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STUDY ON PULMONARY HYPERTENSION &DIASTOLIC DYSFUNCTION IN SCLERODERMA

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CERTIFICATE

This is to certify that this dissertation entitled ***"STUDY ON PULMONARY HYPERTENSION &DIASTOLIC DYSFUNCTION IN SCLERODERMA"*** *submitted by* ***Dr. BALAMURUGAN S.*** *appearing for Part II M.D. Branch I General Medicine Degree examination in September 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India*

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CONTENTS

INTRODUCTION

Systemic sclerosis (scleroderma) is a generalized disorder of connective tissue characterized clinically by thickening & fibrosis of skin & by distinctive forms of involvement of internal organs notably heart, lungs, kidneys, gastrointestinal tract. The etiology & pathogenesis are unknown(7).

It is characterized by fibrotic arteriosclerosis of peripheral & sytemic vasculature

- variable degrees of extracellular matrix accumulation (mainly collagen) occur in both skin & viscera.
- associated with specific antibodies most notably anti-centromere & anti-scl-70 (anti topoisomerase) (1). various subsets with specific clinical features & variable involvement of various organs.

The incidence of PulmHT varies between 6-60% of pts with scleroderma. In diffuse form upto 33% have PulmHT both isolated & in association with interstitial lung disease. In patients with limited scleroderma formerly referred to as CREST (calcinosis cutis, raynauds

phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) upto 60% have pulmonary hypertension (3,4,5).

Pulmonary hypertension is defined as a mean pulmonary artery pressure exceeding 25mmHg at rest or 30 mm Hg in exercise. When it occurs as a manifestation of SSc it is particularly severe & one year survival is approximately 55%. (2)

Studies suggest that both right and left ventricular dysfunction is common in scleroderma and that diastolic ventricular dysfunction may occur independent of systolic dysfunction.(8) Diastolic dysfunction may be primary (myocardial fibrosis) or secondary to pulmonary or systemic hypertension

AIM OF STUDY

- To assess the prevalence of pulmonary hypertension in scleroderma patients with limited & diffuse forms

- To differentiate between those pulmonary hypertension due to interstitial lung disease (secondary PulmHT) from those without ILD (isolated PulmHT)

- To assess the prevalence of ventricular diastolic dysfunction in scleroderma patients

REVIEW OF LITERATURE

EPIDEMIOLOGY;

Its estimated that new cases of scleroderma(SSc) occur at a rare of approximately 18-20 per million of general population per year(9). The prevalence & severity of SSc varies among different racial & ethnic subgroups

The limited variant is found more commonly in caucasions while African-American females appear to have increased risk for diffuse cutaneous type & younger age of onset(10). The average age of onset is approximately 50 years(9).

GENITIC FACTORS

Genetic factors have been suggested to have a possible pathogenic role in scleroderma. There have been suggestions that chromosomal breakage rates are greater in patients with scleroderma. More recent data have been based on assessment of variable number **tandem repeats**, a technique that can show chromosomal abnormalities. Another area of a potential pathogenic relationship is the theory of **microchimerism**, in which the hypothesis is that patients have a reaction to fetal cells from an early

pregnancy or from their parents, after which the patients develop a graft versus host-like reaction that results in scleroderma.

Conversely, the work of Reveille et al(60) Suggests that DQ7 and DQ5 are more common. It was shown that patients with limited scleroderma and anticentromere antibodies were associated with HLA-DR-1, and diffuse scleroderma and antitopoisomerase antibody were associated with HLA-DR-5.

DIAGNOSTIC CRITERIA*;*

American college of rheumatology proposed preliminary criteria for classification based on clinical & lab assessments

Major:

Sclerodermatous skin change in any location proximal to metacarpophalangeal joints was the single major criterion

Minor:

Sclerodactyly, digital pitting scars on fingertips, or loss of digital finger pad substance & bibasilar pulmonary fibrosis

CLASSIFICATION;

Patients with scleroderma are classified into subsets of disease by the degree of clinically involved skin.

1. *diffuse*; skin thickening present on trunk in addition to face, proximal & distal extremities.

2. *limited*: skin thickening limited to sites distal to elbow & knee also involving face & neck

3. *sine scleroderma*: characteristic internal organ manifestations, vascular, serologic, abnormalities but without clinically detectable skin change

4. In overlap.

DIFFUSE CUTANEOUS SCLERODERMA:

In general, patients with diffuse disease have a narrow interval between onset of Raynauds phenomenon, skin thickening & internal organ involvement.the early stage of SScs characteriased by inflamed edematous skin & significant systemic manifestations such as fatigue arthalgias, & elevated ESR.

There is also a significant risk of internal organ involvement particularly in first 3 years(12).

The higher the skin nscore the greater the risk of renal disease& higher mortality. About 10-20% of patients with diffuse disease will develop life threatening internal organ Disease

The later stages are characterised by gradual softening of skin(11). Predictors of higher mortality include higher skin scores (Rodnanscore >20) reduced lung diffusing capacity, elevated ESR & evidence of heart or renal involvement.

LIMITED SCLERODERMA;

The clinical course, survival & clinical features of limited disease are quite different from than in diffuse form. The overall 5 year survival is 80-85% which is significantly better than in diffuse form(13).

They often have many years of Raynauds prior to the development of other signs & symptoms of SSc. The most common first non Raynauds symptom is esophageal dysfunction manifested by dysphagia.

The major cause of morbidity & mortality in limited form are severe Raynauds Phenomenon with occlusive digital vascular disease.& Pulm.HT.

PulmHT is the leading cause of mortality in limited disease patients. This complication occurs in approximately 10-15% of cases with limited disease & often occurs in the absence of interstitial lung disease(ILD)

PATHOPHYSIOLOGY;

The three key pathologic features are

- a unique vascular disease
- abnormal accumulation of extracellular matrix components,
- autoimmunity

RAYNAUDS PHENOMENON;

In SSc over 90% of patients have intense Raynauds phenomenon associated with tissue fibrosis, digital ulceration & on occasion ischemic demarcation , digital amputation.

The severity of Raynauds is a manifestation of both vasospasm & structural abnormalities of digital arteries.

Compared to normals ,SSc patients have a more pronounced decrease of both nutritional & thermoregulatory blood flow skin in response to cold temperatures. The reactive hyperemia which normally follows periods of digital ischemia is absent in SSc.(14)

There is good evidence that a generalized vasospastic disorder exists in SSc (systemic Raynauds phenomenon) involving kidney , heart, lungs & other viscera. The renal crisis of SSc is a clear example of reversible vasoconstriction pf the cortical blood flow to kidney.(15)

CUTANEOUS MANIFESTATION;

The skin disease of scleroderma follows a course characterized by three phases:

- inflammatory edematous phase,
- indurative phase and
- atrophic phase.

In the initial edematous stage, the patient experiences puffiness, swelling and a sense of decreased flexibility of the skin, especially in the forearms, hands and digits, as well as in the feet. The fingers appear puffy

with a moon-like fullness of the fingertip and there is loss of normal digital creases. Loss of the finger pad and tapering of the finger due to fingertip ischemia is often seen during this early phase of SSc..

The face can appear expressionless because of reduced capacity to smile or move the eyelids or cheeks. The opened mouth becomes circular with a remarkable reduction in the maximum oral aperture. Vertical lines or furrowing of the skin around the lips gives **a pursed-lip** The nose becomes pinched and the facial creases smooth so that the face has a **mouse-like appearance** (mauskopf) Pigmentary changes of the skin also occur during the edematous and fibrotic stages of SSc. The vitiligo pattern gives the skin a **salt & pepper** appearance because of perifollicular sparing of pigment loss. On average after 1-3 years of disease activity, the inflammatory and fibrotic process gradually stops. . In the late stage of SSc, the skin becomes atrophic (especially over the fingers, hands and distal limbs) and thinned, with tethering secondary to fibrotic tissue binding to underlying structures. Areas of thinned skin can ulcerate with minor trauma, especially in areas such as the tip of the elbow, the medial or lateral ankle or over sites of a flexion contracture. Flexion contractures of the fingers are very common in the diffuse form. In patients with limited skin disease, the fibrotic skin

changes are usually limited to the fingers(sclerodactyly). More prominent in limited disease are small and large mat-like **telangiectasias** that appear on the face, upper chest, palms, fingertips and mucous membranes. Subcutaneous **calcinosis,** composed of calcium hydroxyapatite deposits at sites of trauma such as the forearms, elbows or fingers.

Pathology in Dermis ;

The pathologic hallmark of systemic sclerosis is an excessive accumulation of extracellular matrix in the dermis, which leads to taut skin. Monotonously similar collagen fibers are present in the reticular dermis and there is thinning of the papillary dermis. Capillary loss can be seen in vivo in the skin by the technique of wide-field nailfold capillaroscopy

MUSCULOSKELETAL INVOLVEMENT

Pain on motion of the ankle, wrist, knee or elbow may be accompanied by a coarse 'friction rub caused by fibrinous deposits on the tendon sheath. These rubs are detected in approximately 30% of patients with diffuse scleroderma(16).

Muscle weakness is a significant problem in scleroderma and often has more than one cause(17). In diffuse scleroderma, muscle atrophy and

weakness can result from deconditioning secondary to restricted mobility and contractures.

GASTROINTESTINAL INVOLVEMENT

Gastrointestinal tract involvement is found in almost every patient with scleroderma and is characterized by abnormal motility secondary to dysfunctions caused by abnormal innervation, smooth muscle atrophy and tissue fibrosis(19).

OROPHARYNX

. Many patients with scleroderma have a sensation of dry eyes and mouth (the sicca complex). In addition, the majority of scleroderma patients with sicca complaints usually do not have antibodies against Ro/SSA or La/SSB, suggesting that the mechanism of dry membranes in scleroderma is a secondary process different from that seen in Sjogren's syndrome(21).

ESOPHAGUS

Esophageal dysfunction affects almost every scleroderma patient, with dysphagia and dyspepsia being the most common symptom. The dysphagia is usually described, as solid foods sticking after normal initiation of swallowing. This sensation is relieved by the intake of extra fluids to clear

the esophagus. Substernal burning pain may be coupled with a feeling of indigestion or nausea. These reflux symptoms are typically worse after meals, with exercise and after bedtime. Severe esophageal reflux and esophagitis occur equally in patients with either limited or diffuse scleroderma..

Low or absent primary and secondary peristalsis of the distal esophagus and low lower esophageal sphincter pressure in the presence of a normal proximal (striated muscle) esophagus are typical manometric findings in scleroderma(22). Excessive air in the esophagus is commonly detected on routine chest X-ray. Although symptoms are a poor guide to the degree of esophageal disease, patients who are asymptomatic on or off treatment are unlikely to have significant complications. Esophagitis appears to occur only in patients with impaired peristalsis and delayed acid clearance(23)

If there is unexplained weight loss with poor caloric intake or other symptoms of esophageal dysfunction, a barium swallow orendoscopic and/or manometric investigation of the esophagus are warranted. A 24-hour pH probe study is a helpful method to quantify the degree and frequency of acid reflux in difficult- to-manage cases.

STOMACH AND SMALL BOWEL

Delayed emptying of the stomach with retention of solid foods aggravates reflux and is a frequent cause of bloating. Antral vascular ectasia (watermelon stomach) can be a cause of gastrointestinal bleeding in scleroderma patients. Endoscopy of these patients reveals antral gastritis and prominent longitudinal vascular folds that resembles the surface of a watermelon (24).

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LARGE BOWEL

The large intestine and rectum are also affected by scleroderma. Scleroderma patients have decreased distensibility of the colon that does not necessarily correlate with symptoms(25). Because of muscular atrophy of the bowel wall, asymptomatic wide mouthed diverticula unique to scleroderma are commonly found in the transverse and descending colon .

PULMONARY INVOLVEMENT

Lung involvement in SSc is almost universal & now accounts for significant lifetime morbidity & is leading cause of death. Both interstitial

fibrosis & pulmonary vascular are present in the lungs of patients with SSc but one pathologic process will be dominant cause of clinical problems.

