Autoimmune diseases and the Heart

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Overview of Presentation

- **Vasculitis**
  - Takayasu arteritis
  - Giant Cell arteritis
  - Kawasaki disease
- **Vasculitis of Small or Medium-Sized Vessels**
  - Churg-Strauss Syndrome
- **Systemic Rheumatological Disorders**
  - Rheumatoid Arthritis
  - HLA-B27–Associated Spondyloarthropathies
  - Systemic Lupus Erythematosus
  - Antiphospholipid Antibody Syndrome
  - Scleroderma
  - Sarcoidosis

Presenting Cardiac Symptoms of Autoimmune Disease

- Pericarditis
- Myocarditis or myocardial fibrosis due to myositis or vasculitis with rhythm and conduction disturbances and diastolic or systolic heart failure
- Ischemic heart disease (coronary arteritis)
- Endocardial involvement with valvular disease and formation of thrombi
- Pulmonary hypertension secondary to concomitant lung disease or recurrent lung embolism
- Unexplained arterial thrombosis
- Syncope
- Arterial hypertension (Malignant)

Ledford DK. Immunologic aspects of vasculitis and cardiovascular disease. JAMA 1997;278:1962–1971

Prevalence of Cardiac involvement in Autoimmune Disease

- Variable
- In general, clinical symptoms are uncommon
- Initial autopsy studies suggested high incidence of cardiac involvement
- Transesophageal echocardiogram and MRI done routinely show prevalence approaching that of autopsy
- Cardiac findings are uncommon at initial diagnosis but do increase in frequency over followup time

Knockaert DC. Eur Heart J. 2007 Aug;28(15):1797-804. Epub 2007 Jun.

Takayasu Arteritis
"The pulseless disease"

- Large vessel vasculitis
- Incidence
  - 1-3 per million in US and northern Europe
  - As high as 1 in 3000 in Japan (features at autopsy)
  - Women affected 10 times more than men
  - Median age 25
- Pathogenesis
  - Exact cause unknown
  - Mononuclear cells infiltrate vessel wall

