STUDY ON CARDIOVASCULAR MANIFESTATIONS IN LUPUS PATIENTS

DISSERTATION

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CERTIFICATE

This to certify that this dissertation entitled, "**A study on cardiovascular manifestations in lupus patients"**, submitted by **Dr.K.JAGANNATHAN,** in partial fulfillment for the award of the degree of Doctor of Medicine in Rheumatology by the Dr.M.G.R. Medical University, Chennai is a bona fide record of the work done by him in the Department of Rheumatology, Madras Medical College, during the academic year 2006-2009.

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INTRODUCTION

STUDY ON CARDIOVASCULAR MANIFESTATIONS IN LUPUS PATIENTS

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease primarily occurs in young women and characterised by varied clinical and laboratory manifestations. Severity ranges from a mild disease with rash and arthritis to a devastating illness with renal failure and central nervous system involvement. Perhaps because of the prominence of cutaneous, musculoskeletal, renal and neurological manifestations cardiac involvement has not received detailed attention. The widespread use of modern echocardiography together with the longer life spans of severe SLE patients has contributed to increased recognition of cardiovascular involvement in these patients.

The heart is frequently involved in systemic lupus erythematosus (SLE). Cardiac involvement in patients with SLE has been described since the early 20th century (1). In recent years, echocardiography has yielded additional information about the heart in patients who have SLE with and without clinical cardiac involvement. Echocardiography is a sensitive and specific technique in detecting cardiac abnormalities, particularly mild pericarditis, valvular lesions and myocardial dysfunction .Very sensitive methods of cardiovascular investigation have found the prevalence of cardiac involvement in SLE to be higher than50 %(2, 3).

SLE can affect most parts of the cardiovascular system. The pathologic involvement includes pericarditis with or without effusion, myocarditis sometimes with involvement of the conduction system and myocardial infarction secondary to coronary arteritis or premature accelerated atherosclerosis. Finally, endocardial involvement in SLE is of particular interest because of its complications which include thromboembolism, infective

endocarditis and ultimately the need for cardiac surgery. Since the original description by Libman and Sacks of sterile vegetations (4), there are many reports of valvular lesions occurring in SLE (5, 6, 7, and 8). Often however, particularly with currently improved therapeutic options, these valve lesions may remain subclinical and produce no symptoms, causing no murmurs of regurgitation or stenosis and thus have no hemodynamic significance. Echocardiography and Doppler with colour flow imaging are currently the only techniques that can detect these lesions during life and better assess the entire spectrum of cardiac pathology.

SLE patients have an increased prevalence of subclinical atherosclerotic disease detected using several modalities. Hypertension and diabetes mellitus are also more prevalent in SLE and traditional risk factors, e.g. hypercholesterolemia, contribute to the development of atherosclerosis in SLE. However, these risk factors alone do not explain the excess CHD risk and after adjusting for traditional risk factors, SLE itself remains independently associated with both clinical and subclinical outcomes. Several lupus-related factors may contribute to the development of accelerated atherosclerosis, for example, there is growing evidence that atherosclerosis itself has a chronic inflammatory component. Premature atherosclerosis is the most frequent cause of coronary artery disease (CAD) in SLE patients.

In addition to chronic inflammation, patients with SLE frequently have lupus anticoagulant (LAC) or associated antiphospholipid antibodies (aPL). A high proportion of SLE patients with cardiac abnormalities have been noted to have high levels of anticardiolipin antibodies. Moreover, antiphospholipid antibodies have been linked to several cardiac manifestations in patients with SLE, including valvular abnormalities and possibly coronary artery disease and there is in *vitro* evidence that certain aPL may be pro-atherogenic as well as pro-thrombotic. Corticosteroid therapy has also been associated with clinical and subclinical disease in several studies (9).

Though the cardiovascular manifestations in SLE have been well documented in literature, there are very few studies done in India addressing this issue. Hence this study was undertaken to establish the frequency and associated risk factors for cardiovascular manifestations in patients of SLE in our geographic area. Although antiphospholipid antibodies (aPL) are associated with arterial and venous thrombosis in systemic lupus erythematosus (SLE), the extent to which they influence other cardiovascular manifestations is either controversial or uncertain. This study was done to examine the relationships of aPL with cardiovascular manifestations in SLE.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Lupus is an autoimmune disease characterized by acute and chronic inflammation of various tissues of the body. Autoimmune diseases are illnesses that occur when the body's tissues are attacked by its own immune system. The immune system is a complex system within the body that is designed to fight infectious agents, such as bacteria and other foreign microbes. One of the ways that the immune system fights infections is by producing antibodies that bind to the microbes. Patients with lupus produce abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents. Because the antibodies and accompanying cells of inflammation can affect tissues anywhere in the body, lupus has the potential to affect a variety of tissues and organ systems. Sometimes lupus can cause disease of the skin, heart, lungs, kidneys, joints, and/or nervous system. When only the skin is involved, the condition is called lupus dermatitis or cutaneous lupus erythematosus. A form of lupus dermatitis that can be isolated to the skin, without internal disease, is called discoid lupus. When internal organs are involved, the condition is referred to as systemic lupus erythematosus (SLE).

HISTORICAL ASPECTS

The term lupus is attributed to the thirteenth century physician **Rogerius**, who described the facial lesions that were reminiscent of a “wolf’s bite” (10). In 1851, **Cazenave** applied the term lupus erythematosus for the first time to a disease described by his teacher **Laurent Biett** (11). In 1845, **von Hebra**, a Viennese physician, used butterfly rash to describe the familiar malar rash of the disease. For most of the nineteenth century, lupus was thought to be a dermatologic disease. Von Hebra, in his 1856 book, published the first illustrations of the disease in the Atlas of Skin Diseases. However, when **Moretz Kaposi** described the visceral forms of the disease in 1872, physicians began to suspect that this disease was a more generalized form of the illness and the term acute disseminated was

included in the description (12). Kaposi proposed two types of lupus: disseminated and discoid. In his early writings, he supposed that the disseminated form consisted of 1) subcutaneous nodules, 2) arthritis, 3) lymphadenopathy, 4) fever, 5) weight loss, 6) anemia, and 7) central nervous system involvement. In 1904, **William Osler** described two women who developed renal failure within 10 months of the appearance of a facial erythema, which in retrospect was the facial rash of von Hebra (13).

Osler described a number of other illnesses at the time, among them, Henoch Schoenlein purpura and disseminated gonococcemia, which could be confused with the lesions in the two women. In Vienna at this time**, Jedasson** described similar syndromes in a few patients. Both he and Osler therefore established SLE as a distinct entity by the turn of the century, even though many practitioners still thought of SLE as a form of skin tuberculosis (14). Very typical cases of SLE were reported under a variety of names, and it was not until the 1920s and 30s that the disease was well defined. The disease, at that time, was carefully described by pathologists who studied the morbid anatomic changes that so characterized someone with lupus.

The atypical bacterial endocarditis of **Emmanuel Libman and Benjamin Sacks**, described in 1924, was a classic example of the pathology found in some patients with SLE and were likely lesions associated with antiphospholipid antibody (4). Following that description, **George Baehr**, published a series of 23 autopsied cases of the renal wire loop lesions of lupus nephritis and described the solar sensitivity we know so well. Thus, pathologists further elucidated the disease known as lupus. In 1936 **Frieberg, Gross and Wallach** autopsied a young woman with lupus and no skin lesions, indicating that the disease was not primarily a skin condition and was even less associated with tuberculosis. **Klempner, Pollack, and Baehr** in 1941 suggested that collagen was a part of the disease because of the many instances of fibrinoid necrosis that they found with the disease. This

gave rise to the name collagen disease as a grouping for all of the diseases that affected connective tissue, a term that is not used widely today.

Hack and Reinhart were the first to describe the false-positive syphilis test in SLE and in 1940 Keil similarly reported ten cases of SLE with false-positive syphilis tests. Haserick and Lang wrote about an additional series of cases where the presence of the false-positive syphilis serology predated the clinical lupus by up to eight years. In all of these cases, the false-positive syphilis tests probably resulted from the presence of antiphospholipid antibodies, the discovery of which was to take an additional 30 years. In 1955, Moore (15) studied another 148 patients who were positive for syphilis and found that some 7% developed lupus with time, whereas 30% had symptoms related to collagen vascular disease. In 1949, Phillip Hench (16) discovered cortisone, and the future of the connective tissue diseases changed. Rheumatoid arthritis patients and those with lupus erythematosus (LE) were manageable, and “cures” were reported.

In 1943, Malcolm M. Hargraves, a hematologist at the Mayo Clinic, found peculiar globular bodies taking purple stain in the marrow aspirate of a child with an undiagnosed disease;2 1/2 years later he made a similar observation. Symptoms in a third case with this finding, in 1946, suggested that this patient had SLE. Two important observations were made in addition to the association of this unusual cell with the diagnosis of SLE: (a) more of these cells were found when the specimen was not fixed immediately; and (b) two similar cells needed to be differentiated. These findings were first reported in January 1948 (17). The tart cell (named after a patient) is not disease specific. Its distinguishing feature is that the secondary nucleus has retained definite chromatin structure.

The LE cell is practically always a mature neutrophilic polymorphonuclear leukocyte in contradistinction to the tart cell which is most often a histiocyte. John R. Haserick at the Cleveland Clinic suggested already in 1948 that the greatest value of the LE

cell lies in its possible presence in suspected cases of acute disseminated lupus erythematosus in which the classic dermatologic manifestations are lacking (18**). Hargraves** (19) in 1949 demonstrated LE cells in the buffy coat of centrifuged specimens of peripheral blood of patients in whose marrow LE cells had been detected. Since it was found to have poor sensitivity and specificity reliability on the LE cell to diagnose SLE, began to diminish after a few years.

In 1957, **Friou et al.** (20) at Yale devised a technique to demonstrate the antibody semi quantitatively by indirect immunofluorescence microscopy. The reactive substance was identified in 1959 as a DNA-histone nucleoprotein and Beck in 1961 in London showed that at least three fluorescent staining patterns could be distinguished (21). In the next decade, refined laboratory methods permitted the discovery of numerous antibodies, some of which could be correlated clinically with subsets of SLE and other diseases. The discovery of the LE cell had initiated the discipline of immunopathology.

In 1957, three laboratories almost simultaneously demonstrated a factor in the serum of some cases of SLE that reacts specifically with DNA (22). Tan et al. (23) in 1966 in New York detected anti-DNA antibodies in SLE sera. Koffler et al. (24) in 1969 in New York found that the detection of native (double-stranded) deoxyribonucleic acid (dsDNA) is more specific for SLE, but less sensitive than antibody to denatured (single-stranded) DNA. Schur et al. (25) in 1971, using more sensitive techniques, confirmed the specificity of the reaction with dsDNA, but obtained positive reactions in only one half of SLE sera. Tan and Kunkel (26) in 1966 in New York detected a cytoplasmic (RNP) antigen in SLE serum that they designated Sm. It was the first antibody to a nonhistone nuclear antigen and highly specific for SLE, although found in only one third of cases.

The next discoveries about the antibody systems that related to SLE were gained from the development of techniques to extract uncomplexed histones from nuclei and

recombining them with DNA, free of other components (27). Histones are small basic proteins associated with nucleic acids in cell nuclei. Some extracted recombined antigens, depending on the precise histone structure, can be used to detect antihistone antibodies. The important findings were that antihistone antibodies occur more frequently in drug-induced than in idiopathic SLE, and that lupus-inducing drugs vary in their ability to induce these antibodies, procaine amide doing so most consistently (28).

The role of antinuclear antibodies (ANAs) in SLE became uncertain when clinically typical cases in which ANAs could not be detected began to be described. These cases comprise fewer than 5% of cases of SLE, and most have antibody reactive against the cytoplasmic RNA antigen Ro (29).

The introduction in 1963 of a convenient pathologic technique complemented the ever-increasing number of serologic tests. The lupus band test determines by immunofluorescence microscopy of skin biopsies as to whether immunoglobulins are deposited at the dermo-epidermal junction (30). In DLE it is positive in lesional but not in uninvolved skin. It also is positive in the normal skin of at least half of cases of SLE, MCTD and psoriasis (31). It has proven not to be a highly specific finding, since it occurs in about 15% of cases of rheumatoid arthritis (32) and in various bullous dermatoses. At Otago Medical School the NZ Brown X NZ White hybrid mouse was discovered (1959) to develop a lethal kidney disease closely resembling Lupus Nephritis - the kidney disease which some people with SLE develop. This mouse has since been studied in laboratories all around the world. Other mice which develop Lupus-like diseases have also been bred particularly in the United States. These mice have aided research tremendously.

EPIDEMIOLOGY

One of the most striking features of SLE is its female predominance. The importance of female hormones in the pathogenesis of SLE has been elegantly studied in

murine models (33). In humans, the ratio of women to men is 9:1, although in a recent study from Rochester, Minnesota, the ratio was less (34). Women with SLE may metabolize estrogen by using pathways that lead to elevated levels of the more active metabolite hydroxyestrone, which would accentuate the effect of estrogen on the immune system (35). Male SLE patients can have decreased androgen levels (36). Thus, an imbalance of estrogen-to-androgen ratio may predispose to SLE in both sexes. The mechanism by which this imbalance leads to autoimmunity is less clear, because sex hormones could act at multiple levels. Sex hormones bind to receptors in the thymus and spleen and to receptors on lymphocytes and increase mitogen-induced immunoglobulin production (37).

SLE is usually a post pubertal disease, with onset of clinical symptoms usually in the 20s to 30s. Childhood and older-onset SLEs differ from the classic presentation, with less female predominance and different clinical presentations. Younger-onset SLE (before age 20) has an increase in cutaneous and renal SLE and is more likely have low serum C4 than older-onset SLE. In a retrospective study of 31 children with SLE, arthritis, anemia, and seizures were associated with a poor prognosis (38). Older-onset (older than 40 years) SLE is less likely to have malar rash, proteinuria, and low serum C4, but more likely to have secondary Sjogren's syndrome.

In both the United States and the United Kingdom (23), SLE is more common in African Americans and African Caribbeans (39,40), yet SLE is not a common autoimmune disease in Africa. SLE does appear to be common in Asia (41,42) and Latin America (43). The LUMINA study in the United States has begun a comparison of SLE in Caucasians, Hispanics, and African-Americans (44). Race affects both the presentation and the course of SLE. Blacks with SLE are more likely than whites to have discoid SLE, lupus nephritis (45), lymphadenopathy, myositis, and pericarditis, but less likely to have malar rash and mouth

ulcers. African-Americans are also more likely to have anti-ribonucleoprotein (anti-RNP) and anti-Sm, but are less likely to have anticardiolipin and lupus anticoagulant than white patients.

Differences in SLE presentation and course that are related to socioeconomic status may actually be due to other factors. In a prospective study of predictors of poor renal outcome (renal insufficiency, renal failure, and chronic nephrotic syndrome), socioeconomic status and race were not found to be significant predictors. Instead, compliance (with visits and medication) and hypertension were the major explanatory variables for poor renal outcomes (45).

Education, however, was associated with major comorbidities of SLE, such as cataracts, hypertension, peptic ulcer, and thrombosis, even after adjustment for race. Education also was associated with several clinical manifestations, including discoid rash, psychosis, and seizures. The apparent association of education with these factors may be due to confounding variables such as diet and social habits.

Systemic lupus erythematosus is rare in India. A prevalence study in India (carried out in a rural population near Delhi) found a point prevalence of 3 per 100,000 (46).This is a much lower figure than reported from the west (Varying from 12.5 per 100,000 adults in England to 39 per 100,000 in Finland and 124 per 100,000 in USA).However, a fair number of cases of SLE are encountered in any large hospital in India. Copcord Bhigwan study (an ongoing, prospective population study from Pune) found a crude incidence rate of 1 per 25,000 person years i.e.4per 100,000 population per year (personal Communication) (47).

Recent work from Rochester, Minnesota, indicates that the incidence of SLE has tripled since the 1970s, from 1.51 in 100,000 (1950-1979) to 5.56 in 100,000 (1980-1992) (34). Prevalence of SLE in the United States is 15–50 per 100,000; the highest prevalence among ethnic groups studied is in African Americans.