Interstitial fibrosis is more likely to be severe in diffuse form while pulmonary vascular disease & PulmHT can be dominant in LC form. Approximately 80% of patients will have abnormal PFT's.(26)

Patients with ILD commonly have a rapid decline in pulmonary function in conjunction with progressive lung disease. Dyspnea on exertion without chestpain is the most common presenting complaint with a dry cough being a late manifestation Of ILD.

The most common changes in PFT are either a reduced diffusion capacity, or a reduced lung volumes(FVC,) typical of restrictive ventilatory defect with associated reduction on gas exchange.

A HRCT scan of chest is a very sensitive indicator for detecting changes in lung parenchyma. Finding of ground glass opacities of lung in HRCT corresponds to active alveolitis & progressive restrictive lung disease.

Broncho-alvelolar lavage is used to detect inflammation & active alveolitis. BAL demonstrates an increased percentage of neutrophils, esinophils or CD 8 cells. When disease progresses, there is worsening interstitial fibrosis & honey combing of lung parenchyma (27,28).

Pulmonary arterial vascular disease with PulmHT is one the most difficult clinical problems in SSc. The pulmonary vascular process can be indolent & remain clinically undetectable until severe irreversible PulmHT & signs of right sided heart failure develops.

Pulmonary hypertension can be detected early and non-invasively by measuring the pulmonary artery pressure with two-dimensional Doppler echocardiography. Pulmonary function testing often reveals an isolated decrease in diffusion capacity when pulmonary vascular disease is present.

The natural history of the lung disease in scleroderma is highly variable; the majority of patients will have an early but modest decline in function and then follow a stable course or improve. Approximately a third will have a more severe progressive decline in lung function that continues for 4-5 years and then appears to stabilize. Patients with diffuse skin changes tend to have serious lung involvement in the first 5 years of disease, while

patients with CREST syndrome usually do not experience clinical symptoms until more than 5 years after diagnosis. Risk factors for serious restrictive lung disease are African-American or Afro-Caribbean race and antitopoisomerase antibodies (29). A low diffusing capacity (less than 40% predicted) (30) or rapidly declining DLco and/or lung volumes predict a high mortality rate.

In predicting the histological pattern, CT, although useful, has not replaced lung biopsy as the ‘gold standard’ investigation. As yet, patients who appear to have early changes on CT should still be considered for a thoracoscopic biopsy for staging of the disease. In systemic sclerosis the predominant histological pattern is NSIP whereas in IPF the majority show UIP.

Less common problems of the lung include aspiration pneumonia (secondary to severe esophageal dysfunction), endobronchial telangiectasias, pulmonary hemorrhage, bronchiolitis obliterans organizing pneumonia, pleural reactions and pneumothorax.

Studies are inconclusive about the association between pulmonary function impairment and abnormal esophageal function(31). There is likely an increased risk of lung cancer in patients with ILD(32).

HISTOLOGY;

The histology of fibrotic lung disease is that of expansion of the normally thin alveolar wall interstitial space with the deposition of collagenand other connective tissue components. Progressive collagen accumulation with diminution of the alveolar air space volume, so that ultimately there is more fibrous tissue than air space a gas diffusion blockade, an increase in the alveolar—arterial Po_2 gradient and ventilation-perfusion inequalities.

PULMONARY HYPERTENSION IN SSC;

Pulmonary arterial hypertension is a life threatening complication of both diffuse & limited scleroderma (including CREST syndrome). pulmonary vascular disease has a particularly adverse effect on prognosis.

The incidence of PulmHT varies between 6-60% of pts with scleroderma(2,3,4) .In diffuse form upto 33% have PulmHT both isolated & in association with interstitial lung disease .In patients with limited scleroderma formerly referred to as CREST (calcinosis cutis, raynauds

phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) upto 60% have pulmonary hypertension

While not all patients. have clinically significant pulmonary hypertension, two thirds of patients with scleroderma will have pathologic evidence of pulmonary vascular disease(33 ,34)

Stupi et al reported two year survival un patients with in patients without pulmonary hypertension to be greater than 80% while patients with pulmonary hypertension had a two year survival of 40%(59).

Sacks et al reported two year survival of patients with pulmonary hypertension & either diffuse or limited forms to be approx. 50%(36).

Koh et al reports 40% survival in patients with scleroderma & pulmonary hypertension compared with higher survival in scleroderma patients without organ failure or with other lung involvement (i.e interstitial lung disease) at two years.(37)

PATHOGENESIS:

The etiology of pulmonary hypertension in scleroderma spectrum disorders remains obscure. There appears to be a direct involvement of

pulmonary circulation with direct involvement of pulmonary circulation with intimal proliferation & medial hypertrophy similar to that seen in primary pulmonary hypertension(38). Some cases may also be related to severe pulmonary parenchymal disease, such as interstitial disease with hypoxemia.

Additionally diastolic dysfunction of right &left ventricles has been seen in patients with scleroderma & may contribute to pulmonary hypertension(39)

Autoimmune processes have been implicated in the pathogenesis of pulmonary hypertension although the mechanism is not known. Positive antinuclear antibodies are frequently found in pulmonary hypertension patients without a diagnosis of connective tissue disease & pulmonary hypertension can occur before the onset of an identifiable connective disease.

AUTO-ANTIBODIES IN SCLERODERMA & PULMONARY HYPERTENSION;

In patients with scleroderma anti-centromere &anti-histone antibodies have been associated with vascular disease. Anti-centromere Ab‘s are primarily seen in limited disease. Since patients with limited form have a higher incidence of pulmonary hypertension than diffuse disease , it is not

surprising that anti-centromere antibodies associated with a higher incidence of pulmonaryhypertension Anti-fibrillarin antibodies (anti-u3- RNP) are frequently found in diffuse form associated with pulm.HT(40). Anti-endothelial Ab's (aECA) are present in 40% & 13% of diffuse form & CREST respectively & are associated with pulm.HT & digital infarcts (41). In scleroderma & pulm.HT ,when accompanied by HLA-B 35 antigen, anti-topoisomeraseII Ab's & antibodies to fibrin bound tissue type plasminogen are more common.(42)

RAYNAUDS & PULM.HT;

Raynauds phenomenon , vasospasm of arterioles in distal systemic circulation, is commonly reported in scleroderma. In one report all patients with Pulm.HT & CREST had raynauds while 68% without Pulm.HT had raynauds .Raynauds is also common in patients with SLE & MCTD & Pulm.HT. but only 10-14% of patients with primary pulmonary hypertension have Raynauds(45). This observation has led to the Pulmonary Raynauds hypothesis that vasospasm contributes to the development of Pulm.HT(46)

Acute hypoxic pulmonary vasoconstriction may be more pronounced in patient's with pulm.HT & scleroderma than in patients with primary Pulm.HT(45). however another report found that pulmonary vasospasm was

not present in patients with raynauds & scleroderma without Pulm.HT.(46) In support of this hypothesis ,patients have defective endothelial dependent vasodilatation &this may be related to decreased endothelial nitric oxide synthse (eNOS). (47) althogh controversial , decreased lung eNOS has been reported in severe primary pulm.HT. while the level of eNOS in connective tissue is not known. decreased production of lung nitric oxie has been found in patients with scleroderma & Pulm.HT. similarly expression of prostacyclin synthasr in pulmonary endothelium may be decreased in patients with severe connective tissue disease associated Pulm.HT Endothelin -1 is increased in serum of patiensts with both diffuse & limited forms(48) & while endothelin levels correlate with survival in patients with scleroderma they are not higher in those with Pulm.HT.(49) In contrast higher serum endothelin levels are found in patients with SLE associated Pulmonary hypertension than in non- Pulmonary hypertension patients.The role of endothelin-1 in Pulmonary hypertension has led to the uase of endothelin antagonists(Bosantan) in connective tissue disease associated in Pulmonary hypertension(50)..Serotonin may also play a role in pathogenesis of Pulmonary hypertension.In scleroderma platelet serotonin levels are decreased & serum levels are increased

DIASTOLIC DYSFUNCTION IN SCLERODERMA

Diastolic dysfunction is defined as the deterioration of the ventricular filling capacity without any compensatory increase in the left atrial pressure. (74) Another definition is the abnormal ventricular filling defect causing cardiac output inadequacy. (75) In patients with diastolic dysfunction, the deterioration of ventricular dilatation (early diastole), decrease in compliance (early late diastole) or an external pressure in pericardium can lead to problems in ventricular filling. Cardiomyopathies, constructive pericarditis, ischemic heart diseases, volume overload (mitral insufficiency, arteriovenous fistulae), mitral and tricuspid valve stenosis may cause diastolic dysfunction.

Guinta et al(39) have pointed out an impaired left ventricular filling in a significant percentage of SSc patients in whom no other cause of diastolic dysfunction had been detected is likely to depend on either myocardial fibrosis or ischemia or both.(52,53) As myocardial fibrosis as well as small intra myocardial coronary vessel are known to affect both right &left ventricle in SSc an altered LV & RV filling is likely to occur in this disease(54,55)

An abnormal right ventricular filling is detected in 40% of SSc patients. Such alteration was detected in many without clinically evident cardiac disease & resulted to be correlated with both left ventricular diastolic abnormalities & Pulmonary hypertension.

Scleroderma heart disease is subclassified into primary & secondary formsPrimary cardiac disease in SSc depends on involvement of myocardium & or pericardium &small intramyocardial vessels by SSc itself. Secondary cardiac involvement develops either in patients with systemic hypertension induced by renal scleroderma (LV disease) & in those with pulmonary vascular & or interstitial lung disease.

SSc myocardial fibrosis is different from that occurring in patients with coronary atherosclerosis. Actually SSC myocardial fibrosis is equally distributed throughout the right & left ventricle, does not involve the immediate subendocardial layers, is not related to the distribution of epicardial coronary vessel & is not associated with hemosiderin deposits.

Left ventricular filling abnormalities in SSc were detected in studies by Maoine et al(52) & Valentine et al.(53) Regarding right ventricular

dysfunction Candell-Riera et al detected a significantly low Tr E/A ratio in 63 % of patients. (56)

PATHOGENESIS:

The pathogenesis of the cardiac lesion in scleroderma is controversial. An intriguing concept is one of repetitive vascular insults secondary to cold induced perfusion changes. Classic pathological changes of contraction band necrosis seen in scleroderma are similar to the findings in hearts subjected to prolonged ischemia and subsequent reperfusion.

MYOCARDIAL INVOLVEMENT:

Myoccardial lesions and fibrosis which are found in up to 80 percent of patients upon autopsy, may be patchy, may present in both ventricles and may be patchy may present in both ventricles and may bear no relationship to myocardial perfusion..

Myocardial dysfunction occurs often although clinical congestive heart failure occurs in less than 5 per cent of patients with progressive systemic sclerosis.

Using extensive noninvasive techniques, left ventricular dysfunction and myocardial perfusion defects can be detected in up to 75% of patients.

Ischemic chest pain and myocardial infarction are uncommon clinical problems in scleroderma. Thallium perfusion defects reflecting vascular disease of the endomyocardial vessels (not larger coronary arteries) are seen among scleroderma patients both at rest and with exercise. Because of this, the scleroderma patient with angina-like chest pain may need angiographic studies to rule out coronary arteriosclerosis because thallium scans are likely be abnormal as a result of the microvascular disease of scleroderma heart.

In fact, cold provocation of Raynaud's phenomenon can temporarily increase the number of thallium scan defects and induce local abnormalities in ventricular wall motion, supporting the notion that reversible vasospasm of the myocardial microcirculation occurs in scleroderma. Thallium scan perfusion defects predict more severe myocardial disease and poor outcome.

Patchy myocardial fibrosis is a fairly common finding at autopsy in scleroderma patients(56) This finding is thought to occur secondary to ischemia-reperfusion events in the heart microvasculature causing contraction band necrosis of heart muscle. A decline in left ventricular ejection fraction is a late clinical manifestation, primarily in patients with diffuse skin disease. An abnormal left ventricular ejection fraction is demonstrated by radionucleotide scanning during exercise in approximately 40-50% of all

patients, and approximately 15% of diffuse scleroderma patients have abnormalities at rest. Echocardiographic studies suggest that both right and left ventricular dysfunction is common in scleroderma and that diastolic left ventricular dysfunction may occur independent of systolic dysfunction. Diastolic dysfunction may be secondary to hypertension (with or without renal disease) or myocardial fibrosis and may manifest with abnormal left ventricular compliance and pulmonary vascular congestion. Unexplained dyspnea on exertion may be the initial clinical manifestation of unappreciated diastolic dysfunction.

