Benghazi university
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ASSESSMENT OF PULMONARY ARTERIAL PRESSURE IN PATIENTS WITH CONNECTIVE TISSUE DISEASES

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Assessment of Pulmonary Arterial Pressure in Patients With Connective Tissue Diseases

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Declaration

This is to declare that I have not submitted this research work to any other university for purpose of obtaining any postgraduate degree in medicine

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Abbreviations

-ACCP - American college of chest physicians.

-ACR – American college of rheumatology.

-ACE-i-Angiotension converting enzyme inhibitor.

-AECAs-Anti-endothelial-cell antibodies.

-ALK1 – Activin receptor-like kinase type 1.

-ANA – Antinuclear antibody.

-ANCA – Antineutrophil cytoplasmic antibody.

-BMPR2 - Bone morphogenetic protein receptor type 2.

-BNP – Brain natriuretic peptide.

-CAD-Coronary artery disease.

-CCB – Calcium channel blocker.

COPD-Chronic obstructive pulmonary disease.

CT-Computed tomography.

-CTD-Connective tissue diseas.

-CTDs – Connective tissue diseases.

-CTEPH – Chronic thromboembolic pulmonary hypertension.

-2D echocardiography-2 Dimention echocardiography.

-EPAP- Estimated pulmonary arterial pressure.

-ET-1-Endotheline-1.

-ET-receptor-Endotheline-receptor.

- GERD - gastroesophageal reflux disease.

-HIV – Human immunodeficiency virus.

-5HTT – 5-Hydroxytryptamine transporter.

-ILD- Interstitial lung disease.

-IPAH – Idiopathic pulmonary arterial hypertension.

-LL edema- Lower limbs edema.

-LV-Left ventricle.

-MCTD-Mixed connective tissue disease.

-6MWT – 6 Minute walk test.

-NIH-National institute of health.

-NT-pro BNP – N-Terminal PRO-Brain natriuretic peptide.

-OSA – Obstructive sleep apnea.

-PAH – Pulmonary arterial hypertension.

-PAP- Pulmonary arterial pressure.

-PASP – Pulmonary artery systolic pressure.

-PCWP – pulmonary capillary wedge pressure.

-PE- Pulmonary embolism.

-PM- Polymyositis

-PVOD – Pulmonary veno-occlusive disease.

-PCH – Pulmonary capillary hemangiomatosis.

-PFT – Pulmonary function test.

-RAD- Right axis deviation.

-RA- Rheumatoid arthritis.

-RAP – Right atrial pressure.

-RBBB- Right bundle branch block.

-RF – Rheumatoid factor.

-RHC- Right heart catheterization.

-RVE – Right ventricular enlargement.

-RVH – Right ventricular hypertrophy.

-RAE – Right atrial enlargement.

-SOB- Shortness of breath

-SRC-Scleroderma renal crisis

-SSc- Systemic sclerosis

-SLE- Systemic lupus erythematosis.

TDI-Tissue Doppler Imaging.

-TR – Tricuspid regurge.

-TRV – Tricuspid regurge jet velocity

-TTE- Transthorasic echocardiography.

-V/Q scan – Ventilation -perfusion scan.

-WHO – World health organization.

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INTRODUCTION

Pulmonary arterial hypertension [PAH]: is characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. It is a life-threatening condition with a poor prognosis if untreated [1].

Definition of Pulmonary Arterial Hypertension :

The definition of pulmonary Arterial hypertension [PAH] is based upon right heart catheterization measurements. PAH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest, a mean pulmonary artery pressure of 8 to 20 mmHg at rest is considered normal, while a mean pulmonary artery pressure of 21 to 24 mmHg at rest has uncertain clinical implication [1].

Two definitions that were previously accepted are no longer used. They include a mean pulmonary artery pressure greater than 30 mmHg with exercise (measured by right heart catheterization) [2] and a systolic pulmonary artery pressure greater than 40 mmHg (measured by Doppler echocardiography) ,The latter corresponds to a tricuspid regurgitant velocity of 3.0 to 3.5 m/sec [3].

Classification of Pulmonary Arterial Hypertension：

PAH was previously classified as either idiopathic pulmonary arterial hypertension (IPAH, formerly called primary pulmonary hypertension) or secondary PAH. However, it became clear that some forms of secondary PAH closely resemble IPAH in their histopathological features, natural history, and response to treatment. In an attempt to organize PAH on a mechanistic basis, the World Health Organization (WHO) classified PAH into five groups [4].

1. Pulmonary arterial hypertension (PAH):

1.1. Idiopathic PAH .

1.2. Heritable .

1.2.1. BMPR2(bone morphogenetic protein receptor type 2).

1.2.2. ALK1 (activin receptor-like kinase type), endoglin (with or without hereditary hemorrhagic telangiectasia).

1.2.3. Unknown.

1.3. Drug- and toxin-induced.

1.4. Associated with .

1.4.1. Connective tissue diseases.

1.4.2. HIV (human immunodeficiency virus) infection .

1.4.3. Portal hypertension .

1.4.4. Congenital heart diseases.

1.4.5. Schistosomiasis .

1.4.6. Chronic hemolytic anemia .

1.5 Persistent pulmonary hypertension of the newborn.

1 . Pulmonary veno-occlusive disease(PVOD) and/or pulmonary capillary. hemangiomatosis (PCH).

2. Pulmonary hypertension owing to left heart disease:

2.1. Systolic dysfunction .

2.2. Diastolic dysfunction.

2.3. Valvular disease .

3. Pulmonary hypertension owing to lung diseases and/or hypoxia:

3.1. Chronic obstructive pulmonary disease .

3.2. Interstitial lung disease .

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing .

3.5. Alveolar hypoventilation disorders.

3.6. Chronic exposure to high altitude .

3.7. Developmental abnormalities .

4. Chronic thromboembolic pulmonary hypertension (CTEPH).

5. Pulmonary hypertension with unclear multifactorial mechanisms.

5.1. Hematologic disorders: myeloproliferative disorders, splenectomy.

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis.

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders .

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis .

Pulmonary Arterial Hypertension in Connective Tissue Diseases:

Pulmonary arterial hypertension (PAH) is a severe complication of many of the seropositive connective tissue diseases (CTDs). It has long been recognized association with systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) [5, 6]; however, it can occur in other connective tissue diseases, including SSc-SLE overlap syndrome [7], mixed connective tissue disease (MCTD) [8–10], inflammatory myositides (dermatomyositis and polymyositis) [11, 12], Sjögren's syndrome [13] and rheumatoid arthritis [1].

Doppler echocardiography has been recommended to screen pulmonary arterial hypertension (PAH) and evaluate for left ventricular systolic and diastolic dysfunction, left-sided ventricular enlargement or valvular heart disease [14]. Right heart catheterization is required to confirm the presence of PAH, establish a specific diagnosis and determine the severity [14]. Using catheterization derived hemodynamic, PAH is defined as a mean pulmonary artery pressure (PAP) ≥25 mmHg and a pulmonary capillary wedge pressure of ≤15 mmHg [15].

Of the CTDs associated with PAH, SSc-PAH and SLE-PAH are the most common [16].

Scleroderma [SSc] is a connective tissue disease with vasculopathy, fibrosis, and autoimmunity. It is rare, with a prevalence of 65–265 per million population [17].SSc is more frequent in women, especially during the childbearing years. The etiology of SSc is largely unknown, with evidence to support both genetic and environmental factors [18,19].

SSc can be classified into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) [20]. In dcSSc, there is skin sclerosis proximal to the knees and elbows and a higher frequency of internal organ involvement. Inflammation is prominent during the first three years of the disease. In lcSSc, skin sclerosis is restricted to the face and distal to the elbows and knees, often only in the hands and face, and the frequency of lung fibrosis is lower. The complications of SSc include gastrointestinal changes (especially gastro esophageal reflux disease [GERD] and dysphagia) and lung (interstitial lung disease) leading to fibrosis or pulmonary arterial hypertension [PAH], heart, and kidney problems, such as SSc renal crisis (SRC). Mortality has improved for SRC with the use of angiotensin-converting enzyme [ACE] inhibitors, so the major causes of premature mortality in SSc are lung and heart complications [21].

For serious complications such as PAH, awareness, a high index of suspicion, and targeted screening programs are important in attaining an early

diagnosis. There are many proven therapies to treat PAH, so there is a pressing need to diagnose SSc and its associated complications as early as possible in order for effective therapy to be initiated. Screening programs for SSc-associated PAH by echocardiograms performed annually have demonstrated that patients with earlier PAH can be detected [22].

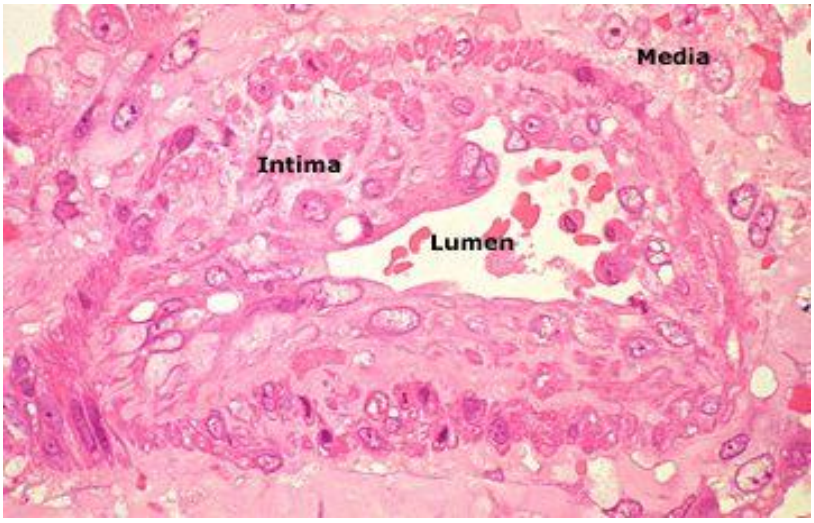
Systemic lupus erythematosus (SLE) or lupus is an autoimmune CTD that occurs in 0.1% of the population and is more common in women [23]. PAH in SLE is more common in Korea, China, and Japan than in North America and Europe [24]. PAH is a major cause of mortality in lupus in some cohorts.

Mixed CTD [MCTD] may have a high frequency of PAH, especially if the manifestations of the disease are SSc-like. MCTD appears to be extremely uncommon in North America. Rheumatoid arthritis, Sjogren's syndrome, poly- and dermatomyositis, and vasculitis may be associated with PAH [25].

Pathogenesis of Pulmonary Arterial Hypertension in CTD:

The pathophysiological mechanisms leading to PAH remain unknown. Histopathological changes in the various recognized forms of PAH have been shown to be qualitatively similar [26]. Even if many pathobiological mechanisms have been identified, exact initiation and perpetuation pathological processes are still not well understood. PAH in patients with CTD is associated with intimal hyperplasia, smooth muscle hypertrophy, and medial thickening, similar to the changes seen in primary PAH.

Figure -1-Vascular changes in pulmonary arterial hypertension



Pulmonary arteriole in pulmonary arterial hypertension showing both mild medial hypertrophy and marked intimal hyperplasia, leading to partial obstruction of the lumen.

CTD associated with occlusive vasculopathy of the small pulmonary arteries and arterioles which lead to increased pulmonary vascular resistance .Endothelial dysfunction may be an important factor in the onset of PAH, possibly by contributing to vasospasm and proliferation of the vasculature occluding flow. A commonly accepted pathophysiological model includes the imbalance between vasoconstrictive, thrombogenic, mitogenic and pro-inflammatory factors as opposed to anti-coagulant, anti-mitotic and vasodilating mechanisms resulting in endothelial dysfunction and vascular remodeling. Chronically impaired production of vasodilators such as nitric oxide and prostacyclin goes along with an over expression of vasoconstrictors such as thromboxane A2 or endothelin-1 (ET1) [27]. In CTD, PAH may occur in association with interstitial fibrosis, but also in isolation (in the absence of overt interstitial lung disease or chronic hypoxia). This might be a result of direct vascular involvement. Deregulated activity of mediators controlling vasomotor tone has been implicated, and levels of ET-1 are elevated in the circulation and in the lungs. By causing enhanced peptide (Brain natriuretic peptide) may be useful in identifying those patients with CTD at highest risk for developing cardiac involvement [28].

There may be a genetic–environmental link that increases PAH in lupus, as reports of PAH are seemingly more frequent in Asia (including China, Korea, and

Japan) than in North America, there may also be increased pulmonary hypertension due to recurrent PE (as SLE may itself be a hypercoaguable state and there are more clotting tendencies in those who are antiphospholipid-antibody-positive). In addition, anticardiolipin antibodies can increase the risk for PAH. There can also be anti-endothelial-cell antibodies (AECAs) [29].

Predisposition to pulmonary vascular disease may be related to genetic mutations in the bone morphogenetic protein receptor type II (BMPR2) [30], activin-like kinase type 1 [31], and /or 5-hydroxytryptamine (serotonin) transporter (5HTT) genes [32].

Prevalence of Pulmonary Arterial Hypertension in CTD:

PAH is an orphan disease, and with all categories included, its prevalence has been estimated to be up to 15 cases per million. However, PAH has been increasingly recognized as a more common and severe complication of CTD. In a population-based study, the prevalence of pulmonary hypertension was 2.6% in over 3500 investigated patients [33]. In the National Institute of Health (NIH) registry, among 236 cases of unexplained PAH, about 8% was associated with CTD [34]. It is a well-recognized phenomenon in PAH associated with CTD that mainly women are affected. However, compared with IPAH, the patients are older, have

a significantly lower cardiac output and there is a trend towards worse survival compared with IPAH patients: 1-, 2- and 3-yr survival rates were reported to be 45, 35 and 28%, respectively, with a median survival of only 1 yr following diagnosis (IPAH: 1- and 3-year survival, 68 and 48%, respectively, with a median survival of 2.8 yrs) [35, 36].

Unfortunately, the risk factors for PAH development in CTD are remain unknown. A British based registry study of PAH in 722 patients with SSc showed a prevalence of about 12% [37]. In another series of 930 patients with SSc, the cumulative incidence was 13% [38], and in the French registry, which included hemodynamic confirmation of PAH, it was calculated to be 10% [39].

PAH is less commonly seen in SLE (0.5–14%, [40]), and is a rare clinical finding in dermatomyositis and rheumatoid arthritis [35].

Symptoms and signs of Pulmonary Arterial Hypertension:

Symptoms of PAH can be subtle or severe. They may include dyspnea, fatigue, and impaired exercise tolerance [40, 41]. These symptoms are non-specific for PAH, so the diagnosis can be missed. There are many other reasons for CTD patients to manifest shortness of breath, such as interstitial lung disease (ILD), cardiomyopathy, pericardial disease, coronary artery disease (CAD), diastolic

dysfunction, pulmonary venous disease from emboli or secondary to congestive heart failure, and myopathy of the diaphragm. ILD and PAH are the main CTD-related reasons to have shortness of breath.

The initial physical finding of PAH is usually increased intensity of the pulmonic component of the second heart sound, which may become palpable. The second heart sound is narrowly split or single in patients with PAH and preserved right ventricular function. Splitting of the second heart sound widens as the right ventricle fails or if right bundle branch block develops. Auscultation of the heart may also reveal a systolic ejection murmur and, in more severe disease, a diastolic pulmonic regurgitation murmur. The right-sided murmurs and gallops are augmented with inspiration. Right ventricular hypertrophy is characterized by a prominent A wave in the jugular venous pulse, associated with a right-sided fourth heart sound, and either a left parasternal heave or a downward subxiphoid thrust. Right ventricular failure results in systemic venous hypertension. This can lead to a variety of findings such as elevated jugular venous pressure, right ventricular third heart sound, and a high-pitched tricuspid regurgitant murmur accompanied by a prominent V wave in the jugular venous pulse if tricuspid regurgitation is present. Hepatomegaly, a pulsatile liver, peripheral edema, ascites, and pleural effusion may exist [42, 43].

Diagnostic tests that may be considered include an echocardiogram to study both the left and right heart, the left heart is spared in PAH, but the right ventricle and atrium may be dilated, The Pulmonary artery pressure is estimated by the tricuspid regurgitant jet on Doppler echocardiogram. Pulmonary function tests (to rule out interstitial or other restrictive defects such as external restriction from a tight chest wall or diaphragm weakness), high-resolution chest computed tomography (CT) for parenchymal disease, spiral CT scan or V/Q scan if pulmonary embolism(PE) is suspected [25].

Right-heart catheterization is necessary to make a diagnosis of PAH where there is increased pulmonary vascular resistance, elevated Pulmonary artery pressure, and a normal wedge pressure [25].

Pulmonary Arterial Hypertension Screening in CTD:

As PAH is common in SS, SLE, MCTD, screening is essential to make an early diagnosis. The WHO recommends annual screening with echocardiography, including Doppler estimates of Pulmonary artery pressure. Findings of PAH on echocardiography can show right ventricular hypertrophy and dilation, even before symptom onset, but ideally the disease should be detected before the right ventricle is damaged [25].

Other Screening Tests:

Endothelin is upregulated in SSc and especially in PAH, but is not a good screening test as there may be elevations in any SSc patient, especially in diffuse SSc [44]. However, N-terminal pro-brain naturetic factor [NTproBNP] has also been used in some studies as screening test [45, 46].

Limitations of Echocardiography for Pulmonary Arterial Hypertension Screening

Echocardiogram is a good screening test, despite the fact that there are both false-positives [not rare] and false-negatives (uncommon in severe elevations of Pulmonary artery pressure, but more frequent in lower pressures that may still be elevated). [47] In addition, a minority of people have no tricuspid regurgitant jet, so the estimate cannot be made. The estimate may also be technician dependent .Thus, if PAH is suspected in the presence of dyspnea in CTD that cannot be explained by other means , referral to a PAH expert is suggested for the possibility of performing a right-heart catheterization regardless of the lack of supportive echocardiogram screening data [25].

Reproducibility in echocardiography:

Reproducibility is defined as the closeness of agreement between independent results, obtained with the same method, on identical test materials, but under different condition [48]. These conditions might be: different human operators, or different time intervals of measurements from a practical and also clinical point of view, reproducibility can be divided in three types. In medicine, and particularly in echocardiography, these types are:

1. Inter-observer reproducibility: In this type of reproducibility, each of two blinded echocardiographers will do the same echocardiographic measurements in one patient, under identical conditions. These measurements are then compared.

2. Intra-observer reproducibility: In this type, one experienced investigator will perform echocardiographical measurements in one patient, and then repeat them several minutes apart, under identical examination conditions. The two measurements are then compared.

3. Test-retest reproducibility: In this type, one experienced investigator will perform echocardiographical measurements in one patient, but several days apart. This type of reproducibility assumes that no important clinical changes have emerged in the time interval between the two examinations. This might not be true, and thus, this type of reproducibility is seldom used in practice. The test-

retest reproducibility is also called “repeatability”. In order to use reproducibility data in clinical practice, three levels of acceptance of the measurements have been defined. A satisfactory limit of reproducibility is defined below 10%. A value of the reproducibility between 10% and 30% may be satisfactory only in some conditions, depending on the magnitude of the use in practice, the cost of the method, and the availability of alternative methods. A variation of the reproducibility level over 30% is unsatisfactory; the method of measurement with such reproducibility needs corrective actions [49].

Reproducibility has a major impact in clinical studies and in the real life evaluation of echocardiographical parameters. Overall, the echocardiographical evaluation has only moderate (acceptable) reproducibility (10-20%). Major exceptions from this moderate reproducibility are: 1) on the good side, high reproducibility (<10%) for 3D echo (only when good images are available); 2) on the bad side, low reproducibility (over 30%) for valvular assessment, particularly for aortic stenosis. TDI (Tissue Doppler imaging) assessment, particularly for diastolic function, has only moderate reproducibility. The measurements of LV dimensions by M-mode or 2D echocardiography have an excellent intra- and inter- observer reproducibility (5% and 10%, respectively) [50].

The measurement of the systolic pulmonary arterial pressure by the maximal velocity of the tricuspid regurgitant jet has excellent reproducibility (in the range of 5%). Moreover, the correlation of the echocardiographical estimate of the pulmonary arterial systolic pressure almost completely overlaps the invasive measurements (r = 0.99) (51).

