Cardiac involvement in rheumatoid disease

George Kitas MD PhD FRCP, Consultant/Clinical Senior Lecturer in Rheumatology, *Dudley Group of Hospitals NHS Trust and University of Birmingham*

Matthew J Banks MRCP, Cardiology Specialist Registrar/Research Fellow, *University of Birmingham*

Paul A Bacon FRCP, Professor of Rheumatology, *University of Birmingham*

Clin Med JRCPL 2001;**1**:18–21

Background

The relationship between joint inflammation and heart disease was first suggested by Bouillaud in 1836. In 1891, Charcot described endocarditis and pericarditis in 'chronic rheumatism', differentiating cardiac disease in rheumatic fever (rheumatic heart disease) from that in other forms of rheumatism (rheumatoid heart disease (RHD)). It is now clear that cardiac pathology is common in rheumatoid arthritis (RA) (Table 1). This may be important. Cardiovascular mortality accounts for 40–50% of all deaths in RA; it is increased and occurs earlier than in the general population and may associate with the severity of RA[1]. The reasons for this remain unclear. RHD, although common, rarely has haemodynamic consequences[2]. Ischaemic heart disease (IHD) is a more likely cause; recent studies suggest similarities of inflammatory pathogenic mechanisms in RA and atherosclerosis, and an increased prevalence of IHD in RA[1,3,4].

Range and clinical presentation of cardiac pathology in rheumatoid arthritis

Pericardial disease

The commonest cardiac complication of RA is pericarditis. It is found in 30–50% of autopsy cases[5–7] and in up to 30% by echocardiography[8,9]. It is commoner in male, seropositive patients with active RA, but can occur in seronegative and quiescent RA or before the onset of synovitis. Histopathology shows chronic inflammation and fibrosis. The pericardial fluid is usually a clear exudate with high protein and lactate dehydrogenase, low glucose, and containing mainly neutrophils[10]. Cholesterol crystals can be seen in persistent effusions; they also occur in tuberculous pericarditis. Staphylococcal pyopericardium has also been described in RA, so infection is an important differential diagnosis. Only 2–4% of patients have symptoms, and fewer than 0.5% experience haemodynamic compromise[2]. The commonest symptom is dull central or sharp pleuritic chest pain. Dyspnoea, peripheral oedema and hepatic or gastrointestinal congestion may occur in constrictive disease. In tamponade, symptoms and shock can rapidly develop and require emergency intervention. Pericardial rub occurs in 30–40% of clinical cases. Other signs (tachycardia, ectopy, diminished heart sounds) are non-specific. Pulsus paradoxus and Kussmaul's sign (rise in height of jugular pulsation during inspiration) may occur. In constriction, a pericardial knock may be heard due to early cessation of ventricular filling. Constriction associates with high jugular vein pulse and a prominent y descent of early ventricular filling; in tamponade, the y descent is diminished, leaving a prominent x descent. Pericardial effusion and constriction can co-exist (effusive-constrictive disease), and this should be suspected if pericardiocentesis fails to rectify haemodynamic compromise[11].

Table 1. Pathological, echocardiographic and clinical prevalence of rheumatoid heart disease.

	Autopsy (%)	Echocardiography (%)	Clinical (%)
Pericarditis	11–50	20–40	1–4
Myocarditis	30	rare	rare
Focal, non-specific	4–30	–	–
Diffuse, necrotising	rare	–	–
Granulomatous	3–5	–	–
Amyloid infiltration	rare	–	–
Conduction system disease	unknown	–	rare
Endocarditis			
Valvular disease	6–50	30–40	rare
Coronary arteritis	15–20	–	rare
Any cardiac lesion	30–50	30–50	1.6–6

Non-specific endocarditis

Non-specific endocarditis is found in 9–70% of autopsy cases. Echocardiographic studies show a high prevalence of valvular thickening, but clinical disease is rare[8,9]. The frequency of valve involvement is similar to rheumatic heart disease (mitral, aortic, tricuspid, pulmonary). Non-specific inflammation and fibrosis cause thickening and calcification, mainly in the base of the valve and the valve ring, but this rarely has haemodynamic consequences. The most distinctive lesions are rheumatoid granulomata within the valve leaflets which can cause incompetence. Most patients have no symptoms because the left ventricle (LV) can adapt to significant mitral or aortic regurgitation without decompensating. The effect on ventricular performance is mainly defined by the rapidity of onset of regurgitation; in severe cases, lesions can develop over a few days and cause rapid LV failure.

