A STUDY OF MEAN PLATELET VOLUME AND RED CELL DISTRIBUTION AS A MARKER OF SEVERITY OF PULMONARY HYPERTENSION

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF

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CHENNAI, TAMILNADU, INDIA

MAY 2022

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**A STUDY OF MEAN PLATELET VOLUME AND RED CELL DISTRIBUTION AS A MARKER OF SEVERITY OF PULMONARY HYPERTENSION**" is the bonafide work of **Dr.R.ANAND** in partial fulfillment of the university regulations of The Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I Examination to be held in May 2022.

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DECLARATION

I **Dr.R.ANAND** solemnly declare that, this dissertation entitled "**A STUDY OF MEAN PLATELET VOLUME AND RED CELL DISTRIBUTION AS A MARKER OF SEVERITY OF PULMONARY HYPERTENSION**" is a bonafide record of work done by me at the Department of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of Professor Dr A.SENTHAMARAI MD., Department of General Medicine, Madurai Medical college, Madurai from June 2021 to November 2021. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, Diploma to any other University, Board either in India or abroad. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I-examination to be held in May 2022.

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CONTENTS

INTRODUCTION

INTRODUCTION

Pulmonary hypertension (PAH) is a chronic and progressive disease characterized by persistent increases in pulmonary artery pressure and pulmonary vascular resistance that eventually led to right heart failure. Regardless of the etiology, thrombotic pulmonary vascular lesions are an integral part of pulmonary vascular pathology, which additionally includes vasoconstriction and remodeling. There are few observations that have shown increased platelet aggregation and activation in patients with PAH.

Method for assessing platelet function. Compared to smaller ones, larger platelets have more granules, aggregate faster with collagen, have higher thromboxane A2 levels, and express more glycoprotein Ib and IIb / IIIa receptors.

RDW can serve as an integrative measure for several processes that occur simultaneously in chronic heart failure, such as kidney dysfunction, liver congestion and nutritional deficiencies. Elevated RDW may simply reflect an underlying inflammatory condition, inpulmonary hypertension, when chronic inflammation is present. Treatment and follow-up care for pulmonary hypertension is difficult and expensive. A simple and inexpensive test, MPV and RDW can help us monitor the progression of pulmonary hypertension.

AIM OF STUDY

AIMS AND OBJECTIVES

To investigate Mean Platelet Volume and Red Cell Distribution width as a marker of severity of pulmonary hypertension.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

PULMONARY HYPERTENSION:

Pulmonary hypertension (PH) is a routine diagnosis in modern cardiology and lung clinics. Significant advances are being made in the treatment of pulmonary arterial hypertension (PAH), which is more readily available in centers specializing in PH.

A**.** Terminology / Definitions. PH is defined as mean pulmonary artery pressure (mPAP)> 25 mm Hg. PH comprises a heterogeneous group of disorders with a common clinical manifestation. The terms PH, a hemodynamic and pathophysiological disorder, and PAH, a clinical disorder, are distinct terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly used in the PH include the following:

1. The transpulmonary gradient (TPG) is defined as the pressure difference between the mean left atrial pressure (LAP) (more often the pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP.

2. Pulmonary vascular resistance (PVR) is defined as TPG divided by cardiac output (CO) (PVR = TPG / CO in Wood units).

3. PAH is hemodynamically defined as PH (i.e., mPAP ≥ 25 mm Hg) with increased PVR (more than 3 Wood units) and normal wedge pressure (<15 mmHg). It is a clinical condition characterized by precapillary PH and pathological changes in the microcirculation of the lungs.

4. Pulmonary venous hypertension is characterized by mPAP 25 mm Hg, PVR> 3 Woodunits and increased wedge pressure (PCWP 15 mm Hg).

B. Classification. The World Health Organization has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics.

C. Epidemiology. The overall PH burden of the disease is substantial as it is an end-stage of several disease processes such as left-sided heart disease, chronic lung disease and PAH, which are very rare. Most patients diagnosed with PH on routine testing (echocardiogram with pulmonary artery systolic pressure [PASP]> 40 mm Hg) end up with left heart disease (nearly 80%), some have lung disease and hypoxia (10%), and only a small minority (4%) will have PAH.

PAH has been linked to environmental factors such as drug use and toxins. Anorexigenic drugs (appetite-suppressing drugs that increase the release of serotonin and block serotonin reuptake) have been linked to PAH, with agents such as fenfluramine.

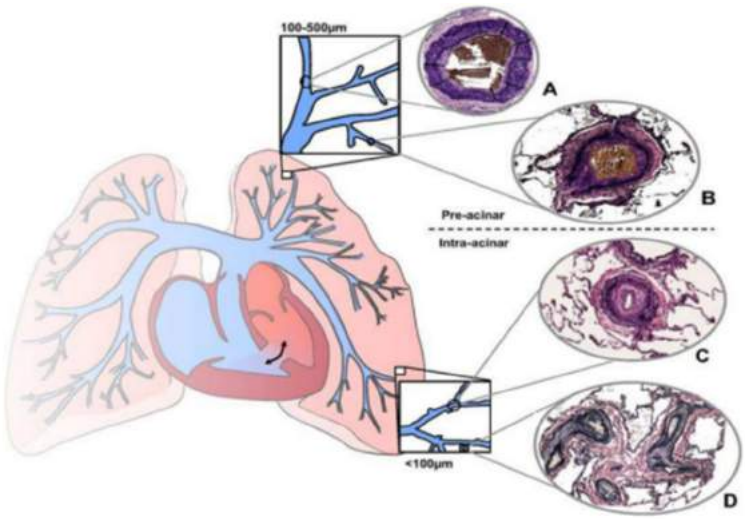
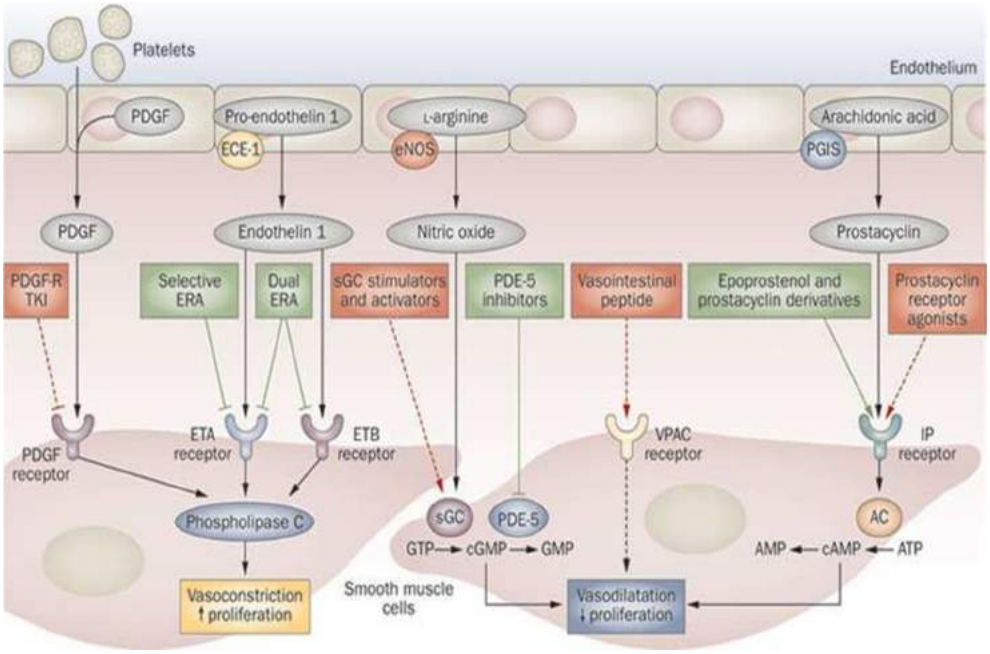


Figure 6. Changes in Pulmonary Vasculature



CLASSIFICATION PULMONARY HYPERTENSION

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, **SMAD9 , CAV1 , KCNK3**
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1". Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart in flow/out flow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due 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 lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Haematologic disorders: **chronic haemolytic anaemia** , myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

* 5th World Symposium on Pulmonary Hypertension, Nice 2013. Main modifications to the previous Dana Point classification are in bold.

Key: BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension

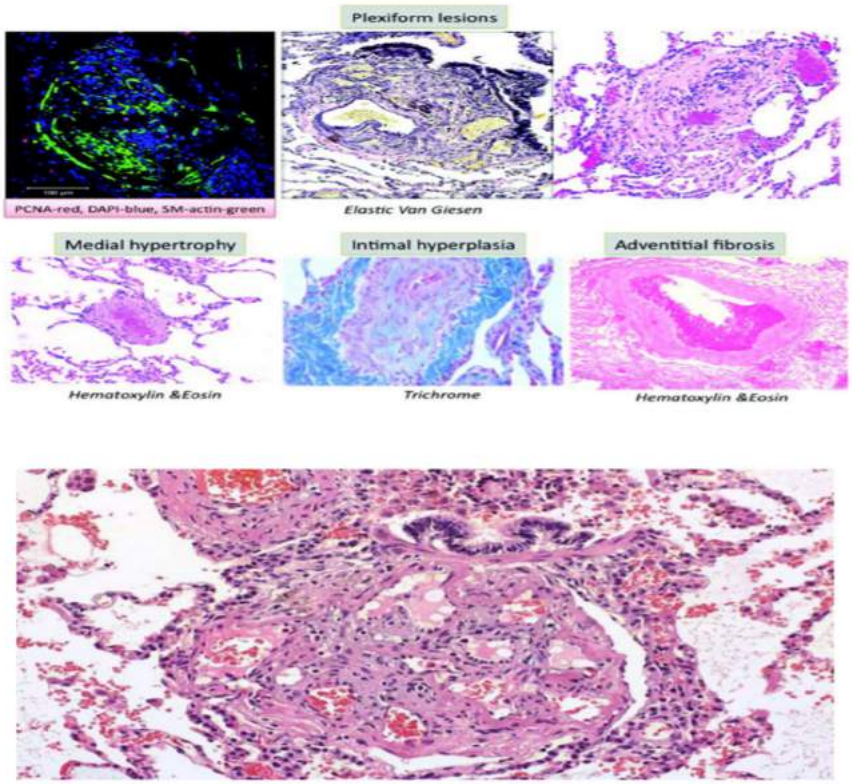


Figure 5. Plexiform Histopathology

GROUP.1 PULMONARY ARTERY HYPERTENSION:

They comprise a group of diseases that cause sustained increases in mPAP greater than 25 mmHg at rest while PCWP or left atrial pressure or left ventricular end diastolic pressure is less than 15 mmHg. In addition, the transpulmonary gradient and the PVR are also increased.

Epidemiology.

Rare disease with prevalence of 15 to 20 cases seen per million population. Most common cause of pulmonary arterial hypertension is idiopathic followed by CTD. Inherited PAH has the least incidence of 4%.

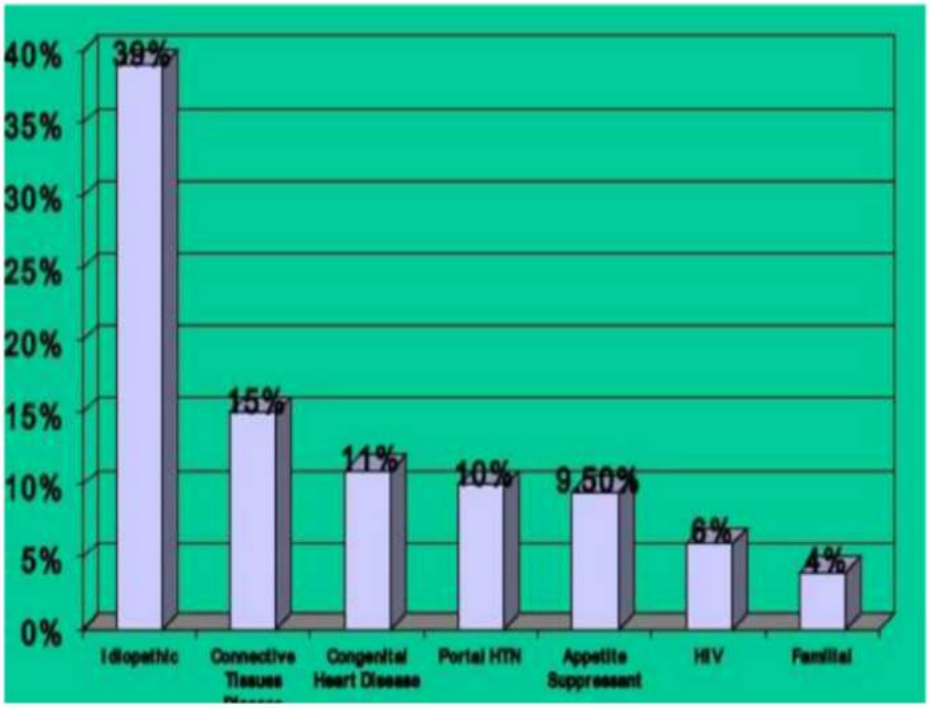


Figure 6. Epidemiology of PAH

Idiopathic pulmonary arterial hypertension:

Formerly known as primary pulmonary hypertension where the cause of the increase in mPAP has not been identified. It is the most common type among PAH15. It was found that patients with no family history or risk factor were sporadic. Females are affected locally, the average value at the presentation is 37 years.

Heritable Pulmonary Arterial Hypertension:

The first case of heritable PAH was diagnosed by Dresdale and colleagues in 1954. Since then, many cases have been reported and a lot of research has been done on genetic analysis of the affected individuals to

identify the genes involved. It is an autosomal dominant triad with complete penetrance showing the phenomenon of anticipation.

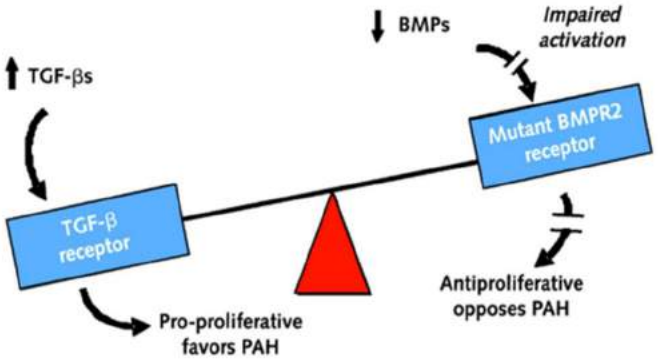
It is present in the long arm of chromosome 2 (2q31-32) 17. It is said to be responsible for the growth and differentiation of lung endothelial cells and smooth muscle cells. The gene is detected in 70 to 80% of cases with a family history and 15 to 20% of sporadic cases. Women are often affected. Patients with this mutation are younger in the age of diagnosis with an aggressive course and have a poor prognosis.

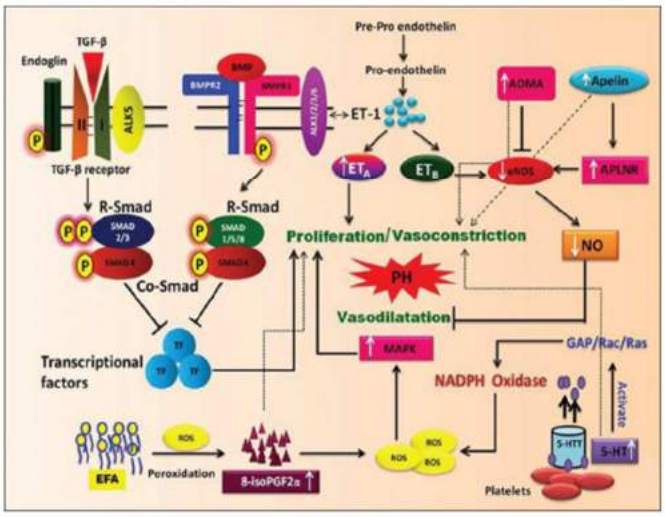
Other genes that are involved are activin a receptor type II like kinase 1(ALK-1), endoglin, SMAD-9, CAV1- involved in TGF- beta signaling pathway.

Drug- and toxin-induced PAH:

In an epidemic outbreak of IPAH due to amino ex fumarate in 1960, it was found that many structurally related compounds such as fenfluramine, dexfenfluramine, which are used as anorexigens, cause PAH and have therefore been withdrawn from the market. Some methamphetamines, L-tryptophan, and canola oil have been found to cause PAH. Dasatinib, a tyrosine kinase inhibitor, was also found to inhibit PAH20.

Figure 7. Genetics in PAH





Definite	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex	• Cocaine • Phenylpropanolamine • St John's Wort • Chemotherapeutic agents • Selective serotonin reuptake inhibitors • Pergolide
Likely	**Unlikely**
• Amphetamines • L-tryptophan • Methamphetamines	• Oral contraceptives • Oestrogen • Cigarette smoking

Figure 8. Drugs Causing PAH

Connective tissue diseases and PAH:

The spectrum of diseases of scleroderma is strongly linked with a prevalence of 8 to 12%. Patients have a poor prognosis with treatment compared to other causes of PAH21. The high-risk patients could be identified with a decrease in carbon monoxide diffusion capacity and an echocardiogram screening to allow for earlier treatment.

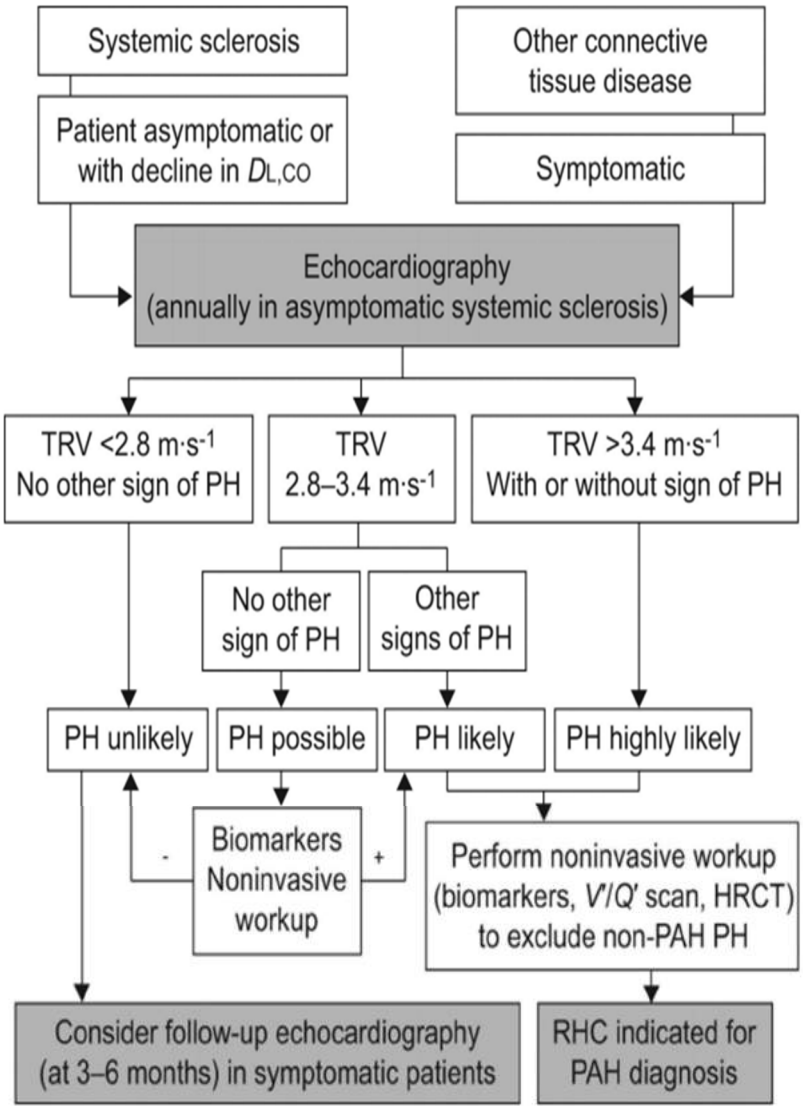


Figure 9. Screening for PAH in CTD

PAH Associated with HIV:

Rare disease with an incidence of 0.5% that does not change with extended antiretroviral therapy unrelated to CD4 + cell counts or the presence of opportunistic infections22,23. The mechanism is unknown, but an association with HIV has been clearly established. Should therefore be suspected in HIV-infected patients for whom no other cause has been identified.

PAH Associated with Portal Hypertension:

Portopulmonary Hypertension (POPH) is the term used when PAH occurs in patients with portal hypertension. There is no association between the severity of liver disease or portal hypertension and the presence or severity of PAH. Also observed in patients with non-hepatic portal hypertension disorders. . The prevalence is 2 to 6% and increases the perioperative risk in patients undergoing liver transplantation.

