DISSERTATION ON

CARDIOVASCULAR MANIFESTATIONS AND PULMONARY HYPERTENSION IN RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that this dissertation entitled **"CARDIOVASCULAR MANIFESTATIONS AND PULMONARY HYPERTENSION IN RHEUMATOID ARTHRITIS"** submitted by **Dr. UDAYAKUMAR.N** appearing for Part II M.D. Branch I General Medicine Degree examination in September 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India

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INTRODUCTION

Is it not disgraceful that a person should, by reason that extraordinary arthritis, be unable to use his hands and should need somebody else to bring food to his mouth and to perform the other necessities for him… and even if overlooks the disgraceful aspect of this, yet one cannot overlook the pain these people suffer, night and day.

Galen (128 – 200 A.D)

Rheumatoid arthritis (RA) is the most common inflammatory arthritis and hence an important cause of potentially presenting disability. Rheumatoid arthritis is a chronic multi system disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of Rheumatoid arthritis is a persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in the joint integrity is the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable.

Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, where as others will have a relentless progressive polyarthritis with marked functional impairment.

Long- term survival of patients with rheumatoid arthritis is shorter compared with the general population or control population without RA[1] Among the different causes of death, increased mortality from heart disease with high mortality from congestive cardiac failure was reported in many studies. [1,2] Necropsy studies showed a high incidence of pericardial, myocardial and endocardial involvement in RA patients. [3] However, cardiac disease is clinically silent and is rarely a life threatening complication in RA. Cardiac failure is the result of either systolic or diastolic dysfunction, or both. Left ventricular diastolic dysfunction is usually attributable to common structural abnormalities such as hypertrophy or interstitial fibrosis and impaired myocyte relaxation resulting from ischemia. [4] In RA, the cardiac disease can present in various forms in relation with granulomatosis and vasculitis. In patients with RA, all layers of the heart can be inflamed and pericarditis is the most common form of involvement. Moreover valvular disease, myocardial involvement, coronary vasculitis and diastolic dysfunction can be identified.

Lung involvement in rheumatoid arthritis is not uncommon, comprising pleural effusion, interstitial fibrosis, pulmonary rheumatoid nodules, and involvement of small airways.

Pulmonary hypertension has also been described in RA patients. This is usually the result of RA- associated lung disease.[5] Isolated case reports of primary pulmonary hypertension have also been published.[6] Primary pulmonary hypertension is often clinically silent until well advanced. Sub clinical pulmonary hypertension may be more common in rheumatoid arthritis, since Dawson et al.[7] reported that 21% of all the rheumatoid arthritis patients had pulmonary hypertension identified by echocardiography, without significant cardiac disease or lung disease evident upon pulmonary function testing. In fact, at the initial stages of pulmonary hypertension, symptoms may be absent or may be quite unspecific, causing this diagnosis to be missed or delayed.

Doppler echocardiography is a sensitive and non-invasive method of detecting cardiac abnormalities and systolic and/or diastolic function and for detecting pulmonary hypertension.

There have been no studies from the Indian sub continent on the prevalence of left ventricular filling abnormalities and pulmonary hypertension in Rheumatoid arthritis patients. So we decided to study these parameters and investigated whether they correlate with the disease duration.

AIMS AND OBJECTIVES

1. To study the prevalence of cardiovascular manifestations using echocardiography in rheumatoid arthritis (RA) patients without clinically evident cardiovascular manifestations.

2. To evaluate the left ventricular filling abnormalities, analyzing transmitral flow in rheumatoid arthritis (RA) patients without clinically evident cardiovascular manifestations with special regard to disease duration.

3. To study the prevalence of pulmonary hypertension using Doppler echocardiography in rheumatoid arthritis (RA) patients without clinically evident cardiovascular manifestations and to correlate it with the duration of disease.

REVIEW OF LITERATURE

Historical review:

The delineation of Rheumatoid Arthritis (RA) as a disease entity in the contemporary medical literature began to emerge in the 18 th century. It was Alfred Baring Garrod (1859) who first used the term Rheumatoid arthritis.

In the early days of modern medicine, RA like other diseases of unknown causes was thought to result from foci of infection. (Hunter 1901: Wilcox 1935). The microscopic observation of fibrinoid changes in rheumatoid joints and nodules prompted Klemperor et al in 1942 to consider that the disease might result from diffuse primary degeneration of collagen. This led to the inclusion of RA in the group of connective tissue diseases, however this theory was hampered by the observations that the hydroxyproline and collagen content of the subcutaneous nodule was normal.

The discovery by Waaler (1940) of IgM Rheumatoid factor in the blood of patients was the first immunological marker of rheumatoid disease to be recognized. Examinations of ancient medical literature and mediaeval paintings have yielded evidence of RA prevalent in those periods.

Prevalence:

The prevalence of RA is approximately 0.8 % of population (range 0.3 to 2.1%): women are affected approximately three times more often than men. The prevalence increases with age, and sex differences diminish in the older age groups. RA is seen throughout the world and affects all races. However, the incidence and severity seem to be less in rural sub Saharan Africa and in Caribbean blacks. The onset is more frequent during the fourth and fifth decades of life, with 80 % of all patients developing the disease between the ages of 35 and 50.

Genetic Factors:

Family studies indicate a genetic predisposition. Approximately 10 % of patients with RA will have an affected first degree relative. Moreover monozygotic twins are at least four times more likely to be concordant for RA than dizygotic twins. The class II major histocompatibilty complex allele HLA-DR4 and related alleles are known to be major genetic risk factors for RA. In some groups, including Asian Indians like ours, however there is no association between the development of RA and HLA-DR4. In these

individuals there is an association between RA and the closely related HLA-DR1.

Additional genes in the HLA-D complex may also convey altered susceptibility to RA. Certain HLA-DR alleles, including HLA-DR5, HLA-DR2, HLA-DR3 and HLA-DR7 may protect against the development of RA in that they tend to be found at lower frequency in RA patients than in controls. Moreover, polymorphisms in the tumor necrosis factor (TNF) and the interleukin (IL) 10 genes are also associated with RA, as is a region on chromosome 3 (3q13).

Environmental factors:

A number of possible causative agents have been suggested, including Mycoplasma, Epstein-Barr virus, Cytomegalovirus, parvovirus and rubella virus. The mechanism by which these produce damage is not clear, probably by producing persistent infection of articular structures and by acting as super antigens. Of all the potential environmental structures, the only one clearly associated with the development of RA is cigarette smoking.

Pathology and Pathogenesis:

The precise mechanism by which bone and cartilage destruction occurs has not been completely resolved. Although the synovial fluid contains a number of enzymes potentially able to degrade cartilage, the majority of destruction occurs in juxtaposition to the inflamed synovium or pannus. This vascular granular granulation tissue is composed of proliferating fibroblasts and a variable number of mononuclear cells and produce a large number of degradative enzymes, including collagenase and stromelysins. The cytokines IL-1 and TNF play an important role in stimulating the cells of the pannus to produce proteases. These cytokines may contribute to the local demineralization of bone by activating osteoclasts. Systemic manifestations of RA can be accounted for by release of inflammatory molecules from the synovium. These include IL-1, TNF, IL-6, which account for many of the manifestations of active RA.

Clinical Manifestations:

Articular Disease:

Pain in the affected joints, aggravated by movement, is the most common manifestation of established RA. Generalized stiffness is frequent and is usually greater after periods of inactivity. Morning stiffness of greater than 1- hour duration is an almost invariable feature of inflammatory

arthritis and may serve to distinguish from non- inflammatory joint disorders.

Clinically, synovial inflammation causes swelling, tenderness and limitation of motion. Pain originates predominantly from joint capsule, which is abundantly supplied with pain fibers and is markedly sensitive to stretching or distention. Joint swelling results from accumulation of synovial fluid, hypertrophy of the synovium and thickening of the joint capsule.

Although inflammation can affect any diarthroidal joint, RA most often causes symmetric arthritis with characteristic involvement of certain specific joints such as the proximal interphalangeal and metacarpophalangeal joints. The distal interphalangeal joints are rarely involved. Axial involvement is limited to the upper cervical spine. Involvement of lumbar spine is not seen, and lower back pain cannot be ascribed to RA. On occasion, inflammation from the synovial joints and bursae of the upper cervical spine lead to atlantoaxial subluxation. With persistent inflammation, a variety of characteristic changes are seen, particularly in the hands.

1. Radial deviation of the wrist with ulnar deviation of the digits, often with palmar subluxation of the proximal phalanges. (“Z” deformity)

2. Hyperextension of the proximal interphalangeal joints with compensatory flexion of the distal interphalangeal joints. (Swan neck deformity)

3. Flexion contractures of the proximal interphalangeal joints and extension of the distal interphalangeal joints. (Boutonniere deformity)

4. Hyperextension of the first interphalangeal joint and flexion of the first metacarpophalangeal joint.

5. Typical joint changes in the foot, including eversion at the hind foot, plantar subluxation of the metatarsal heads, widening of the forefoot hallux valgus and lateral deviation and dorsal subluxation of the toes.

The 1987 Revised Criteria for the classification of RA

CRITERIA	DEFORMITY
a. Morning stiffness	**Stiffness in and around the joints lasting 1 hour before maximal improvement**
b. Arthritis of three or more joint areas	**At least three joint areas observed by a physician simultaneously- right or left Proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle and metatarsophalangeal joints.**
c. Arthritis of hand joints	**Arthritis of wrist, metacarpophalangeal or proximal interphalangeal joint.**
d. Symmetric arthritis	**Simultaneous involvement of the same joint areas on both sides of the body.**
e. Rheumatoid nodules	**Subcutaneous nodules over bony prominences, extensor surfaces or juxtaarticular regions observed by a physician**
f. Serum Rheumatoid Factor	**Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.**
g. Radiographic changes	**Typical changes of RA on postero anterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.**

Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).

Patients with two or more clinical diagnosis are not excluded.

In 1987, the American College of Rheumatology developed revised criteria for the classification of RA. These criteria demonstrate a sensitivity of 91 to 94 % and a specificity of 89% for the diagnosis of RA. Although these criteria were developed as a means of disease classification for investigational purposes, they can be useful as guidelines for establishing the diagnosis.