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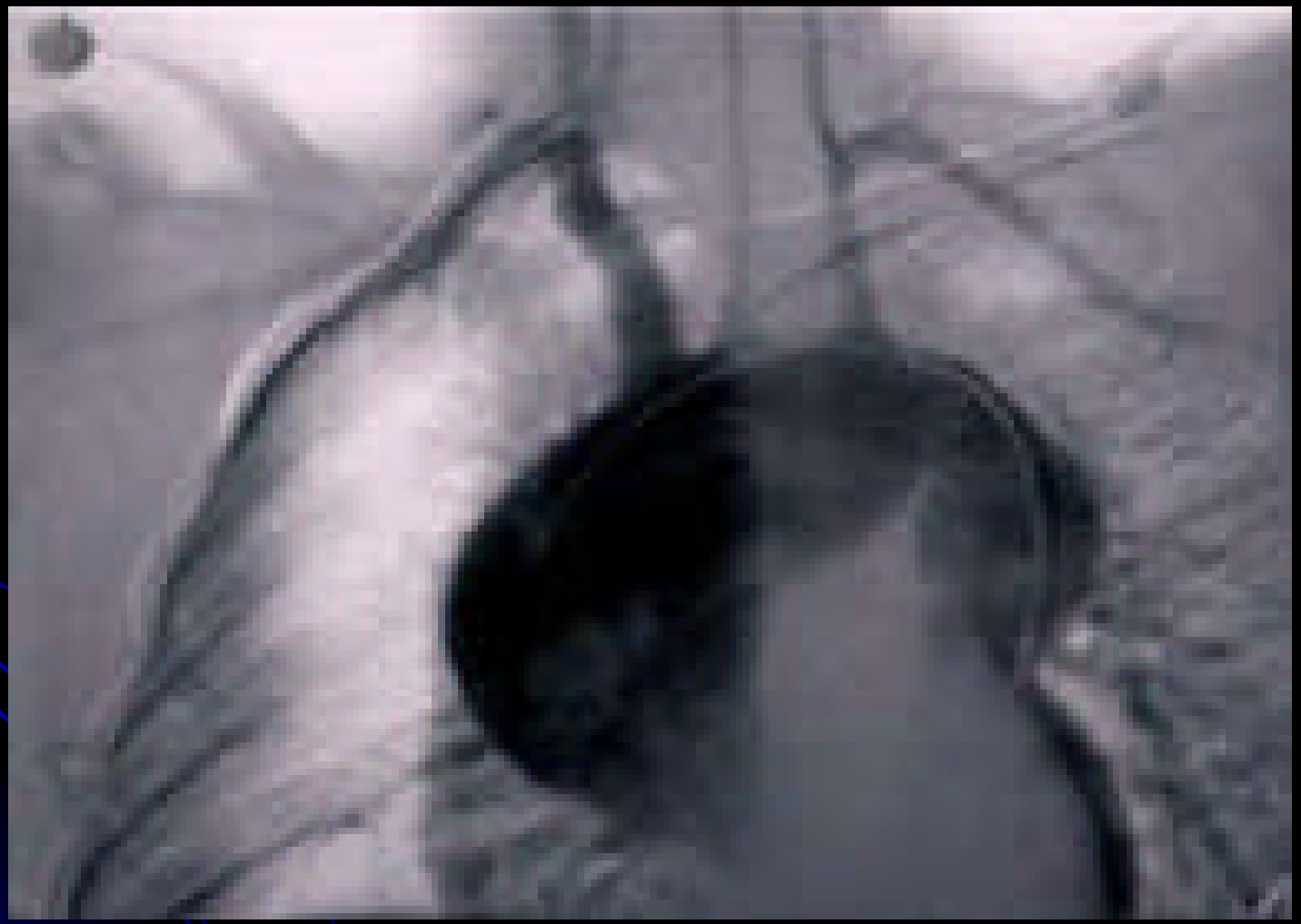
Aortic root dilation in Takayasu Arteritis



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Features of Takayasu Arteritis

- Stenosis 3-4x more common than aneurysms
- Upper (and lower) extremity claudication
- Asymmetric pulses
- Aortic valve regurgitation due to aortic root aneurysms
- Hypertension associated with renal artery stenosis
- Coronary vasculitis in <5% of cases
- Mortality estimates of 3-35% in 5 years

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Diagnosis of Takayasu Arteritis

- Suspect in young patient with hypertension
  - Very common cause of hypertension in adolescents in Asia, India, and Mexico
  - Asymmetric pulses
  - Vascular bruits
- Malaise, myalgias, arthralgias, night sweats, and fever
- ESR usually elevated with active disease but may be normal
- No single diagnostic test

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Imaging Takayasu Arteritis

- MRI, CT
  - Visualize vessel aneursym/stenosis
- PET
  - Visualize inflammatory activity in vessel wall
- Echocardiography
  - Left ventricular dysfunction in 20%
- Angiography

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Treatment of Takayasu Arteritis

- High dose (1 mg/kg/day) prednisone
  - Tapering dose
- Refractory cases
  - cyclophosphamide (2 mg/kg) or
  - methotrexate (20 mg weekly)
- Relapse/Remission cycles common
- Long term immunosuppression often needed
- TNF blockade may be helpful

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Mechanical therapy for Takayasu Arteritis

- Consider intervention for clinically important vascular stenosis
  - Stents more prone to restenosis than bypass grafts
- Aortic surgery with or without valve surgery for aortic aneurysm

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Giant Cell arteritis

- Incidence of 18 in 100,000 in US
- Mean age 74
- Females > Males by 2-3:1
- 50% have features of polymyalgia rheumatica

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Pathophysiology of Giant Cell arteritis