Most studies report a high correlation [0.57 to 0.93] between transthoracic echocardiogram (TTE) and right heart catheterization (RHC) measurements of pulmonary artery systolic pressure (PASP) [52]. Reported sensitivity of TTE-estimated PASP for detecting PAH ranges from 79 % to 100 % and specificity from 60 % to 98 % [52-53].

Correlation coefficient between systolic pulmonary arterial pressure estimated from echocardiography versus measured by right heart catheterization in one study was 0.70 (95% CI 0.67 to 0.73; n=27). The summary sensitivity and specificity for echocardiography for diagnosing pulmonary hypertension was 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85; n=12), respectively [54].

Right Heart Catheterization:

Cardiac catheterization remains the gold standard for diagnosing pulmonary hypertension, assessing disease severity, and determining prognosis and response to therapy. By directly measuring pressures and indirectly measuring flow, right heart catheterization allows for determination of prognostic markers such as right atrial pressure, cardiac output, and mean pulmonary artery pressure. This procedure has been shown to be safe. In addition, a recent study reported a procedure-related mortality of 0.055% [55]. Right heart catheterization determines the presence or absence of pulmonary hypertension, may define the underlying etiology, and allows for prognostication.

Treatment of Pulmonary Arterial Hypertension:

Treatment of PAH associated with CTD mirrors the diagnosis and treatment for PAH of any other etiology [56]. As prognosis of CTD patients with PAH, especially SSc, is substantially worse than that of patients with IPAH [57, 58], intensive efforts are underway to develop effective treatment options. However, treatment appears more complex as compared with other forms of PAH. The risk-to-benefit ratio of oral anti-coagulation is not yet well-understood. Also, the rate of acute

vasoreactivity and of a long-term favorable response to calcium channel blocker treatment is suggested to be lower when compared with IPAH [59].

Therapeutic agents like prostacyclins or drugs that modulate the synthesis of nitric oxide and additional agents targeting the ET-1 signaling system are under ongoing investigation. Intravenous epoprostenol has been shown to be effective in a 3-month randomized trial of patients suffering from scleroderma spectrum. It has been shown that epoprostenol treatment can improve exercise capacity, symptoms and hemodynamic [60]. However, no improvement in survival was observed, and further retrospective analyses have shown that the effect of intravenous epoprostenol on survival of IPAH patients seems to be better when compared with its effects in SSc patients [61]. Prostacyclin application by another route, a continuous subcutaneous administration of treprostinil, was evaluated in a subset of 90 patients with PAH and CTD who were enrolled in a larger randomized controlled trial. After 3 months, an improvement in exercise capacity, symptoms and hemodynamic too was shown [62]. Also, the endothelin receptor antagonist's bosentan and sitaxsentan have shown favorable results. The clinical efficacy of the dual ET-receptor antagonist bosentan was demonstrated in BREATHE-1: 213 PAH patients (either idiopathic or associated with CTD) were randomized to placebo or bosentan [63]. Compared with placebo, administration

of bosentan improved exercise capacity, as measured by the 6-min walk test, and WHO functional class, and significantly improved the overall time to clinical worsening [63]. In the subgroup of SSc patients included in this trial, bosentan just prevented deterioration and did not significantly improve exercise capacity. Interestingly, a recent post hoc analysis revealed that the survival rate has improved after first-line bosentan therapy also in this subset of patients: 82% after 1 yr, 66.6% after 2 yrs and 63.5% after 3 yrs [63, 64]. Additionally, the selective ET-A receptor antagonist sitaxsentan has also shown favorable results in patients with PAH associated with CTD, in a recently performed trial [65].

Another treatment strategy in PAH is the inhibition of phosphodiesterase-5. In a randomized controlled study, sildenafil had improved the exercise capacity and hemodynamic also in a subgroup of patients with CTD [66].

Lung transplantation is the last option for patients with severe PAH. However, the presence of CTD with possible multi-organ involvement may represent a contraindication for lung transplantation in advanced cases not responsive to medical treatment. Thus, each patient needs to be considered individual increased risks as a consequence of the presence of multisystem disease. In conclusion, long-term survival has improved in CTD associated with

PAH but is still worse compared with IPAH patients receiving a ‘specific PAH’ medication.

Upcoming combination strategies might result in higher survival rates of patients with PAH and CTD. Further investigations have to be performed to understand the pathophysiology of PAH in CTD more clearly.

Aim of the study:

The aim of the study is to evaluate pulmonary artery pressure in patients attending Rheumatology clinic in Al-Hwari Hospital.

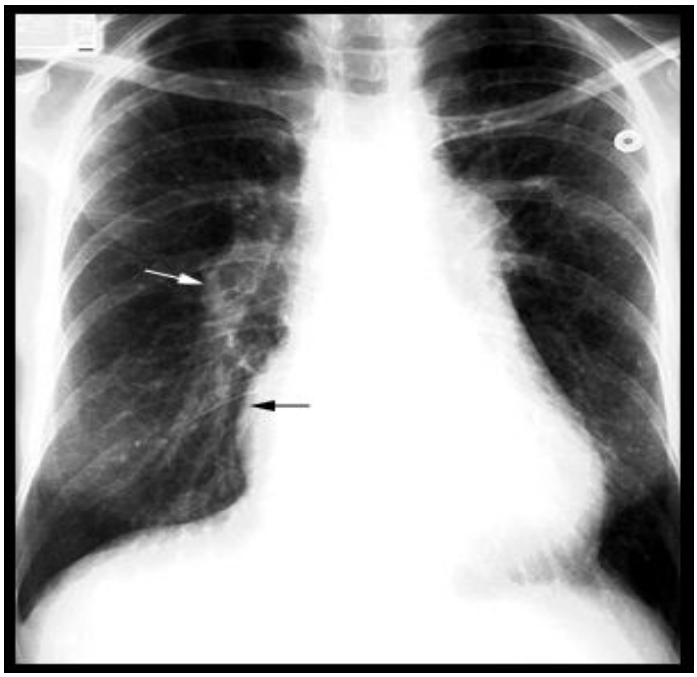
Method:

This is cross sectional study done at Rheumatology unit-Al-Hwari hospital-Benghazi during the year 2012. Data analyzed statistically for evidence of PAH.

100 Libyan Patients with CTD including RA, SLE, Scleroderma, MCTD, and PM diagnosed according to ACR Criteria. These patients are examined clinically for symptom and sign of PAH & the following investigation was done to detect PAH:

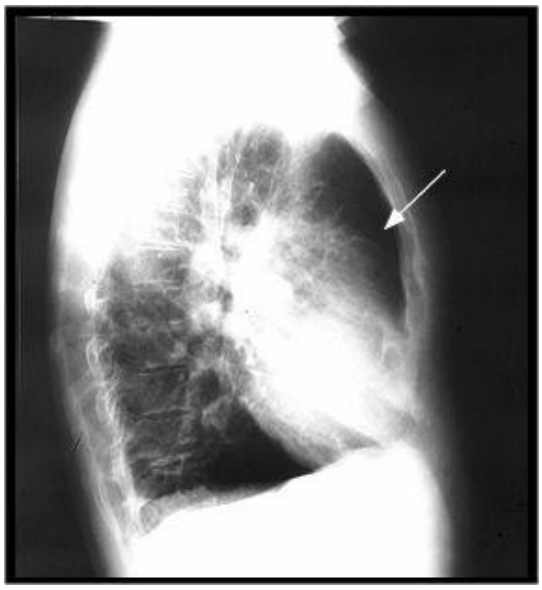
1- Chest radiograph: The classic chest radiograph shows enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in oligemic lung fields. Right ventricular enlargement (diminished retrosternal space) and right atrial dilatation (prominent right heart border) may also be seen. Occasionally, the underlying cause of the PAH is apparent on the chest radiograph (for example: interstitial lung disease).

Figure -2- chest radiograph(frontal view) in patient with PAH



This plain frontal chest radiograph demonstrates prominence of the interstitial pulmonary markings with enlargement of the right and left ventricle and the right atrium (black arrow). Additionally, large central, but attenuated peripheral pulmonary arteries are noted (white arrow), all features characteristic of pulmonary hypertension.

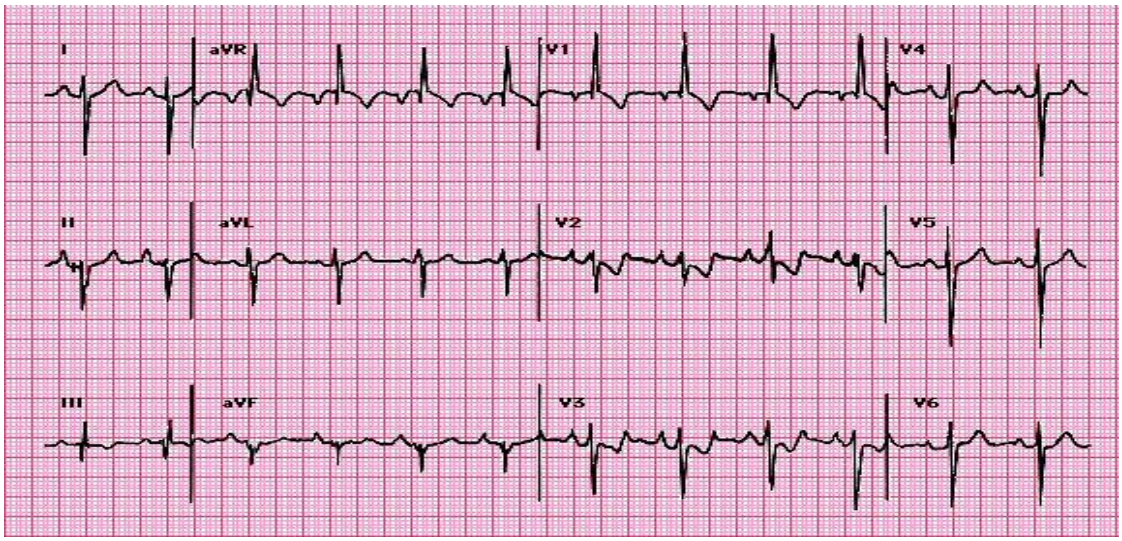
Figure-3-Lateral view Chest radiograph in patient with PAH



Chest radiograph in lateral view showing decreased retrosternal space (arrow) due to right ventricular enlargement in pulmonary hypertension.

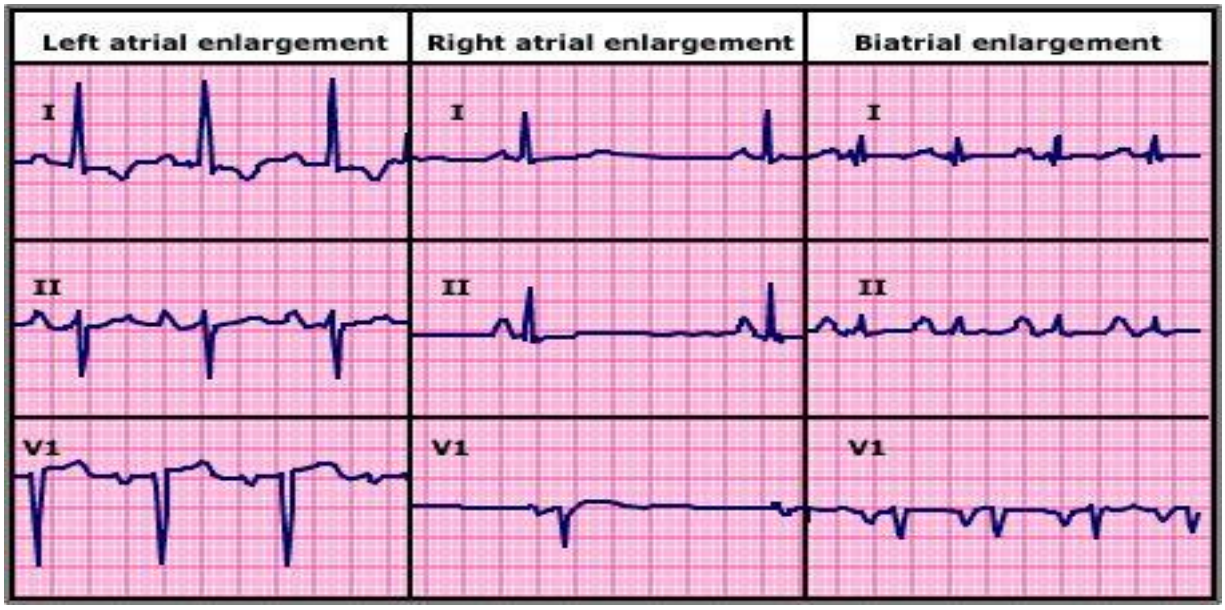
2- Electrocardiogram (ECG): may demonstrate signs of right ventricular hypertrophy or strain , including right axis deviation, an R wave/S wave ratio greater than one in lead V1, incomplete or complete right bundle branch block, or increased P wave amplitude in lead II (P pulmonale) due to right atrial enlargement. Most ECG signs are specific but not sensitive for the detection of right ventricular disease. ECG changes cannot determine disease severity or prognosis [41, 42].

Figure-4- ECG with right ventricular hypertrophy.



Right ventricular hypertrophy. The characteristic features include marked right axis deviation, tall R wave in V1, delayed precordial transition zone with prominent S waves in leads V5 and V6, inverted T waves and ST depression in V1 to V3 consistent with right ventricular "strain", and peaked P waves in lead II consistent with concomitant right atrial enlargement.

Figure-5-Electrocardiographs with left, right and both atrial enlargement.



P wave morphology with atrial enlargement in leads I, II, and V1. The P waves in left atrial enlargement (left panel) are wide, and notched in leads I and II and the terminal segment has a negative deflection that is deep and delayed in V1. In right atrial enlargement (middle panel), the P wave amplitude is increased in lead II. Biatrial enlargement (right panel) has characteristics of both atrial abnormalities.

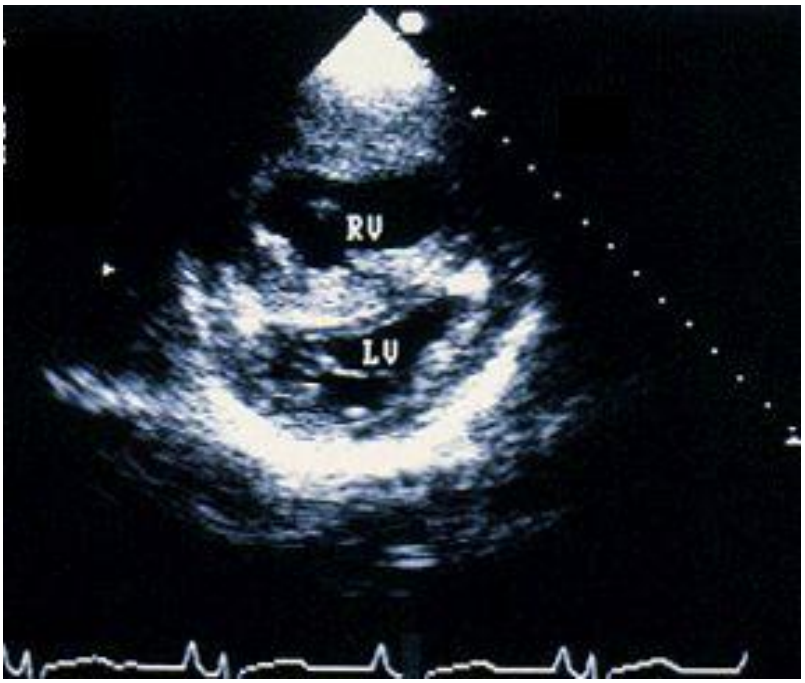
3-Echocardiography:

Echocardiography is performed(by different expert operator) to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function , In addition, evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts (69,70).Transthoracic Doppler echocardiography used to estimate the pulmonary artery systolic pressure. This technique takes advantage of the tricuspid regurgitation that usually exists. The maximum tricuspid regurgitant jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is then calculated:

PASP = (4 x TRV squared) + RAP

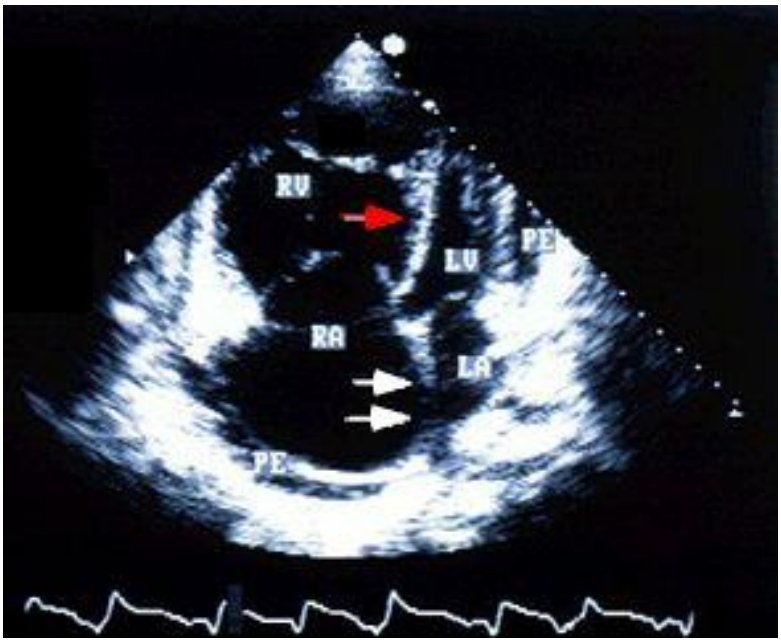
where TRV is the maximum tricuspid regurgitant jet velocity and RAP is the right atrial pressure estimated from the size and respiratory variation of flow in the inferior vena cava. An estimated right ventricular systolic pressure [ERVSP] ≥40 mm Hg was considered PAH [71].

Figure-6- Echocardiography from a patient with pulmonary arterial hypertension.



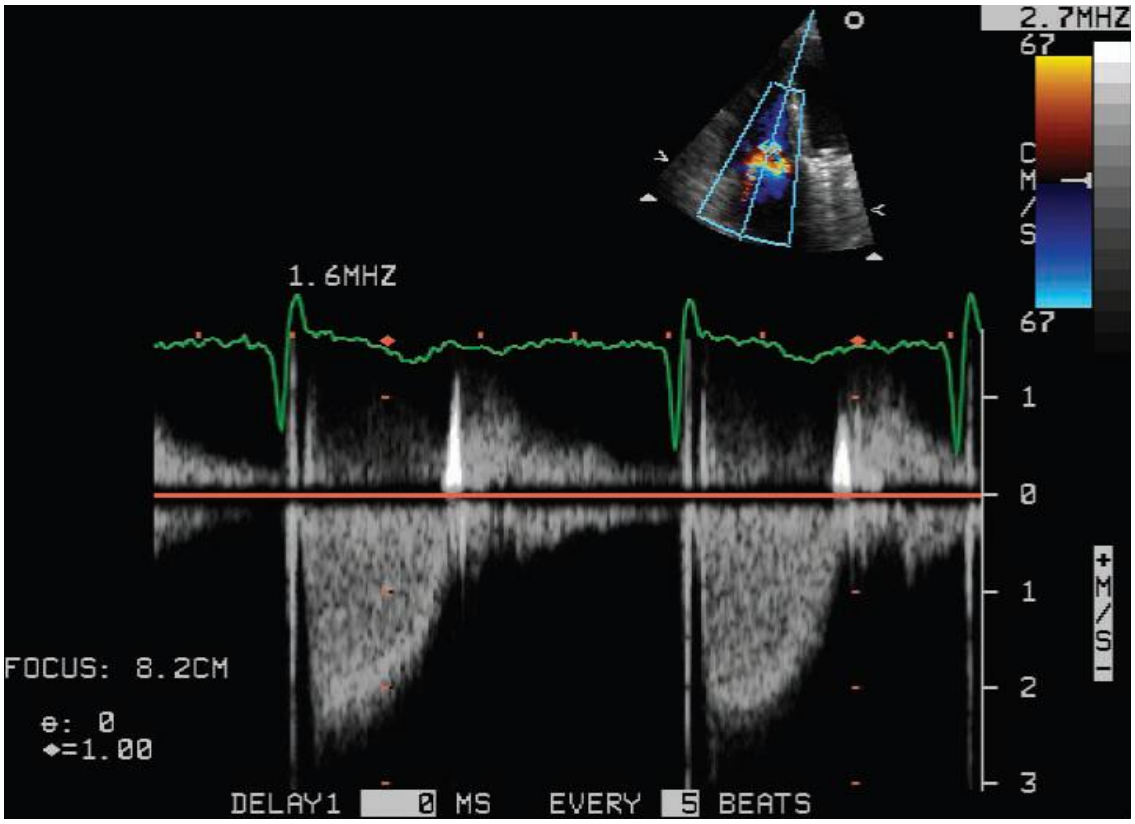
The short axis view at the level of the mitral chordae from a patient with advanced pulmonary hypertension shows severe hypertrophy of the right ventricular (RV) wall, dilation of the RV chamber and hypertrophy of the right side of the septum. The septum is flattened, strongly suggesting pressure overload in the RV; this septal shape imparts a "D shape" to the left ventricle (LV) which has relatively thin walls.