PERICARDIAL INVOLVEMENT

Autopsy series report pericardial involvement in up to 50 per cent of patients with systemic sclerosis. Pericardial involvement includes fibrinous pericarditis, pericardial adhesions and pericardial effusions

ECG changes in SSC

Electrocardiography or Holter monitoring often shows conducting system disease or arrhythmias, which are usually clinically silent. Premature ventricular contractions are the most common arrhythmia; frequently they are in couplets or are multifocal. Premature atrial contractions,

supraventricular tachycardia, AV or intraventricular conduction disorders are seen less commonly(57).

RENAL INVOLVEMENT;

The most important clinical manifestation of scleroderma kidney is accelerated hypertension and/or rapidly progressive renal failure: the scleroderma renal crisis(58) Surveys suggest that only about 10-15% of all scleroderma patients develop a crisis. The majority of patients who develop renal crisis have diffuse cutaneous disease and approximately 80% of cases of renal crisis occur within 4 years of disease onset. Risk factors for renal crisis include rapidly progressing diffuse skin disease, tendon friction rubs, new unexplained anemia and the presence of anti-RNA polymerase III antibody. Antecedent use of corticosteroids is also associated with a higher risk of developing renal crisis. Non-malignant hypertension, abnormalities on urinalysis, plasma renin level and the presence of anticentromere or antitopoiso-merase antibodies are not predictors of a scleroderma renal crisis.

Patients with renal crisis may present with typical signs of malignant hypertension, including headache, altered vision, signs of heart failure and confusion or neurologic signs such as seizures in the setting of an abnormally high blood pressure (>150/90mmHg) .

The typical vasculopathy of scleroderma is present in the renal vessels of patients with or without renal crisis. This suggests that other factors, such as vasospasm, probably contribute to the development of renal crisis. Scleroderma patients may have a reduced creatinine clearance, proteinuria, microscopic hematuria and non-malignant hypertension, but often another cause for these abnormalities is found. For example, an immune complex process may be the cause for glomerulonephritis in patients with an overlap syndrome of SLE and scleroderma. A reversible proteinuria or even a crescentic glomerulonephritis may occur secondary to treatment with D-penicillamine

CLINICAL PRESENTATION & EVALUATION:

. Popular clinical measurements include skin score, hand extension, oral aperture/ finger flexion and global patient and physician assessments of disease activity. Most clinical observations detail the cutaneous manifestations because the skin is directly measurable by observation and palpation. Although the natural course of the skin changes is reasonably well described in diffuse scleroderma, it must be remembered that the cutaneous disease may not be the ideal surrogate for the overall disease activity. For example, significant cardiopulmonary and gastrointestinal disease can emerge later in the course,

at a time when the skin may be improving or thinning. In limited scleroderma, the skin fibrosis is minimal and does not parallel the vascular disease such as pulmonary hypertension and digital loss.

Recently, a quantitative measure of disease severity has been developed that documents Degree of severity of involvement of each major organ graded from 0 (normal) to 4 (end-stage) . This scale has been externally validated on a large group of scleroderma patients and may be helpful in comparing groups of patients in clinical trials and for following disease in individual patients.

Dyspnea is the most common presenting symptom of SSc associated pulmonary hypertension. the clinical evaluation is similar to that of primary pulmonary hypertension. History & physical examination often reveal findings of underlying connective tissue disease.

Since around 15% SSc patients may develop PAH & in most cases asymptomatic its important to monitor them regularly for this complication . The British cardiac society guidelines recommend that patients with LCC particularly those whom are anticentromere antibodies positive should be screened by transthroacic echo annually even if they have no symptoms(2).

Screening for PAH is certainly worthwhile in these high risk patients since it's the only way to identify PAH earlier & begin treatment earlier. Although PAH is incurable, it can now be contained for many years through use of new effective treatments for this condition .We now have a greater incentive to identify PAH patients & manage them through combined clinics with rheumatologist working together with cardiologist, pulmonologist & pulmHT nurses(2). Doppler echo has emerged .as a reliable & reproducible means of non invasively assessing pulmonary artery systolic pressure(PASP) & has been employed to detect Pulm.Ht in patients with connective tissue disease.

.Denton et al (61) performed Doppler echocardiography to estimate the trucuspid gradient(TG), an indirect & observer dependent measure of pul;monary artery elevation on 33 consecutive SSc patients clinically suspected to have PAH.they subsequently confirmed the diagnosis in 21 of these patients (64%). Echo correctly identified 19 of these patients , giving a sensitivity of 90% & specificity of 75%. Interestingly they noted a difference of upto 29 mm Hg between echo & catheter Findings. The authors concluded echo is a useful non-invasive, initial screening tool. The role of

carbon monoxide diffusing capacity as a non- invasive measure of PAH is less certain.

Stupi et al (59) & Ungerer et al (6) have demonstrated an association between DLCO <40-55% & isolated SSc PAH in a total of 89 patients.

Burke et al (60)& Jezek & widimsky etal(62) were unable to confirm a clear link between low DLCO & PAH.

Mukerjee (76)et al suggested echo estimated TG or PASP & DLCO, most commonly used screening tools for SScPAH, perform well only in the diagnosis of advanced pulm.HT.

Echo perfomed better in identifying patients who require urgent referral & treatment for advanced disease. Patients suspected of advanced disease in SSc & Pah have an annual mortality of 40%. Relying on echo alone to identify these patients results in a high false negative rate of 42% .however combining 3D echo & clinical findings (modified NYHA dyspnea grade) identifies > 90% of patients with advanced PAH.

Echo has been used to evaluate ventricular diastolic function M – mode techniques have been used to record the rate of relaxation of

ventricular cavity. This technique utilizes digitalization of the borders of left ventricular cavity, with which the left ventricular dimension increases in early diastole being noted

Doppler echo currently is the primary technique used for evaluating ventricular diastolic function.. With normal pressures the early diastolic mitral velocity (E) exceeds that following atrial systole or late mitral(A) velocity (E/A greater than 1)

Under several conditions one of which is normal aging , the velocity in early diastole decreases & the late velocity increases. Among the pathologic states that. produce this change are LV hypertrophy. & myocardial ischemia.both conditions produce abnormal relaxation & decreased early velocity into LV. This situation will commonly produce elevated LV diastolic pressures unusually low filling pressures in lefty atrium may also have a similar pattern.

If the LV filling pressure is markedly elevated, as may occur in severe heart failure, then the LV inflow velocity pattern changes dramatically. Now there is a marked increase in early diastolic velocity with an increase in E velocity.

The atrial velocity is now reduced. This type of mitral flow may also occur if there is a restrictive pattern of filling of LV as may occur with restrictive cardiomyopathy.

ABNORMAL PATTERNS

Impaired Myocardial Relation Pattern

In nearly all types of cardiac disease, the initial abnormality of diastolic filling is slowed or impaired myocardial relaxation , include LV hypertrophy, hypertrophic cardiomyopathy, and myocardial ischemia/infarction. The Isovolumic relaxation time(IVRT) is prolonged. Mitral E velocity is decreased and A velocity is increased, roducing and E/A ratio<1, with prolonged DT.

Whenever the E/A ratio is below 1, impaired relaxation is usually present.

RESTRICTIVE FILLNG (or Decreased Compliance) PATTERN:

The term restrictive diastolic filling, or restrictive physiology, should be distinguished from restrictive cardiomyopathy. Restrictive physiology can be present in any cardiac abnormality or in a combination of abnormalities that produce decreased LV compliance and markedly increased LA pressure. Examples include patients with decompensated

congestive heart failure, advanced restrictive cardiomyopathy, severe coronary artery disease, acute severe aortic regurgitation, and consrtrictive pericarditis.

The increase in LA pressure result in earlier opening of the mitral valve, shortened IVRT, and a greater initial transmitral gradient(high E velocity). Early diastolic filling into a noncompliant LV cause a rapid (increase in early LV diastolic pressure, with rapid equalization of LV and LA pressures producing a shortened DT, Atrial contraction increased LA pressure increases even more rapidly, when LV diastolic pressure is markedly increased, there sure is markedly increased, there may be diastolic mitral regurgitation during mid-diastole or with atrial relaxation. Therefore, restrictive physiology is characterized by mitral flow velocities that show increased E velocity, decreased A velocity (<<E), and shortened DT(<160 msec) and IVRT (<7 msec). Typically, the E/A ratio is greater than 2...

PSEUDONORMALIZED PATTERN:

As diastolic function deteriorates, a transition from impaired relaxation to restrictive filling occurs. During this transition, mitral inflow pattern goes through a phase resembling a normal diastolic filling pattern, that is, E/A ratio of 1 to 1.5 and normal DT (160 to 200 ms). This is referred

to as the pseudonormalized filling pattern and it represents a moderate stage of diastolic dysfunction. The pseudonormal pattern can be distinguished from a true normal pattern by Doppler Tissue Imaging(DTI)

GRADING OF DIASTOLIC DYSFUNCTION:

. Therefore, diastolic dysfunction can be graded as follows according to the diastolic filling pattern.

Grade 1 = impaired relaxation

Grade 2 = pseudonormalized pattern

Grade 3 = reversible restrictive pattern

Grade 4 = irreversible restrictive pattern.

As previously discussed, patients with scleroderma should be considered an “at risk” group for the development of pul-monary hypertension, and echocardiography may reveal right ventricular hypertrophy and dilatation even before the onset of symptoms

. Ultimately, as with primary pulmonary hypertension, right-heart catheterization is needed to confirm the diagnosis, assess hemodynamic

severity, and exclude other possible contributing factors, such as an occult congenital heart defect. While it is generally thought that patients with scleroderma- associated pulmonary hypertension are less likely to demonstrate a favorable response to vasodilator therapy than patients with primary pulmonary hypertension (in whom the response rate is approximately 20%)to its still advocated by some experts.

MATERIALS AND METHODS

STUDY POPULATION

All patients were prospectively identified from rheumatology department of our college. There were 40 patients of SSc defined according to previously mentioned ACR criteria were studied. Of them 36 were females and 4 were males. Of them thirty patients satisfied the criteria for limited disease & ten had diffuse disease.

Mean age of forty patients is 38.5 years. The average duration of illness is 3.5 years. All patients except three had raynauds phenomenon. Twenty patients were affected with digital pitting scars & ulcers , & two had digital amputation.

For comparison twenty normal persons were selected(seventeen females, three male) of the same age group. All patients & controls gave consent for the study.

None of the subjects included in the study had evidence of cardiac disease, hypertension, diabetes mellitus, chronic obstructive pulmonary

disease, pulmonary tuberculosis or pulmonary thromboembolism as assessed by history, physical examination

CLINICAL EVALUATION:

A questionnaire prepared noted the duration of SSc, extra-cutaneous complications, the use of current and previous disease-modifying drugs, . Questions were asked relating to previous chest disease, cough, dyspnea, sputum production, chest pain, weight loss and risk factors for respiratory disease, including smoking, medications, and occupation(exposure to silica,solvent industry) .A detailed clinical examination was performed. All patients had venous blood taken for full blood count, renal and liver function, C-reactive protein and antinuclear antibodies. Patients also underwent skin biopsy.

All patients had a physical examination for signs of pulmonary hypertension (Jugular venous distension, Right ventricualar heave, Accentuated pulmonary closure sound) & Signs of interstitial lung disease(Velcro rales)

ELECTROCARDIOGRAM: .

Patients also had 12 lead ECG that was reviewed for presence of left or right atrial enlargement and left or right ventricular hypertrophy.

ECHOCARDIOGRAM;

All echocardiograms were performed by two Cardiologists. Whenever possible, these cardiologists, who were blinded to clinical details, determined pulmonary artery pressure All studies were performed using a phased array ultrasonoscope (ALOKA) with a combined 2.5 MHz. Imaging/continuous wave Doppler and colour Doppler transducer.