- Inflammation in Adventitial layer
- Initially high concentration of proinflammatory cytokines in vessel wall
  - IL-1
  - IL-6
  - TNF
  - Interferon-gamma
- High concentration of T cells
- Later stages demonstrate growth factors, promoting intimal growth and stenosis

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Clinical features of Giant Cell Arteritis

- Severe headaches of new onset
- Temporal tenderness
- Visual loss
- Pain with chewing

- With elevated ESR, treatment should be initiated
  - If symptoms not improved in 1-3 days then alternative diagnosis should be considered

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Cardiac Involvement of Giant Cell Arteritis

- 15% may involve aorta, subclavian artery
  - Similar features as Takayasu
  - Thoracic and abdominal aortic aneurysms
- Half of patients have cardiac disease
  - Secondary to aging vs Giant Cell arteritis?

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Treatment of Giant Cell Arteritis

- Prednisone 0.7-1.0 mg/kg/day
  - Symptom improvement 1-3 days
  - Symptom resolution 1 week
  - Taper 2-4 weeks after ESR and Clinical symptoms resolved
- Low dose aspirin reduces incidence of blindness and stroke
- Anti-TNF monoclonal antibodies have not demonstrated efficacy

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Kawasaki Disease

- Main cause of acquired heart disease in children in the US and Japan
- Mainly affects children <5 years of age
  - Rare after 8 years of age
- Male to Female predominance 1.5:1
- Incidence in Asian children 50-200/100,000
- Incidence in US 6-15/100,000
- Siblings have higher incidence (2%) than general

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Pathogenesis of Kawasaki Disease

- Possible infectious cause?
  - Fever, rash, conjunctivitis, adenopathy
- Acute phase
  - Widespread inflammation
  - Macrophages, T lymphocytes
  - Increased levels of many cytokines

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Clinical Definition of Kawasaki Disease

- Fever ≥5 days, without other explanation, plus at least four of the following:
  1. Bilateral conjunctival injection
  2. Mucous membrane changes—injected or fissured lips; injected pharynx or “strawberry” tongue
  3. Extremity abnormality—erythema of palms, soles, edema of hands, feet, or generalized or peripheral desquamation (hands, feet)
  4. Rash (polymorphous)
  5. Cervical lymphadenopathy (usually a single node >1.5 cm)

- Associated manifestations
  - Irritability
  - Sterile pyuria, meatitis
  - Perineal erythema and desquamation
  - Arthralgias, arthritis
  - Abdominal pain, diarrhea
  - Aseptic meningitis
  - Hepatitis
  - Obstructive jaundice
  - Hydrops of gallbladder
  - Uveitis
  - Sensorineural hearing loss
  - Cardiovascular changes

Barron K: Kawasaki disease: Etiology, pathogenesis and treatment. Cleve Clin J Med 69(Suppl 2):69, 2002

Cardiac manifestations of Kawaskai disease

- Pericardial effusion (30%)
- Mitral regurgitation (30%)
- Coronary aneurysms
- Myocarditis
- Aortitis
- Congestive heart failure
- Arrhythmias
- EKG changes
  - ST depression, T wave flattening/inversion
  - PR and/or QT prolongation