Extraarticular Manifestations:

Extra articular manifestations may precede the onset of articular symptoms. Predictors for the development of extra-articular manifestations include severe joint disease, a positive antinuclear antibody assay, IgA (but not IgG or IgM) RF, rheumatoid nodules, and certain *HLA-DR* haplotypes [8]. Rheumatoid arthritis is a systemic disease with a variety of extraarticular manifestations.

Rheumatoid Nodules:

This develops in 20 to 30 % of patients with rheumatoid arthritis. They are usually found on periarticular structures, extensor surfaces

or other areas subjected to mechanical pressure, but they can also develop elsewhere, including the pleura and meninges. Common sites include the olecranon bursa, the proximal ulna, the Achilles tendon and the occiput.

Skin Abnormalities:

Livedo reticularis is a blotchy, erythematous to purplish discoloration of the skin due to the presence of an obliterative cutaneous capillaropathy. This lesion is sometimes associated with the antiphospholipid-antibody syndrome; a hypercoagulable state linked to antiphospholipid antibodies and characterized by recurrent vascular thrombosis and second trimester miscarriages.

Rheumatoid arthritis is one of the causes of pyoderma gangrenosum, a necrotizing, ulcerative, noninfectious neutrophilic dermatosis. Sweet's syndrome, a neutrophilic dermatosis usually associated with myeloproliferative disorders, viral infections, and drug reactions, also occurs in rheumatoid arthritis.[9] Other complications include erythema nodosum, lobular panniculitis, atrophy of digital skin, palmar erythema, diffuse thinning (rice paper skin), and skin fragility.

Hematological Abnormalities:

a. Anemia- Iron utilization is impaired.

Iron deficiency

Reduced Erythropoeitin

It is normally normocytic and normochromic, unless complicated by blood loss, poor nutrition, hemodilution, intercurrent infections.

b. Thrombocytosis and thrombocytopenia

c. Eosinophilia

d. Lymphadenopathy

Felty's syndrome:

This is defined as a combination of rheumatoid arthritis in combination with splenomegaly and leukopenia. The syndrome occurs in patients with long-standing, seropositive, nodular, deforming RA. There is also increased risk of bacterial infections and lymphoproliferative and other malignancies.

Renal Manifestation

Renal disease is rare in patients with rheumatoid arthritis. When it does occur, it is often related to treatment with nonsteroidal anti-inflammatory

drugs (NSAIDs), cryoglobulinemia, or vasculitis. Renal manifestations include glomerulonephritis, azotemia, interstitial nephritis, and papillary necrosis. Patients with secondary renal amyloidosis due to long-standing chronic inflammation may have proteinuria. [10].

Hepatic Abnormalities:

Active RA may be associated with an increase in liver enzymes. (Especially serum aspartate aminotransferase and alkaline phosphatase). Liver involvement varies from portal fibrosis to nodular regenerative hyperplasia.

Eye Abnormalities:

The Rheumatoid process involves the eye in less than 1% of patients.

a. Episcleritis
b. Scleritis
c. Scleromalacia Perforans

Rheumatoid Vasculitis:

It is seen in patients with severe RA and high titers of circulating Rheumatoid factor. In its most aggressive form, rheumatoid vasculitis can cause polyneuropathy and mononeuritis multiplex, cutaneous ulcerations and dermal necrosis, digital gangrene and visceral infarction. Myocardial Infarction secondary to rheumatoid vasculitis has been reported, as has vasculitic involvement of lungs, bowel, liver, spleen, pancreas, lymph nodes and testes.

Pleuropulmonary Manifestations:

Interstitial pulmonary fibrosis

Pleural disease

Pleuritis with or without effusion

Sterile or septic empyema

Necrobiotic rheumatoid nodules associated with bronchopleural fistula

Pyopneumothorax

Rheumatoid (Necrobiotic) Nodules; Pneumoconiotic nodules (Caplan's syndrome)

Bronchiolitis obliterans organizing pneumonia (BOOP)

Airway disease

- Bronchiolitis obliterans
- Follicular bronchiolitis
- Bronchiectasis
- Upper airway dysfunction secondary to cricoarytenoid arthritis

Respiratory tract infection, especially typical and atypical tuberculosis

Drug induced lung disease

- Penicillamine
- Methotrexate
- Gold

Apical Fibrobullous disease

Thoracic cage immobility

Pulmonary vascular lesions

Pulmonary Hypertension- Primary and secondary to lung disease

Cardiac Manifestations:

Cardiac involvement occurs in the majority of patients with seropositive rheumatoid arthritis. The most common manifestation is pericarditis. Although symptomatic pericarditis is relatively uncommon, both random electrocardiographic evaluation in patients with RA and

autopsy studies reveal evidence of pericardial inflammation in 50% of patients. Although it is usually asymptomatic, rheumatoid pericarditis can be associated with pericardial effusion and the development of acute or chronic pericarditis with tamponade. The restrictive pericarditis of rheumatoid arthritis responds poorly to medical therapy and generally requires pericardiectomy. Pericarditis usually occurs in seropositive patients with nodules.

Myocardial disease resulting from nodular granulomatous lesions or more diffuse fibrosing lesions has been seen in RA. Non-specific myocarditis is usually a symptomatic and rarely affects cardiac size or function. Male patients with RA may suffer a greater frequency of congestive cardiac failure than persons without RA, and even in a symptomatic patient, left ventricular diastolic function more often impaired than in those without RA in spite of normal left ventricular systolic function. Abnormalities in the conduction pathways have also been described. Endocardial involvement may be diffuse, but it is rarely clinically significant.

Echocardiographic evidence for some degree of valve involvement is detected in about 30% of patients, but it is usually hemodynamically insignificant. Lesions typical of RA in the absence of symptomatic cardiac

disease include posterior pericardial effusion, aortic root abnormalities and valvular thickening. However, a few patients develop valvular incompetence. Coronary arteritis can occur as part of systemic rheumatoid arthritis. Because myocardial and endocardial diseases associated with RA is usually a result of vasculitis and nodule formation, appropriate treatment of the underlying disease is necessary. RA itself may be an independent risk factor for coronary artery disease. It has been suggested that coronary artery disease may be associated with monoclonal proliferation of CD4 + CD 28 null T cells in patients with or without RA in the absence of vasculitis- another mechanism by which coronary ischemia can occur.

Long-term survival of patients with rheumatoid arthritis (RA) is shorter compared with the general population or control subjects without RA.[1] Among the different causes of death, increased mortality from heart disease with high prevalence of congestive cardiac failure was reported in many studies.[1, 2] However, cardiac disease is often clinically silent and is rarely a severe life threatening complication in RA. Cardiac failure is the result of either systolic or diastolic dysfunction or both. Left ventricular diastolic dysfunction is usually attributable to common structural abnormalities such as hypertrophy or interstitial fibrosis and impaired myocyte relaxation resulting from ischemia.

Diastolic dysfunction is defined as the deterioration of the ventricular filling capacity without any compensatory increase in the left atrial pressure. [11] Another definition is the abnormal ventricular filling defect causing cardiac output inadequacy. [12] In patients with diastolic dysfunction, the deterioration of ventricular dilatation (early diastole), decrease in compliance (early late diastole) or an external pressure in pericardium can lead to problems in ventricular filling. Cardiomyopathies, constructive pericarditis, ischemic heart diseases, volume overload (mitral insufficiency, arteriovenous fistulae), mitral and tricuspid valve stenosis may cause diastolic dysfunction. [13, 14]

In echocardiography, there are various methods measuring diastolic dysfunction. The early diastolic filling wave ‘E’, subsequently the deceleration phase and then the ‘A’ wave formed as a result of the atrial contraction are determined during the diastolic phase. [15]

Most researchers have measured the peak velocity of the E wave and the A wave by transmitral pulsed-wave Doppler and calculated the relation between these two parameters as the rate of E/A. When taken alone, normally E/A is bigger than 1; in late relaxation it decreases to below 1 and this is an indicator of diastolic dysfunction. [16, 17] The E/A rate can be

measured as below 1 especially in most of the people over the age of 60–70 years. [15]

The reasons of diastolic dysfunction in RA cannot yet be fully explained. It is thought to be linked with myocardial ischemia or cardiac autonomic neuropathy caused by cardiovascular disease, which is common in RA. Additionally, it is thought that in patients with RA, pericardial perfusion may cause diastolic filling defects by exerting external pressure on ventricles. In autopsy studies on RA, non-specific myocarditis, granulomatous lesions, secondary amyloidosis and coronary vasculitis were reported. These lesions may deteriorate the left ventricular diastolic filling. Prospective studies proved that long-lasting diastolic dysfunction increases the rate of mortality due to cardiac insufficiency. In a study assessing diastolic filling functions by calculating the rate of isovolumetric relaxation period and peak filling, a significant deterioration was detected in left ventricular filling in patients with RA, when compared with the control group. [18]

Some studies have shown that cardiovascular disease is the commonest cause of premature mortality in patients with rheumatoid arthritis (RA) [19]. In RA, the risk of death caused by cardiovascular disease was considered to be doubled compared with an age-matched population

[20.] Additional reports have confirmed an increased prevalence of cardiovascular complications in patients with RA [21, 22]. del Rincon et al [21] have observed that the higher incidence of cardiovascular complications in these patients was independent of the influence of traditional cardiovascular risk factors. With respect to this, they have recently confirmed the presence of endothelial dysfunction in long-term, actively treated patients with RA [23]. As vascular endothelial dysfunction is closely linked to the development of atherosclerosis, this finding may, at least in part, explain the increased mortality observed in these patients [23.]

Besides coronary complications, classic studies showed a high prevalence of congestive heart failure in RA [2, 23]. A high incidence of myocardial, endocardial, and pericardial involvement also was reported in necropsy studies [2]

It is hypothesized that the systemic inflammation associated with rheumatoid arthritis (RA) promotes an increased risk of cardiovascular (CV) morbidity and mortality. In a population-based study from Mayo clinic of the risk of congestive cardiac failure in rheumatoid arthritis patients, they found that compared with persons without RA, patients with RA have twice the risk of developing CHF. This excess risk is not explained by traditional CV risk factors and/or clinical ischemic heart disease. [24]

Thirteen years ago, Finnish investigators showed abnormalities in left ventricular diastolic function in 12 young men with RA without clinically evident cardiac disease compared with 14 healthy controls [18.] Later, Italian investigators described the presence of diastolic abnormalities in both men and women with RA [25]. Diastolic dysfunction was observed despite normal left ventricular systolic function, compared with matched controls. Abnormal relaxation was mainly responsible of the impairment in left ventricular filling [25].