PATHOGENESIS

In SLE, interactions between susceptibility genes and environmental factors result in abnormal immune responses. Those responses include 1) activation of innate immunity (dendritic cells) by DNA, DNA in immune complexes, and RNA in RNA/protein self-antigens; 2) lowered activation thresholds of adaptive immunity cells (antigen-specific T and B lymphocytes);3) ineffective regulatory and inhibitory CD4+ and CD8+ T cells; and 4) reduced clearance of apoptotic cells and of immune complexes. Self-antigens (nucleosomal DNA/protein; RNA/protein in Sm, Ro, and La; phospholipids) are available for recognition by the immune system in surface blebs of apoptotic cells; thus antigens, autoantibodies, and immune complexes persist for prolonged periods of time, allowing inflammation and disease to develop. Immune activation of circulating and tissue-bound cells is accompanied by increased secretion of proinflammatory tumor necrosis factor (TNF) and type 1 and 2 interferons (IFNs), and the B cell–driving cytokines B lymphocyte stimulator (BLyS) and interleukin (IL) 10. Up regulation of genes induced by interferons is a genetic "signature" of SLE. However, lupus T and natural killer (NK) cells fail to produce enough IL-2 and transforming growth factor (TGF) to induce regulatory CD4+ and inhibitory CD8+ T cells. The result of these abnormalities is sustained production of pathogenic autoantibodies and immune complexes, which bind to target tissues, with activation of complement and phagocytic cells that recognize Ig-coated circulating blood cells. Activation of complement and immune cells leads to release of chemotaxins, cytokines, chemokines, vasoactive peptides, and destructive enzymes. In the setting of chronic inflammation, accumulation of growth factors and products of chronic oxidation contribute to irreversible tissue damage in glomeruli, arteries, lungs, and other tissues.

DIAGNOSIS

The diagnosis of SLE is based on the characteristic clinical features and autoantibodies. In 1971, the American Rheumatism Association (ARA) published preliminary criteria for the classification of SLE. These criteria were developed for clinical trials and population studies rather than for diagnostic purposes (48). The 1982 revised criteria, is a simplified and updated version of the 1971 preliminary criteria that incorporated newer immunologic criteria and aggregates of some organ system manifestations into single criteria. It consists of 11 items, compared with 14 in the initial criteria. Because the presence of antiphospholipid antibodies and the antiphospholipid syndrome (APS) was increasingly recognized in SLE patients, the Diagnostic and Therapeutic Criteria Committee of the ACR updated the 1982 revised criteria for SLE in 1997(49).

The 1997 Revised Criteria for the Classification of Systemic Lupus Erythematosus (SLE)

Criterion	Definition
1. Malar rash	Fixed malar erythema, flat or raised
2. Discoid rash	Erythematous-raised patches with keratic scaling and follicular plugging; atrophic scarring may occur in older
3. Photosensitivity	Skin rash as an unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulcers, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a. Pleuritis (convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion) OR b. Pericarditis (documented by ECG, rub, or evidence of pericardial effusion)
7. Renal disorder	a. Persistent proteinuria (>0.5 g/d or >3+) OR

	b. Cellular casts of any type
8. Neurologic disorder	a. Seizures (in the absence of other causes) OR b. Psychosis (in the absence of other causes)
9. Hematologic disorder	a. Hemolytic anemia OR b. Leukopenia (<4,000/mL on two or more occasions) OR c. Lymphopenia (<1,500/mL on two or more occasions) OR d. Thrombocytopenia (<100,000/mL in the absence of offending drugs)
10. Immunologic disorder	a. Anti-double-stranded DNA OR b. Anti-Sm OR c. Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody (ANA) by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus syndrome

Any combination of ≥4 of 11 criteria, well documented at any time during an individual's history, makes it likely that the patient has SLE. (Specificity and sensitivity are 95% and 75%, respectively.)

CARDIOVASCULAR MANIFESTATIONS OF LUPUS

The heart is a major target for disease in patients with systemic lupus erythematosus (SLE). Several clinical and postmortem studies have demonstrated a high incidence of cardiovascular manifestations involving the pericardium, myocardium, endocardium, cardiac valves, and coronary vessels. (50, 51) Although the association of raised anticardiolipin antibodies with SLE and other lupus like syndromes has been well described, (52, 53) there is little prospective data on their possible role in the development of cardiovascular abnormalities (54). There are now a few reports (6,55) describing an association between valvular lesions and raised anti cardiolipin antibodies in patients with SLE, but the spectrum of cardiac pathology and the predictive value of high levels of anti cardiolipin antibodies to the presence of cardiac involvement have not been fully established. This has been made possible with increased use of two-dimensional echocardiography and Doppler techniques in the living population with SLE.

PERICARDIAL DISEASE

Pericarditis is the most common form of cardiac involvement in SLE, although often it is not evident clinically. Its prevalence is also greater in autopsy samples, thus indicating that asymptomatic pericardial involvement is quite common (57). Echocardiographic evidence of pericardial thickening or effusion is detected in 18% to 54% of SLE patients (58, 59), whereas pericardial disease at autopsy has been reported in up to 61 % (57). Evaluating several clinical studies in the literature, **Doherty and Siegel** (5) found a 25.6% prevalence of pericarditis in 1,194 patients with SLE, but a prevalence of 62.1% in the 254 cases at autopsy. A great amount of the pericarditis may consist of small effusions in asymptomatic patients. Although pericarditis can occur at any time during the course of SLE, it can even be the first manifestation of lupus. Coexistent pleurisy or effusions are common,

occurring in 14 of 28 cases in one series (60). Pericarditis usually appears as an isolated attack or as recurrent episodes, with or without symptoms. In a French series of 28 cases of pericarditis, 23 had pain, 12 had a rub, and 4 required pericardiocentesis because of tamponade (60).

The clinical presentation is usually typical and includes fever, tachycardia, substernal pain (which worsens during breathing, coughing or leaning forward), and by the presence of pericardial rub on auscultation. ECG findings in acute pericarditis include PR segment depression and widespread, upwardly concave ST segment elevation. T-wave inversions usually occur several days into the clinical course which is not different from that seen in other causes of pericarditis (61, 62).

Electrical alternans and reduced QRS voltage are most often seen when large effusions are present. The inflammation may reach the sinoatrial node or the atrioventricular node and provoke arrhythmias. In one study, only patients with moderate or severe pericardial effusion had clinical or ECG evidence of pericarditis (63). Chest radiographs may reveal an enlarged cardiac silhouette when an effusion is present, and pericardial fat lines may be visible. When present, pericardial effusions are usually small and do not cause hemodynamic problems. Pericardial tamponade has been reported but rare. In the modern era, most pericardial effusions do not cause hemodynamic problems (61). Constrictive pericarditis is very rare. Pericardial fluid in SLE is usually exudative, the amount of fluid varying from 100 to more than 1,000 ml.

M-mode and two-dimensional echocardiography are currently considered the main complementary methods used for the diagnosis of pericardial effusion. However, the absence of pericardial effusion on echocardiography should not exclude the possibility of a clinically suspected pericarditis. In cases of pericardial constriction, computerized tomography (CT)

and magnetic resonance imaging (MRI) are superior to echocardiography for the visualization of pericardial thickening and calcifications.

The pericardial fluid of patients with SLE frequently contains lupus erythematosus cells and low complement levels compared with that found in serum. Antinuclear antibodies, anti DNA antibodies, and rheumatoid factor may also be found in the pericardial effusion (61). The eventual finding of antinuclear antibodies is considered virtually pathognomonic of pericarditis associated with SLE.

For symptomatic patients with a small effusion, treatment should include the use of nonsteroidal anti-inflammatory drugs, such as indomethacin with or without antimalarial medication. For the more severe cases, or those that do not respond to the above measures, usually steroids are used in dosages that vary from 0.5-1mg/kg/day of prednisone, according to the seriousness of the involvement. Pericardial drainage and pericardiectomy rarely need to be performed.

MYOCARDITIS AND CARDIOMYOPATHY

Myocarditis is the most characteristic feature of myocardial involvement in SLE. However, in SLE patients myocardial dysfunction may be the consequence of other features, particularly coronary artery disease (CAD) due to premature atherosclerosis, hypertension, renal failure, valvular disease and toxicity from medications, such as cyclophosphamide and chloroquine(3).The recognition of myocardial involvement as a result of SLE has been considerably enhanced as a result of the hemodynamic and echocardiographic findings of systolic and diastolic dysfunction, in several patients with lupus who did not show clinical evidence of heart disease (5,63). Nowadays, clinically overt myocarditis is uncommon and reported in 7–10% of cases (64), probably as the consequence of the introduction of steroid therapy. However, as for other cardiac manifestations, subclinical involvement is probably

more frequent. A greater frequency of myocarditis (40% to 80%) is observed on autopsy. The lower frequency of myocarditis in a series of necropsies more recently studied may be attributed to the greater use of steroids in patients with SLE (63).

In myocarditis, histological findings show small foci of fibrinoid necrosis with infiltrates of plasma cells and lymphocytes and small foci of myocardial fibrosis, common in patients treated with corticosteroids (64). Immunofluorescence studies demonstrate fine granular immune complexes and complement deposition in the walls and perivascular tissues of myocardial blood vessels, supporting the hypothesis that lupus myocarditis is an immune complex-mediated vascular phenomenon (64). Some reports demonstrate an association between anti-Ro/SSA antibodies and myocarditis (65).

The clinical identification of lupus myocarditis may be more difficult due to the frequent occurrence in SLE of other factors potentially responsible for myocardial damage, such as anemia, hypertension, systemic infection, valvular disease, water retention related to renal disease or the use of steroids. Patients who present with acute myocarditis usually have associated pericarditis. They also frequently have fever and tachycardia, which may be disproportionate to fever and thoracic pain. Such patients may only occasionally have signs of heart failure, arrhythmias, electrical conduction disorder, and intraventricular or atrioventricular blocks (63).

Thus ventricular dysfunction caused by lupus myocarditis usually is not of a great magnitude, and therefore the so-called lupus cardiomyopathy is of high intensity rarely with symptoms and sometimes even without symptoms (66). Cardiac failure may occur occasionally, mostly in association with severe dilated cardiomyopathy, resulting from isolated myocarditis, or of several repeated episodes of myocarditis. However, congestive heart failure, as an independent event, is reported in less than 5% of lupus patients, which

makes it secondary in importance to hypertension, sometimes resulting from use of steroids (63).

Asymptomatic lupus myocardial dysfunction seems to be a frequent occurrence. There are several promising noninvasive investigations for diagnosing myocardial involvement in SLE. Echocardiography shows findings that, although not specific, are indicative of myocardial inflammation and/or dysfunction such as global, regional or segmental wall motion abnormalities, decreased ejection fraction, increased chamber size and prolonged isovolumetric relaxation time. Scintigraphy using gallium citrate 67 or indium 111-labelled Fab fragments of antimyosin antibody, MRI with T1 spin echo and T2 relaxation time (67) may be useful in the diagnosis of myocardial inflammation. In general terms, the electrocardiogram, which can show atrial and ventricular premature beats with nonspecific alterations in the ST segment and T waves and the chest X-ray, which only in cases of severe systolic dysfunction shows enlargement of the cardiac silhouette, have low-specificity in lupus myocarditis, usually producing results similar to those of other causes of cardiomyopathy.

An increase in muscle enzymes may be present in patients with lupus carditis, which is a condition eventually associated with peripheral myositis, where the dosage of total creatine phosphokinase (CPK) and the muscle - brain fraction of creatine phosphokinase (CK - MB) in these patients would certainly be useful. The acute lupus myocarditis with serious clinical and hemodynamic involvement is treated with a high dosage of prednisone (1mg/kg/day). A minimum 7 - 14 days of treatment is recommended. Diuretics, vasodilators and digitalis can be used. Immuno-suppression agents, such as azathioprine and cyclophosphamide have also been occasionally used.

VALVULAR HEART DISEASE

Anatomical and functional valvular abnormalities have been described in SLE. Libman–Sacks endocarditis, also termed ‘atypical verrucous endocarditis’, is the most characteristic lesion (4). However, valvular thickening and regurgitation are more frequently observed than verrucous endocarditis. Anatomical lesions were observed in 15–75% in necroscopy studies, in 40–50% of cases with the transthoracic echocardiography (TTE) and in 50–60% with transesophageal echocardiography (TEE). Therefore, TEE is more sensitive than TTE in revealing valve abnormalities. (68)

Libman - Sacks endocarditis (atypical verrucous endocarditis, noninfectious) is considered a characteristic, even pathognomonic, finding of SLE. The name refers to verrucous vegetation, usually ranging in diameter from 1 - 4 mm. This vegetation can be found isolated or in conglomerates, usually strongly adhered to the endocardium of valve cusps, but also to chordae tendineae, papillary muscles and the atrial walls or ventricular endocardium. The four heart valves may be involved, the most common site being the mitral valve (posterior leaflet), and the second most common site, the aortic valve (5). Microscopic examination of the lesions shows degenerative cells, fibrin, fibrous tissue and occasionally hematoxylin corpuscles with a variable degree of inflammation. An association between valvular abnormalities and antiphospholipid antibodies (aPL) has also been reported, but this association remains a matter of controversy. Two major pathogenetic hypotheses could explain the development of valvular abnormalities in SLE patients: 1) aPL and anti-endothelial antibodies bind to and activate endothelial cells, leading to platelet aggregation with thrombus formation; and 2) deposition of immune complexes between the endothelium and the basal membrane, leading to an infiltration of inflammatory cells.

Libman - Sacks endocarditis is primarily an anatomopathological and not a clinical finding. The lesions in this type of involvement are usually silent, and the occasional clinical

problems associated with them are related more to embolic phenomenon or overlying valvular dysfunction or heart failure (66). The real prevalence of this type of involvement is hard to determine during clinical examinations alone, considering the fact that most of the murmurs heard on auscultation in lupus, which usually result from fever, anemia, tachycardia and cardiomegaly, are not associated with organic valvular disease.

On the other hand, Libman - Sacks endocarditis is frequently reported on necropsies of patients who had no indication of murmurs during clinical examination. The cardiac vegetations, usually small, are difficult to detect on echocardiogram, although this method might be useful when the vegetations are larger than 2mm. Vegetations of 10mm in diameter or larger may be found in some patients with Libman - Sacks endocarditis (5). The incidence of this type of endocarditis has progressively declined during the last four decades, because of the use of more efficient therapeutics for SLE in recent years, compared with the initial period of 1920 and 1930 when the lesions were first described. Corticosteroids' specific mechanism of action is controversial. Some people attribute the possible reduction in the incidence of these lesions in lupus to an increase in corticoid use (5), and also a possible reduction in valvular dysfunction, because they promote healing of scars caused by verrucous lesions, which would result in fibrotic retraction of valve cusps (63). Another possible explanation for the lower frequency of verrucous endocarditis described in recent years is that the diagnosis of SLE is now carried out before death through clinical criteria, and not by the postmortem finding of cardiac vegetations, as in the past, when the recognition of the high specificity of the lesions and the absence of other diagnostic criteria for SLE stimulated a search for them on necropsies (5). Although Libman - Sacks endocarditis rarely results in considerable hemodynamic involvement, some complications, such as rupture of the chordae tendineae, aortic stenosis, localized thrombosis and cerebral embolism, are reported. Infectious endocarditis may complicate Libman - Sacks endocarditis. Doherty and Siegel (5)

demonstrated this in a meta-analysis of 15 reports showing that 4.9% of cases of verrucous endocarditis identified at necropsy and 33% of cases clinically diagnosed had infectious endocarditis as a complication. Such frequencies are greater than in the general population or even in patients with other diseases of the connective tissue. Therefore, the prophylactic use of antibiotics in dental and surgical procedures is indicated in patients with Libman - Sacks endocarditis (63).

Valvular thickening, whether or not due to Libman – Sacks endocarditis, visualized with M-mode or two dimensional echocardiography may be observed in about half of patients with SLE. Valvular thickening predominantly occurs in the mitral and aortic valves (8), and may, in some cases, be correlated with surgical findings of verrucous endocarditis (63). The most common valvular dysfunction in lupus is regurgitation, which in most cases is of small magnitude with no clinical significance. However, valvular malfunction, with considerable clinical and hemodynamic importance to an extent where they require surgical replacement by prosthesis may occur in certain patients. Aortic regurgitation, which may result from Libman - Sacks endocarditis, valvulitis, fibrosis, mucous degeneration, bacterial endocarditis and aortic dissection, is considered to be the valve dysfunction usually associated with severe hemodynamic importance in SLE (5).

Severe cases of mitral regurgitation have also been reported, however less frequently. Mitral regurgitation may be caused by fibrosis, thickening and calcification of the mitral leaf and chordae tendineae, rupture of the chordae tendineae, and fibrinoid necrosis of papillary muscles. Cases of aortic stenosis, mitral stenosis, and tricuspid stenosis resulting from in situ thrombosis, some requiring valve replacement, have also been described, however in limited numbers (5, 8). The valvular evaluation in lupus includes the conventional findings of clinical examination and electrocardiogram, chest X-ray and echocardiogram. The transthoracic echocardiography is presently the method most used for diagnosis of valvular

disease associated with SLE. The transesophageal echocardiogram is also beginning to be used in studies for evaluation of the frequency of valvular involvement in lupus (8). **Roldan et al (**8) found a 74% frequency of valvular involvement in SLE using this method. A greater frequency of regurgitation in the right chambers in relation to the left chambers, as identified in patients with SLE through Doppler echocardiography, has been associated with pulmonary vascular lesions, resulting in pulmonary hypertension.