Doppler recordings were made from the parasternal, apical and subcostal positions using a modified views when appropriate. A systematic search was performed using two dimensional and colour flow Doppler to identify the most complete tricuspid regurgitant jet followed by continuous wave Doppler acquisition of spectral envelopes of greatest maximal velocity and density. The systolic transtriuspid gradient was calculated using the modified Bernoullie equation

P=4V2

Where V represents maximal regurgitant velocity in metres per second

TWO DIMENSIONAL ECHOCARDIOGRAPHY

PulmHT is easily recognized when the following M-mode and 2D echocardiographic features are present( )

Diminished or absent “a”(atrial) wave of the pulmonary valve

Midsystolic closure or notching of the pulmonary valve

Enlarged chambers on the right side of the heart

D-shaped left ventricular (LV)caviry caused by a flattened ventricular septum

Estimated Right Atrial Pressure(RAP):

Measurement of inferior vena cava (IVC) diameter was made from long axis subxiphoid views. RAP was estimated using caval respiratory index as. when the caval respiratory index exceeded 50% the assumed RAP was 5mm Hg. When the caval respiratory index was less than 50% the assumed RAP was 15 mm Hg.

Estimated Pulmonary Artery Systolic Pressure(PASP):

PASP was calculated as the sum of transtricuspid gradient and the estimated RAP. This method is highly accurate over a wide range of Pulmonary Artery Pressure.

Pulmonary hypertension is defined as a PASP of 25 mm Hg.or greater.. In the absence of pumonic stenosis or RV outflow obstruction, RV systolic pressure is equal to pulmonary artery systolic pressure. The normal TR velocity is 2.0 to 2.5 m/sec. A higher velocity indicates pulmonary hypertension, RV outflow tract obstruction, or pulmonic stenosis.

Mitral Flow Velocities;

The initial classification of diastolic filling is usually attempted from peak mitral flow velocity of the early rapid filling wave(E), peak velocity of the late filling wave due to atrial contraction(A), and the E/A ratio. To measure E and A velocities reliably, the Doppler velocity recording shoud be satisfactory. As mentioned previously, When taken alone, normally E/A is bigger than 1; in late relaxation it decreases to below 1 and this is an indicator of diastolic dysfunction. (53) We have taken E/A ratio of less than 1 as suggestive of diastolic dysfunction.

DECELERATION TIME;

The diastolic filling pattern is characterized further by measuring deceleration time(DT), the interval from the peak of the E velocity to its extrapolation to baseline. DT is prolonged in patients with a relaxation abnormality as the predominant diastolic dysfunction, because it takes longer for LA and LV pressures to be equilibrated with a slower and continued decrease in LV pressure until mid to late diastole.

Tricuspid Flow Velocities

Just as mitral flow velocity variables characterize the LV diastolic filling pattern, so tricuspid flow velocity recordings characterize the RV diastolic filling pattern, using the same criteria. Left and right diastolic filling patterns are not necessarily the same in a patient. The main difference between mitral and tricuspid velocities is a respiratory variation in tricuspid flow velocities in normal subjects.

In order to differentiate pseudo- normalization pattern (grade 2 diastolic dysfunction) from a normal one Doppler tissue imaging was performed.

Mitral&Tricuspid Annulus Velocities by Doppler Tissue Imaging(DTI):

Doppler tissue imaging (DTI), or tissue Doppler, has been applied to evaluate diastolic function by measuring mitral & tricuspid annulus velocity during diastole. The mitral & tricuspid annulus velocity profile during diastole reflects the rate of changes in the long axis dimension and in LV & RV volume respectively. When myocardial relaxation is abnormal, the ratio of mitral & tricuspid annulus motion during atrial systole to the total diastolic annular motion is increased. Sohn et al(77) demonstrated that mitral annulus velocity determined by DTI is relatively preload-independent and is useful in differentiating pseudonormal(grade 2 diastolic dysfunction) from normal mitral inflow velocity pattern.

Left Ventricular Ejection Fraction(LVEF):

LVEF was used as an index of LV systolic pump function and was calculated by Simonsons formula

Right Ventricular Accelerated Fractional Shortening(RVAFS):

The percentage of shortening of RV area during systole was used as an index of RV systolic function and was calculated.Fractional shortening was calculated as the difference between diastolic and systolic diameters divided by diastolic dimension.

The following variables were also assessed:

The left atrial (LA) and right atrial (RA) areas were traced manually and measured at end-systole from the two-dimensional apical four-chamber view.& ,right ventricular dimension

Pulmonary artery pressure control group:

For the normal population, limited data are available on pulmonary artery pressure estimated by Doppler echocardiography. A study of 20 normal healthy adults by Vachiery et al. (65) using Doppler echocardiography found that the maximum estimated pulmonary artery pressure was 24 mmHg

To assess the diagnostic validity of the results of the echocardiogram, a control group of 20 normal persons were subjected for echocardiogram & readings were incorporated into the study. Echocardiography was undertaken with the same ALOKA echocardiogram machine by the same cardiologists who performed the echocardiography in the patients with SSc.

Those patients who had PAH (echowise) are advised to undergo PFT.

DEFINITIONS

Pulmonary hypertension:

The gold standard for pulmonary artery pressure measurement is invasive right-heart catheterization. Pulmonary hypertension, defined by right-heart catheterization of the pulmonary artery is a pressure of 25 mmHg or greater at rest and at least 30 mmHg during exercise (2).

Echocardiography has now been used widely in patients with cardiac disease. Reported correlations between Doppler and catheter measurements range from 0.89 to 0.97; the average standard error for systolic pulmonary artery pressure ranges from 5 to 9 mmHg, and interobserver variability is <3% (83). We have taken Denton et al.'s definition of pulmonary hypertension on Doppler echocardiography as an estimated PASP of 25 mmHg or greater .

Pulmonary Function Tests;

Of the 40 patients, 18 patients (9 with limited-type SSc, and 9 with diffuse-type SSc) underwent lung function testing within period of 1 week after the echocardiography examination. Of these 18 patients, none were being treated for pulmonary disease. . Pulmonary function testing was performed (Jaeger Masterlab, Body Box 10151, Transfer 10154; Jaeger;

Wuerzburg, Germany) according to the recommendations of the American Thoracic Society. Values are presented as a percentage of the predicted value.

Significant lung disease:

Significant lung disease that could be causing pulmonary hypertension was defined as pulmonary function measurements outside the normal range: a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio of less than 65% or a vital capacity lung volume of less than 80% of the predicted value (80,81)

High-resolution CT (HRCT) of lungs:

When PFT is abnormal patients were advised to undergo HRCT of lungs to see whether they have radiographic evidence of ILD. High resolution CT was performed in eighteen of the patients (Philips Tomoscan LX; Philips; Eindhoven, the Netherlands).

Scans were performed at full inspiration in the supine position with 120 kV and 175 mA, including continuous scans through the lungs with 10-min thickness followed by scans with 1.5-mm thickness with a slice spacing of 30 mm.

When they had ILD they are called secondary pulmonary hypertension. When there is no ILD in the presence of significant PulmHT they are likely to have isolated PulmHT.

STATISTICAL ANALYSIS

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

RESULTS & OBSERVATION

There were forty cases with mean age of 35.58+10 years.

TABLE 1: DURATION OF DISEASE

DURATION	*NO. OF FEMALES*	*NO. OF MALES*
1 YR	3	1
2YRS	15	1
3YRS	8	1
4YRS	3	-
5YRS	4	1
>5YRS	3	-

Adequate images & Doppler spectral envelopes of tricuspid regurgitatin were obtained in 37 of 40 patients. The calculated pulmonary artery pressure ranged from 16-72 mm of Hg with a mean of 24.41(SD 15.30)

Similarly TR JET was identified in 16 controls with a mean PASP of 18.2(3.55) mm of Hg. Nine patients had PulmHT with calculated PASP ranging from 34- 72 mm of Hg. Of them 4 had values above 50 mm Hg No patient had impaired left ventricular function, as assessed by left ventricular ejection fraction, which could explain pulmonary hypertension. Of those 9 patients with Pulm.HT 5 had limited disease ; 4 had diffuse form. there were 8 females & 1 male.

Chest HRCT showed that 4(10%) (1 of limited: 3 of diffuse) patients had interstitial lung disease with a fibrosing alveolitis pattern. All the 4 patients, had lung disease was sufficiently severe to cause significant volume loss (as defined above, under significant lung disease) on pulmonary function testing.& hence had secondary pulmonary hypertension . So the remaining (5) 12.5 % of patients had isolated pulmonary hypertension without lung disease evident on pulmonary function testing. [Table 2]

The One remaining female patient in diffuse category had no evidence of ILD (had a moderately high pulmonaryartery pressure). For this patient a second echo was done three months later on the advice of rheumatologist & was found to have a tricuspid gradient which had become lower (reversible)

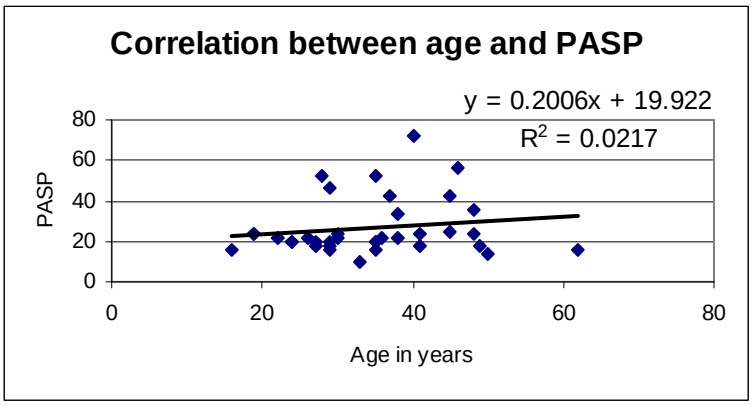
TABLE 2: SUBGROUPING THE PATIENTS WITH PulmHT

	LIMITED (N=5)		DIFFUSE(N=4)	
	NO. OF MALES	NO.OF FEMALES	NO.OF MALES	NO.OF FEMALES
WITH ILD	0	4	1	2
WITHOUT ILD	0	1	0	1

6 other patients who were symptomatic underwent respiratory function tests which showed restriction & HRCT evidence of ILD but without increased PASP.

The clinical features of the SSc patients with pulmonary hypertension were compared with those of SSc patients who had a pulmonary artery pressure below 25 mmHg. (The findings are shown in the tables3,4,5,6).| There was No statistically Significant difference found between the two SSc groups in type of SSc, age,sex and disease duration(table). . Also the acute phase response as assessed by C-reactive protein did not differ significantly between the two groups.

