KJC 4

Kerala Journal of Cardiology

Focus Topic: **Pulmonary Hypertension**

Courtesy

Every image has a story that brings it to life. And the power to inspire.

Kathleen Sheffer received a heart-lung transplant on the 1st of July 2016, after a 17 year long fight with Idiopathic Pulmonary Hypertension. Now 24, she follows her passion for photography in San Francisco, California (Kathleen Sheffer Photography) and shares her experience in her column, Life after PH. The image on the cover page is an abstract rendering of her explanted heart that she commissioned with the artist Rachel Wadlow (www.rachelwadlowart.com), on the occasion of Valentine's Day, 2019. She sends her wishes to KJC.

I am indeed in fantastic health! Thank you for your kind words and interest in my story. I would love to be included in your issue. Thank you for the work you are doing. There is so much more to do to raise awareness of Pulmonary Hypertension.

Best,

Kathleen

KJC

Kerala Journal of Cardiology

CONTENTS

Editorial

KJC Diamonds
Focus topic : Pulmonary Hypertension (PH)

KJC Pearls

Close Encounters of the Fourth Kind

Sajan Ahmad Z

Assistant Professor, Department of Cardiology,
Pushpagiri Medical College, Thiruvalla, Kerala, India.

My Heart Leaps Up

William Wordsworth, 1802

Greetings from Kerala Journal of Cardiology and Indian College of Cardiology Kerala Chapter.

2019. Our journey of a different kind continues.

After Congenital Heart Disease, Valvular Heart Disease and Interventions of the Interatrial Septum in the previous issues, KJC 4 will focus on *Pulmonary Hypertension* (PH) in the *KJC Diamonds* section. The definition and classification is followed by clinical, ECG, echocardiographic and cardiac catheterisation features. Management approach and the entity of PH in HFpEF are also addressed. Since the Child is Father of the Man, pediatric perspective is also included with articles on Eisenmenger syndrome and PPHN. We hope it will be a comprehensive coverage of the subject that will be useful to both the Residents and Consultants in Cardiology. It is our firm belief that knowledge and science have no boundaries. Therefore, in this issue, we have eminent Teachers not only from Kerala, but also from our friendly neighbouring states.

The *KJC Pearls* section continues with a few upgrades :

* The advent of the Heart Team concept makes it imperative that the cardiology community be aware of important surgical procedures and outcomes. Hence we have a peep into *The Surgeon's Den*.

* *Beyond the Heart* is a section aimed at showcasing clinical conditions in other specialities that are relevant to the cardiologist. A gastroenterologist is our first guest.

* The coronary circulation finds its rightful space in a *Case report* of PCI in anomalous LCX.

* *Statistics Simplified* is a new series which kicks off with an introduction to the famous, yet elusive p value.

* *KJC Classroom* is in the novel format of an earnest and educational personal letter from our previous (and dear) Editor-in-Chief.

* The past is prologue. *History of Cardiology* pays a fitting and poetic tribute to Dr Paul Wood, THE legend in pulmonary hypertension.

* The future is now. And the young brigade of residents have now been given a slot in the *Resident's Corner* to share information that will be useful to their peers.

At the heart of KJC is a love for Cardiology, and a desire to learn, share and celebrate it's science, practice and art. This has been made possible by the unconditional and unflinching support and vision of the ICC Kerala Office-bearers, both current & past. Thanks will be an understatement. We are also happy that this issue is being released on the occasion of the 26th National Conference of ICC, 2019 and thank the Organising Team and the Office-bearers of the National ICC.

And ofcourse, a big thanks to our readers, young and old, novices and veterans alike, for sharing our enthusiasm and for the encouragement. Together, let us Read and Rise!

Warm regards from the heart

Sajan Ahmad Z
Editor-in-Chief
For the Editorial Team

Address for correspondence: Dr. Sajan Ahmad Z, MD, DM, DNB, 16 FG, Skyline Edge, Thirumoolapuram, Thiruvalla, Kerala, India – 689115.
Ph: 9447097965, Email: sajanahmad@gmail.com

KJC Diamonds

Definition and Classification of Pulmonary Hypertension

Sunitha Viswanathan

Professor and Head, Department of Cardiology,
Government Medical College, Thiruvananthapuram, Kerala.

EVOLUTION

Since the 1st World Symposium on Pulmonary Hypertension (WSPH) at Geneva in 1973, pulmonary hypertension (PH) has been arbitrarily defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, measured by right heart catheterisation. What is actually the upper limit of normal mean Pulmonary artery Pressure (mPAP)? In 2009, Kovacs *et al*. analysed all available data obtained by RHC studies in healthy individuals to determine normal values of mPAP at rest and exercise. Data from 1187 normal subjects from 47 studies were analysed. mPAP at rest was 14.0±3.3 mmHg; this value was independent of sex and ethnicity, and was only slightly influenced by age and posture.

Recent data from normal subjects has shown that normal mPAP was 14.0±3.3 mmHg. Two standard deviations above this mean value would suggest mPAP>20 mmHg as above the upper limit of normal (above the 97.5th percentile).

This definition is no longer arbitrary, but based on a scientific approach. However, this abnormal elevation of mPAP is not sufficient to define pulmonary vascular disease as it can be due to an increase in cardiac output or pulmonary arterial wedge pressure. This definition continued till the 6th Task force in order to avoid over diagnosis and overtreatment Thus, this 6th WSPH Task Force proposes to include pulmonary vascular resistance ≥3 Wood Units in the definition of all forms

Address for correspondence: Dr. Sunitha Viswanathan, MD, DM, Professor and Head, Department of Cardiology, Government Medical College, Thiruvananthapuram, Kerala. Email: sunithaviswan@gmail.com

of pre-capillary PH associated with mPAP>20 mmHg. Prospective trials are required to determine whether this PH population might benefit from specific management.

Further, the patients with PH are further divided into precapillary PH and post capillary PH. Precapillary PH has been defined as mPAP of ≥25 mm Hg with Pulmonary capillary wedge pressure (PCWP) of ≤ 15 mm Hg and PVR of ≥ 3 WU while, post capillary PH has been defined as when mPAP ≥ 25 mm Hg and the PCWP is ≥ 15 mm Hg. In the present clinical classification of PH, pre-capillary PH concerns patients from groups 1, 3 and 4, some patients from group 5, and rarely patients from group 2 with combined pre- and post-capillary PH.