Figure-7-Echocardiography from a patient with right side dilatation of the heart .



The four chamber view shows severe dilation of the right ventricle (RV) and right atrium (RA) with evidence of high right sided filling pressure; the interventricular septum (red arrow) and the interatrial septum (white arrows) bulge into the left ventricle (LV) and left atrium (LA) respectively.

Figure -8- Tricuspid regurgitant jet velocity.



4-CT chest: done in patients who discovered with PAH by Echocardiography.

5-PFTs: are performed to identify and characterize underlying lung disease that may be contributing to PAH. An obstructive pattern is suggestive of COPD while restrictive disease suggests interstitial lung disease, neuromuscular weakness, or chest wall disease [72].

Results:

The study included 100 Libyan patients with CTD. Sixty seven patients (67%) have RA, 21 patients have SLE (21%) , 8 patients have SS (8%), 2 patients have MCTD (2%), and 2 patients have PM (2%) (Figure 9).

Eighty seven patients were females (87%) and 13 patients were males (13%) (Figure 10).

The mean age of the study patients was 48.79 ±13.49 (range 20-82) years, whereas the mean age of male patients was 48.38±18.23 (range 24-82) year, and of female was 48.85± 12.77 (range 20-75) years.

Twelve patients were black (12%), 88 of them were white (88%) (Figure 11).

Nineteen patients (19%) were complaining of SOB.

On physical examination 3 patients (3%) have pedal edema, 6 patients (6%) have left parasternal heave and 6 patients (6%) have loud S2.(Figure 12).

ECG features in the study patients included: 6 patients (6%) with P pulmonale, 3 patients (3%) with RVH, 6 patients (6%) with RAD, and 6 patients (6%) with RBBB (Figure 13). On CXR 7 patients (7%) have pulmonary fibrosis, 4 patients (4%) have prominent pulmonary vessels, and 16 patients (16%) have cardiomegaly (Figure 14).

By Echo 9 patients were found to have PAH (Figure 8). Out of the 9 patients who have PAH (by ECHO), 3 (33.3%) patients were male, 6 (66.7%) patients were female. Four patient (44.4%) with PAH have pulmonary fibrosis and 5 (55.6%) patients have no CT evidence of pulmonary fibrosis.

In the 9 patients with PAH(Table 1), 4 patients (44.4%) have SLE(19% of all SLE patients), 3 patients (33.3%) have SS(37.5% of all SS patients), one patient (11.1%) has RA(1.5% of all RA patients), and one patient (11.1%) has MCTD(50% of all MCTD patients).

The mean age of patients with PAH 47±16.05 (range 26-74) year, the mean duration of diseases was 13.67 ±11.94 year. Six of the 9 patients (66.7%) with PAH have SOB, 2 patients (22.2%) have LL edema, 6 patients (66.7%) have left parasternal heave, and 6 patients (66.7%) have loud S2. CXR findings in patients with PAH included: pulmonary fibrosis in 4 patients (44.4%), prominent pulmonary vessels in 4 patients (44.4%) and cardiomegaly in 6 patients (66.7%) patients.

CT scan Chest showed evidence of ILD in 4 out of the 9 patients (44.4%) with PAH and all of them had restrictive pattern on PFT. By ECG: 6 patients (66.7%) of those with PAH have P-pulmonale, 5 patients (55.6%) have RBBB, 3 patients (33.3%) have RVH, and 6 patients (66.7%) have RAD.

Table 1:Characteristics of 9 patients with elevated pulmonary artery pressure in the study:

Diagnosis	Age [year]	Sex	Duration of disease [year]	Race	Symptom	Examination	ECG	CXR	CT scan	Spirometry	ECHO [EPAP In mmhg]
SLE	26	M	4	White	NO	Normal	Normal	Normal	Normal	Normal	42
SLE	28	M	2	White	NO	Normal	Normal	Normal	Normal	Normal	40
MCTD	62	M	20	White	NO	Normal	Normal	Prominent pulmonary vasculature	Normal	Normal	44
SS	74	F	40	Black	SOB	Pedal edema Lt parasternal heave,Laud S2.	P pulmonale, RAD, RBBB	Pulmonary fibrosis Prominent pulmonary vasculatur, cardiomegaly	ILD	Restrictive	46
SLE	39	F	6	White	SOB	Pedal edema Lt parasternal heave,Laud S2.	P pulmonale, RAD, RBBB	Prominent pulmonary vasculatur, cardiomegaly	Normal	Normal	48
SS	50	F	12	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	46
RA	52	F	21	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB,RVH	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	49
SLE	41	F	8	White	SOB	Pedal edema Lt parasternal heave,Laud S2	P pulmonale, RAD, RBBB,RVH	Prominent pulmonary vasculature cardiomegaly	Normal	Normal	48
SS	55	F	12	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB,RVH	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	48

Figure -9

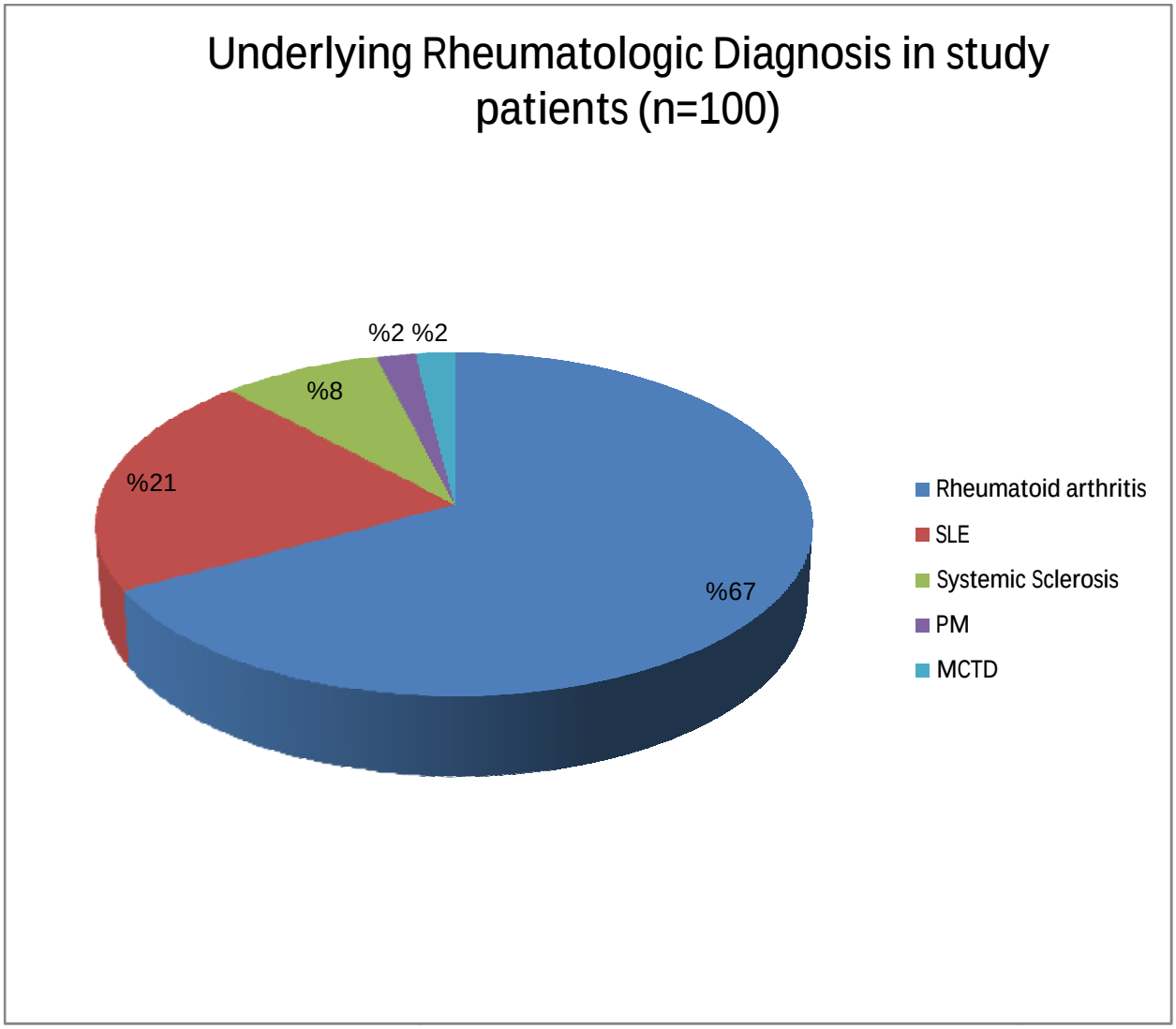

Underlying Rheumatologic Diagnosis in study patients (n=100)
%2 %2
%8
%21
%67
Rheumatoid arthritis
SLE
Systemic Sclerosis
PM
MCTD

Figure -10

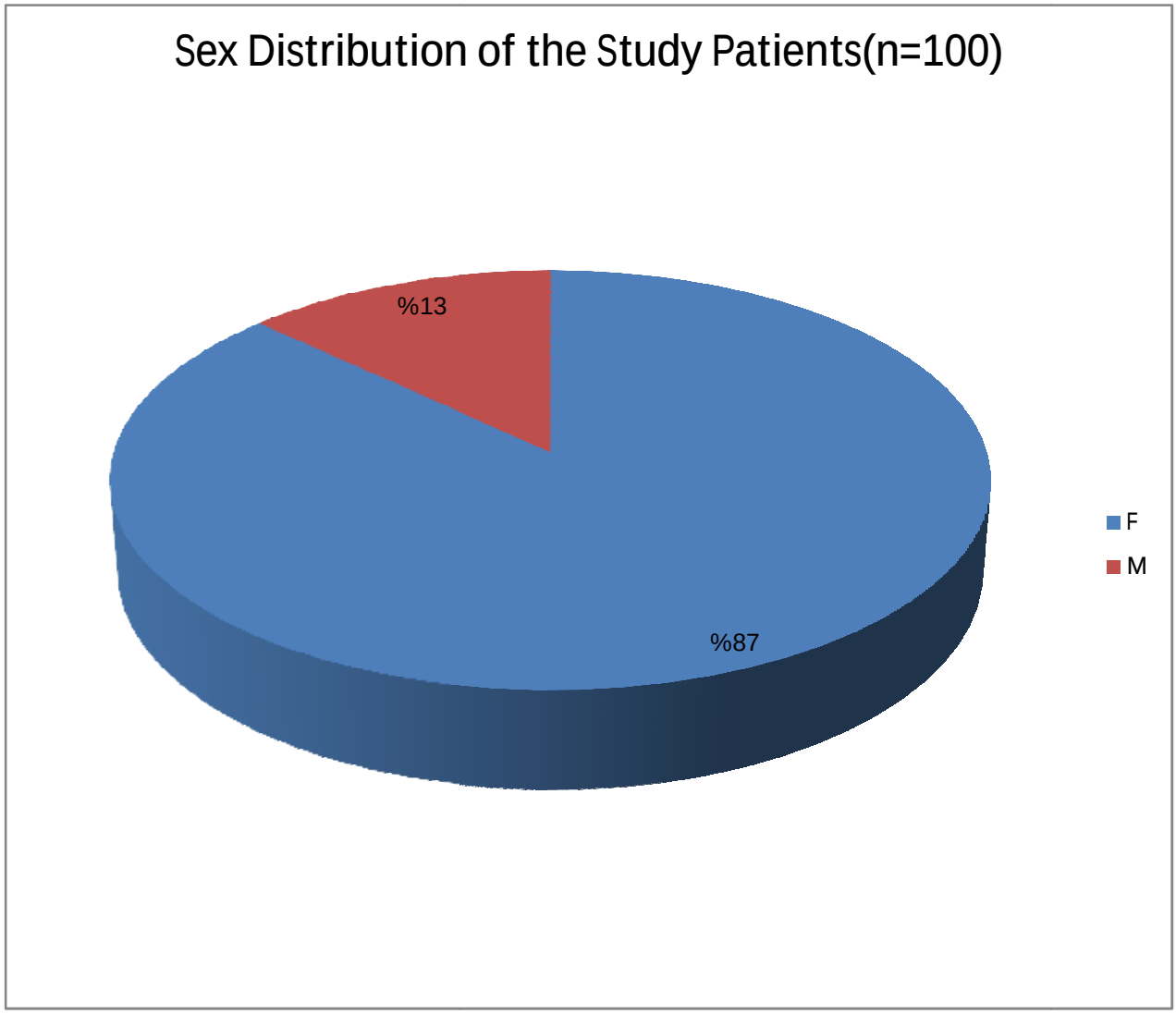


Figure -11

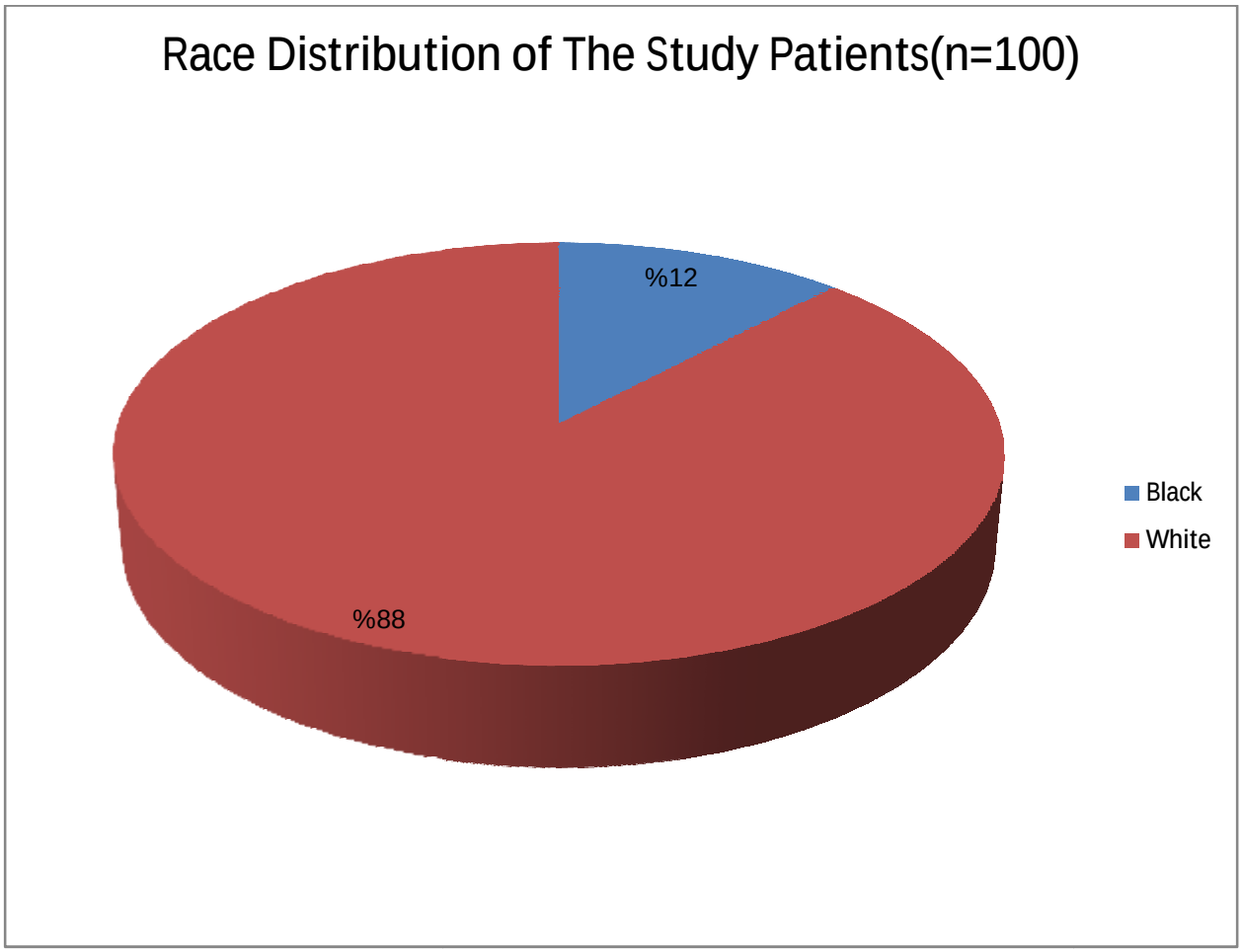

Race Distribution of The Study Patients(n=100)
%12
%88
Black
White

Figure -12

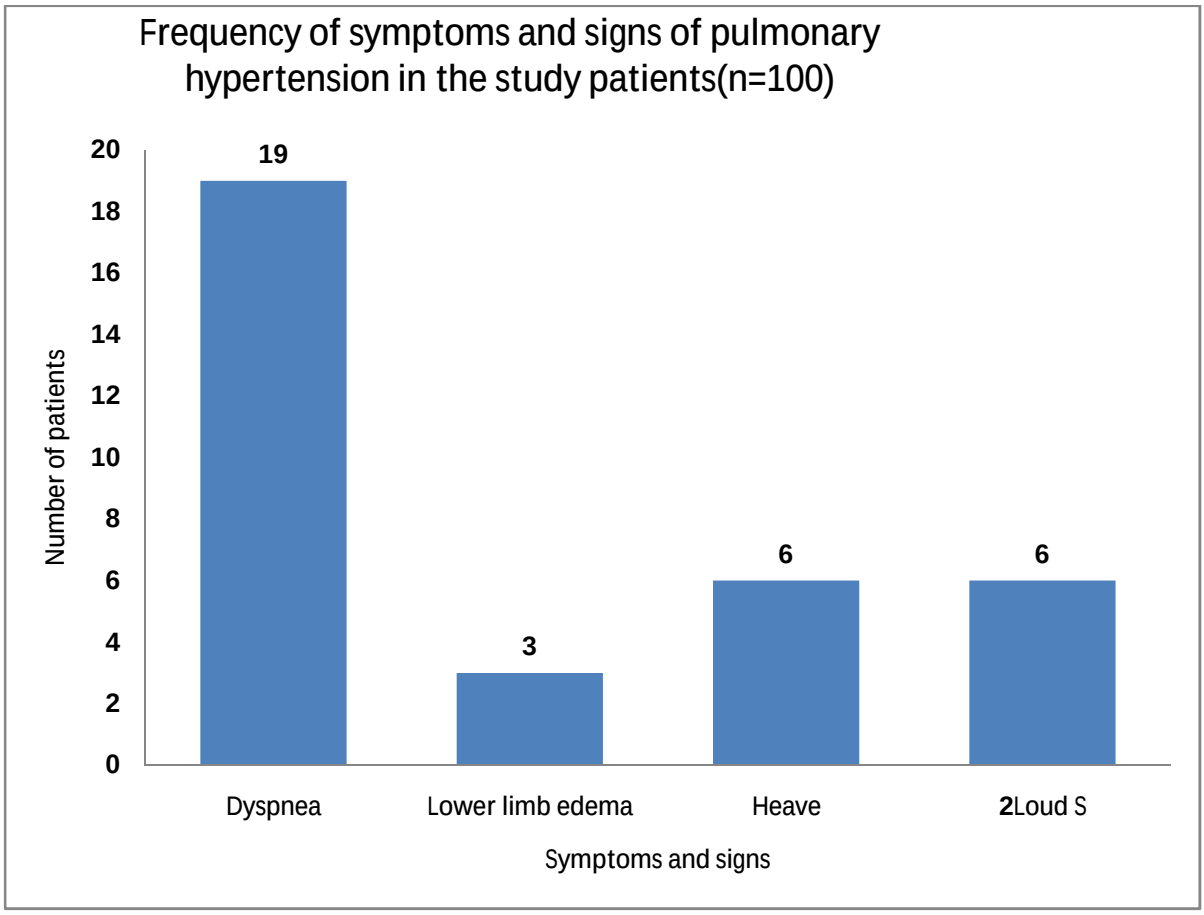

Frequency of symptoms and signs of pulmonary hypertension in the study patients(n=100)
Number of patients
20
18
16
14
12
10
8
6
4
2
0
19
3
6
6
Dyspnea
Lower limb edema
Heave
2Loud S
Symptoms and signs