Jansen-Urstad et al (69) recently reported a close association between valvular abnormalities and cardiovascular disease (CVD) as well as raised levels of homocysteine and triglycerides in SLE patients. Therefore, patients with valvular disease should be screened for clinical and subclinical atherosclerotic features.

Since Libman–Sacks endocarditis is clinically silent in the majority of cases, it is generally not treated. When it is found in an early active stage, corticosteroids (prednisone 1 mg/kg/day) are recommended, especially if antiphospholipid antibodies and lupus anticoagulant are negative. Valvular abnormalities frequently resolved over time (62).

When endocarditis is detected at a later stage during the course of the disease, careful clinical surveillance is necessary and, if the lesion becomes hemodynamically significant, valve surgery is needed. It is necessary to carefully evaluate the type of surgical treatment. Mechanical valve replacement seems to be the best choice in lupus patients (70).

RHYTHM AND CONDUCTION TISSUE ABNORMALITIES

Sinus tachycardia is the most frequent rhythm abnormality and is quite common in SLE patients. Atrioventricular block and bundle branch block are also observed. However, they are rare in adults (71) and occur in only 2% of children born from mothers with anti-Ro/SSA antibodies (72). Rhythm and conduction abnormalities are mostly asymptomatic or may lead to some mild complaints such as palpitation or fatigue. In some cases syncope may

occur. Sinus tachycardia can be due to fever, anaemia or cardiac abnormalities including pericarditis and myocarditis. Conduction defects can also be the result of anti malarial use (71). In SLE patients with rhythm and conduction abnormalities, electrolyte balance and thyroid hormonal status should be investigated. The treatment is based on the use of common anti arrhythmic drugs and in the most severe cases the implant of a pacemaker is necessary.

PULMONARY HYPERTENSION

Association of pulmonary hypertension with diseases of the connective tissues has been most frequently described in the combination of connective tissue disease and systemic sclerosis, this last especially in CREST syndrome (calcinosis, Raynaud's phenomenon, sclerodactyly, esophageal involvement and telangiectasia). Although acute pulmonary arterial hypertension continues to be considered a rare manifestation, it has been demonstrated to be common in patients with subclinical or mild cases of SLE, and a current trend exists to recognize pulmonary arterial hypertension as a complication of SLE (63). The determination of the real prevalence and magnitude of pulmonary hypertension in SLE has been difficult over the years due to the fact that the only method with sufficient sensitivity for determining pulmonary pressures and confirming the existence of pulmonary hypertension has been the catheterization of the right chambers with direct measurement of pulmonary pressures (73), an invasive method that one is naturally reluctant to use before symptoms and signs of advanced disease are present. In fact, in older reports a trend can be observed of studying patients with SLE with well defined clinical manifestation of pulmonary arterial hypertension (74), which usually is associated with high pressure levels in the pulmonary artery.

The advent of two-dimensional Doppler echocardiography, a method thought to be of similar sensitivity as right chamber catheterization for measuring pulmonary pressure, allowed the study of a greater number of patients, with or without symptoms. **Simonson et al**

(73), by way of Doppler echocardiography, found a frequency of pulmonary artery hypertension (defined as systolic arterial pressure >30mmHg) of 14% in 36 patients with SLE, observing in these patients a slight increase pulmonary pressures, suggesting that pulmonary arterial hypertension in SLE is common, although of light intensity. A gradually progressive pulmonary hypertension in lupus was demonstrated by **Winslow et al** (75), when reevaluating this same group of patients five years later and concluding that the prevalence of pulmonary hypertension increased from 14% to 43%. The real causes of pulmonary hypertension in SLE are yet unknown. The hypothesis of pulmonary vasculitis, with deposits of immune complexes and complements on the pulmonary artery walls, thromboembolic blockage in pulmonary vessels, possibly related to antibodies, and vasospasms, are suggested by a greater frequency of Raynaud's phenomenon in these patients (63, 73).

In lupus, the rare forms of pulmonary arterial hypertension produce symptoms that usually develop insidiously and gradually progress. Dry cough, thoracic pain and shortness of breath are usually the first symptoms, which may not be noticed because the physical examination and chest X-ray are frequently normal during the initial phase. Later, the second heart sound in the pulmonary area intensifies, and X-ray of the thorax shows an enlargement of the pulmonary vessels. The electrocardiogram shows overload of the right chambers. At this point, the Doppler echocardiography or catheterization of the right chamber clearly shows pulmonary hypertension.

The prognosis for the acute form of the disease is somber. More than 50% of the patients die within a period of two years. A large number of the patients reported here have undergone treatment with vasodilators, anticoagulants, corticoids and cytotoxic agents, and in spite of several reports of improvement of the symptoms, the hemodynamic response has generally been unsatisfactory. Supportive therapy with oxygen supplementation, diuretics and

anticoagulation is indicated for those with cardiac failure. The joint heart-lung or lung only transplant has been carried out with success in some patients.

ANTIPHOSPHOLIPID ANTIBODIES (APLS) AND THE HEART IN LUPUS

Antiphospholipid antibodies (aPLs) are most commonly identified through coagulation tests. They have been associated with thrombotic manifestations, low platelet counts and miscarriages as frequently in patients with SLE as in a variety of situations, such as connective tissue diseases, patients with neoplasia, acquired immunodeficiency syndrome, the use of certain drugs (phenytoin, interferon, quinidine, cocaine) or even with no identifiable illness (76). aPLs were identified in 1952 when Conley and Hartman discovered a coagulation inhibitor in lupus patients, named lupus anticoagulant (LAC) . Later on it was discovered that the coagulation inhibitor came from the immunoglobulins IgA, or IgM, or perhaps both of these directed against the natural phospholipids in the coagulation cascade, and also that the hemorrhagic disturbances were not frequent. In fact a paradoxical increase in thrombosis in patients with LAC occurred, by mechanisms not yet well explained, but whichmay include a lesion of the endothelium by aPLs (77). On the other hand, it was also observed that the LAC was frequently associated with the presence of false-positive serum tests for syphilis, which also commonly occurs in lupus patients.

Based on this observation cardiolipin, a phospholipid originally extracted from bovine hearts and used for serum tests for syphilis, was introduced as an antigen in solid phase immunology studies, such as radioimmunoassay and enzyme-linked immunosorbent assay (ELISA) . Presently, ELISA is the most commonly used method for the research on aPLs and for the detection of anticardiolipin antibodies (aCL) of the IgM, IgG, or IgA type, or all of these.

A spectrum of cardiac involvement has been reported in several types of patients with aPLs, which suggests the possibility of aPLs also being responsible for the basic

immunological events related to the onset of heart disease, and that certain cardiac manifestations may, in fact, be part of the primary or secondary so-called antiphospholipid antibody syndrome (aPL syndrome) defined as a set of clinical manifestations associated with the presence of these antibodies (78). Although some authors have not found any association between cardiac manifestation in lupus and the presence of aPLs (8, 79) other authors demonstrate a significant frequency of aPLs in lupus patients with different forms of cardiomyopathy. Among cardiac manifestations of SLE Libman - Sacks endocarditis and especially valvular defects and valvular thickening are the most frequently reported as being associated with aPLs (6, 7, 80). These findings have been reinforced by the fact that valvular lesions similar to those found in lupus have been found in patients with primary aPL syndrome (78). Whether the aPLs are the cause of valvular lesions, or simple coincidence accompanied by other immunological disorders, is not known. The findings of selective immunoglobulin deposits and complements along with cardiac vegetations in patients with Libman - Sacks endocarditis, suggesting involvement of a part of the immune complexes in the onset and growth of the lesions (78), should be emphasized, however, as should the more recent and suggestive findings of anticardiolipin antibody deposits in the sub endothelial layer of valves in patients with aPL syndrome.

Several cases of myocardial infarction have been documented in patients with primary aPL syndrome or aPL associated with lupus. The antiphospholipid antibodies may in this way become additional risk factors for coronary disease in patients with SLE, in addition to arteritis and classic accelerated atherosclerosis (78). The observation that antibodies against low density lipoproteins (LDL), which are also considered antiphospholipid antibodies due to the presence of phospholipids and apolipoprotein B in the LDL molecules have been found to be more clearly associated with atherosclerotic phenomenon than with the thrombotic phenomenon itself, which suggests the interesting possibility of aPLs being

directly responsible for the development of atherosclerosis in patients with SLE (81). Some evidence of the possible relation between the aPLs and myocardial infarction is also reported in studies of patients who do not have SLE or aPL syndrome. **Hamsten et al** (82) evaluated 62 survivors of a first myocardial infarction, less than 45 years old, and found high levels of anticardiolipin (aCL) in 13 (21%). Eight of the 13 patients with aCL levels persistently high experienced additional cardiovascular events during a 36 - 64 month follow-up, which suggests that aCL should be interpreted as a risk factor for recurrent cardiovascular events after the first myocardial infarction.

Zuckerman et al (83) evaluated 124 non lupus patients less than 65 years old who survived an acute myocardial infarction, and similarly observed that the incidence of thromboembolic events and re-infarction during a variable follow-up period of 12 to 27 months was significantly higher in patients positive for anticardiolipin antibodies.

Pulmonary hypertension in SLE has also been associated with the presence of aPLs. **Asherson et al.** (84) found a frequency of aPLs of 68% in 24 patients with pulmonary hypertension, 22 of these with SLE, one with primary aPL and one with overlying SLE/sclerodermatitis syndrome.

Leung et al (61) evaluated 75 patients with SLE by Doppler echocardiography, ELISA for aCL and various tests for LA and concluded that of five patients with myocardial dysfunction, four (80%) were positive for aPLs ($p<0.05$). Thrombotic closures of the myocardial microcirculation, in the absence of vasculitis (cardiac microangiopathy), may be a possible explanation for this type of anomaly in patients with aPLs (78).

Other cardiac manifestations in lupus, such as pseudo infectious endocarditis - which is a type of acute thrombosis of Libman - Sacks endocarditis, related to periods of activity of SLE with clinical findings quite similar to those of bacterial endocarditis - and the

intra cavity thrombus, have also been associated with the presence of aPLs (78), which correlates with a greater frequency of cerebral, ischemic events found in patients with aPLs.

ACCELERATED ATHEROSCLEROSIS

Atherosclerosis is emerging as a significant cause of death and illness in patients with systemic lupus erythematosus. The mortality rate from coronary artery disease in patients with systemic lupus erythematosus is estimated to be nine fold greater than predicted population-based rates (85). Severe atherosclerotic narrowing of coronary arteries has been well documented on autopsy studies, even in patients younger than 35 years of age.

Although the pathogenesis of accelerated atherosclerosis is unknown, it is believed to be multifactorial. Traditional cardiac risk factors, such as hypertension, obesity, and hyperlipidemia, are observed with high frequency in patients with systemic lupus erythematosus. Fifty-three percent of these patients have three or more risk factors; this prevalence greatly exceeds the prevalence seen in a matched population (6). Glucocorticoid-induced dyslipoproteinemia (86) and complications that result from disease involvement in other organ systems (for example, renal disease leading to hypertension and hyperlipidemia) may also potentiate the atherosclerotic process. Circulating immune complexes may promote intracellular cholesterol accumulation and therefore may be an additional compounding factor (87).

Risk factors for atherosclerosis in SLE

In SLE patients the role of traditional and nontraditional risk factors for atherosclerosis is still debated. Patients with SLE have abnormalities in their lipid profile.

Corticosteroid therapy has been implicated in the development of vascular disease in SLE patients (88). Patients with more active, severe SLE will receive higher doses of corticosteroid therapy for a longer time, although the relationship between corticosteroids and vascular disease in SLE patients remains controversial. Most ultrasound studies in SLE patients have found an association between carotid plaque and corticosteroid therapy. Moreover, corticosteroid therapy seems to increase the serum concentration of lipoproteins, (9) whereas hydroxychloroquine seems to reduce them in SLE patients. Other studies (9, 89) have shown an important role of hypertension, sedentary lifestyle and hyperhomocysteinemia in the development of atherosclerosis. Corticosteroids and nephropathy could lead to an increase of homocysteine.

Among the SLE-related risk factors, besides cumulative dosage (89) and/or length of corticosteroid therapy, (9) disease duration, high scores of activity (measured by scoring systems such as SLAM, SLEDAI or ECLAM) or damage (SLICC DI), (90) could contribute to the development of atherosclerotic plaque. However, it is not yet clear whether patients with mild or with severe disease are more at risk.

More recently, some novel risk factors for atherosclerosis have been proposed and reviewed (91). They are inflammatory markers (CRP and other pentraxines), immunological factors (anti-b2 glycoprotein I, antioxidized LDL, anti-heat shock protein 60/65), lipoproteins or coagulation parameters which are abnormal in SLE patients due to the disease itself. Therefore SLE is an intriguing model from this point of view. Unfortunately, data on the role of novel predictors in SLE cohorts are limited.

CAROTID IMT IN SLE

Noninvasive imaging techniques have been used to explore why SLE predisposes women to excess CVD risk. Both carotid IMT and plaque can be measured using B-mode ultrasound in women with SLE. Using these modalities, studies have shown increased rates of carotid focal plaque in women with SLE compared with controls.

Manzi S et al (92) studied a group of 175 women with SLE [predominantly white (87%)] with a mean age of 44.9 years and found that older age, elevated pulse pressure, a previous coronary event, and a higher SLICC disease damage score were independently related to increased IMT ($P < 0.05$). Independent determinants of plaque ($P < 0.05$) were older age, higher systolic blood pressure, higher levels of LDL cholesterol, prolonged treatment with prednisone, and a previous coronary event. Older age, a previous coronary event, and elevated systolic blood pressure were independently associated with increased severity of plaque ($P < 0.01$).

Roman MJ et al (93) in his study of 197 SLE patients and equal number of controls noted that the risk factors for cardiovascular disease were similar among patients and controls. Carotid plaque was more prevalent among patients than controls (37.1 percent vs. 15.2 percent, P<0.001). But the mean carotid IMT was comparatively lower in the patient group. Independent predictors of plaque were a longer duration of disease, a higher damage index score, a lower incidence of the use of cyclophosphamide, and the absence of anti-Smith antibodies.

S. Jime´nez et al. (94) found that SLE patients had a higher prevalence of traditional atherosclerosis risk factors: hypertension and dyslipidaemia and higher levels of

total cholesterol, triglycerides and apolipoprotein. The prevalence of carotid plaque was higher and appeared earlier in SLE patients than in the primary APS patients or controls. The IMT was similar in the three groups. Plaque prevalence in patients with primary APS (8%) was similar to that of controls (15%) and inferior to that of SLE patients with secondary APS (28.6%). SLE patients had a high prevalence of early carotid atherosclerosis that was associated with cumulative disease damage and disease activity and older age at the time of study (47.3±8.44 yrs vs 37.38±11.28 yrs, P<0.003) and found no correlation between IMT and the different antiphospholipid antibodies (aPL) or their titers. But in another study, in patients with primary APS, the IMT correlated with the anticardiolipin antibody titer and was greater in thrombotic than in non-thrombotic subjects.

Trina Thompson et al (95) noted that in the lupus patients, the frequency of plaque progression was higher (27% versus 10%) and the degree of IMT progression was similar (0.011 mm/year versus 0.008 mm/year) compared with those in a control group. The prevalence of carotid plaque was found in 31% of SLE patients, similar to that in women with SLE.

Bhatt SP et al (96) compared 50 patients with SLE with 50 age- and sex-matched healthy control subjects. Patients with lupus (mean ± SD age 31.6 ± 10.05 years, median age 30.5 years; mean± SD disease duration 52.3 ± 36.7 months, median disease duration 46 months) exhibited significantly greater intima-media thickness (IMT) than controls (mean ± SD 0.417 ± 0.07 mm versus 0.362 ± 00.07 mm; $P < 0.003$). Carotid plaques were seen in 7 patients (14%). None of the control population had plaques ($P< 0.006$). The IMT was significantly associated with age, systolic blood pressure (SBP), disease duration and menopausal status in this study.