Variable	Normal	Mild	Moderate	Severe
NYHA class	—	I-II	II-III	II-IV
mPAP (mmHg)	15-24	25-34	35-44	>45
CI (L/min/m^2)	2.5-4	>2.5	>2.5	<2.0
PVR (dynes/s/cm^5)	<80	240-500	500-800	>800
RAP (mmHg)	0-5	0-5	5-10	>10
Prognosis	—	Favorable	Questionable	Poor
Specific therapy	—	No	Questionable	Yes
Reversibility after LT	—	Yes	Questionable	No

NYHA = New York heart association, mPAP = Mean pulmonary arterial pressure, CI = Cardiac index, PVR = Pulmonary vascular resistance, RAP = Right atrial pressure, LT = Liver transplantation

It should be differentiated from hepatopulmonary syndrome which is due to vasodilatation that occurs in pulmonary vasculature causing intrapulmonary shunting resulting in hypoxemia and dyspnoea

PAH Associated with Congenital Heart Defects:

Considered a complication due to uncorrected congenital heart disease with increased pulmonary blood flow and systemic and pulmonary shunt. The condition is defined as Eisenmenger syndrome, which is characterized by progressive pulmonary vasculopathy with shunt reversal and cyanosis. The prognosis is better than the right ventricular adaptive response in congenital heart disease25 compared to other causes23 of PAH

Eisenemenger Physiology	Reversible PAH	Irreversible PAH
Symptoms	Most Class 1 and few class 2	All class 4 And most class 3
Functional capacity	6 minutes > 400mts walk	6 minutes walk < 250 m
Systemic O2 saturation	> 90-95 %	< 90 % At room Air
Signs of increased pulmonary flow	Well Split S2 Dynamic RV LV still felt Mitral MDM	Quiet pre-cardium No-Mitral MDM Absent LV impulse
Signs of gross RV failure	Definitely Irreverisble (Simple TR, V waves not enough to diagnose RV failure .Mean JVP should be elevated)	
Pulmonary artery Systolic pressure (PASP)	Use-less for two reasons 1.In any large VSD RV systolic pressure is at near equilibrium of LV . 2. RV function has a major impact on PASP	
Pulmonary Diastolic pressure (PADP)	< 40mmhg	> 40mmhg
Pulmonary artery pulse pressure (PAPP)	< 30 mmhg	> 50mmhg
Note : Operability depend upon many factors other than reversibility of PAH. *Reversibility and operability are not synonymous* .There have been many instances of low PVR doing badly after VSD closure. So The intrinsic RV function can be crucial determinant of surgical outcome		

Figure 11. Eisenmenger Physiology

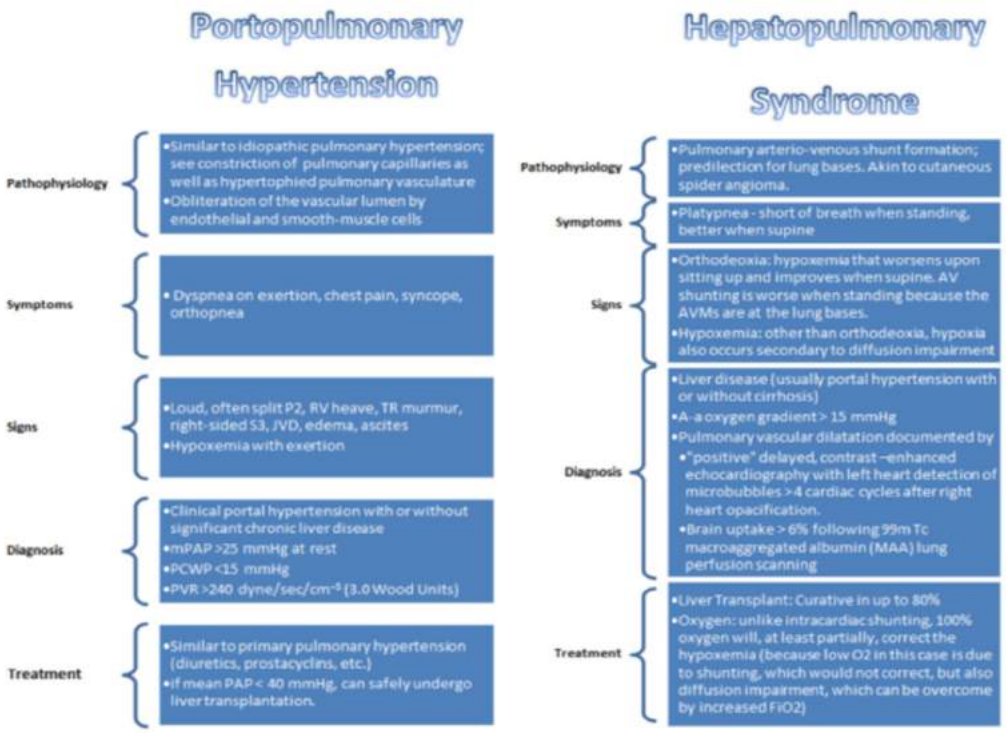


Figure 10. Port-Pulmoary & Hepato-Pulmonary

Diagnosis:

Symptoms:

Exercise dyspnea is the most common with symptoms occurring in 60% of cases. Followed by increased fatigue in 19% of the cases. Syncope more common in IPAH. As the disease progresses, the patient develops syncope, increasing dyspnea, later right ventricular failure24, which leads to flatulence and pedal edema26. The symptoms of risk factors that cause PH, such as CTD, COPD, heart disease, can mask or worsen the symptoms of PH. This has resulted in a delay in diagnosis averaging 2 years from the onset of symptoms.

Electrocardiogram:

In expensive and non-invasive instrument, but not sensitive or specific to PH. Common findings are right axis deviation, right atrial and ventricular enlargement, sometimes right ventricular hypertrophy with a stress pattern.

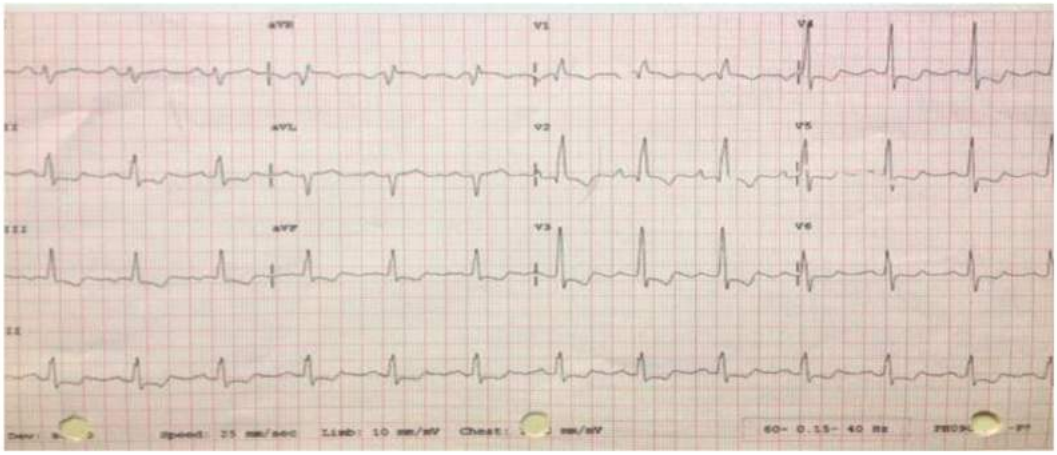


Figure 12. ECG in Pulmonary Hypertension

Chest X-ray:

A right ventricular enlargement can be seen on the side view. The presence of swollen pulmonary artery shadows in the center with circumcision of the periphery helps in the diagnosis of pulmonary hypertension. Pulmonary vein congestion is in left-sided heart disease. Emphysematous chest shows hyperinflation with flattening of the diaphragm in COPD28

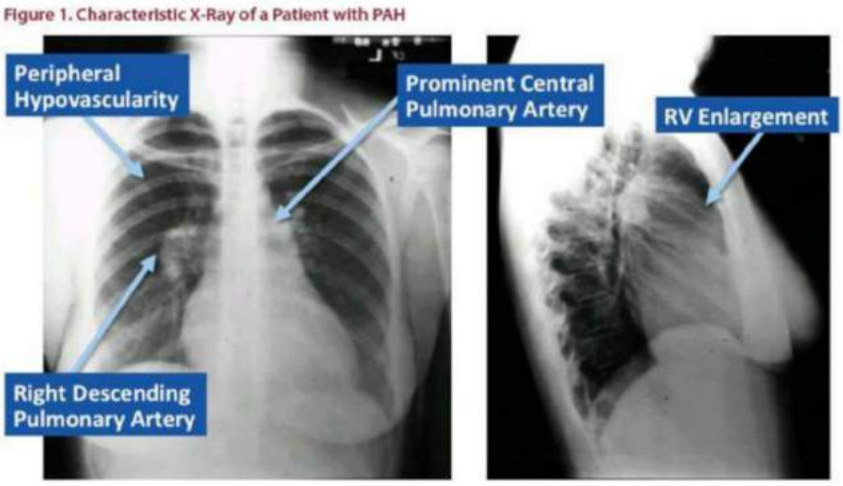


Figure 13. X - Ray

ECHOCARDIOGRAM:

It is a non-invasive screening tool used in patients with suspected pulmonary artery hypertension. The pulmonary artery pressure of more than 35 mmHg determined by Doppler echocardiography is cut off for the diagnosis of pulmonary hypertension.

Echocardiogram measures the following parameters:

1. Pulmonary artery systolic pressure (PASP)
2. Assessment of left ventricular –systolic, diastolic function and valves
3. Assessment of RV dysfunction
4. Presence of poor prognostic factors.

Pulmonary artery systolic pressure (PASP):

This depends on the principle that in the absence of right ventricular outflow tract obstruction PASP equals the right ventricular systolic pressure (RVSP) PASP = RVSP= 4 $(VTR)^2$+ RAP according to the Bernoulli equation When VTR is less than 2.8 m/s and PASP less than 36 mmhg PH is less likely.

	Grading of pulmonary arterial hypertension*		
	Systolic	Diastolic	Mean
Grade 1 (Mild)	30-50	20-25	>30
Grade 2 (Moderate)	50-70	26-35	>40
Grade 3 (severe)	70-110	36-45	>50
Grade 4 (Systemic or supra systemic)	>110	46-55	>60

*Data from 100 patients of PAH and rheumatic heart disease. Quintile 1 & 2 (Grade 1) quintile 3 & 4 (Grade 2) quintile 5 (Grade 3) top 3%(Grade 4)

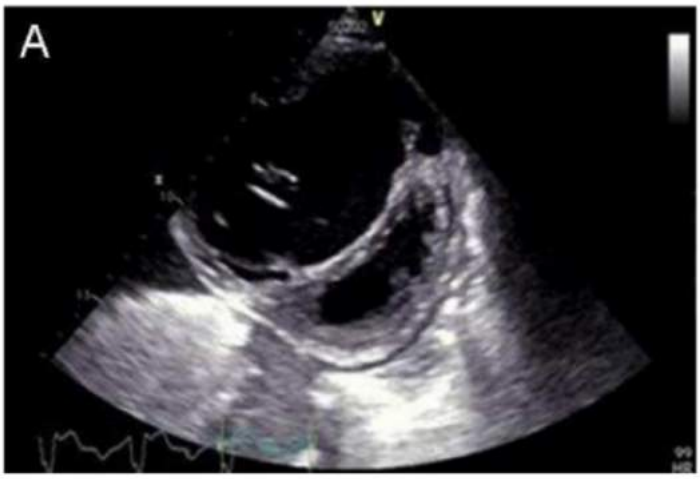
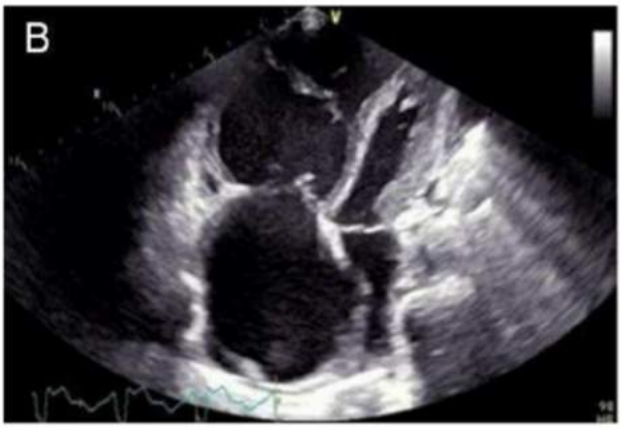


Figure 14. Echocardiogram, A,B,C

Dilated Right ventricle compressing the left ventricle causing 'D' shaped left ventricle[30,31].



VENTILATION PERFUSION SCAN:

It is ideal and more specific in diagnosing pulmonary hypertension due to CTEPH. Segmental or large perfusion defects occur during the VP scan. If the CTEPH is still inconclusive, an invasive contrast pulmonary angiogram must be performed showing pouches, tissue, ligaments, and even complete vascular occlusion.

LUNG FUNCTION TEST:

In Group 1 PAH there will be a moderate pattern of lung restriction so it may be evident on the lung function test. In patients with scleroderma, there is a decreased diffusion capacity of carbon monoxide, which is a warning sign of the development of pulmonary arterial hypertension.

CARDIAC MAGNETIC RESONANCE IMAGING (CMRI):

It is not useful in diagnosing PAH, but helps in assessing the right ventricular function and also in assessing the CHD. Right ventricular ejection fraction less than 35% on CMR is predictive of mortality

OXIMETRY:

A overnight oximetry is done in identifying the patient with obstructive sleep apnea. Formal polysomnography is done in patients with desaturation at night.

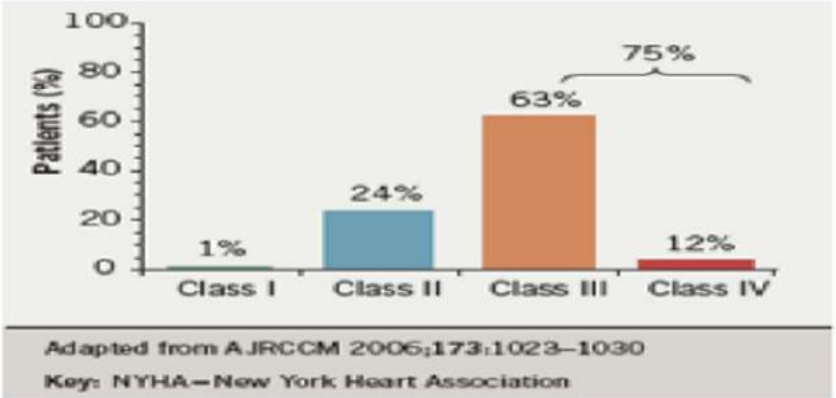
FUNCTIONAL EVALUATION:

Functional evaluation based on disease progression or response to treatment is based on the 6-minute Hall walk (6 MW). It is one of the prognostic indicators used to assess patients with PAH. It is still under research but is still the primary endpoint in clinical trials evaluating the PAH.

The WHO gave the functional classification of patients for pulmonary hypertension similar to the NYHA. Is useful in initial assessment, further prognosis, and response to treatment.

Table 2 – World Health Organization functional classification for pulmonary hypertension

Functional class	Symptoms
Class I	*Symptoms do not limit physical activity.* Ordinary physical activity does not cause undue discomfort.
Class II	Slight limitation of physical activity. The patient is comfortable at rest, yet experiences *symptoms with ordinary physical activity*.
Class III	Marked limitation of activity. Patient is comfortable at rest, yet experiences *symptoms with minimal physical activity.*
Class IV	Inability to carry out any physical activity. The patient may experience *symptoms even at rest.* Discomfort is increased by any physical activity. Manifest signs of right-sided heart failure.



Adapted from AJRCCM 2006;173:1023–1030
Key: NYHA—New York Heart Association

The other important method for assessing physical performance and gas exchange is by performing cardiopulmonary exercises. The maximum systolic blood pressure of less than 120 mmHg and the maximum oxygen uptake of less than 10.4 ml / kg / min are a poor prognostic indicator.

RIGHT HEART CATHETERISATION:

It is the invasive procedure done at the end, if all other non-invasive procedure proved to be inconclusive but still PAH could not beruled out.

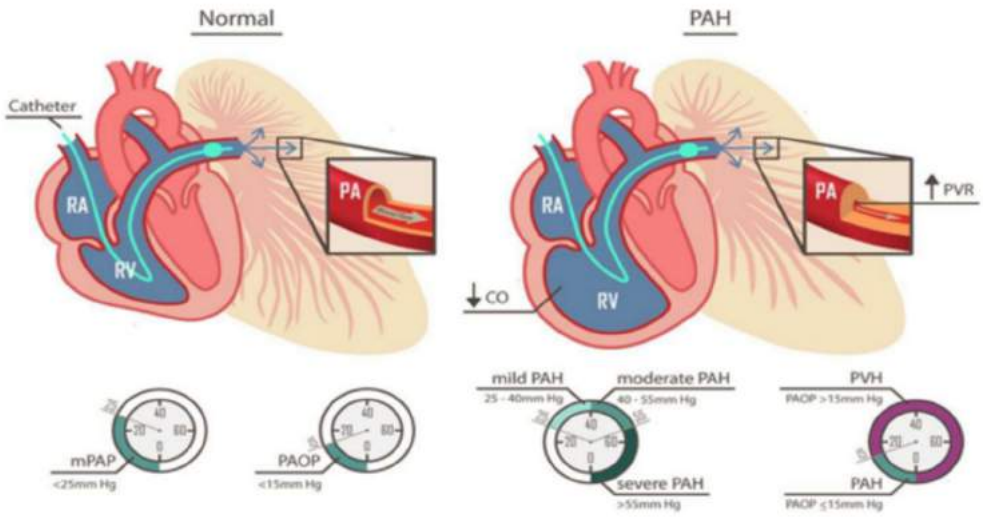
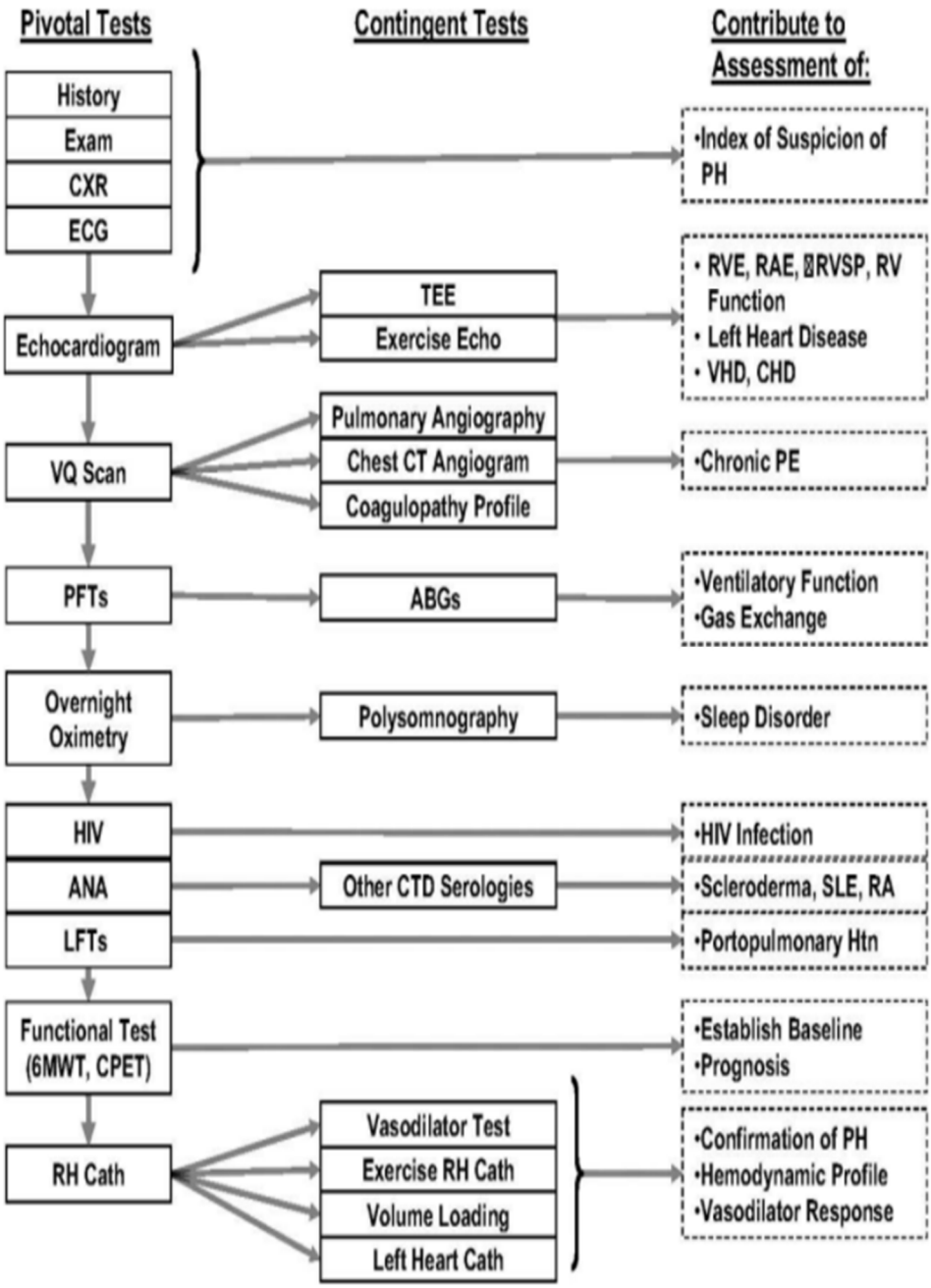


Figure 15. Right Heart Catheterisation

The measurements that are done during the RAH are:

1. Oxygen saturation in SVC, IVC, pulmonary and systemic arteries
2. Right Atrial and Right Ventricular pressure
3. Pulmonary artery pressure
4. Left side filling pressure
5. CO/ cardiac index
6. PVR
7. Systemic blood pressure
8. Heart rate
9. Response to acute vasodilators

The commonest mistake in diagnosing the PAH is misinterpreting the PAWP values. It should be measured at different segments of the pulmonary vasculature and at the end expiration. Acute vasodilator testing should be performed in the patients with IPAH.



TREATMENT:

Goals of the treatment in PAH are to improve the symptoms, right ventricular function, hemodynamics, exercise tolerance and thereby improving the survival.

GENERAL MEASURES:

- Low level graded aerobic exercise is allowed.
- Heavy physical exertion and isometric exercise should be avoided.
- In some patients, intensive pulmonary rehabilitation has proven useful.
- Oxygen therapy to keep satiety at 92% or above. (may not be possible in patients with intracardiac shunt)
- A reduced sodium diet (<2400 mg / day) is particularly advisable for inpatients with right heart failure.
- Influenza and pneumococcal vaccinations are mandatory.

  Hemodynamic fluctuations during pregnancy are very difficult to control and maternal mortality reaches almost 50%. Therefore, it is better to terminate pregnancy in patients with PAH.

ANTICOAGULANTS AND DIURETICS

Anticoagulants are useful in treating patients with PAH, particularly those with idiopathic PAH. Warfarin is the prescribed drug and dosages are adjusted to keep the INR between 1.5 and 2.5

Diuretics are used in patients with right-sided heat failure with volume overload. Care should be taken to ensure that there is no electrolyte imbalance or deterioration in kidney function.

CALCIUM CHANNEL BLOCKER

It is helpful in patients with PAH who respond well to the acute vasodilator test. A positive response to this test is defined as a drop in mPAP from at least 10 mmHg to an mPAP of 40 mmHg or less with unchanged or increased CO.

Patients who met these criteria but did not improve on this drug should not be considered chronic responders and should seek alternative PAH therapy. IPAH responds to calcium channel blockers in some patients (<7%). Drugs used are nifedipine, diltiazem and amlodipine38. Verapamil should be avoided because of its negative inotropic effects.

PROSTANOIDS

The missing or reduced prostacyclin synthase in PAH is one of the most important pathophysiological mechanisms. Prostacyclin I2, a vasodilator with an antiproliferative effect, is not synthesized in PAH39.

Many treatment protocols aim at this. Frequently used prostanoids are: 40 epoprostenol continuously intravenously, dosage at the beginning of 2 ng / kg / min and can be titrated up with a maximum dose of 25 40 ng / kg / min40,41,42.

Treprostinil inhaled continuously subcutaneously, intravenously and intermittently.

The maximum dosage is 75 150 ng / kg / min43,44,45. Iloprost inhaled intermittently46. Inhaled prostacyclin analogs show superior results in improving pulmonary hemodynamics and functional capacity, and also in reducing the worsening of pulmonary hypertension.

Endothelin Receptor Antagonist:

Endothelin-1 is a potent vasoconstrictor that contributes to the pathogenesis of PAH. The endothelin receptor antagonists commonly used in the treatment of PAH are:

1. Bosentan It is helpful and highly effective in patients with congenital systemic pulmonary shunts and eisenmenger physiology. After drug

therapy, there are improvements in PVR, mPAP and 6 MW distance, and there is also no deterioration in oxygen saturation. Liver function monitored.

2. Ambrisentan Like bosentan. Liver dysfunction is not that significant.

3. Macitentan It is used at a dosage of 3 mg or 10 mg per day.

PHOSPHODIESTERASE INHIBITORS:

Disruption of the cyclic guanosine monophosphate (cGMP) pathway due to reduced NO synthesase is the other pathogenesis of PAH. PDE5 inhibitors like Sildenafil 20 mg three times a day help to inhibit the hydrolysis of cGMP, thereby improving the symptoms of PAH51. Tadalafil is another drug that is given as a single 40 mg dose.