Figure -13

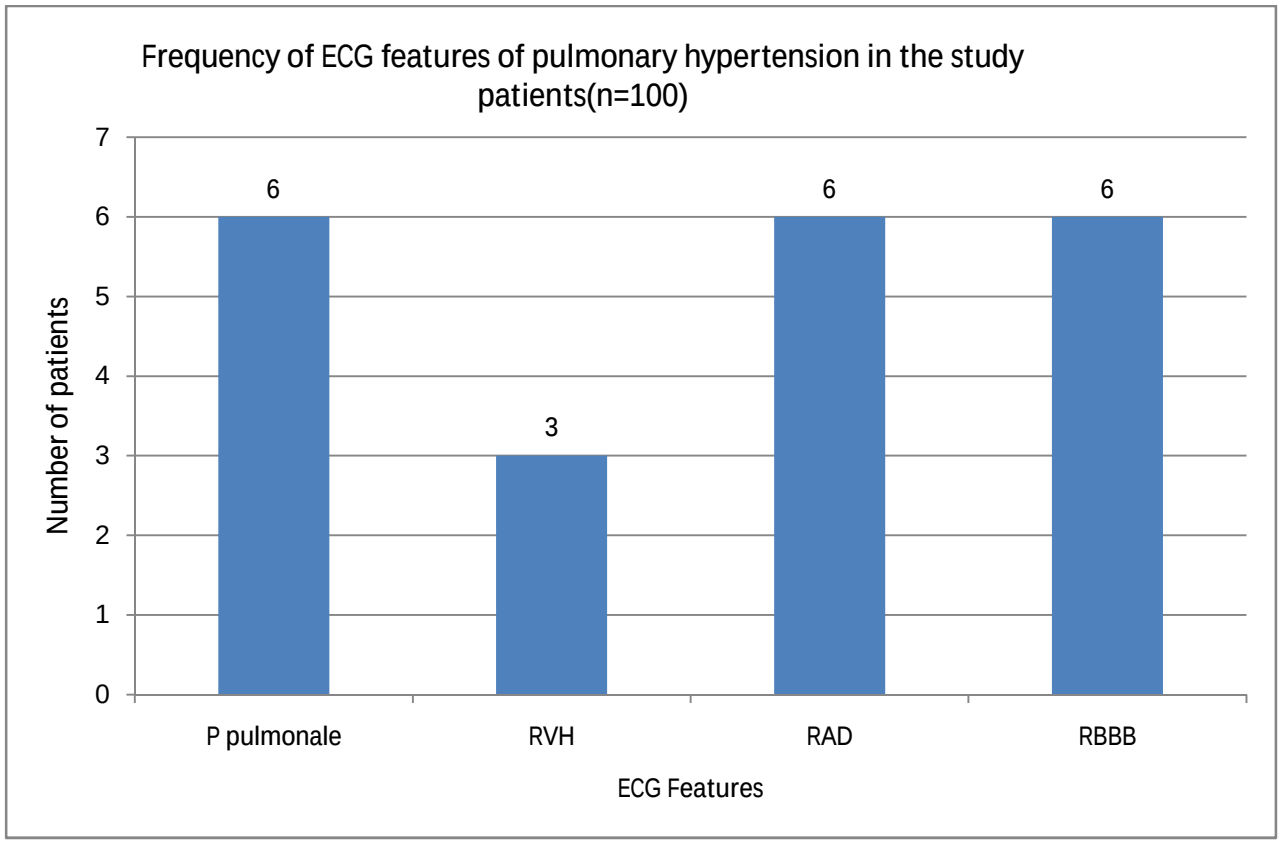

Frequency of ECG features of pulmonary hypertension in the study patients(n=100)
Number of patients
7
6
5
4
3
2
1
0
6
3
6
6
P pulmonale
RVH
RAD
RBBB
ECG Features

Figure -14

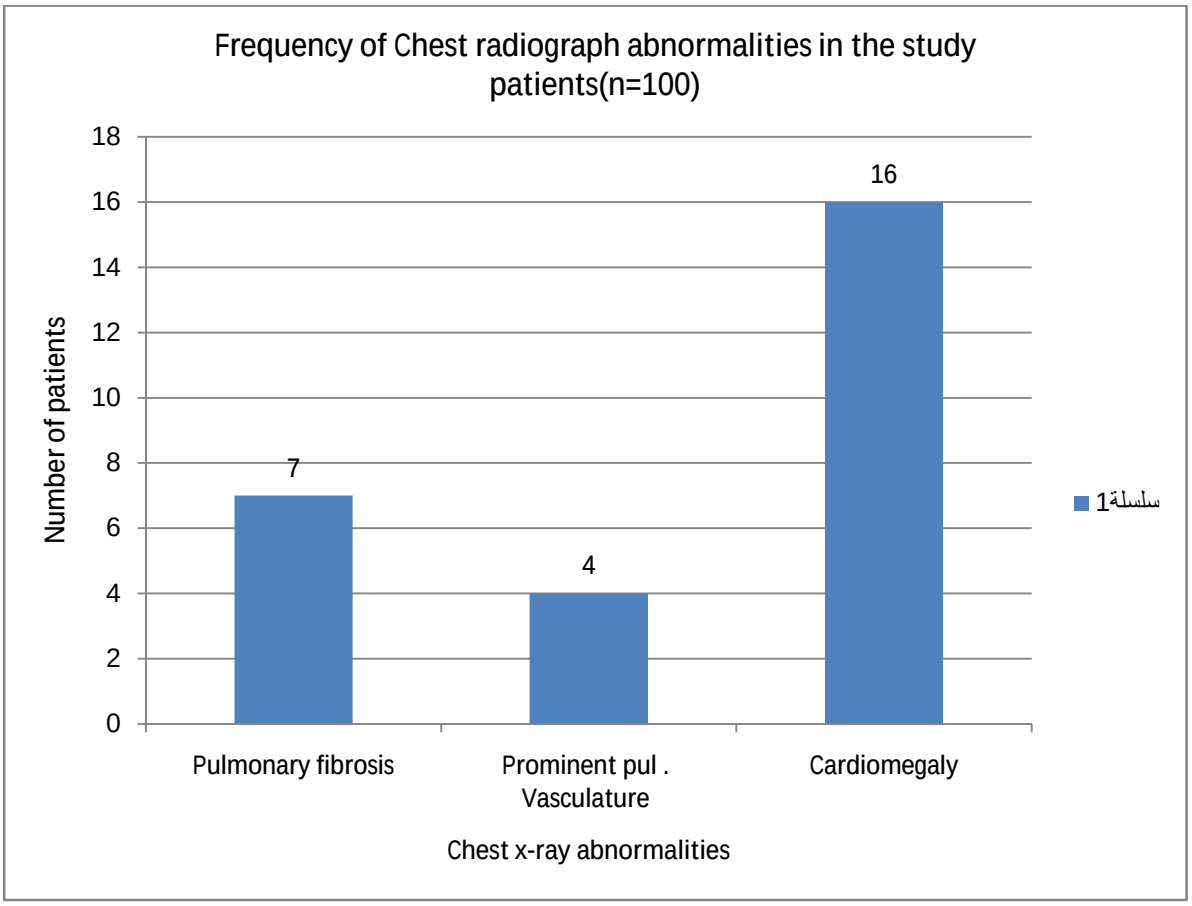
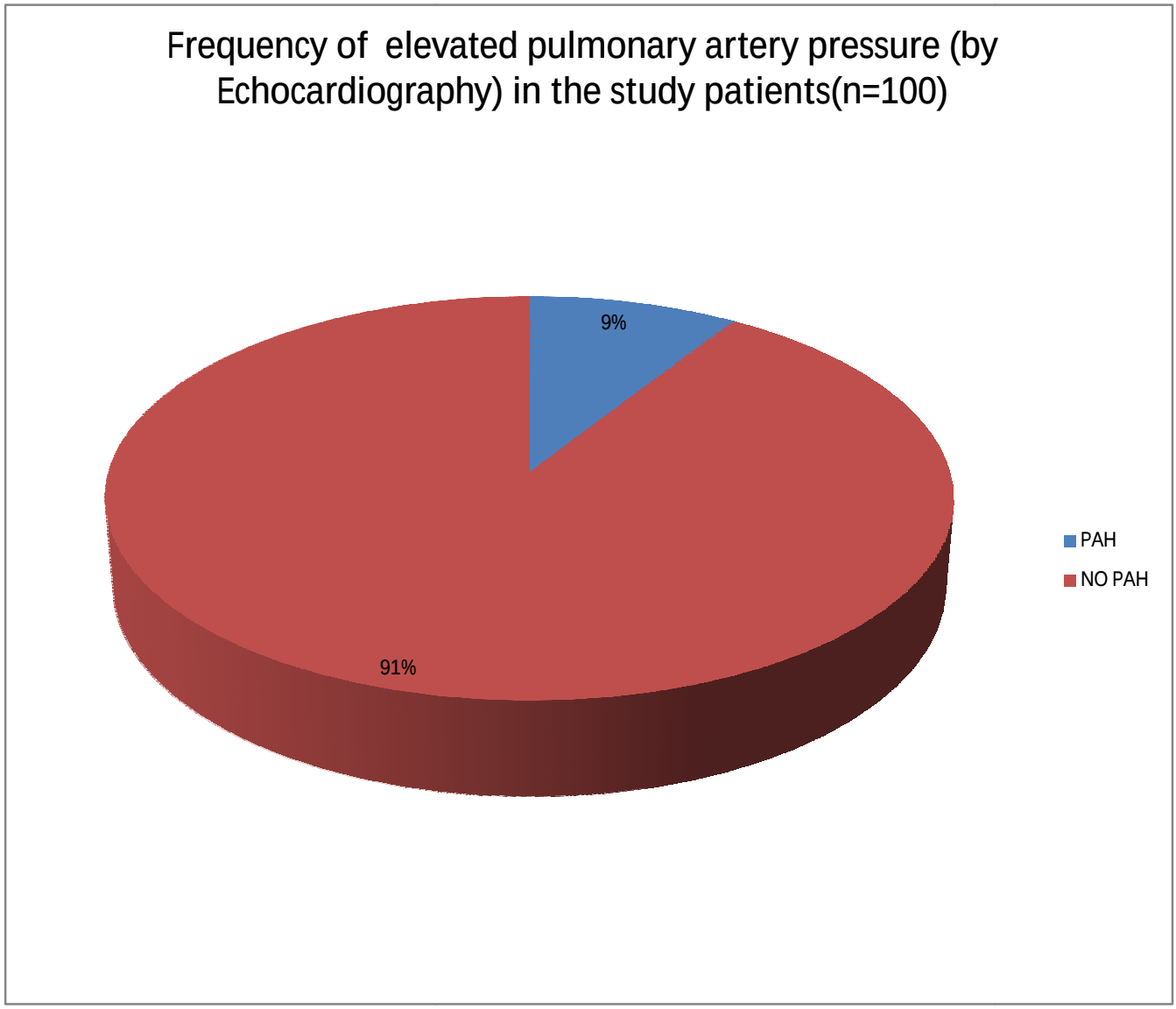

Frequency of Chest radiograph abnormalities in the study patients(n=100)
Number of patients
18
16
14
12
10
8
6
4
2
0
7
4
16
Pulmonary fibrosis
Prominent pul . Vasculature
Cardiomegaly
Chest x-ray abnormalities
سلسلة1

Figure -15


Frequency of elevated pulmonary artery pressure (by Echocardiography) in the study patients(n=100)
9%
91%
PAH
NO PAH

Discussion:

PAH in CTD is considered to be a killer that we often miss, said investigator Frederick M. Wigley, MD, professor of medicine, rheumatology division, Johns Hopkins University, Baltimore, Maryland. PAH is easy to overlook in simple examinations, and can progress to an irreversible state. It is more prevalent in patients with scleroderma and CTD than we knew.

RELATIONSHIP BETWEEN CTD AND PAH:

Analysis of cause of death in MCTD has drawn attention to the involvement of PAH in CTD. That is, PAH was found to be the primary cause of death in MCTD, which had been thought to display good prognosis. This led to investigation of the prevalence of PAH in other CTD.

In 1998, the Ministry of Health and Welfare's MCTD Research Committee carried out the world's first national epidemiological survey [73]. Complications of PAH were seen in 83 of 1, 651 (5.02%) MCTD patients, 82 of 9, 015 (0.90%) SLE patients, 100 of 3,778 (2.64%) SSc patients, and 19 of 3,349 (0.56%) PM /DM patients. These prevalence can be considered very high, since the prevalence of idiopathic pulmonary arterial hypertension (IPAH) in the general population is 1-5 per million. Patients were diagnosed with PAH by physicians because they had

shown clinical symptoms. On the consideration that other patients with latent PAH exhibiting no clinical signs were probably present, a separate Research Committee of Ministry of Health, Labour and Welfare in 2003 investigated PAH in CTD patients who were randomly selected, regardless of the presence/absence of symptoms [74]. PAH was detected in 16.0% of MCTD, 9.3% of SLE and 11.4% of SSc patients, and patients with asymptomatic PAH were at least as numerous as those with clinical signs of PAH. This suggests that a similar investigation is needed in patients with CTD who present with no signs raising suspicion of PAH. The above results generated in Japan have been supported by a similar survey performed at 50 institutions in North America.[75] That is, PAH was diagnosed by the primary physician and by echocardiography, showing rates of 11.7% and 19.1% in MCTD patients and 18.9% and 27.7% in SSc patients, respectively. A World Health Organization (WHO) symposium on PAH recommended annual echocardiography screening for patients with SSc-related diseases (SSc and MCTD), regardless of whether symptoms or changes in symptoms had been noted.

- 8% to 27% of patients with SSc may also have PAH [75].
- As many as 25% of patients with MCTD may also have PAH [71].

- Prevalence of PAH in systemic lupus erythematosus [SLE]: 0.5% to 14% [76, 77].
- In a 5-year follow-up study of PAH in 28 patients with SLE, the prevalenc of PAH increased from 14% at the first study to 43% at follow-up. [78].

Overall mortality was 25% to 50% 2 years after PAH diagnosis [76, 77].

- In the UNCOVER study: 791 CTD patients in community-based rheumatology practices were screened for the presence of PAH [71].

26.7% had suspected PAH, using Doppler echocardiography as a screening tool.

13.3% were found to have previously unidentified PAH (89 of 669 patients not previously screened).

Over 20% of patients with previously unidentified PAH had evidence of advanced disease. [71].

For purposes of the study, an estimated right ventricular systolic pressure [ERVSP] ≥40 mmHg was considered PAH. [71].

Advanced disease was defined as ERVSP ≥50 mm Hg, increased right ventricular dimensions, or right atrial enlargement [71].

A total 33 patients have PAH were included in a study of pulmonary arterial hypertension among Filipino patients with connective tissue diseases, of the total

33 patients, there were 32 women ,and 1 man. The mean age of patients was 43±14 years. The mean age at PAH diagnosis was 38±14 years and mean duration of CTD to PAH diagnosis was 53±52 months. The most common underlying CTD was (42%) SLE, (36%) SS,(15%) MCTD, (3%) antiphospholipid syndrome, and (3%) dermatomyositis [79].

Eighty-two (3.7%) patients with CTDs (75 females and 7 males), were found to have PAH. The underlying diseases included MCTD, SSc, primary sjogren´s syndrome, SLE, and Behcet disease. The most common clinical manifestations were dyspnea on exertion (84.1%) [80].

Our study included 100 Libyan patients with CTD who were registered at Al-Hwari Rheumatology clinic. Nine patients [9%] were found to have PAH, which in the range of other study (3.7-13.3%) [71, 80], estimation of the real prevalence of PAH in CTD remains open for discussion due to the lack of a consistent epidemiological data. Available data are highly variable according to the definition and the method used for assessing PAP and the potential biases concerning the study populations investigated.

Of the total 9 patients, 3 patients were males[33.3%],and 6 patients were females [66.7%],and this is comparable with other study were number of

females found to have PAH is more than males, and this because connective tissue disease is more common in females[80].

The mean age of patients with PAH is 47±16.05 years, and this is comparable with other study were the mean age of patients have PAH was 43±14 years [79].

The underlying diseases included are Systemic lupus erythematosus(SLE) ,Systemic scleroderma(SSc) ,Mixed connective tissue disease(MCTD) ,Rheumatoid arthritis(RA),and this is because PAH is a common complication among these Connective tissue diseases[79].

Four patients (44.4%) SLE, 3 patients (33.3%) SSc, and one patient (11.1%) MCTD, found to have PAH. This comparable to other study were 42% SLE, 36 % SS, and 15% MCTD with PAH [79]. One patient RA (11.1%) has PAH ,this is comparable to other study were 10.6 % with RA found to have PAH [81].

The mean duration of connective tissue disease at the diagnosis of PAH 13.67±11.94 years, and this reinforcing the need for vigilance in recognition of this complication.

Dyspnea, accentuated P2, and cardiomegaly were among the most common manifestations in our patients, for which conditions careful examinations should be conducted, and these are comparable to other study [79,

80]. These conditions are easily detected during routine check-up and can be further verified by a chest radiograph and an echocardiogram. ACCP has included the chest radiograph and the echocardiogram as part of patient´s evaluation if there is a reason to suspect PAH[82].

The chest radiograph is obtained to reveal features supportive of a diagnosis of PAH and to lead to the diagnosis of the underlying disease, whereas echocardiogram is performed as a noninvasive screening test that can detect PAH, although it may be imprecise in the determination of the actual pressures when compared with invasive evaluation in a group of patients [82].

This suggest that PAH in CTD is an important cause of morbidity & mortality that is often missed .It is recommended that the Echo evaluation of patients with CTD is important for detection of patients who may require further evaluation or care for pulmonary arterial hypertension. These conclusions were based on the results of the undiagnosed pulmonary hypertension in patients with CTD attending community rheumatology clinics (UNCOVER) Study [71].

The recommendation carries a corresponding strength of evidence as stated by the ACCP committee [83].

Conclusion:

The prevalence of PAH, the sex distribution and the underlying etiology in Libyan patients with CTD is comparable to other studies and often clinically missed. Routine screening with Echo is needed for detection of patients who may require further evaluation & treatment.

Recommendation:

We recommend that all patients with confirmed connective tissue diseases should be screened regularly by echocardiography for possible elevated pulmonary artery pressure.

All cases found to have elevated pulmonary artery pressure should be referred to specialized center for further more invasive test to confirm the disease and possible treatment.

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Assessment of pulmonary arterial pressure in patients with connective tissue diseases

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Submitted for fulfillment of MSC in Internal medicine.

Under the supervision of

Professor Imhemed Abdulsalam Mealif

2013


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VAIO

Introduction

The definition of pulmonary Arterial hypertension :

The definition of pulmonary Arterial hypertension (PAH) is based upon right heart catheterization measurements.

PAH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest.[1]

- 1.Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54:S55-S66.

Classification of PAH

World Health Organization (WHO) classified PAH into five groups : [1]

1. Pulmonary arterial hypertension (PAH):

- 1.1. Idiopathic PAH .
- 1.2. Heritable .
- 1.2.1. BMPR2(bone morphogenetic protein receptor type 2).
- 1.2.2. ALK1 (activin receptor-like kinase type), endoglin (with or without hereditary hemorrhagic telangiectasia).
- 1.2.3. Unknown.
- 1.3. Drug- and toxin-induced.
- 1.4. Associated with :
- 1.4.1. Connective tissue diseases.
- 1.4.2. HIV (human immunodeficiency virus) infection .
- 1.4.3. Portal hypertension .
- 1.4.4. Congenital heart diseases.
- 1.4.5. Schistosomiasis .
- 1.4.6. Chronic hemolytic anemia .
- 1.5 Persistent pulmonary hypertension of the newborn.
- 1′. Pulmonary veno-occlusive disease(PVOD) and/or pulmonary capillary. hemangiomatosis (PCH).

- 1. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54:S43.

Classification of PAH (cont'd)

2. Pulmonary hypertension owing to left heart disease:

- 2.1. Systolic dysfunction .
- 2.2. Diastolic dysfunction.
- 2.3. Valvular disease .