More recently, a different group reported the presence of diastolic dysfunction in 32 Italians with RA without clinically evident cardiac disease [26]. Similar abnormalities have been observed in patients with ankylosing spondylitis and psoriatic arthritis [27, 28]. Thus, primary diastolic dysfunction is a finding that is present in different chronic inflammatory rheumatic diseases.

Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction [29], knowledge of this complication in patients with RA without clinically evident cardiac disease may be important to improve patient survival. A

correlation between diastolic dysfunction and disease duration in active patients with RA has also been reported in one study. [30.]

In literature, rheumatoid valvular involvement was reported as 6–62% in autopsy series. [31] In a study performed with the aim of determining the aetiologies of 1051 patients, who underwent surgery due to mitral stenosis, RA was detected only in two patients (less than 1%). [32] Thus, valvular involvement in RA usually is asymptomatic and number of cases that require surgery is relatively limited. In a study of RA patients for the determination of valvular involvement, the rate of mitral valvular involvement was 40%, aortic valve involvement 20% and variations in the aortic root was 34.3% and all these findings were evaluated to be significantly higher than the control group. [33] In another study, it was observed that there was no significant relation between valvular involvement and the disease duration. [34] In another research, it was detected that 25% of the patients with RA suffer from valvular involvement and it was found that especially the patients with valvular involvement had high levels of (66%) IgG anticardiolipin antibodies, but there was no significant difference in terms of valvular involvement between patients whose anticardiolipin antibodies were positive and negative. [35]

Conduction defects were reported in rates of 8–10% in various studies. [34] In these studies, complex or different levels of heart blocks were defined. In postmortem studies, mononuclear cell infiltration, significant vascular degeneration and moderate fibroelastosis were detected in the conduction system. [36] On the other hand, though rarely, atrioventricular blocks may develop as a complication of methotrexate and chloroquine therapies. [37, 38] Nevertheless, methotrexate therapy can cause ventricular tachycardia. [39] In a study with a 24-hour ECG monitorization, arrhythmias were detected in 43 of 70 patients with RA, whereas arrhythmias were reported to be detected only at a rate of 6–8% with 12-leads standard ECG.

Pulmonary hypertension in Rheumatoid arthritis may be secondary to pulmonary fibrosis (derived from its structural alterations and chronic hypoxia) and to hyperviscosity [40] or it may occur isolated, similarly to primary pulmonary hypertension.

Pulmonary hypertension has been observed in patients with RA [7]. Using Doppler echocardiography, a pulmonary artery pressure of 30 mm Hg

or greater was found in 45 (31%) of 146 unselected patients with RA in England [7]. In that series 21% of the patients had an estimated pulmonary artery systolic pressure of 30 mm Hg or greater without clinically evident cardiac disease [7].

With this background, we did a study to study the prevalence of echocardiographic abnormalities, diastolic dysfunction and pulmonary hypertension in rheumatoid arthritis patients and correlated them with the disease duration.

MATERIALS AND METHODS

The study was carried out on 45 patients (nine men and 36 women, mean (SD) age 34.8 (6.7), range 21-50 years) attending the rheumatology out patient department of Madras Medical College and General Hospital with an established diagnosis of RA, as defined by the American Rheumatism Association 1987 criteria. Duration of the disease ranged from 1 to 17 years. Informed consent was obtained from subjects enrolled and the study was approved by the local ethics committee. 45 normal subjects (nine men and 36 women, mean (SD) age 35.4 (6.5), range 23-52 years) were selected as controls.

None of the subjects included in the study had evidence of cardiac disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, pulmonary tuberculosis or pulmonary thromboembolism as assessed by history, physical examination, Chest radiography and standard 12-lead ECG. In view of the radiation exposure involved in the study, patients were excluded if they were pregnant or planning a pregnancy. Patients with moderate mitral regurgitation, mitral stenosis or a left ventricular ejection

fraction below 64% were considered to have a cardiac cause for their PASP and so were excluded.

All had been treated with nonsteroidal anti-inflammatory drugs (diclofenac, 100-150 mg/day) daily. All of them have been treated and were in treatment with 1 or more DMARD, including chloroquine, sulphasalazine, and methotrexate. Treatment with a DMARD was initiated when a diagnosis of RA was made.

Patients were considered seropositive if the rheumatoid factor (by nephelometry) was positive on at least 2 separate occasions during the course of the disease.

A questionnaire prepared noted the duration of RA, extra-articular complications, the use of current and previous disease-modifying drugs, corticosteroid use, and early morning joint stiffness. Questions were asked relating to previous chest disease, cough, dyspnea, sputum production, chest pain, weight loss and risk factors for respiratory disease, including smoking, medications, domestic pets and occupation. Cigarette consumption was evaluated in pack years (1 pack yr = 20 cigarettes/day for 1 yr). A detailed

clinical examination was performed. All patients had venous blood taken for full blood count, renal and liver function, C-reactive protein and plasma proteins. Immunological investigations included rheumatoid factor (latex agglutination test) and antinuclear antibodies.

All patients underwent echocardiography, Electrocardiogram (ECG), chest radiography, High Resolution Computerized Tomography (HRCT) and full pulmonary function testing (PFT). Patients with pulmonary hypertension without significant lung disease were also evaluated for the presence of anticardiolipin antibodies.

Echocardiography:

Two-dimension and M mode echocardiography was performed with the patient in the left lateral position, using ALOKA echocardiogram. One senior cardiologist performed the echocardiography. Whenever possible, this cardiologist, who was blinded to clinical details, determined pulmonary artery pressure. The following variables were assessed: aortic root diameter, left atrial diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, thickness of the interventricular septum,

thickness of the left ventricular posterior wall, and right ventricular end-diastolic diameter. Fractional shortening and ejection fraction were calculated according to Simpson's formula.

Special attention was paid to the structure of the mitral, aortic, tricuspid, and pulmonary valves (different grades of regurgitation and stenosis were assessed), and the pericardial space to detect pericardial effusion.

Doppler echocardiography was used to obtain transmitral flow from the apical four-chamber view. To record transmitral flow the sample volume was positioned at the tip of the leaflets of mitral valve. The following variables were examined as parameter of left ventricular filling: Peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio, and isovolumic relaxation time (IVRT). When taken alone, normally E/A is bigger than 1; in late relaxation it decreases to below 1 and this is an indicator of diastolic dysfunction. [16, 17] We have taken E/A ratio of less than 1 as suggestive of diastolic dysfunction.

Tricuspid regurgitation was identified in continuous-wave mode at the apex. The peak instantaneous drop in systolic pressure from the right ventricle to the atrium was calculated from the peak signal velocity of the tricuspid regurgitant signal by the simplified Bernoulli equation, $\Delta P=4v2$, where ΔP is the trans-tricuspid gradient and v is the peak velocity measured.

The final estimate of the pulmonary artery systolic pressure was obtained by adding the patient's jugular venous pressure to the estimate of the trans-tricuspid gradient [41].

Pulmonary function tests:

Pulmonary function tests comprised spirometry, static lung volume and flow loops. In all cases the pulmonary function tests were performed on the same day as the echocardiogram.

Definitions

Pulmonary hypertension:

The gold standard for pulmonary artery pressure measurement is invasive right-heart catheterization. Pulmonary hypertension, defined by

right-heart catheterization of the pulmonary artery is a pressure of 20 mmHg or greater at rest and at least 30 mmHg during exercise [42.]

Echocardiography has now been used widely in patients with cardiac disease. Reported correlations between Doppler and catheter measurements range from 0.89 to 0.97; the average standard error for systolic pulmonary artery pressure ranges from 5 to 9 mmHg, and interobserver variability is <3% [43-45.] Similar to the study by Dawson et al, we have taken Denton et al.'s definition of pulmonary hypertension on Doppler echocardiography as an estimated PASP of 30 mmHg or greater.

Significant lung disease:

Significant lung disease that could be causing pulmonary hypertension was defined as pulmonary function measurements outside the normal range: a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio of less than 65% or a vital capacity lung volume of less than 80% of the predicted value [46,47].

Pulmonary artery pressure control group:

For the normal population, limited data are available on pulmonary artery pressure estimated by Doppler echocardiography. A study of 20 normal healthy adults by Vachiery et al. [48] using Doppler echocardiography found that the maximum estimated pulmonary artery pressure was 24 mmHg

To assess the diagnostic validity of the results of the echocardiogram, a control group for echocardiogram readings was incorporated into the study. Patients with RA were excluded. Echocardiography was undertaken with the same ALOKA echocardiogram by the same cardiologist who performed the echocardiography in the patients with RA.

STATISTICAL ANALYSIS

Continuous data were described as mean and standard deviation (mean +/- SD), and categorical variables as numbers. Comparisons between 2 categories were made using Student t test (2 tailed) for continuous variables. To analyze categorical data we performed the chi square test. Pearson correlation was used to correlate the continuous variables like disease duration and pulmonary artery pressure and parameters of diastolic dysfunction.

RESULTS

The main demographic, clinical and laboratory features of the 45 patients with RA without clinical evidence of cardiovascular disease are shown in Table 1. Women outnumbered men. [Figure 1] The mean age at the time of diagnosis was 34.82± 6.67 years. During the course of the disease, extra-articular manifestations were observed in almost 58% (26) of the patients. Rheumatoid nodules were found in 10 patients, all of whom were rheumatoid factor positive.

Table 1 Demography, Clinical and Laboratory features of 45 patients with RA

Variable	Number (%)
Mean age at the time of study (yr) ± S .D	**34.82 ± 6.67**
Men/ Women	**9/36**
Proportion of men	**20 %**
Mean disease duration (yrs)	**5.07 years**
Extra articular manifestations	**26 (57.78%)**
Rheumatoid factor positive	**28 (62.22%)**

40 patients (88.89%) had sufficient Tricuspid regurgitation visible for their pulmonary artery pressure to be assessed by Doppler echocardiography. Contrary to the literature, Of note, only 1 patient with RA had mild pericardial effusion. The structural findings in for the RA patients are listed in table 2.