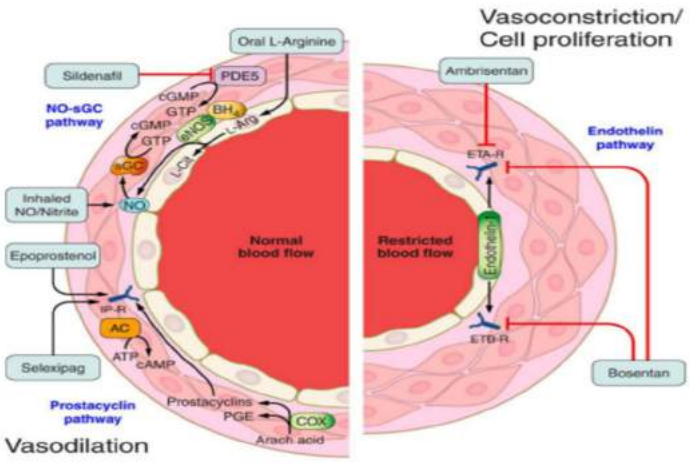


Figure 17. Sites of drug action in Pulmonary Vasculature

INTERVENTIONAL THERAPIES:

1. Atrial septostomy: It creates an increased right-to-left interatrial shunt and decreases the filling pressure of the right heart, thereby improving the symptoms of PAH.
2. Graduated balloon dilatation of the oval fossa is the other procedure
3. Transplant Lung or heart-to-lung transplant is used as a last resort.

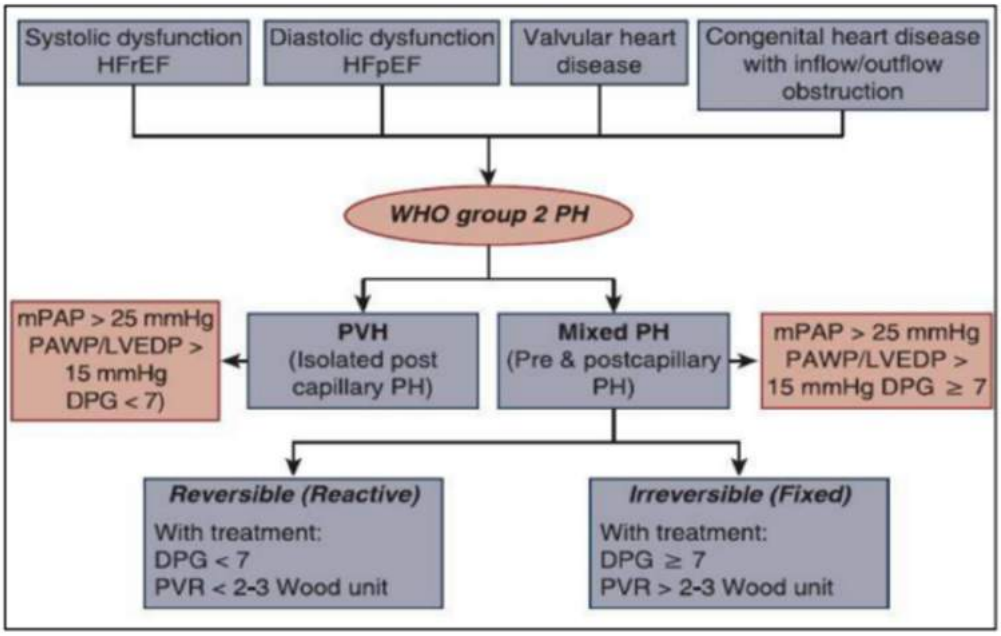
GROUP 2. PULMONARY HYPERTENSION DUE TO LEFT SIDE HEART DISEASE:

The presence of chronic left ventricular systolic or diastolic dysfunction or valve lesions leads to a sustained increase in left atrial pressure there due to passive re-transfer of pressure into the topulmonary veins.

Characterized by an increase in pulmonary artery wedge pressure of more than 15 mmHg, with normal transpulmonary gradient and pulmonary venous resistance.

Common causes are mitral and aortic valve diseases, pericardial diseases, cardiomyopathies, left ventricular dysfunction, age-related changes. Of all heart failure, the received ejection fraction (HFpEF) is the more common cause today.

Figure 18. Management of Group 2 PHT



DIAGNOSIS:

HFpEF is the most common cause and is often confused with IPAH in diagnosis. It occurs in patients older than Group 1. Orthopnea, paroxysmal nocturnal dyspnea are pathognomonic.

Figure 19. Difference between PAH & HFpEF

CHARACTERISTIC	PAH MORE LIKELY	HFPEF MORE LIKELY
Age	Younger	Older
Comorbid conditions—DM, HTN, CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms—PND, orthopnea	Often absent	Often present
Cardiac examination	RV heave, loud P_2, TR murmur	Sustained LV impulse, LS4
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, atrial fibrillation, no RAD
Natriuretic peptides	Often elevated	Often elevated
Echo—LAE, LVH	Absent	Often present
Echo—diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo—right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo—pericardial effusion	Sometimes	Rare

Chest X Ray – pulmonary vascular congestion, interstitial edema on radiograph

CT Chest – Mosaic perfusion pattern and ground glass opacities

ECG – Left ventricular and atrial enlargement, atrial fibrillation.

Echocardiogram – Left ventricular hypertrophy, left atrial enlargement and Doppler showing diastolic dysfunction.

Two types of hemodynamic profiles are observed:

1. Increase in pulmonary artery pressure with only a small increase in the transpulmonary gradient (mPAP - PAWP). A high systolic pressure is created in the preserved right ventricle in order to maintain sufficient forward blood flow. Therefore a moderate pH value is characteristic and favorable.
2. Some patients have increased pulmonary artery pressure due to reactive pulmonary vasoconstriction. They show a characteristic increase in diastolic pressure in the pulmonary artery.

TREATMENT:

1. Treat the underlying cause.
2. Blood pressure to be controlled.
3. Volume management.
4. Sodium Restriction Diet.
5. Comorbid diseases like obesity. Diabetes can be treated.
6. Maintain sinus rhythm as these patients do not tolerate atrial fibrillation.
7. No role in PAH-specific therapy.

GROUP 3:

PULMONARY HYPERTENSION CAUSED BY CHRONIC RESPIRATORY DISEASES:

Chronic lung disease results in alveolar hypoxia, which leads to pulmonary vasoconstriction and remodeling, which leads to pulmonary hypertension. In general, the mPAP in airway pathology is less than 40 mmHg, i.e. less than 40 mmHg. H. mild to moderate pulmonary hypertension. Severe pulmonary hypertension is rare

The progression of the natural history of pulmonary hypertension is small (0.5 mmHg / year) in patients with COPD.

Echocardiographic screening in patients with COPD is difficult and therefore the severity could not be assessed. mPAP correlates inversely with PaO2. With the knowledge of FEV1, PaO2 and mPAP, the patients could be divided into 4 groups, namely

1. Normal mPAP, moderately low FEV1 and PaO2.

2. Moderate mPAP and PaO2, greatly reduced FEV1.

3. High mPAP, greatly reduced PaO2, FEV1.

4. Severe mPAP and greatly reduced PaO2 and moderate reduction in FEV1.

The last group has high FEV1 and mPAP, but lower PaO2 than the other groups, which suggests a change in the pulmonary vasculature. These patients may have other comorbidities that favor diastolic and systolic

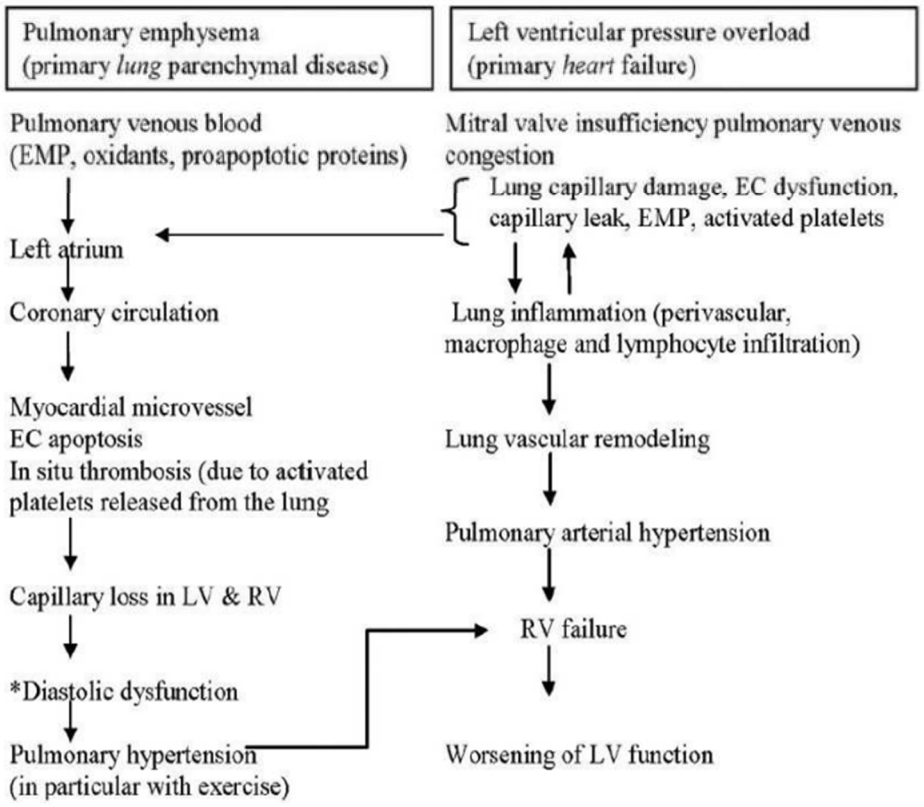
dysfunction, obstructive sleep apnea, etc. These patients have severe exertional dyspnea and a poor prognosis than other COPD patient.

DIAGNOSIS:

Since patients have nonspecific signs and symptoms of cardiac and respiratory pathology, it is difficult to distinguish the two. Spirometry, arterial blood gas analysis, and diffusion capacity for carbon monoxide are important for the diagnosis. The BNP is also elevated, but it can occur in both left and right heart failure. Doppler echocardiography 48 is suboptimal for diagnosing COPD-induced PH.

However, the gold standard in PH diagnosis is the RHC, which determines precapillary PH and hemodynamic severity without the postcapillary component. It is always important to keep an eye on the comorbidities like left heart failure, obstructive sleep apnea, etc. as they also contribute to the clinical findings.

Figure 21. PH due to Cardiac & Lung Disorder



TREATMENT:

Smoking cessation is very important and is primarily intended to prevent further disease progression. Long-term oxygen therapy is helpful and leads to a decrease in mPAP. Pharmacological drugs such as calcium channel blockers, PDE5 inhibitors are tried, but they have a deleterious effect on alveolar gas exchange.

The ideal management for end-stage disease is a lung transplant. Even PH from other lung conditions such as sarcoid, interstitial lung disease, pulmonary Langerhans cell histiocytosis, and lymphangioleiomyomatosis all lead to end-stage lung disease that warrants a lung transplant.

GROUP 4. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

It is a curable form of pulmonary hypertension that often requires surgical treatment. It is diagnosed by certain findings that persist after 3 months of continuous anticoagulant therapy. These findings include at least one segmental perfusion defect observed on CT angiography or lung scanning and the presence of precapillary pulmonary hypertension. CTEPH is due to a pulmonary embolism that occludes the main pulmonary arteries.

An incidence of 3 to 30 million people is often misdiagnosed. Errors mainly due to referral errors, difficulties in diagnosing pulmonary hypertension in acute pulmonary embolism due to the lack of specific symptoms in the acute stage. Acute venous thromboembolism is an independent risk factor. Prothrombotic factors lupus anticoagulant, antiphospholipid antibodies, factor 8 are associated with it.

Due to hypercoagulation, an increase in platelet count and the inability to break down fibrinogen contribute to the obliteration of the pulmonary arteries. The median age at diagnosis is 63 years and occurs equally in both sexes.

DIAGNOSIS:

Nonspecific signs and symptoms of right heart failure such as edema, flat stomach are found. In contrast to IPAH, these patients have haemoptysis; a disease exists if risk factors are suspected. Imaging procedures such as CT and ventilation perfusion scan help with the diagnosis.

The presence of at least one defect that affects more than half of a lung segment is diagnostic in the ventilation perfusion scan. However, some patients may have non-segmental and minor defects, particularly with PAH and PVOD. RHC shows a precapillary PH. The prognostic indicator after the operation is the PVR.

Contrast enhanced CT shows stenosis, complete obstruction, arterial wall irregularities, pulmonary artery tissue and ligaments.Lateral selective pulmonary angiography in both the anteroposterior and lateral 51 views helps assess proximal segment involvement and assess surgical accessibility.

TREATMENT:

Surgery is the treatment of choice at CTEPH. Embolectomy and pulmonary endarterectomy are the surgical procedures performed at CTEPH. Based on the preparation, it can be divided into four types:

Type I: Involved main and pulmonary arteries with red thrombus and white obstruction.

Type II: intimal thickening and fibrosis in proximal to segmental arteries.

Type III: Thickening, fibrosis and intimal tissue with involvement of the distal segmental and subsegmental arteries.

Type IV: Microscopic distal arteriolar vasculopathy with no visible thrombus.

Type IV is not functional.

Operable criteria:

NYHA functional class II, III or IV.

Preoperative PVR of more than 300 dyn-s.cm-5.

Surgical accessibility of thrombi in main, lobar or segmental arteries most patients are relieved of symptoms and normal hemodynamic stability occurs.

Medical treatment has also been attempted at CTEPH61 and are life-long anticoagulants with vitamin K antagonists, diuretics, and oxygen supplementation.

The soluble guanylate cyclase stimulator riociguat helps improve 6 MW and PVR.

GROUP 5.

PH WITH SMALL OR MULTIFACTORIAL CAUSE:

Several mechanisms contribute to the pathogenesis of pulmonary hypertension, such as:

Splenectomized individuals, either post-traumatic or post-haematological, favor the development of distal CTEPH or IPAH. Some haemolytic anemias such as sickle cell anemia62 and beta-thalassemia are associated with PH.

They can cause postcapillary PH from hyperdynamic circulation or precapillary PH from pulmonary vasculature. Most commonly associated with sickle cell anemia, the incidence is 6%.

Systemic diseases:

Sarcoid: It is a chronic granulomatous disease of unknown etiology. It causes fibrosis of the pulmonary capillary bed leading to hypoxia. Since the degree of severity is disproportionate to the degree of destruction, other causes such as cardiac sarcoidosis, mediasternal lymphadenopathy, which causes compression of the pulmonary vessels, etc. were considered. Tried treatment with steroids63.

Pulmonary Langerhans Cell Histiocytosis:

Although it is a rare condition, it is seen in younger people with a history of smoking. Causes parenchymal destruction and changes in vasculopathy. Bad prognosis. Treatment consists of a lung transplant64.

Other systemic diseases, such as lymphangioleiomyomatosis and neurofibromatosis, have also been linked to PH with several unclear causal mechanisms.

Metabolic diseases:

Enzyme deficiency diseases such as type 1 a glycogen storage disease due to a glucose-6-phosphate deficiency, Gauchers disease due to a 54 lysosomal B-glucosidase deficiency can cause thromboembolic or restrictive lung disease which is due to pulmonary hypertension

Miscellaneous:

Rare conditions like pulmonary artery sarcomas, metastatic tumor emboli from breast,lung or gatric cancers, fibrosing alveolitis, end stage liver disease on lomg term haemodialysis are also associated with pulmonary hypertension.

Platelets:

They are auclear small (3.0 x 0.5 m) disc-shaped cells, fragmented from megakaryocytes that are stimulated by thrombopoietin produced by the liver65. These stimulated megakaryocytes go through an endomitosis and send out cytoplasmic projections called propellets. Each megakaryocyte produces 1,000 to 2,000 platelets. The normal cytoplasmic volume of the pallets is 7 fl. Due to the abundance of cytoplasm, younger platelets are larger than those in the circulatory system. They are

sometimes counted with red blood cells due to their larger size. The half-life of platelets is 8 to 10 days

Platelet morphology:

The approximately 1 trillion platelets that circulate in an adult human are small, anucleate cell fragments that are adapted to adhere to damaged blood vessels, aggregate with one another, and facilitate the formation of thrombin strength through the action of thrombin, the fibrinogen into strands of fibrin converts. To accomplish these tasks, platelets have surface receptors that can bind adherent glycoproteins; These include the GPIb / IX / V complex, which supports platelet adhesion by binding the von Willebrand factor, especially under conditions of high shear, and the IIb3 (GPIIb / IIIa) receptor, which is platelet-specific and platelet aggregation by binding of fibrinogen and / or of conveys the Willebrand factor.

Other receptors for adhesive glycoproteins (integrin 21 [GPIa / IIa], GPVI and maybe others for collagen; integrin 51 [GPIc * / IIa] for fibronectin; integrin 61 [GPIc / IIa] for laminin and CLEC-2 for podoplanin) also contribute to platelet adhesion, but their precise contributions are less well defined. Activated platelets express both surface P-selectin, which mediates interactions with leukocytes, and CD40 ligand, which activated a Number of proinflammatory cells and release

chemokines and a soluble form of the CD40 ligand, thereby initiating an inflammatory response.

Platelet coagulation activity results from exposure to negatively charged phospholipids on the surface of platelets and the generation of platelet microparticles along with the release and activation of platelet factor V and possibly exposure of specific receptors for activated coagulation factor. Platelets change shape when activated as a result of a complex reorganization of the platelet membrane skeleton and cytoskeleton.

Upon activation, the platelets release granules, dense bodies, and lysosomes, the contents of which restore vascular integrity. The activation process includes a number of receptors for agonists such as adenosine diphosphate, epinephrine, thrombin, collagen, thromboxane A2, vasopressin, serotonin, platelet activating factor, lysophosphatidic acid, sphingosine-1-phosphate and thrombospondin, as well as multiple metabolic pathways including phosphine, Arachidonic acid release and conversion to TXA2 and phosphorylation of a number of different target proteins. Elevations in intracellular calcium result from and further contribute to platelet activation. Platelet activation leads to a change in the conformation of the integrin IIb3 receptor, which leads to high-affinity ligand binding and platelet aggregation.

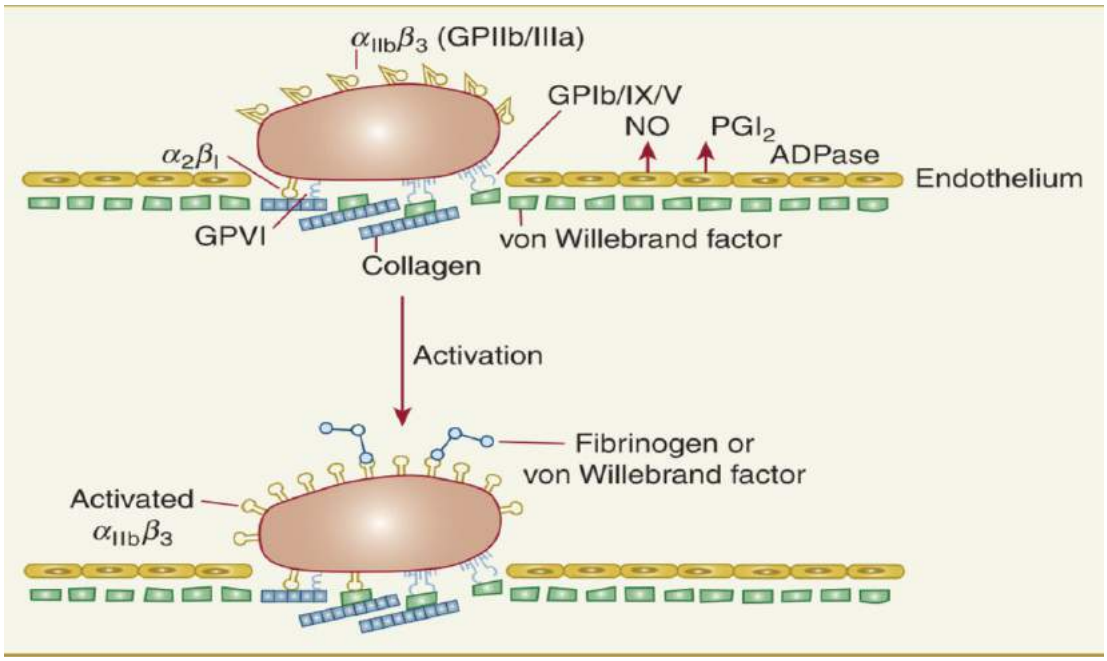
OVERVIEW OF PLATELET ADHESION, AGGREGATION, AND PLATELET THROMBUS FORMATION

The hemostatic system is under sophisticated controls so that the response is either not inadequate to meet the haemorrhagic challenge or results in inappropriate thrombosis in response to a trivial provocation. Developmental pressures likely favoured a more active hemostatic system. Active hemostatic systems were more likely to prevent death from bleeding prior to sexual maturity or in connection with childbirth. Our active hemostatic system may be less well adapted to our modern age, which is characterized by long lifespan and progressive vascular disease, since the deposition of a platelet-fibrin thrombus on a damaged atherosclerotic plaque is the cause of most myocardial infarctions and many strokes The main function of the platelets is to close openings in the vascular tree.

It is therefore appropriate that the initiating signal for platelet deposition and activation is exposure of the underlying parts of the blood vessel wall that are normally hidden from circulating platelets by an intact endothelial lining (Fig. 112-1) .1 Other parameters likely to be the platelet response control are: (1) the depth of the injury, with deeper damage exposing more platelet-reactive materials and tissue factors (2) the vascular bed, where the blood vessels serve mucosal tissues that are particularly dependent on blood platelets for haemostasis, in contrast to the vascular beds in muscles and joints.