3. Pulmonary hypertension owing to lung diseases and/or hypoxia:

- 3.1. Chronic obstructive pulmonary disease .
- 3.2. Interstitial lung disease .
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep-disordered breathing .
- 3.5. Alveolar hypoventilation disorders.
- 3.6. Chronic exposure to high altitude .
- 3.7. Developmental abnormalities .

4. Chronic thromboembolic pulmonary hypertension (CTEPH).

Classification of PAH (cont'd)

- 5. Pulmonary hypertension with unclear multifactorial mechanisms.
- 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy.
- 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis.
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders .
- 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis .

Pulmonary Arterial Hypertension in Connective Tissue Diseases:

Pulmonary arterial hypertension (PAH) is a severe manifestation of many of connective tissue diseases(CTDs) :

-Systemic sclerosis (SSc)

-Systemic lupus erythematosus(SLE)

-SSc-SLE overlap syndrome

-Mixed connective tissue disease (MCTD)

-Inflammatory myositides(dermatomyositis and polymyositis),

-Sjögren's syndrome

-Rheumatoid arthritis .

Of the CTDs associated with PAH, SSc-PAH and SLE-PAH are the most common.[1]

1 .Denton CP, Pope JE, Peter HH, et al . *Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheum Dis 2008; 67: 1222–1228.*

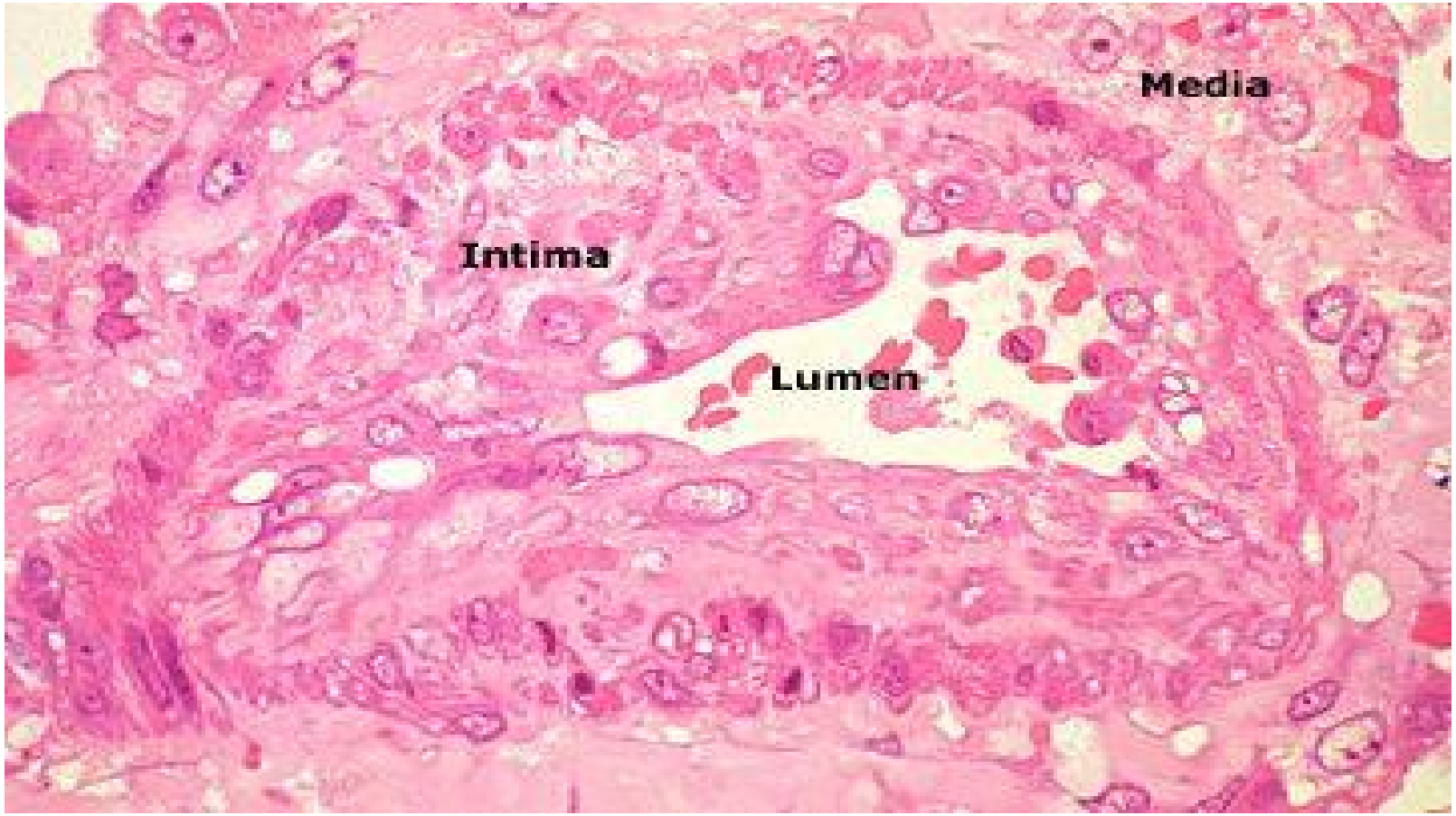
Pathogenesis of Pulmonary Arterial Hypertension in CTD

The pathophysiological mechanisms leading to PAH remain unknown.

Pathogenesis of Pulmonary Arterial Hypertension in CTD (cont'd)

- Increased pulmonary vascular resistance (occlusive vasculopathy).

- Endothelial dysfunction .



- PAH in pateints with CTD is associated with intimal hyperplasia,smooth muscle hpertrophy and medial thickening .

Pathogenesis of Pulmonary Arterial Hypertension in CTD (cont'd)

- Interstitial fibrosis.

- Genetic–environmental factor.

Prevalence of Pulmonary Arterial Hypertension in CTD

- In the National Institute of Health (NIH) registry, among 236 cases of unexplained PAH, about 8% was associated with CTD .
- In the UK a prevalence of about 12% in 722 patients with SSc .
- In another series of 930 patients with SSc, the cumulative incidence was 13%, and in the French registry, which included hemodynamic confirmation of PAH, it was calculated to be 10% .[1,2,3,4]
- PAH is less commonly seen in SLE (0.5–14%), and is a rare clinical finding in dermatomyositis and rheumatoid arthritis. [5,6]

1 Rich S, Dantzker DR, Ayres SM et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216–23.

2 Mukerjee D, St George D, Coleiro B et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–93.

3. MacGregor AJ, Canavan R, Knight C et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology 2001;40:453–459.

4 Humbert M, Chaouat A, Bertocchi M et al. ItinerAIR-HTAP: A French National Prospective Registry of Pulmonary Arterial Hypertension. Am J Respir Crit Care Med 2004;169:A169.

5.Haas C.Pulmonary hypertension associated with with systemic lupus erythematosus.BullAcad Natl Med 2004;188:985-997.

6. Galie N, Manes A, Farahani KV et al. Pulmonary arterial hypertension associated to connective tissue diseases. Lupus 2005;14:713–717.

- In PAH associated with CTDs there is a trend towards worse survival compared with IPAH patients: 1-, 2- and 3-yr survival rates were reported to be 45, 35 and 28%, respectively, with a median survival of only 1 yr following diagnosis (IPAH: 1- and 3-year survival, 68 and 48%, respectively, with a median survival of 2.8 yrs) .

- Galie N, Manes A, Farahani KV et al. Pulmonary arterial hypertension associated to connective tissue diseases. Lupus 2005;14:713–7.
- Humbert M, Simonneau G. Drug Insight: endothelin-receptor antagonists for pulmonary arterial hypertension in systemic rheumatic diseases. Nat Clin Pract 2005;1:93–101.

Pulmonary Arterial Hypertension Screening in CTD

- The WHO recommends annual screening with echocardiography, including Doppler estimates of Pulmonary artery pressure.

- Right-heart catheterization is necessary to make a diagnosis of PAH.

- Most studies report a high correlation [0.57 to 0.93] between TTE and RHC measurements of PASP .

- Reported sensitivity of TTE-estimated PASP for detecting PAH ranges from 79% to 100% and specificity from 60% to 98% .[1,2,3]

- 1. Denton C, Cailes J, Phillips G, Wells A, Black C, Du Bois R. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. Br JRheumatol 1997;36:239–43.
- 2. Bossone E, Avelar E, Bach DS, Gillespie B, Rubenfire M, Armstrong WF. Diagnostic value of resting tricuspid regurgitation velocity and right ventricular ejection flow parameters for the detection of exerciseinduced pulmonary arterial hypertension. Int J Card Imaging 2000;16:429–36.
- 3. Penning S, Robinson K, Major C, Garite T. A comparison of echocardiography
- and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. Am J Obstet Gynecol 2001;184:1568–70.

correlation coefficient between systolic pulmonary arterial pressure estimated from echocardiography versus measured by right heart catheterization in one study was 0.70 The summary sensitivity and specificity for echocardiography for diagnosing pulmonary hypertension was 83% and 72% respectively.[1]

1. Janda S, Shahidi N, Gin K, et al. , Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis, Heart. 2011; 97(8):612-622.

- The measurement of the systolic pulmonary arterial pressure by the maximal velocity of the tricuspid regurgitant jet has excellent reproducibility (in the range of 5%). Moreover, the correlation of the echocardiographical estimate of the pulmonary arterial systolic pressure almost completely overlaps the invasive measurements .[1]

1 Lanzarini L, Fontana A, Lucca E, Campana C, Klersy C – Noninvasive Estimation of both Systolic and Diastolic Pulmonary Artery Pressure from Doppler Analysis of Tricuspid Regurgitant Velocity Spectrum inPatients with Chronic Heart Failure. *Am Heart J.* 2002; 144:1087-1094.

Limitations of Echocardiography for Pulmonary Arterial Hypertension Screening

- false-positives .
- false-negatives .
- A minority of people have no tricuspid regurgitant jet , so the estimate cannot be made.
- The estimate may also be technician dependent.

Aim of the study

- The aim of the study is to evaluate pulmonary artery pressure in patients attending Rheumatology clinic in Al-Hwari Hospital.

Method

- This is cross sectional study done at Rheumatology unit-Al-Hwari hospital-Benghazi during the year 2012. Data analyzed statistically for evidence of PAH.
- 100 Libyan Patients with CTD including RA, SLE, Scleroderma, MCTD, PM diagnosed according to ACR Criteria.

Method (cont'd)

- These patient are examined clinically for symptoms and signs of PAH & the following investigation were done to detect PAH :

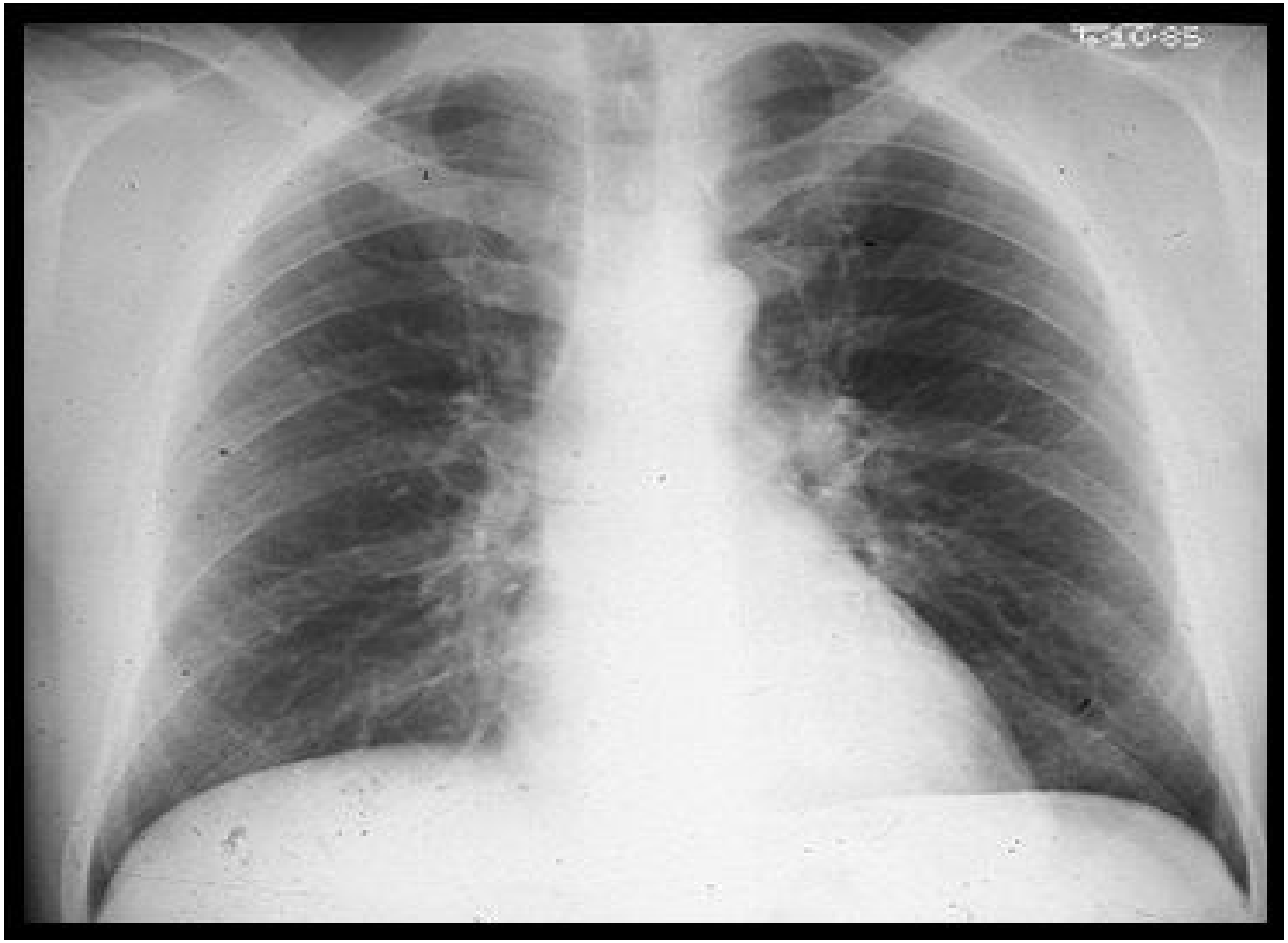
  1-Chest radiograph .

  2- Electrocardiogram (ECG).

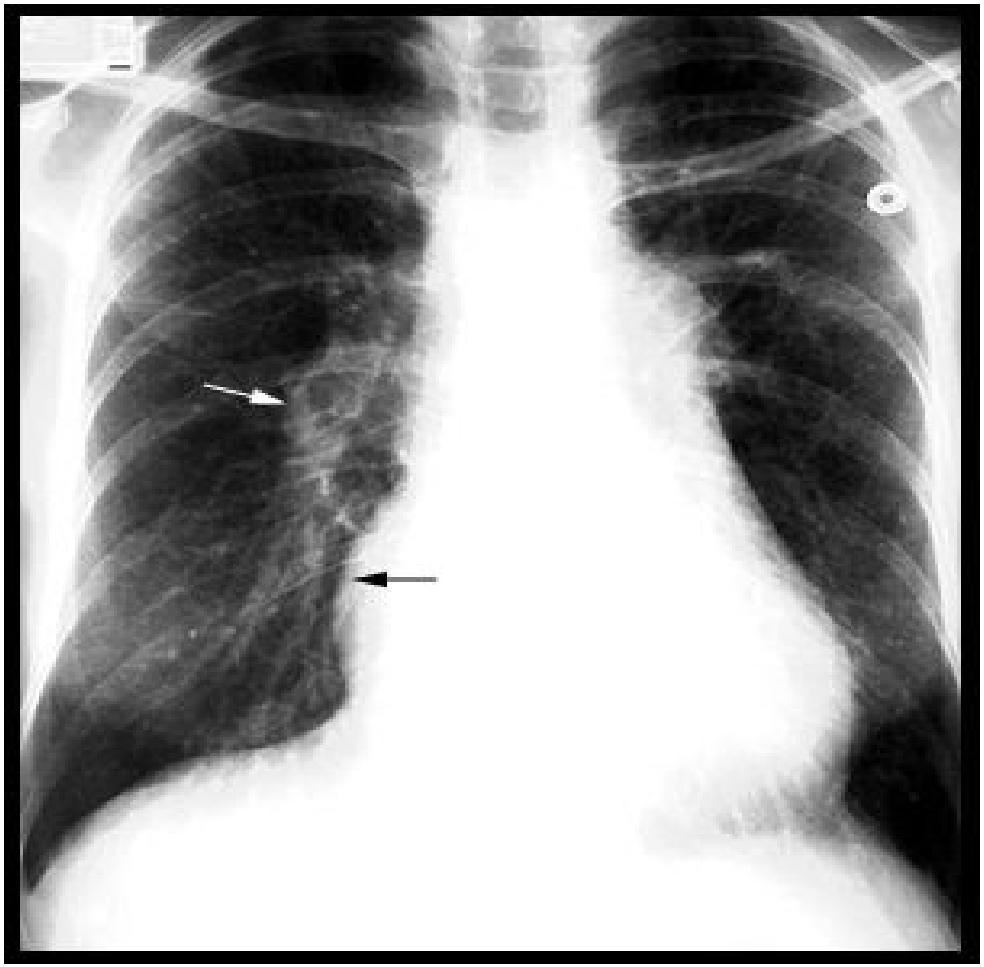
  3-Echocardiography .

  4-CT scan chest .

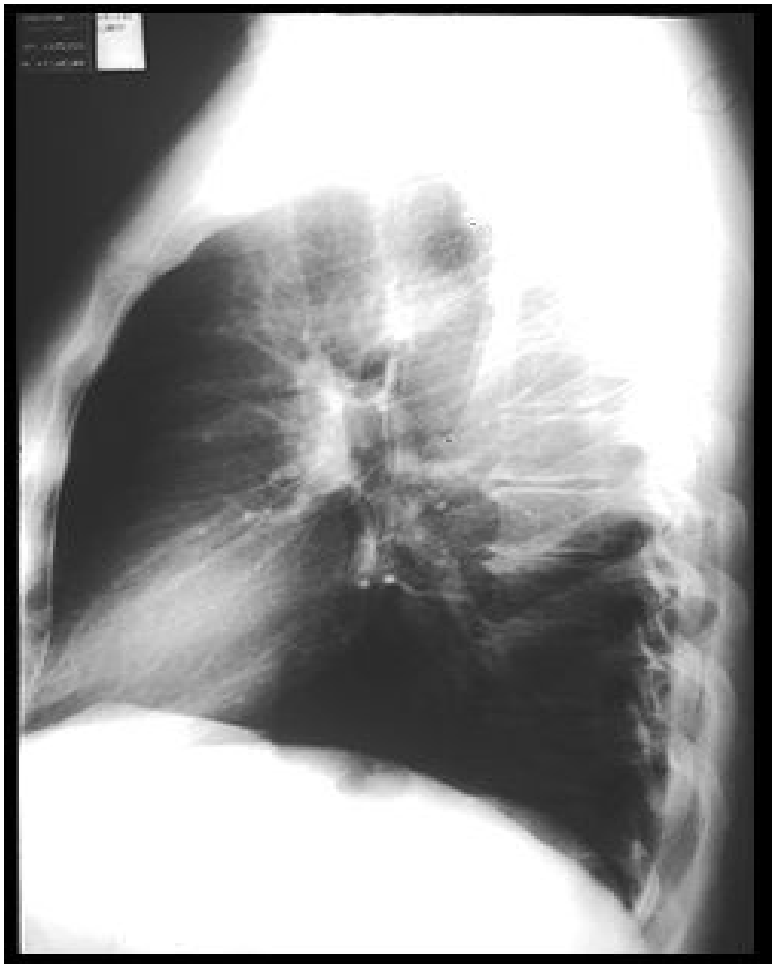
  5-Pulmonary function test .