Myocarditis

Myocarditis is found in up to 30% of autopsy cases[5–7]. It can be diffuse or focal, non-specific or pathognomonic nodular rheumatoid myocarditis. Its

clinical significance is unknown. The overwhelming majority of patients are asymptomatic. However, the compact anatomy and relationship of the atrioventricular node to the aortic root and interventricular septum make it vulnerable to damage from inflammation of adjacent structures and can lead to conduction defects. Complete heart block has been reported in RA and penicillamine-induced myositis[12,13].

Arteritis

Arteritis is present in up to 20% of autopsy cases, affecting mainly medium and small intramyocardial arteries[5–7]. This may lead to patchy myocardial necrosis due to microinfarction or ischaemia. Severe arteritis of the epicardial vessels has been reported and tends to be non-occlusive. Its relationship to myocardial infarction (MI) is controversial[14,15].

Myocardial dysfunction

Several processes operating alone or in tandem may lead to myocardial dysfunction in RA. Heart failure may be one of the main causes of increased cardiovascular mortality in RA, particularly in men[1]. Diastolic LV dysfunction on Echo-Doppler, found in 30–40% of RA patients without overt heart disease[16], is thought to be an early sign of IHD or heart failure and has adverse prognostic significance. Restriction due to amyloid can lead to diastolic heart failure; in the past it was found in 10–20% of rheumatoid hearts, but is now rare. Pancarditis and small vessel vasculitis can lead to systolic pump failure[17], while pulmonary fibrosis can cause right ventricular failure. Overall, however, heart failure in RA, as in the general population, is more likely to be the result of atherosclerotic disease. Symptoms of myocardial dysfunction such as dyspnoea are unusual in RA, possibly due to reduced physical activity, while signs are non-specific. Patients suddenly developing overt heart failure should be investigated for many possible causes, including acute MI or hypertensive heart disease, but also vasculitis, valvular disease/bacterial endocarditis, cor pulmonale or constrictive pericarditis.

Ischaemic heart disease

Myocardial perfusion imaging under pharmacological stress detects IHD in about 50% of RA patients, a prevalence double that of matched controls[18]. This is reflected in the incidence of MI and heart failure as causes of cardiovascular mortality in RA[1]. Alarmingly, more than half of RA patients with IHD have no ischaemic symptoms. Classical cardiovascular risk factors appear to be important, but RA, like diabetes, confers significant extra risk[18]. The long-term significance of this is obvious, but strategies to prevent it are yet to be established.

Investigation of cardiovascular involvement in rheumatoid arthritis

Overall cardiovascular risk in RA, as in other conditions, can be assessed on the basis of history, blood pressure, lipids and ECG. A range of other investigations is also available to identify specific cardiac pathologies, assess their effects and allow targeted treatment. These should be used judiciously, and they require collaboration between rheumatologists and cardiologists.

ECG and chest X-ray are useful, but are insensitive and non-specific first-line investigations. Echocardiography allows evaluation of both cardiac anatomy and function, and may be helpful in several situations[8,9,16]:

- pericarditis (fluid and thickening)
- imminent tamponade (diastolic collapse)
- constriction (preserved LV function but abrupt termination of ventricular filling)
- valvular lesions (grading of regurgitation and serial assessment of LV end-diastolic dimension)
- amyloidosis
- assessment of LV systolic and diastolic function.

In cases of constriction, computed tomography (CT) scanning is useful to confirm pericardial thickening, and helps to differentiate constrictive pericarditis from restrictive cardiomyopathy (Table 2). Cardiac catheterisation is essential if pericardectomy is considered.

Exercise testing provides evidence of ischaemia, but may be impossible or difficult due to physical disability. A useful alternative is nuclear perfusion imaging under pharmacological stress. This may show ischaemia, whether due to epicardial or small vessel abnormalities, and inform the need for further invasive investigation[18,19]. Coronary angiography will reveal epicardial disease, but can neither differentiate

Table 2. Differential diagnostic features between constrictive pericarditis and restrictive cardiomyopathy.

Diagnostic feature	Constrictive pericarditis	Restrictive cardiomyopathy
S_3 Gallop	Absent	May be present
Pericardial knock	May be present	Absent
Palpable systolic apical impulse	Absent	May be present
Pulsus paradoxus	May be present	May be present
Pericardial calcification	Present 50%	Absent
CT scan, MRI, echocardiography	Thickened pericardium	Normal pericardium
Equal RV and LV diastolic filling pressures	Usually present	LV>RV
Rate of LV filling	80% in first half of diastole	40% in first half of diastole

CT = computed tomography; MRI = magnetic resonance imaging; LV = left ventricle; RV = right ventricle.