(4) the haematocrit, as an increased number of erythrocytes increases the platelet interactions with the blood vessel wall by forcing the platelets into the periphery of the bloodstream (since the erythrocytes occupy the axial area disproportionately) by adding radially directed energy to the platelets when the erythrocytes in flip-flop movements and possibly by releasing the platelet activator adenosine diphosphate (ADP) at points of vascular injury24; and (5) the rate of blood flow and the size of the blood vessel which determines the number of platelets that pass a single point in a given time interval, the length of time it takes for a platelet to interact with the blood vessel wall or other platelets that The rate of dilution of platelet activating agents and the forces that tend to pull a platelet off the vessel wall or another platelet (shear rate) .2,46 The vasospastic response associated with vascular injury to which the platelets are caused by the release of thromboxane (TX) A2 and. Serotonin, believed to play a key role in reducing bleeding and facilitating platelet and fibrin deposition via its effect on blood flow

A


$\alpha_{IIb}\beta_3$ (GPIIb/IIIa)
GPIb/IX/V
NO
PGI_2
ADPase
$\alpha_2\beta_1$
Endothelium
GPVI
von Willebrand factor
Collagen
Activation
Fibrinogen or
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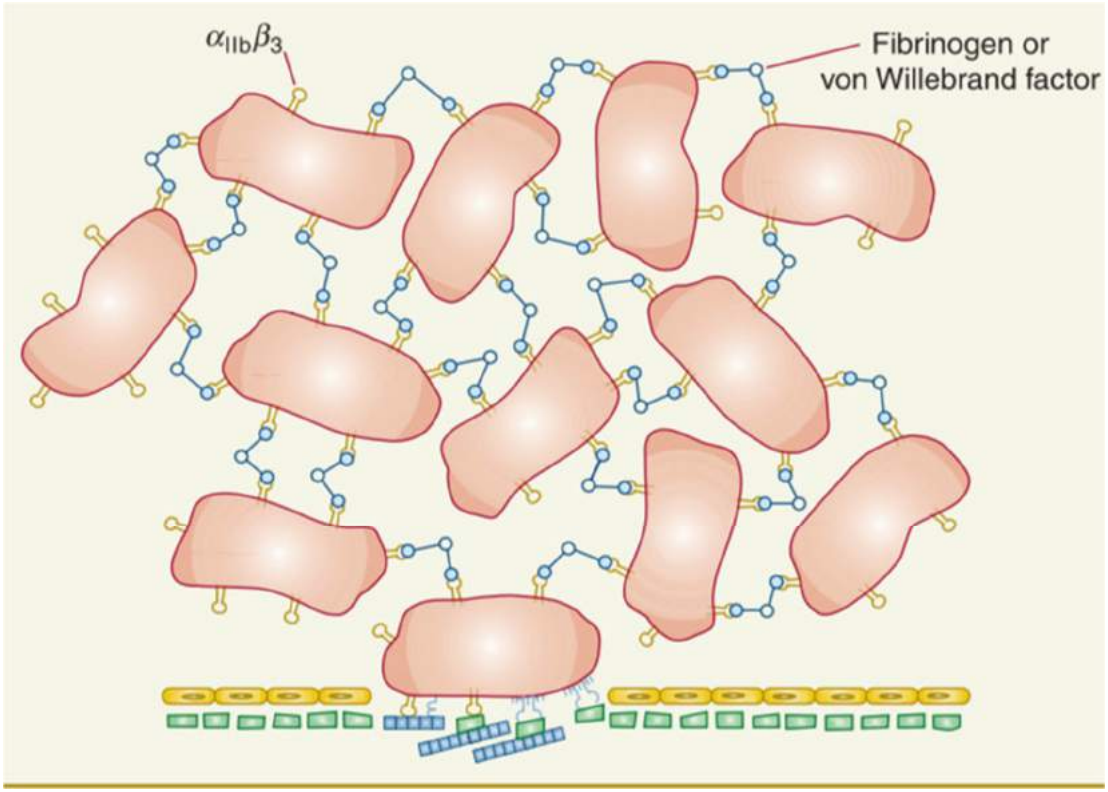
Activated
$\alpha_{IIb}\beta_3$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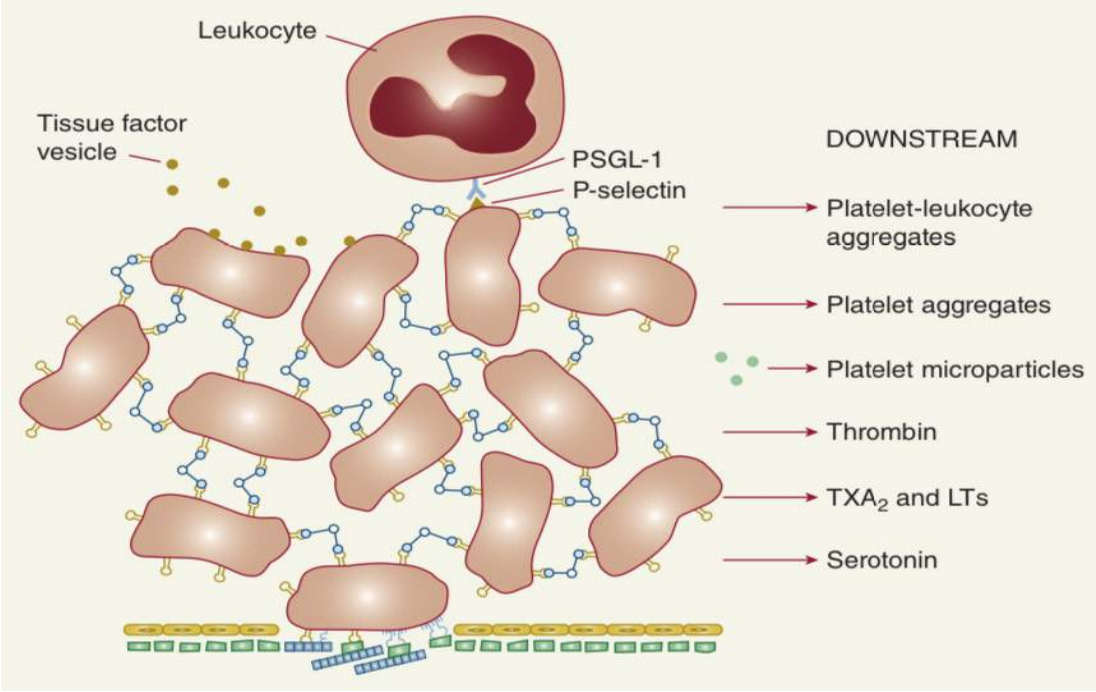


Platelets also interact directly with exposed collagen, including types I, III, and VI, via GPVI and integrin (GPIa / IIa) or perhaps one or more of the many other receptors involved in platelet-collagen interactions (e.g., CD36 [GPIV], p65) .1729 The interaction of blood platelets with collagen is most pronounced at relatively low shear rates. Depending on the vascular bed, the adhesive glycoproteins available, and the shear conditions, it is likely that various combinations of platelet receptors, including GPIb, integrin 21 (GPIa / IIa), GPVI, and integrin IIb3, work together to transform the tethering and slow translocation of platelets, initiated by the interaction of GPIb with VWF resulted in stable platelet adhesion. For platelet plug formation to occur, the platelets must undergo both activation and adhesion.

The adhesion of platelets to subendothelial structures, particularly VWF at high shear, can itself lead to platelet activation, including the formation of TXA2, the release of ADP and serotonin, and the activation of the integrin IIb3 receptors on the luminal side of the platelets, see above that they adopt their high affinity ligand binding conformation. These positive feedback mechanisms ensure an adequate hemostatic response. Depending on the type of surface they adhere to, platelets also go through different spreading reactions and are anchored through a process that at least partially involves integrin IIb3 ligation and clustering, resulting in external signal transmission, reorganization of the cytoskeleton and leads to tyrosine phosphorylation; these reactions also help initiate the release reaction.

The binding of adhesive ligands to platelet receptors then repeats itself, resulting in the recruitment of additional platelet layers and ultimately the formation of a hemostatic plug. Intravital video microscopy of the mesenteric and cremasteric circulation of mice after endothelial cell damage shows that platelet thrombus formation, at least in these vascular beds, is initially a very dynamic process in which many platelets are deposited, but then embolize. The thrombus grows relatively slowly compared to how it was Growth would be if all of the deposited platelets adhered to the surface.

The integrin αIIbβ3 receptor occupies a central role in determining the extent of platelet aggregation, in part because it is present at an extraordinarily high density on the platelet surface (approximately 50,000 receptors per platelet, such that receptors are probably less than 20 nm apart). This permits it to rapidly initiate platelet aggregation. On the other hand, the receptor is not in its high-affinity ligand-binding state on resting platelets but rather needs to be activated by agonists, including ADP, serotonin, thrombin, collagen, and TXA, that are localized to sites of vascular injury.

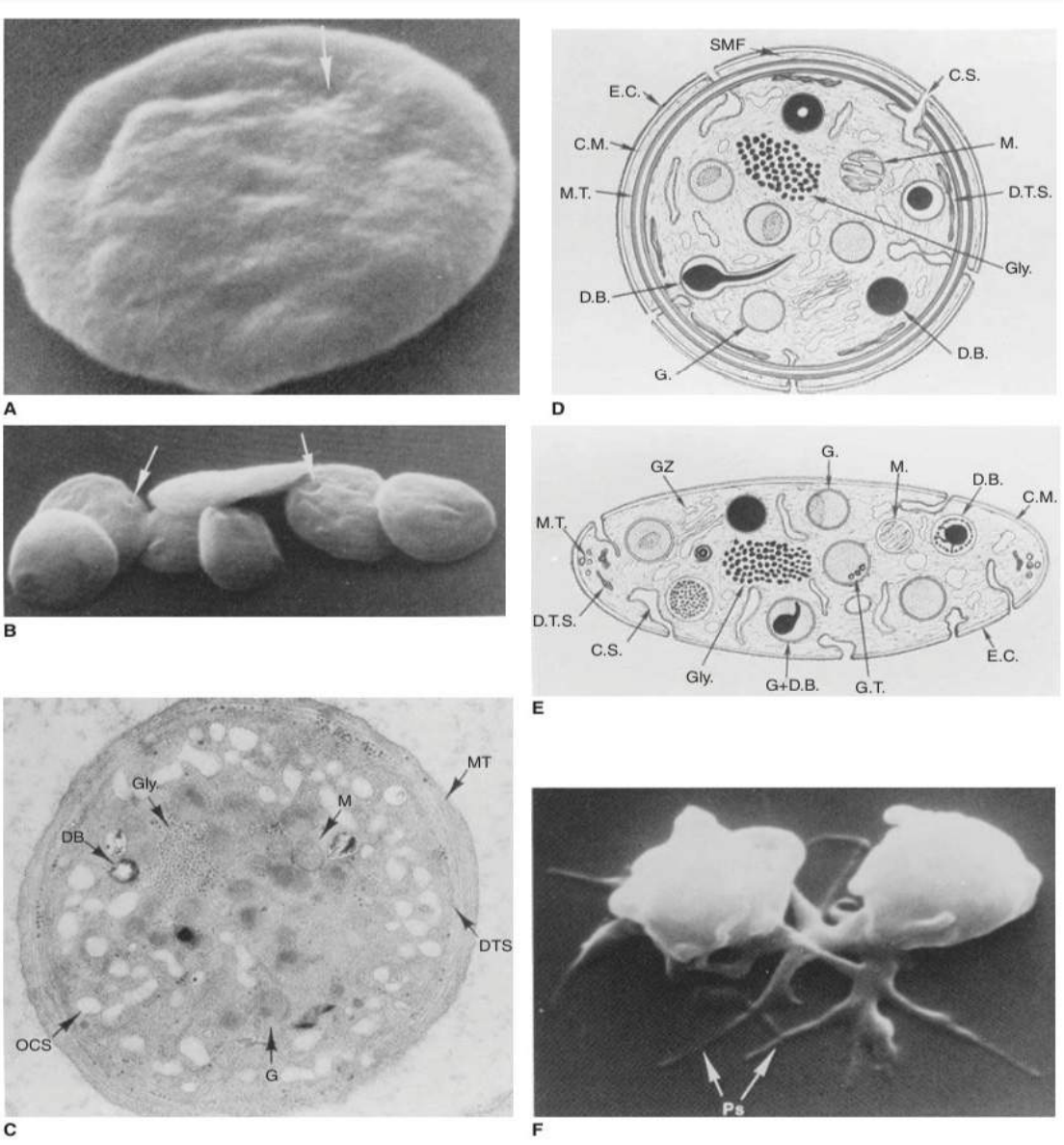
As a result, platelets can circulate in plasma containing high concentrations of the integrin αIIbβ3 ligands fibrinogen and VWF without ongoing platelet thrombus formation. The agonists that activate the integrin αIIbβ3 receptor are likely to work in combination in vivo. In fact, the mixture of agonists present is likely to change as the process unfolds, with collagen perhaps more important at the beginning, thrombin more important later on, and the other agonists in varying mixtures throughout. The platelet activation effects of multiple agonists may be additive or synergistic, depending on the mechanism(s) involved.

PLATELET MORPHOLOGY AND BIOCHEMISTRY

MICROSCOPIC APPEARANCE:

On films made from blood that has been anticoagulated with the strong calcium chelating agent ethylenediaminetetraacetic acid (EDTA) and treated with Wright stain, platelets appear as small bluish-Gray, oval to round cell fragments with several purple-red granules. The mean diameter of the platelets varies in different individuals and ranges from about 1.5 to 3.0 m, about one third to one fourth the diameter of the red blood cells. There is also considerable variability in the size of platelets in a single individual, with platelets in normal blood samples occasionally having diameters greater than half the diameter of erythrocytes. Overall, the platelet size appears to follow a logarithmic normal distribution with an average volume of approximately 7 fL. When non-anticoagulated blood is used to form blood films, platelets are subject to variable activation and spreading, and therefore platelet aggregates are often observed; Platelets from such specimens may have three or four very long finger-like appendages extending from the body of the platelet (filopodia), and some platelets may be free of granules. Indentations on the platelet surface are thought to be the openings of the open canalicular system, which is an elaborate channel system composed of invaginations of the plasma membrane that extend throughout the platelet (see Fig. 112–2 and “Membrane Systems” below). The contents of platelet granules can gain

access to the outside when the granules fuse with either the plasma membrane or any region of the open canalicular system. Similarly, glycoproteins contained within granule membranes can join the plasma membrane after granule fusion with either the plasma membrane or the open canalicular system.



PLATELET SECRETION

A complicated pathway of protein-protein interactions has been proposed for platelet secretion, in which granules attach and dock to the inner sail of the plasma membrane, whereupon the fusion of the two opposing lipid bilayers mediates the release of charge. It is assumed that docking and attachment in Part mediated by small GTP-binding proteins of the Rab family. Platelets have been reported to contain at least 11 Rabs, although few have been shown to be functionally relevant. Rab27s a and b are important for both granule biogenesis and secretion, while Rab 4 seems to play a role in secretion.

It has been shown that the granule-associated Rab6 is involved in a protein kinase C (PKC) upon thrombin stimulation. -dependent way is phosphorylated and phosphorylation appears to increase its GTP load. Platelet granule–plasma membrane fusion is analogous to exocytosis in neurons, where detailed studies have shown the importance of a core set of integral membrane proteins called soluble N-ethylmaleimidesensitive factor (NSF) attachment protein receptors (SNAREs). It is generally accepted that vesicle/granule-target membrane fusion is governed by the binding of a SNARE from the cargo-containing granule or vesicle (v-SNARE), with a heteromeric protein complex in the target membrane (t-SNAREs).

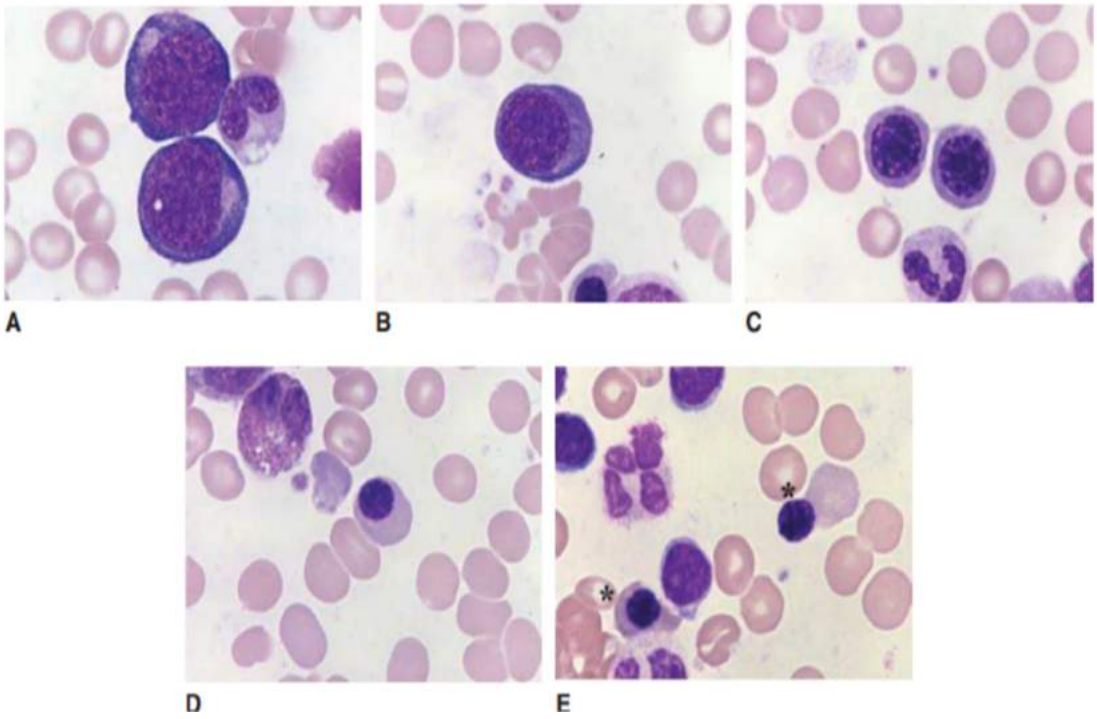
The resulting, trans-bilayer complex is minimally sufficient for membrane fusion. In human platelets, the v-SNAREs are vesicle-associated membrane protein (VAMP)-2/synaptobrevin, VAMP-3/cellubrevin, VAMP-7/TI-VAMP, and VAMP-8/endobrevin, with the latter being most abundant. There are two classes of t-SNAREs: the synaptosome-associated protein (SNAP)-23/25/29 type and the syntaxin type. Human platelets contain the syntaxins 2,4,7 as well as SNAP-23, -25 and functional studies with in vitro assays and genetically engineered mice have shown that VAMP-8 is the primary v-SNARE. is required for secretion from all three classes of granular platelets. VAMP-2 or VAMP-3 can also play a role with higher stimulation strengths. As with t-SNAREs, SNAP-23 and Syntaxin 2 are required for every secretion event. Syntaxin 4 also appears to play a role, but only in granule and lysosome release.

ERYTHROID PROGENITORS AND PRECURSORS

Early Progenitors

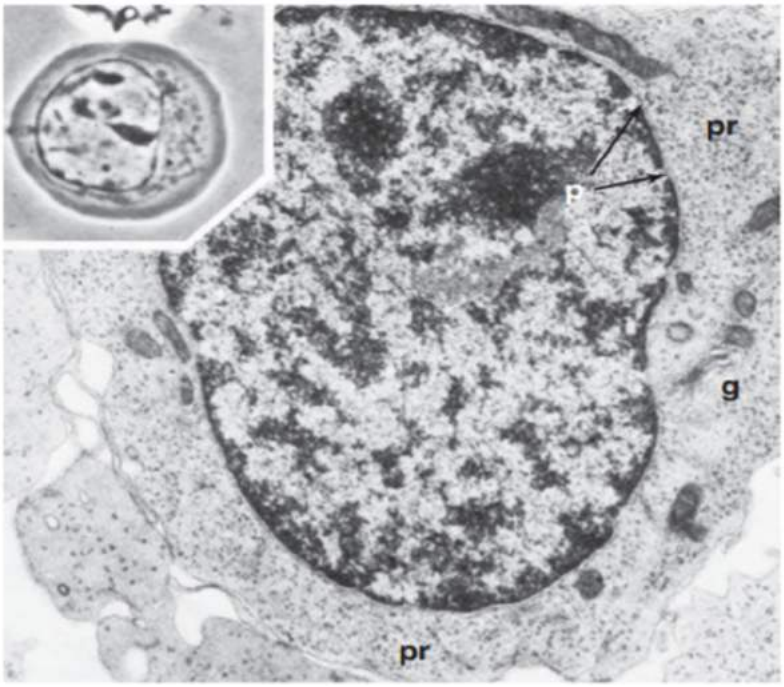
A precursor in the hematopoietic system is defined as a marrow cell which, through the differentiation process, is a derivative of the pluripotent hematopoietic stem cell and precedes a progenitor cell, the latter being identifiable by its morphological feature using a light microscope In erythropoiesis, the earliest precursor is proerythroblast. Erythroid progenitor cells are identified as marrow cells capable of forming erythroid colonies in vitro in semi-solid medium under conditions in which the

appropriate growth factors are present. Progenitor cells can also be identified by characteristic profiles of surface CD antigens using flow cytometry. Numerically, erythroid precursors, BFU-E and CFU-E, represent only a tiny fraction of human bone marrow cells. BFU-E range from 300 to 1700 mononuclear cells and CFU-E range from 1500 to 5000 106 mononuclear cells. 5 In vitro cultures with CD34 + cells from blood, umbilical cord blood and bone marrow as starting material have identified the critical cytokines, required for the differentiation and maturation of erythrocytes and enabled the identification and isolation of pure cohorts of erythroid precursors and erythroblasts in all stages of terminal erythroid maturation.



Basophils Erythroblasts

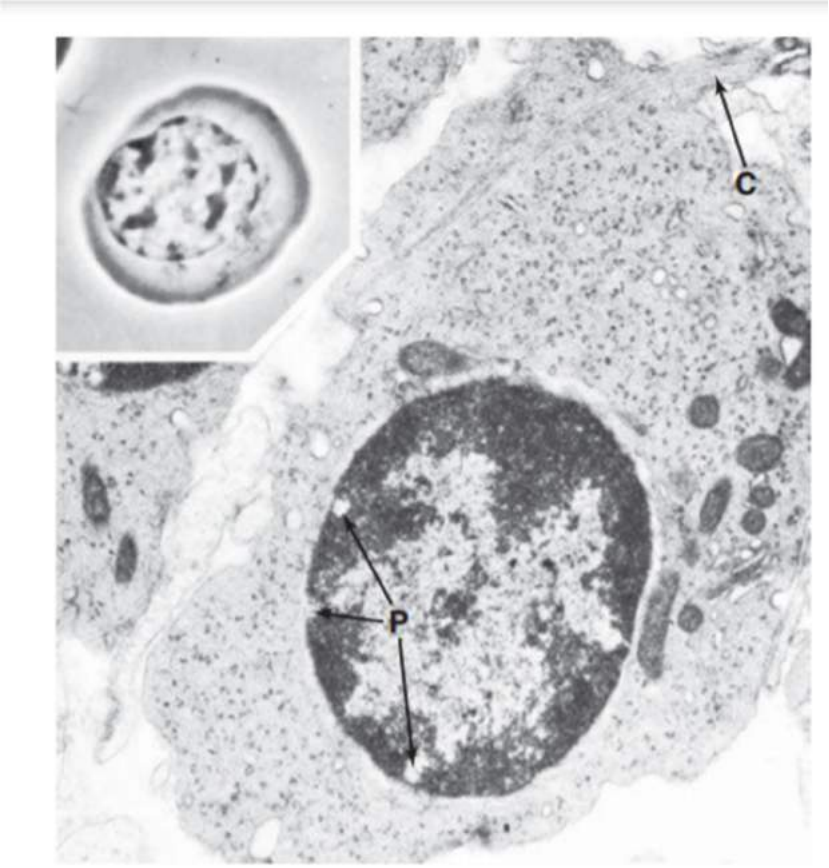
Basophils are smaller than pro-erythroblasts. The core takes up three-quarters of the cellar and consists of characteristic dark purple heterochromatin interspersed with pink-colored clumps of euchromatin connected by irregular strands.13 The entire arrangement often resembles wheel spokes or a dial. The cytoplasm turns deep blue and leaves a perinuclear halo that expands around the Golgi apparatus to form a juxtanuclear clear zone. Cytoplasmic basophilia at this stage results from the persistent presence of polyribosomes.