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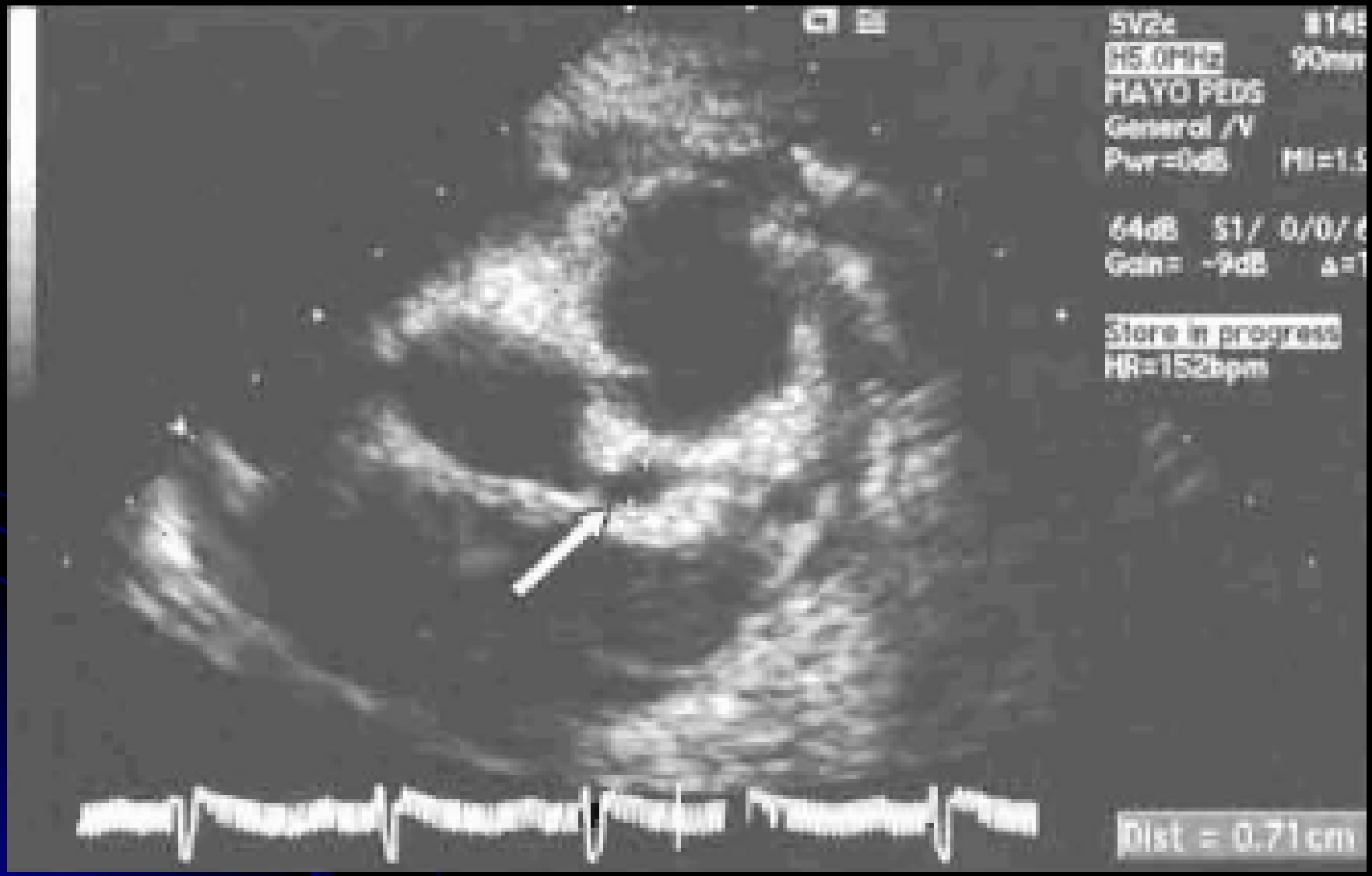
Coronary aneurysms

- Develop in 20-25% if untreated for 2 weeks
  - Usually appear 1-4 weeks after symptoms
  - Proximal artery > Distal
  - Half of the aneurysms will regress in 2 years
  - Giant aneurysms (>8mm) rare, but persist
  - Overall 2% mortality
    - Death occurs due to thrombosis and occlusion
- IVIG treatment decreases incidence to 5%
- May be clinically silent until 3rd or 4th decade!

Braunwald's Heart Disease, 8th ed.
•Pinna GS, Kafetzis DA, Tselkas OI, Skevaki CL. Kawasaki disease: an overview. Curr Opin Infect Dis. 2008 Jun;21(3):263-70.