Key Points

- Cardiovascular disease causes almost half of all deaths in rheumatoid arthritis (RA)
- Cardiovascular mortality is greater and occurs earlier in RA than in the general population
- Rheumatoid heart disease is commonly found at autopsy or by echocardiography, but is rarely clinically apparent
- RA associates with a higher prevalence of ischaemic heart disease

between arteritis and atherosclerosis nor detect smaller vessel involvement. Endomyocardial biopsy may provide histological diagnosis and allow prompt treatment in myocarditis or diffuse vasculitis[17]. Other investigations that may be useful in experienced hands include:

- ^{67}Gallium scanning (inflammation)[17]
- stress echocardiography (ischaemia)
- electron-beam CT (coronary artery calcification)
- cardiac magnetic resonance imaging.

Treatment of cardiac complications in rheumatoid arthritis

The majority of cardiac complications in RA are silent and do not require symptomatic treatment.

Pericarditis

Silent pericarditis is benign in the long term, without progression to constriction. Symptomatic pericarditis without haemodynamic upset is treated with non-steroidal anti-inflammatory drugs or steroids, but abrupt cessation of steroids may result in rapid deterioration. The course of aggressive pericarditis is unfavourable. Compression due to effusion or constriction associates with up to 37% mortality[2], and steroids or slow-acting antirheumatic drugs (SAARDs) have little influence on such disease. Pericardiocentesis may be life-saving in tamponade, but re-accumulation is common despite systemic or intrapericardial steroids. This procedure has a risk of myocardial or coronary laceration, and should be performed by experienced hands under echocardiographic guidance. Extensive pericardial resection should be considered in all patients with cardiac compression, if they will tolerate thoracotomy.

Valve lesions

Valve replacement depends on the lesion, its clinical and haemodynamic effects, and the patient's state. The optimum time for this procedure is before development of irreversible LV dysfunction but after the risk of significant LV damage outweighs the operative risks. Pre-operative cardiac catheterisation is essential to confirm echocardiographic findings and exclude coexistent coronary artery disease. In milder cases or patients unsuitable for valve replacement, medical treatment with vasodilators, angiotensin-converting enzyme inhibitors and diuretics may be appropriate. There is no evidence for using steroids or SAARDs in treating valve lesions. Bacterial endocarditis should be actively excluded if there is rapid deterioration in the condition of a valve.

Fulminant coronary vasculitis/myocarditis

Fulminant coronary vasculitis and/or myocarditis presenting with congestive heart failure are usually diagnosed at *post-mortem*. There is no consensus as to the best treatment. Steroids have been the mainstay of therapy, but they are also recognised to provoke coronary arteritis. More aggressive regimens involving cyclophosphamide may be useful, but have not been formally evaluated. Fortunately, such cases are rare.

Conclusion

There is an urgent need for further research into the causes, significance and prevention of IHD in RA. At present, it would be sensible to suggest that practising rheumatologists should assess and correct the modifiable cardiovascular risk factors of their patients, and have a high index of suspicion and a low threshold for cardiology referral and investigation.

References

1 Manzi S, Wasko MCM. Inflammation-mediated rheumatic diseases and atherosclerosis. *Ann Rheum Dis* 2000;**59**:321–5.
2 Escalante A, Kaufman R, Fransisco P, Quisimorio FP Jr, Beardmore TD. Cardiac compression in RA. *Semin Arthritis Rheum* 1990;**20**:148–63.
3 Pasceri V, Yeh ETH. A tale of two diseases. Atherosclerosis and rheumatoid arthritis. *Circulation* 1999;**100**:2124–6.
4 Kitas GD, Banks MJ, Bacon PA. Accelerated atherosclerosis as a cause of cardiovascular death in rheumatoid arthritis. *Pathogenesis* 1998;**1**:73–83.
5 Sokolof L. The heart in rheumatoid arthritis. *Am Heart J* 1953;**45**:635–43.
6 Cathcart ES, Spodick DH. Rheumatoid heart disease. *N Engl J Med* 1962;**266**:959–64.
7 Bonfiglio T, Atwater EC. Heart disease in patients with seropositive rheumatoid arthritis; a controlled autopsy study. *Arch Intern Med* 1969;**124**:714–9.
8 Bacon PA, Gibson DG. Cardiac involvement in rheumatoid arthritis. An echocardiographic study. *Ann Rheum Dis* 1974;**33**:20–4.
9 MacDonald WJ Jr, Crawford MH, Klippel JH, Zvaifler NJ, O'Rourke RA. Echocardiographic assessment of cardiac structure and function in rheumatoid arthritis. *Am J Med* 1977;**63**:890–6.
10 Travaglio A, Anaya J-M. Rheumatoid pericarditis: new immunopathological aspects. *Clin Exp Rheumatol* 1994;**12**:313–6.
11 Hancock EW. Subacute effusive-constrictive pericarditis. *Circulation* 1971;**43**:183–92.
12 Ahern M, Lever JV. Complete heart block in rheumatoid arthritis. *Ann Rheum Dis* 1983;**42**:389–95.
13 Christensen PD, Sorensen KE. Penicillamine induced polymyositis with complete heart block. *Eur Heart J* 1989;**10**:1041–4.
14 Voyles WF, Searles RP, Bankhurst AD. Myocardial infarction caused by rheumatoid vasculitis. *Arthritis Rheum* 1980;**23**:860–3.
15 Morris PB, Imber MJ, Heinsimer JA, Hlatky MA, Reimer KA. Rheumatoid arthritis and