Polychromatophilic Erythroblasts

After the mitotic division of the basophilic erythroblast, the cytoplasm changes from deep blue to gray, as hemoglobin dilutes the polyribosome content. Cells at this stage are smaller than basophilic

erythroblasts. The cell nucleus takes up less than half of the cell area. The heterochromatin is found in well-defined clumps that are regularly distributed around the nucleus.

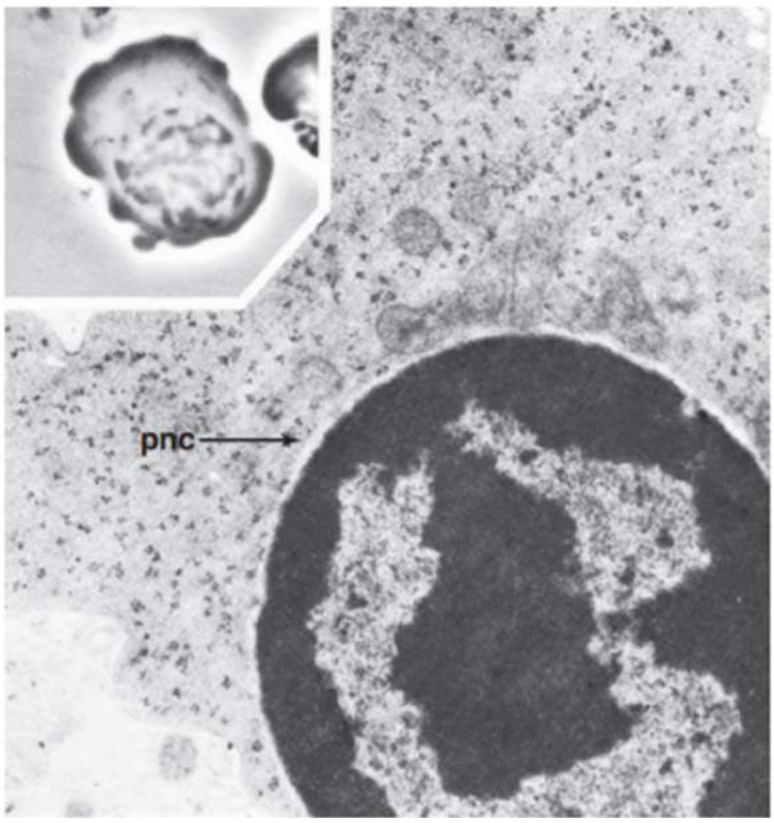


Polychromatophilic erythroblast

Orthochromic (syn. Orthochromatic) erythroblasts

After the last mitotic division of the erythropoietic series, the hemoglobin concentration within the erythroblasts increases. Under the light microscope, the core appears almost completely dense and structureless. It is measurably reduced. This cell is the smallest of the erythroblastic series.The cell nucleus takes up about a quarter of the cell area and is eccentric. The cell movement can be seen under the phase

contrast microscope. Round projections suddenly appear indifferent parts of the cell periphery and are withdrawn just as quickly. The movements are probably made in preparation for ejection of the thenucleus. The cellular infrastructure is characterized by irregular edges that reflect its mobility. The heterochromatin forms large masses. Mitochondria are reduced in number and size



Orthochromic erythroblast

.

Normal Sideroblasts

All normal erythroblasts are sideroblasts because they contain iron in structures called siderosomes, as seen by transmission electron microscopy. These structures are essential for the transfer of iron for heme

(hemoglobin) synthesis. By light microscopy, under the usual Prussian blue staining conditions for iron, a minority of normal erythroblasts (approx. 15 to 20 percent) can be identified as containing siderosomes, and those that can be so identified have very few (one to four) small Prussian blue positive granules.

Pathological sideroblasts

A heterogeneous group of erythrocyte diseases is accompanied by ineffective erythropoiesis, abnormal erythroblast morphology, and hyperferemia. These diseases include acquired megaloblastic anemia , congenital dyserythropoietic anemia , thalassemia, hereditary and acquired sideroblastic anemia, pyridoxine-responsive anemia, alcohol-induced sideroblastic anemia, and lead intoxication. Some of these conditions are characterized by the presence of pathological sideroblasts.

Pathological sideroblasts are of two types. One type are anerythroblasts, which have an increase in the number and size of Prussian blue stained siderotic granules throughout the cytoplasm. Another type is the erythroblast, which shows ferrous granules arranged in an arc or complete ring around the nucleus. These pathological sideroblasts are known as ring sideroblasts or ring sideroblasts. Electron microscopic examinations show that granules in ring sideroblasts are iron-laden mitochondria. In cells with iron-laden mitochondria, many ferritin molecules are deposited between adjacent erythroblast membranes.

RETICULOCYTE

Birth

Prior to enucleation at the late orthochromatic erythroblasts stage, intermediate filaments and the marginal band of microtubules disappear.

tubulin and actin are concentrated where the nucleus exits. These changes, accompanied by microtubular rearrangements and actin polymerization, play a role in nuclear expulsion. In vitro expulsion of the nucleus is not an instantaneous phenomenon; it takes 6 to 8 minutes. The process begins with several vigorous contractions around the central part of the cell, followed by the cell dividing into unequal parts.

Maturation

After nuclear extrusion, the reticulocyte retains mitochondria, a small number of ribosomes, the centriol and remains of the Golgi apparatus. It does not contain an endoplasmic reticulum. Supravital staining with brilliant cresyl blue or new methylene blue creates aggregates of ribosomes, mitochondria and other cytoplasmic organelles. These aggregates turn deep blue and, arranged in reticular strands, give the reticulocyte its name.

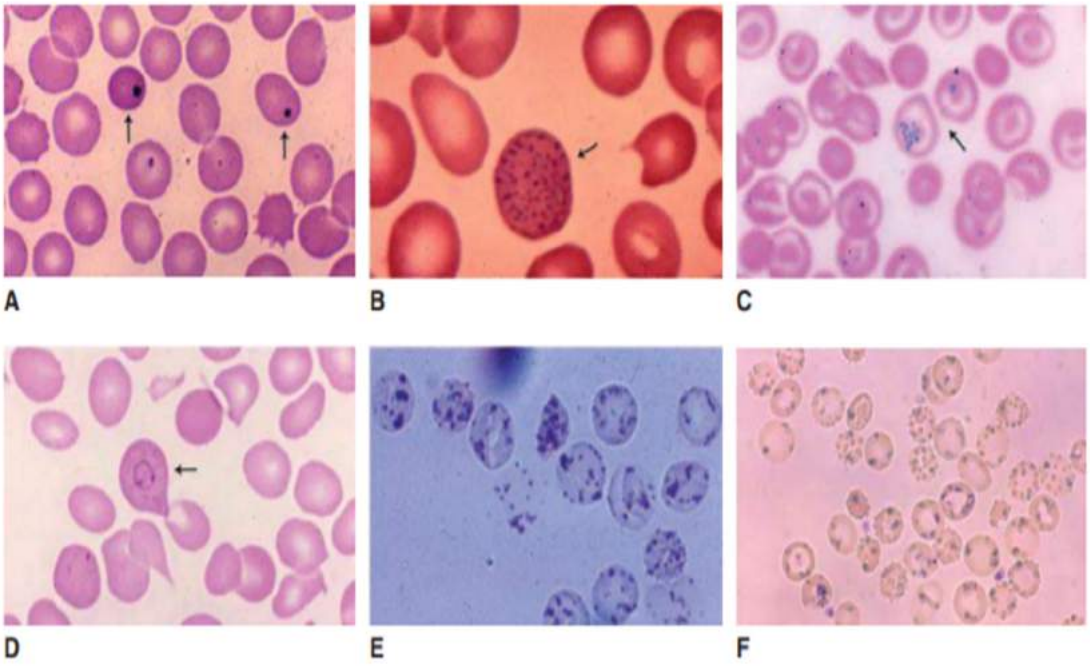
The maturation of the reticulocytes takes 48 to 72 hours. During this time, approximately 20 percent of the membrane surface area is lost and the cell volume decreases by 10 to 15 percent and the final assembly of the membrane skeleton is complete. Living reticulocytes observed by phase

contrast microscopy are irregularly shaped cells with a characteristically warped exterior and texture movable membrane.

When examined by electron microscopy, reticulocytes are irregularly shaped and contain many remaining organelles. The organelles, small smooth vesicles, and occasionally a centriole, are grouped in the area of the cell where the nucleus is expelled. In young reticulocytes, the vast majority of the ribosomes distributed in the cytoplasm are in the form of polyribosomes.

RED CELL INCLUSIONS

Howell-Jolly Bodies Howell-Jolly bodies are small nuclear remnants that have the color of a pyknotic nucleus on Wright-stained films and give a positive Feulgen reaction for DNA.



HowellJolly bodies can be numerous, although generally there is only one. In pathological situations, they appear to represent chromosomes that have separated from the mitotic spindle during abnormal mitosis and contain high levels of centromeric material along with heterochromatin. More often they arise during normal ripening due to nucleus fragmentation or incomplete expulsion of the nucleus. Howell-Jolly bodies are enucleated from reticulocytes as they pass through the interendothelial slits of the splenic sinus. They are characteristically present in the blood of splenectomized individuals and inpatients suffering from megaloblastic anemia and hyposplenic conditions.

Smallpox (or holed) erythrocytes

When viewed by interference phase microscopy, red blood cells with smallpox appear to have surface depressions or craters. The vesicles or depressions that characterize these cells represent autophagic vacuoles that are adjacent to the cell membrane. The vacuoles appear to play a role in clearing up cell debris as the erythrocytes pass through the microcirculation of the spleen. Within a week after the splenectomy, the number of red blood cells in smallpox begins to rise and reaches a plateau after 2 to 3 months. The pocket red blood cell count is sometimes used as a substitute test for spleen function.

Cabot Rings

The ring-shaped or figure-of-eight structures sometimes found within reticulocytes in megaloblastic anemia and in an occasional, heavily spotted late-intermediate megaloblast, are called Cabot rings.40,41 Their composition is nuclear. Some researchers have suggested that Cabot rings are made from spindle material that was mishandled during abnormal mitosis. Others have found no evidence of DNA or spindle filaments, but have shown that the rings are attached to adherent granular material containing arginine-rich histone and non-hemoglobin iron.

Basophilic speckle

The basophilic speckle consists of granules of different sizes and numbers that turn deep blue with Wright's stain. Electron microscopic studies have shown that punctiform basophilia represents aggregated ribosomes.42 As the cells dry and stain postvital, clumps form, similar to how the reticulum in reticulocytes precipitates from the ribosomes during supravital staining. The clumped ribosomes can include forming mitochondria and siderosomes. In conditions such as lead intoxication (Chapter 52), pyrimidine-5-nucleotidase deficiency (Chapter 47) and thalassemia (Chapter 48), the altered reticulocyte ribosomes have a greater tendency to aggregate. As a result, the basophilic granulation appears larger and is referred to as coarse basophilic puncture.

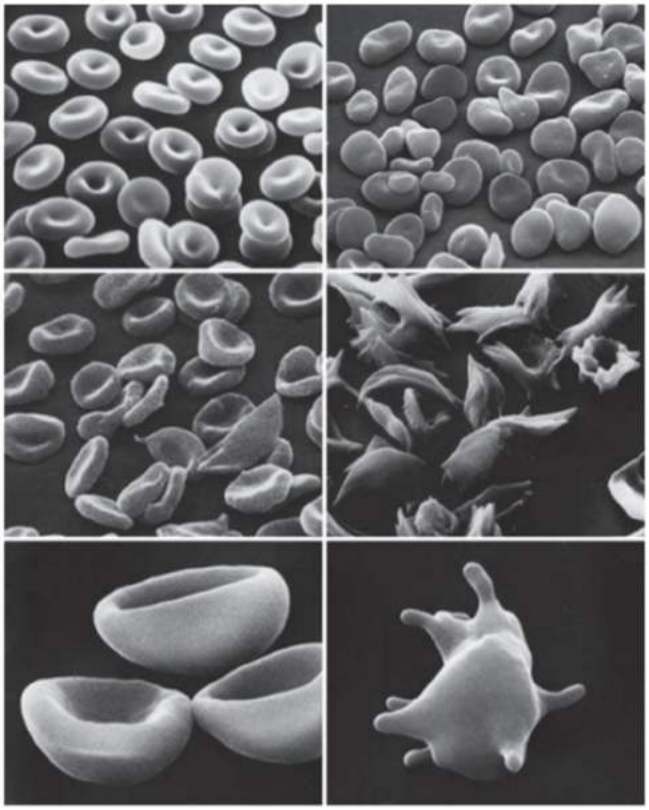
Heinz bodies

They are made up of denatured proteins, mainly hemoglobin, that form in erythrocytes as a result of a chemical attack; with hereditary defects of the hexose monophosphate shunt; in thalassemia (Chapter 48); and in unstable hemoglobin syndromes (Chapter 49) .43 Heinz bodies cannot be seen on normal Wright or Giemsa stained blood smears. Heinzbodies are easily visible in erythrocytes stained supravitally with brilliant cresyl blue or crystal violet and are eliminated when erythrocytes cross the endothelial slits of the spleen sinus.

STRUCTURE AND SHAPE OF ERYTHROCYTES

The membrane is in sufficient excess to allow the cell to swell to a sphere approximately 150 fL or to deform to penetrate a 2.8 m diameter capillary. The normal erythrocytes stain reddish brown with Wright stained blood smears and pink with Giemsa stain. The middle third of the cell appears relatively pale compared to the periphery, reflecting its biconcave shape. Many artifacts can be created in the preparation of the blood smear. They can result from contamination of the slide or the cover glass with grease, cleaning agents or other impurities. Friction and surface tension, which are involved in making the blood smear, create fragmentation, donut cells or anulocytes and crescent-shaped cells. When observed under a phase-contrast or interference microscope, the red blood cells show a characteristic internal scintillation known as red cell fibrillation.48

Scintillation results from thermally excited waves of the red cell membrane. The frequency analysis of the surface waves has provided an estimate of the elastic constants of the membrane curvature and the changes in these constants due to alcohol.



PATHOPHYSIOLOGY OF ERYTHROCYTE SHAPES:

Spherocytes and stomatocytes Spherocytes (Chapter 46) represent erythrocytes with the most reduced SA: V ratio in hereditary spherocytosis, immunohemolytic anemia, blood reserves, Heinz body hemolytic anemia and stomatosis caused by cell fragmentation.49,61 observed, as well as in hereditary spherocytosis, alcoholism, cirrhosis, obstructive liver disease and defects in the erythrocyte sodium pump.49,62,63 red blood cells

sensitized with antibodies, complement or immune complexes lose cholesterol and surface. As a result, they are less malleable and more osmotically fragile. The Heinz body formation leads through fragmentation to membrane depletion with spherocyte formation. A spherogenic mechanism common in Heinz body hemolytic anemia and immune hemolysis is the partial phagocytosis of parts of the cell which contain aggregates of denatured hemoglobin or parts of the sensitized membrane.

Spherocytes and stomatocytes Spherocytes

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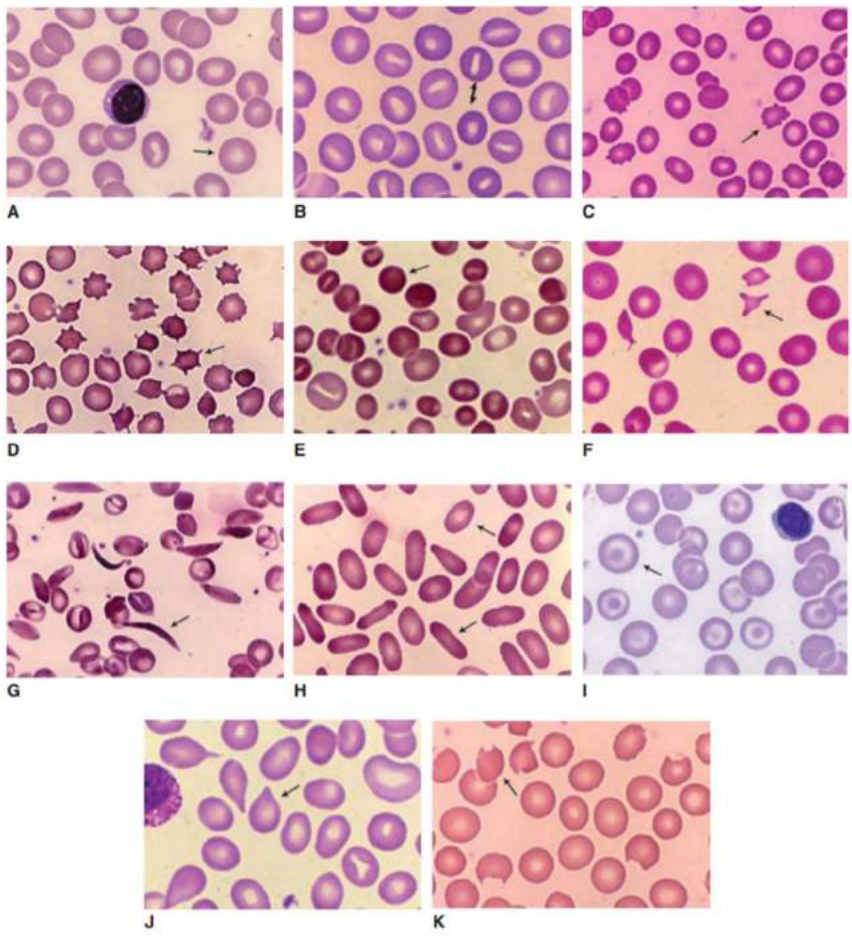


A. Normal blood. B. Stomatocytes. C. Echinocytes. D. Acanthocytes. E. Spherocytes. F. Schizocytes G. Sickle cells (Drepanocytes). H. Elliptocytes and ovalocytes. J. Tear-drop–shaped cells (Dacryocytes). K. Horn cell (Keratocyte).

The acanthocyte

It is irregularly shaped, with two to 10 hemispherical pointed spicules of different lengths and diameters. The bases of the spiculums on the acanthocyte are of different size, in contrast to the spiculae on echinocytes, which are remarkably uniform in dimensions. Acanthocytes are observed in neuroacanthocytosis and in abetalipoproteinemia.65 The

absence of anemia in these diseases suggests that these cells in the circulatory system have an almost normal lifespan.

Target cells (codocytes)

A relative excess of the membrane surface or a reduced cell volume, which leads to an increased SA: V ratio, leads to target cells. Target cells can be observed in obstructive liver disease, hemoglobinopathies (S and C), thalassemia, iron deficiency, post-splenectomy and lecithin-cholesterol acetyltransferase deficiency. The activity of lecithin cholesterol acetyltransferase is decreased in patients with obstructive liver disease. This increases the cholesterol-to-phospholipid ratio and leads to an absolute increase in the surface area of the erythrocyte membrane. In contrast, the membrane excess in patients with iron deficiency anemia and thalassemia is only relative due to the reduced cell volume. In contrast to spherocytes, which have an increased osmotic fragility, the red target cells are osmotically resistant.

Sickle cells (Drepanocytes)

The spindle-shaped, crescent-shaped cell with two pointed extremities is most commonly found in deoxygenated blood samples as a result of the polymerization of sickle hemoglobin. When sickle cell formation is observed by phase contrast microscopy, the earliest change in deoxygenation is a loss of fibrillation, followed by a slight deformation at the discocyte boundary with a shift in hemoglobin to a region of the cell.

The cell then expands and becomes rigid due to the polymerization of hemoglobin S. During reoxygenation, the sickle cell reassumes its discocyte shape and loses its membrane through microspheres and fragmentation when long spicules are withdrawn. There is evidence that the more typical sickle-shaped cells form with slow deoxygenation. With each sickle-sickle cycle, membrane damage accumulates, leading to the formation of irreversible sickle cells (ISCs). These cells cannot return to the biconcave disc shape even if they are completely oxygenated. They have increased hemoglobin levels, increased cation permeability, decreased potassium, and increased sodium

Fragmented cells (schistocytes).

severe burns and marching hemoglobinuria. Strands of fibrin in damaged blood vessels can be arranged to sift through the passing red blood cells. When a passing red blood cell folds over or otherwise attaches itself to the cord, the bloodstream pulls, stretches, and eventually fragments the arrested cell.70 The spleen quickly removes the shale cells with a low relative SA: V ratio; the rest can circulate for many days

MATERIALS AND METHOD

MATERIALS AND METHODS

SOURCE OF DATA:

The study will be conducted in patients whom on evaluation was diagnosed to have pulmonary hypertension with echocardiographic evidence attending general medicine department of govt Rajaji hospital Madurai.

INCLUSION CRTIERIA:

All patients with the echocardiographic evidence of pulmonary hypertension greater than 18 years of age who are willing to participate in the study are included

EXCLUSION CRITERIA:

- Patients already under treatment of anti coagulants and anti-platelet drugs
- Presence of any underlying liver disease
- Renal failure
- Malignancies
- Disorder of platelet function and morphology
- Fever with thrombocytopenia
- Pregnant patients
- Renal failure patients on haemodialysis
- Primary bone marrow disorders
- More than 60 years of age

ANTICIPATED OUTCOME :

- There will be Significant co-relation between severity of pulmonary hypertension and Mean Platelet Volume , Redcell Distribution Width There will be significant co-relation between RV diameter , PASP and MPV , RDW.

DATA COLLECTION:

Informed consent will be obtained from all patients to be enrolled for the study. In all patients, relevant information will be collected in a predesigned proforma.The patients are selected based on a thorough history taking, clinical examination and ECHO findings.

DESIGN OF STUDY : Cross sectional study

PERIOD OF STUDY :6 months

COLLABORATING DEPARTMENTS :

DEPARTMENT OF CARDIOLOGY, GRH.

DEPARTMENT OF PATHOLOGY, GRH.

ETHICAL CLEARANCE : obtained from institute of Ethical Committee Madurai Medical College, Madurai.

CONSENT : Individual informed and written consent

ANALYSIS : Statistical analysis will be performed using appropriate tests required according to data collected.

CONFLICT OF INTEREST : Nil

FINANCIAL SUPPORT : Self

- **PARTICIPANTS :** 50 Pulmonary hypertension patients with ECHO evidence , after getting informed consent.

PROFOMA:

Name:

Age/Sex:

Occupation:

Presenting Complaints:

PastHistory:T2DM/SHT/CAD/CKD/Thyroid disorders

Clinical Examination:

General Examination:

Consciousness

Febrile/Afebrile

Pallor

Icterus

Cyanosis

Clubbing

Generalised Lymphadenopathy

Pedal oedema

VITALS:

PR:

BP:

RR:

SPO2:

SYSTEMIC EXAMINATION:

CVS:

RS:

ABDOMEN:

CNS:

LAB INVESTIGATIONS:

- Complete blood count and peripheral smear
- Bleeding time and clotting time
- Blood urea and Serum creatinine
- Liver function test
- PT – INR
- Pulmonary function test
- ECG
- Ct chest
- Echocardiogram

RESULTS AND ANALYSIS

OBSERVATIONS AND RESULTS

RESULTS:

Statistical analysis:

The data were entered in MS office excel sheet and analyzed using SPSS version 16. Continuous data with normal distribution was expressed as mean with standard deviation. Categorical data were expressed as frequency with %. One Way Anova with Bonferroni post hoc test was used to compare the variance between three groups. Unpaired 't' test was used to compare the mean values between the two groups. Pearson's correlation test was performed to measure the direction and degree of association between various parameters. $P<0.05$ was considered statistically significant.