Coronary Aneurysm in Kawasaki Disease



Kane GC, Keogh KA. Involvement of the heart by small and medium vessel vasculitis. Curr Opin Rheumatol. 2009 Jan;21(1).

Treatment of Kawasaki Disease

- Early identification!
- IVIG 2g/kg single IV infusion
- Aspirin 80-100mg/kg/day until afebrile
  - Then 3mg/kg/day for about 8 weeks
  - Low dose aspirin indefinitely for coronary aneurysms?
- Steroids? Controversial!
- Consider bypass, percutaneous intervention in cases of giant aneurysms or stenosis

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Churg-Strauss Syndrome

- Incidence of 2.4/1,000,000
- Peak age 35-50
- Allergic angiitis and granulomatosis
  - Asthma
  - Eosinophilia
  - Pulmonary infiltrates
  - Upper airway inflammation
- May involve
  - Kidneys
  - Neurologic system
  - Cutaneous lesions
  - Cardiovascular system
- Eosinophilic granulomatous infiltrates and vasculitis.

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Pathogenesis of Churg-Strauss

- Not well understood
- May be precipitated by environmental exposure?
- P-ANCA more common than C-ANCA
- Th1 and Th2 lymphocytes
- Eosinophils

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Cardiovascular involvement of Churg-Strauss

- Most common cause of death in Churg-Strauss
- 15-55% of Churg-Strauss cases
- Pericarditis
- Myocarditis
- Coronary arteritis
- Congestive heart failure (15-30%)
- Mesenteric ischemia

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Treatment of Churg-Strauss

- Acute phase
  - Prednisone 1mg/kg/day
    - Consider IV methylprednisolone 1 gm/day if kidney, cardiac, or neurologic involvement
  - Also cyclophosphamide 2mg/kg/day (watch renal function)
- Chronic
  - Azathioprine (daily) or
  - Methotrexate (weekly)

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Rheumatoid Arthritis

- Most common form of chronic inflammatory polyarthritis
- 1-3% incidence in general population
- Female to Male ratio 2:1
- Genetic predisposition but unknown cause

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Clinical features of Rheumatoid Arthritis

- Symmetric polyarthritis
- Small and large joints
  - Metacarpophalangeal joints and wrists
  - Spares lumbar and thoracic spine and distal interphalangeal joints

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Pericarditis in Rheumatoid Arthritis

- Symptomatic involvement in 0.5%
  - But may see activity in up to 40%
- Coexistent pericardial effusion common
  - Usually blood tinged fluid with neutrophils
- Can evolve into constrictive pericarditis
- Treated with NSAIDS, steroids, pericardiocentesis, pericardial window as needed

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Other cardiac involvement of Rheumatoid Arthritis

- Frequent involvement of mitral and aortic valves
  - Rarely causes clinical problems
- Secondary pulmonary hypertension can develop form rheumatoid lung disease
- Heart block is rare

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Prognosis of Rheumatoid Arthritis