Table 2 Structural Findings found on Echocardiography of patients with RA

Finding on Echocardiogram	Number of Patients (%)
Aortic stenosis	**2 (4.4%)**
Aortic regurgitation	**7 (15.55%)**
Mitral regurgitation	**12 (26.67%)**
Pericardial effusion	**1 (2.2%)**
Tricuspid regurgitation	**40 (88.89%)**
Aortic root dilatation	**11 (24.44%)**

Main Echocardiographic and Doppler Finding in Patients With RA:

The main echocardiographic and Doppler findings in this series of patients with RA without clinical evidence of cardiovascular disease are summarized in Table 3. The mean values of diameters in the left cavities were within the normal ranges. It was also the case for the mean left ventricular ejection fraction (Table 3).

Nodules were present in the aortic valve in 5 patients. Mild aortic regurgitation was found in 7 (15.55%) of 45 patients (Table 2). 19 (42.22%) of the patients exhibited left ventricular diastolic dysfunction (E/A <1) due to impaired relaxation

Echocardiographic and Doppler Differences Between Patients With RA and Controls:

There was a significant difference between the two groups regarding the ventricular cardiac chamber dimensions, both end systolic and end diastolic compared to controls. ($p< 0.05$) But there was no difference between the ejection fraction and fractional shortening of the left ventricle.

In RA patients, we found abnormalities of left ventricular filling characterized by increased late diastolic mitral filling velocity A cm/s (76.92+ 11.62 vs. 70.11+ 5.33,p=0.001), prolonged isovolumic relaxation time ms (75.77+ 8.13 vs. 70.43+ 2.94, p=0.001) and by a reduced E/A ratio. (0.98+ 0.23 vs. 1.09 + 0.11,p= 0.004) compared to controls. (Table 3)

Moreover in the group of patients we found a relation between the isovolumic relaxation time and disease duration (r= 0.67, p=0.001), late diastolic mitral filling velocity A cm/s and disease duration (r= 0.61, p=0.001) and a negative correlation between the E/A ratio and disease duration. (r= -0.19, p=0.21) [Figure 2, 3, 4]

19 patients (42.22%) in the RA group had E/A ratio of less than 1and this was taken as an indicator of diastolic dysfunction. Among the control population, only 2 patients (4.44%) had evidence of diastolic dysfunction. Moreover the mean age of patients was 34.8 $\pm$ 6.7 years and this age cannot explain the diastolic dysfunction. The RA patients with evidence of diastolic dysfunction were then compared with RA patients with E/A ratio more than 1 and the results are summarized in table 4.

Table 3 ECHOCARDIOGRAPHIC AND DOPPLER VARIABLES IN PATIENTS AND CONTROL SUBJECTS

	PATIENTS N=45	CONTROLS N=45	P Value
Left Atrium Diameter (mm)	27.60 ± 4.47	24.96± 2.45	0.01
Aorta Diameter (mm)	29.91± 1.50	30.18± 1.15	0.35
Left Ventricular end diastolic dimension (mm)	50.04± 3.78	45.99± 3.42	0.001
Left Ventricular end systolic Dimension (mm)	30.48+2.47	29.04+2.29	0.005
Ejection Fraction (%)	70.72+ 2.26	70.58+ 1.94	0.75
Fractional Shortening (%)	38.32+ 3.29	39.07+ 3.37	0.22
Early Diastolic flow velocity E (cm/s)	73.32+ 9.04	76.32± 5.59	0.06
Late Diastolic flow velocity A (cm/s)	76.92± 11.62	70.11± 5.33	0.001
Isovolumic Relaxation Time (ms)	75.77± 8.13	70.43± 2.94	0.001
E/A	0.98+ 0.23	1.09 ± 0.11	0.004
Pulmonary Artery Pressure (mm of Hg)	27.49± 12.66	20.40± 8.88	0.003

Differences between Patients with RA with and without Left Ventricular Diastolic Dysfunction

To further investigate the implication of the left ventricular diastolic dysfunction in patients with RA without clinically evident cardiovascular disease, we assessed whether patients with RA who had left ventricular diastolic dysfunction had some clinical or investigational peculiarities that might help identify these patients.

Rheumatoid factor was significantly positive in patients with RA with left ventricular diastolic dysfunction (89.5% versus 42.3%; P=0.02). However, no statistically significant differences in sex, presence of extra articular manifestations, cumulative prednisone dose were found (data not shown). Also there was a significant difference in the estimated pulmonary artery systolic pressure between patients with and without left ventricular diastolic dysfunction (32.47$\pm$ 12.09 vs. 23.85$\pm$ 12, p=0.02).

Table 4 ECHOCARDIOGRAPHIC AND DOPPLER VARIABLES IN PATIENTS WITH AND WITHOUT DIASTOLIC DYSFUNCTION

	PATIENTS (N=19) [E/A < 1]	PATIENTS (N=26) [E/A > 1]	P Value
Left Atrium Diameter (mm)	27.26 ± 6.49	27.85± 2.17	0.67
Aorta Diameter (mm)	30.11± 1.91	29.77± 1.10	0.46
Left Ventricular end diastolic dimension (mm)	53.17± 2.33	47.75± 2.88	0.001
Left Ventricular end systolic Dimension (mm)	32.80±1.50	28.78+1.42	0.001
Ejection Fraction (%)	70.71+ 1.73	70.73+ 2.61	0.97
Fractional Shortening (%)	35.22+ 2.53	40.59+ 1.35	0.001
Early Diastolic flow velocity E (cm/s)	65.18+ 4.94	79.27± 6.24	0.001
Late Diastolic flow velocity A (cm/s)	87.85± 7.73	68.92± 6.10	0.001
Isovolumic Relaxation Time (ms)	83.57± 5.34	70.07± 3.94	0.001
E/A	0.75+ 0.09	1.15 ± 0.11	0.001
Pulmonary Artery Pressure (mm of Hg)	32.47± 12.09	23.85± 12.00	0.02

PULMONARY HYPERTENSION IN RA

All RA patients

Forty-five RA patients underwent all the investigations. 40 (88.8%) RA patients had sufficient tricuspid regurgitation visible for their pulmonary artery pressures to be assessed by Doppler echocardiography.

RA patients with raised pulmonary artery pressure

Twelve RA patients (26.7%) had a pulmonary artery pressure of more than 30 mmHg. [Table 5] No patient had impaired left ventricular function, as assessed by left ventricular ejection fraction, which could explain pulmonary hypertension. Chest HRCT showed that 4 patients had interstitial lung disease with a fibrosing alveolitis pattern. Among the 4 patients, in three of these patients the lung disease was sufficiently severe to cause significant volume loss (as defined above, under significant lung disease) on pulmonary function testing. Clinically, 3 patients (6.7 %) of the RA population studied had pulmonary hypertension that was secondary to lung disease. So the remaining (9) 20 % of patients had pulmonary

hypertension without lung disease evident on pulmonary function testing. [Table 6]

The clinical features of the patients with primary pulmonary hypertension without lung or heart disease were compared with those of RA patients who had a pulmonary artery pressure below 30 mmHg. The findings are shown in the table 7. Significant difference was found between the two RA groups in age and disease duration. Patients with pulmonary hypertension had a higher mean age (39.16+ 5.18) vs. patients without pulmonary hypertension (33.53+ 6.38, p= 0.008), and it was statistically significant. Patients with pulmonary hypertension also had higher mean duration of disease (10+ 4.67 vs. 5.18+ 3.31, p value = 0.003). No significant difference was found between the two RA groups when sex, smoking, corticosteroid treatment were compared. Also the acute phase response as assessed by C-reactive protein did not differ significantly between the two groups. We subsequently investigated the patients with primary pulmonary hypertension for the presence of anticardiolipin antibodies, but none of the patients tested was found to have a significantly elevated concentration (normal range, IgG 0–9 GPL U/ml, IgM 0–4 MPL U/ml).

In the control group, 2 patients (4.5%) had pulmonary artery pressure above 30 mm of Hg. Both these patients had no secondary lung or cardiac disease. The pulmonary artery systolic pressure was higher in patients with RA (27.49 +/- 12.66 mm Hg) than in controls (20.40 +/- 8.88) (P =0.003). Incidence of pulmonary artery systolic pressure >30 mm Hg indicating pulmonary hypertension was significantly higher in patients with RA (26.7 % versus 4.5 % in controls; P =0.03). [Table 7] Among these 3 patients (6.7%) had pulmonary hypertension that was secondary to lung disease. So the remaining 20 % of patients had pulmonary hypertension without lung disease evident on pulmonary function testing or cardiac disease. Among the 12 patients with pulmonary hypertension, 7 patients (15.6%) had pulmonary artery pressure more than 40 mm of Hg, while 5 patients (11.1%) had pulmonary artery pressure between 30 and 40 mm of Hg indicating mild pulmonary hypertension. Among the 7 patients, 3 patients had significant lung disease sufficiently severe to cause significant volume loss and hence pulmonary hypertension. So 4 patients (8.9%) had moderate pulmonary hypertension (> 40 mm of Hg) primarily due to RA.