Table 1. Description of age category of patients with PHT observed in the study

S.No	Age category	n	%
1	20 – 40 years	13	26
2	41 – 60 years	33	66
3	>60 years	4	8

Data are expressed as n with %. Total N = 50. The mean age is 46.3 years with standard deviation of 8.6 years. The minimum age is 27 years and the maximum age is 64 years.

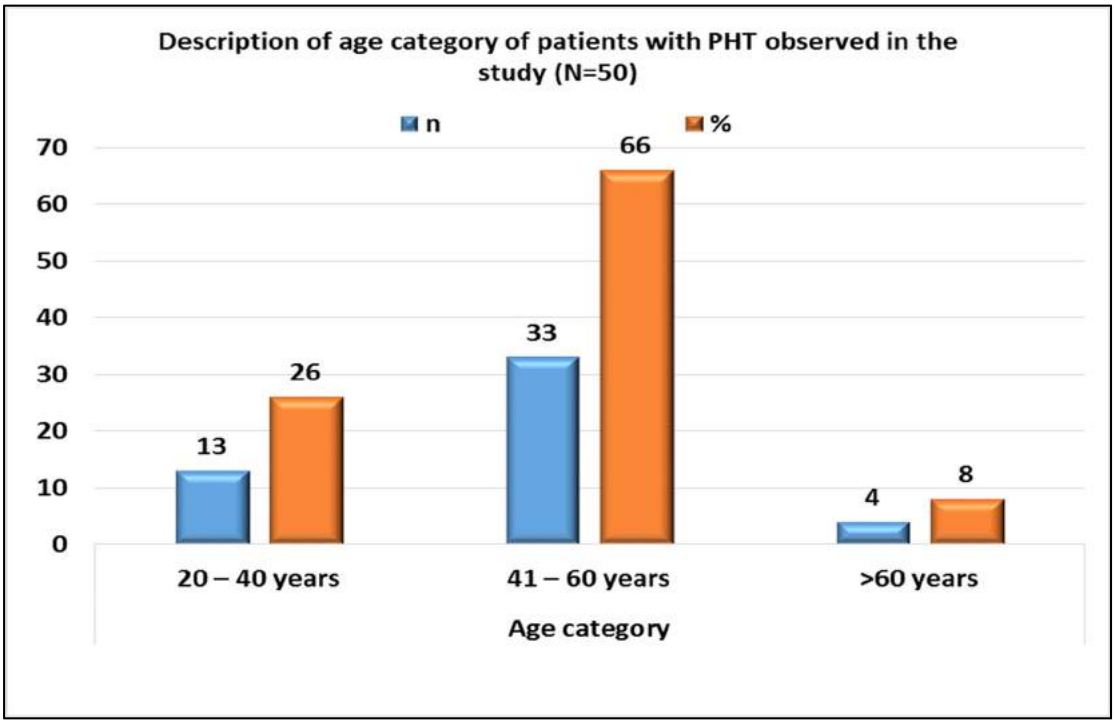


Table 2. Description of gender category of patients with PHT observed in the study

S.No	Gender category	n	%
1	Female	27	54
2	Male	23	46

Data are expressed as n with %. Total N = 50.

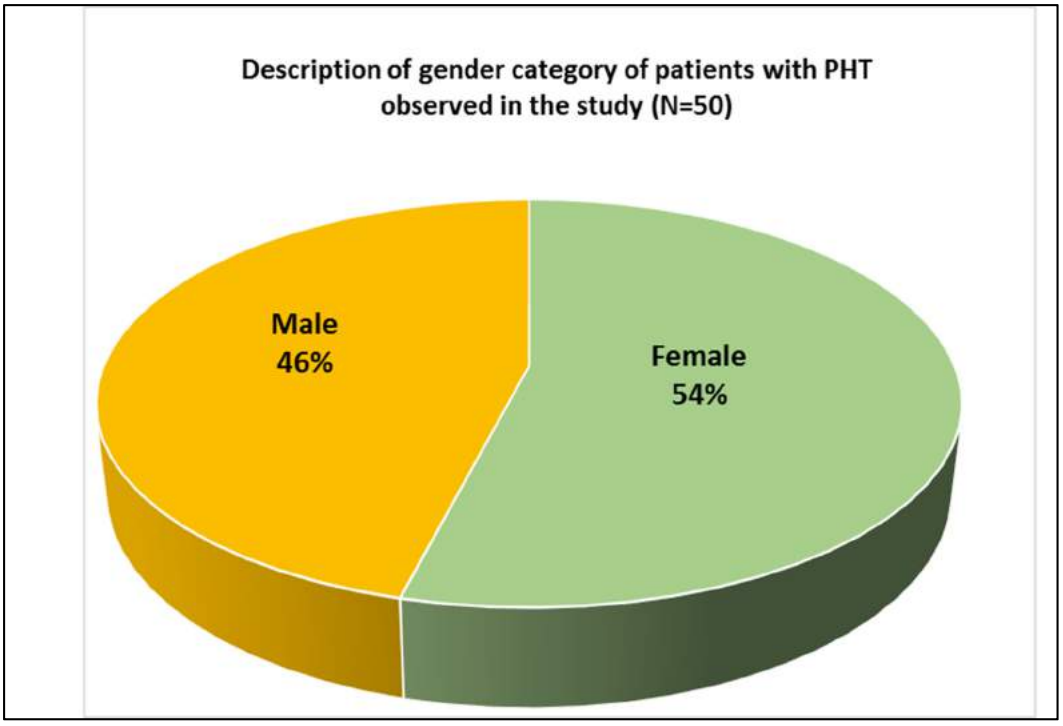


Table 3. Description of etiology of pulmonary hypertension observed in the study

S.No	Etiology	n	%
1	ASD	1	2
2	COPD	19	38
3	CTD	5	10
4	CTEPH	2	4
5	Idiopathic PAH	4	8
6	Old PTB-COPD	4	8
7	OSA	3	6
8	Valvular HD	10	20
9	VSD	2	4

Data are expressed as n with %. Total N = 50.

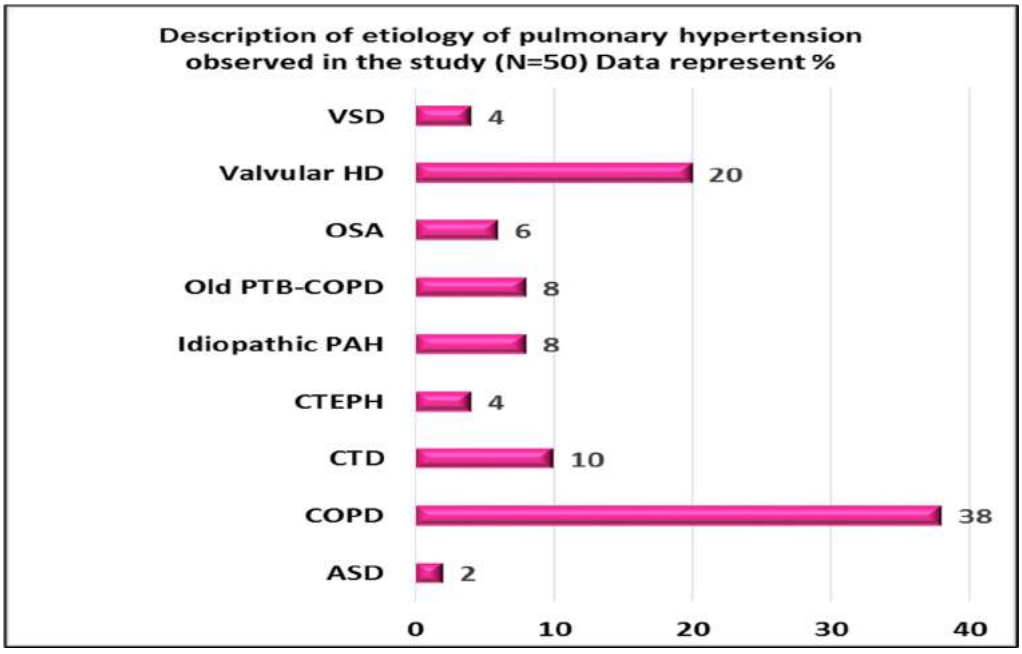


Table 4. Description of etiology of pulmonary hypertension observed in the study

S.No	Class of PHT	n	%
1	Class 1	10	20
2	Class 2	12	24
3	Class 3	26	32
4	Class 4	2	4

Data are expressed n with %. Total N = 50.

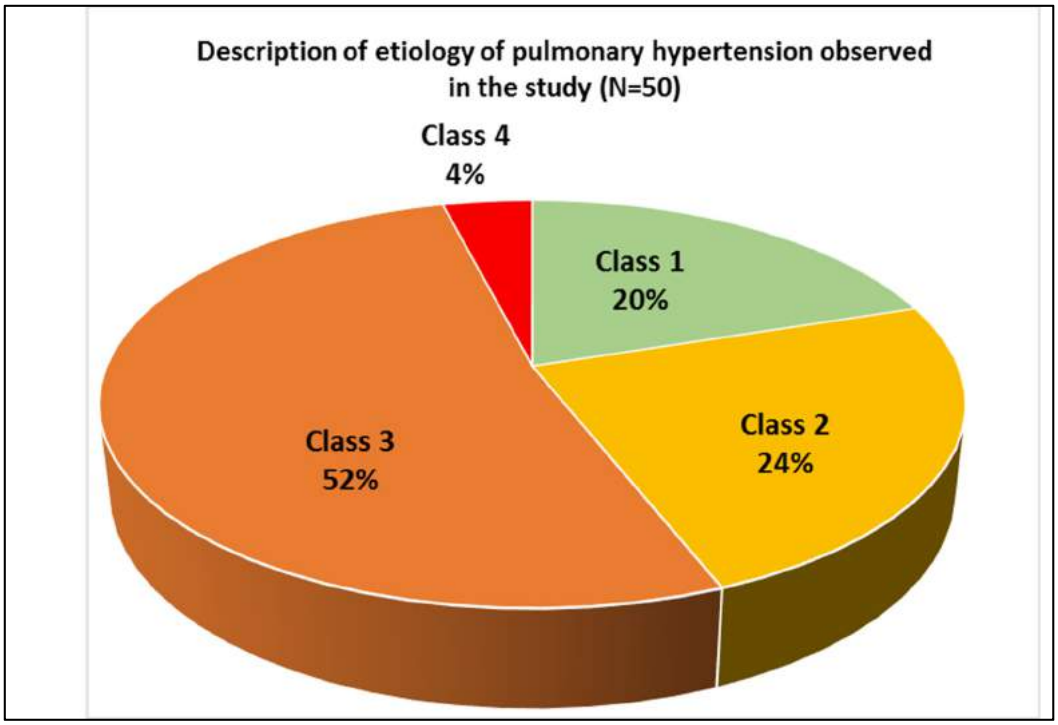


Table 5. Description of RA RV dimension in patients with pulmonary hypertension observed in the study

S.No	RA RV dimension	n	%
1	Dilated	40	80
2	Normal	10	20

Data are expressed as n with %. Total N = 50.

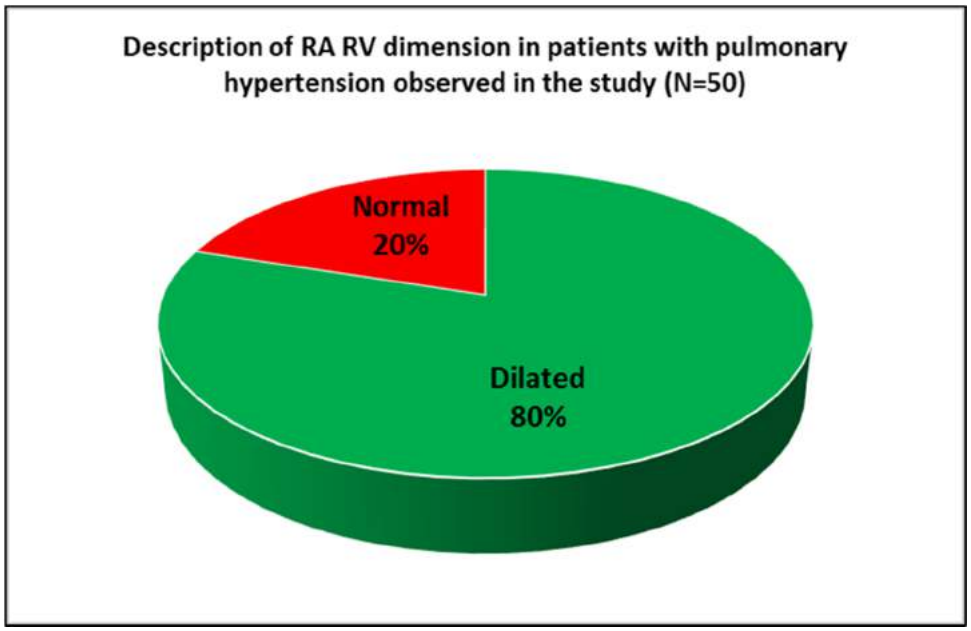


Table 6. Description of mPAP categroy in patients with pulmonary hypertension observed in the study

S.No	mPAP category	n	%
1	30 – 40 mmHg	11	22
2	>40 – 50 mmHg	27	54
3	>50 – 60 mmHg	10	20
4	>60 mmHg	2	4

Data are expressed as n with %. Total N = 50.

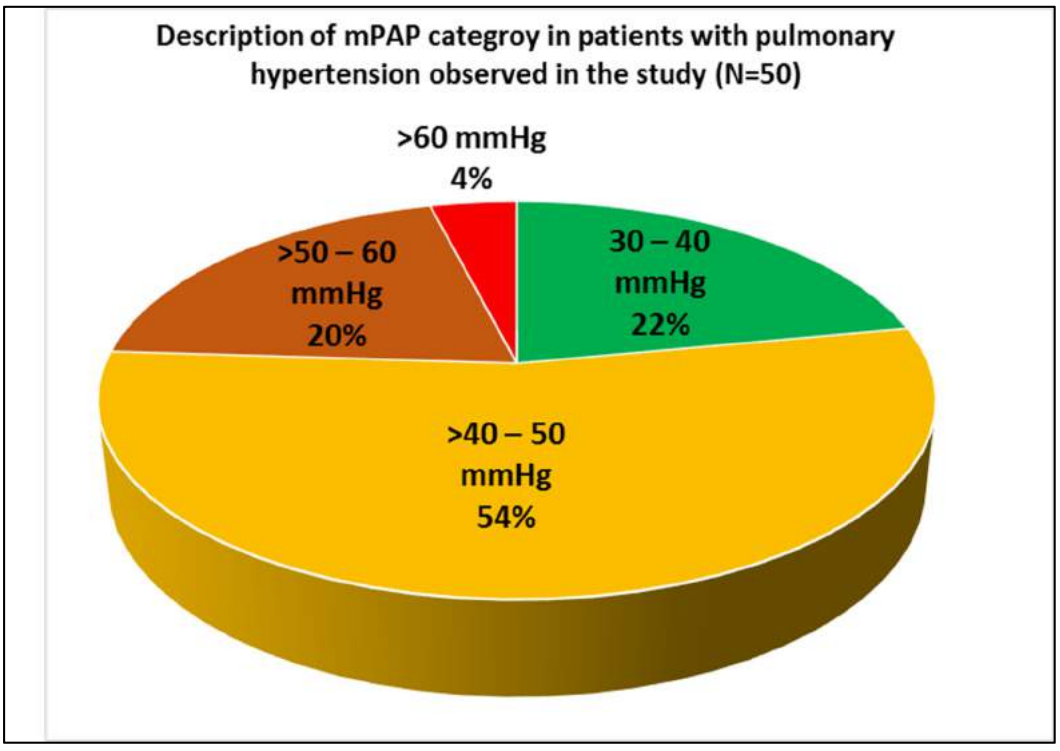


Table 7. Description of EF categroy in patients with pulmonary hypertension observed in the study

S.No	EF category	n	%
1	40 – 60%	20	40
2	>60%	30	60

Data are expressed as n with %. Total N = 50.

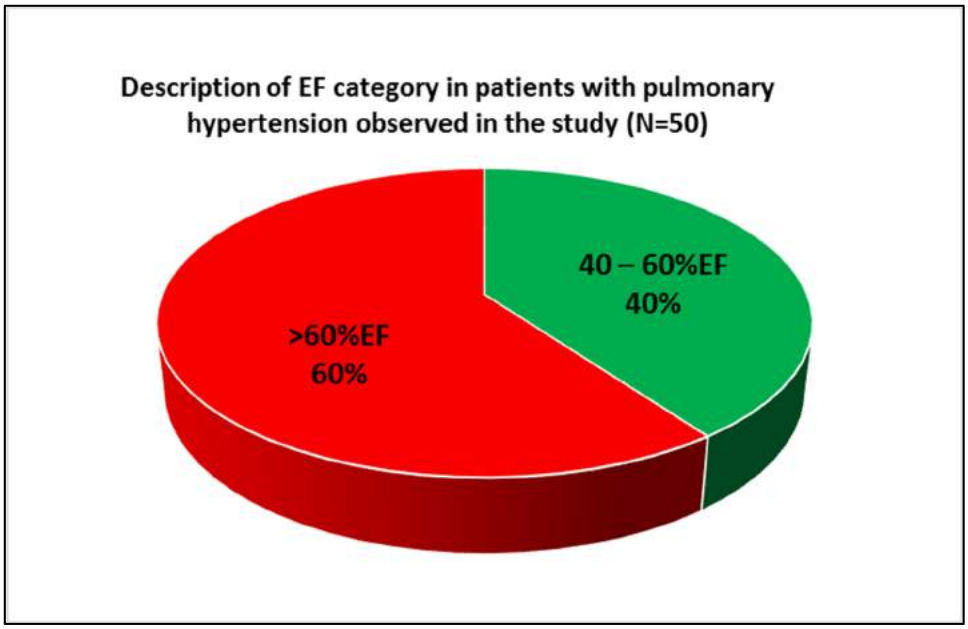


Table 8. Description of TRPG categroy in patients with pulmonary hypertension observed in the study

S.No	TRPG category	n	%
1	35 – 55mmHg	12	24
2	>55 – 75 mmHg	26	52
3	>75 mmHg	12	24

Data are expressed as n with %. Total N = 50.

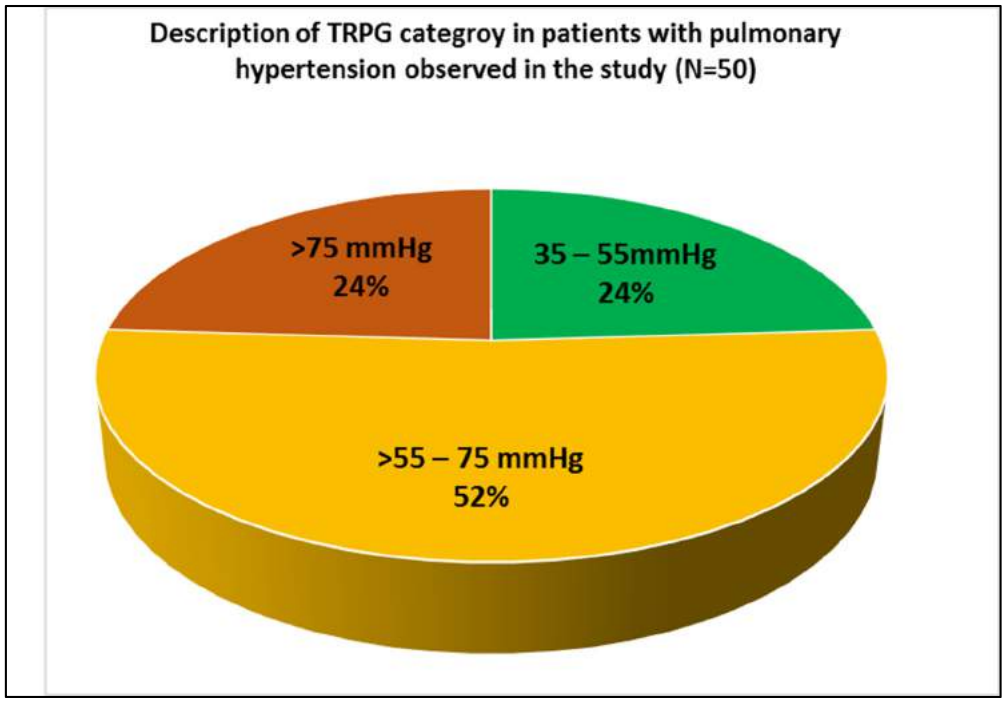


Table 9. Description of severity of pulmonary hypertension observed in the study

S.No	Severity of PHT	n	%
1	Mild	12	24
2	Moderate	26	52
3	Severe	12	24

Data are expressed as n with %. Total N = 50.

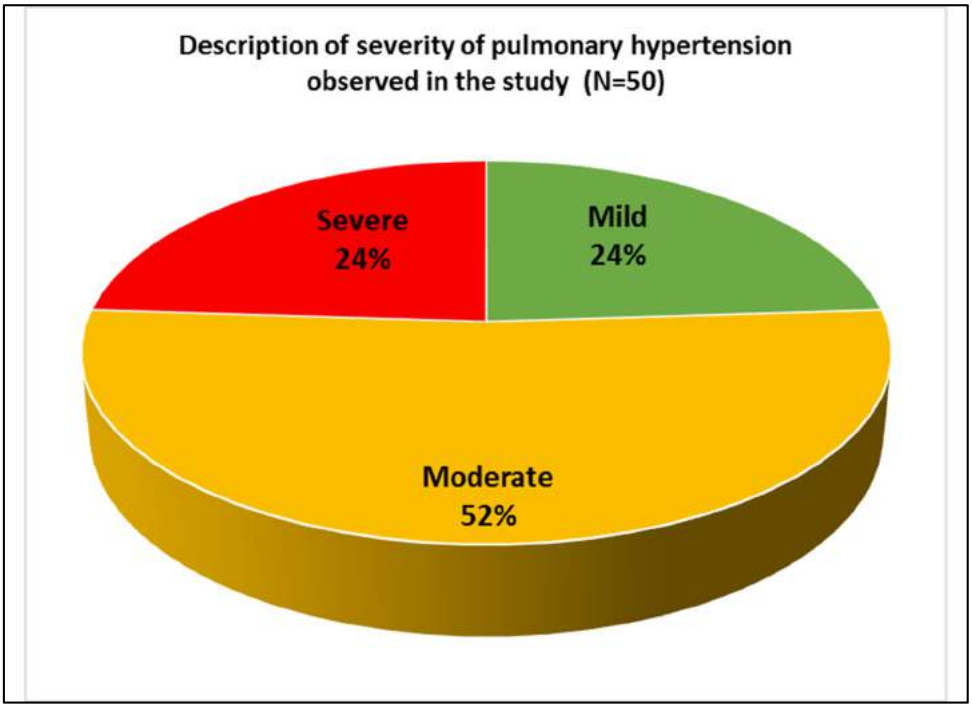


Table 10. Description of various parameters observed in the study

(N=50)

S.No	Parameter	N	Minimum	Maximum	Mean	Std. Deviation
1	TAPSE (mm)	50	12	19	15.46	1.64
2	EF %	50	54	68	62.12	3.54
3	mPAP (mmHg)	50	34	62	46.85	7.81
4	TRPG (mmHg)	50	42	114	67.2	16.1
5	MPV (fL)	50	8	15	11.20	1.65
6	PDW	50	14	21	17.40	1.80
7	Plateletcount (Lakhs/cc)	50	1.40	4.20	2.56	0.74
8	RDWSD (fL)	50	32	54.8	44.1	5.77

Table 11. Comparison of mean platelet volume with respect to severity of pulmonary hypertension observed in the study.