In the control group, none of them had pulmonary artery pressure above 25 mm of Hg. . The pulmonary artery systolic pressure was higher in patients with SSc (24.18+ 15.51 mm Hg) than in controls (18.2+3.55 mm) (P =0.003).There was also a weak correlation between the pulmonary artery pressure and the age of the patient (r=0.02,). [Figure 1]



A comparison of clinical variables in patients with normal & elevated PASP is shown in tables 3,4&5

Table 3:

Limited Type	Pul. Hypertension				Total	
	No		Yes			
	Count	%	Count	%	Count	%
No	6	19.4	4	44.4	10	25.0
Yes	25	80.6	5	55.6	30	75.0
Total	31	100.0	9	100.0	40	100.0

Not significant

Table 4:

Diffused Type	Pul. Hypertension				Total	
	No		Yes			
	Count	%	Count	%	Count	%
No	25	80.6	5	55.6	30	75.0
Yes	6	19.4	4	44.4	10	25.0
Total	31	100.0	9	100.0	40	100.0

Not significant

Table 5:

Sex	Pul. Hypertension				Total	
	No		Yes			
	Count	%	Count	%	Count	%
Female	28	90.3	8	88.9	36	90.0
Male	3	9.7	1	11.1	4	10.0
Total	31	100.0	9	100.0	40	100.0

Not significant

Table 6:

	Pul. Hypertension				t	Df	Sig. (2-tailed)
	No (n = 31)		Yes (n = 9)				
	Mean	S D	Mean	S D			
Age	34.74	11.12	38.44	7.13	-0.94	38	0.353

Not significant

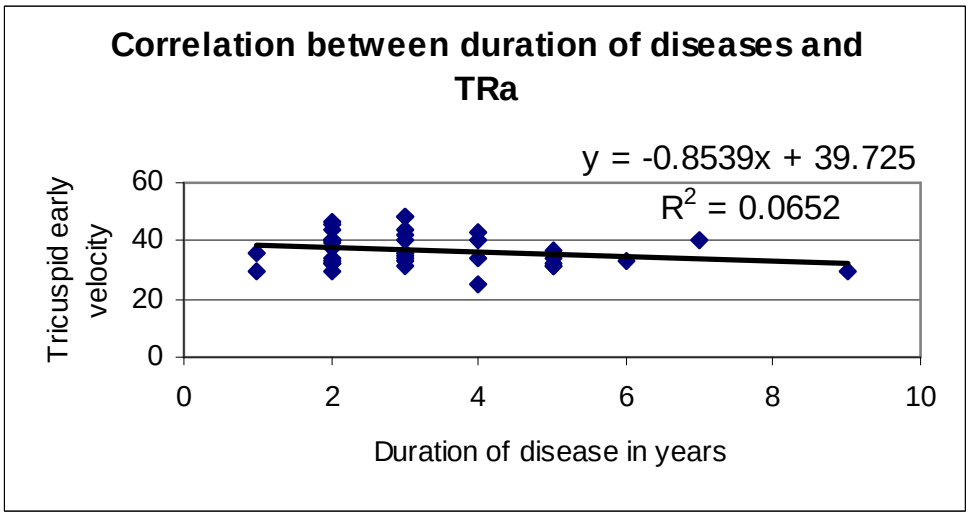
There is no statistically significant differences at baseline in patients with or without elevated PASP.

Echocardiographic and Doppler Differences Between Patients With SSc and Controls:

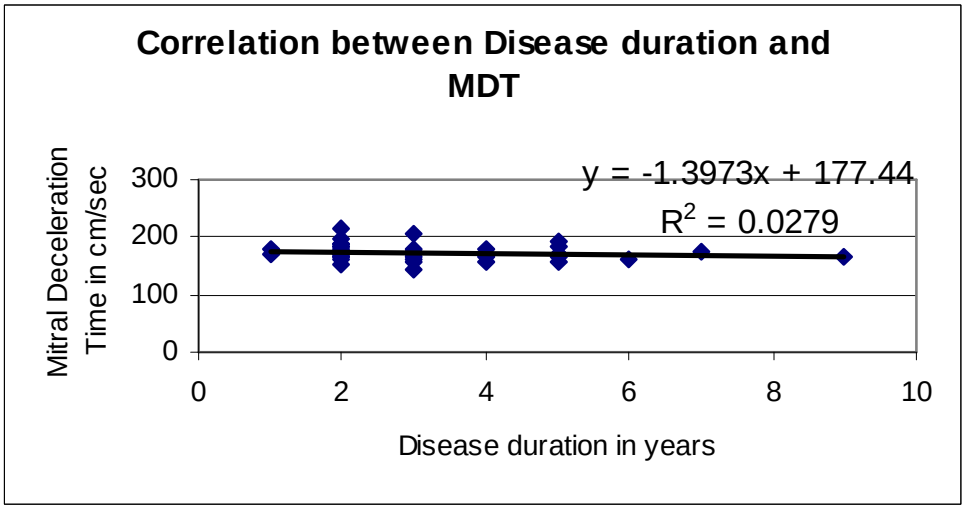
There was a significant difference between the two groups regarding the right ventricular cardiac chamber dimensions (17.7+2.9), compared to controls(14.5+3.1)($p< 0.05$). But there was no difference between the ejection fraction of left ventricle and fractional shortening of the right ventricle.[table 7]

In SSc patients, we found abnormalities of left ventricular filling characterized by increased late diastolic mitral filling velocity A cm/s (52.05+10.1vs45+4.20, p=0.006), prolonged deceleration time (172.9+14.01vs158.1+5.82, p=0.001) .

Moreover in the group of patients we found a weak correlation between the deceleration time and disease duration (r= -0.1,), late diastolic tricuspid filling velocity A cm/s and disease duration (r= -0.2,) correlation_0 .2



Correlation -0.1



7 patients (17.5%) in the group had E/A ratio of less than 1and this was taken as an indicator of diastolic dysfunction. Among the control population, none of patients had evidence of diastolic dysfunction. Moreover the mean age of patients was 35.8 $\pm$ 10.1 years and this age cannot explain the diastolic dysfunction. The patients with evidence of diastolic dysfunction were then compared with SSc patients with E/A ratio more than 1 and the results are summarized in table 4.

Table 7:

	TYPE				T	df	Sig. (2-tailed)
	Control (n = 20)		Case (n = 40)				
	Mean	S D	Mean	S D			
Rt. Ventricular Dimension	14.50	3.00	17.70	2.90	3.98	58	0.000
Rt. Vetricular thickness	3.95	0.83	4.65	1.61	1.82	58	0.073
Age	30.35	7.92	35.58	10.39	1.98	58	0.053
Lt. Ejection Fraction	64.60	3.03	66.15	5.41	1.19	58	0.240
Diastolic Dysfunction	0.00	0.00	0.18	0.38	2.03	58	0.047
Pul. Artery Sys. Pressure	18.20	3.55	24.18	15.51	1.69	58	0.096
DTI Mitral	1.20	0.17	1.24	0.18	0.81	58	0.418
DTI Tricuspid	1.22	0.17	1.28	0.20	1.30	58	0.200
Mitral early velocity	.	.	71.75	6.76			
Mitral late velocity	45.15	4.20	52.05	10.41	2.84	58	0.006
Mitral DT	158.10	5.82	172.90	14.01	4.52	58	0.000
Tricuspid early velocity	.	.	43.53	4.98			
Tricuspid late velocity	38.65	4.74	36.95	5.60	1.16	58	0.249
Tricuspid early by late	1.20	0.16	1.16	0.27	0.50	58	0.620
Tricuspid DT	177.15	5.75	175.85	14.62	0.38	58	0.704
RV fraction shortening	41.80	2.02	43.18	3.63	1.57	58	0.121

7 patients had diastolic dysfunction.one male & six females. The male patient had severe Pulm.HT & diastolic dysfunction of both RV & LV.

Of the 6 female patients 4 had right ventricular diastolic function (3 had associated Pulm.HT), 2 had left ventricular diastolic dysfunction (no associated systemic hypertension).[table8]

Table 8: Subgrouping Of Patients With Diastolic Dysfunction

	RV diastolic dysfunction		LV diastolic dysfuntion		Both RV & LV diastolic dysfuntion	
	With PHT	With out PHT	With SHT	Without SHT	With PHT	Without PHT
No. of females	3	1	0	2	0	0
No. of males	1	0	0	0	1	0

Differences between Patients with SSc with and without Ventricular Diastolic Dysfunction

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

However, no statistically significant differences in sex, age were found (data not shown). But there was a significant difference in the estimated pulmonary artery systolic pressure between patients with and without ventricular diastolic dysfunction (40.+19.32vs 20.82+12.53,P=0.00).[table9]

Two patient had pericardial effusion. One 22 year old female patient had dilated left atrium & left ventricle with global hypokinesia without previous history of myocarditis or infarction. One patient had ECG evidence of left bundle branch block.

Table 9:

	DDYS						F	Sig.
	No (n = 33)		Yes (n = 7)		Control (n = 20)			
	Mean	S D	Mean	S D	Mean	S D		
Tricuspid late velocity	35.39	4.41	44.29	4.92	38.65	4.74	11.82	0.000
Tricuspid DT	171.48	11.09	196.43	11.63	177.15	5.75	19.17	0.000
Tricuspid early by late	1.22	0.24	0.91	0.22	1.20	0.16	6.13	0.004
Mitral late velocity	49.33	5.39	64.86	17.81	45.15	4.20	18.24	0.000
Mitral Early by late	1.45	0.17	1.23	0.32	1.21	0.16	11.79	0.000
Mitral DT	171.67	13.20	178.71	17.28	158.10	5.82	11.41	0.000
Pul. Artery Sys. Pressure	20.82	12.53	40.00	19.32	18.20	3.55	9.88	0.000

DISCUSSION

As per study by Fredrick M Wigley & Laura K Hummers et al(1) the prevalence of SSc is higher in females than in males(3:1), & the difference is greater in younger age group(7:1) .(9)

In my study also there is a female preponderance with a female :male ratio of 12:1.The average age of onset is 50 years.(1). This is in contrast to my cohort of patients where age of onset is much younger(mean age is 35.8 years+SD 10)

The results indicate that unrecognized elevation of PASP is present in significant (22.5%) of patients in my study. Only 3 patients in total cohort had evidence of Pulm. HT by physical examination & ECG or both .the prevalence of pulmonary symptoms were similar in patients with or without Pulm.HT. Thus clinical assessment did not have Discriminant power with regard to presence or absence of Pulm.HT.

In a study by R.W.Battle,M.A Davitt(3) et al the prevalence of patients with limited type was 85% & that of diffuse was 15% . in my study the ratio of limited to diffuse was 75:25%(30:10).

In the same study the prevalence rate of Pulm.HT in their cohort of 34 patients was 12 (35%). In my study the prevalence was lower (22.5%).

The gold standard for assessing pulmonary artery pressure is right heart catheterization. However as catheterization is invasive & As Doppler echocardiography and cardiac catheterization have been reported to have a correlation of between 0.89 and 0.97 in cardiac causes of pulmonary hypertension (83), we have not undertaken catheterization of our SSc patients.

Six other patients who had undergone PFT & HRCT for symptoms of dyspnea Had ILD but no Pulm.HT.

In a study by Ungerer RG, Tashkin et al(6), indicate that specific noninvasive studies are helpful in assessing the likelihood of normal or definitely elevated pulmonary artery pressures in patients with progressive systemic sclerosis, but patients with mild pulmonary hypertension are not likely to be identified by these noninvasive studies.

SSc pulmHt patients are unusual in that they become symptomatic & develop reduced cardiac output at relatively low pulmonary pressures.

Echo assessment of TG is traditionally regarded as accurate technique. However under or overestimation are well known to occur. Overestimates are rare. underestimation is are due to either absence of TR Jet or inability to obtain full alignment with regurgitation jet.(83)

Rich etal(45) & Richards et al(68) have demonstrated variations upto 30 % within 24 hours in pulmonary artery pressure.

One patient had reversible elevation of pulmonary artery pressure.Its probably due to raynauds phenomenon occurring in pulmonary vasculature.

Pulmonary parenchymal abnormalities are recognized with increased with increased frequency as a complication of SSc patients. In patients with CREST syndrome as many as 60-70% develop abnormal results in PFT's despite significantly lower incidence of either symptoms of dyspnea or radiographic abnormalities.

In this setting four major pattern of Pulmonary injury have been described, including vascular changes with or without PulmHT, an usual interstitial pneumonitis pattern(UIP) , small airways disease or a combination of these. Lung biopsy was not done since it may have harmful complications

Of these isolated Pulmonary vascular injury is most common histologic feature occurring in upto 50 % of autopsy in CREST syndrome. Typically patients present with exertional dyspnea . Early identification of PulmHT at a potentially reversible stage can modify the natural course of disease.

Because primary diastolic dysfunction is an important cause of heart failure, as it often is a silent alteration preceding systolic dysfunction (39), knowledge of this complication in patients with SSc without clinically evident cardiac disease may be important to improve patient survival. The early detection of cardiopulmonary involvement in SSc is clearly desirable both for optimal treatment and for implementation of preventive measures in the early stages of the disease.

The extent of RV diastolic dysfunction was not related to the duration of the disease or to the SSc skin score. in the present group of patients with SSc, LV function was normal, RV systolic function was preserved, but BV diastolic function was disturbed. This was evidenced by abnormal relaxation and filling properties, together with RV hypertrophy

These abnormalities were defined using both conventional Doppler echocardiography and Doppler tissue imaging (DTI). The hallmarks of SSc heart disease are myocardial fibrosis and ischemia. Studies (55) have demonstrated that intermittent coronary vasospasm, similar to Raynaud phenomenon, is prevalent in patients with SSc. The pattern of RV &LV diastolic disturbance seen in the present study could therefore be related to myocardial fibrosis and/or ischemia, both of which are known to affect ventricular relaxation and filling and are characterized by reduced E-wave velocity.

