence of “primary” myocardial disease. Nearly half (23 of 52) of patients with systemic sclerosis (mean age of 45 years and 67% female) who underwent autopsy at Johns Hopkins Hospital had focal areas of contraction band necrosis, a reperfusion lesion, and fibrosis in both ventricles despite patent epicardial coronary arteries and normal intramural coronary arteries. The severity of these lesions was unrelated to concomitant pulmonary and systemic hypertension, Raynaud’s phenomenon, and renal disease but was related to the presence of congestive heart failure, conduction abnormalities, ventricular arrhythmias, and cardiovascular death. Given the absence of large- or small-vessel disease, the authors speculated that intermittent obstruction due to vasospasm of the intramyocardial arteries might be responsible for the myocardial abnormalities.

The presence of myocardial disease, including segmental wall motion abnormalities and impaired coronary flow reserve, in the absence of epicardial coronary artery disease, has been confirmed repeatedly. Furthermore, a recent angiographic study of 172 systemic sclerosis patients with suspected coronary artery disease (based on the presence of angina or exertional dyspnea) detected rates of epicardial coronary disease similar to those in a comparison population with similar symptoms, age, and gender. Further support for the existence of microvascular disease, particularly spasm, derives from the demonstration of improvement in myocardial perfusion with oral nifedipine therapy and the detection of cold-induced perfusion defects and wall motion abnormalities in systemic sclerosis patients with Raynaud’s phenomenon. The presence of endothelial damage is supported by the presence of markedly increased numbers of circulating endothelial cells that, in turn, were related to an index of disease activity.

The right ventricle may likewise be abnormal in systemic sclerosis, even in the absence of pulmonary hypertension, likely due to microvascular disease similar to that detected in the left ventricle. Significantly lower right ventricular (RV) ejection fractions determined by radionuclide ventriculography in the setting of normal pulmonary artery pressure estimated by Doppler echocardiography were reported in 42 patients with systemic sclerosis compared with control subjects. After administration of oral nicardipine, RV ejection fraction improved significantly; because changes in estimated pulmonary pressure were not reported, it is uncertain whether the increase in RV ejection fraction was related to a reduction in afterload or to improvement in functional microvascular disease. A more recent report of reductions in RV systolic function and diastolic relaxation measured by tissue Doppler imaging, with reduced RV ejection fraction being unrelated to pulmonary artery systolic pressure, supports the earlier observation.

**Vascular Stiffness**

Although systemic sclerosis is usually associated with microvascular abnormalities, abnormalities of the large conduit arteries have been reported recently. Carotid artery stiffness was increased in 52 patients with both limited and diffuse cutaneous disease compared with control subjects, whereas stiffness of the muscular femoral artery was not abnormal. Of note, intimal-medial thicknesses of the carotid and femoral arteries were not increased in systemic sclerosis patients after adjustment for relevant covariates. A large study of 106 systemic sclerosis patients reported reduced aortic distensibility in comparison to control subjects. Distensibility was independently (versely) related to systolic pressure gradient across the tricuspid valve (an estimate of pulmonary artery systolic pressure), although the mechanism for this association is not apparent from the data provided. The large artery stiffening parallels that described above in RA and SLE. The contributions of microvascular disease, possibly of the vasa vasorum, or of inflammation to arterial stiffening in systemic sclerosis are unknown.

**Conduction Disease**

Fibrosis of the sinus node and bundle branches at autopsy and diffuse conduction abnormalities and arrhythmias detected by ambulatory electrocardiography have been described in patients with systemic sclerosis. Invasive electrophysiological studies have confirmed the presence of diffuse conduction system disease and increased susceptibility to tachyarrhythmias. The extent to which conduction abnormalities and arrhythmias are primarily related to fibrosis, as opposed to ischemic microvascular disease, likely varies with underlying anatomic and functional vascular and myocardial disease.