Carotid ultrasonography has consistently showed more atherosclerotic plaques in SLE patients than in matched controls, but measurement of the intima-medial thickness, which is also indicative of subclinical atherosclerosis, has yielded conflicting results. The conflicting results for IMT in different studies, as mentioned by **Westerweel et al** (97), could be attributable to varying criteria used to select control groups. For example, **Manzi et al** (92) included as a control group, women participating in a lifestyle project at their institution. These women were older (mean age 49.0 years) compared with lupus patients (mean age 44.9 years). Also, the patient and control groups were not matched for menopausal status, race, or other cardiovascular risk factors. Similarly, the control population in the study by **Roman MJ et al** (93) included both normotensive and hypertensive patients, and the control subjects had significantly higher blood pressure than the patients, at the time of study. Both age and hypertension influence IMT and could have accounted for an increase in IMT of the control population in the aforementioned studies, thereby blunting the difference in IMT between control subjects and patients with lupus. Asian Indian patients with lupus, despite being relatively young and having shorter disease duration, exhibited premature atherosclerosis in the form of significantly thicker intima-media and plaque (96).

STUDIES FROM INDIA

Most studies from India reported the overall clinical/immunological profile of SLE. There are only a limited number studies on cardiovascular manifestations reported from India. The prevalence of cardiac involvement was from 5.3% to 58.5**%. Surjit Singh et al** (98) in their retrospective analysis, found 18.7 % patients to have cardiac involvement among the 16 children with SLE analysed. Cardiovascular involvement was seen in the form of pericarditis, myocarditis, endocarditis and right heart failure. One child had severe myocarditis and another had large pedunculated (1 cm x 0.7 cm) vegetation on the mitral valve without any valvular compromise. The study from south India (**A N Chandrasekaran et al**) (99) noted 10.2% cardiac involvement in childhood SLE. Another study from Madras found 28% cardiac involvement among 330 SLE patients (100).

Cardiac involvement was seen in 5.3% of patients with SLE, in a study from Northern Kerala (101). Two had pericardial effusion and two had mitral regurgitation. One patient had an isolated right bundle branch block.

S Kalke et al (59) in his case control study, performed echo for 54 patients with SLE and 20 age, sex matched controls, whom nine (17%) had significant cardiac involvement (four left ventricular hypertrophy, one moderate pericardial effusion, one severe aortic regurgitation, and three ventricular systolic dysfunction). Anticardiolipin antibodies (both IgG and IgM) were elevated in five patients (13 studied). One of them had severe mitral regurgitation, one had trace mitral and aortic regurgitation and one had diastolic dysfunction. There was no linear correlation between disease activity and diastolic dysfunction.

An autopsy study of 27 SLE patients from India (103) noted that the valvular lesions were the commonest cardiac lesions noted with non-bacterial thrombotic endocarditis

in nine (33.33%), valvular thickening in two (7.41%), Libman-Sacks endocarditis and infective endocarditis in one (3.70%) each. Myocarditis and myocardial scarring were seen in 10 (37.03%) and seven (25.92%) cases, respectively. Fibrinous pericarditis was noted in seven (25.92%). Thrombosis/ embolism, vasculitis and severe coronary atherosclerosis were seen in nine (33.33%), five (18.52%) and one (3.70%) subjects, respectively. Renal disease [48.14%] and cardiovascular manifestations [29.62%] were the leading causes of mortality.

In a recent cross sectional study (104), 58.5% patients had some form of cardiovascular abnormality detected by either ECG or Echo. There were 78 females and 4 males (F: M=19.5:1) with mean age of 28.4 ± 9 years. Echo abnormality was detected in 38/82 patients (46%) that ranged from pericardial effusion in 20 patients (24%), mitral regurgitation in 10 (12%), tricuspid regurgitation in five (9%) and mitral valve prolapse in 2 (2%). Dilated cardiomyopathy was detected in seven patients (8%). Diastolic dysfunction was detected in eight patients (10%) and pulmonary artery hypertension was noted in three patients (4%). ECG abnormality was detected in 31 patients (38%). This comprised of sinus tachycardia in 22 (26%), LVH in three (4%), non-specific ST-T changes in three (4%) and low voltage complex in three patients (4%). They did not find any relationship between cardiovascular status of SLE patients and disease duration, steroid dose or disease activity (SLEDAI scores).

A I M

AIM OF THE STUDY

1) To identify the various cardiac manifestations in patients with systemic lupus erythematosus.

2) To detect the risk of association of anti cardiolipin antibodies and lupus anticoagulant with cardiac involvement in lupus patients.

3) To determine the correlation between the risk factors for atherosclerosis and carotid intima medial thickness in lupus patients

MATERIALS AND METHODS

MATERIALS AND METHODS

In this prospective study, 100 consecutive patients (95 females, 5 males) with systemic lupus erythematosus (who fulfilled the1997 revision of ACR 1982 classification criteria for classification of systemic lupus erythematosus) attending the rheumatology outpatient clinic or as inpatients in the rheumatology ward of Government General Hospital, Chennai constituted the study group. This study was done during March 2007- March 2009.

Inclusion criteria

Patients who fulfilled the 1997 revision of ACR 1982 classification criteria for systemic lupus erythematosus were included.

Exclusion criteria:

Patients with overlap syndrome

Preexisting cardiac illness due to other causes.

Patients with renal failure (defined by a serum creatinine level of 3.0 mg/dl [265moles/liter] or acreatinine clearance of 30 ml/minute).

Apart from age and sex, detailed history including mode of onset, duration of illness, constitutional, mucocutaneous, musculoskeletal and symptoms pertaining to the cardiovascular system i.e. chest pain, palpitation, breathlessness, leg swelling and relevant history of other organ involvement was obtained. History of recurrent abortion if relevant, venous or arterial thrombosis and dose of steroid therapy at the time of study were noted. All patients were questioned for history of rheumatic fever, infective endocarditis, hypertension, diabetes, alcohol and smoking habits.

Clinical examination included general examination, pulse rate, blood pressure, detailed cardiovascular system, musculoskeletal and other organ system examination done in all patients. Patients were considered to be hypertensive when they had systolic BP≥ 140 mm

Hg and/or diastolic BP ≥90 mm Hg (The JNC 7 Report. JAMA 289:2560, 2003) and/or when they were taking antihypertensive drugs.

Laboratory investigations including complete haemogram, urine analysis including microscopic examination and urine PCR were noted. Biochemical parameters including blood glucose, urea, serum creatinine, serum electrolytes, liver function tests and fasting lipid profile were done for all patients.

Hypercholesterolemia is defined as Total Cholesterol >200mg/dl, LDL-Cholesterol as >130mg/dl, hypertriglyceridemia as TGL >150mg/dl and HDL- Cholesterol <40mg/dl. Dyslipidemia is defined as presence of one or more than one abnormal serum lipid concentration (**third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285:2486, 2001, Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines: SM Grundy et al for the Coordinating Committee of the National Cholesterol Education Program. Circulation 110:227, 2004**). Persons with fasting blood glucose >126mg/dl or symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl or 2-hr plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT or who were on medication for diabetes was considered as having diabetes mellitus.

Immunological investigations:

C - reactive protein was done by latex agglutination method, a value >6mg/L taken as positive. ANA and anti- ds DNA were done by ELISA method (Enzyme Immunoassay Kit, Binding Site, U.K.). Anti-Sm antibodies were detected by ELISA method by using Varelisa kit for the semi quantitative and qualitative determination of anti-Sm D antibodies in

human serum or plasma. aCL IgG and IgM by ELISA was done by using commercial ELISA kit (CAL BIOTECH, INC).

Principle

Microwells are pre-coated with purified antigen/antigens. The pre-diluted controls, together with diluted patient samples, are added to the wells, autoantibodies recognizing one or a combination of antigens bind during the first incubation. After washing the wells to remove all unbound proteins,peroxidase labeled rabbit anti-human IgG (γ chain specific) conjugate is added. The conjugate binds to the captured human autoantibody and the excess unbound conjugate is removed by a further wash step. The bound conjugate is visualized with 3,3',5,5' tetramethylbenzidine (TMB) substrate which gives a blue reaction product, the intensity of which is proportional to the concentration of autoantibody in the sample. Acid is added to each well to stop the reaction. This produces a yellow end point colour, which is read at 450nm by using ELISA reader.

Cut-off value for ANA

ANA Result	Interpretation
≤ 10.0	Negative
>10.0	Positive

Cut-off value for anti ds-DNA

Interpretation	
<30 IU/mL	Negative result
30-75 IU/mL	Borderline
>75 IU/mL	Positive result

Interpretation of results for anti-Sm antibodies

Assessment	Semi quantitative evaluation	Qualitative evaluation
Negative	<10 U/ml	Ratio < 1.0
Equivocal	10-15U/ml	Ratio 1.0-1.4
Positive	>15 U/ml	Ratio >1.4

Interpretation of results for aCL IgG and IgM antibodies

aCL IgG		aCL IgM	
<10 GPL units/ml	Negative	<15 MPL units/ml	Negative
10-15 GPL units/ml	Borderline positive	15-20 MPL units/ml	Borderline positive
>15-80 GPL units/ml	Moderate Positive	>20-80 MPL units/ml	Moderate Positive
>80 GPL units/ml	High positive	>80 MPL units/ml	High positive

The complement levels were measured using Single Radial Immune Diffusion plates. The procedure consists of immunoprecipitation in agarose gel between an antigen and its homologous antibody. It is performed by incorporating the anti C3 and anti C4 antibodies uniformly throughout a layer of agarose gel and antigen is added into the wells duly punched in the gel. Antigen diffuses radially out of the well into the surrounding gel and a visible ring of sharp precipitation forms where the antigen and antibody reacted in the zone of equivalence. A quantitative relationship does exist between ring diameters and complement concentration. The reference value for C3 is 80-160mg/dl and for C4 is 20-40mg/dl. Lupus Anticoagulant Study including activated partial prothrombin time, dilute Russel viper venom test and Kaolin clotting time were done.

Cardiac evaluation

A standard 12-lead electrocardiogram and chest x-ray were taken on each patient. The echocardiograms were recorded in all selected patients. Two dimensional, continuous wave (CW), pulse wave (PW) and color flow Doppler examinations were performed in

parasternal and apical views for structural and hemodynamic findings and valvular function. Left ventricular systolic function was determined by measuring the ejection fraction (EF) and fractional shortening (FS) from standard parasternal long-axis view by M-mode echocardiogram. Diastolic function of left ventricle was evaluated by measuring peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), E/A ratio (a measure of relative blood volume, filling the left ventricle in early versus late diastole), isovolumetric relaxation time (IRT) (the time between aortic valve closure and mitral valve opening) and deceleration time (DT) (time between peak E to zero point of velocity) by PW Doppler echocardiogram. Valvular function was assessed by CW and color flow Doppler echocardiography. Pulmonary artery systolic pressure was calculated from the peak velocity of the tricuspid regurgitation jet and estimated central venous pressure. Pulmonary hypertension was defined as pulmonary artery systolic pressure >30 mm Hg. Echocardiographic studies were performed with Philips iE33 ultrasound system.

Duplex ultrasonography

Carotid arteries were evaluated using the ALOKA P3500 machine equipped with a linear probe (3.5–15 MHz).The intima-media thickness (IMT) was measured at common carotid artery (10 mm before the bulb), bulb(5–10 mm cranially to the start of the bulb) on each side. Mean IMT calculated from four values for patients (n=70) and controls (n=20). The vessels were imaged using multiple planes, and searched for focal plaques. Plaque was defined as a distinct area of hyperechogenicity and/or focal protrusion of the vessel wall into the lumen.

Disease activity was assessed in the study with the use of the Systemic Lupus Erythematosus Disease Activity Index.

Statistical Analysis

The statistical analysis was performed using the SPSS (version 17.0). Results are presented as the mean ± SD, except for frequencies, which are expressed as percentages. Comparisons between groups were made by means of 2-sample t-test, and chi square test used when appropriate. Binary logistic regression analysis was used to predict the possibility of having an overall cardiac disease and valvular heart disease from the predictor variables like blood pressure, CRP, LDL, TGL, HDL, Complements, LAC, aCL and from a history of recurrent abortion in patients with lupus. Pearson correlation was used to identify significant relationships between variables and carotid IMT. P values less than 0.05 (2-tailed) were considered significant.

RESULTS

RESULTS

There were 95 females and 5 males in the study group (Fig 1). The age of the patients varied from 11 years to 45 yrs (Fig 2). The mean age of the patients was 23±6.77 years. Disease onset in the second or third decade was common (mean age 20.83± 6.29 years). Almost one quarter of patients had childhood onset of the disease (Fig 3). The mean disease duration was 2.5±2 years.

Table 1

Cross-tabulation: Disease duration vs. cardiovascular status (by either ECG or Echo)

Disease duration	Cardiac status				Total
	Normal		Abnormal		
≤3 yrs	40	54.79%	33	45.20%	73
>3 yrs	18	66.66%	9	33.33%	27
Total	58		42		100

$\chi 2 = 1.14$; ns

The results of the chi square test (Table 1) implied that cardiac involvement is independent of disease duration in SLE patients.

Symptoms like dyspnea on exertion (27 %), chest pain (15%), palpitation (21%) and leg swelling (19%) were present. Hypertension and tachycardia were present in 15%. Cardiac failure was present in 4% of patients. Pulsus paradoxus due to cardiac tamponade was seen in one patient, for which pericardiocentesis was done. Systolic thrill in the mitral area was present in one patient. On auscultation muffled heart sound was present in5%, loud P2 in 7%, third heart sound in 15%, fourth heart sound in 4%, mid systolic click in the mitral area in 5%, pan systolic murmur in the mitral area in 4% and pericardial rub was heard in 3% of patients. 40% of patients with cardiac involvement (by echo) did not have any symptoms or signs related to cardiovascular system.