There was also a strong correlation between the pulmonary artery pressure and the disease duration ($r= 0.68$, $p< 0.001$) and a relationship was found between the pulmonary artery pressure and the age of the patient ($r=0.32$, $p= 0.03$). [Figure 6 and 7]

Table 5 Pulmonary Artery Pressure in Rheumatoid Arthritis (RA) patients

Pulmonary Artery Systolic Pressure	Number of patients	Number of patients with Primary pulmonary hypertension
31-40 mm of Hg	5 (11.11%)	5 (11.11%)
41-50 mm of Hg	6 (13.33%)	3 (6.6%)
> 50 mm of Hg	1 (2.2%)	1 (2.2%)

Table 6 PFT/HRCT findings in RA patients

No of Patients	PFT/ HRCT findings	Pulmonary artery pressure
3	Obstructive/ Fibrosing Alveolitis pattern	42, 47, 44
1	Normal/ Fibrosing alveolitis pattern	48

PFT is Pulmonary Function tests

HRCT is high-resolution computerized tomography

Table 7 Characteristics of RA patients according to pulmonary artery pressure

(A) Continuous variables of RA patients

	Primary pulmonary hypertension (N=9)	Pulmonary artery pressure < 30 mm of Hg (N= 33)	P value
Age (yr) +/- SD	39.16+/-5.18	33.53+/-6.38	0.008
RA Duration (yr)	10+/-4.67	3.31+/-5.18	0.0003
Cigarette Pack yr	6.5+/-7.1	13.1+/- 14.2	0.21
C-reactive protein (mg/l)	30.2+/- 23.2	30.1+/- 24.1	0.72

(B) Discrete Variables of RA patients

	No of Patients with PPH (N=9)	No of Patients with PAP < 30 mm of Hg (N= 33)	P value
Rheumatoid Factor Positive	8	28	0.86
Anti nuclear antibody Positive	3	11	0.93

Table 8 Characteristics of RA patients and controls

	Patients	Controls	P value
Age (yr) +/- S.D	34.8 +/-6.7	35.4 +/-6.5	0.80
Sex/ No. Of men	9	9	1
PASP in mm of Hg	27.49 +/- 12.66	20.40 +/- 8.88	0.003
30-40 mm of Hg	5 (11.1%)	0	0.03
> 40 mm of Hg	7 (15.55%)	2 (4.4%)	0.03

Figure 1 Sex Distribution of RA patients

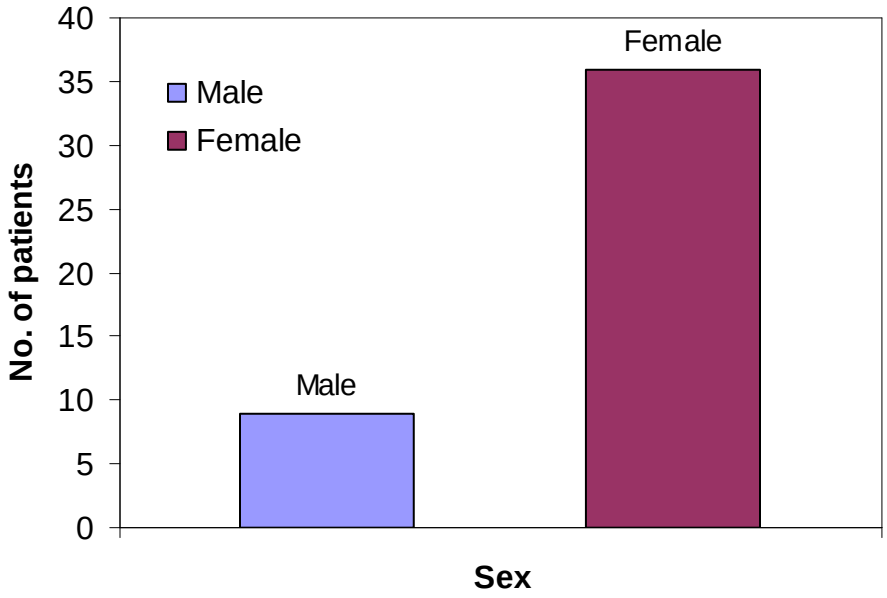
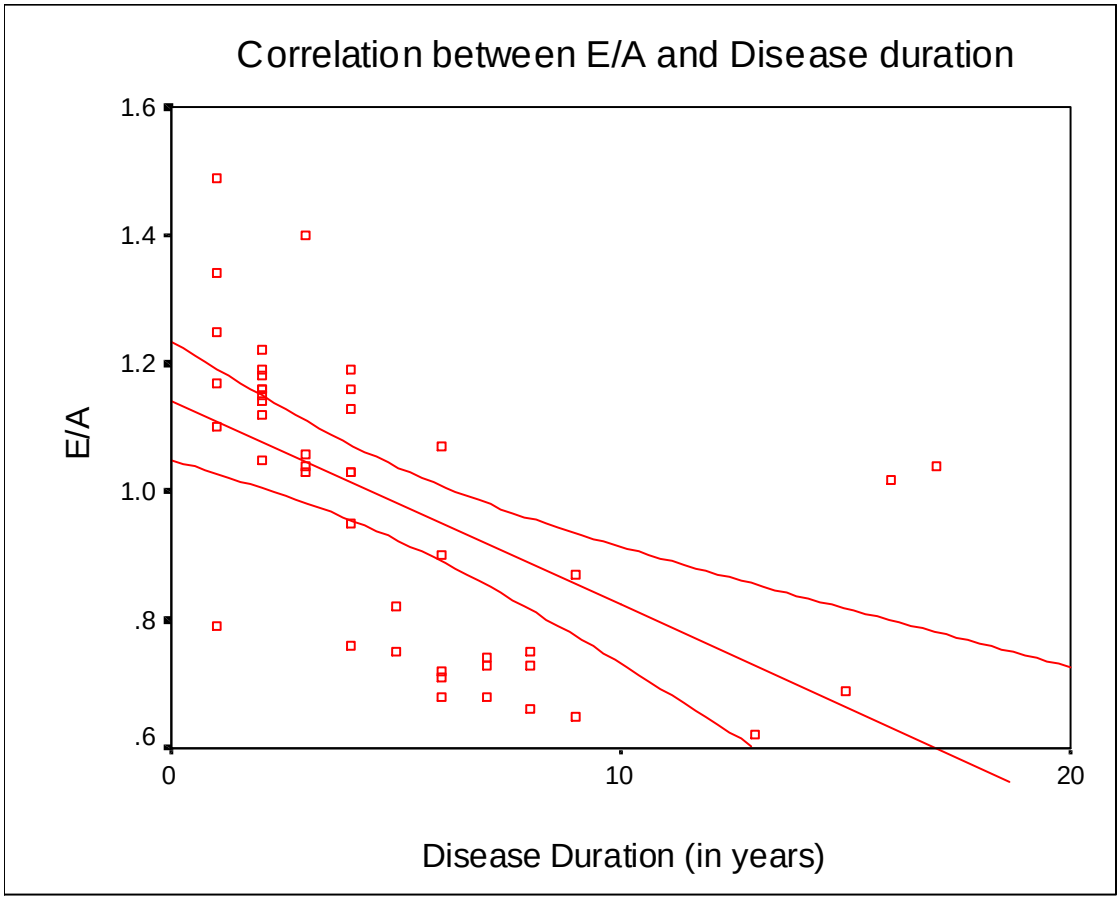


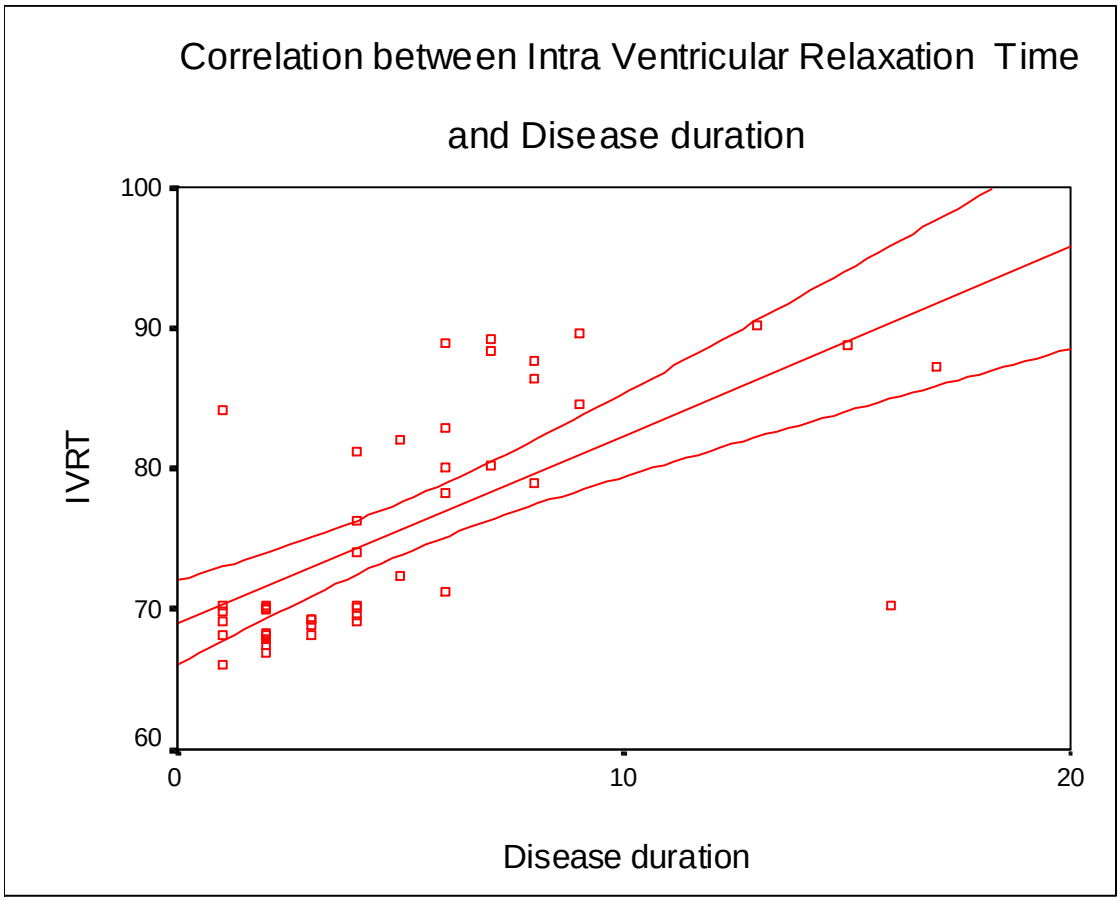
Figure 2 Correlation between Diastolic dysfunction and Disease Duration



Correlation coefficient r= -0.19

Slope p=0.21 (not significant)