Recently, another variable that has been taken into consideration is Diastolic pressure gradient (DPG). DPG is defined as difference between diastolic PAP and mean PCWP. Post capillary PH is defined as DPG of ≤ 7 mm Hg and /or PVR of ≤ 3 WU, while DPG of ≥ 7 mm Hg and /or PVR ≥ 3 WU is a condition with existence of both precapillary and post capillary PH.

SHOULD EXERCISE INCREASE IN PH BE INTRODUCED ?

In 2004, PH was defined as resting mPAP>25 mmHg or exercise mPAP>30 mmHg. At the 4th WSPH in 2008, however, the "exercise" part of the definition was removed. This was largely due to uncertainties concerning the interrelationship between normal ageing, Cardiac Output (CO) changes with exercise and pulmonary vascular physiology. This question was revisited again at the 6th WSPH in 2018.

WHY MIGHT EXERCISE PH BE RELEVANT?

A rise in resting PH pressure is a late event in the natural history of PVDs, because of microvascular "reserves". PAP rises only when ≥50% of the microcirculation has been lost. Much effort has been directed towards detecting PVD at an earlier (and potentially more treatable) stage. Intuitively, "unmasking" PVD by increasing CO to demonstrate increased resistance is a logical idea. Furthermore, PH patients first develop symptoms on exercise.

A number of studies have tried to unmask PVD by "stressing" the pulmonary circulation, by lung flow redistribution with upright posture or by increasing CO . This has led to the concept of "multipoint mPAP–CO" curves, where the rate of rise of mPAP with increasing CO has been informative. In general, mPAP rises by ≥1 mmHg per litre of CO in normal subjects; PVD patients have a rise of ≥3 mmHg per litre of CO, reflecting increased resistance. Generating such data is, however, challenging as exercise RHC measurements are time consuming, difficult, and potentially complicated by errors due to rapid respiratory cycles and inaccuracies in exercise CO and PAWP measures. Thus, generating mPAP–CO graphs for individual patients is impractical as a clinical routine.

Although there is intuitive appeal to measuring exercise haemodynamics to detect PVD at an earlier stage than can be revealed by measurements at rest, too many uncertainties persist to allow the reintroduction of a clinically useful definition of exercise PH. More information is required concerning normal changes with ageing, high CO and especially about distinguishing exercise-elated changes in PAWP (due to LHD) from changes due to PVD. These areas will certainly be fruitful areas for future investigation.

CLASSIFICATION

1. Second World Symposium on PH - 1998

In 1998, at the Second World Symposium on PH at Evian, a clinical classification of PAH was proposed classifying PH into groups that share similar pathophysiologic and hemodynamic characters.

Five groups of disorders that cause PH were identified: pulmonary arterial hypertension (Group 1); pulmonary hypertension due to left heart disease (Group 2); pulmonary hypertension due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic pulmonary hypertension (Group 4); and pulmonary hypertension due to unclear multifactorial mechanisms (Group 5). During the successive world meetings, a series of changes were carried out, reflecting some progresses in the understanding of the disease

2. Dana Point Classification - 2008

The classification system of Pulmonary hypertension (PH) was revised at the 4th World Symposium on PH held at Dana Point California, in 2008.

3. Updated Clinical Classification - 2013

The 5th World symposium on PH was held in Nice, France in 2013[1,2]. The key classification systems are provided (Tables 1,2,3).

Table 1 Classification of Pulmonary Hypertension[1,2]

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 hemangiomatosis
    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 inflow/outflow 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   Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
    5.2   Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
    5.3   Metabolic disorders: glycogenstorage disease, Gaucher disease, thyroiddisorders
    5.4   Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

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

Table 2 Updated Classification for Drug- and Toxin-induced PAH[1,2]

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Interferon α and β
SSRIs	Amphetamine-like drugs
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

Table 3 Clinical Classification of PAH Associated with Congenital Heart Disease[1,2]

1. **Eisenmenger syndrome**

   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.

2. **Left-to-right shunts**

   - Correctable
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.

3. **Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease**

   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.

4. **Post-operative PAH**

   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

4. 6th World Symposium on PH - 2018

The 6th WSPH comprised 124 experts, divided into 13 task forces, that began their work in January 2017 and presented their consensus opinions to an audience of 1376 participant attendees between February 27 and March 1, 2018 in Nice, France[3]. A newly created task force dedicated to patients' perspectives, including representatives of patients' associations worldwide, was added for the 6th WSPH.

After consideration of the changes in the general definition of PH the proposed haemodynamic definition of PH in left heart disease (LHD) was:

1) isolated post-capillary PH: PAWP >15 mmHg and mPAP>20 mmHg and PVR <3 WU;

2) combined post- and precapillary PH: PAWP >15 mmHg and mPAP>20 mmHg and PVR ≥3 WU.

The importance of the differential diagnosis between idiopathic PAH and PH due to heart failure with preserved left ventricular ejection fraction has been emphasised.

The task force has therefore proposed including a pulmonary vascular resistance (PVR) ≥3 WU into the definition of pre-capillary PH associated with mPAP>20 mmHg, irrespective of aetiology[4]. Future trials should assess the efficacy of pulmonary arterial hypertension (PAH) medications (currently approved based on a mPAP≥25 mmHg) in patients with mPAP from 21 to 24 mmHg and PVR ≥3 WU. Due to limited data, the task force declined to identify a clinically useful definition of exercise PH, encouraging additional outcome studies instead.

The clinical classification of PH was simplified, maintaining the traditional five-group structure.

Regarding clinical classification, the main Task Force changes were the inclusion in group 1 of a subgroup "pulmonary arterial hypertension (PAH) - long-term responders to calcium channel blockers", due to the specific prognostic and management of these patients, and a subgroup "PAH with overt features of venous/capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement", due to evidence suggesting a continuum between arterial, capillary and vein involvement in PAH[5].