FIGURE 1

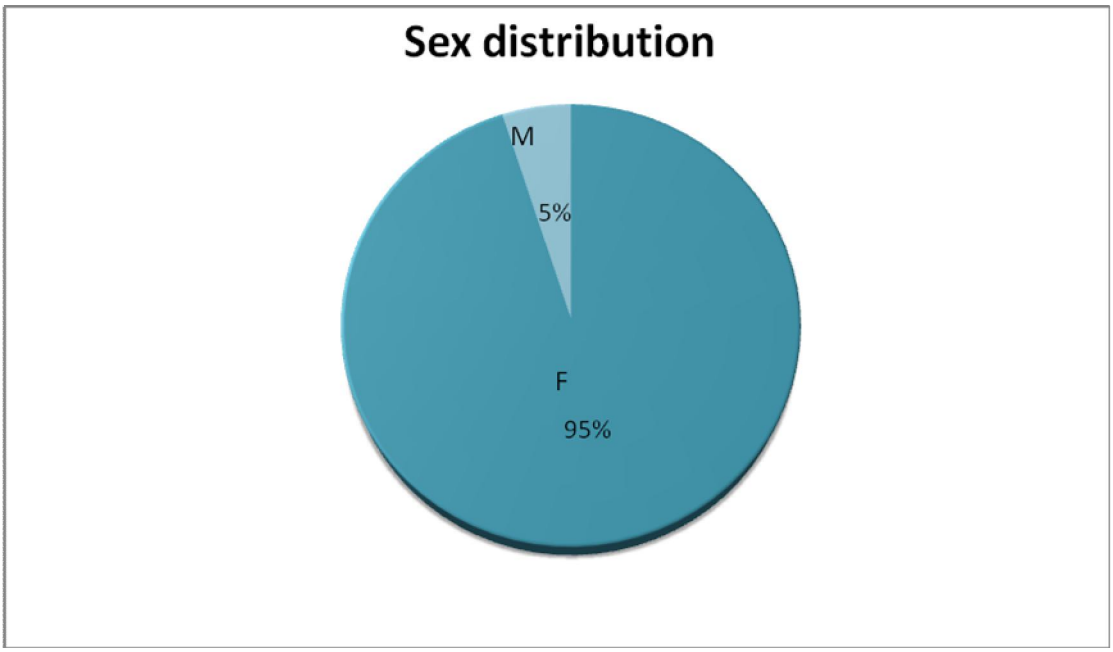


FIGURE 2

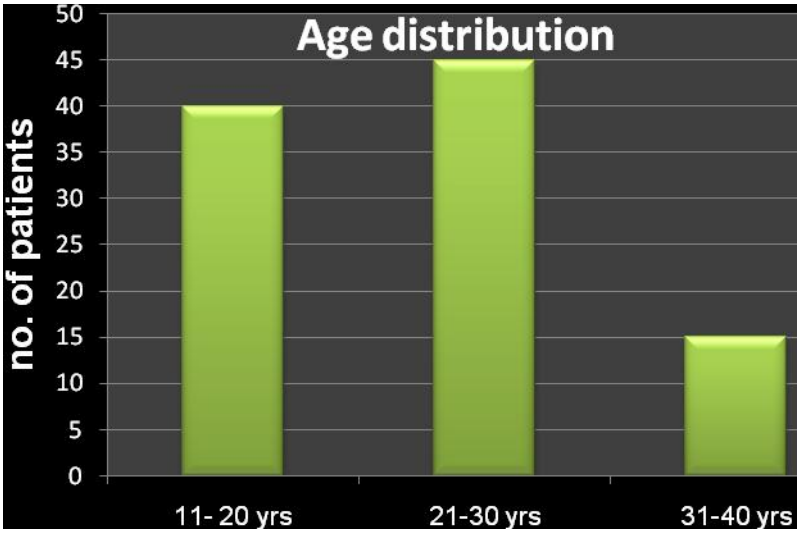


FIGURE 3

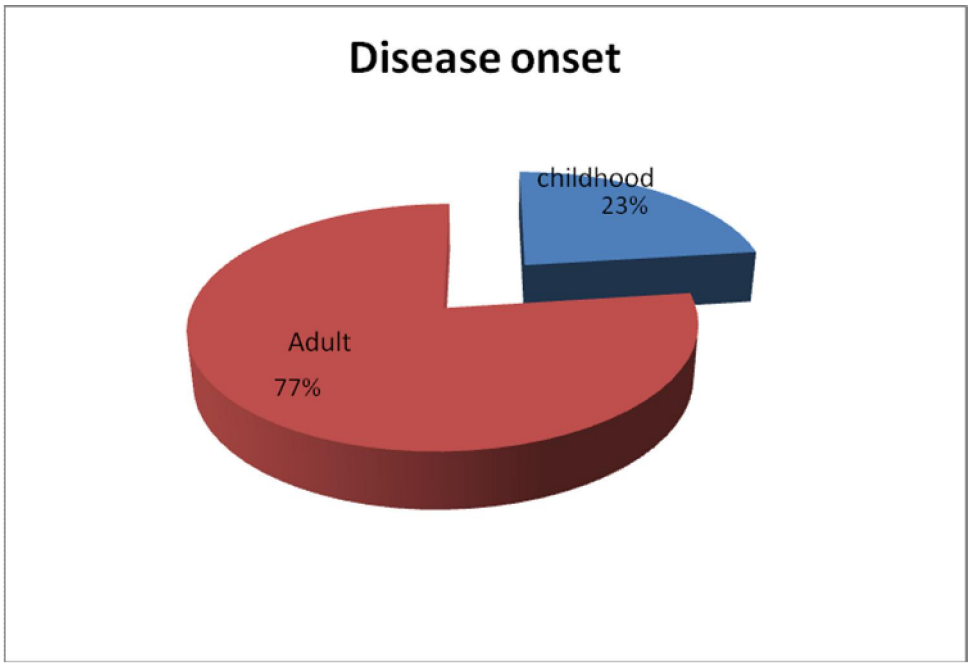
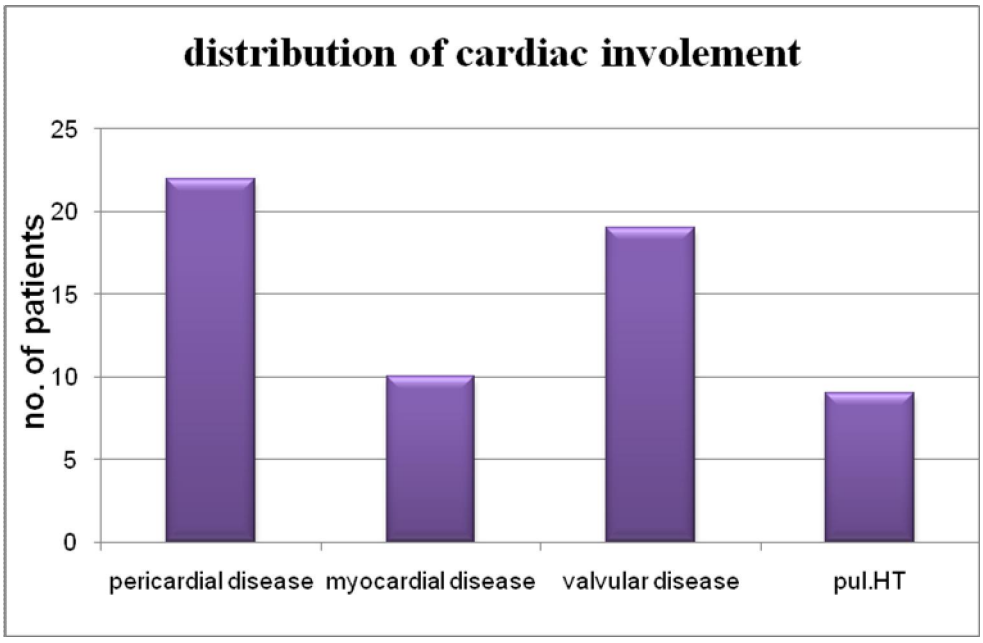


FIGURE 4



Cardiac abnormalities were found in 42% of patients. 58% patients had no cardiac involvement. The electrocardiogram (ECG) was abnormal in 25% of cases. The abnormal findings were sinus tachycardia in 16%, ST-T changes in 5%, conduction abnormalities in 3 % of cases (AVNRT, RBBB and complete heart block in 1 patient each), RVH pattern and low voltage complexes were present in each of 1% of patients. In the chest X-ray PA view, unilateral & bilateral pleural effusion each was present in 5 % cases. Cardiomegaly was noted in 7% of patients and pneumonitis in 2%.

Echocardiographic abnormalities were found in 41% of patients (Fig 4). Out of 100 patients, mild pericardial effusion was present in 15%, moderate in 3% and large effusions in 4% of cases. One patient had large pericardial effusion with tamponade and pericardial strands were noted in another one. Global hypokinesia due to myocarditis was found in 3%. LV diastolic and systolic dysfunction was found in 6% and 3% of cases respectively. 2% of patients had mild to moderate concentric LVH.

Valvular abnormalities were seen in 19% of our patients, comprising mitral valve involvement in (15%), followed by tricuspid in (9%) and then aortic valve in (3%) (Fig. 5). Mild, moderate, severe mitral regurgitation, mild tricuspid regurgitation and aortic regurgitation was found in10%, 2%, 1%, 7%, and 3% of cases respectively. Mitral valve thickening in 1% and mitral valve prolapse was noted in 5% of cases. None had stenotic valvular lesions. Pulmonary hypertension was seen in 9% of patients (mild- 4, moderate - 3, severe - 2).

Mucocutaneous and musculo skeletal manifestations were common among the clinical features noted in the study group. Recurrent abortion was noted in 4%, digital gangrene in 5% and deep venous thrombosis of left leg in 1%. None of the patients had diabetes mellitus, history of consumption of alcohol or smoking habits.

FIGURE 5

Valvular disease distribution

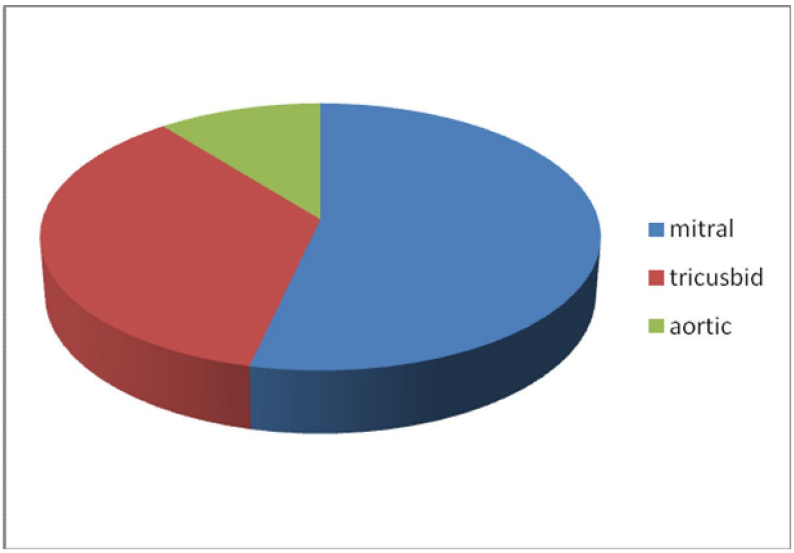


FIGURE 6

Echo - Pericardial effusion

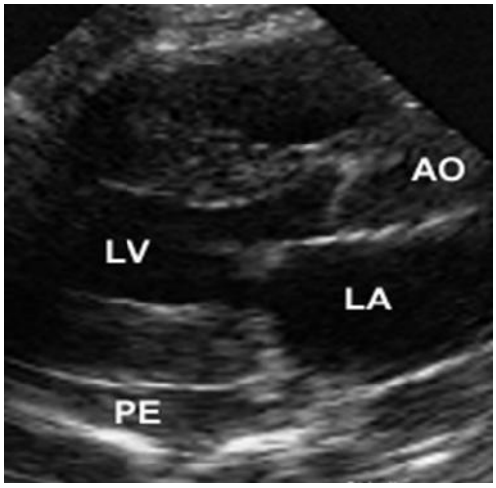


FIGURE 7

Echo – thickening of the mid portion of the posterior mitral valve leaflet (arrow)

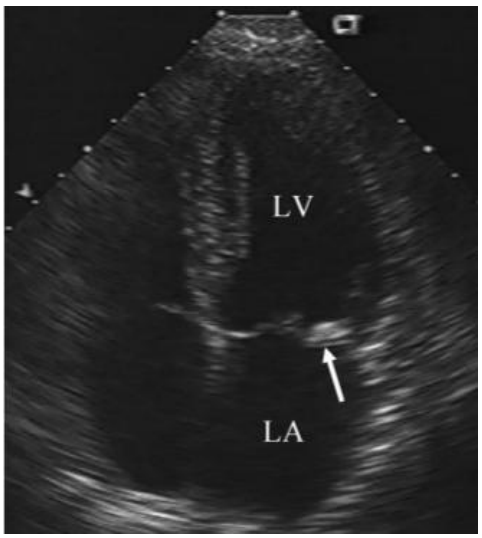


FIGURE 8

Echo – Mitral regurgitation

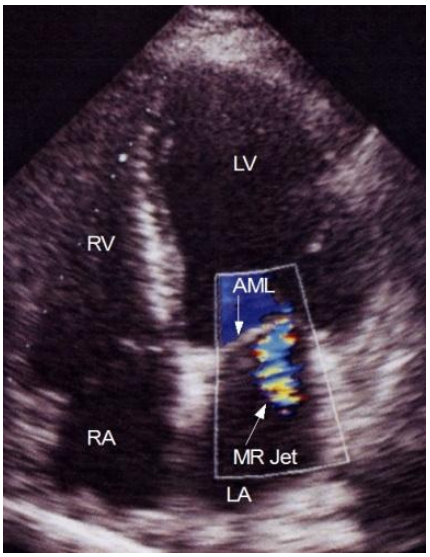
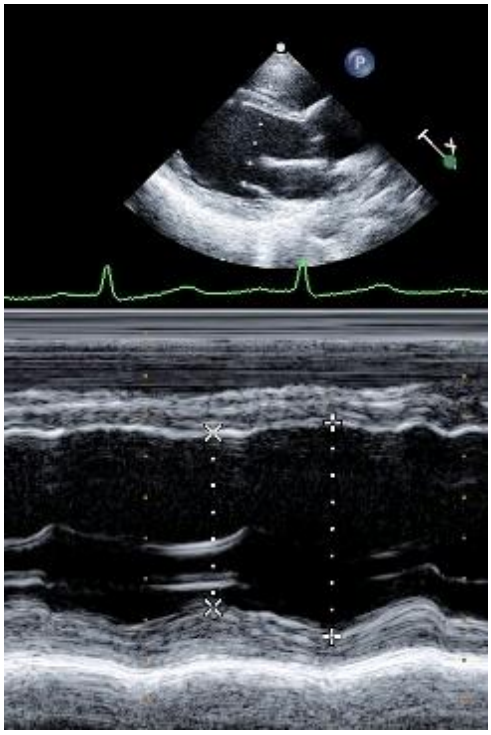


FIGURE 9

Echo – Dilated cardiomyopathy



On laboratory investigations, majority of patients (65%) were anaemic (<10 gm), thrombocytopenia in 15%, elevated ESR in 59% and positive CRP was present in 38% of patients. Dyslipidaemia was present in half of the patients (54%). Elevated total cholesterol in 44%, hypertriglyceridaemia in 54%, increased low density lipoproteins in 35% and low high-density lipoprotein (HDL) levels in 21% were noted.

ANA was positive in 97%, anti dsDNA in 71% and Sm antibodies in 34% of cases. LAC and anticardiolipin antibodies were present in 8% and 52% of cases respectively. Reduced complements C3 in39% and C4 were found in 27% of cases. Overall the disease activity was high (mean±SD = 18.21±10.64). All patients were on steroid therapy. The mean steroid dose was 16.12 ± 7.25 mg.

Table 2

Comparison of demographic and clinical parameters -

Cardiac Vs without cardiac involvement

s.no	**Parameters**	SLE **with cardiac** involvement **(n=42)**	**%**	SLE **without cardiac** involvement (**n=58**)	**%**	**T-value**	**P value**
1	Age in yrs(mean±SD)	22.79±6.21		23.48±6.71		0.523	NS
2	M:F	1:41		1:14			
3	Duration of disease in months (mean ±SD)	27.5± 23.24		31.1±24.86		0.734	NS
4	Recurrent abortions (no. of pts)	3	7.14%	1	1.72%	1.365	NS
5	Digital gangrene/DVT	3	7.14%	3	5.17%	0.410	NS
6	Heart rate/min (mean ±SD)	89.5±11.97		85.01±11.13			
	Tachycardia>100 /min (no. of pts)	7	16.66%	8	13.79%	0.397	NS
7	hypertension(no. of pts)	9	21.42%	6	10.34%	1.352	NS

The analysis in the Tables 2 & 3 show that there exists no statistically significant difference between SLE patients with cardiac Vs without cardiac involvement in demographic, clinical and laboratory parameters, SLEDAI was also included.

Table 3

Comparison of lab parameters - cardiac Vs without cardiac involvement

s.no	**Parameters**	SLE **with cardiac** involvement(**n= 42**)	**%**	SLE **without cardiac** involvement(**n= 58**)	**%**	**T-value**	**P value**
1	Hb in gm (mean ±SD)	8.82±2.14		9.42±1.79			
	Aneamia <10 gm (no. of pts)	29	69.04 %	36	62.06 %	0.722	NS
2	Platelets in lakhs/cmm (mean ±SD)	1.95±0.82		1.72±0.78			
	Thrombocytopenia <1 lakh/cmm (no. of pts)	6	14.28 %	9	15.51 %	0.170	NS
3	ESR in mm/1 hr(mean ±SD)	66.95±31.82		66.03±41.75			
4	ESR > 50 mm/1hr (no. of pts)	28	66.66 %	31	53.44 %	1.326	NS
5	CRP positivity (no. of pts)	17	40.47 %	21	36.20 %	0.434	NS
6	T. cholesterol >200mg (no. of pts)	19	45.23 %	25	43.27 %	0.354	NS
7	LDL cholesterol >130mg (no. of pts)	13	30.95 %	22	37.93 %	0.722	NS
8	Triglycerides >150mg (no. of pts)	24	57.14 %	30	51.72 %	.025	NS
9	HDL cholesterol <40mg (no. of pts)	10	23.80 %	11	18.96 %	0.578	NS
10	LAC Study detected (no. of pts)	5	11.90 %	3	5.17%	1.225	NS
11	aCL positivity (no. of pts)	25	59.52 %	27	46.55 %	1.212	NS
12	Complement C3 Low(no. of pts)	19	45.23 %	20	34.48 %	1.088	NS
13	Complement C4 Low(no. of pts)	11	26.19 %	16	27.58 %	0.155	NS
14	SLEDAI score(mean ±SD)	19.79±11.86		17.08±9.61		1.261	NS

Table 4

Comparison of demographic and clinical parameters –

Valvular heart disease Vs without cardiac involvement

s. no	**parameters**	SLE **with valvular heart disease(n=19)**	**%**	SLE **without cardiac** involvement **(n=58)**	**%**	**T-value**	**P value**
1	Age in yrs (mean ±SD)	24.16±5.69		23.48±6.71		0.397	NS
2	M:F	1:18		1:14			
3	Duration of disease in months (mean ±SD)	26.63± 22.08		31.1±24.86		0.698	NS
4	Recurrent abortion no. of pts)	3	15.78%	1	1.72%	2.398	<0.02*
5	Digital gangrene/DVT	1	5.26%	3	5.17%	0.015	NS
6	Heart rate/min (mean ±SD)	87.21±10.39		85.01±11.13		0.760	NS
	Tachycardia >100/min (no. of pts)	2	10.52%	8	13.79%	0.368	NS
7	Hypertension (no. of pts)	4	21.05%	6	10.34%	1.205	NS

* Significant (<0.05)

In Tables 4 & 5 - Comparison of demographic, clinical parameters and SLEDAI between SLE patients with valvular heart disease Vs without cardiac involvement show that recurrent abortions were significantly higher in the former group and also the LAC & anticardiolipin antibody positivity group.