Detection of abnormalities in RV diastolic function might provide a means of identifying patients at risk for progressive heart failure.

CONCLUSIONS

Scleroderma is higher in females than in males.

Pulmonary hypertension occurs in a significant proportion of patients with scleroderma. More often its is asymptomatic.

Symptoms consistent with PAH have no Discriminant power to differentiate those with or without elevated PASP.

Its more commonly associated with ILD in diffuse disease, but can occur without lung or heart abnormalities in limited form (isolated PulmHT).

The ratio of patients with limited to diffuse is 3:1.

Mild or early intermittent pulmonary hypertension are not likely to be identified by these non-invasive studies & hence mild PulmHT cannot be excluded in other patients.

There is no statistically significant difference between patients with or without PulmHT when compared by type of SSc ,age ,sex ,duration of disease or CRP

When comparing Echo and Doppler differences between Patients With SSc and controls there was a significant difference between the two groups regarding the right ventricular cardiac chamber dimensions.

There was a significant difference in the estimated pulmonary artery systolic pressure between patients with and without ventricular diastolic dysfunction.

Raynaud phenomenon within the lung is a possibility.

Diastolic dysfunction of RV, LV or both can occur in SSc, which can occur with or without the presence of PulmHT or systemic hypertension. More often it is asymptomatic.

The extent of RV diastolic dysfunction was not related to the duration of the disease or to the SSc skin score.

The hallmarks of SSc heart disease are myocardial fibrosis and ischemia. Intermittent coronary vasospasm, similar to Raynaud phenomenon, is prevalent in patients with SSc. The pattern of RV &LV diastolic disturbance seen in the present study could therefore be related to myocardial fibrosis and/or ischemia.

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

Since so many therapeutic options are in the offing for management of PulmHT early detection is useful in altering the natural course of disease & in decreasing morbidity & mortality & to monitor the progression of disease.

Detection of abnormalities in diastolic function might provide a means of identifying patients at risk for progressive heart failure.

LIMITATION OF THE STUDY

- In my study, I did not do diffusing capacity of carbon monoxide (DLCO) because of its limited availability and cost.

- For patients with isolated pulmonary hypertension, I did not rule out states of hypercoagulability like antiphospholipid antibody syndrome (or) thromboembolic phenomena by investigations like pulmonary angiography and ventilation / perfusion scans.

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PROFORMA

STUDY ON PULMONARY HYPERTENSION &DIASTOLIC DYSFUNCTION IN SCLERODERMA

NAME:

AGE:

SEX:

DISEASE DURATION:

HISTORY OF PRESENTING COMPLAINTS:

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

TREATMENT HISTORY:

HISTORY OF DRUG INTAKE: YES/NO HOW MANY YEARS

GENERAL EXAMINATION

- Conscious
- Temperature
- Pallor

- Icterus
- Cyanosis
- Clubbing
- Lymphadenopathy
- Pedal edema

Pulse Rate: Blood pressure:

EXAMINATION OF SYSTEMS

Cardiovascular System:

CHEST WALL DEFORMITIES: YES/NO

MURMURS YES/NO

RVH YES/NO

RESPIRATORY SYSTEM:

INSPIRATORY CREPTS : YES/NO

PLEURAL EFFUSION :YES/NO

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS

1. COMPLETE BLOOD COUNT

Hemoglobin

Total Count

Differential Count

ESR

2. C REACTIVE PROTEIN
3. BLOOD GLUCOSE
4. BLOOD UREA
5. SERUM CREATININE
6. SERUM ELECTROLYTES

Albumin

Globulin

7. ANA
8. SKIN BIOPSY
9. X-RAY CHEST PA VIEW

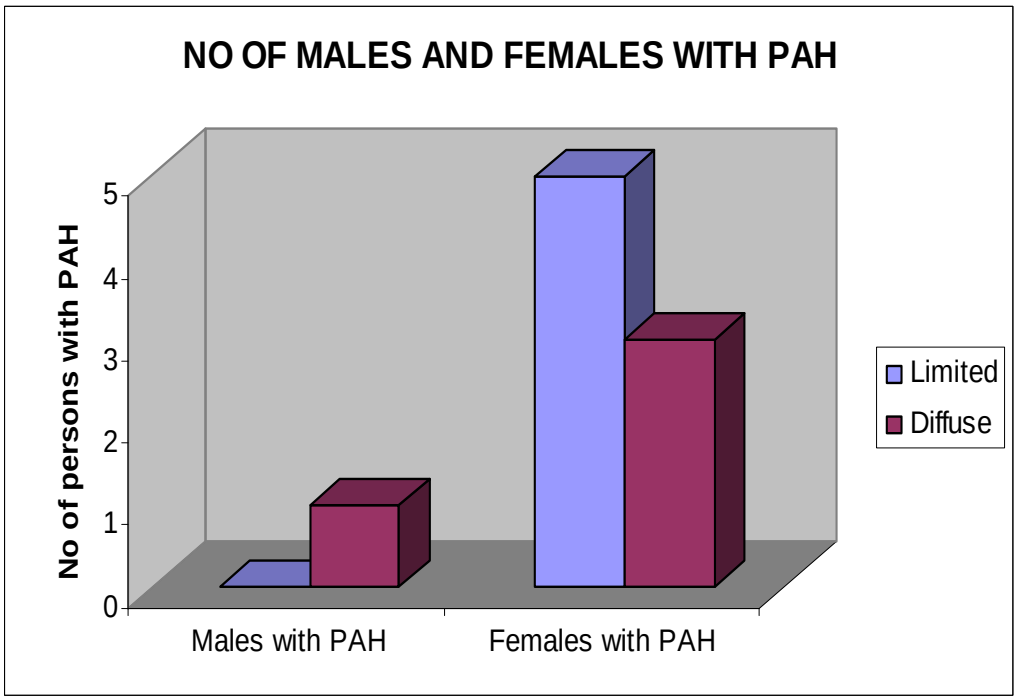
12. ELECTROCARDIOGRAPY

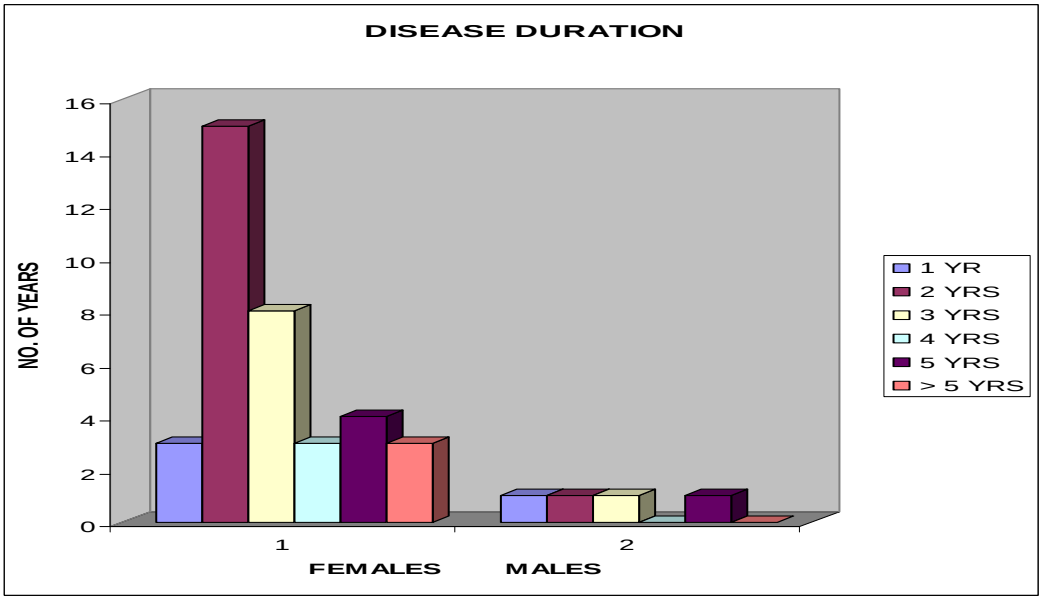
13. HRCT

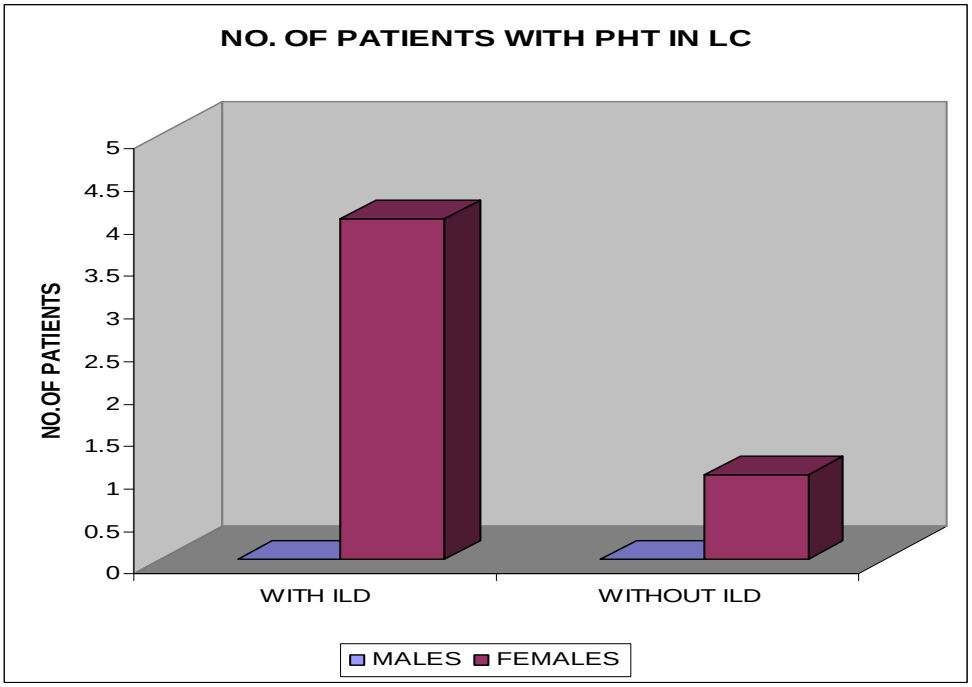
14. ECHOCARDIOGRAPHY (Inclusive of Doppler)

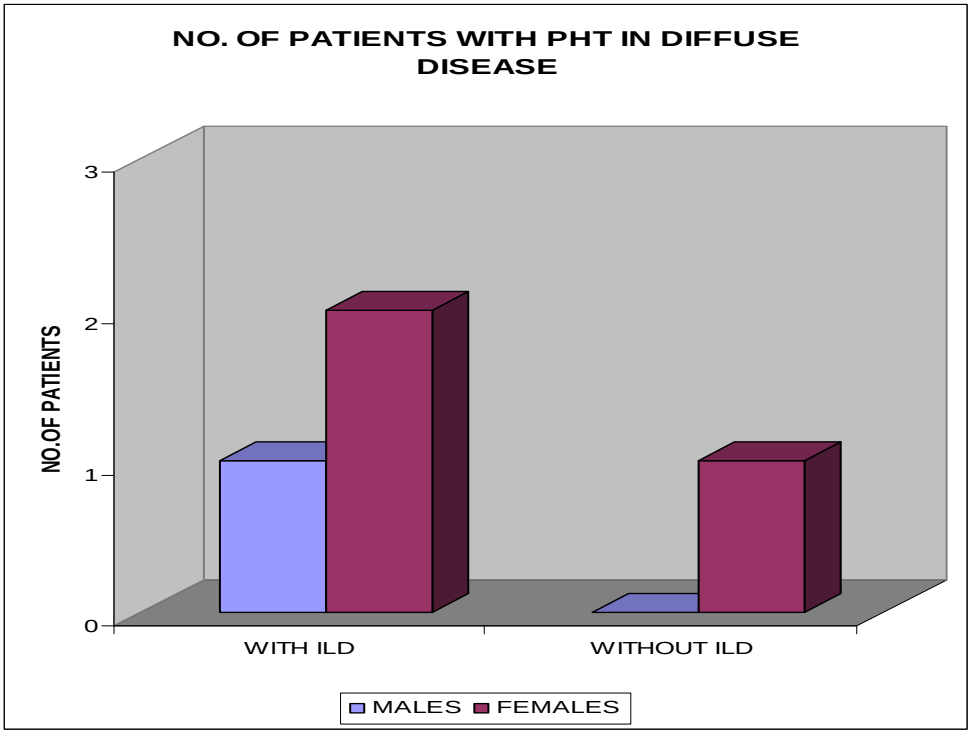
1. Left atrial enlargement
2. Right atrial enlargement
3. Pericardial effusion
4. Left ventricle ejection fraction (EF %)OF LV
5. Fractional shortening (FS %) OF RPH
6. Tricuspid regurgitation / TRPG
7. Transmitral flow velocity (Em/Am Velocity)
8. Transtricuspid flow velocity (Et/At Velocity)
9. Deceleration time
10. Pulmonary artery pressure (PAP)