**Pericardial Disease**

Pericardial disease unrelated to uremia and characterized histologically by chronic inflammatory changes has been
described in autopsy studies of patients with systemic sclerosis. Clinically important pericardial disease, however, appears to be very rare. Two large echocardiographic studies reported small pericardial effusions in 14% of 77 patients and none of 106 patients.98

Conclusions
The most prominent cardiovascular abnormalities associated with systemic sclerosis are microvascular perfusion abnormalities of the ventricular myocardium resulting in ischemia, fibrosis, systolic dysfunction, and conduction disease. In addition, fibrosis may occur independent of ischemia. Stiffening of the conduit arteries develops as a consequence of inflammation and/or microvascular disease. Prognosis in systemic sclerosis is adversely affected by evidence of cardiac involvement. Although short-term nifedipine therapy may improve myocardial perfusion in patients with Raynaud’s phenomenon, long-term effects of such therapy in limiting cardiovascular complications of systemic sclerosis are unknown.

Ankylosing Spondylitis
Ankylosing spondylitis, the prototypical spondyloarthropathy, is a systemic, inflammatory disorder that involves the entire spine and sacroiliac joints, with lesser effects on peripheral joints. The characteristic musculoskeletal lesion is enthesitis, inflammation of the enthesis (the site where tendons and ligaments attach to bone). Associated extra-articular manifestations include uveitis, fibrocavitary apical lung lesions, and serum amyloid A–related amyloidosis. The prevalence of ankylosing spondylitis is ~1 to 2 per 1000 among whites with a 3:1 to 4:1 male predominance.1,105,106 Onset of clinical features usually begins in the third to fourth decades. Roughly 90% of affected individuals are HLA-B27 positive, with racial prevalences of ankylosing spondylitis varying according to HLA-B27 frequency (lower in blacks and higher in American Indians).1 The likelihood of developing ankylosing spondylitis among HLA-B27–positive individuals is 1.3% based on a Dutch study but substantially higher (21%) if an HLA-B27–positive relative has ankylosing spondylitis.107 Its cause is unknown, but it is thought to be triggered by an as yet undefined infection in a genetically predisposed host. TNF-α antagonists have been shown only recently to treat this disorder effectively; thus, few data are available to demonstrate their capacity to ameliorate associated cardiovascular disease.

Aortic Disease
Aortic disease and aortic regurgitation associated with ankylosing spondylitis were recognized even before ankylosing spondylitis (previously termed rheumatoid spondylitis) was distinguished from RA. In 1973, Bulkley and Roberts described autopsy findings in 8 male patients with ankylosing spondylitis and congestive heart failure due to severe aortic regurgitation.108 Distinctive features included thickening of the aortic wall due to adventitial scarring and intimal proliferation that was limited to the aortic root but extended into the membranous ventricular septum. Conduction abnormalities present in 6 of 8 patients were attributed to fibrous scarring of the interventricular septum. In addition, aortic valve leaflets were diffusely thickened and shortened and thereby rendered incompetent. The presence of aortic root and aortic valve thickening has been described in subsequent transthoracic and transesophageal echocardiographic studies. Echocardiographic evidence of aortic regurgitation, in most instances mild, has been described in 5% to 13% of patients with ankylosing spondylitis, although higher estimates have been reported in small studies or in select populations undergoing transesophageal echocardiography.115 Detection of aortic regurgitation may precede development of joint manifestations.108,109 Although mild aortic root dilatation has been described in ankylosing spondylitis, the impact of age and body size on diameters has not always been considered.116 In addition, it is possible that increases in aortic diameter are due to the presence of significant aortic regurgitation rather than a direct consequence of aortitis.117 Other studies have not detected increases in aortic diameter.

Conduction Disease
Conduction disease may develop in ankylosing spondylitis as a consequence of postinflammatory scarring of myocardial tissue. Prevalences of conduction abnormalities in clinical series of patients with ankylosing spondylitis range from 2% to 20%.109–113,117 First-degree atrioventricular block is most common; however, higher-grade atrioventricular block and right and left bundle-branch block have also been reported. Interestingly, heart block appears to occur more frequently in HLA-B27–positive individuals, even in the absence of clinical manifestations of rheumatologic disease.

Myocardial Disease
Diastolic filling abnormalities have been described in ankylosing spondylitis. Among 59 patients without clinical cardiovascular disease, 12 (20%) had abnormal filling patterns characterized as E/A ratio <0.9 in 7, prolonged deceleration time and isovolumic relaxation time in 2, and a restrictive filling pattern in 3.121 Similarly, lower E/A ratio on average was found in 88 patients compared with 31 healthy control subjects; however, no adjustment was made for the presence of aortic regurgitation (which may influence E/A ratio) in the patients.111 In contrast, early diastolic relaxation as assessed by the more specific technique of tissue Doppler imaging did not differ between 40 ankylosing spondylitis patients and 35 control subjects.122 LV systolic dysfunction and hypertrophy have not been reported in the absence of significant aortic regurgitation.