Table 5

Comparison of lab parameters - valvular heart disease Vs without cardiac involvement

s. no	Parameters	SLE with valvular heart disease(n=19)	%	SLE without cardiac involvement (n=58)	%	T-value	P value
1	Hb in gm(mean ±SD)	9.58±2.34		9.42±1.79		0.313	NS
	Aneamia <10 gm(no. of pts)	12	63.15%	36	62.06%	0.085	NS
2	Platelets in lakhs/cmm(mean ±SD)	1.72±0.77		1.72±0.78		0.00	NS
	Thrombocytopenia <1 lakh/cmm(no. of pts)	3	15.78%	9	15.51%	0.028	NS
3	ESR in mm/1 hr(mean ±SD)	66.58±35.29		66.03±41.75		0.052	NS
4	ESR > 50 mm/1 hr (no. of pts)	11	57.89%	31	53.44%	0.338	NS
5	CRP positivity(no. of pts)	8	42.10%	21	36.20%	0.461	NS
6	T. cholesterol >200mg (no. of pts)	8	42.10%	25	43.27%	0.076	NS
7	LDL cholesterol >130mg (no. of pts)	7	36.84%	22	37.93%	0.085	NS
8	Triglycerides >150mg(no. of pts)	8	42.10%	30	51.72%	0.728	NS
9	HDL cholesterol <40mg (no. of pts)	4	21.05%	11	18.96%	0.199	NS
10	LAC Study detected(no. of pts)	4	21.05%	3	5.17%	2.090	<0.04*
11	aCL positivity(no. of pts)	15	78.94%	27	46.55%	2.461	<0.02*
12	Complement C3 Low(no. of pts)	8	42.10%	20	34.48%	0.599	NS
13	Complement C4 Low(no. of pts)	2	10.52%	16	27.58%	1.525	NS
14	SLEDAI score(mean ±SD)	19.11±11.32		17.08±9.61		0.764	NS

* Significant (<0.05)

Table 6

Comparison of demographic and clinical parameters - aCL positive Vs aCL negative

s.no	Parameters	aCL positive (n=52)	%	aCL negative (n=48)	%	T-value	P value
1	Age in yrs (mean ±SD)	22.63±6.34		23.79±6.65		0.893	NS
2	M:F	3:49		2:46			
3	Duration of disease in months (mean ±SD)	26.71±22.79		32.6±25.4		1.222	NS
4	Recurrent abortions (no. of pts)	3	5.76%	1	2.08	0.946	NS
5	Digital gangrene/DVT	4	7.69%	2	4.16%	0.742	NS
6	Heart rate/min (mean ±SD)	86±9.98		87.79±13.26		0.766	NS
	Tachycardia >100/min(no. of pts)	6	11.53%	9	18.75%	1.009	NS
7	Hypertension (no. of pts)	8	15.38%	7	14.58%	0.112	NS

Tables 6 &7 shows that valvular heart disease was more common in those patients with anticardiolipin antibody positivity. But there was no significant relationship between anticardiolipin antibodies and other cardiac manifestations like pericardial disease, systolic & diastolic left ventricular dysfunction, global hypokinesia due to myocarditis and pulmonary hypertension.

Table 7

Comparison of lab parameters - aCL positive Vs aCL negative

S. no	Parameters	aCL positive (n=52)	%	aCL negative (n=48)	%	T-value	P value
1	Hb in gm (mean ±SD)	9.21±2.27		9.15±1.59		0.152	NS
	Aneamia <10 gm (no. of pts)	31	59.61%	34	70.83%	1.175	NS
2	Platelets in lakhs/cmm (mean ±SD)	1.74±0.84		1.72±0.76		0.124	NS
	Thrombocytopenia <1 lakh/cmm(no. of pts)	8	15.38%	7	14.58%	1.009	NS
3	ESR in mm/1 hr (mean ±SD)	68±36		65±40		0.395	NS
	ESR > 50 mm/1 hr (no. of pts)	32	61.53%	27	56.25%	0.537	NS
4	CRP positivity (no. of pts)	19	36.53%	19	39.58%	0.313	NS
5	T. cholesterol >200mg (no. of pts)	20	38.46%	24	50%	1.161	NS
6	LDL cholesterol >130mg (no. of pts)	16	30.76%	19	39.58%	0.923	NS
7	Triglycerides >150mg(no. of pts)	28	53.84%	26	54.16%	0.032	NS
8	HDL <40mg (no. of pts)	10	19.32%	11	22.91%	0.452	NS
9	Complement C3 Low(no. of pts)	23	44.23%	16	33.33%	1.116	NS
10	Complement C4 Low(no. of pts)	15	28.84%	12	25%	0.433	NS
11	Valvular disease	15	26.92%	4	8.33%	2.417	<0.02*
12	Sys. LV dysfunction	2	3.84%	1	2.08%	0.516	NS
13	Diast. LV dysfunction	4	7.69%	2	4.16%	0.742	NS
14	Global hypokinesia	2	3.84%	1	2.08%	0.516	NS
15	Pericardial disease	13	26.92%	9	18.75%	0.970	NS
16	PUL. HT	4	7.69%	5	10.41%	0.476	NS
17	SLEDAI score(mean ±SD)	18.63±10.67		17.75±10.69		0.412	NS

* Significant (<0.05)

Table 8

Binary logistic Regression for cardiac involvement -Classification Table

observed		Predicted		
		Cardiac disease		Percentage Correct
		.00	1.00	
Cardiac disease	.00	50	8	87.2
	1.00	23	19	45.2
Overall Percentage				70.4

Table 9

Variables in the Equation

Variables	B	B S.E.	Wald	df	Sig.	Exp(B)
BP	1.014	.666	2.319	1	.128	2.758
CRP	-.127	.464	.074	1	.785	.881
LDL	-.631	.498	1.604	1	.205	.532
TGL	.259	.449	.331	1	.565	1.295
HDL	-.036	.571	.004	1	.949	.964
LAC	.542	.821	.436	1	.509	1.720
C3	.656	.539	1.478	1	.224	1.926
C4	-.491	.599	.673	1	.412	.612
aCL positivity	.324	.445	.530	1	.467	1.328
Abortion	1.860	1.281	2.107	1	.147	6.423
constant	-.733	.476	2.369	1	2.369	.481

Table 10

Binary logistic Regression for Valvular heart disease -Classification Table

Observed		Predicted		
		Valvular heart disease		Percentage Correct
		.00	1.00	
Valvular heart disease	.00	77	2	97.5
	1.00	12	7	36.7
Overall Percentage				85.7

Table 11

Variables in the Equation

Variables	B	B S.E.	Wald	df	Sig.	Exp(B)
BP	.642	.829	.600	1	.438	1.900
CRP	.466	.671	.482	1	.487	1.594
LDL	-.318	.710	.200	1	.655	.728
TGL	-.559	.632	.783	1	.376	.572
HDL	.107	.786	.019	1	.891	1.113
LAC	1.123	.930	1.458	1	.227	3.073
C3	.741	.668	1.232	1	.267	2.098
C4	-2.122	.996	4.541	1	.033*	.120
aCL positivity	1.479	.686	4.647	1	.031*	4.388
Abortion	2.968	1.403	4.477	1	.034*	19.453
constant	-2.486	.759	10.722	1	.001	.083

*significant ($p < 0.05$)

In table 9 binary logistic regression analysis showed that there was no significant relationship between dependent (cardiac involvement) and other independent covariates (BP, CRP, LDL, TGL, HDL, LAC, C3, C4, aCL positivity, abortion).

But in table 11, the analysis showed that history of recurrent abortion and aCL positivity were significant predictors for having valvular heart disease in SLE patients. Other variables (hypertension, positive CRP, dyslipidaemia and C3) were not significantly related to the valvular heart disease. SLE patients who have recurrent abortions and aCL positivity are 19 times and 4 times more likely to have valvular heart disease respectively when compared to their counterparts.

Table 12 -Bivariate analysis (Pearson correlation)

Parameters	AGE	Disease duration in months	Systolic BP mmHg	Diastolic BP mmHg	ESR	T.Chol	LDL	TGL	HDL	aCL IgG	aCL IgM	SLEDAI
CAROTID IMT in mm	.653** (.000)	.149 (.218)	.273* (.022)	.191 (.113)	.023 (.850)	.069 (.570)	.243* (.043)	.102 (.400)	-.137 (.259)	.169 (.162)	.027 (.822)	.025 (.835)

Figures in parentheses indicate 'P' value; *: Significant ($P \leq 0.05$);
**: Very significant ($P \leq 0.01$)

The mean carotid IMT in the study group (n=70) was (mean±SD) 0.573± 0.093 mm and in the control group (n= 20) 0.47± 0.056 mm (p value <0.001). Patients with lupus (mean age 23.28±7.07, disease duration 30.91±24.24 months) exhibited a significantly greater IMT than controls (mean age 22.75±3.22 yrs). Carotid plaques were seen in 4 (5.71%) cases. None of the control population had plaques (p =NS). On bivariate analysis, the IMT was significantly affected by age, systolic blood pressure and LDL cholesterol (table 12).

DISCUSSION

DISCUSSION

SLE is a multisystem disorder and the manifestations can be variable. In atypical cases the diagnosis may be missed if the index of suspicion is not high. The present study was done on 100 SLE patients conforming to the 1997 revision of ACR 1982 classification criteria. There were 95 females and 5 males. The Female to Male ratio was 19:1. Indian series by **Malaviya *et al*** (104) had a female to male ratio of 8:1. There are reports from southern and eastern part of India, similar to the observations in the present study (100, 103).

The age of the patients varied from 11 years to 45 yrs. The mean age of the patients was 23±6.77 years. Disease onset was in the second or third decade was common. Median age at disease onset was 20.83±6.29 years. **Masi *et al*** and **Hochberg *et al*** observed a median age of disease onset at 31 and 30 years respectively *(105)*. In India, **Binoy J. Paul *et al*** and **Ghosh B *et al*** noted a median age of onset of 21.6 and 26.5±9 years respectively (101,103). Almost one quarter of patients had childhood onset of disease. The mean disease duration was 2.5±2 years. Majority of our study cases had short disease duration and renal involvement was found in 32 patients (32%).

Musculoskeletal and mucocutaneous involvement were the commonest clinical manifestations noted in the study group as reported in studies from India and abroad (100, 104).

Symptoms like dyspnea on exertion (27 %), chest pain (15%), palpitation (21%) and leg swelling (19%) were present. These symptoms may also occur due to other causes (respiratory, anaemia, renal and steroid use). Hypertension and tachycardia were present in 15% of cases. Hypertension is closely related to disease duration and nephropathy. Cardiac failure was present in 4% of patients. Cardiac tamponade was seen in one patient. Systolic thrill in the mitral area was present in one patient. On auscultation muffled heart sound was

present in5%, loud P2 in 7%, third heart sound in 15%, fourth heart sound in 4%, mid systolic click in the mitral area in 5%, pan systolic murmur in the mitral area in 4% and pericardial rub was heard in 3% of patients. Clinical cardiac manifestations were infrequent in our study which was similar to the study by **Ramonda R et al** (106).

ECG abnormalities were detected in 25% of cases comprising sinus tachycardia in 16%, ST-T changes in 5%, conduction abnormalities in 3 % of cases (AVNRT, RBBB and complete heart block in each 1 patient), RVH pattern and low voltage complexes were present in each 1% of patients. This is in agreement with the findings of **Uri Elkayam et al** (107) except for sinus tachycardia which was comparatively more frequent in our study. **Ghosh B et al** (103) found sinus tachycardia in 22 patients (26%) followed by non-specific ST-T change in three patients (4%).

On echocardiogram cardiac abnormalities were found in 41% of patients which was similar to **Gentile et al.** (46.3%) and **B Ghosh et al** (46%) (103, 108). Echo findings comprised of pericardial effusion in 22%, valvular abnormalities in 19% and over all myocardial involvement in 10% of cases.

Pericardial disease is usually asymptomatic, and is generally diagnosed by echo. It was the most common lesion in the present study. Mild pericardial effusion was present in 15%, moderate in 3% and large effusion in 4% of cases. **Cervera R et al** (7) in a case control prospective study found pericardial effusion in 27% of patients (20% mild effusion and 7% moderate to large effusion). There are rare reports of pericardial tamponade in SLE. Pericardiocentesis was done for 1 patient for large pericardial effusion with tamponade and pericardial strands noted in another one. Evaluating several clinical studies in the literature, **Doherty and Siegel** (5) found a 25.6% prevalence of pericarditis in 1,194 patients with SLE, but a prevalence of 62.1% in the 254 cases at autopsy.

Compared to the present study (10%), **Cervera R et al** (7) found increased frequency (20%) of myocardial abnormalities. In the present study, global hypokinesia with decreased EF due to myocarditis was found in 3% of patients. LV diastolic and systolic dysfunction was found in 6%, 3% cases respectively. 2% of patients had mild to moderate concentric LVH. **Kalke S et al** (59) observed more or less similar frequency in their 54 SLE patients.

Myocarditis is an uncommon, often asymptomatic manifestation of SLE with a prevalence of 8 to 25% in different studies. Lupus myocarditis can be diagnosed by clinical suspicion and echocardiographic evidence of impaired LV EF and wall motion abnormality, if other etiologies such as viral and ischemic cardiomyopathy are excluded.

Involvement of the mitral valve was most commonly encountered followed by aortic valve (62**)**. However, any valve or multivalvular affection can occur. Functionally, valvular regurgitation was reported to occur in up to 74% of patients, 7~41% of cases having moderate to severe regurgitation, while valvular stenosis was seen in only 3~4% of patients (62**)** and usually accompanies regurgitation. Valvular abnormalities was seen 19% of our patients, comprising mitral valve involvement in (15%), followed by tricuspid (9%) and then aortic valve (3%).Mild, moderate and severe mitral regurgitation was found in10%, 2%, and 1% of cases respectively. Mitral valve thickening was seen in 1%. Mitral valve prolapse was noted in 5% of cases. None had stenotic valvular lesions or vegetations. Similar findings had been reported by **Ghosh B et al** (103) in a recent study. The incidence of this type of endocarditis has progressively declined during the last four decades, because of the use of more efficient therapies for SLE in recent years, compared with the initial period of 1920 and 1930 when the lesions were first described. Some people attribute the possible reduction in the incidence of these lesions in lupus to an increase in corticosteroid use (5). Also attributed to steroids is a possible reduction in valvular dysfunction, because they promote healing of

scars caused by veruccous lesions, which would result in fibrotic retraction of valve cusps (63).

There exists no relationship between cardiovascular status of SLE patients, disease duration and disease activity (SLEDAI scores). **Lolli C et al** (109) also observed similar findings as by **Ghosh B et al** from India (103).

There was no statistically significant difference in the parameters (table 2 & 3) between the patients who had cardiac involvement and those with normal cardiac status including anticardiolipin antibodies. Higher percentage of recurrent abortions, anticardiolipin antibodies and LAC were present in patients with valvular heart disease (p value < 0.05) (table4, 5).

In the present study, the frequency of anticardiolipin antibodies was 52% while two studies from our country, the north and from Madras reported 28% and 41% respectively. When patients were divided on the basis of anticardiolipin antibodies, valvular abnormalities was higher in the positive group (p value < 0.02) (table 7) and no significant difference was found with other cardiac manifestations including pulmonary hypertension and other parameters between the groups. This is in agreement with the findings of **Gentile et al** (108) in which pericardial effusion was detected in 19 patients without any statistical difference between aPL positive and negative groups, but more frequent valvular involvement being noted in aPL positive patients. But as opposed to Gentile et al there was no significant difference in myocardial involvement between the groups (table 7). Some studies also have suggested an association between the valvular disease and antiphospholipid antibodies (6, 7, 80**)**. However, other reports have not confirmed the relationship between antiphospholipid antibodies and valvular heart disease (8, 110**).**

Binary logistic regression analysis (table 10 & 11) showed that history of recurrent abortions and aCL positivity were significant predictors for valvular heart disease in SLE

patients. SLE patients who have recurrent abortions are 19 times and those who have aCL positivity are 4 times more likely to have valvular heart disease, compared to their counterparts.

Dyslipidemia is a significant problem in SLE. Untreated SLE is associated with endogenous dyslipidemia, increased very low density lipoprotein (VLDL), triglycerides, low high-density lipoprotein (HDL) levels, and altered chylomicron metabolism. Treatment with steroids is associated with increased low density lipoproteins and triglyceride concentrations. Dyslipidemia was present in half of our patients (54%). Elevated total cholesterol in 44%, hypertriglyceridemia in 54%, increased low density lipoproteins in 35% and low high-density lipoprotein (HDL) levels in 21% were noted.