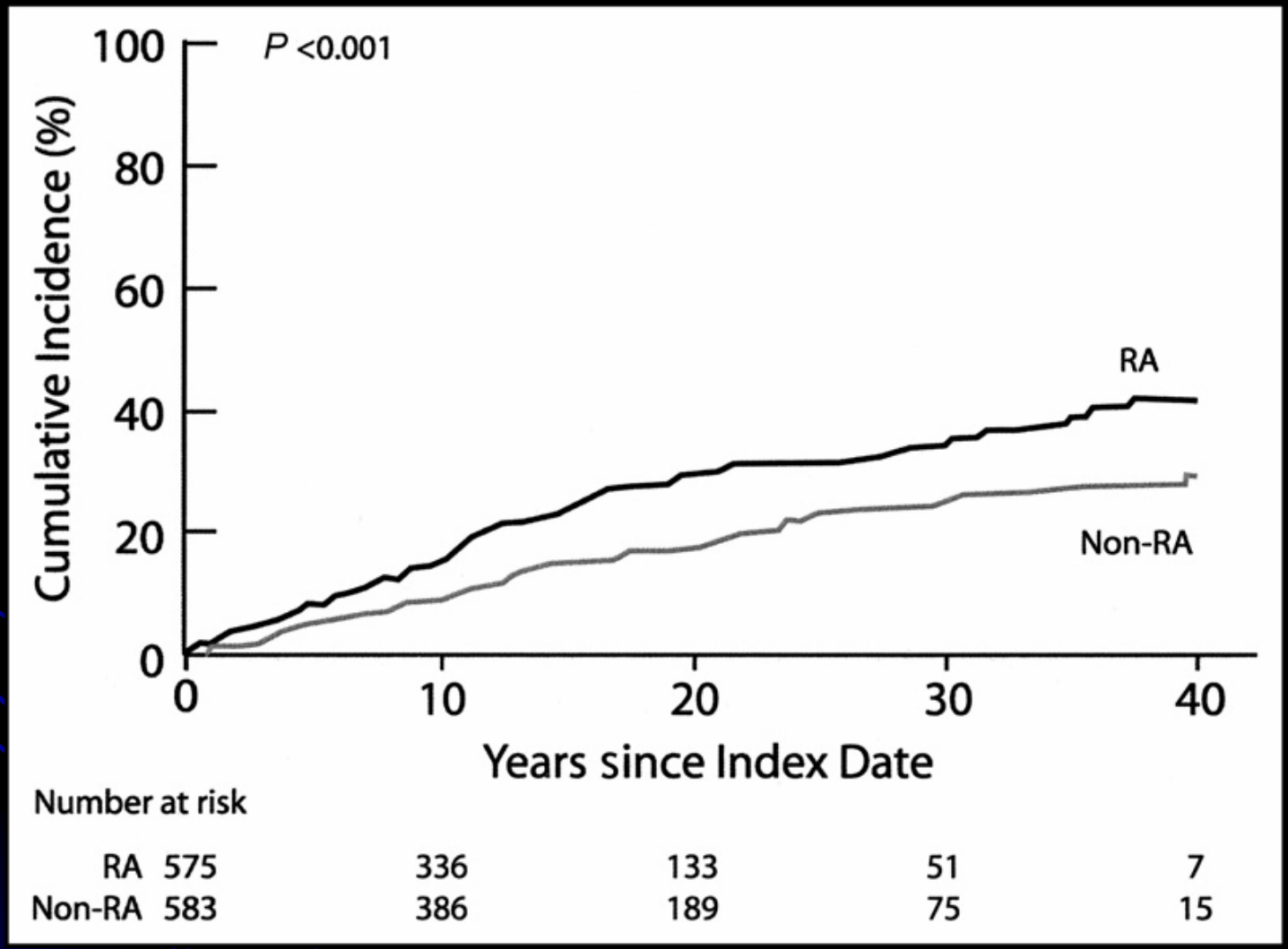
- Decreased life expectancy
- Main cause of death is cardiovascular
  - Chronic inflammation
  - Chronic NSAID use
  - Atherogenic HDL production

Braunwald's Heart Disease, 8th ed.

Survival in Rheumatoid Arthritis

Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum.* 2003;48:54-58.

Incidence of CHF in Rheumatoid arthritis



Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52:412-420.

Treatment of Rheumatoid Arthritis

- Anti TNF agents
  - Careful in patients with CHF
- Methotrexate
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine
- Low-dose prednisone
- NSAIDS increase cardiovascular risk

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HLA-B27–Associated Spondyloarthropathies

- Ankylosing spondylitis
- Psoriatic arthritis
- Inflammatory bowel disease–associated arthritis
- Postinfectious reactive arthritis

- Most people with HLA-B27 gene (10% of US caucasian population) do **not** have spondyloarthropathy!