S.No	Parameter	Severity of PHT						F value	df	P value
		Mild (N=12)		Moderate (N=26)		Severe (N=12)				
		Mean	SD	Mean	SD	Mean	SD			
1	Mean platelet volume (fL)	9.05	0.55	11.2	0.67	13.3	1	99.2	2, 47	<0.0001*
Post hoc analysis										
S.No	**Group vs Group**	**P value**								
1	Mild Vs Moderate	<0.0001*								
2	Mild Vs Severe	<0.0001*								
	Moderate Vs Severe	<0.0001*								

Data are expressed as n with %. One way ANOVA with Bonferroni post hoc test was used to compare the variances between the groups. *indicates $p<0.05$ and considered statistically significant.

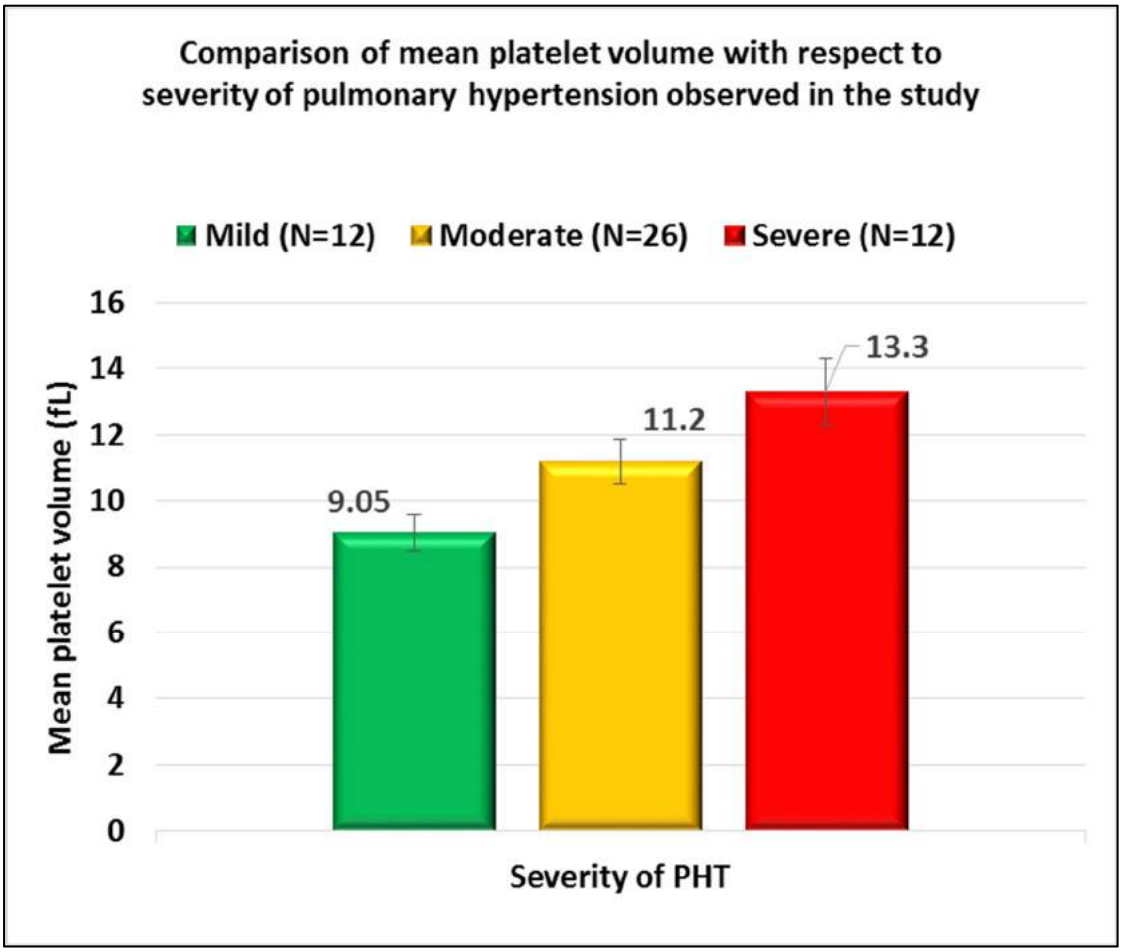

Comparison of mean platelet volume with respect to severity of pulmonary hypertension observed in the study
Mild (N=12)
Moderate (N=26)
Severe (N=12)
Mean platelet volume (fL)
16
14
12
10
8
6
4
2
0
9.05
11.2
13.3
Severity of PHT

Table 12. Comparison of Platelet distribution width with respect to severity of pulmonary hypertension observed in the study.

S.No	Parameter	Severity of PHT						F value	df	P value
		Mild (N=12)		Moderate (N=26)		Severe (N=12)				
		Mean	SD	Mean	SD	Mean	SD			
1	Platelet distribution width	15.2	1.05	17.5	1.02	19.4	1.16	45.7	2, 47	<0.0001*

Post hoc analysis

S.No	Group vs Group	P value	S.No	Group vs Group	P value
1	Mild Vs Moderate	<0.0001*	3	Moderate Vs Severe	<0.0001*
2	Mild Vs Severe	<0.0001*			

Data are expressed as n with %. One way ANOVA with Bonferroni post hoc test was used to compare the variances between the groups. *indicates $p<0.05$ and considered statistically significant.

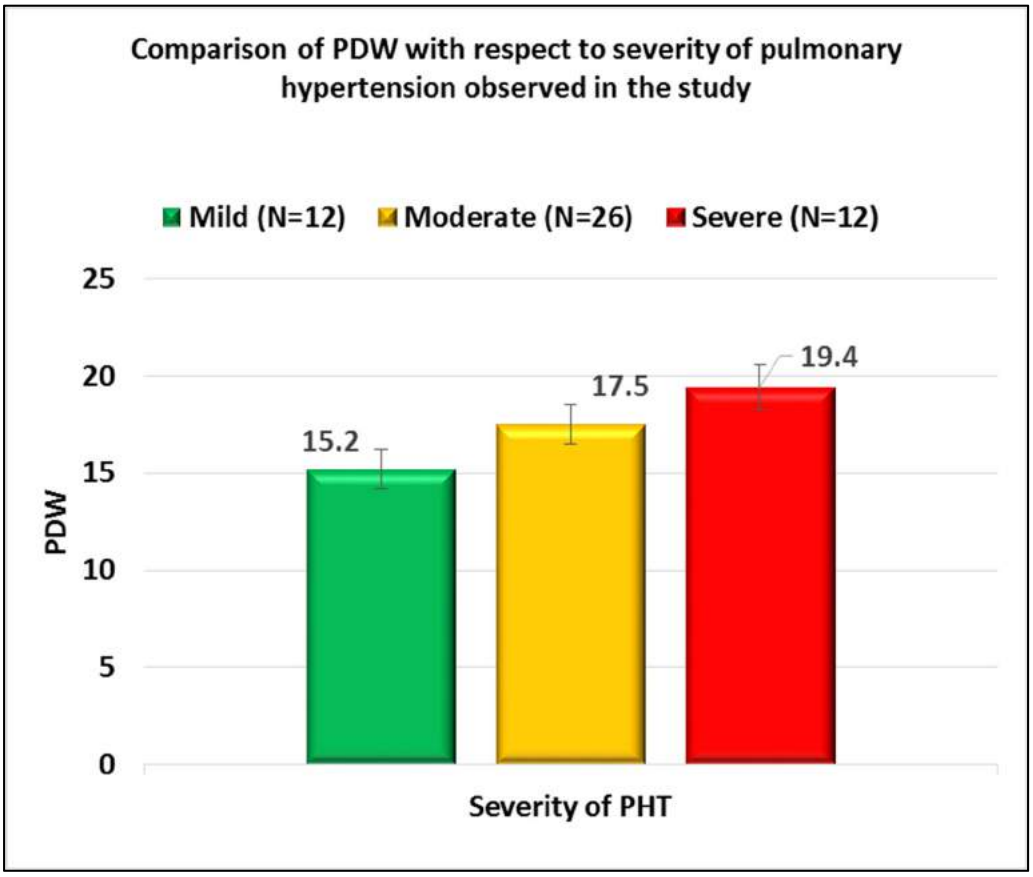

Comparison of PDW with respect to severity of pulmonary hypertension observed in the study
Mild (N=12)
Moderate (N=26)
Severe (N=12)
25
20
15
10
5
0
PDW
15.2
17.5
19.4
Severity of PHT

Table 13. Comparison of platelet count with respect to severity of pulmonary hypertension observed in the study.

S.No	Parameter	Severity of PHT						F value	df	P value
		Mild (N=12)		Moderate (N=26)		Severe (N=12)				
		Mean	SD	Mean	SD	Mean	SD			
1	Platelet count (Lakhs/cc)	2.88	0.87	2.59	0.73	2.22	0.49	2.49	2, 47	0.093 (NS)
Post hoc analysis										
S.No	Group vs Group	P value	S.No	Group vs Group	P value					
1	Mild Vs Moderate	0.657 (NS)	3	Moderate Vs Severe	0.536 (NS)					
2	Mild Vs Severe	0.091 (NS)								

Data are expressed as n with %. One way ANOVA with Bonferroni post hoc test was used to compare the variances between the groups. *indicates $p<0.05$ and considered statistically significant.

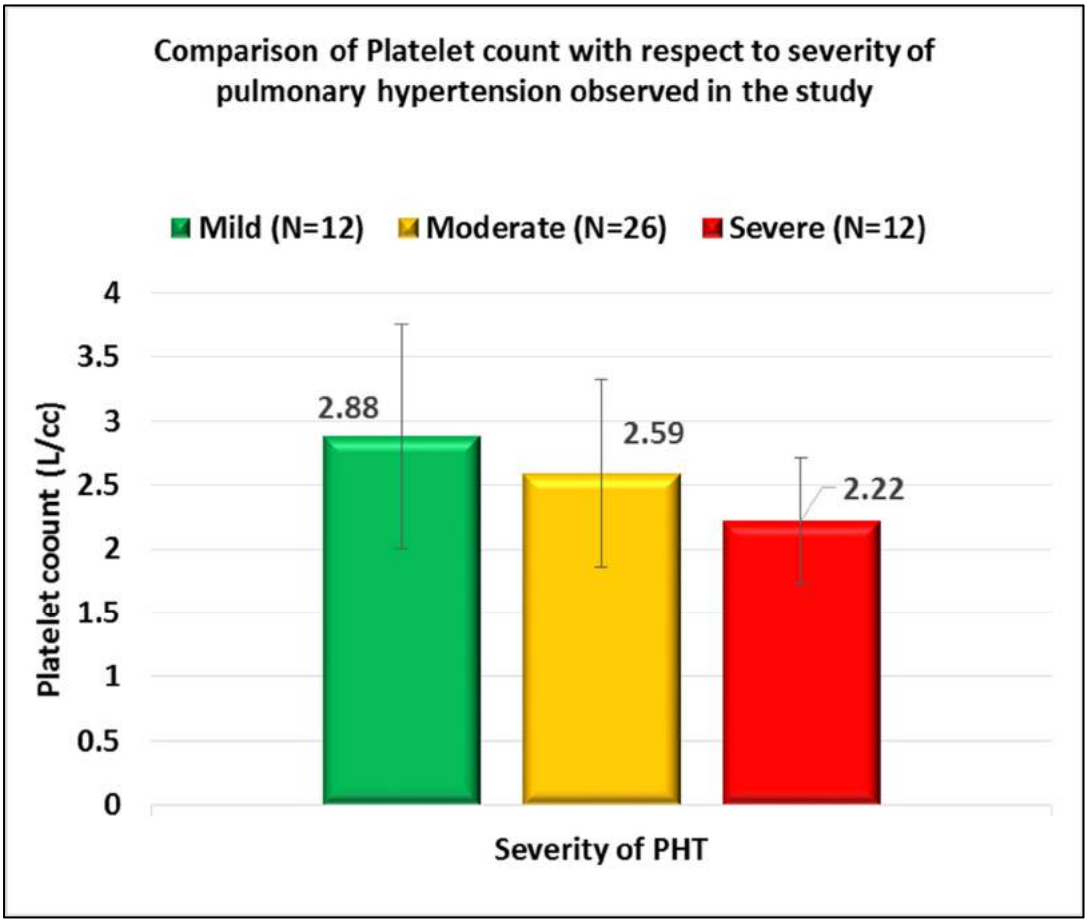

Comparison of Platelet count with respect to severity of pulmonary hypertension observed in the study
Mild (N=12)
Moderate (N=26)
Severe (N=12)
Platelet coount (L/cc)
4
3.5
3
2.5
2
1.5
1
0.5
0
2.88
2.59
2.22
Severity of PHT

Table 14. Comparison of RDW-SD with respect to severity of pulmonary hypertension observed in the study.

S.No	Parameter	Severity of PHT						F value	df	P value
		Mild (N=12)		Moderate (N=26)		Severe (N=12)				
		Mean	SD	Mean	SD	Mean	SD			
1	RDW-SD (fL)	36.5	3.03	44.4	3.04	50.8	2.5	71.9	2, 47	<0.0001*

Post hoc analysis

S.No	Group vs Group	P value	S.No	Group vs Group	P value
1	Mild Vs Moderate	<0.0001*	3	Moderate Vs Severe	<0.0001*
2	Mild Vs Severe	<0.0001*			

Data are expressed as n with %. One way ANOVA with Bonferroni post hoc test was used to compare the variances between the groups. *indicates $p<0.05$ and considered statistically significant.

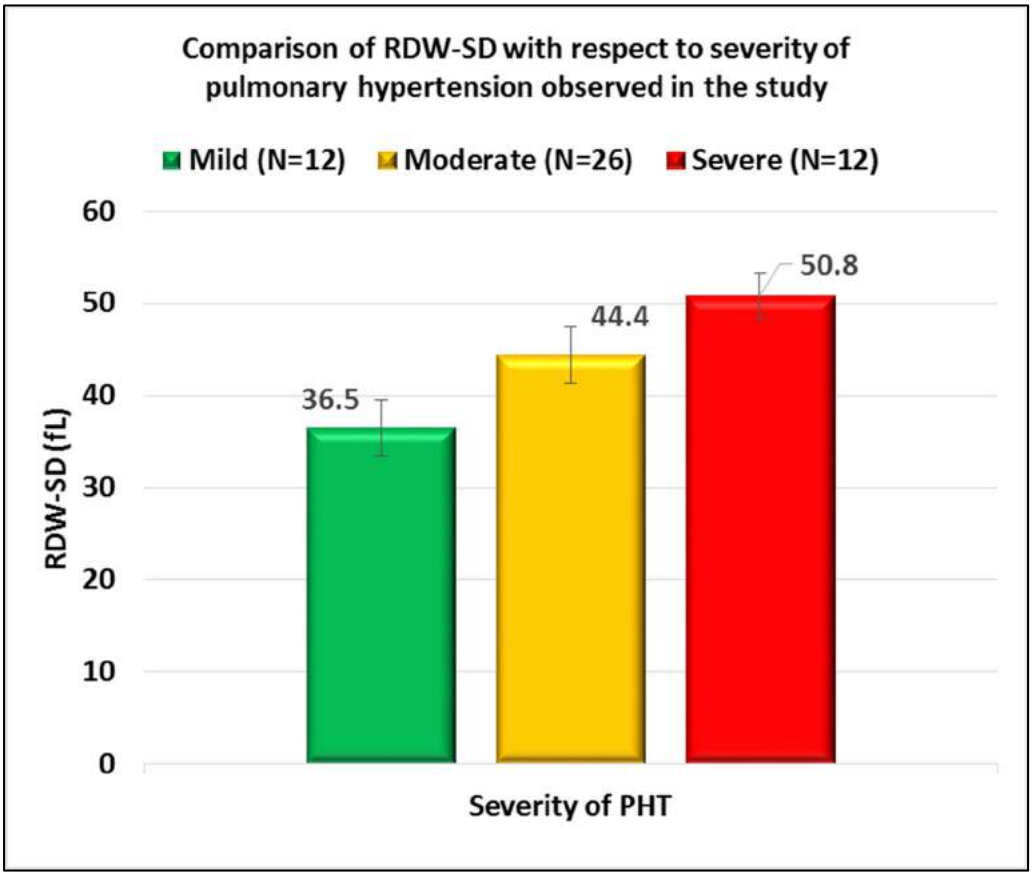
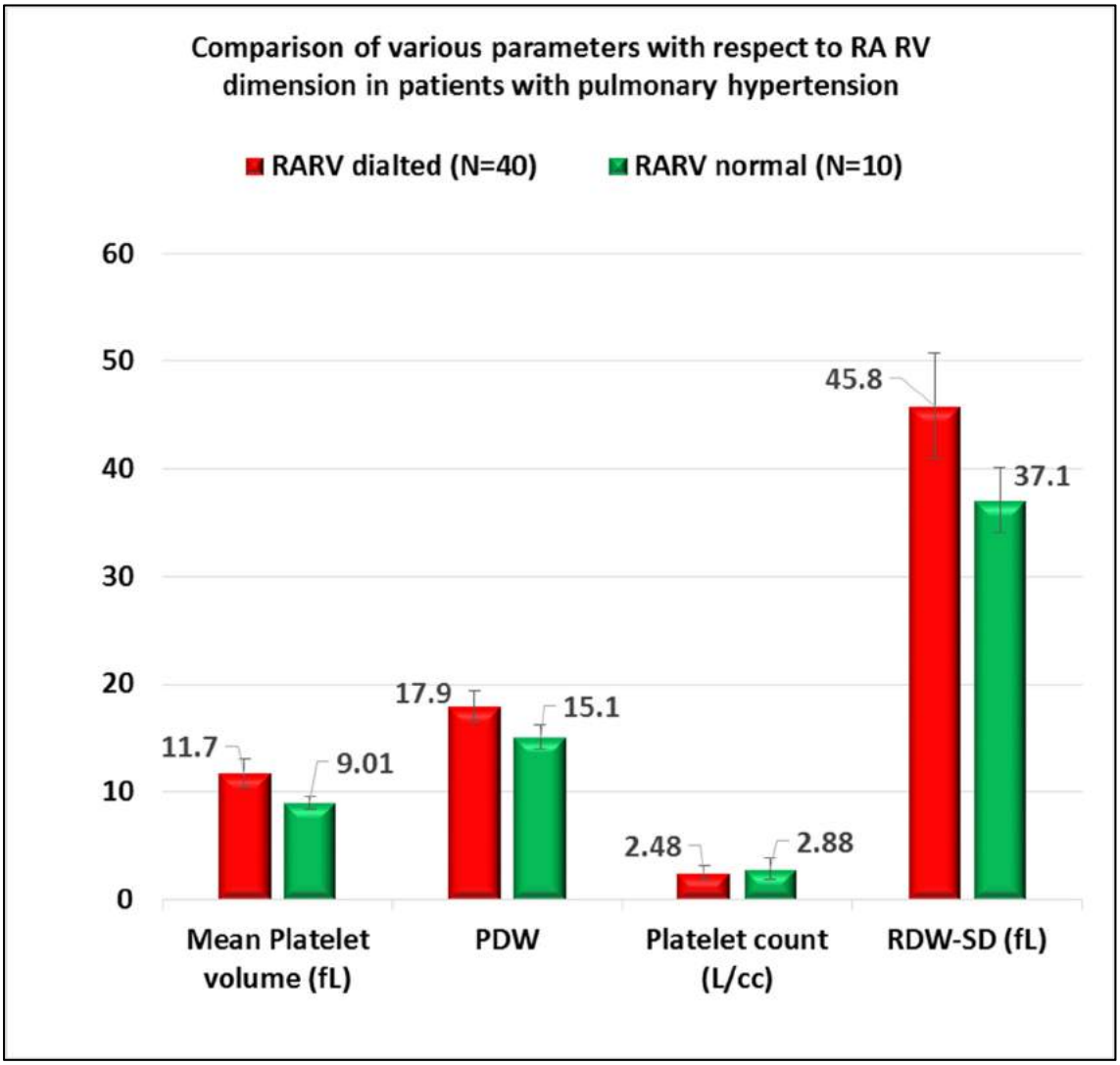

Comparison of RDW-SD with respect to severity of pulmonary hypertension observed in the study
Mild (N=12)
Moderate (N=26)
Severe (N=12)
60
50
40
30
20
10
0
RDW-SD (fL)
36.5
44.4
50.8
Severity of PHT

Table 15. Comparison of various parameters with respect to RA RV dimension in patients with pulmonary hypertension.

S.No	Parameter	RA-RV dimension				t value	df	P value
		Dilated (N=40)		Normal (N=10)				
		Mean	SD	Mean	SD			
1	Mean Platelet volume (fL)	11.7	1.34	9.01	0.58	6.23	48	<0.0001*
2	PDW	17.9	1.44	15.1	1.1	5.87	48	<0.0001*
3	Platelet count (L/cc)	2.48	0.66	2.88	0.96	1.53	48	0.132 (NS)
4	RDW-SD (fL)	45.8	4.9	37.1	3	5.32	48	<0.0001*

Data are expressed as n with %. Unpaired 't' test was used to compare the mean between the two groups. *indicates $p<0.05$ and considered statistically significant.


Comparison of various parameters with respect to RA RV dimension in patients with pulmonary hypertension
RARV dialted (N=40)
RARV normal (N=10)
60
50
40
30
20
10
0
11.7
9.01
17.9
15.1
2.48
2.88
45.8
37.1
Mean Platelet volume (fL)
PDW
Platelet count (L/cc)
RDW-SD (fL)

DISCUSSION

DISCUSSION

- Data were analyzed using SPSS version 16
- Continuous data with normal distribution was expressed as mean with standard deviation.
- The mean age is 46.3 years with standard deviation of 8.6 years.The minimumage is 27 years and the maximum age is 64 years.
- The study population is 50 and of those 27 females and 23 males.
- The study population was divided into age group.
- The study population was categorised according to the etiology
- Data are expressed as n with %. One way ANOVA with Boneerroni post hoc test was used to compare the variances between the groups.
- Correlation was performed using Pearson' correlation test. Degree and direction of asoociation was represented using r value.
- MPV and platelet count are compared with severity of pulmonary hypertension of different etiology.
- MPV and platelet count was compared with RA, RV diameter and TAPSE.
- RDW was compared with pulmonary hypertension of different etiology with severity of pulmonary hypertension.
- There was significant correlation between severity of pulmonary hypertension and MPV , RDW.