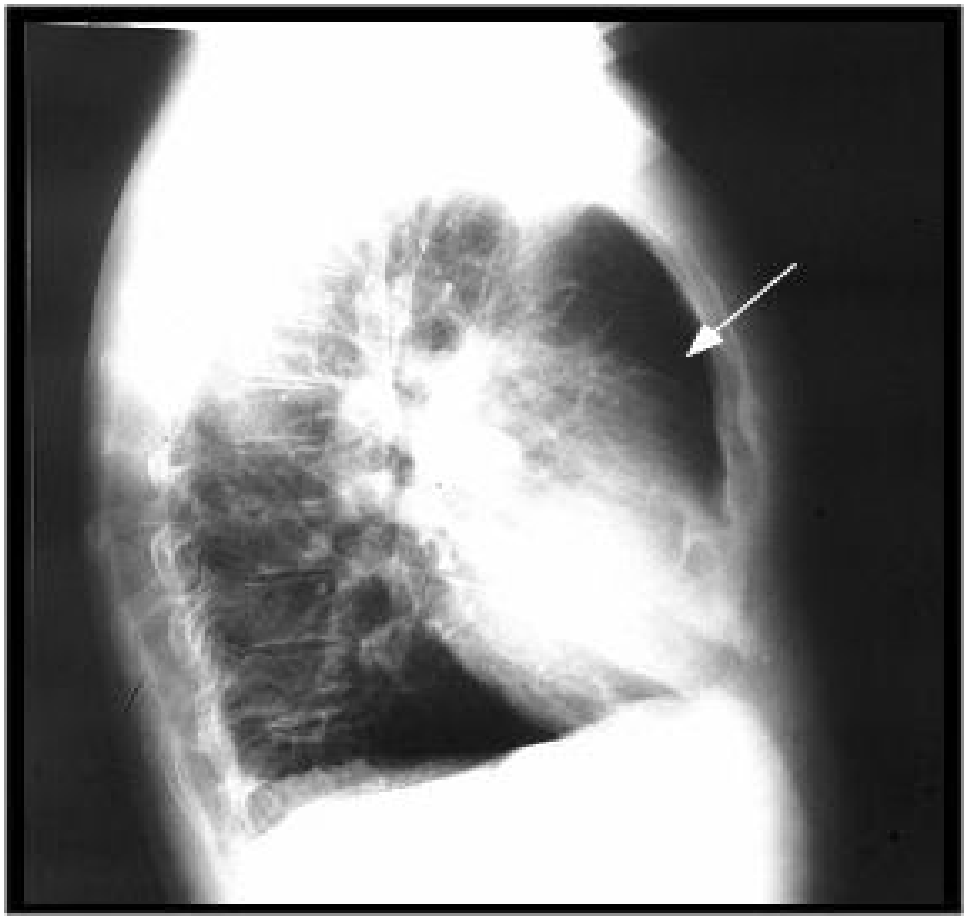
- Posteroanterior view of a normal chest radiograph.



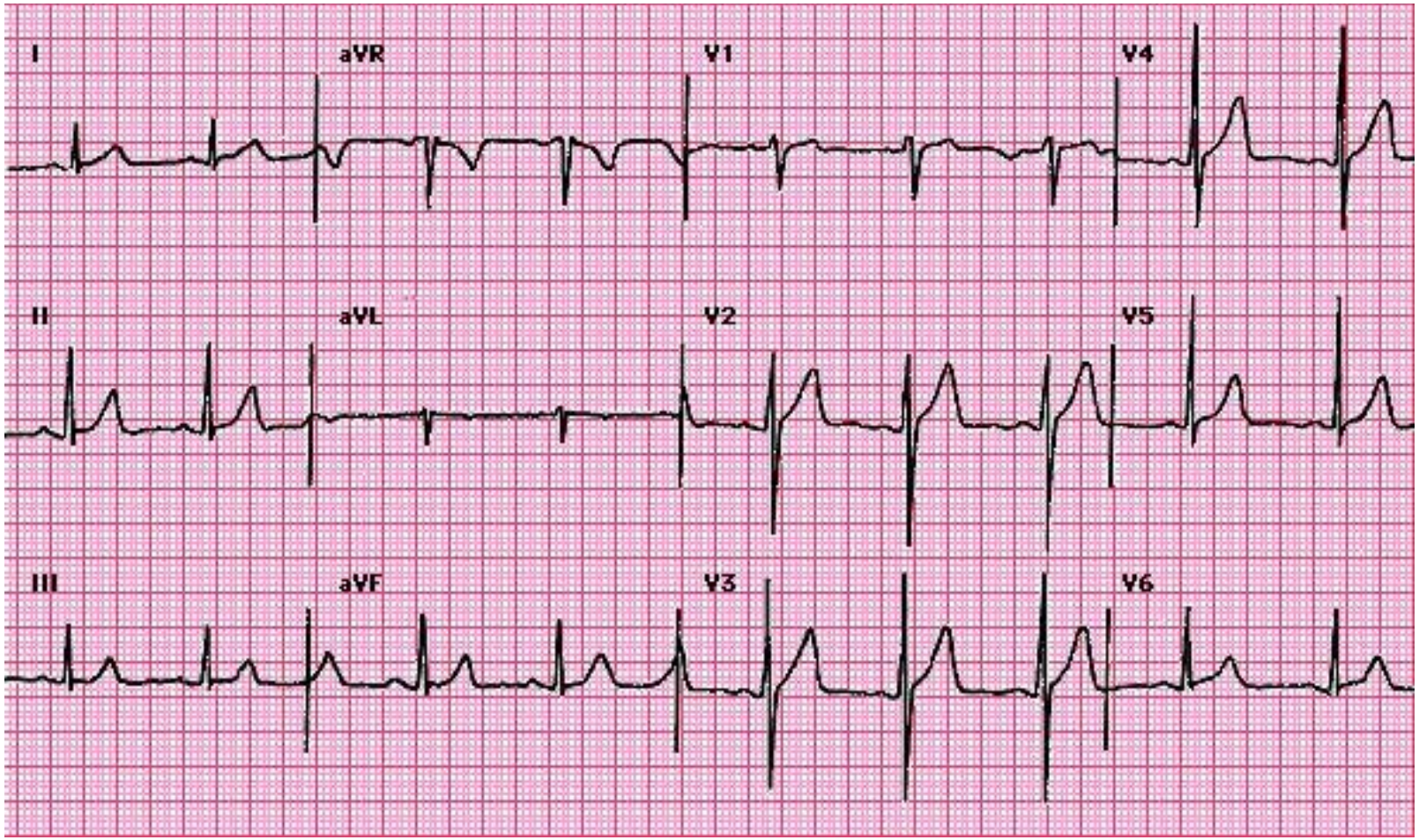
- This plain frontal chest radiograph from a 50-year-old male demonstrates prominence of the interstitial pulmonary markings with enlargement of the right and left ventricle and the right atrium (black arrow). Additionally, large central, but attenuated peripheral pulmonary arteries are noted (white arrow), all features characteristic of pulmonary hypertension.



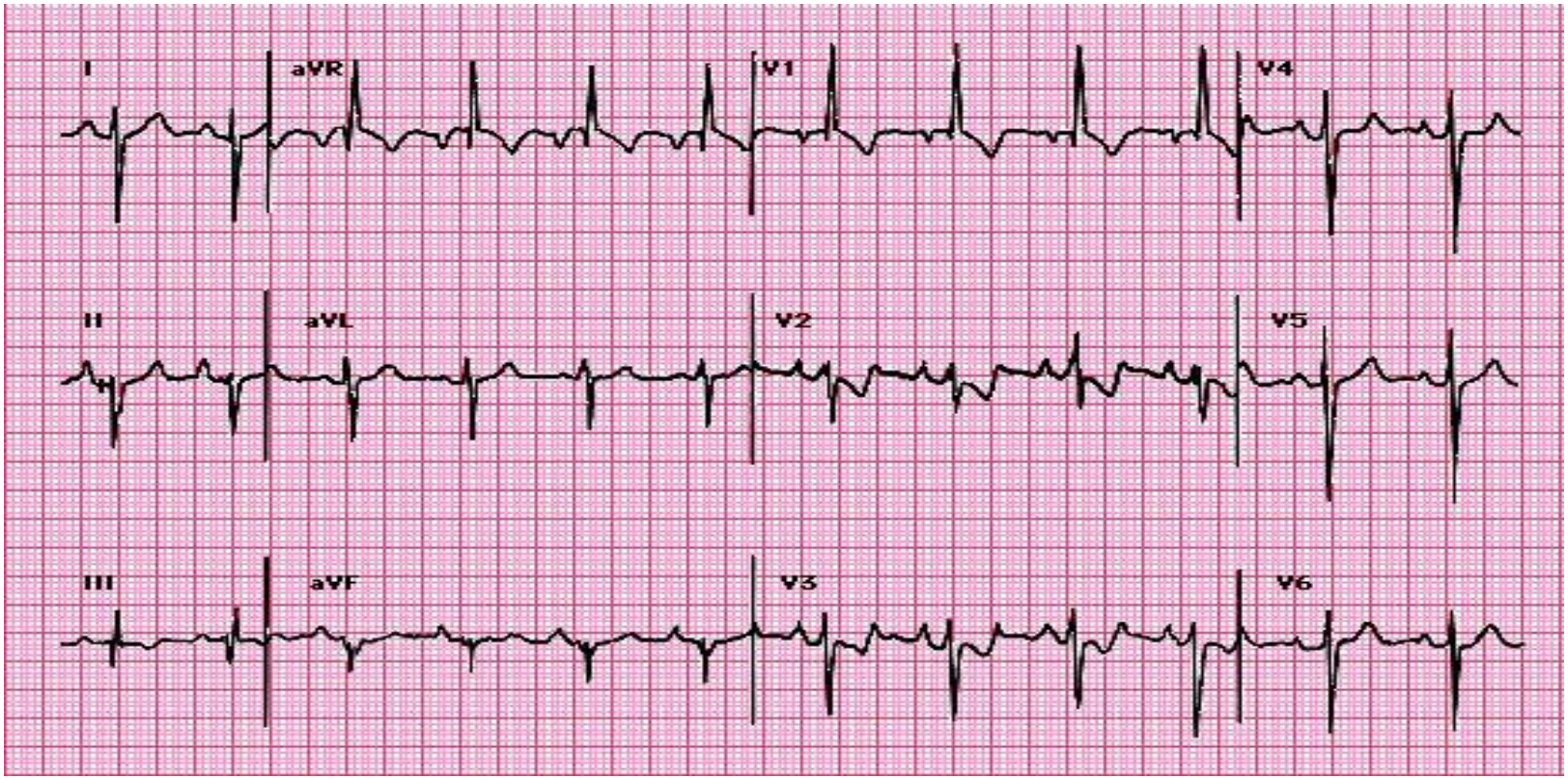
Normal lateral chest radiograph



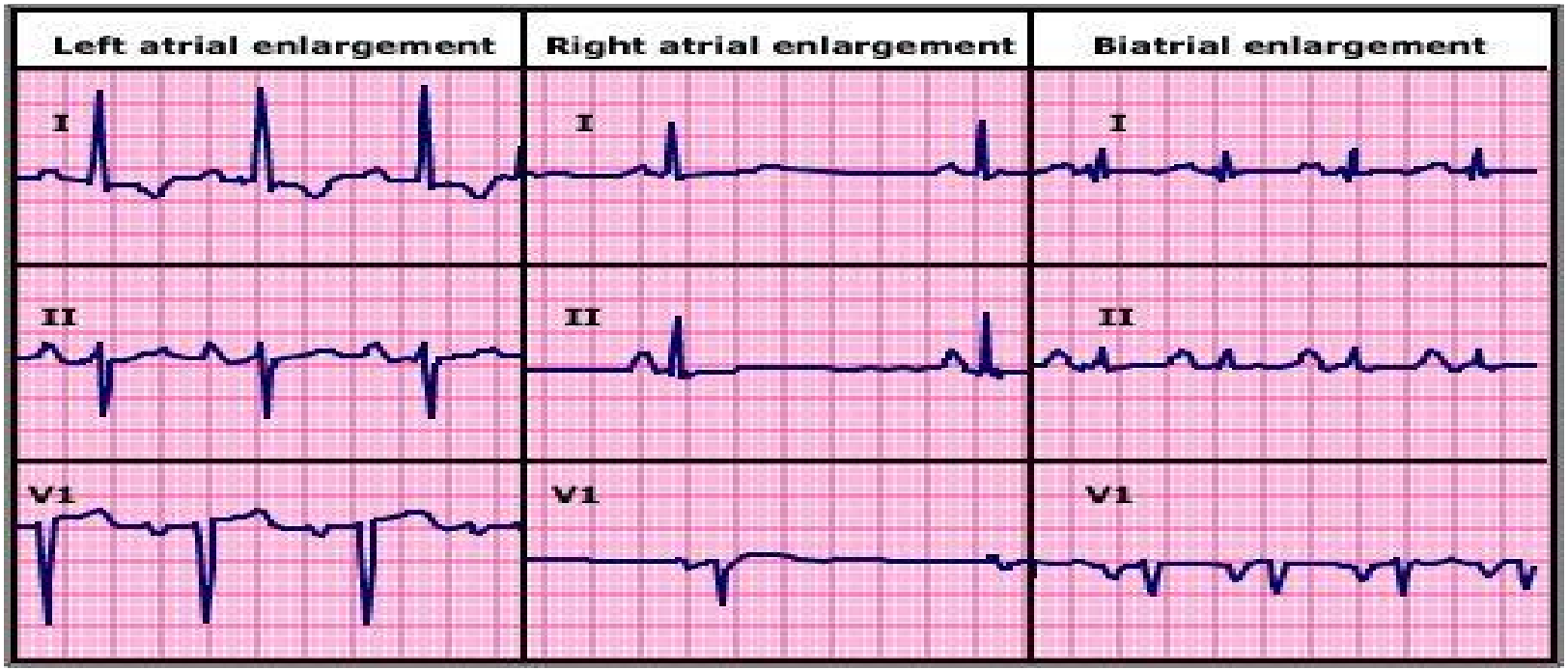
- Chest radiograph in lateral view showing decreased retrosternal space (arrow) due to right ventricular enlargement in pulmonary hypertension.



Normal ECG



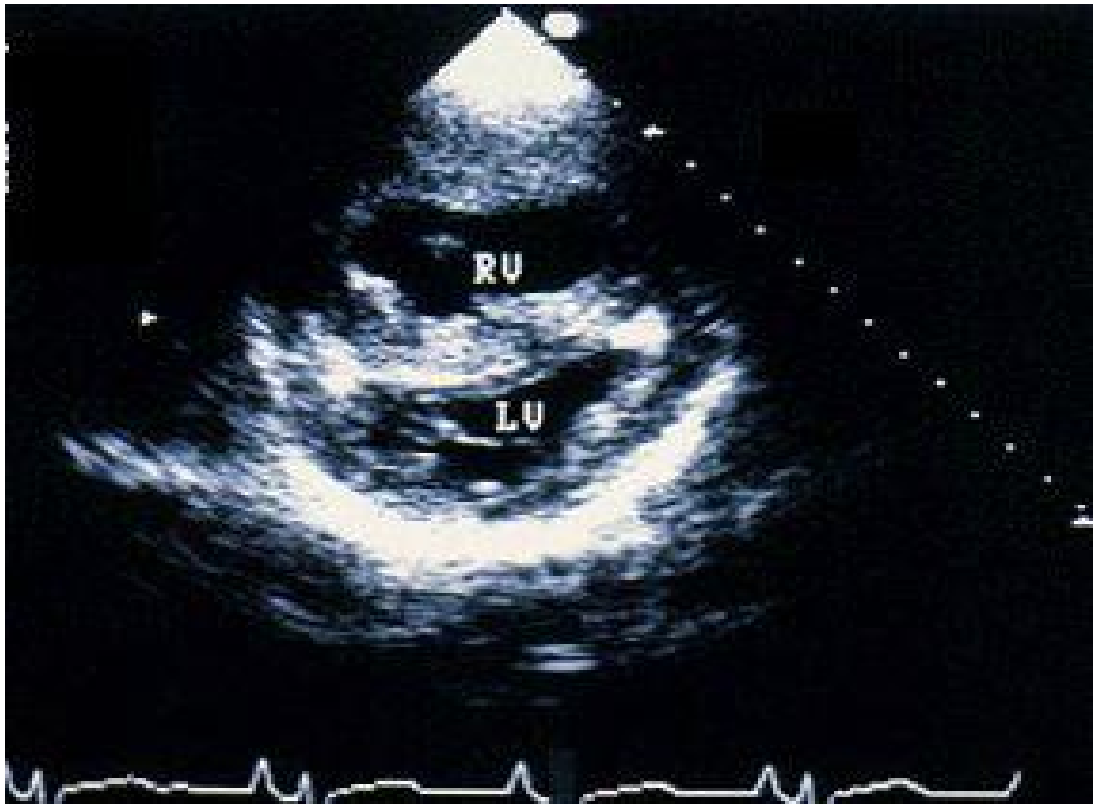
- Right ventricular hypertrophy. The characteristic features include marked right axis deviation , tall R wave in V1 , delayed precordial transition zone with prominent S waves in leads V5 and V6, inverted T waves and ST depression in V1 to V3 consistent with right ventricular "strain", and peaked P waves in lead II consistent with concomitant right atrial enlargement.



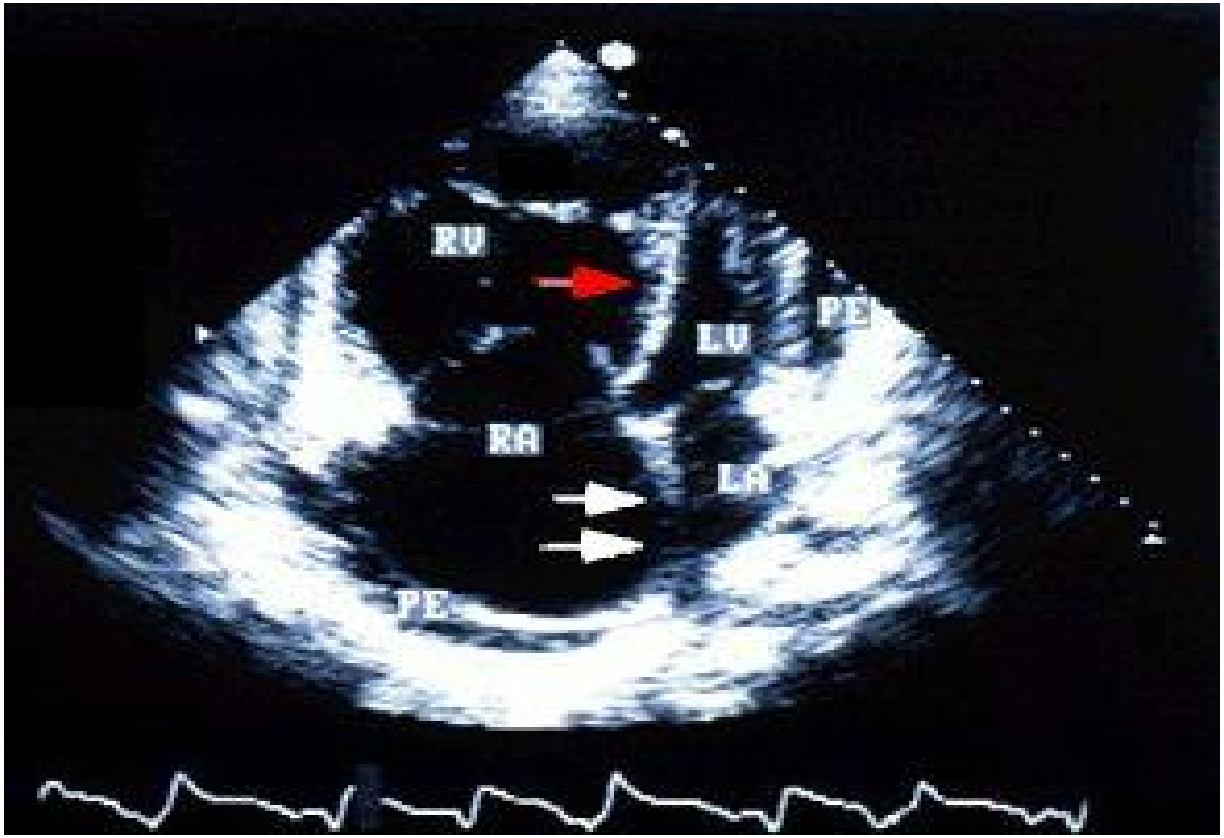
- P wave morphology with atrial enlargement in leads I, II, and V1. The P waves in left atrial enlargement (left panel) are wide (>0.12 sec) and notched in leads I and II and the terminal segment has a negative deflection that is deep and delayed in V1. In right atrial enlargement (middle panel), the P wave amplitude is increased (0.28 mV) in lead II. Biatrial enlargement (right panel) has characteristics of both atrial abnormalities: the P wave amplitude (0.22 mV) and duration (0.12 sec) are increased in lead II and there is deep terminal negativity in V1.