coronary arteritis. *Am J Cardiol* 1986;**57**: 689–90.
16 Corrao S, Salli L, Arnone S, Scaglione L, *et al*. Echodoppler abnormalities in patients with rheumatoid arthritis without clinically evident cardiovascular disease. *Eur J Clin Invest* 1996;**26**:293–7.
17 Slack D, Waller B. Acute congestive heart failure due to the arteritis of rheumatoid arthritis. Early diagnosis by endomyocardial biopsy. *Angiology* 1986;**6**:477–81.
18 Banks MJ, Flint EJ, Bacon PA, Kitas GD. Rheumatoid arthritis is an independent risk factor for ischaemic heart disease. *Arthritis Rheum* 2000;**43**:S385.
19 Banks MJ, Kitas GD. Patients' physical disability in RA may influence doctors' perceptions of suitability for risk assessment of coronary heart disease. *Br Med J* 1999; **319**:1266–7.

Address for correspondence:
Dr G D Kitas, Department of Rheumatology, Dudley Group of Hospitals NHS Trust, The Guest Hospital, Tipton Road, Dudley, West Midlands DY1 4SE.
E-mail: g.d.kitas@bham.ac.uk

The real connective tissue diseases

Paul Wordsworth MA MB FRCP, Professor of Clinical Rheumatology, *University of Oxford*
Dorothy Halliday MB MRCP, British Heart Foundation Clinical Research Fellow

Clin Med JRCPL 2001;**1**:21–4

Rheumatologists and immunologists, in particular, are familiar with the connective tissues as a battlefield for a wide variety of inflammatory diseases, many of which are covered in this issue. The heritable disorders of connective tissue constitute a second, less familiar group which in recent years has yielded many of its mysteries to the techniques of molecular biology. Classification and accurate diagnosis of these conditions, affecting a wide variety of mesenchymal tissues, have benefited significantly from advances in basic science. A brief review is able only to scratch the surface of this fascinating group of conditions which have been extensively reviewed elsewhere[1,2]. Examples of disorders affecting the hard and soft musculoskeletal system will be used to illustrate general points.

Skeletal dysplasias

Skeletal dysplasias may be divided into those that affect bone (eg osteogenesis imperfecta) or the cartilage component of the bones (chondrodysplasias)[3]. The latter can be separated into those predominantly affecting the epiphyses or the metaphyses. Together with the presence or absence of spinal involvement, these simple descriptions form the basis of a clinical classification system:

- epiphyseal dysplasia
- metaphyseal dysplasia
- spondyloepiphyseal dysplasias, etc.

The presence of skeletal disproportion and its distribution can be useful clinically, for example:

- rhizomelic short limbs in achondroplasia
- relatively short trunk in spondyloepiphyseal dysplasia.

Several distinct families can be recognised within the skeletal dysplasias based on the underlying genetic abnormalities. The first to be well studied was osteogenesis imperfecta in which the diversity of clinical phenotypes correlates well with the mutations involving Type I collagen. Briefly, substitutions of cysteine for glycine in the critical central core of the collagen triple helix significantly impair formation of the classic triple helix of α chains, and lead to overmodification of the mature collagen by excessive glycosylation and hydroxylation. This type of mutation ('dominant negative') may reduce the amount of normal collagen by 7/8ths and lead to severe phenotypes (lethal or severely deforming). In contrast, mutations that create an effective null allele (eg premature stop codons) reduce the amount of normal collagen by smaller amounts and cause milder forms of disease. Similar attempts at classification based on the underlying biochemical and genetic defects have been possible in the chondrodysplasias (Table 1). The major cartilage collagen (more than 90%) is Type II. A large number of mutations have now been described in the gene *COL2A1*, identifying a family of chondrodysplasias[4]. These conditions are associated not only with abnormalities of the epiphyses but also frequently of the eye (Type II collagen is a major constituent of vitreous humour).

Soft connective tissues disorders

The heritable disorders of the soft connective tissues are best exemplified by the heterogeneous Ehlers-Danlos syndrome (EDS), characterised broadly by excessive skin elasticity, joint hypermobility and bruising, and the Marfan syndrome.

Ehlers-Danlos syndrome

Although 10 classic forms of EDS are described, many patients cannot be