As knowledge and data regarding pulmonary hypertension continue to accumulate, newer definitions and classifications shall continue to emerge with the common goal of enhancing patient survival and quality of life.

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Clinical Examination in Pulmonary Hypertension

Prabhavathi

Professor, Department of Cardiology
Sri Jayadeva Institute of Cardiovascular Sciences and Research,
Bangalore, Karnataka.

INTRODUCTION

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) >25 mmHg, measured during cardiac catheterization. It may involve multiple clinical conditions and can complicate majority of cardiovascular and respiratory diseases. PH is divided into 5 groups, based on the clinical presentation, pathophysiology and treatment implications (ESC/ERC 2015 guidelines)[1]. Natural history of PH varies according to the etiology of the condition. PH is a progressive disease characterized by increased pulmonary vascular resistance (PVR) and diminished right ventricular (RV) function due to increased RV afterload.

Most common causes of PH are left heart diseases and lung diseases. Pulmonary artery hypertension (PAH) is due to remodelling at the level of the small pulmonary muscular arterioles. Most important causes are congenital left to right shunts, PH related to connective tissue diseases and idiopathic PAH (IPAH). PAH is a precapillary cause of PH. Other important causes of precapillary PH are lung diseases and chronic thromboembolic PH (CTEPH). PH due to left heart diseases is post capillary PH.

Clinical examination can be subtle or nonspecific, especially during the early phase of PH. But most often, clinical findings can help in the diagnosis of PH and may give a clue to the etiology. Certain clinical findings can reliably reflect the severity of the PH and right heart failure (RHF). Disorders like IPAH and CTEPH have the purest expressions of PH.

Physical appearance

General physical examination may suggest a possible underlying cause for PH (Table 1)[2]. Cutaneous telangiectasia, digital ulceration and sclerodactyly are signs of scleroderma spectrum of diseases, which has the highest prevalence of PH among the connective tissue diseases. Raynaud's phenomenon occurs commonly in patients with PH related to connective tissue diseases. Spider naevi, testicular atrophy, and palmar erythema suggest liver diseases. Obesity and kyphoscoliosis may be possible substrates for disordered ventilation. Peripheral edema may be present late in the course of PH, when right heart failure (RHF) sets in.

Clubbing

Clubbing may be present in Eisenmenger syndrome (ES), hypoxic lung diseases and liver diseases. Differential clubbing, where toes show more clubbing than the fingers, can be seen in patent ductus arteriosus (PDA) with reversal of shunt.

Cyanosis

Central Cyanosis is a feature of ES and hypoxic lung diseases. Differential cyanosis, where cyanosis is more in lower limbs than in upper part of the body, is typically seen in patients with Eisenmenger PDA. Patients with IPAH may have peripheral cyanosis especially during effort, due to low cardiac output. Occasionally they may have mild central cyanosis, which results from right to left shunt through patent foramen ovale.

Address for correspondence: Dr. Prabhavathi, MD, DM, DNB, S 201, Wilson court apartment, No 48, 6th cross, Wilson Garden, Bangalore 560027, Karnataka
Ph: 9845020533, Email: prabhavathi_in@yahoo.com

Table 1: Physical signs that suggest possible underlying cause or associations of PH (Modified from reference 2)

Sign	Underlying Cause
Central cyanosis	Eisenmenger Syndrome, lung diseases
Clubbing	Eisenmenger Syndrome, liver diseases, lung diseases
Cardiac findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop.	Congenital or acquired heart diseases
Rales, dullness, or decreased breath sounds.	Pulmonary congestion or effusion or both
Fine rales, accessory muscle use, wheezing, protracted expiration	Pulmonary parenchymal diseases
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorders
Peripheral venous insufficiency or obstruction	Possible deep vein thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic PH, Peripheral Pulmonary Stenosis
Splenomegaly, spider angiomata, palmary erythema, icterus, caput medusa, ascites	Portal hypertension

Pulse oximetry

Pulse oximetry is considered as the 5th vital sign. Clinically cyanosis can be detected when the saturation is <85% with normal haemoglobin levels. To detect desaturation between 85 to 94%, pulse oximetry is helpful. One distinction between ES and other forms of PH is the presence of desaturation. Pulse oximetry at rest and with exercise is a useful way to uncover a missed intracardiac shunt. Patients with bidirectional shunt may have normal saturation at rest, which falls during exercise, reflecting shunt reversal. A saturation difference of 4-5% between fingers and toes qualifies for differential cyanosis in Eisenmenger PDA. Overnight oximetry may help to identify patients with obstructive sleep apnea.

Pulse & Blood pressure (BP)

Arterial pulse is usually normal. In severe PH, pulse may be of small volume with narrow pulse pressure because left ventricular (LV) stroke volume is reduced. Rarely pulse pressure may be wide in patients with Eisenmenger PDA with severe pulmonary regurgitation (PR)[5]. Here aortic diastolic pressure is low because diastolic run off occurs from aorta through the ductus into the pulmonary artery (PA), and then across the incompetent pulmonary valve (PV) into the RV.

An increased resting heart rate from baseline without another explanation is a sensitive sign of impending or overt decompensated RV failure.

In severe PH, BP is frequently low but tolerated, representing "warm" shock. Systemic hypertension may suggest obstructive sleep apnea or LV diastolic dysfunction as a cause of PH.

Jugular venous pulse (JVP)

Prominent "a" wave is the characteristic finding in JVP. It may become "giant" when PA pressure (PAP) becomes equisystemic or suprasystemic. This results from forceful right atrial (RA) contraction against noncompliant RV, secondary to RV hypertrophy (RVH). Paul Wood aptly described it as: "This presystolic venous pulse is abrupt and collapsing in quality; is little influenced by change in posture and may be more noticeable on inspiration"[3]. It is best seen when the patient sits upright or stands up, when the "v" wave usually disappears. "a" wave is absent in patients with atrial fibrillation (AF).

However, in Eisenmenger ventricular septal defect (VSD), JVP is usually normal because RV systolic pressure cannot exceed the systemic level, and the RV copes with this pressure without any help from RA. Even in PDA with suprasystemic PVR, "a" wave is relatively unimpressive because the RV adapts to systemic pressure without augmented RA contraction.