Atherosclerosis
Patients with ankylosing spondylitis may have higher death rates than the general population.105,123 Congestive heart failure and peripheral vascular disease, but not ischemic heart disease, appear to develop earlier on the basis of analyses using a large health plan database; however, the heightened risk may be due to greater burden of hypertension and dyslipidemia.124 Coronary flow reserve, a measure of microvascular function, measured from transthoracic Doppler evaluation of flow in the left anterior descending artery was significantly reduced in 40 ankylosing spondylitis patients compared with 35 control subjects.122 This result was based largely on 2 outliers in the control group with otherwise
complete overlap of the ankylosing spondylitis and control groups. Severity of sacroiliitis and TNF-α level were independently, negatively related to coronary flow reserve. Although the authors concluded that C-reactive protein was inversely related to coronary flow reserve, C-reactive protein was eliminated in multivariate analyses including as many as 15 independent variables in a study population of only 40 patients. Interestingly, carotid intimal-medial thickness is not increased in patients with ankylosing spondylitis compared with controls,125 similar to observations in SLE and RA.15,53,58

Conclusions
Ankylosing spondylitis causes thickening of the aortic root and aortic valve resulting in aortic regurgitation. Associated enlargement of the aortic root, independent of age, body size, and the hemodynamic impact of aortic regurgitation, has not been clearly established. Conduction abnormalities, primarily atrioventricular block, are more commonly encountered in ankylosing spondylitis. Tissue Doppler imaging of velocity of early myocardial relaxation (Em) is not altered in ankylosing spondylitis, whereas less specific measures (reduced E/A ratio) are abnormal. Definitive evidence of microvascular disease and premature atherosclerosis or coronary heart disease is lacking.

Psoriatic Arthritis
Psoriatic arthritis is defined as the coexistence of an inflammatory arthritis with psoriasis and affects 6% to 11% of individuals with psoriasis.126,127 Data from population-based studies in Norway and the United States indicate a prevalence of 1 to 2 per 1000, with men and women being affected equally.126,128 Its exact cause is unknown; however, similar to other rheumatologic diseases, its expression appears to be modulated by immunologic, genetic, and environmental factors. Recent research has differentiated it immunologically and pathologically from RA. Like ankylosing spondylitis, it fits into the group of disorders called spondyloarthropathies. However, only 25% of patients develop spine and sacroiliac joint disease, and the arthritis usually involves <4 large, lower-extremity joints or the distal interphalangeal joints. In addition, nail involvement with pitting of the nails and onycholyis, separation of the nail from its bed, is frequently present, and patients can develop uveitis.

Data from Olmstead County, Minnesota, indicate comparable death rates in individuals with psoriatic arthritis and the general population.126 Consistent with this observation, a recent echocardiographic study from Spain involving 50 patients with psoriatic arthritis and no cardiovascular disease risk factors or clinical disease found prevalences of valvular regurgitation, normal pulmonary artery pressures, and abnormal diastolic relaxation comparable to those in 50 matched control subjects.129 In contrast, data from Canada suggest that death rates are higher in both men and women with psoriatic arthritis. However, only deaths due to respiratory diseases, and not those due to cardiovascular disease (the leading cause of death), were increased in comparison to the general population.130 A recent US study based on health plan data found that patients with psoriatic arthritis had higher prevalences of both cardiovascular disease risk factors and ischemic heart disease, peripheral vascular disease, and congestive heart failure than age- and sex-matched control subjects.124 However, the higher prevalences of diseases were not adjusted for risk factors. Interestingly, the risk of incident myocardial infarction was increased in a large UK study of 130 976 psoriasis patients, particularly in younger patients and in those with more severe disease (defined by type of therapy), even after adjustment for traditional risk factors.131 Unfortunately, a subgroup analysis was not performed on patients with psoriatic arthritis.

Conclusions
Although psoriatic arthritis may be associated with an excess prevalence of cardiovascular disease risk factors, it remains uncertain whether higher rates of clinical cardiovascular disease are independently associated with the disease itself.

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Disclosures
None.

References


Cardiovascular Manifestations of Rheumatologic Diseases
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