Jimenez S. et al. (94) noted in their study that SLE patients had a significantly higher prevalence of hypertension (31%) and hypercholesterolemia (38.6%) than primary APS patients and controls, and higher incidence of hypertriglyceridemia (31.4%) than controls. SLE patients had higher total cholesterol, triglycerides and apolipoprotein B levels than controls at the time of ultrasound study. A recent study from eastern India (103) reported dyslipidaemia in 49 SLE patients (60%) in the form of high triglyceride (32%), high total cholesterol (26%), low HDL (48%) and high LDL (36%).

The mean carotid IMT in the study group (n=70) was (mean±SD) 0.573± 0.093 mm and in the control group (n= 20) 0.47± 0.056 mm (p value <0.001). Contrary to some western studies, the frequency of carotid plaques was less (5.71%) and the patients with lupus exhibited a significantly greater IMT than controls. This was in full agreement with Bhatt SP et al from India and Zhang CY et al from China (96).

Bivariate analysis (table 12) showed that age, systolic blood pressure and LDL cholesterol were independently related to increased carotid IMT which was similar to the study by Bhatt SP et al. Disease duration did not correlate with carotid IMT in the present

study as opposed to that of Bhatt SP et al., where disease duration had a positive correlation with carotid IMT. There was no relation between anticardiolipin antibodies and the carotid IMT which was similar to the study by **Jimenez** S**. et al** (94).

CONCLUSION

CONCLUSION

1. Pericarditis was the most common observation followed by valvular heart disease.
2. Myocarditis, conduction abnormalities, impairment of systolic and diastolic function and pulmonary hypertension occur less frequently.
3. Significantly higher number of patients had valvular heart disease in the anticardiolipin antibody positive group.
4. SLE patients with anticardiolipin antibody positivity are 4 times more likely to have valvular heart disease, compared to their counterparts.
5. The risk of valvular heart disease is 19 times higher in lupus patients who also have secondary antiphospholipid antibody syndrome with history of recurrent abortions.
6. Dyslipidemia was found in half of the patients.
7. Patients with lupus exhibited a significantly greater IMT than controls.
8. The carotid IMT was independently related to age, systolic blood pressure and LDL cholesterol.
9. There was no relation between anticardiolipin antibodies and the carotid IMT.

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APPENDICES

ABBREVIATIONS

aCL IgM, IgG	Anticardiolipin antibody IgM, IgG
ACR	American college of Rheumatology
ANA	Antinuclear antibodies
anti-RNP	Anti-ribonucleoprotein
aPL	Antiphospholipid antibody
AVNRT	Atrioventricular nodal reentry tachycardia
C3,C4	Complement
CAD	Coronary artery disease
CRP	C-reactive protein
DLE	Discoid Lupus Erythematosus
dsDNA	Double stranded DNA
IMT	Intima-media thickness
LAC	Lupus anticoagulant
MCTD	Mixed connective tissue disease
SLE	Systemic Lupus Erythematosus
Sm Ab	Anti –Smith antibody
TEE	Trans esophageal echocardiography
TTE	Trans thoracic echocardiography

PATIENT CONSENT FORM

Study title : A study on cardiovascular manifestations in lupus patients"

Study Centre : Department of Rheumatology,Government General Hospital,Chennai.
Patient's Name : _____
Patinet's Age : _____
Identification Number : _____

Patients may check (✓) these Boxes

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that the investigator, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current tsudy and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identify will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any detorieration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby agree to allow the investigator to take around 30ml of blood from me for the laboratory investigations until the completion of study. ☐

I hereby give permission to undergo complete physical examination, and diagnostic tests including hematological, Biochemical, Radiological and urine examination. ☐

Signature / Thumb Impression of the patient. _____ Place _____ Date

Patient's Name&Address : _____
_____

Signature of the Investigator : _____ Place _____ Date
Study Investigator's Name : _____

PROFORMA

CARDIOVASCULAR MANIFESTATIONS OF SLE

NAME: AGE/SEX: OP/IP No:

RCC No :

ADDRESS: OCCUPATION:

FEATURES AT ONSET:

DURATION:

DURING COURSE:

H/O PRESENT ILLNESS:

Fever	Malaise	Fatigue	photosensitivity
Malar rash	Discoid lesion	Palatal ulcer	Alopecia
Purpura	Striae	Vasculitic ulcer	Raynaud's
Gangrene	Arthritis -poly	Pauci	Arthralgia
Mayalgia	Weakness	Headache	visualsym
Psychosis	Seizures	insomnia	Chest pain
Palpitation	Dyspnea	Syncope	Pedal edema
Cough	Expectoration	Hemoptysis	Hematuria
Periorbital edema	Facial puffiness	Oliguria	

OTHERS

PAST HISTORY: PERSONAL:

TREATMENT HISTORY:

PHYSICAL EXAMINATION:

Fever Aneamia clubbing cyanosis LN PE JVP

MUCOCUTANEOUS OTHERS

PULSE BP RR

CVS RS ABDOMEN

CNS MSS:

INVESTIGATIONS:

Hb TC DC ESR 1 hr Platelets BT CT

Urea Cr Uric acid Sugar T.Bilirubin ALT AST

SAP LDH CPK Electrolytes Na K HCO 3 Cl

Lipid profile

Urine R/E PCR 24 hrs protein

ANA Anti dsDNA Sm Ab

LAC aCL Complement

CRP

ECG CXR PA View

ECHO Carotid IMT

ASSESSMENT

SLEADAI

MANAGEMENT

NSAIDS STEROIDS Pulse Oral

IMMUNOSUPPRESSANTS ANTICOAGULANTS/ANTIPLATELETS

OTHERS

SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX
SELENA MODIFICATION

Physicians Global Assessment _____

0 None 1 Mild 2 Med 3 Severe

SLEDAI SCORE

Check box: If descriptor is present at the time of visit or in the proceeding 10 days

Wt	Present	Descriptor	Definition
8	☐	Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	☐	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary Casts	Heme-granular or red blood cell casts
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	New Rash	New onset or recurrence of inflammatory type rash.
2	☐	Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.
2	☐	Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations

2	□	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	□	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2	□	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	□	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	□	Fever	>38°C. Exclude infectious cause
1	□	Thrombocytopenia	<100,000 platelets/mm3
1	□	Leukopenia	<3,000 White blood cell/mm3. Exclude drug causes.

____ TOTAL SCORE (Sum of weights next to descriptors marked present)

Mild or Moderate Flare □	**Severe Flare** □
□ Change in SLEDAI > 3 points	□ Change in SLEDAI > 12
□ New/worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE)	□ New/worse CNS-SLE Vasculius Nephritis Myositis Pk < 60.000 Home anemia: Hb <7% or decrease in Hb > 3% **Requiring:** double prednisone Prednisone>0.5 mg/kg/day hospitalization
□ Increase in Prednisone, but not to >0.5 mg/kg/day	□ Prednisone >0.5 mg/kg/day
□ Added NSAID or Plaquenil	□ New Cytoxan, Azathioprine, Methotrexate, Hospitalization (SLE)
□ ≥1.0 Increase in PGA, but not to more than 2.5	□ Increase in PGA to > 2.5

SL. NO	AGE	SEX	RCC No	DOD	CARDIOVASCULAR SYMPTOMS	RECURRENT ABORTION	EVID OF THROMBOSIS	PULSE/min	BP mmHg	HB gm	PLATELETS lakhs/cmm	ESR	CRP
1	20	F	49958	4m	dyspnea, palpitation	nil	nil	86	110/80	8.2	1.6	70	P
2	25	F	46284	3yr	chest pain,dysnea	yes	nil	110	100/70	5.6	3.14	145	p
3	18	M	49937	2yr	nil		nil	82	110/70	11.2	1.6	55	p
4	15	F	49992	3m	nil		nil	102	120/80	9.8	1.2	40	p
5	15	F	49963	3m	nil		nil	122	120/70	8.7	0.85	43	n
6	19	F	47327	4yr	dyspnea, palpitation		nil	86	116/70	12	1.66	45	P
7	22	F	49880	1.5yr	chest pain,PE, palpitation		nil	96	130/90	12.2	1.4	85	P
8	20	F	44990	6yr	nil		nil	96	100/70	10	1.32	25	p
9	26	F	42505	6yr	dyspnea, palpitation		nil	80	110/70	11.3	1.15	10	n
10	24	F	47565	6yr	PE,palpitation		nil	90	90/60	8.3	3.34	102	P
11	29	F	49108	3yr	nil		gangrene Lt. hand	92	110/70	6.8	0.55	80	P
12	22	F	49970	2yr	nil	nil	nil	92	100/70	9.2	1.4	50	P
13	32	F	49607	1yr	dyspnea, palpitation,chest pain		nil	74	84/66	11.8	0.95	28	n
14	23	F	50057	3m	nil	nil	nil	102	90/66	9	2.24	42	n
15	29	F	48313	1yr	dyspnea, palpitation,chest pain	nil	nil	88	96/74	7.8	1.2	65	n
16	19	F	48397	2yr	nil		gangrene toes	92	140/80	14.3	1.95	34	n
17	19	F	50086	6m	dyspnea, palpitation,chest pain		nil	96	112/70	11.4	1.24	20	n
18	36	M	49169	3yr	dyspnea, PE		nil	100	120/70	8	2.37	128	n
19	32	F	48556	3yr	dyspnea	nil	nil	82	110/80	8.2	1.8	25	n
20	22	F	40603	4m	PE		nil	96	110/76	11.4	1.75	95	n
21	21	F	50178	1yr	nil		nil	78	90/70	9.6	1.8	120	n
22	19	F	48398	9m	dyspnea		nil	102	110/80	7.9	1.36	125	p
23	22	F	44347	4yr	nil	nil	nil	82	100/80	9.4	0.5	56	p
24	20	F	50072	3yr	nil		nil	80	120/76	7	1.45	98	n
25	14	F	46785	3yr	chest pain,PE		nil	110	160/100	8.1	0.5	68	n

SL. NO	AGE	SEX	RCC No	DOD	CARDIOVASCULAR SYMPTOMS	RECURRENT ABORTION	EVID OF THROMBOSIS	PULSE/min	BP mmHg	HB gm	PLATELETS lakhs/cmm	ESR	CRP
26	18	F	47112	2yr	nil		nil	86	110/80	10	2.6	46	P
27	18	F	47643	1.5yr	nil		nil	84	114/80	10	0.85	52	n
28	16	F	46142	6yr	nil		nil	98	100/70	8.5	1.6	80	n
29	24	F	45302	7yr	nil		nil	76	110/76	12.7	2.79	40	p
30	37	F	50331	6m	PE	nil	nil	80	96/50	6.8	0.4	102	n
31	18	F	50251	3m	chest pain, dyspnea, PE	preterm	nil	96	140/116	6.9	1.45	80	p
32	20	F	50344	1m	nil		nil	78	110/80	8.1	0.92	58	p
33	21	F	50402	2.5yr	PE	nil	nil	78	110/70	8	2.1	80	n
34	18	F		6m	chest pain, dyspnea, PE,palpitation		gangrene toes,fingers	96	110/90	4	1.14	150	n
35	16	F	50390	4m	chest pain, dyspnea, PE,orthopnea		nil	90	90/70	8.4	3	76	n
36	16	F	48461	2yr	dyspnea , palpition		nil	126	140/86	8	1.92	105	p
37	33	F	50454	1yr	nil	nil	nil	92	110/70	9.3	1.91	80	n
38	20	F	45625	9yr	nil		nil	76	110/70	10.7	1.7	25	n
39	15	F	49310	7m	nil		nil	90	110/70	7.4	1.55	120	n
40	21	F	50508	4yr	dyspnea		nil	78	116/70	10.5	1.01	33	n
41	21	F	49701	1.5yr	dyspnea		nil	100	90/60	5	1.82	85	n
42	24	F	50517	4m	PE		nil	74	110/80	9.8	1.2	50	n
43	18	m	49628	7m	nil		nil	82	110/90	8.4	1.56	47	n
44	25	F	49978	4.5yr	dysnea		nil	80	140/96	12.4	2	8	p
45	30	F	45373	3yr	nil	nil	nil	76	110/80	11	1.4	65	p
46	25	F	50547	3m	nil	nil	nil	78	110/70	8.5	0.64	54	n
47	18	F	50529	3yr	chest pain, dyspnea, palpitation		DVT Lt leg	90	116/80	9.4	1.65	42	n
48	25	F	50564	2m	dyspnea		nil	116	122/80	8	1.56	135	n
49	24	F	50531	4m	chest pain, palpitation	yes	nil	110	110/80	6.6	1.67	82	n
50	19	F	47497	2.5yr	nil		nil	78	100/70	5.3	0.56	138	p

SL. NO	AGE	SEX	RCC No	DOD	CARDIOVASCULAR SYMPTOMS	RECURRENT ABORTION	EVID OF THROMBOSIS	PULSE/min	BP mmHg	HB gm	PLATELETS lakhs/cmm	ESR	CRP
51	17	F	50636	1yr	nil		nil	76	120/80	11	1.56	10	n
52	20	F	49538	2yr	palpitation		nil	75	110/80	11.8	1.82	10	n
53	22	F	49641	3m	PE,dyspnea		nil	90	100/80	6	1.6	40	n
54	32	F	50643	6m	nil	nil	nil	102	106/80	9	1.6	135	n
55	23	F	49985	6m	palpitation		nil	85	110/80	7.8	1.8	85	p
56	18	F	44341	4yr	nil		nil	76	110/80	9.8	1.93	100	p
57	16	M	46417	3yr	nil		nil	76	100/70	11.4	1.3	45	n
58	22	F	41235	1.5yr	Chestpain		nil	88	116/80	12.2	2.26	43	n
59	23	F	46939	4yr	dyspnea		nil	76	100/70	10.3	2.11	70	n
60	25	F	48459	2yr	nil		nil	88	140/70	11.2	2.01	35	n
61	30	F	44263	1.5yr	nil	nil	nil	76	124/80	9.2	4.53	33	n
62	40	F	43441	5yr	nil	nil	nil	74	130/90	7	0.45	98	n
63	15	F	49266	1yr	nil		nil	76	110/80	8	1.24	56	n
64	22	F	48754	2yr	dyspnea		nil	70	110/70	8.4	1.76	114	n
65	37	F	50363	1.5yr	PE	nil	nil	82	106/80	9.8	1.62	80	n
66	25	F	48491	2yr	nil	yes	nil	78	110/70	11.4	2.75	20	n
67	22	F	41516	3.5yr	nil	nil	nil	76	110/76	10.7	2.77	30	n
68	20	F	44138	5yr	dyspnea		nil	78	110/82	6.7	2,74	120	p
69	36	F	46304	3yr	nil	nil	nil	80	126/80	10.2	0.85	95	p
70	27	F	50654	2yr	nil	yes	nil	74	130/80	8.8	1.53	65	p
71	38	F	43814	5yr	nil	nil	nil	78	120/78	12	2	20	n
72	18	F	47628	2yr	nil		nil	92	96/70	10.8	1.5	15	p
73	24	F	49424	6m	dyspnea, palitation	nil	nil	110	100/70	7	4.26	68	n
74	20	F	50727	2yr	chest pain, dyspnea		nil	88	110/70	11.2	1.68	35	p
75	23	F	50785	6m	nil		nil	90	110/70	9.6	1.53	65	p