A large "v" wave may appear when there is increasing tricuspid regurgitation (TR) which attenuates the "x" descent and exaggerates the "y" trough. In this scenario, prominent "v" wave may be confused with the carotid arterial pulsation.

Positive hepatojugular reflux suggests RV dysfunction. When RV failure sets in, there will be elevation of mean JVP. Normal inspiratory collapse of JVP disappears or it may even increase with inspiration in RV failure (Kussmaul's sign).

Precordial movement and palpation
(Table 2)

RV impulse varies in prominence with the severity and duration of PH, and with the size and function of the RV. An enlarged RV displaces the LV from the apex resulting in a diffuse apical impulse (AI) of RV type. LV can no longer be palpated in severe PH. However, when patients with mitral regurgitation (MR) or aortic valve (AV) disease develop PH, apical impulse continues to be of LV type. Similarly, in patients with truncus arteriosus with biventricular regurgitation and PAH, both ventricles are palpable[5].

A parasternal RV heave is often palpable at the left lower sternal border (LLSB) ranging from grade I to III, depending on the severity of PH. It is characterised by sustained (>50% of systole) outward movement of the left sternal border in 3rd and 4th intercostal spaces, which is augmented during inspiration. This also results in systolic epigastric pulsations which is better appreciated in held inspiration and in supine position. This is particularly useful in patients with chronic obstructive pulmonary disease (COPD), obesity or muscular chest and chest deformities, when the RVH is suspected but left parasternal heave (LPH) is not felt. In Eisenmenger VSD and PDA, LPH is insignificant and not more than grade I to II[4] as RV pressure cannot become suprasystemic.

An increased force of right atrial (RA) contraction generates a palpable right-sided S4 which parallels the "a" wave of the jugular venous waveform. This causes presystolic distention, which is palpated at the LLSB and subxyphoid area. Like the "a" wave of JVP, palpable RV S4 is not a feature of PH in VSD and PDA (4).

Palpation in the 2nd left intercostal space detects 2 important events –
1. Systolic impulse of a dilated hypertensive PA
2. Loud pulmonary component of the second heart sound (P2).

Graham Steell wrote in 1888, "the closure of the semilunar valve being generally perceptible to the hand placed over the pulmonary area as a sharp thud".

In general, palpable P2 in left 2nd intercostal space correlates with a PA systolic pressure of 75 mm Hg[5].

In patients with mitral stenosis (MS), palpable P2 accurately detects PA pressures of 50 mm Hg or more[5a].

Occasionally a transmitted pulmonic ejection click may be palpable in the second left intercostal space. PR murmur may be associated with thrill in 10% of cases.

It is often possible to see as well as feel the PA and RV impulses and even the presystolic distention. Held exhalation makes these impulses more apparent.

Table 2: Findings of precordial examination in PH

- RV apical impulse
- Left parasternal heave
- Systolic epigastric pulsations
- Palpable RV S4
- Pulmonary artery pulsation
- Palpable P2
- Palpable pulmonary ejection click (rare)
- Thrill of PR murmur (10%)

Percussion

Dullness in the 2nd intercostal space to the left of the sternum indicates dilated PA, which is a feature of PH.

Auscultation

8 auscultatory signs may be found in PH: abnormal second heart sound, pulmonary ejection click, Graham Steell murmur due to PR, tricuspid regurgitation (TR) murmur, pulmonary midsystolic murmur, RV S3, RV S4, and a mid-diastolic-presystolic murmur (Fig1), (Table 3)[3]

Table 3: Auscultatory features of PH

- Abnormal S2
- Pulmonary ejection click
- RV S4, S3
- TR murmur
- Graham Steell (PR) murmur
- Midsystolic pulmonary murmur (rare)
- Middiastolic murmur (rare)

Hallmark of PH is loud P2, which is the most consistent finding and is found in 93% of cases. Others are less commonly heard. Right-sided S3 and S4 are found in 23% & 38% of cases respectively. Murmur of TR and PR are audible in 40% and 13% of cases respectively[4].

Second heart sound (S2): The pulmonary component of the S2 (P2) is altered in its timing, intensity, and precordial location.
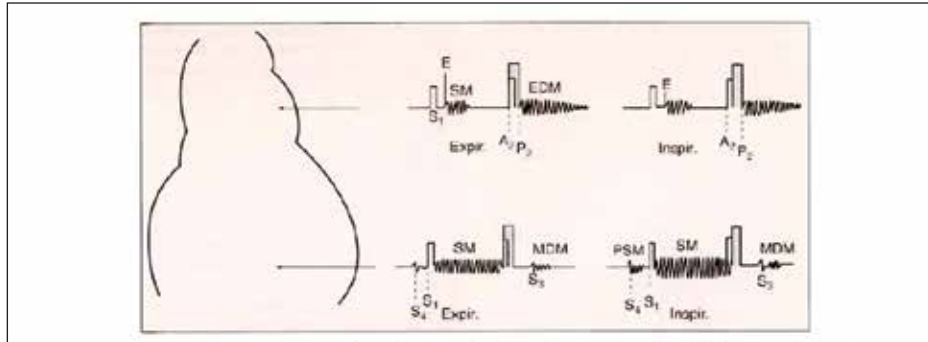
Figure 1: Auscultatory features of PH (from Perloff's Clinical Recognition of Congenital Heart Disease; 6th edition, 2012)

S2 Splitting in PH: The degree of splitting is the net effect of two variables:

1. Decreased capacitance and increased resistance in the pulmonary vascular bed due to PH, which decreases hang out interval and narrows the split due to early P2.
2. Prolongation of RV systole in RV dysfunction increases the split due to delayed P2.

When RV function is normal, inspiratory splitting is usually preserved. However, a loud P2 in the second left interspace can obscure a closely preceding aortic component. But auscultation at the right base, LLSB, or apex helps to analyse the transmitted but attenuated P2 and allows the detection of splitting.

A functionally depressed RV is associated with prolonged RV systole, resulting in delayed P2. It cannot increase its stroke volume with inspiration, so the split becomes fixed. Hence, in patients with severe PH and RV failure, S2 may be wide split and fixed.