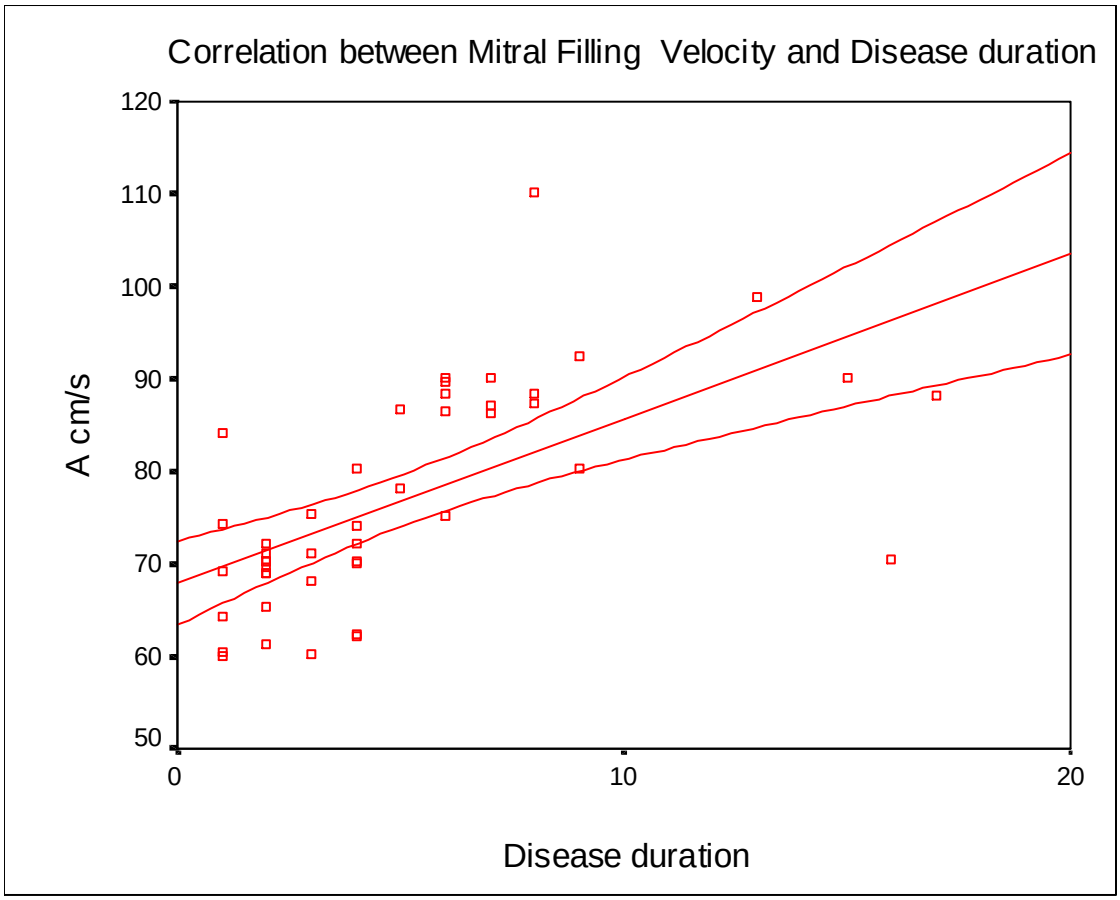
Figure 3 Correlation between Diastolic dysfunction (IVRT) and Disease Duration



Correlation coefficient r= 0.67

Slope p=0.001

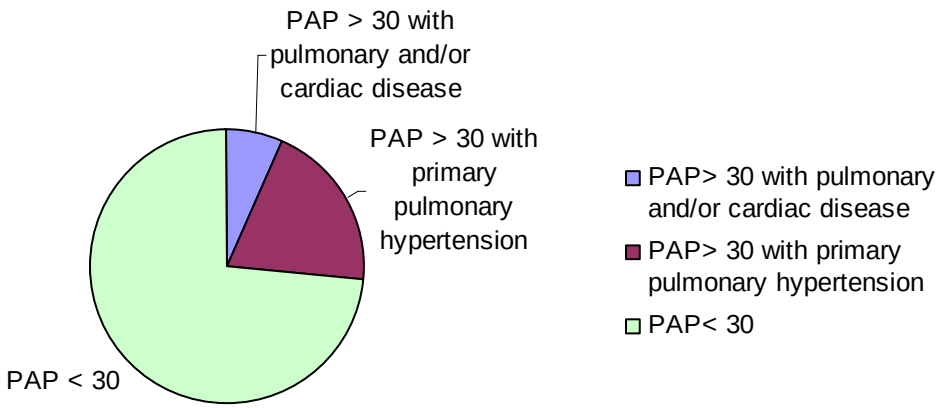
Figure 4 Correlation between Mitral Filling Velocity (A) and Disease Duration



Correlation coefficient r= 0.61

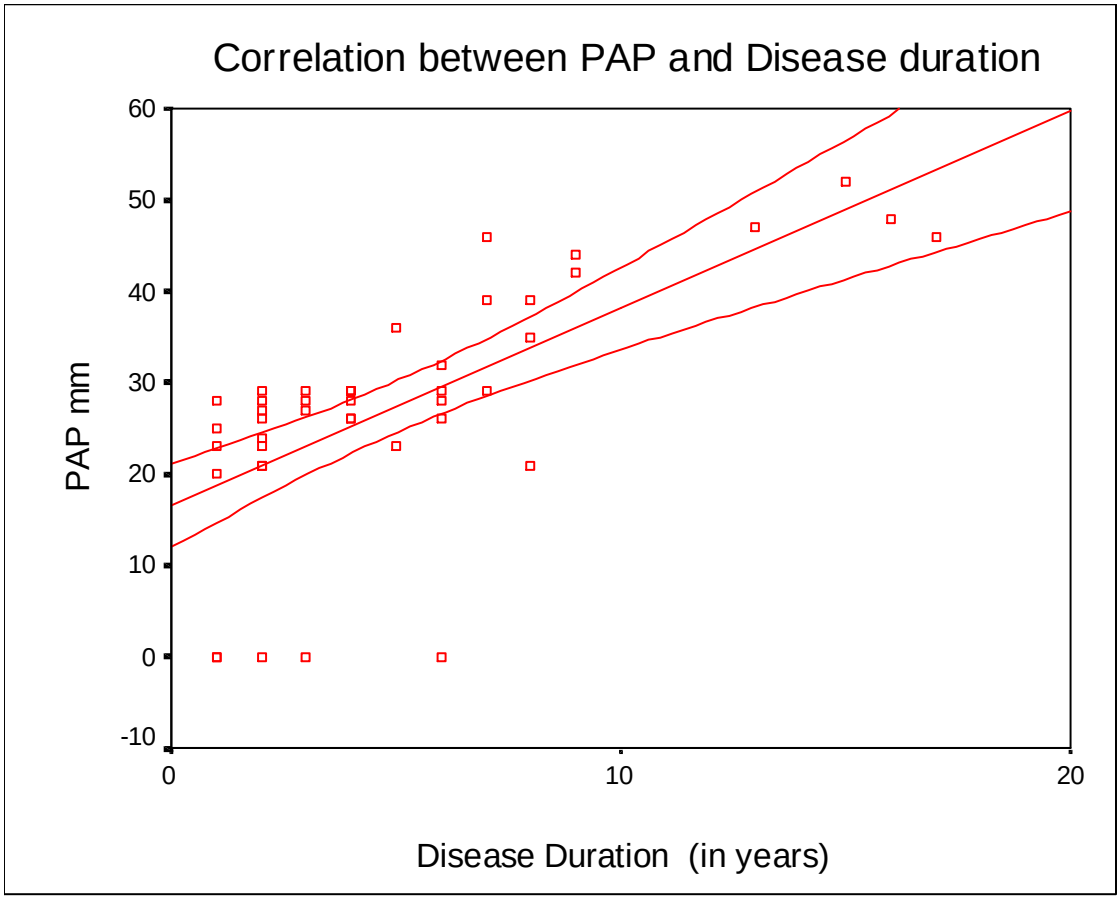
Slope p=0.001

Figure 5 Pulmonary Artery Pressure distributions in RA patients



PAP is Pulmonary artery pressure [9 patients (20 %) had Primary Pulmonary hypertension]

Figure 6 Correlation between pulmonary artery pressure and disease Duration

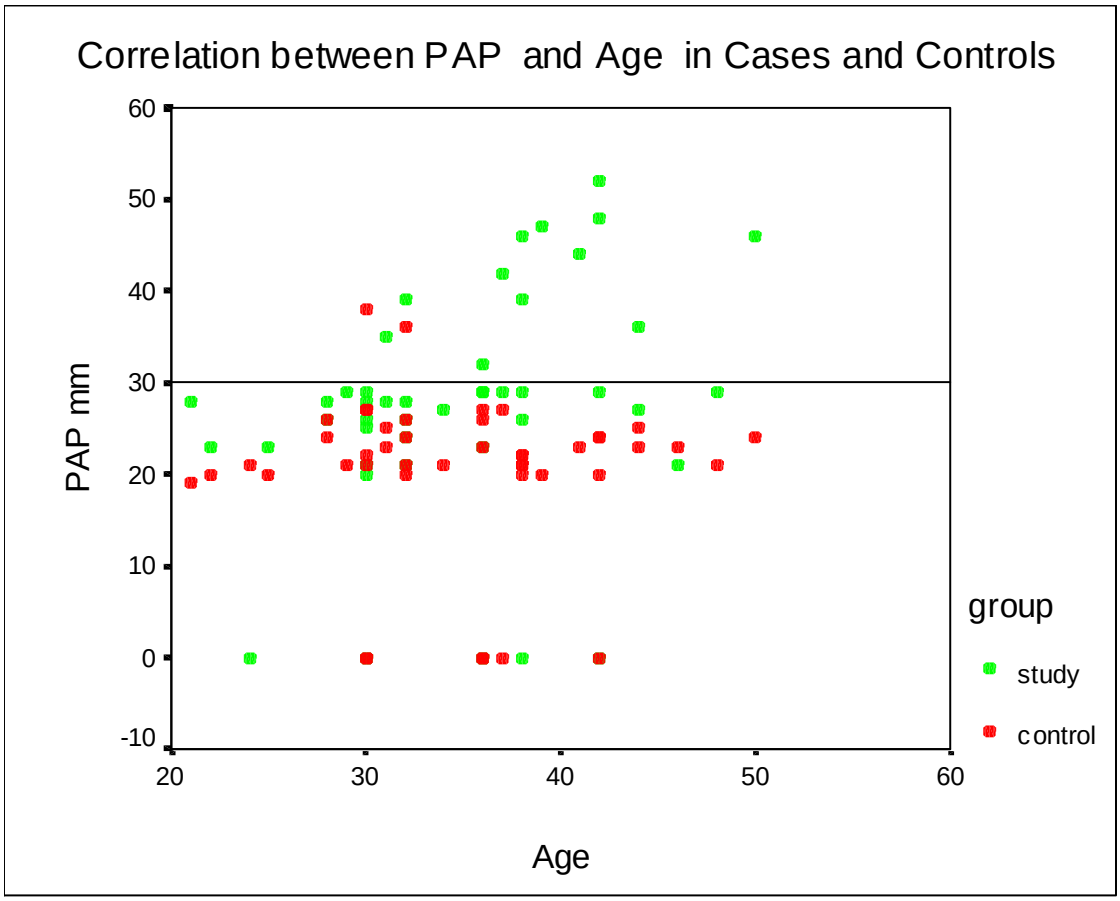


Correlation coefficient r = 0.68

Slope p < 0.001

PAP is Pulmonary artery Pressure

Figure 7 Correlation between pulmonary artery pressure and age



Correlation coefficient for study group r = 0.32

Slope p = 0.03

Correlation coefficient for control group r = -0.03

Slope p = 0.84 (not significant)

DISCUSSION

Cardiovascular Abnormalities in Rheumatoid Arthritis

In unselected patients with RA a wide spectrum of echocardiographic and Doppler abnormalities has been observed [7.] An important step forward in our understanding cardiovascular disease in RA may be to confirm whether cardiac abnormalities also are present in actively and uniformly treated patients with RA in whom underlying cardiac disease or concomitant cardiovascular risk factors that might be implicated in the development of cardiac abnormalities have been excluded.