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Clinical features of Spondyloarthropathies

- Entire spine involved
  - Frequent sacroiliac joint involvement
- Large joint involvement asymmetric
- “Sausage digits”

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Cardiovascular involvement in Spondyloarthropathies

- Frequent Aortic root disease
  - Dilatation
  - Aortic valve regurgitation
- Conduction disease in up to one third
  - Generally progressive
- Very rare involvement of pericardium, coronary arteritis

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Treatment of Spondyloarthropathies

- Anti TNF agents
- NSAIDS
- Physical therapy

- Unclear whether these influence cardiovascular complications

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Systemic Lupus Erythematosus

- Serositis
- Arthritis
- Glomerulonephritis
- Neurologic dysfunction
- Hemolytic anemia
- Thrombocytopenia
- Leukopenia
- 20% have antiphospholipid antibodies
  - Arterial and venous thrombosis
  - Pulmonary hypertension
  - Miscarriage

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Pericarditis in SLE

- Clinically significant pericarditis in 25%
  - Autopsy series have shown 60-80% involvement
  - Tamponade <2%
  - Constrictive pericarditis is rare
- Pericardial effusion
  - Neutrophils
  - Elevated protein level
  - May occur as complication of renal failure

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Knockaert DC. Eur Heart J. 2007 Aug;28(15):1797-804. Epub 2007 Jun.

Coronary involvement in SLE

- Coronary arteritis infrequent
- But coronary atherosclerosis is prevalent
  - Chronic inflammation
  - Immune complex deposition
  - Antiphospholipid antibodies
- Acute coronary syndrome
  - Thrombosis related to antiphospholipid antibody
  - Embolism from Libman-Sacks endocarditis

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Conduction problems in SLE

- Unusual in patients with SLE
- But infants born to mothers with SLE have higher incidence of complete heart block
  - Occurs in small number of mothers with anti-RO/SSA and anti-LA auto-antibodies

Braunwald's Heart Disease, 8th ed.

Knockaert DC. Eur Heart J. 2007 Aug;28(15):1797-804. Epub 2007 Jun.

Valvular disease in SLE

- Sterile vegetations
  - Libman-Sacks endocarditis
  - Seen in up to 60% of patients by TEE
  - Not related to disease severity, disease activity, or disease duration
- Most commonly mitral valve
- Valvular regurgitation
- Valvular thickening
  - May lead to stenosis

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Treatment of SLE

- Systemic treatment courses vary
- Pericarditis
  - NSAIDS
  - Steroids
- Pericardial effusions
  - Pericardiocentesis for large effusions or tamponade
  - Pericardial window for recurrent effusions

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Antiphospholipid Antibody Syndrome

- Recurrent venous or arterial thrombosis (or miscarriage) combined with Antiphospholipid Antibody or Lupus anticoagulant
- Most commonly venous thrombosis
- Cardiac involvement similar to SLE

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Cardiac Involvement in Antiphospholipid Antibody Syndrome

- Valve abnormalities
  - Thickening of leaflets
  - Irregular nodular excrescences
  - Vegetations (sterile)
  - Valve dysfunction
- Thrombotic and atherosclerotic coronary occlusion
- Intracardiac thrombus
- Pulmonary hypertension
- Ventricular hypertrophy and dysfunction

Tenedios F, Erkan D, Lockshin MD. Cardiac manifestations in the antiphospholipid syndrome. Rheum Dis Clin North Am. 2006 Aug;32(3):491-507.