S2 split in some common diseases with PH: In MS with PH, split is physiological or narrower due to early P2. In mitral regurgitation (MR) with PH, split may be wide due to early A2. In VSD with hyperkinetic PH, split is wide due to early A2, whereas in Eisenmenger VSD, S2 is single. In atrial septal defect (ASD), both with hyperkinetic or obstructive PH, split is fixed but may become narrower in severe obstructive PH. In PDA with hyperkinetic PH, split may be physiological or reverse, whereas in Eisenmenger PDA, split is normal. In idiopathic PAH, inspiratory splitting is narrower (Table 4).

Intensity of P2: Of all the auscultatory signs, **loud P2 is the most consistent finding of PH and comes closest to being unique to PH.** Graham Steell wrote that

Table 4: S2 split in various conditions with PH

Underlying Heart Disease	S2 Split
MS	Narrow split
MR	Wide variable split
VSD	
Hyperkinetic PH	Wide variable split
Eisenmenger VSD	Single S2
ASD	Wide and fixed Split narrows in obstructive PH
PDA	
Hyperkinetic	Normal/Reverse split
Eisenmenger PDA	Normal split
IPAH	Narrow split
RV Failure	Wide and fixed split

Table 5: Grading of PH based on intensity of P2 (Modified from Reference 6)

	Grading	Description
1	Mild or grade 1 (+)	When intensity of P2 is equal to A2
2	Moderate or grade 2 (++)	When intensity of P2 is louder than A2
3	Severe or grade 3 (+++)	When P2 is loud and banging and is audible beyond the pulmonary area

"accentuation of the pulmonary second sound is always present". The intensity of the P2 is a representation of the PA systolic pressure. Normally even in left 2nd intercostal space, A2 is louder than P2. If intensity of P2 is equal to A2, it suggests mild PH. P2 louder than A2

indicates moderate PH. P2 is loud, banging and becomes audible all over the precordium, up to the apex in severe PH (Table 5)[7].

Audible splitting at the apex indicates significant PH and this finding is better correlated with PH in IPAH[8]. P2 may be loud in ASD without significant PH, due to proximity of the dilated PA to the chest wall. In this situation P2 may be audible at the apex (causing audible splitting of S2), as volume overloaded RV occupies the apex. Rarely, intensity of P2 may be normal inspite of severe PH, in patients with RV failure and low cardiac output. This is more likely to happen in patients with IPAH with RV failure

Pulmonary ejection click (EC): It is identified by its high-pitched sharp clicking quality, and its maximal intensity in the second left intercostal space. The timing of the EC coincides with the interval between the onset of RV systole and opening of the pulmonary valve (PV) (isovolumetric contraction period). The origin of this sound is less certain. It could be due to opening movement of the leaflets that resonate or due to reverberations of the proximal arterial wall of dilated PA. This click does not vary with respiration (constant click), because RV end diastolic pressure cannot exceed the PA end diastolic pressure in severe PH, which prevents premature opening of PV. A prominent pulmonic EC radiates to the LLSB and apex, especially when the RV occupies the apex.

TR murmur: TR murmur becomes increasingly apparent when the RV pressure increases. In general, **RV systolic pressure >55 mmHg** will cause functional TR due to annular dilatation (9). It is maximal at the LLSB; but when the RV occupies the apex, the murmur is well heard at the apex, and when the RA is enlarged, the murmur is heard to the right of the sternum. TR murmur is holosystolic and high-pitched, because regurgitation is holosystolic and has high velocity. It may be loud enough to cause a thrill or may be barely audible.

An increase in intensity during active inspiration, Rivero-Carvallo sign, is an important finding. But if the breath is held in inspiration, the intensity fades. The murmur is sometimes audible only during deep inspiration or passive leg raising. Amplification during inspiration depends on a RV that is functionally capable of converting an inspiratory increase in venous return into an increase in stroke volume and regurgitant flow. This capacity is lost with RV failure, so Carvello's sign disappears.

Pulmonary Regurgitation (PR) Murmur: PR murmur is popularly known as **Graham Steell** murmur. It may be appreciated in patients with a dilated main PA, which usually represents longstanding elevated pressures, most prominent in ES, long-term survivors from effective therapies, or CTEPH. Presence of PR murmur in PH indicates equisystemic or suprasystemic PA pressure.

PR murmur starts with loud P2. It is typically located in the 2nd and 3rd left intercostal spaces adjacent to the sternum, but when it is loud, it is heard at the LLSB or even to the right of the sternum. Marked difference between the diastolic pressure in the PA and RV exists from the beginning to the end of diastole, so the murmur is prolonged and high frequency. The configuration is decrescendo, but vibrations can be almost equal throughout diastole. Length of the murmur varies. It may be pan diastolic in PAH due to ES, where RV diastolic pressure may remain normal. Murmur may be brief in PR due to post capillary PH. Intensity can be enough to generate a thrill or soft or even inaudible. PR murmur may or may not increase with inspiration, depending on the RV function.

When the PR murmur is rough with a diastolic thrill, it is often mistaken for a systolic murmur of VSD or pulmonic stenosis. This type of murmur is more likely in PH due to PDA and IPAH. In this setting, one should carefully auscultate to identify the sounds first and by inching the stethoscope from the apex to the base[9].

RV S4: RV S4 should parallel the "a" wave of the jugular venous waveform. S4 accompanies presystolic distention of the RV and are best detected with the bell of the stethoscope (low pitched sound) applied lightly at the LLSB, but it may be heard at the apex when the RV forms the apex. The low frequency S4 can be more readily palpated than heard, a feature recognized by Potain who stated that "if one applies the ear to the chest, it affects the tactile sensation more than the auditory sense"[3]. RV S4 becomes louder and occurs earlier during inspiration because the greater force of RA contraction is translated into earlier and more vigorous presystolic filling of the RV. In VSD, when Eisenmenger complex is present from infancy, the RV copes with this level of systolic pressure without the help of augmented atrial contraction. Thus, S4 is not a feature of PH in this context. RV S4 is absent in AF.