Method (cont'd)

- Echocardiography is performed (by different expert operator) to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function , In addition, evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts .



- The short axis view at the level of the mitral chordae shows severe hypertrophy of the right ventricular (RV) wall, dilation of the RV chamber and hypertrophy of the right side of the septum. The septum is flattened, strongly suggesting pressure overload in the RV; this septal shape imparts a "D shape" to the left ventricle (LV) .



- The four chamber view shows severe dilation of the right ventricle (RV) and right atrium (RA) with evidence of high right sided filling pressure; the interventricular septum (red arrow) and the interatrial septum (white arrows) bulge into the left ventricle (LV) and left atrium (LA) respectively.

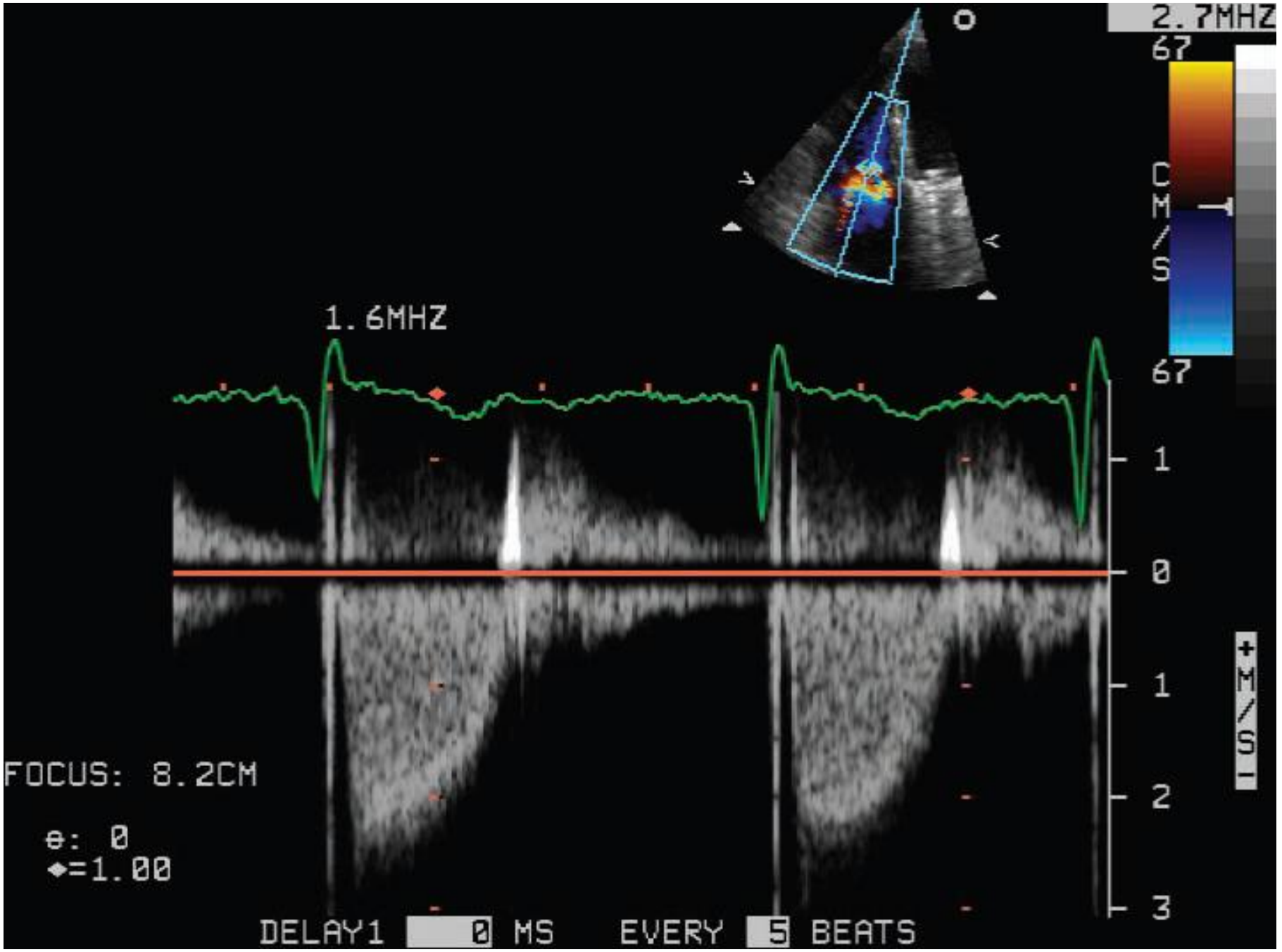
- Transthoracic Doppler echocardiography used to estimate the pulmonary artery systolic pressure. This technique takes advantage of the tricuspid regurgitation that usually exists. The maximum tricuspid regurgitant jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is then calculated:

$$PASP = (4 \times TRV \text{ squared}) + RAP$$

where TRV is the maximum tricuspid regurgitant jet velocity and RAP is the right atrial pressure estimated from the size and respiratory variation of flow in the inferior vena cava.

An estimated right ventricular systolic pressure [ERVSP] ≥40 mm Hg was considered PAH .[1]

1.Wigley FM, Lima JA, Mayes M, McLain D, Chapin JL, Ward-Able C. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). *Arthritis Rheum*. 2005;52:2125-2132.


2.7MHZ
67
CM/S
67
1.6MHZ
1
0
1
2
3
+M/S-
FOCUS: 8.2CM
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DELAY1 0 MS EVERY 5 BEATS

Method (cont'd)

- 4-CT chest: done in patients who discovered with PAH by Echocardiography.
- 5-PFTs: are performed to identify and characterize underlying lung disease that may be contributing to PAH. An obstructive pattern is suggestive of COPD while restrictive disease suggests interstitial lung disease, neuromuscular weakness, or chest wall disease .

Results

- The study included 100 Libyan patients with CTD.

Sixty seven patients (67%) have RA.

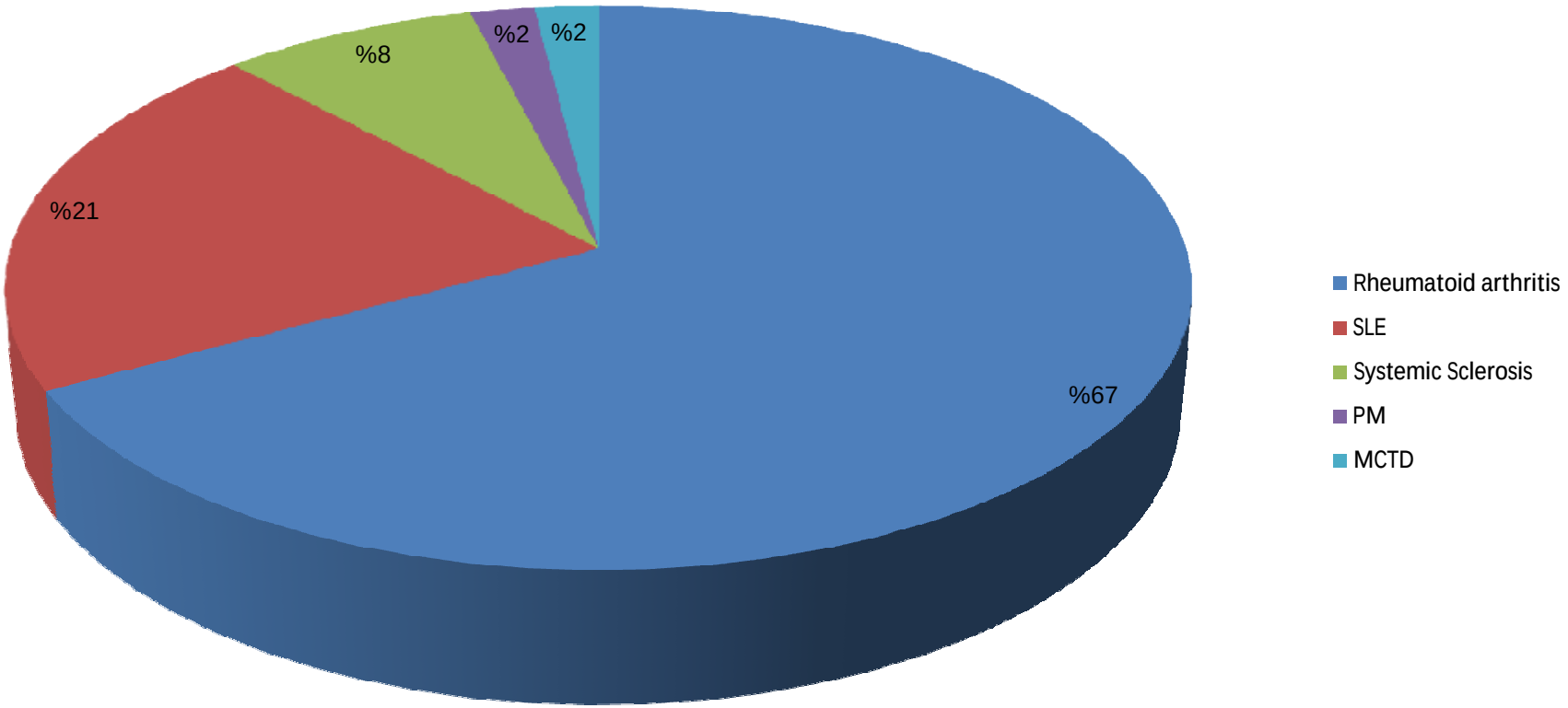
21 patients have SLE (21%) .

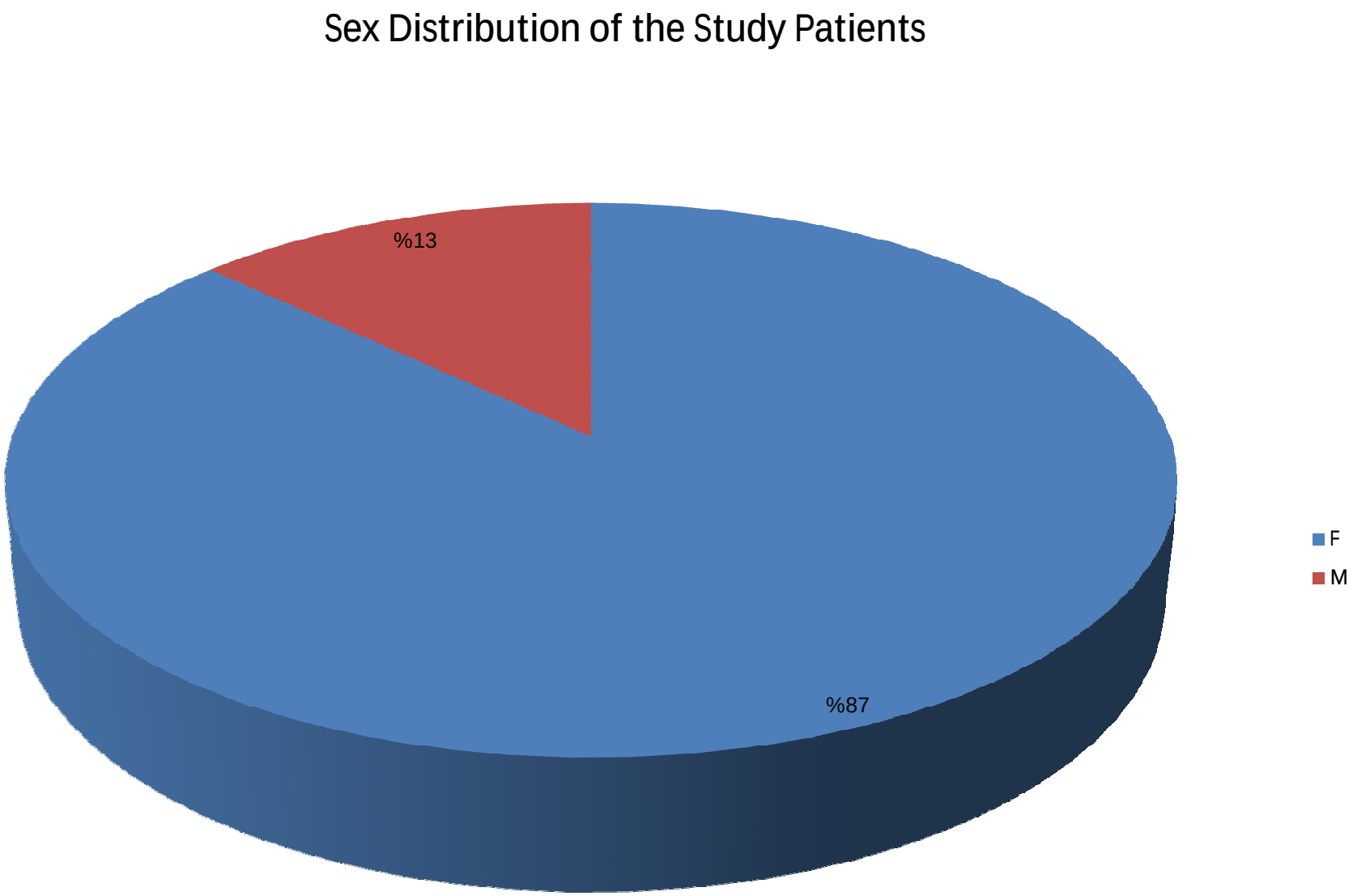
8 patients have SS (8%).

2 patients have MCTD (2%).

and 2 patients have PM (2%) .

Diagnoses of The Study Patients



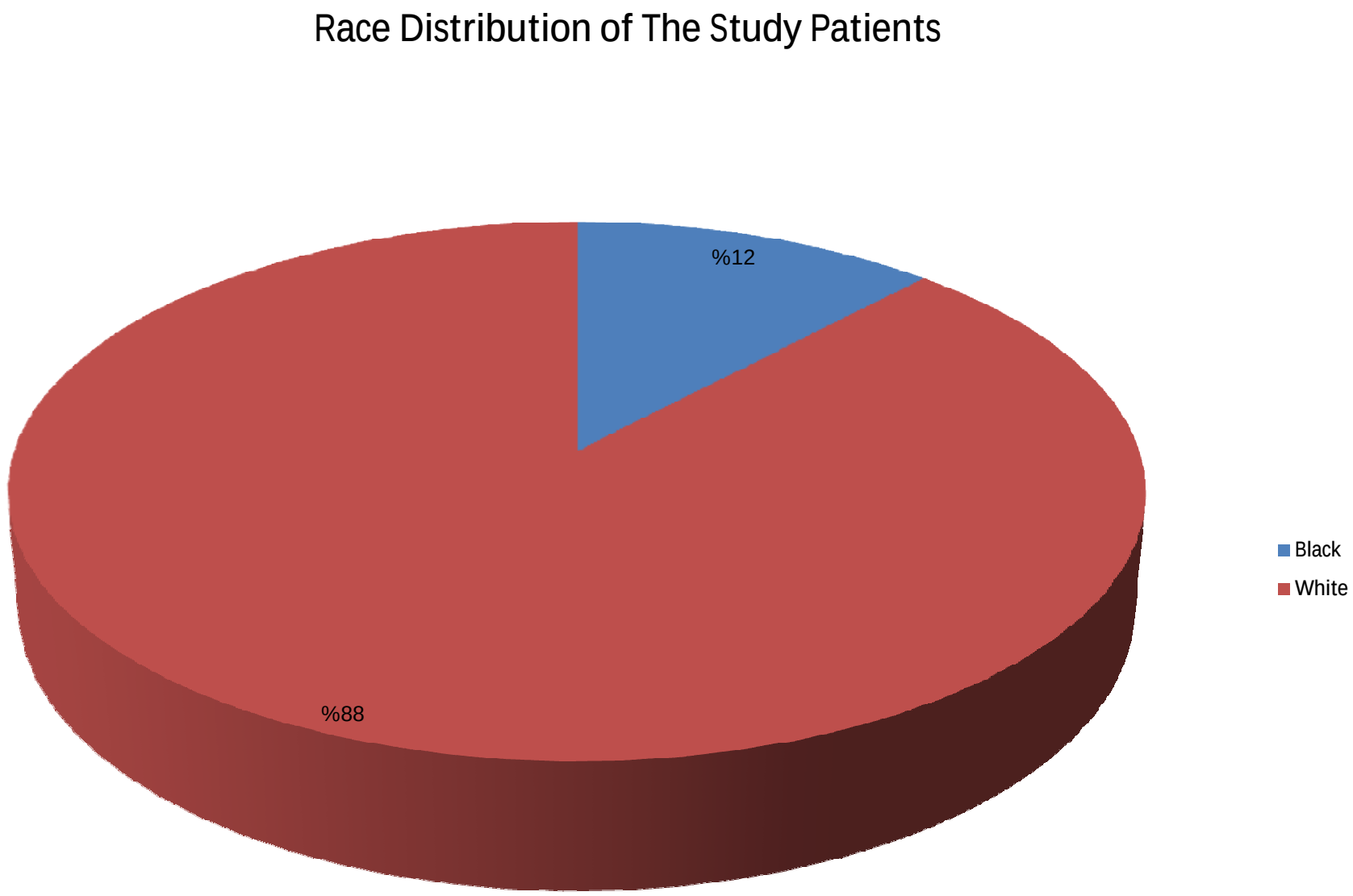

Sex Distribution of the Study Patients
%13
%87
F
M

Results (cont'd)

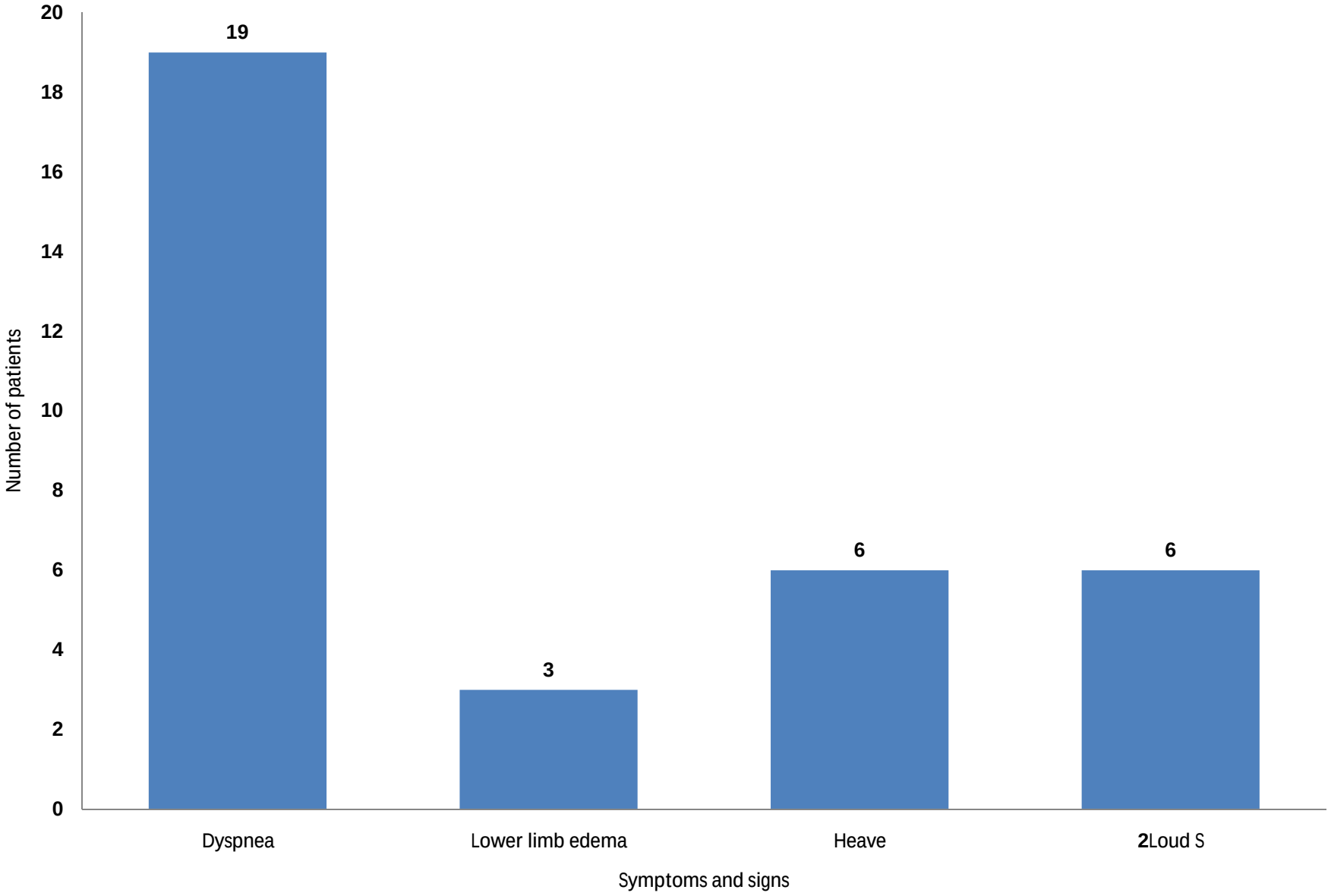
The mean age of the study patients was 48.79 ±13.49(range 20-82) years.