Treatment of Antiphospholipid Antibody Syndrome

- Longterm secondary prevention
- Coumadin for venous thrombosis
  - INR 2.0-2.5
- Aspirin for arterial thrombosis

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Scleroderma

- Progressive systemic scleroderma
- CREST syndrome
  - Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia

- Initially inflammatory, fibrosis in later stage
- Cutaneous and parenchymal fibrosis
  - Microvascular occlusive disease
  - Vasospasm
  - Vascular intimal proliferation
- Average age of onset 45-65 years
- Female predominance

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Clinical Features of Scleroderma

- Raynaud phenomena in 90%
- Arthralgias (>90%)
- Proximal weakness (>60%)
- Esophageal dysmotility (>80%)
- Telangiectasias (90% in CREST, 60% in generalized disease)
- Pulmonary fibrosis (70% in generalized, 35% in CREST)

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Cardiovascular involvement in Scleroderma

- Pulmonary hypertension
- Renal crisis
  - Hypertension, LV dysfunction
  - Treatment with ACE inhibitors
- Pericarditis
- Pericardial effusion
- Coronary vasospasm
- Coronary microvascular disease

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Treatment of Scleroderma

- ? Cyclophosphamide may slow progression of pulmonary hypertension
- Endothelin antagatonists and prostanoids improve pulmonary hypertension
  - Bosentan/Ambrisentan
  - Epoprostenol/treprostinil/iloprost
- Steroids can precipitate renal crisis

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Sarcoidosis

- Noncaseating granulomatous inflammatory disease
  - lung parenchyma
  - Adenopathy
  - Arthropathy
  - Myositis
  - Fever
  - Renal, liver, skin, eye, and cardiac disease
- Incidence
  - 10 per 100,000 in whites
  - 35 per 100,000 in African Americans
  - 50 to 60 cases per 100,000 in Scandinavians

Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. Am Heart J. 2009 Jan;157(1):9-21. Epub 2008 Nov 12.

Cardiovascular Involvement in Sarcoidosis

- Granulomatous infiltration of heart (25%)
  - Often asymptomatic (up to 95%)
  - Endomyocardial biopsy may miss patchy infiltrates
  - Nuclear imaging can detect fibrosis/scar
- Clinically heterogeneous effects
  - Dilated cardiomyopathy
  - Congestive Heart Failure
  - Pericarditis
  - Conduction system disease
  - Pulmonary artery hypertension (due to pulmonary fibrosis)

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Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. Am Heart J. 2009 Jan;157(1):9-21. Epub 2008 Nov 12.

Incidence of Cardiac Findings in Sarcoidosis

AV block	26%-62%
Bundle Branch Block	12%-61%
Supraventricular Tachycardia	0%-15%
Ventricular Tachycardia	2%-42%
Congestive Heart Failure	10%-30%
Sudden Cardiac Death	12%-65%

Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. Am Heart J. 2009 Jan;157(1):9-21. Epub 2008 Nov 12.

Diagnosing Cardiac Sarcoidosis

- History, EKG nonspecific
- Endomyocardial biopsy has low sensitivity (due to patchy granulomas) but high specificity
- Echocardiography nonspecific
  - Wall motion abnormality in non-coronary distribution is suspicious
- Gallium-67 Scintigraphy detects inflammation, but has a low sensitivity
- FDG-PET demonstrates hypermetabolic activity in cardiac granulomas
- MRI with Gadolinium delayed enhancement
  - Myocardial necrosis and wall motion abnormalities in noncoronary distribution
  - High sensitivity and specificity

Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. Am Heart J. 2009 Jan;157(1):9-21. Epub 2008 Nov 12.

Treatment of Sarcoidosis

- Corticosteroids
- Methotrexate can be added

- Some studies suggest stabilization of cardiac findings with therapy

- Questionable duration of therapy
- Imaging with MRI or PET to guide therapy?
- No data on cardiac outcomes

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Summary

- Chronic inflammatory diseases have variable cardiac sequelae
  - Autopsy/imaging involvement greater than clinical expression
- Generally treatment targeted to underlying autoimmune disease as well as cardiac issues
- Unclear what effect treating autoimmune disease has on cardiac disease
- No clear guidelines on followup for most autoimmune diseases

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