RV S3: S3 occurs during the rapid filling phase of the cardiac cycle and is a sign of RV failure. With the advent of TR, S3 intensifies due to accelerated flow across the tricuspid valve (TV). S3 is low frequency sound best detected with the bell of the stethoscope applied over the RV, but it is audible at the apex when apex is occupied by the RV.

Pulmonary midsystolic murmur results from ejection into the dilated hypertensive PA. This murmur is

confined to the left 2nd intercostal space, is introduced by the pulmonary EC, and is symmetric, short, impure, and soft (grade 1/6 or 2/6). Intensity and length of this murmur may increase when there is significant PR, due to increased flow across the PV.

Occasional occurrence of **mid-diastolic/presystolic murmur** represents prolonged vibrations of third or fourth heart sounds. Mid-diastolic murmurs increase during inspiration and are more likely to occur when the TV is incompetent, which increases TV flow. In addition, "right sided Austin Flint" murmurs have been described with PR of PH.

Influence of PH on coexisting Congenital/Acquired Heart Diseases

Both congenital and acquired cardiac defects can initiate PH, and then in turn be influenced by it[10].

Shunt lesions: In VSD with advancing PAH, the pansystolic murmur may become early systolic, and finally when the shunt is reversed (Eisenmenger's complex), the murmur is abolished completely. In addition, when high PVR diminishes the left-to-right shunt and consequently the mitral flow, the mid-diastolic apical rumble also disappears. LV also regresses. Similar changes occur in PDA, when PVR increases and left to right shunt reverses. Both shunt murmur and flow murmur disappear.

Mitral stenosis (MS): When PH causes RV hypertrophy and dilatation, the LV tends to rotate away from the chest wall and may no longer form the apex. In addition, high PVR may decrease cardiac output and diminish the rate of flow across the stenotic mitral valve (MV). When PH is severe enough to cause both displacement of the LV apex and a decline in MV flow, the auscultatory signs of MS may be attenuated or even abolished, resulting in "silent MS"

PH due to intrinsic lung diseases: Emphysema is the most common cause of chronic parenchymal lung disease associated with PH.

2 factors influence clinical analysis of the PH:
1. Wheezes, rhonchi and rales in the distended emphysematous lung may make cardiac auscultation almost impossible.

2. Large, over expanded chest may obscure the heart so that cardiac dullness is absent, precordial pulsations are imperceptible, and heart sounds and murmurs are difficult to hear.

Precordial auscultation may improve, if the patient sits and leans forward.

A loud P2 may be damped, so that a moderate increase in intensity may suggest severe PH.

Other system examination

Chest examination: The findings on lung examination are nonspecific but may point to the underlying cause of PH. For instance, wheezing may lead to a diagnosis of COPD, and basilar crackles may indicate the presence of interstitial lung disease[11]. Pulmonary vascular bruits may be heard in CTEPH[11]. Peripheral PA stenosis may cause a systolic or continuous murmur over the back or precordium.

Abdominal examination: RHF results in hepatomegaly and/ascites. A pulsatile liver may be present in the setting of severe TR.

Assessment of severity of PH: In a recent study by Daniel Vis, JVP of > 4 cm above the sternal angle, and a loud P2 had reasonable sensitivity to detect moderate to severe PH. Right-sided S3 and S4 had reasonable specificity[12]. Physical signs that suggest moderate to severe PH are listed in Table 6[8].

Table 6: Physical signs that suggest moderate to severe PH (Modified from reference 8)

- Prominent jugular "a" wave
- Hepatojugular reflux
- Increased jugular v waves
- Left parasternal heave (Grade 3)
- Loud P2 (audible at apex in over 90%)
- Ejection systolic click
- RV S4 (in 38%)
- Tricuspid regurgitation
- Pulmonary regurgitation
- Pulsatile liver

Elevated JVP, hepatomegaly, ascites, peripheral oedema and cold extremities characterize patients with advanced disease (Table 7).

Table 7: Advanced PH with RV failure (Modified from reference 8)

Sign	Implication
RV S3 (in 23%) Elevated JVP Hepatomegaly	RV dysfunction or TR or both
Peripheral edema (in 32%) Ascites	RV dysfunction or TR or both
Low blood pressure, diminished pulse pressure, cold extremities	Reduced cardiac output, peripheral vasoconstriction

CONCLUSION

PH is a common clinical condition characterized by nonspecific signs and symptoms with multiple potential causes. A high index of suspicion, meticulous history and careful clinical examination are paramount in the diagnosis of PH. Physical examination can provide a wealth of information about the presence and severity of PH. However various diagnostic modalities are required to confirm the presence and severity of PH, and unravel the etiology.

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ECG in Pulmonary Hypertension

Rajesh G Nair

Professor of Cardiology, Government Medical College, Calicut, Kerala.

Introduction

Though the classical triad of dyspnoea or fatigue on exertion, normal lung parenchyma on chest X-ray and normal pulmonary function test results doesn't have much differential diagnosis other than pulmonary hypertension(PH), the average delay in diagnosis of PH after the onset of symptoms is a mean of 27 months[1]. Speich in an editorial in Eur Respir J 2011 states that there is not only a diagnostic triad but also a ''fatal triad'' regarding the early detection of precapillary PH, namely the low specificity of symptoms, the inconspicuous clinical findings and the lack of the awareness of treating physician. Though the gold standard for screening PH is echocardiography, it is expensive, and not freely available to all physicians and hence we need a revival of the old and neglected tool the ECG. The echocardiographic analysis has decreased our dependency on the ECG and catheterization to diagnose PPH. Structural changes in right atrium and right ventricle such as hypertrophy or dilation are reflected by several ECG changes. Although of limited value, standard ECG has diagnostic[2] and prognostic[3] potential in PH. The role of ECG for the diagnosis of PH has been investigated in a large US registry initiated in the early 1980s. Rich et al reported that electrocardiographic RVH was present in 87% and right axis deviation in 79% of patients with idiopathic PH.[4]

Basis of ECG abnormalities

RV forces are normally masked by dominant LV. RVH is defined as RV weight > 71 g or RV enlargement when RV is > 30% of the total ventricular mass. Since V1 is the lead closest to RV, it is the lead which is most sensitive to changes in PH, similarly leads V3R and V4R may also be useful in detection of RVH.