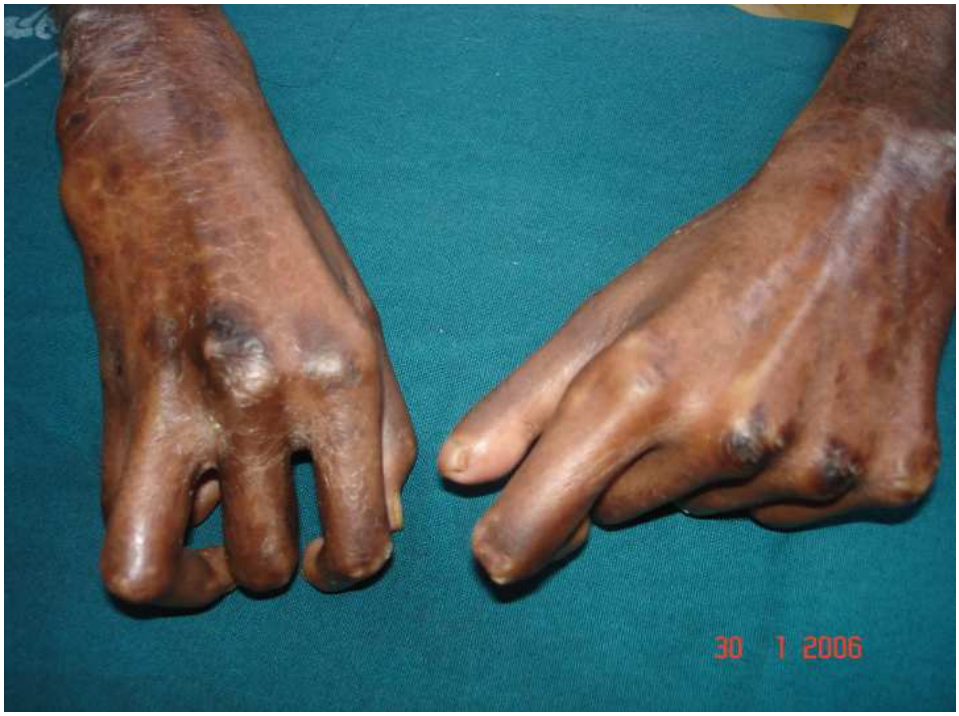
11Doppler Tissue Imaging (Mitral annulus / Tricuspid annulus)

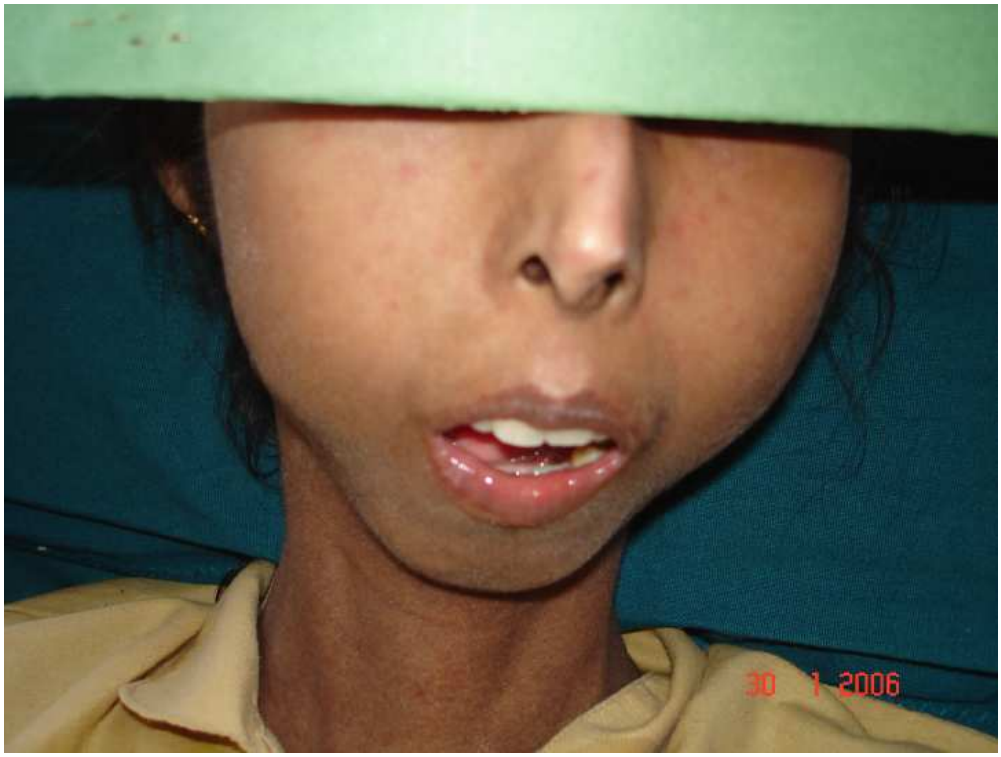

NO OF MALES AND FEMALES WITH PAH
No of persons with PAH
0
1
2
3
4
5
Males with PAH
Females with PAH
Limited
Diffuse

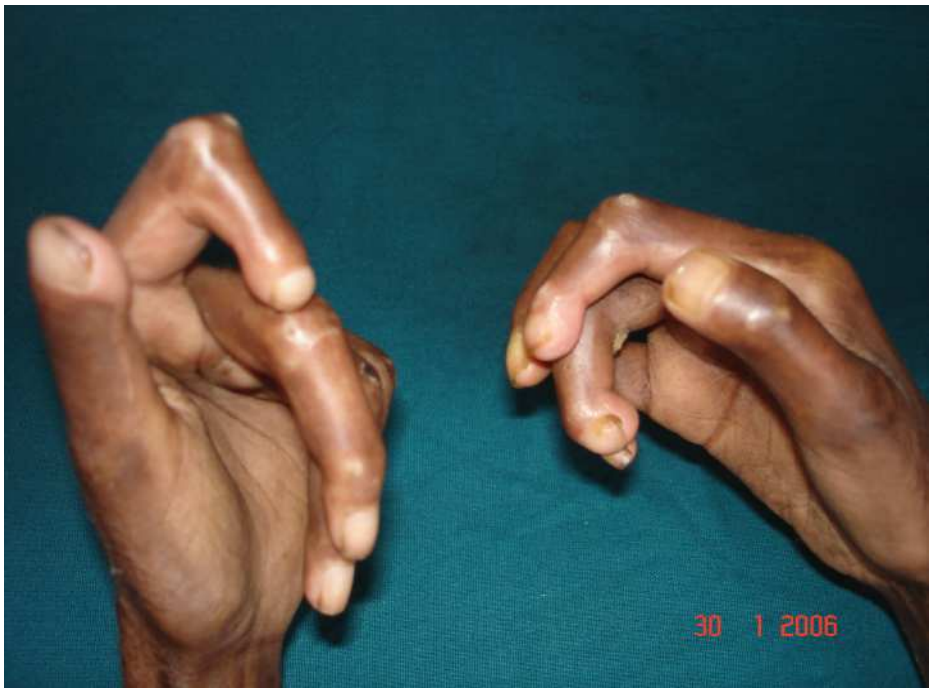

DISEASE DURATION
NO. OF YEARS
0
2
4
6
8
10
12
14
16
1
2
FEMALES
MALES
1 YR
2 YRS
3 YRS
4 YRS
5 YRS
> 5 YRS


NO. OF PATIENTS WITH PHT IN LC
NO.OF PATIENTS
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
WITH ILD
WITHOUT ILD
MALES
FEMALES