In our study of patients with RA from South India without cardiovascular risk factors or clinically evident cardiac disease, a number of echocardiographic abnormalities were observed. Besides valvular involvement, left ventricular diastolic dysfunction was observed in 19 of 45 patients. (42.2%)

Diastolic dysfunction is defined as the deterioration of the ventricular filling capacity without any compensatory increase in the left atrial pressure. [11] Another definition is the abnormal ventricular filling defect causing cardiac output inadequacy. [12] In patients with diastolic dysfunction, the deterioration of ventricular dilatation (early diastole), decrease in

compliance (early late diastole) or an external pressure in pericardium can lead to problems in ventricular filling. Cardiomyopathies, constructive pericarditis, ischemic heart diseases, volume overload (mitral insufficiency, arteriovenous fistulae), mitral and tricuspid valve stenosis may cause diastolic dysfunction. [13, 14]

In echocardiography, there are various methods measuring diastolic dysfunction. The early diastolic filling wave 'E', subsequently the deceleration phase and then the 'A' wave formed as a result of the atrial contraction are determined during the diastolic phase. [15]

Most researchers have measured the peak velocity of the E wave and the A wave by transmitral pulsed-wave Doppler and calculated the relation between these two parameters as the rate of E/A. When taken alone, normally E/A is bigger than 1; in late relaxation it decreases to below 1 and this is an indicator of diastolic dysfunction. [16, 17]

Thirteen years ago, Finnish investigators showed abnormalities in left ventricular diastolic function in 12 young men with RA without clinically evident cardiac disease compared with 14 healthy controls [18]. Later, Italian investigators described the presence of diastolic abnormalities in both men and women with RA [25]. Diastolic dysfunction was observed despite normal left ventricular systolic function, compared with matched

controls. Abnormal relaxation was mainly responsible of the impairment in left ventricular filling [25].

More recently, a different group reported the presence of diastolic dysfunction in 32 Italians with RA without clinically evident cardiac disease [26.] Similar abnormalities have been observed in patients with ankylosing spondylitis and psoriatic arthritis [27,28]. Thus, primary diastolic dysfunction is a finding that is present in different chronic inflammatory rheumatic diseases.

Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction [29], knowledge of this complication in patients with RA without clinically evident cardiac disease may be important to improve patient survival. Similar to our study, a correlation between diastolic dysfunction and disease duration in active patients with RA has also been reported in one study. [30.]

Our results indicate that patients with RA have a different mitral flow velocity pattern compared to controls. In the patients we found an increased mitral flow velocity pattern at atrial contraction and a decreased E/A ratio. As the subjects were selected to clinically exclude loading alterations and other factors that can affect diastolic filling, there is no reason to think that the two groups are not homogeneous and comparable.

Thus our results confirm diastolic abnormalities in RA patients and also point out that these abnormalities also concern left ventricular filling detected by echo Doppler examination of transmitral flow.

What is the clinical outcome of such abnormalities? Diastolic dysfunction has been recognized as a primary cause of CCF. In RA patients, an increased prevalence of congestive cardiac failure is well documented. Such an increased morbidity does not seem to be related to hypertension or ischemic heart disease. It could be due to more extensive involvement of the heart with consequent changes in left ventricular structure that might manifest themselves in abnormalities of left ventricular diastolic function, afterwards leading to systolic dysfunction. As no specific tissue typing studies were performed in our patients, we can only guess that these diastolic abnormalities could be caused by left ventricular structural alterations (i.e. an increase or modification of interstitial connective tissue within the myocardium)

In autopsy studies of RA, pericarditis was detected at a rate of 30–50%, whereas the frequency of symptomatic pericarditis was reported only 2–10%. [31, 35] In a prevalence study, pericardial effusion was detected at a rate of 6%. Nevertheless, pericarditis is the most common type of cardiac involvement reported in the literature. Clinically, pericarditis was reported in

patients with high RF titers, subcutaneous nodules, anemia and high rate of sedimentation. [35] In a study of 39 patients, echocardiographic pericardial Involvement was detected in four patients; three of these had effusion, whereas one of them had pericardial adhesion. [49] In our study, pericardial effusion was detected in only 1 of 45 patients (2.2%). The reason could be that we see a different population and the susceptibility factors would be different.

In our study, we found a statistically significant correlation between disease duration and alteration of diastolic function expressed as late diastolic mitral filling velocity (A) and isovolumic relaxation time (IVRT). The relation between transmitral flow alteration and disease duration suggests a sub-clinical myocardial involvement with disease progression. This observation could be of a therapeutic benefit in sensitizing the doctors about the benefits of controlling the disease progression and periodic screening by echocardiography of RA patients.

Pulmonary Hypertension in Rheumatoid Arthritis

PHT is an increasingly recognized complication of the autoimmune rheumatic diseases, including RA [50.] The largest series belongs to Dawson et al [7], who screened 146 RA patients with DE and found that 31% had PHT. When the RA patients with cardiopulmonary diseases were excluded; the frequency of PHT became 21% — approaching our figure [7].

Concurrence of rheumatoid arthritis and pulmonary hypertension is not common in clinical practice. Pulmonary hypertension may be an extra-articular manifestation of rheumatoid arthritis or may be secondary to other diseases [51].

All our patients were submitted to high-resolution computed tomography of the thorax and spirometry. As none of these tests showed evidence of other causes for increased pulmonary artery pressure, we considered this patient as having pulmonary hypertension secondary to rheumatoid arthritis. Lung biopsy was not done since it may have harmful complications. Reported lung biopsies of pulmonary hypertension secondary to rheumatoid arthritis usually show a mixed pattern of hypertrophy and fibroelastic proliferation of the media and the intimae of small- to medium-sized pulmonary arteries [52]. In the absence of vasculitis, these histological

findings are identical to that of primary pulmonary hypertension [53.] Chest HRCT performed on these patients identified early fibrosing alveolitis in 4 patients in the pulmonary hypertension group. Without volume loss on pulmonary function testing, the fibrosing alveolitis is unlikely to be at a stage to be causing secondary pulmonary hypertension. Whether or not fibrosing alveolitis on HRCT predicts the rate at which pulmonary hypertension progresses are yet to be determined.

Doppler echocardiography is both sensitive and specific for the diagnosis of pulmonary hypertension [33, 54] However; recently Arcasoy et al [55] compared the PASP estimated by DE and measured by cardiac catheterization in 166 patients with advanced lung disease. Although the correlation was good ($r \sim 0.69$, $p < 0.0001$), they found that 52% of the PASP measurements using DE were inaccurate, and 48% of the patients were misclassified as having PHT if the diagnosis was based on DE alone. But his study was undertaken in patients with advanced lung disease and none of our patients had significant lung disease demonstrated on PFT/HRCT imaging. Impairment of left ventricular function can cause elevation of pressure on the left atrium and raise pulmonary artery pressure. It would seem unlikely that this is the cause of the raised pulmonary artery pressure, as patients with a reduced left ventricular ejection fraction have been excluded. As Doppler

echocardiography and cardiac catheterization have been reported to have a correlation of between 0.89 and 0.97 in cardiac causes of pulmonary hypertension [56, 57], we have not undertaken catheterization of our RA patients.

The limitations of our study were that other causes of possible primary pulmonary hypertension like porto-pulmonary hypertension, Human Immunodeficiency virus infections were not ruled out before ascribing pulmonary hypertension to be due to RA. HIV testing was not undertaken in view of the ethical considerations. How ever it would seem unlikely that this is the cause of the raised pulmonary artery pressure, as patients were asymptomatic for other features of this disease. Another limitation of our study was that we did not measure the serum viscosity, as pulmonary hypertension in RA has been rarely reported with hyperviscosity syndromes. [40]

One more significant new observation of our study, as compared to the study by Dawson et al was the statistically significant correlation between the disease duration and pulmonary artery pressure and age and pulmonary artery pressure. This difference could be attributed to the different race of population we see, where the involvement of the pulmonary vessels could be a manifestation as the disease duration increases and also

may be related to yet unidentified susceptibility genes in our population. RA patients with pulmonary hypertension were older compared to patients without pulmonary hypertension. Also a positive relationship between age and pulmonary artery pressure raises an issue whether pulmonary hypertension develops as the RA patients become older and as the disease duration increases. Also there was a statistically significant difference in disease duration also, probably indicating patients with pulmonary hypertension had a longer duration of the disease. Also surprisingly no correlation was observed between the pulmonary artery pressure and age in control population. [Figure 7]

This study continues to raise an important issue—we have found that 26.7% of hospital RA patients have pulmonary hypertension on echocardiography. In 6.7% of our RA patients this was due to lung disease. The remaining 20 % probably had primary pulmonary hypertension. Further research into the pathogenesis and progression of raised pulmonary artery pressure in RA patients is needed. It is possible that mild to moderate PHT may also contribute to the high incidence of cardiovascular related deaths in RA. The relationship between the pulmonary artery pressure and disease duration and age suggests a sub clinical involvement of the pulmonary

vasculature with disease progression and may be relevant to the high incidence of cardiovascular deaths observed in patients with RA. Long-term follow-up is obviously necessary to ascertain the impact of mild to moderate PHT on the prognosis and mortality rate of RA patients.