PH causes elevated RV wall stress which leads to RVH, both result in ECG changes. The ECG changes depend on the degree of the PA pressure, the degree of hypertrophy of RV and aetiology of PAH. Studies in rats and humans have illustrated that even mildly increased RV pressure is associated with significant changes in myocardial electrical properties, detectable in a standard 12-lead ECG. The classic ECG criteria rely on depolarization characteristics of hypertrophied RV. As RV hypertrophy occur relatively late in the course, it becomes apparent only in advanced stages of PH. Therefore, regular surface ECG criteria may not be well suited for early detection of elevated PA pressure.

Address for correspondence: Dr. Rajesh G Nair, MD, DM, Professor of Cardiology, Government Medical College, Calicut, Kerala.
Email:drrajeshgnair@gmail.com

Importance of clinical correlation in ECG analysis.

Bossone E et al[5] studied the importance of clinical information in interpreting ECG of PH cases. They showed that the cardiologist blinded to clinical data most often characterized RV strain as non-specific or inferior or as antero-lateral ischemia. The electrocardiogram has a high degree of sensitivity for the detection of abnormalities in symptomatic patients with isolated PH provided there is correlation with the clinical parameters to optimize the usefulness of the ECG.

ECG Changes in RVH

1. QRS changes
   a. Right axis deviation
   b. R wave dominance in right leads
   c. Delay in intrinsicoid deflection > 0.02 sec
   d. RS or rS complexes in left leads
   e. RS complexes in transition zone
   f. RBBB
   g. Clockwise rotation
   h. Initial incident r, rR' complex

2. ST-T & U wave changes
   a. T inversion V1-V4
   b. Convex up ST depression
   c. U wave inversion

3. P wave changes
   a. Tall peaked P wave in lead II
   b. P axis to > +60

Predicting region of RV hypertrophied in RVH from ECG

1. Dominant free wall hypertrophy
   a. Tall R in right precordial leads.
   b. Mean QRS axis towards 120 degrees.

2. Dominant right paraseptal hypertrophy
   a. Tall R of RS complex in transition zone
   b. Mean WRS axis +90 to +120

3. Dominant right basal hypertrophy
   a. rS complexes in V1 – V6 with deep S in V5,6
   b. qR in aVR
   c. SI SII SIII syndrome
   d. Mean WRS axis in right superior quadrant.

Type of RV hemodynamic loads from ECG.

1. RV systolic overload
   a. Tall R with inverted T in right precordial leads
   b. Diminished/inverted U in right leads

2. RV diastolic overload
   a. Incomplete/complete RBBB

Type of heart disease and usefulness of ECG criteria.

In congenital heart disease sensitivity of such criteria is over 90%, in mitral stenosis it is 65% and in COPD it is only 30%. RVH in presence of COPD is most difficult to diagnose.

Sets of ECG Criteria for Diagnosing Anatomic RVH

A. Criteria of Maurice Sokolow and Thomas P. Lyon

They published their study on RVH in American Heart Journal in 1949 (Fig 1). Sixty patients with RVH who suffered from cyanotic congenital cardiac disease, TOF, mitral stenosis, cor pulmonale, or kyphoscoliosis were studied. They stated that ECG findings are reliable and consistent in the well-established case of RVH such as occurs in PS or TOF. RVH can be strongly suspected if axis is greater than +110 degrees. Definitive criteria required a study of Leads V 1, V5, and occasionally aVR. Abnormal findings in lead aVR were rarely observed unless diagnostic changes were also seen in Leads V1 and/or V5.

I. Voltage of the R and S waves and various ratios:
   1. The R wave in V_1 is 7.0 mm. or more.
   2. The S wave in V_1 is less than 2.0 millimeters.
   3. The S wave in V_5 or V_6 is 7.0 mm. or more.
   4. The sum of the amplitudes of the R wave in V_1 and the S wave in V_5 and V_6 exceeds 10.5 mm. in individuals over 5 years of age.
   5. The R wave in V_5 or V_6 is less than 5.0 millimeters.
   6. The ratio of the R to the S wave in V_5 or V_6 is 1.0 or less.
   7. The R wave in aV_R is 5.0 mm. or more.
   8. The ratio of $\frac{R/S \text{ in } V_5}{R/S \text{ in } V_1}$ is 0.4 or less.
   9. The ratio of the R wave in V_1 to the S wave in V_1 exceeds 4.0 in individuals under the age of 5.
   10. The ratio of the R wave to the S wave in V_1 exceeds 1.0 in individuals over the age of 5 years.

II. Delayed onset of the intrinsicoid deflection (delayed ventricular activation time) 0.04 to 0.07 second in V_1 and/or V_2.

III. Depression of the RS-T segment and inversion of the T wave in:
   a. V_1, less often V_2 and V_3 when the R wave equals or exceeds 5.0 millimeters.
   b. aV_L or aV_F when the R wave equals or exceeds 5.0 millimeters.

IV. Marked right axis deviation, greater than +110° suggests, but is not in itself diagnostic of, right ventricular hypertrophy.

Fig 1 Criteria of Maurice Sokolow and Thomas P. Lyon (Am Heart J, 1949)

B. Other criteria of RVH
(Fig 2)
1. WHO criteria
2. Heikkila criteria
3. Louridas criteria
4. Butler and Legget criteria
5. Lehtonen criteria
6. Cabrera Index
7. Milnor criteria
8. Murphy's criteria