SL. NO	AGE	SEX	RCC No	DOD	CARDIOVASCULAR SYMPTOMS	RECURRENT ABORTION	EVID OF THROMBOSIS	PULSE/min	BP mmHg	HB gm	PLATELETS lakhs/cmm	ESR	CRP
76	38	F	46952	3yr	nil	nil	nil	84	140/80	8	1.9	34	p
77	34	F	47403	7yr	nil	nil	nil	98	70/60	8.2	2.88	67	p
78	27	F	44660	5yr	chest pain, palpitation	nil	nil	86	100/70	10	3.78	25	n
79	27	F	50798	1yr	nil	nil	nil	102	110/80	9.8	1.37	65	n
80	25	F	41105	5yr	palpitation	nil	nil	90	90/60	9.4	1.56	5	n
81	21	F	46800	5yr	palpitation		nil	82	160/110	10.2	2.5	20	p
82	18	F	48442	3yr	nil		nil	70	110/70	12.6	2.76	65	n
83	37	F	49675	5yr	nil	nil	nil	76	130/86	11	2.6	34	n
84	12	F	50287	4m	nil		nil	88	90/60	9	1.56	112	n
85	11	F	50800	8m	dyspnea		nil	82	110/70	8.2	0.212	110	n
86	30	F	42698	8yr	nil	nil	nil	76	140/86	9.2	1.9	30	n
87	27	M	46708	5yr	nil		nil	87	130/90	9.8	1.6	32	p
88	22	F	50812	5yr	chest pain, palpitation		nil	88	130/90	9	1.72	20	n
89	32	F	47858	4yr	nil		nil	76	160/100	7.2	1.8	95	p
90	20	F	47303	3yr	dyspnea,palpitation		nil	79	120/82	11	1.68	10	p
91	17	F	50955	6m	PE		nil	92	110/80	9	0.87	152	n
92	13	F	51046	2yr	PE		nil	86	110/70	6.2	1.58	95	P
93	29	F	51037	3m	nil	nil	nil	70	100/80	9.8	3.12	116	n
94	21	F	51067	2yr	PE		nil	82	110/80	8.4	1.52	130	P
95	24	F	51009	5yr	palpitation, dyspnea, PE		gangrene digits	110	146/96	9.4	0.44	96	p
96	20	F	47971	2.5yr	nil		gangrene digits	84	110/76	8.8	2.4	25	p
97	28	F	50963	3yr	nil	nil	nil	90	110/70	10.4	1.84	100	n
98	15	F	51034	1yr	palpitation, dyspnea, PE		nil	80	160/110	10.6	1.69	78	n
99	21	F	51061	6m	PE	1 abortion	nil	78	124/80	4	1.8	70	n
100	32	F	48810	4yr	chest pain, palpitation	nil	nil	76	130/84	6.3	2.8	82	n

SL. NO	T.Chol	LDL	TGL	HDL	ANA	dsDNA	Sm Ag	LAC	ACL IgG	ACL IgM	C3	C4	ECG	CXR	ECHO
1	200	116	220	40	p	p	NG	NG	MP	MP	L	N	N	N	PE+, MR trivial,Global hypokinesia of LV, EF 50%
2	180	114	142	38	P	BLP	P	NG	MP	MP	N	L	ST	N	PE+, MR &AR Mild
3	130	67	124	40	P	BLP	P	NG	MP	MP	N	N	N	N	N
4	180	80	226	56	p	P	NG	NG	MP	MP	N	N	N	N	PE+
5	208	129	176	44	P	BLP	P	NG	NG	NG	N	N	ST	N	N
6	166	93	126	48	p	p	NG	NG	MP	MP	L	L	ST	N	N
7	219	153	119	42	p	NG	NG	NG	MP	MP	L	N	ST	B/L PL. Effusion	trivial MR
8	130	76	70	40	p	P	NG	NG	NG	NG	L	L	RBBB,T↓inV2-V5&II,III,aVF	cardiomegaly	severe PHT,RA&RV dilated, PE
9	156	86	110	48	P	BLP	P	P	MP	MP	L	N	RVH	N	RA&RV dilated,TR mild,PG 50mmHg, PHT mod
10	280	216	140	36	HP	p	NG	NG	NG	NG	L	N	N	N	Severe MR, PHT &TR
11	213	121	189	54	HP	P	NG	NG	MP	MP	L	L	**T↓**I,II,AvI &v1-v4	B/L PL. Effusion	N
12	174	98	166	43	P	NG	NG	NG	MP	MP	N	N	N	N	N
13	258	180	164	45	HP	P	NG	NG	MP	MP	N	N	N	Lt.PL.Effusion	MR,AR,TR mild PHT mod.,mild conc LVH
14	163	90	287	39	P	HP	NG	NG	NG	NG	N	N	N	N	N
15	208	130	164	44	P	P	P	NG	NG	NG	L	L	N	N	Global hypokinesia of LV,mod LV dysfunt,EF 46%
16	252	190	91	44	P	NG	NG	P	MP	HP	N	N	N	N	trivial MR
17	165	76	250	41	P	MP	NG	NG	MP	MP	N	N	ST	N	Massive PE with tamponade
18	218	118	343	46	P	BLP	P	NG	MP	NG	N	N	N	N	N
19	183	84	280	43	P	NG	NG	NG	NG	NG	N	L	N	N	mild PE
20	113	57	131	34	P	BLP	P	NG	MP	MP	N	N	N	N	N
21	194	122	125	47	P	P	NG	NG	NG	NG	L	L	N	N	N
22	170	84	262	36	P	NG	NG	NG	NG	NG	N	N	ST	N	MVP, Tachycardia
23	205	123	184	46	P	NG	NG	P	NG	MP	N	L	N	N	N
24	265	163	253	52	P	NG	NG	NG	NG	NG	N	N	ST	N	N
25	246	134	498	38	P	P	P	NG	NG	MP	L	L	ST	cardiomegaly	mod. PE

SL. NO	T.Chol	LDL	TGL	HDL	ANA	dsDNA	Sm Ag	LAC	ACL IgG	ACL IgM	C3	C4	ECG	CXR	ECHO
26	229	147	176	47	P	P	NG	NG	MP	MP	L	L	N	N	N
27	154	83	132	45	p	BLP	P	NG	NG	NG	N	N	ST	N	trivial PE
28	470	210	245	48	p	NG	NG	NG	NG	NG	N	N	N	N	Mild diastolic LV
29	160	70	195	52	p	BLP	NG	NG	MP	MP	L	N	N	N	N
30	245	145	275	40	p	p	P	NG	MP	NG	L	N	N	N	N
31	212	112	385	36	p	BLP	NG	NG	MP	MP	L	L	N	Rt.pl.effusion, cardiomegalyy	mild PE
32	146	81	92	47	p	P	NG	NG	NG	NG	N	N	N	N	N
33	200	97	320	43	HP	p	P	NG	MP	MP	N	N	ST	increased BVM	N
34	176	109	124	42	P	P	P	NG	MP	MP	L	N	N	N	N
35	179	107	91	54	p	P	P	NG	MP	MP	N	N	low voltage complexes	Lt.pl.effusion, cardiomegaly	large PE,no tamponade
36	165	80	250	38	p	P	NG	NG	NG	NG	L	L	AVNRT	N	N
37	233	168	141	37	p	P	NG	NG	MP	MP	N	N	N	N	mild TR
38	239	164	126	50	p	P	P	NG	MP	MP	N	N	N	increased BVM	N
39	154	70	250	38	p	p	NG	p	MP	HP	L	N	ST	N	Mild PE, mod MR,LVH
40	224	165	74	44	NG	NG	NG	NG	NG	NG	N	N	N	Rt.pl.effusion	N
41	186	114	97	52	p	NG	NG	NG	MP	MP	N	N	N	Rt pl effusion	mod. PE
42	165	101	94	45	p	P	P	NG	NG	NG	N	N	N	N	N
43	224	156	425	37	p	NG	P	NG	NG	NG	N	N	N	N	N
44	228	114	245	65	HP	NG	NG	NG	MP	MP	N	N	N	N	N
45	198	116	161	60	p	BLP	P	NG	MP	BLP	N	N	N	straightening of lt heart border	thickened mitral valve , mild MR
46	221	134	317	54	P	P	NG	NG	MP	MP	N	N	N	N	mild MR
47	194	112	205	52	P	P	NG	P	BLP	BLP	L	L	N	N	mild global hypokinesia, EF 50%
48	169	76	177	48	P	P	NG	NG	NG	NG	N	N	N	N	N
49	155	78	238	46	p	P	NG	NG	MP	MP	L	N	N	B/L PL. Effusion	MVP,mild MR
50	130	57	186	47	p	P	NG	NG	MP	NG	L	L	N	N	N

SL. NO	T.Chol	LDL	TGL	HDL	ANA	dsDNA	Sm Ag	LAC	ACL IgG	ACL IgM	C3	C4	ECG	CXR	ECHO
51	157	90	78	52	p	P	P	NG	NG	NG	L	N	N	N	N
52	199	133	119	42	p	p	P	NG	NG	MP	L	N	N	N	N
53	181	112	134	42	p	NG	NG	NG	MP	MP	N	N	ST	cardiomegaly	PE,EF 62%
54	270	165	362	45	p	NG	NG	NG	NG	NG	L	L	ST	B/L PNEUMONITIS	N
55	162	90	99	52	p	P	NG	NG	NG	NG	N	N	N	N	N
56	147	70	281	50	p	BLP	P	NG	NG	NG	N	N	N	N	N
57	212	151	116	48	p	P	P	NG	NG	NG	L	L	N	N	N
58	216	124	341	43	P	P	NG	NG	NG	NG	N	N	AVD, CHB	N	mildTR, Trivial AR
59	187	117	151	40	p	P	P	NG	NG	NG	N	L	N	N	N
60	178	116	109	50	p	NG	NG	NG	NG	MP	N	N	**T↓**v5-v6	N	mild PHT, RA &RV dilated, TR trivial
61	138	67	133	54	p	NG	P	NG	MP	MP	N	N	N	N	N
62	209	150	112	37	p	NG	NG	NG	NG	NG	N	N	N	N	N
63	190	102	154	47	p	P	NG	NG	NG	BLP	N	N	N	N	N
64	266	164	224	38	p	P	NG	NG	NG	NG	L	N	N	N	Mild PE
65	170	96	368	50	p	P	P	NG	NG	NG	N	N	N	N	N
66	234	155	123	54	p	NG	NG	NG	NG	NG	N	N	N	N	N
67	294	212	154	45	p	P	P	p	MP	MP	N	N	N	N	N
68	240	124	387	39	p	p	NG	NG	NG	NG	N	N	N	N	mod.PHT
69	234	154	182	43	p	NG	NG	NG	NG	NG	N	N	N	N	MILD PHT
70	212	145	98	47	p	P	P	p	MP	BLP	N	N	N	N	MOD. MR
71	270	195	177	40	N	NG	P	NG	NG	NG	N	N	N	N	N
72	153	84	168	42	p	NG	P	NG	NG	NG	N	N	N	N	N
73	187	110	118	53	p	NG	NG	NG	NG	NG	N	N	N	B/L PL. Effusion	large PE,no tamponade,stands+
74	166	106	83	44	p	p	NG	NG	NG	NG	N	N	N	N	severe PHT,RA&RV pul A dilated,TR mod
75	110	56	205	48	p	p	NG	NG	NG	NG	N	N	N	N	N

SL. NO		T.Chol	LDL	TGL	HDL	ANA	dsDNA	Sm Ag	LAC	ACL IgG	ACL IgM	C3	C4	ECG	CXR	ECHO
76		243	176	144	38	NG	BLP	NG	NG	NG	NG	L	L	N	N	N
77		198	125	152	42	p	NG	NG	NG	NG	NG	N	N	ST-T CHANGES	B/L PL. Effusion	MILD PE
78		242	154	203	48	p	P	NG	NG	NG	MP	N	N	N	N	N
79		217	124	273	35	p	NG	P	NG	NG	NG	L	L	N	N	N
80		165	77	201	50	P	P	NG	NG	NG	NG	N	N	N	N	N
81		245	174	174	36	P	P	P	NG	NG	NG	N	N	N	N	N
82		187	118	146	39	p	BLP	P	NG	NG	MP	L	L	N	N	N
83		145	87	233	40	HP	HP	NG	NG	MP	MP	N	N	N	N	N
84		122	50	130	46	HP	HP	NG	NG	MP	BLP	L	L	N	N	N
85		228	118	242	56	p	HP	NG	NG	NG	MP	L	L	N	N	MILD PE,MVP
86		236	156	144	51	p	NG	P	NG	NG	NG	N	N	N	N	N
87		176	102	134	47	p	NG	NG	NG	NG	NG	N	N	N	cardiomegaly	MILD MR. MVP. MILD PE
88		233	167	101	46	p	BLP	P	NG	NG	NG	L	N	N	N	N
89		280	207	176	38	p	NG	NG	NG	NG	NG	L	N	SR, T Inv. V1-V3	N	PE
90		248	170	165	45	p	NG	NG	NG	NG	NG	N	N	N	N	N
91		166	99	132	41	p	P	NG	NG	NG	NG	N	N	N	N	N
92		172	103	126	44	P	P	NG	NG	NG	NG	L	L	ST	N	N
93		243	160	156	52	p	P	NG	NG	NG	NG	N	N	N	N	N
94		212	112	267	35	HP	p	NG	NG	NG	MP	L	L	N	N	N
95		256	146	234	37	p	p	P	P	NG	NG	L	N	N	N	N
96		253	156	256	47	p	P	NG	NG	NG	NG	L	L	N	N	MILD PE
97		222	148	97	52	p	p	NG	NG	MP	MP	N	L	N	N	N
98		198	106	282	44	p	p	NG	NG	BLP	NG	L	L	ST	Haziness in both mid, LZ	mild PE
99		210	130	237	40	p	p	NG	NG	NG	NG	L	N	ST	Large cardiomegaly	large PE
100		187	114	145	45	p	NG	NG	NG	MP	MP	L	N	N	N	MVP, MR-mild.ASD, TR, PHT-mild. RA,RV slightly dilated

S. no	CAROTID IMT in mm	SLEDAI	steroid dose mg
1	0.54mm	16	15
2	0.65mm	23	17.5
3	0.56mm	15	10
4	0.48mm	7	17.5
5	0.5mm	9	10
6		14	22.5, pulse, dexa
7	0.65mm	41	30
8	0.45mm	17	15, dexa
9	0.55mm	6	7.5
10	0.4mm	24	20
11	0.75mm,plaque rt CCA	42	45, dexa
12		29	30, dexa
13	0.72mm	10	10
14		11	12.5
15	0.6mm	12	15
16	0.45mm	27	17.5
17		16	30
18	0.7mm, plaque+ LT C bulb	22	15
19	0.58mm	16	20
20		13	12.5
21	0.6mm	23	25
22		27	15
23	0.64mm	12	12.5
24		21	10
25	0.68mm	37	20
26	0.48mm	32	12.5
27	0.58mm	24	15
28	0.47mm	15	10
29	0.55mm	11	12.5
30	0.78mm	31	15, dexa
31		18	15
32		13	10
33	0.59mm	19	17.5, dexa
34		26	27.5, pulse
35	0.46	22	30, pulse
36	0.58mm	45	25
37		20	15
38	0.64mm	21	20
39	0.47mm	45	40
40		9	12.5
41		8	10
42	0.6mm	19	17.5
43	0.48mm	12	15
44		10	10
45	0.62mm	15	15
46	0.59	16	12.5
47	0.53	36	30
48	0.5	30	22.5, dexa
49		34	15
50	0.62mm	27	20

S. no	CAROTID IMT in mm	SLEDAI	steroid dose mg
51		17	15
52	0.6	2	10
53		9	10
54	0.64	43	25
55		9	10
56	0.65	7	7.5
57	0.45	13	10
58	0.5	10	12.5
59		9	10
60	0.6	7	10
61	0.6	4	7.5
62	0.8	7	10
63	0.47mm	11	10
64	0.61	14	10
65	0.47	11	7.5
66		8	10
67	0.61	4	5
68	0.5	7	7.5
69	0.72mm,laque in lt CCA	6	7.5
70		16	15
71	0.65mm,plaque in rt. C bulb	12	15
72	0.54	17	17.5
73	0.56	12	10
74	0.6mm, plaque rt. C bulb	11	12.5
75	0.58	16	15
76		35	22.5, dexa
77	0.5	43	25
78		9	10
79	0.6	32	30, pulse
80	0.56	6	10
81	0.56	10	15
82		12	15
83	0.85	15	12.5
84	0.42	17	15
85	0.4	24	17.5
86		11	12.5
87		11	20
88	0.56	9	10
89	0.75	14	15
90	0.52	15	17.5
91	0.4	13	15
92	0.42	33	25
93	0.61	14	15
94	0.6	22	17.5
95		31	20
96	0.56	14	12.5
97		19	15
98		35	25
99		40	30, dexa
100	0.61	7	10

CAROTID INTIMA MEDIAL THICKNESS IN CONTROL GROUP

S.no	age	sex	Controls - CAROTID IMT in mm
1	30	M	0.35
2	22	M	0.5
3	21	F	0.45
4	22	F	0.5
5	23	F	0.5
6	22	F	0.45
7	20	F	0.5
8	22	F	0.55
9	23	F	0.45
10	22	M	0.5
11	23	F	0.55
12	18	F	0.42
13	19	F	0.48
14	21	F	0.45
15	27	F	0.5
16	22	F	0.45
17	30	F	0.55
18	25	F	0.48
19	19	F	0.35
20	24	F	0.42

INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE, CHENNAI-600 003.

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K.Dis.No.16328 P & D3/Ethics/Dean/GGH/08 Dated: 8.9.2008

Title of the work : "Study on cardiovascular Manifestation in Lupus patients."

Principal Investigator : Dr. R. Jagannathan, M.D.,

Department : Rheumatology, MMC, Ch.3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10th September 2008 at 2 P.M in Government General Hospital, Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH,CHENNAI

DEAN
GGH &MMC, CHENNAI

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