CONCLUSION

The following are the conclusions from the study

1. Cardiovascular manifestations are common in Rheumatoid arthritis patients.
2. The relation between transmitral flow alteration and disease duration suggests a sub-clinical myocardial involvement with disease progression and may be related to the high incidence of cardiovascular deaths in patients with RA.
3. The relationship between the pulmonary artery pressure and disease duration and age also suggests a sub clinical involvement of the pulmonary vasculature with disease progression and may be relevant to the high incidence of cardiovascular deaths observed in patients with RA

PROFORMA

CARDIOVASCULAR MANIFESTATIONS AND PULMONARY HYPERTENSION IN RHEUMATOID ARTHRITIS

AIM:

To study the prevalence of left ventricular filling abnormalities and pulmonary hypertension in patients with rheumatoid arthritis without clinically evident cardiovascular manifestations.

NAME:

AGE:

SEX:

DISEASE DURATION:

RHEUMATOID FACTOR:

SMOKING STATUS:

HISTORY OF PRESENTING COMPLAINTS:

1.	COUGH	YES/NO
2.	EXPECTORATION	YES/NO
3.	DYSPNEA	YES/NO
4.	ORTHOPNEA	YES/NO
5.	PND	YES/NO
6.	CHEST PAIN	YES/NO
7.	PALPITATIONS	YES/NO
8.	SYNCOPE	YES/NO
9.	CYANOSIS	YES/NO
10.	WEIGHT LOSS	YES/NO
11.	OTHER COMPLAINTS	YES/NO
12.	RAYNAUDS PHENOMENON	YES/NO

TREATMENT HISTORY:

1.	HISTORY OF NSAID INTAKE: HOW MANY YEARS	YES/NO
2.	HISTORY OF INTAKE OF DMARD: HOW MANY YEARS	YES/NO

GENERAL EXAMINATION

- Conscious
- Temperature
- Pallor
- Icterus
- Cyanosis
- Clubbing
- Lymphadenopathy
- Pedal edema

Pulse Rate: ***Blood pressure:***

EXAMINATION OF SYSTEMS

Cardiovascular System:

CHEST WALL DEFORMITIES:	YES/NO
MURMURS	YES/NO
ESM	YES/NO
EDM	YES/NO
PSM	YES/NO
RVH	YES/NO

Respiratory System:

INSPIRATORY CREPTS:	YES/NO
PLEURAL EFFUSION	YES/NO

Abdomen:

SPLENOMEGALY YES/NO

Central Nervous System:

INVESTIGATIONS

1. COMPLETE BLOOD COUNT

   Hemoglobin
   Total Count
   Differential Count
   ESR

2. C REACTIVE PROTEIN

3. BLOOD GLUCOSE

4. BLOOD UREA

5. SERUM CREATININE

6. SERUM ELECTROLYTES

7. LIVER FUNCTION TESTS

   Serum bilirubin- Total
   Direct
   Indirect
   SGOT
   SGPT
   SAP
   Serum Proteins- Total
   Albumin
   Globulin

8. ANA

9. ANTIPHOSPHOLIPID ANTIBODIES

10. X-RAY CHEST PA VIEW

12. ELECTROCARDIOGRAPY

13. HRCT

14. ECHOCARDIOGRAPHY (Inclusive of Doppler)

1. Left atrial enlargement
2. Right atrial enlargement
3. Aortic regurgitation
4. Aortic stenosis
5. Aortic root dilatation
6. Mitral regurgitation/Mitral valve prolapse
7. Pericardial effusion
8. Left ventricle ejection fraction (EF %)
9. Fractional shortening (FS %)
10. Tricuspid regurgitation
11. Transmitral flow velocity (E/A Velocity)
12. Wall motion abnormalities
13. Isovolumic relaxation time
14. Pulmonary artery pressure (PAP)

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ECHOCARDIOGRAPHIC MEASUREMENTS IN 45 RHEUMATOID ARTHRITIS PATIENTS

PATIENT S.NO	AGE	SEX	DURATION OF DISEASE (Years)	LEFT ATRIUM DIAMETER (mm)	AORTA (mm)	LVED (mm)	LVESD (mm)	EF %	FS %	E cm/s	A cm/s	E/A	IVRT (ms)	RF	PAP (mm of Hg)
1	44	F	5 YEARS	21	27	57.2	33.2	71	40.3	60.2	86.8	0.75	72.3	YES	36
2	38	F	8 YEARS	32	30	52.1	37.3	64.5	32.1	72.3	110.1	0.66	79	YES	39
3	36	F	6 YEARS	30	28	50.2	31.2	70	39.8	79	88.4	0.9	78.2	YES	32
4	24	F	2 YEARS	83	28	48.4	26.5	72	40.6	79.6	71.2	1.12	70.1	N0	0
5	22	F	1 YEAR	22	28	47.2	25.8	74	39.2	80.8	69.2	1.17	69.1	N0	23
6	44	M	3 YEARS	32	30	50.2	30.3	71	38.9	70.2	68.1	1.03	69.2	YES	27
7	36	M	4 YEARS	30	32	47.4	29.2	69	42.3	72.4	70.1	1.03	69.5	N0	29
8	28	M	2 YEARS	32	30	46.2	29.8	70	41.3	64.6	61.3	1.05	67.8	N0	26
9	30	F	6 YEARS	28	26	56.4	33.1	70	38.2	61.2	89.6	0.68	82.9	N0	0
10	32	F	7 YEARS	31	30	54.4	32.4	71	36.9	64.7	87.2	0.74	80.2	YES	39
11	30	F	1 YEAR	28	30	46.2	28.3	70	41.3	80.6	64.2	1.25	70.3	N0	25
12	30	M	4 YEARS	30	32	56.1	33.2	73	38.2	61.2	80.2	0.76	81.2	YES	26
13	32	F	2 YEARS	26	29	48.2	29.5	70	40.1	80.1	70.2	1.14	70.2	YES	24
14	38	F	1 YEAR	28	30	46.2	28.2	72	42.3	81.1	74.3	1.1	69.8	YES	0
15	37	F	9 YEARS	30	32	56.2	33.6	71	34.2	60.1	92.4	0.65	89.6	YES	42
16	42	F	3 YEARS	30	30	45.2	28.4	69	41.2	74.3	71.2	1.04	68.9	NO	0
17	34	M	2 YEARS	29	31	47.1	28.3	71	40.1	80.2	68.9	1.16	68.3	NO	27
18	32	F	2 YEARS	30	32	46.9	27.9	72	39.9	82.3	68.9	1.19	70.1	NO	28
19	39	F	13 YEARS	34	32	54.2	34.5	70	35.9	61.1	98.9	0.62	90.2	YES	47
20	42	M	4 YEARS	29	30	49.2	29.9	69	41.2	74.2	72.3	1.03	70.1	YES	29
21	36	F	6 YEARS	3	32	51.3	33.2	72	35.4	64.3	90.2	0.71	88.9	YES	29

22	38	F	4 YEARS	28	29	46.4	28.8	75	40.2	72.1	62.4	1.16	70.2	NO	29
23	21	F	1 YEAR	27	29	44.5	26.1	76	41.1	88.4	60.1	1.34	66.1	NO	28
24	25	M	2 YEARS	30	31	46.2	28.4	70	40.2	80.1	65.4	1.22	68.2	YES	23
25	32	F	8 YEARS	30	33	54.2	32.1	71	32.4	64.2	87.4	0.73	87.6	YES	21
26	30	F	1 YEAR	28	30	51.2	30.2	71	34.1	66.2	84.2	0.79	84.2	YES	20
27	32	F	6 YEARS	29	30	48.1	27.6	70	39.5	80.2	75.2	1.07	71.2	YES	26
28	30	M	2 YEARS	27	31	46.5	29.1	71	40.2	81.2	70.2	1.16	66.9	YES	21
29	41	F	9 YEARS	28	29	54.2	33.1	70	33.5	69.6	80.2	0.87	84.6	YES	44
30	36	F	5 YEARS	27	28	50.1	31.2	72	35.2	68.9	78.1	0.82	82.1	YES	23
31	46	F	2 YEARS	28	30	47.4	29.3	68	39.2	83.1	72.1	1.15	67.5	NO	21
32	29	F	4 YEARS	29	31	49.8	31.2	70	36.1	70.2	74.2	0.95	74.1	NO	29
33	30	F	6 YEARS	29	30	51.2	32.4	71	34.3	62.5	86.4	0.72	80.1	YES	28
34	48	F	3 YEARS	26	30	49.8	30.1	66	39.8	80.2	75.4	1.06	68.2	YES	29
35	42	F	15 YEARS	26	32	54.2	32.2	72	32.4	62.3	90.1	0.69	88.8	YES	52
36	38	F	4 YEARS	28	30	49.8	31.1	71	39.9	79.6	70.2	1.13	69.1	NO	26
37	31	F	8 YEARS	25	29	52.1	32.8	71	32.9	66.2	88.4	0.75	86.4	YES	35
38	30	F	7 YEARS	28	30	51.2	33.1	71	32.1	63.1	86.2	0.73	89.2	YES	29
39	50	F	17 YEARS	26	28	58.3	31.2	64.2	36.9	92.2	88.2	1.04	87.2	YES	46
40	42	F	16 YEARS	26	28	53.1	31.2	73	41.9	72.1	70.4	1.02	70.2	NO	48
41	31	F	4 YEARS	27	30	47.1	28.5	71	41.1	74.2	62.1	1.19	76.3	YES	28
42	38	F	7 YEARS	29	31	53.9	33.1	72	35.1	61.1	90.2	0.68	88.3	YES	46
43	28	F	3 YEARS	26	29	45.9	28.8	70	42.1	84.5	60.2	1.4	69.2	NO	28
44	37	F	2 YEARS	28	30	44.9	28.1	69.8	41.4	82.3	69.7	1.18	69.9	NO	29
45	36	M	1 YEAR	26	29	45.1	27.9	75	43.5	90.4	60.5	1.49	68.2	YES	0