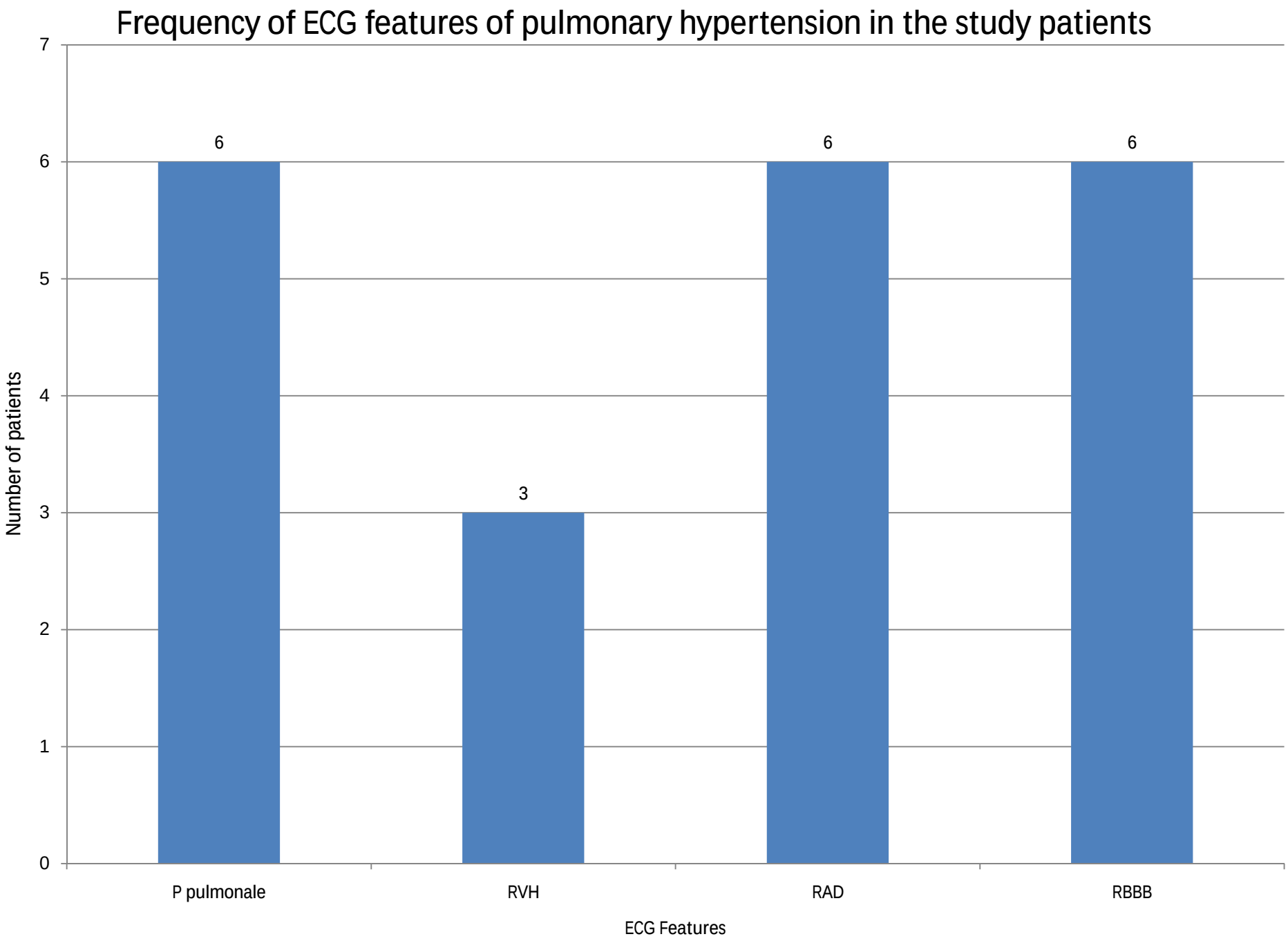
The mean age of male patients was 48.38±18.23(range 24-82)year .

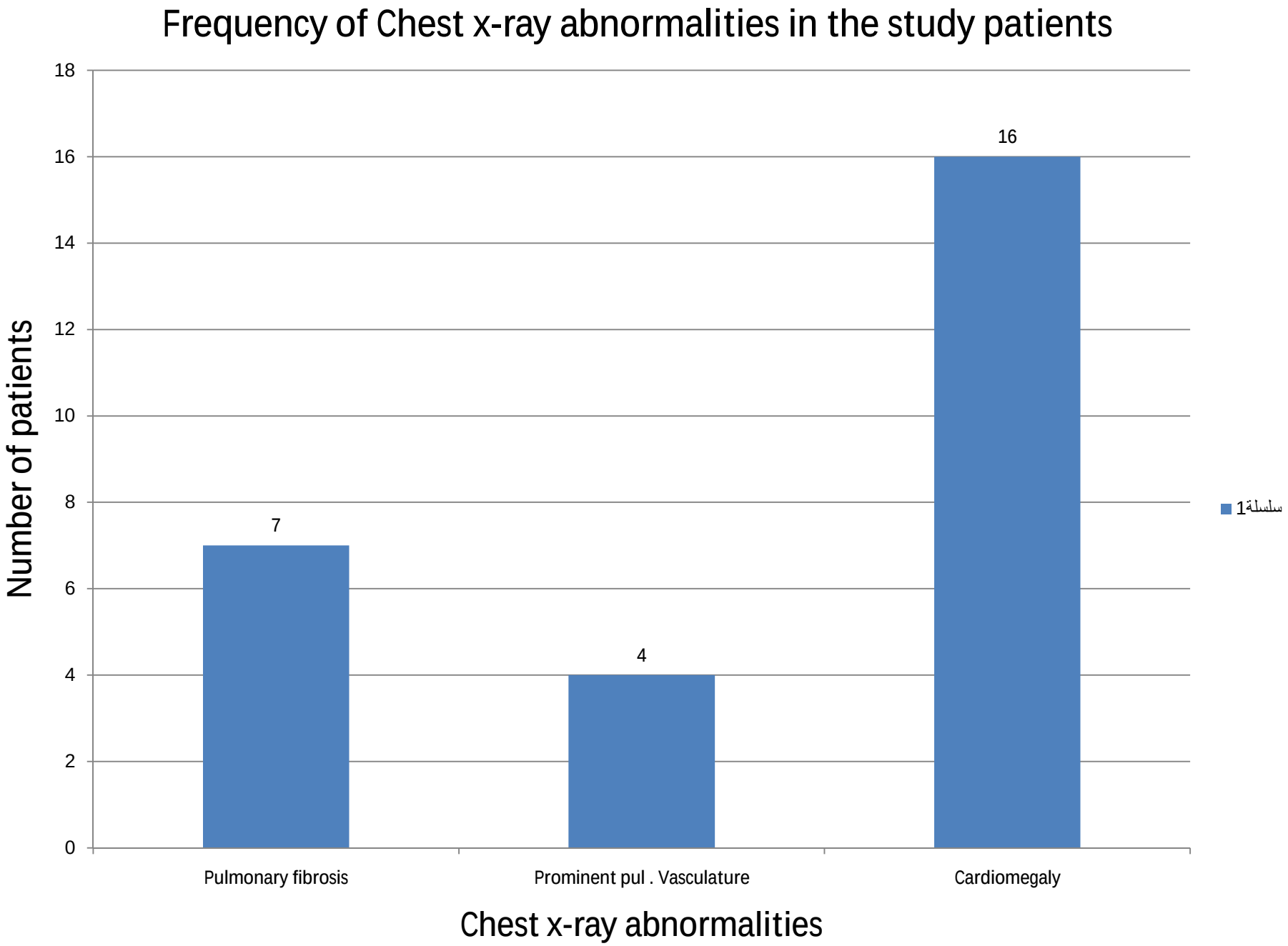
The mean age of female was 48.85± 12.77 (range 20-75) year.


Race Distribution of The Study Patients
%12
%88
Black
White

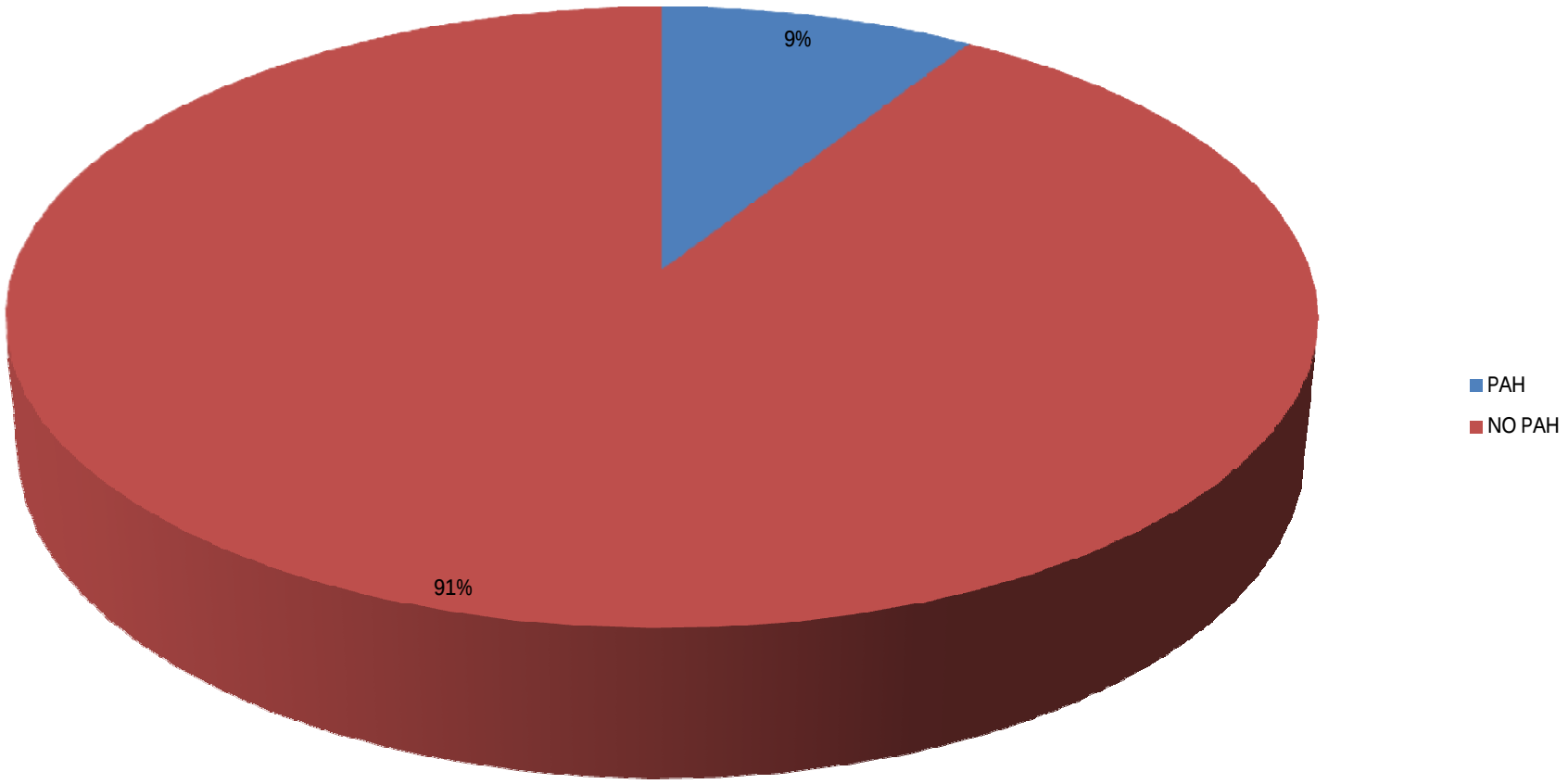
Frequency of symptoms and signs of pulmonary hypertension in the study patients




Frequency of ECG features of pulmonary hypertension in the study patients
Number of patients
0
1
2
3
4
5
6
7
6
3
6
6
P pulmonale
RVH
RAD
RBBB
ECG Features


Frequency of Chest x-ray abnormalities in the study patients
Number of patients
18
16
14
12
10
8
6
4
2
0
7
4
16
Pulmonary fibrosis
Prominent pul . Vasculature
Cardiomegaly
Chest x-ray abnormalities
سلسلة1

Frequency of PAH(by ECHO) in the study patients



Results (cont'd)

- By Echo 9 patients were found to have PAH.
- Out of the 9 patients who have PAH (by ECHO) :

  3 (33.3%) patients were male .

  6 (66.7%) patients were female.

  Four patient (44.4%) with PAH have pulmonary fibrosis and 5 (55.6%) patients have no CT evidence of pulmonary fibrosis.

Results (cont'd)

- In the 9 patients with PAH:

  4 patients (44.4%) have SLE(19% of all SLE patients).

  3 patients (33.3%) have SS(37.5% of all SS patients).

  one patient (11.1%) has RA(1.5% of all RA patients).

  and one patient (11.1%) has MCTD(50% of all MCTD patients).

Results (cont'd)

- The mean age of patients with PAH 47±16.05(range 26-74) year.
- The mean duration of diseases was 13.67 ±11.94 year.
- Six of the 9 patients (66.7%) with PAH have SOB.
- 2 patients (22.2%) have LL edema.
- 6 patients (66.7%) have left parasternal heave.
- and 6 patients (66.7%) have loud S2.

Results (cont'd)

- CXR findings in patients with PAH included: pulmonary fibrosis in 4 patients (44.4%), prominent pulmonary vessels in 4 patients (44.4%) and cardiomegaly in 6 patients (66.7%) .
- CT scan Chest showed evidence of ILD in 4 out of the 9 patients (44.4%) with PAH and all of them had restrictive pattern on spirometry.
- By ECG: 6 patients (66.7%) of those with PAH have P-pulmonale , 5 patients (55.6%) have RBBB , 3 patients (33.3%) have RVH , and 6 patients (66.7%) have RAD.

Diagnosis	Age [year]	Sex	Duration of disease [year]	Race	Symptom	Examination	ECG	CXR	CT scan	Spirometry	ECHO [EPAP In mmhg]
SLE	26	M	4	White	NO	Normal	Normal	Normal	Normal	Normal	42
SLE	28	M	2	White	NO	Normal	Normal	Normal	Normal	Normal	40
MCTD	62	M	20	White	NO	Normal	Normal	Prominent pulmonary vasculature	Normal	Normal	44
SS	74	F	40	Black	SOB	Pedal edema Lt parasternal heave,Laud S2.	P pulmonale, RAD, RBBB	Pulmonary fibrosis Prominent pulmonary vasculatur, cardiomegaly	ILD	Restrictive	46
SLE	39	F	6	White	SOB	Pedal edema Lt parasternal heave,Laud S2.	P pulmonale, RAD, RBBB	Prominent pulmonary vasculatur, cardiomegaly	Normal	Normal	48
SS	50	F	12	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	46
RA	52	F	21	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB,RVH	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	49
SLE	41	F	8	White	SOB	Pedal edema Lt parasternal heave,Laud S2	P pulmonale, RAD, RBBB,RVH	Prominent pulmonary vasculature cardiomegaly	Normal	Normal	48
SS	55	F	12	White	SOB	Lt Parasternal heave,laud S2	P pulmonale, RAD, RBBB,RVH	Pulmonary fibrosis cardiomegaly	ILD	Restrictive	48

Discussion

- Our study included 100 Libyan patients with CTD who were registered at Al-Hwari Rheumatology clinic. Nine patients [9%] were found to have PAH, which in the range of other study (3.7-13.3%) .[1,2]
- estimation of the real prevalence of PAH in CTD remains open for discussion due to the lack of a consistent epidemiological data. Available data are highly variable according to the definition and the method used for assessing PAP and the potential biases concerning the study populations investigated.

1.Ji YQ,Zhang ZL,Lu WX The clinical analysis of pulmonary arterial hypertension in connective tissue disease (Article in Chinese).

2.Wigley FM, Lima JA, Mayes M, McLain D, Chapin JL, Ward-Able C. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). *Arthritis Rheum*. 2005;52:2125-2132.

Discussion (cont'd)

- Of the total 9 patients, 3 patients were males [33.3%], and 6 patients were females [66.7%],and this is comparable with other study were number of females found to have PAH is more than males, and this because connective tissue disease is more common in females.[1]
- The mean age of patients with PAH is 47±16.05 years ,and this is comparable with other study were the mean age of patients have PAH was 43±14 years.[2]

1. Ji YQ,Zhang ZL,Lu WX The clinical analysis of pulmonary arterial hypertension in connective tissue disease (Article in Chinese).

2.Paul V.Santos Estrella.Yih Chang Lin.Santos V.Navarra Pulmonary arterial hypertension among Filipino patients with connective tissue diseases.

Discussion (cont'd)

- The underlying diseases included are Systemic lupus erythematosus(SLE) ,Systemic scleroderma(SSc) ,Mixed connective tissue disease(MCTD) ,Rheumatoid arthritis(RA),and this is because PAH is a common complication among these Connective tissue diseases.

Discussion (cont'd)

- Four patients (44.4%) SLE , 3 patients (33.3%) SSc ,and one patients (11.1%) MCTD,found to have PAH.This comparable to other study were 42% SLE, 36 % SS,and 15% MCTD with PAH .1 One patient RA (11.1%) has PAH ,this is comparable to other study were 10.6 % with RA found to have PAH .2

- The mean duration of connective tissue disease at the diagnosis of PAH 13.67±11.94 years,and this reinforcing the need for vigilance in recognition of this complication.

- 1.Paul V.Santos Estrella.Yih Chang Lin.Santos V.Navarra Pulmonary arterial hypertension among Filipino patients with connective tissue diseases.

2.V.Santos Estrella.Yih Chang Lin.Santos V.Navarra Pulmonary arterial hypertension among Filipino patients with connective

Discussion (cont'd)

- Dyspnea, accentuated P2, and cardiomegaly were among the most common manifestations in our patients, for which conditions careful examinations should be conducted, and these are comparable to other study [1,2]. These conditions are easily detected during routine check-up and can be further verified by a chest radiograph and an echocardiogram.

1. Paul V.Santos Estrella.Yih Chang Lin.Santos V.Navarra Pulmonary arterial hypertension among Filipino patients with connective tissue diseases.
2. Ji YQ,Zhang ZL,Lu WX The clinical analysis of pulmonary arterial hypertension in connective tissue disease (Article in Chinese).

Discussion (cont'd)

- ACCP(American college of chest physician) has included the chest radiograph and the echocardiogram as part of patient´s evaluation if there is a reason to suspect PAH.
- The chest radiograph is obtained to reveal features supportive of a diagnosis of PAH and to lead to the diagnosis of the underlying disease, whereas echocardiogram is performed as a noninvasive screening test that can detect PAH, although it may be imprecise in the determination of the actual pressures when compared with invasive evaluation in a group of patients.

Conclusion

- The prevalence of PAH, the sex distribution and the underlying etiology in Libyan patients with CTD is comparable to other studies and often clinically missed . Routine screening with Echo is needed for detection of patients who may require further evaluation & treatment.

Recommendation

- We recommend that all patients with confirmed connective tissue diseases should be screened regularly by echocardiography for possible elevated pulmonary artery pressure.
- All cases found to have elevated pulmonary artery pressure should be referred to specialized center for further more invasive test to confirm the disease and possible treatment.