LIMITATIONS

LIMITATIONS OF THE STUDY

- The study was done with a population size of 50.
- MPV and RDW can also be altered due to multiple causes.
- No large general population studies had been conducted so far and poor literature support.
- Individual causes of pulmonary hypertension and their correlation with MPV and RDW couldn’t be established.

CONCLUSION

CONCLUSIONS

- There is a significant co-relation between MPV and RDW and severity of pulmonary hypertension.
- There is a significant co-relation between RV diameter , PSAP and MPV , RDW.
- MPV and RDW can predict the progression of pulmonary hypertension.
- Hence MPV and RDW can be used as a prognostic marker and can also be used to assess the progression of the disease in low resource settings.

ANNEXURE

BIBLIOGRAPHY

1. N. Galiè, M. Humbert, J.-L. Vachiery et al., “2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension,” *European Heart Journal*, vol. 37, no. 1, pp. 67–119, 2016.
2. V. Thakkar and E. M. T. Lau, “Connective tissue disease-related pulmonary arterial hypertension,” *Best Practice & Research Clinical Rheumatology*, vol. 30, no. 1, pp. 22–38, 2016.
3. A. J. Peacock, N. F. Murphy, J. J. V. McMurray, L. Caballero, and S. Stewart, “An epidemiological study of pulmonary arterial hypertension,” *European Respiratory Journal*, vol. 30, no. 1, pp. 104–109, 2007.
4. V. Cottin, “Pulmonary arterial hypertension in connective tissue disease,” *Revue des Maladies Respiratoires*, vol. 23, Supplement 4, pp. 13S61–13S72, 2006.
5. J. Avouac, P. Airò, C. Meune et al., “Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies,” *The Journal of Rheumatology*, vol. 37, no. 11, pp. 2290–2298, 2010.
6. L. Cavagna, E. Prisco, C. Montecucco, and R. Caporali, “Pulmonary arterial hypertension in antisynthetase syndrome: comment on the article by Chatterjee and Farver,” *Arthritis Care & Research*, vol. 63, no. 4, pp. 633-634, 2011.
7. M. J. Ruiz-Cano, P. Escribano, R. Alonso et al., “Comparison of baseline characteristics and survival between patients with

idiopathic and connective tissue disease-related pulmonary arterial hypertension," *The Journal of Heart and Lung Transplantation*, vol. 28, no. 6, pp. 621–627, 2009.

8. N. F. Chaisson and P. M. Hassoun, "Systemic sclerosis-associated pulmonary arterial hypertension," *Chest*, vol. 144, no. 4, pp. 1346–1356, 2013.

9. N. Galiè, L. Rubin, M. Hoeper et al., "Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial," *The Lancet*, vol. 371, no. 9630, pp. 2093–2100, 2008.

10. J. G. Coghlan, C. P. Denton, E. Grünig et al., "Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study," *Annals of the Rheumatic Diseases*, vol. 73, no. 7, pp. 1340–1349, 2014.

11. T. C. Evans and D. Jehle, "The red blood cell distribution width," *The Journal of Emergency Medicine*, vol. 9, pp. 71–74, 1991.

12. C. J. Rhodes, J. Wharton, L. S. Howard, J. S. R. Gibbs, and M. R. Wilkins, "Red cell distribution width outperforms other potential circulating biomarkers in predicting survival in idiopathic pulmonary arterial hypertension," *Heart*, vol. 97, no. 13, pp. 1054–1060, 2011.

13. A. Smukowska-Gorynia, I. Tomaszewska, K. Malaczynska-Rajpold et al., "Red blood cells distribution width as a potential prognostic biomarker in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension," *Heart, Lung and Circulation*, vol. 27, no. 7, pp. 842–848, 2018.

14. J. Zhao, H. Mo, X. Guo et al., “Red blood cell distribution width as a related factor of pulmonary arterial hypertension in patients with systemic sclerosis,” *Clinical Rheumatology*, vol. 37, no. 4, pp. 979–985, 2018.

15. M. Hui, J. Zhao, Z. Tian et al., “Red blood cell distribution width as a potential predictor of survival of pulmonary arterial hypertension associated with primary Sjogren’s syndrome: a retrospective cohort study,” *Clinical Rheumatology*, vol. 38, no. 2, pp. 477–485, 2019.

16. L. G. Rudski, W. W. Lai, J. Afilalo et al., “Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography,” *Journal of the American Society of Echocardiography*, vol. 23, no. 7, pp. 685–713, 2010.

17. O. O. Olumuyiwa-Akeredolu and E. Pretorius, “Platelet and red blood cell interactions and their role in rheumatoid arthritis,” *Rheumatology International*, vol. 35, no. 12, pp. 1955–1964, 2015.

18. L. L. Abrahan IV, J. D. A. Ramos, E. L. Cunanan, M. D. A. Tiongson, and F. E. R. Punzalan, “Red cell distribution width and mortality in patients with acute coronary syndrome: a meta-analysis on prognosis,” *Cardiology Research*, vol. 9, no. 3, pp. 144–152, 2018.

19. B. D. Horne, J. B. Muhlestein, S. T. Bennett et al., “Extreme erythrocyte macrocytic and microcytic percentages are highly

predictive of morbidity and mortality," *JCI Insight*, vol. 3, no. 14, 2018.

20. N. Farkas, A. Szabó, V. Lóránd et al., "Clinical usefulness of measuring red blood cell distribution width in patients with systemic sclerosis," *Rheumatology*, vol. 53, no. 8, pp. 1439–1445, 2014.

21. S. R. Johnson, J. R. Swiston, and J. T. Granton, "Prognostic factors for survival in scleroderma associated pulmonary arterial hypertension," *The Journal of Rheumatology*, vol. 35, no. 8, pp. 1584–1590, 2008.

22. M. I. Acosta Colmán, G. Avila Pedretti, M. E. Acosta, C. P. Simeón Aznar, V. Fonollosa Plá, and M. Villardel Torrés, "Can we predict the severity of pulmonary hypertension in patients with scleroderma?" *Reumatología Clínica*, vol. 8, no. 5, pp. 259–262, 2012.

23. P. Herve, M. Humbert, O. Sitbon et al., "Pathobiology of pulmonary hypertension. The role of platelets and thrombosis," *Clinics in Chest Medicine*, vol. 22, no. 3, pp. 451–458, 2001.

24. N. Galiè, V. V. McLaughlin, L. J. Rubin, and G. Simonneau, "An overview of the 6th World Symposium on Pulmonary Hypertension," *European Respiratory Journal*, vol. 53, no. 1, article 1802148, 2019

MASTER CHART

S.NO	AGE	SEX	ETIOLOGY	CLASSIFICATION OF PHT	ECHOCARDIOGRAPHY						MPV fL	PDW	PLATELET COUNT	RDW-SD fL
					RA,RV DIMENSION	TAPSE mm	EF %	mPAP mmHg	TRPG mmHg	SEVERITY OF PHT				
1	52	M	COPD	3	DILATED	16	65	47	68	MODERATE	10.5	17	2.0 LAKHS/CU.mm	44.2
2	50	F	IDIOPATHIC PAH	1	DILATED	15	60	50	72	MODERATE	12	18	2.2 LAKHS/CU.mm	48
3	45	F	VALVULAR - HD	1	NORMAL	16	60	36.8	48	MILD	8.8	14	1.8 LAKHS/CU.mm	32
4	48	F	CTD	1	DILATED	13	64	58	88	SEVERE	12.4	19	1.7 LAKHS/CU.mm	52.4
5	42	M	VALVULAR - HD	2	DILATED	16	62	41	58	MODERATE	11	17	3.2 LAKHS/CU.mm	46.5
6	62	M	OSA	3	DILATED	12	56	60.6	102	SEVERE	15	18	2.4 LAKHS/CU.mm	49.3
7	56	F	OLD PTB - COPD	3	NORMAL	17	65	37.2	48	MILD	9.2	16	3.5 LAKHS/CU.mm	36.2
8	38	F	VALVULAR - HD	2	DILATED	15	58	47.6	68	MODERATE	11	17	2.2 LAKHS/CU.mm	47.8
9	39	M	COPD	3	DILATED	18	68	34.6	44	MILD	9	16	2.9 LAKHS/CU.mm	34.6
10	44	F	CTD	1	DILATED	16	66	46.4	65	MODERATE	11.5	19	1.9 LAKHS/CU.mm	45.4
11	52	F	IDIOPATHIC PAH	1	DILATED	13	62	57.8	84	SEVERE	13.4	21	2.0 LAKHS/CU.mm	50
12	54	M	COPD	3	DILATED	15	60	48.6	70	MODERATE	12	18	2.6 LAKHS/CU.mm	43.5
13	30	F	ASD	2	NORMAL	17	62	36	48	MILD	8.4	15	4.2 LAKHS/CU.mm	36.4
14	45	F	COPD	3	DILATED	14	64	56.5	80	SEVERE	14	20	2.0 LAKHS/CU.mm	49.8
15	51	M	COPD - OLD PTB	3	NORMAL	17	66	39	50	MILD	9.4	16	2.2 LAKHS/CU.mm	39.2
16	44	F	VALVULAR - HD	2	DILATED	17	56	43	60	MODERATE	10.8	16	1.5 LAKHS/CU.mm	48.4
17	44	F	IDIOPATHIC PAH	1	DILATED	12	62	62	114	SEVERE	13.5	19	1.8 LAKHS/CU.mm	54.2
18	47	M	COPD	3	NORMAL	18	68	43	46	MILD	9	14	2.3 LAKHS/CU.mm	38.2
19	55	F	CTEPH	4	DILATED	14	62	49	72	MODERATE	11.2	17	1.4 LAKHS/CU.mm	49.6
20	39	M	COPD	3	DILATED	12	58	60	96	SEVERE	12.8	18	2.2 LAKHS/CU.mm	54
21	37	F	VALVULAR - HD	2	DILATED	15	60	49	70	MODERATE	12	18	2.5 LAKHS/CU.mm	44.5
22	45	M	COPD	3	DILATED	14	54	55.6	82	SEVERE	13.5	21	2.0 LAKHS/CU.mm	50.2
23	46	F	VALVULAR - HD	2	DILATED	19	58	35	44	MILD	9.6	16	2.9 LAKHS/CU.mm	33
24	64	F	OSA	3	DILATED	15	66	47	68	MODERATE	10.6	17	1.9 LAKHS/CU.mm	42
25	52	F	COPD - OLD PTB	3	DILATED	13	60	59	90	SEVERE	14.8	20	1.9 LAKHS/CU.mm	54.8
26	51	M	COPD	3	DILATED	15	62	50	72	MODERATE	12.5	19	2.3 LAKHS/CU.mm	48
27	43	M	COPD	3	NORMAL	17	66	36	48	MILD	8.6	14	3.8 LAKHS/CU.mm	39.6
28	41	F	CTD	1	DILATED	16	64	45.8	66	MODERATE	12	19	1.4 LAKHS/CU.mm	44
29	62	M	CTEPH	4	DILATED	15	56	46	68	MODERATE	11.5	18	4.0 LAKHS/CU.mm	45.6

S.NO	AGE	SEX	ETIOLOGY	CLASSIFICATION OF PHT	ECHOCARDIOGRAPHY					SEVERITY OF PHT	MPV fL	PDW	PLATELET COUNT	RDW-SD fL
					RA,RV DIMENSION	TAPSE mm	EF %	mPAP mmHg	TRPG mmHg					
1	52	M	COPD	3	DILATED	16	65	47	68	MODERATE	10.5	17	2.0 LAKHS/CU.mm	44.2
2	50	F	IDIOPATHIC PAH	1	DILATED	15	60	50	72	MODERATE	12	18	2.2 LAKHS/CU.mm	48
3	45	F	VALVULAR - HD	1	NORMAL	16	60	36.8	48	MILD	8.8	14	1.8 LAKHS/CU.mm	32
4	48	F	CTD	1	DILATED	13	64	58	88	SEVERE	12.4	19	1.7 LAKHS/CU.mm	52.4
5	42	M	VALVULAR - HD	2	DILATED	16	62	41	58	MODERATE	11	17	3.2 LAKHS/CU.mm	46.5
6	62	M	OSA	3	DILATED	12	56	60.6	102	SEVERE	15	18	2.4 LAKHS/CU.mm	49.3
7	56	F	OLD PTB - COPD	3	NORMAL	17	65	37.2	48	MILD	9.2	16	3.5 LAKHS/CU.mm	36.2
8	38	F	VALVULAR - HD	2	DILATED	15	58	47.6	68	MODERATE	11	17	2.2 LAKHS/CU.mm	47.8
9	39	M	COPD	3	DILATED	18	68	34.6	44	MILD	9	16	2.9 LAKHS/CU.mm	34.6
10	44	F	CTD	1	DILATED	16	66	46.4	65	MODERATE	11.5	19	1.9 LAKHS/CU.mm	45.4
11	52	F	IDIOPATHIC PAH	1	DILATED	13	62	57.8	84	SEVERE	13.4	21	2.0 LAKHS/CU.mm	50
12	54	M	COPD	3	DILATED	15	60	48.6	70	MODERATE	12	18	2.6 LAKHS/CU.mm	43.5
13	30	F	ASD	2	NORMAL	17	62	36	48	MILD	8.4	15	4.2 LAKHS/CU.mm	36.4
14	45	F	COPD	3	DILATED	14	64	56.5	80	SEVERE	14	20	2.0 LAKHS/CU.mm	49.8
15	51	M	COPD - OLD PTB	3	NORMAL	17	66	39	50	MILD	9.4	16	2.2 LAKHS/CU.mm	39.2
16	44	F	VALVULAR - HD	2	DILATED	17	56	43	60	MODERATE	10.8	16	1.5 LAKHS/CU.mm	48.4
17	44	F	IDIOPATHIC PAH	1	DILATED	12	62	62	114	SEVERE	13.5	19	1.8 LAKHS/CU.mm	54.2
18	47	M	COPD	3	NORMAL	18	68	43	46	MILD	9	14	2.3 LAKHS/CU.mm	38.2
19	55	F	CTEPH	4	DILATED	14	62	49	72	MODERATE	11.2	17	1.4 LAKHS/CU.mm	49.6
20	39	M	COPD	3	DILATED	12	58	60	96	SEVERE	12.8	18	2.2 LAKHS/CU.mm	54
21	37	F	VALVULAR - HD	2	DILATED	15	60	49	70	MODERATE	12	18	2.5 LAKHS/CU.mm	44.5
22	45	M	COPD	3	DILATED	14	54	55.6	82	SEVERE	13.5	21	2.0 LAKHS/CU.mm	50.2
23	46	F	VALVULAR - HD	2	DILATED	19	58	35	44	MILD	9.6	16	2.9 LAKHS/CU.mm	33
24	64	F	OSA	3	DILATED	15	66	47	68	MODERATE	10.6	17	1.9 LAKHS/CU.mm	42
25	52	F	COPD - OLD PTB	3	DILATED	13	60	59	90	SEVERE	14.8	20	1.9 LAKHS/CU.mm	54.8
26	51	M	COPD	3	DILATED	15	62	50	72	MODERATE	12.5	19	2.3 LAKHS/CU.mm	48
27	43	M	COPD	3	NORMAL	17	66	36	48	MILD	8.6	14	3.8 LAKHS/CU.mm	39.6
28	41	F	CTD	1	DILATED	16	64	45.8	66	MODERATE	12	19	1.4 LAKHS/CU.mm	44
29	62	M	CTEPH	4	DILATED	15	56	46	68	MODERATE	11.5	18	4.0 LAKHS/CU.mm	45.6

30	36	F	VALVULAR - HD	2	NORMAL	16	64	39	52	MILD	9.5	17	2.1 LAKHS/CU.mm	38.2
31	42	F	VALVULAR - HD	2	DILATED	17	60	44	60	MODERATE	9.8	15	3.0 LAKHS/CU.mm	44.8
32	48	M	COPD	3	DILATED	15	62	48	70	MODERATE	11	18	2.2 LAKHS/CU.mm	43.2
33	56	M	COPD	3	DILATED	15	66	53	78	SEVERE	12	19	2.8 LAKHS/CU.mm	49.2
34	44	F	CTD	1	DILATED	14	60	60	92	SEVERE	13.8	21	1.8 LAKHS/CU.mm	46.2
35	27	M	VSD	2	DILATED	15	60	50	72	MODERATE	12	18	2.2 LAKHS/CU.mm	44
36	51	F	COPD	3	DILATED	16	66	46.5	66	MODERATE	10.5	17	3.0 LAKHS/CU.mm	42
37	48	M	COPD	3	NORMAL	18	60	35.6	44	MILD	10	16	4.2 LAKHS/CU.mm	32
38	38	M	COPD	3	DILATED	16	62	44.6	64	MODERATE	11.4	17	2.9 LAKHS/CU.mm	40
39	61	F	OSA	3	DILATED	17	60	42.4	58	MODERATE	10.2	16	4.0 LAKHS/CU.mm	39.6
40	32	M	VSD	2	DILATED	14	56	58.4	86	SEVERE	12	19	2.9 LAKHS/CU.mm	50.2
41	52	M	COPD	3	DILATED	15	62	49.2	70	MODERATE	11.8	19	3.0 LAKHS/CU.mm	42.4
42	36	F	COPD	3	DILATED	16	64	45.6	64	MODERATE	11	17	2.5 LAKHS/CU.mm	46.4
43	58	M	COPD	3	DILATED	17	60	41	58	MODERATE	10.2	16	2.2 LAKHS/CU.mm	40.8
44	46	F	IDIOPATHIC PAH	1	DILATED	14	68	49	72	MODERATE	11.5	18	2.8 LAKHS/CU.mm	48.2
45	36	F	COPD	3	NORMAL	18	66	34.8	42	MILD	8	14	2.9 LAKHS/CU.mm	40.2
46	39	M	VALVULAR - HD	2	DILATED	16	60	42	60	MODERATE	11.2	18	4.0 LAKHS/CU.mm	38.4
47	42	M	COPD	3	DILATED	15	68	44	66	MODERATE	11.4	18	2.9 LAKHS/CU.mm	41.4
48	54	F	CTD	1	DILATED	15	62	49	70	MODERATE	11	17	3.0 LAKHS/CU.mm	47.2
49	36	F	VALVULAR - HD	2	NORMAL	17	64	36	48	MILD	9.2	15	1.8 LAKHS/CU.mm	39.4
50	57	M	OLD PTB - COPD	3	DILATED	15	66	53	78	SEVERE	12.5	18	3.2 LAKHS/CU.mm	50.2

INSTITUTIONAL ETHICS COMMITTEE
MADURAI MEDICAL COLLEGE & GOVT. RAJAJI HOSPITAL, MADURAI
CDSCO:Reg.No.ECR/1365/Inst/TN/2020 &
DHR Reg.No.EC/NEW/INST/2020/484

Study Title	:	A study of Mean Platelet Volume and Red Cell distribution width as a marker of severity of pulmonary hypertension
Principal Investigator	:	Dr.R.Anand
Designation	:	PG in MD., General Medicine
Guide	:	Dr.A.Senthamarai, MD (General Medicine) Professor of General Medicine
Department	:	Department of General Medicine, Government Rajaji Hospital & Madurai Medical College, Madurai

The request for an approval from the Institutional Ethics Committee (IEC) was considered on the IEC meeting held on **20.07.2021** at GRH Auditorium, Govt. Rajaji Hospital, Madurai at 10.00 A.M

The Members of the committee, the Secretary and the Chairman are pleased to inform you that your proposed project mentioned above is **Approved.**

You should inform the IEC in case of any changes in study procedure, methodology, sample size investigation, Investigator or guide or any other changes.

1. You should not deviate from the area of work for which you had applied for ethical clearance.

2. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions. If encountered during from study.

3. You should abide to the rules and regulations of the institution(s)

4. You should complete the work within the specific period and if any extension is required, you should apply for the permission again for extension period.

5. You should submit the summary of the work to the ethical committee on completion of the study.

MEMBER SECRETARY,
IEC, Madurai Medical College,
Madurai
Dr.K.RAADHIKA, M.D(Pharm)
Associate Professor
Member Secretary
IEC - Madurai Medical College
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22 JUL 2021

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IEC Madurai Medical College
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ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு:

"மூன்றாம் நிலை மருத்துவமனைகளில் அனுமதிக்கப்படும் நுரையீரல் புடைச்சவ்வு ஊறணியுடன் கூடிய புற்று நோய்(malignant pleural effusion) நோயாளிகளில் நுரையீரல் புடைச்சவ்வொட்டலுக்கு(pleurodesis) பயன்படுத்தப்படும் மருந்துகளின் செயல்திறனை கண்டறிதல் "

பங்கேற்பாளரின் பெயர்: முகவரி:

இந்த ஆய்வின் விவரங்களை எழுத்து மூலமாகவும் எனது சொந்த மொழியிலும் எனக்கு கூறப்பட்டது. இந்த ஆய்வு குறித்த சந்தேகங்களும் அதன் விளக்கங்களையும் கேட்க எனக்கு வாய்ப்பளிக்கப்பட்டது. நான் தன்னார்வத்தோடு இந்த ஆய்வில் பங்கேற்கிறேன். மேலும் எனக்கு வழக்கமாக வழங்கப்படும் மருத்துவ சிகிச்சைகள் பாதிக்காதபடி, எந்த நேரத்திலும் நான் இந்த ஆய்விலிருந்து விலகிக்கொள்ளலாம் என்பதை அறிந்து கொண்டேன். இந்த ஆய்வின் மூலம் பெறப்படும் தரவுகள் மருத்துவ ஆராய்ச்சிக்கு மட்டுமே பயன்படுத்தபடும் என்பதை அறிந்து கொண்டு, இந்த ஆய்வில் கலந்துகொள்ள முழுமனதுடன் சுயநினைவுடன் சம்மதிக்கிறேன்.

பங்கேற்பாளரின் கையொப்பம்: தேதி: _____

சாட்சி: மருத்துவர் கையொப்பம்:

CONSENT FORM

Title of the project: **"A study of mean platelet volume and red cell distribution as a marker of severity of pulmonary hypertension**"

Participant's name: **Address:**

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant: _____

Date: _____

Witness: _____ Doctor's sign: _____

ABBREVIATIONS

MPV	-	MEAN PLATELET VOLUME
RDW	-	RED CELL DISTRIBUTION
PAH	-	PULMONARY ARTERIAL HYPERTENSION
PASP	-	PULMONARY ARTERY SYSTOLIC PRESSURE
TRPG	-	TRICUSPID REGURGITATION PRESSURE GRADIENT
TAPSE	-	TRICUSPID ANNULAR SYSTOLIC PLANE EXCRUSION
PDW	-	PLATELET DISTRIBUTION WIDTH
COPD	-	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
CTEPH	-	CHRONIC THROMBO EMBOLISM ASSOCIATED PULMONARY HYPERTENSION
RA	-	RIGHT ATRIUM
RV	-	RIGHT VENTRICLE
ASD	-	ATRIAL SEPTAL DEFECT
VSD	-	VENTRICULAR SEPTAL DEFECT