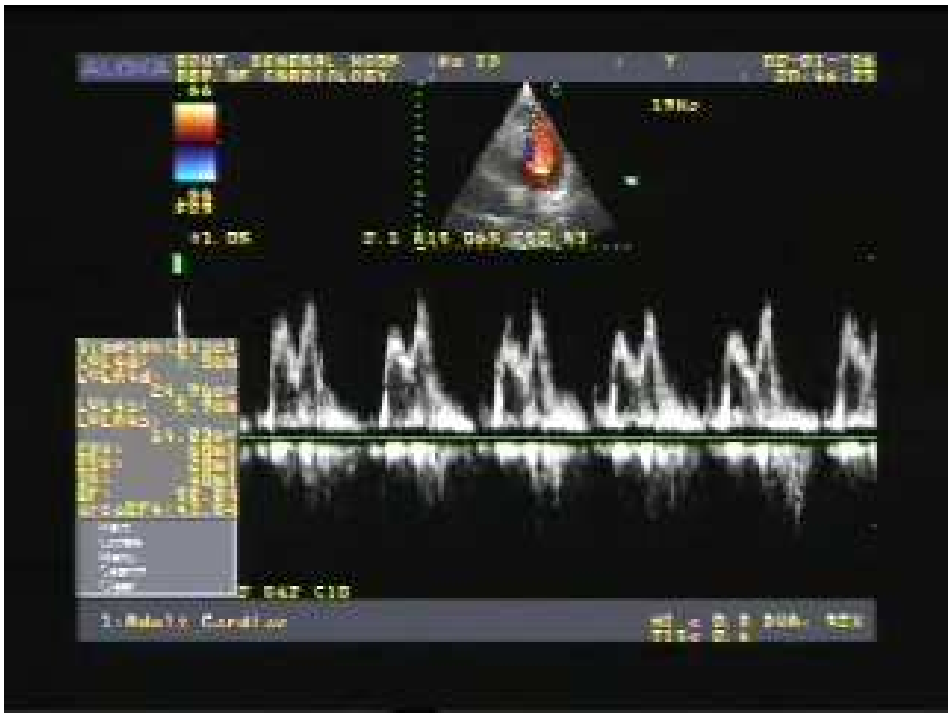

NO. OF PATIENTS WITH PHT IN DIFFUSE DISEASE
NO.OF PATIENTS
3
2
1
0
WITH ILD
WITHOUT ILD
MALES
FEMALES

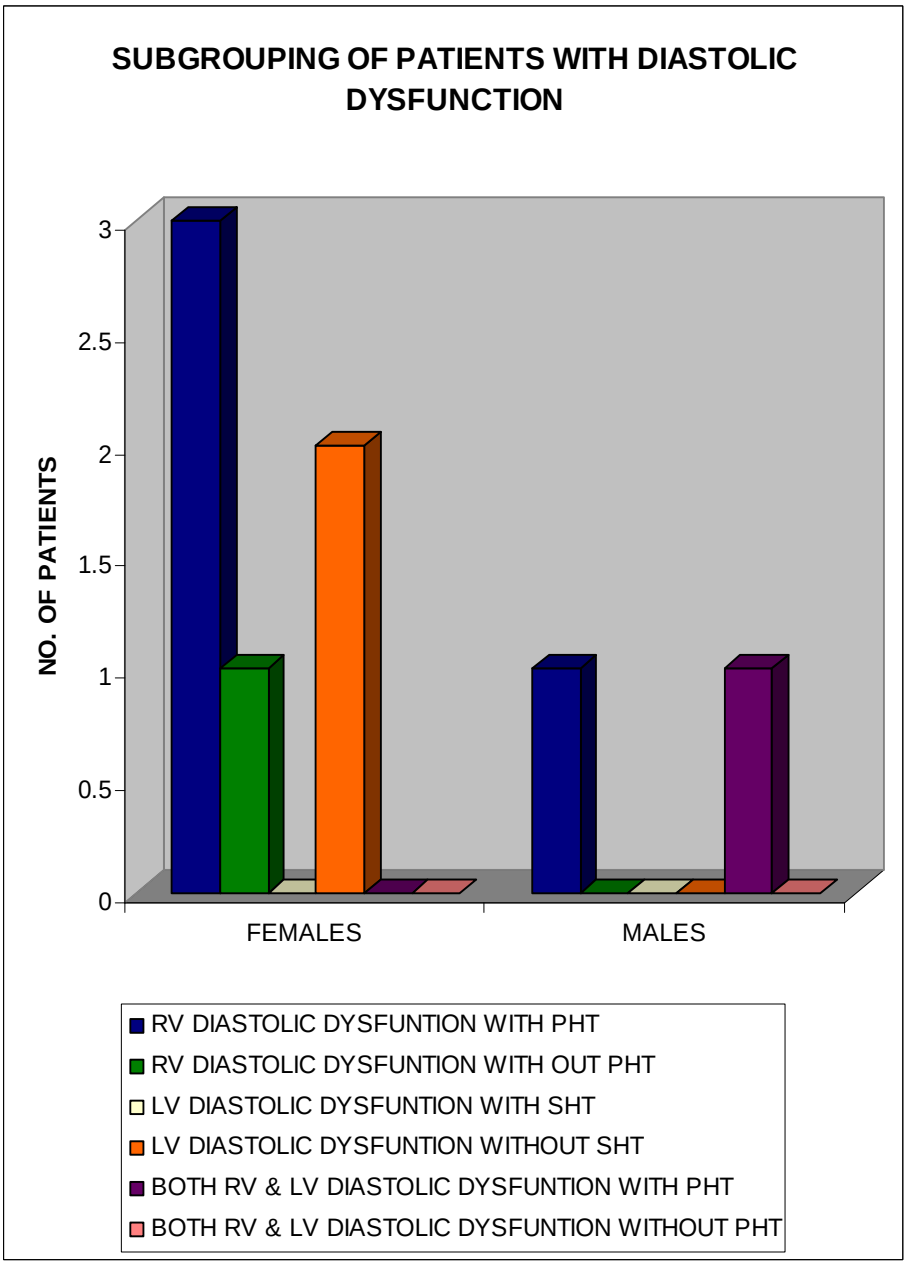

30 1 2006





DIASTOLIC DYSFUNCTION-2D ECHO




SUBGROUPING OF PATIENTS WITH DIASTOLIC DYSFUNCTION
NO. OF PATIENTS
3
2.5
2
1.5
1
0.5
0
FEMALES
MALES
RV DIASTOLIC DYSFUNTION WITH PHT
RV DIASTOLIC DYSFUNTION WITH OUT PHT
LV DIASTOLIC DYSFUNTION WITH SHT
LV DIASTOLIC DYSFUNTION WITHOUT SHT
BOTH RV & LV DIASTOLIC DYSFUNTION WITH PHT
BOTH RV & LV DIASTOLIC DYSFUNTION WITHOUT PHT

MASTER CHART

	age	sex	pasp	RA	LA	RVTH	FAS	EF	TRE/A	DT	MIITE/A	DT	EM
Meenakshi	24	0	18	9.4	10.4	4	40	65	1.4	185	1.3	155	
Mallika	34	0	16	8.4	9.6	3	44	66	1	176	1.2	160	
Vasanthi	20	0	24	10.4	8.4	5	38	70	1.3	170	1.4	145	
Dharmalingam	40	1	22	9.4	10.4	4	40	65	1.4	165	1.2	150	
Parimala	35	0	12	12.2	12	4	44	60	1.3	170	1.4	155	
Thangam	28	0	21	8.2	20	6	40	62	1	174	1	157	
Krishnan	20	1	19	10.4	14.2	30	41	63	1.2	171	1.4	168	
Mohamed Ali	42	0	13	12.8	10	18	40	64	1.1	180	1.1	156	
Renuka	33	0	15	11.7	17.4	23	41	62	1.4	175	1.3	166	
Chandrasekar	41	1	23	8.4	21.6	40	45	64	1	178	1	153	
Rathnakiumari	30	0	14	14.6	18.2	28	44	66	1.3	181	1.2	159	
Pitchayee	20	0	20	12.8	14.2	21	42	61	1.2	178	1.4	164	
Lakshmi	22	0	16	13	9.2	12	40	66	1.3	180	1.3	159	
Muthulakshmi	25	0	22	17	18.2	8	41	60	1	175	1	161	
Radha	40	0	16	19.4	17.6	31	43	68	1.4	188	1	160	
Janagam	32	0	18	10.2	12.2	33	42	63	1.2	182	1.4	163	
Jeyalaksmi	38	0	21	21.4	13.8	22	40	67	1	172	1.1	152	
Rajeswari	24	0	15	14.8	11.6	12	44	70	1.3	179	1	161	
Jamela Begum	21	0	22	20	18.2	25	42	62	1.1	184	1.3	165	
Tamilarasi	38	0	17	15.2	16.4	24	45	68	1	180	1.2	153	

MASTER CHART

	RVD	RVTH	DUR	LVEF	**DDYS**	**PAH**	**AGE**	LCC	dif	SEX	**ILD**	EM/AM	ET/AT	MITE	MITA	E/A	DT	TR E	TR A	E/A	DT	FAS
vijayalak	2.4	4	4	66	**0**	**0**	**22**	**1**	0	0	**0**	1.12	1.28	70	45	1.6	166	52	34	1.52	176	44
laksmi	2	4	2	74	**0**	**25**	**45**	1		0	**0**	1.4	1.25	68	52	1.3	170	40	33	1.21	188	42
banumathi	1.8	3	3	65	**1**	**0**	**48**	1		**0**	**0**	1.2	0.8	72	50	1.4	172	39	48	0.92	206	42
RAJESWARI	1.8	5	3	66	**0**	**0**	**36**	1		0	**0**	1.23	1.34	70	48	1.5	157	36	31	1.16	160	40
v jaya	1.5	5	2	70	**0**	**56**	**46**		1	0	**1**	1.36	1.42	66	40	1.7	178	48	40	1.2	176	40
kanaga	15	4	9	75	**0**	**0**	**24**	1		0	**1**	1.42	1.38	64	54	1.2	166	36	30	1.2	165	43
chinnamal	14	4	2	72	**0**	**0**	**27**	1		0	**0**	1.33	1.24	71	48	1.5	214	47	40	1.17	160	40
veronica	16	3	2	68	**0**	**0**	**29**		**1**	0	**0**	1.37	1.18	84	46	1.8	168	39	32	1.21	175	42
kala	2	4	5	65	**0**	**46**	**29**	0	**1**	0	**0**	1.18	1.55	73	53	1.4	170	44	36	1.22	166	44
rajammal	2.4	4	2	62	**0**	**0**		1				1.24	1.16	69	52	1.3	186	46	40	1.15	186	45
rukmini	2	4	6	68	**0**	**42**	**45**	1		0	**0**	1.4	1.54	66	40	1.7	162	48	33	1.45	160	50
naseera	2.2	5	5	70	**0**	**42**	**37**	1		0	**0**	1.32	1.61	80	49	1.6	170	39	31	1.25	166	44
anitha	1.6	4	5	62	**0**	**0**	**16**	1		0	**0**	1.37	1.42	80	55	1.5	164	42	34	1.23	154	46
susela	17	4	5	63	**0**	**0**	**49**	1		0	**0**	1.28	1.54	76	50	1.5	192	45	37	1.21	176	48
maliga	2.2	6	2	75	**0**	**0**	**35**	1				1.26	1.37	70	48	1.5	182	46	40	1.15	170	45
shanthi	1.4	5	7	63	**0**	**0**	**38**	1		0	**0**	1.2	1.28	68	44	1.5	176	50	40	1.22	160	41
padmavathi	2.5	4	4	74	**0**	**0**	**30**	1		0	**1**	1.39	1.29	83	50	1.7	156	38	25	1.52	166	43
manimegalai	1.4	4	3	75	**0**	**0**	**41**	**1**				1.34	1.33	66	42	1.6	174	48	33	1.45	166	46
chinapa	18	4	5	66	**0**	**0**	**41**	1		**1**		1.26	1.65	82	52	1.6	157	46	32	1.43	149	48
malliga	14	5	2	60	**0**	**0**	**35**	**1**		**0**	**0**	1.14	1.38	77	47	1.6	182	39	30	1.3	176	32
gandimathi	19	8	2	68	**0**	**0**	**33**	1		**0**	**0**	1.3	1.28	80	60	1.3	166	47	40	1.17	172	50
prabavati	19	5	3	65	**0**	**0**	**33**	0	**1**	**0**	**1**	1.4	1.36	60	49	1.2	142	44	36	1.2	157	48
PARTHBAN	18	3	1	60	**0**	**0**	**50**		**1**	**1**	**1**	1	1.45	70	50	1.4	170	40	30	1.3	167	41

	RVD	RVTH	DUR	LVEF	**DDYS**	**PAH**	**AGE**	LCC	dif	SEX	**ILD**	EM/AM	ET/AT	MITE	MITA	E/A	DT	TR E	TR A	E/A	DT	FAS
citra	16	4	3	65	**0**	**0**	**27**		**1**	**0**	**1**											
sujatha	14	4	2	55	**0**	**0**	**19**		1	**0**	**0**	1.36	1.18	60	42	1.4	152	48	34	1.4	176	45
boomadevi	18	6	2	65	**0**	**34**	**38**	1		0	**0**	1.27	1.34	67	49	1.4	170	40	32	1.25	180	40
revathi	16	5	4	62	**0**	**22**	**26**	1		0	**0**	1.38	1.42	72	54	1.3	168	49	40	1.21	172	42
jamina	15	5	1	62	**0**	**0**	**24**	1		0	**0**	1.54	1.29	79	50	1.6	178	42	36	1.16	186	45
bhimrao	20	5	3	56	**0**	**0**	**29**	1		1	**0**	1.2	1.18	64	42	1.5	180	44	35	1.25	188	46
rajammal	16	4	2	66	**0**	**20**	**50**	**1**	**0**	**0**	**0**	1.36	1.26	78	52	1.5	164	46	38	1.21	190	48
saraswathy	18	4	5	64	**0**	**0**	**62**	**1**	**0**	**0**	**1**	1.32	1.24	60	43	1.4	182	38	31	1.22	174	42
kamala	16	3	3	58	**0**	**0**	**45**	**1**	**0**	**0**	**0**	1.16	1.35	66	48	1.4	170	48	40	1.2	180	40
sulochana	20	8	2	77	**1**	**52**	**35**	1		0	**0**	0.9	1.33.	80	60	1.3	173	38	47	0.8	206	44
malati	16	4	3	74	**1**	**24**	**19**	1		0	**0**	0.8	1.23	76	52	1.5	163	40	48	0.83	198	45
anthoniam	16	4	4	66	**1**	**52**	**28**	0	**1**	0	**1**	0.78	1.1	74	62	1.2	179	36	43	0.84	188	40
devaki	16	4	2	60	**1**	**20**	**35**	1		0	**0**	1.25	0.8	80	50	1.6	160	40	46	0.76	201	46
Jeeva	17	12	2	70	**1**	**72**	**40**	1		1	**1**	0.77	0.82	70	90	0.8	198	35	44	0.79	202	38
paremes	16	5	3	64	**1**	**36**	**48**	0	1	0	**1**	1.2	0.84	75	90	0.8	206	48	34	1.4	174	40
Sankari	20	4	2	65	**0**	**0**	**30**	**0**	**1**	**0**	**0**	1.3	1.2	66	60		190	49	39	1.25	182	38
bimarao	16	4	3	65	**0**	**0**	**29**	**1**		**0**	**0**	**1.3**	**1.4**	**76**	**60**		**176**	**55**	**44**	**0**	**186**	**40**