Table 1: ECG Criteria of RVH

Criteria	Description
World Health Organisation Criteria 1.qR pattern with intrinsicoid deflection > 0.03 s in V1 2.R < S in V5 3.R or R' < S in I 4.Incomplete RBBB with QRS < 0.12 sec 5.P >/= 0.25 mm in 2 6.RAD >/= 110 degree 7.T inversion in V1-V4 or in leads 2,3	ECG is diagnostic for RVH if criterion 1 or two or more of criteria 2-4 are met. Criteria 5-7 reinforce the diagnosis
Heikkila Criteria 1.RAD > 110 degree, no RBBB 2.R or R' >/= S in V1 or V2 3.R </=S in V6, No anterior myocardial infarct 4.P>0.25 mV in leads 1,2 or avF 5.P axis +60 - +90 degree (P in avF>P in lead 2)	ECG is diagnostic for RVH if one or more of criteria 1-3 is met. Criteria 4-5 reinforce the diagnosis
Louridas Criteria 1.R or R' > S in V1 2.R < S in V5 or V6 3.ST depression and T inversion in V1 and V2 4.Intrinsicoid deflection >0.04 s	ECG is diagnostic for RVH if two or more of the criteria are met
Butler Criteria 1.A + R – PL >/= 0.7 mV 2.R </=0.2 mV in lead I 3.P >/=0.25 mV in leads 2,3,avF,VI or V2 A = maximal R or R' amplitude in V_1 or V2 R = maximal S in lead I or V6 PL = minimal S in V1 or minimal r in lead I or V6	ECG is diagnostic for RVH if two or more of the criteria are met

Cabrera Index

Cabrera Index = RV1/ (RV1 + SV1)

Values greater than 0.5 suggest the presence of RVH. Values near1 indicates severe degree of RVH. In RHD, Cabrera Index near 1 indicates complicating severe PAH.

Diagnosing RVH in presence of RBBB

a. A high amplitude R' wave exceeding 15 mm in V1
b. Clockwise rotation, transition shifted to V5/V6
c. Right axis deviation of initial forces in frontal plane
d. A very wide S wave in lead I

Diagnosing Biventricular Hypertrophy

a. Right axis deviation in LVH
b. Clockwise rotation with LVH
c. Relatively tall R in presence of LVH
d. Katz-Wachtel phenomenon (large amplitude equiphasic QRS complexes in V2, V3, V4 reflecting RV systolic and LV diastolic overload)
e. P wave reflecting LA abnormality in combination with any of following
   1. R:S ratio in V5/V6 < 1
   2. S in V5/6 > 7 mm
   3. Right QRS axis beyond + 90 degrees

Diagnosing RVH in Paediatric age group.

RVH in Newborn

a. Pure R (without S) in V1 > 10mm
b. R in V1 > 25mm, R in aVR > 8mm
c. qR in V1
d. Upright T in V1 more than 3 days of age with upright T in V6
e. RAD > +180 degrees

ECG findings of Right Atrial Enlargement

1. qR morphology in V1 (without infarction)- specificity is 100%
2. P wave > 2.5 mm in lead II
3. P wave > 1.5 mm in V1
4. Mean P wave axis > +75 degrees
5. V2/V1 QRS voltage ratio 5 with QRS voltage in V1 < 4mm – specificity 90%
6. Early terminal negativity in V1 < 0.03 second.

Types of RVH (Chou Types)

Type A -RVH occur in severe PH, critical valvular PS and severe MS. It is characterised by Tall R in V1 and prominent S in V5,6.

Type B -RVH occur in volume overload states like ASD and moderate forms of MS. It is suggested by incomplete RBBB pattern, normal QRS in V5,6.

Type C RVH- has no classical signs of RVH. RAE and a vertical QRS axis suggest the diagnosis. rS in V1 and RS in V5,6 are the only QRS findings.

The value of Lead v3R in the diagnosis of right ventricular hypertrophy

A prominent R wave, which is abnormal in amplitude and duration both in comparison with the S wave of the same lead and with the R wave in leads farther to the left. The sharply inverted T waves associated with the abnormal R in Lead V3R offeres further support to the diagnosis of RVH.

Sensitivity of commonly used ECG criteria for RVH

Flowers and Horan examined 819 hearts using the chamber dissection technique. They found that criteria based on V1 are the most specific but least sensitive. Including criteria involving left leads improve sensitivity.

Prevalence of ECG findings in Primary Pulmonary Hypertension

Eduardo Bossone et al showed that ECG criteria for RVH was present using the criteria of Lehtonen et al in 96%, Heikkila in 90%, Louridas in 60%, the WHO in 48%, and by Butler in 38%. ST-T depression (1 mm) and T wave inversions suggestive of ischemia or strain were very common in inferolateral leads (II, III, aVF, V4, V5,V 6) and right precordial leads.

Predictive values of the ECG in diagnosing pulmonary hypertension

Though ECG patterns focusing on the R and S amplitude in V1 and QRS axis deviation≥110° have excellent positive predictive values in diagnosing PH, the absence of ECG criteria of RVH cannot exclude with certainty the presence of PH.

Table 2 : Prevalence and predictive values of ECG patterns

ECG patterns	Prevalence (%)	Positive predictive values (%)	Negative predictive values (%)
R V1 >/= 7 mm	2.8	72.7	24.5
R V5 </= 5 mm	13.5	30.8	26.3
R in I </= 2 mm	8	81.5	25.1
S V1 </= 2 mm	4	100	25.4
R/S V1 >/= 1	7.1	72.7	35.8
R/S V6 </= 1	2.9	80	24.8
R V1 + S V5 >/= 10 mm	1.4	71.4	24.4
QRS axis >/= 110 degree	8.1	88.5	25.6
qR in V1	6.3	94.7	25.6

ECG patterns using V1 appears to have better positive predictive values than criteria using V5 and V6 as the amplitude of R and S and their ratios in leads V5 and V6 are more dependent on the LV wall thickness than the RV wall thickness.

Usefulness of RV strain in PAH

RV strain pattern is defined as ST-segment deviation and T-wave inversion in leads V1–V3. Despite the fact that post-capillary PH may cause an RVS pattern on ECG, RVS remained the strongest predictor of pre-capillary PH in one study[21]. ST-T changes in V1-3 depicts repolarisation of RV, and appears to be a sensitive and immediate marker of RV strain. The presence of RVS correctly identified 78.8% of pre-capillary PH cases in the study[21]. Bonderman in the study to assess whether standard non-invasive diagnostic procedures are able to safely exclude pre-capillary PH showed that ECG and NT-proBNP in addition to TTE predict significant pre-capillary PH with sensitivity of 100% and specificity of 19.3%.

ECG findings with prognostic impact in PH

qR in lead $V1$[13-15], p wave amplitude in lead II[13], restingheart rate[14], p wave duration[17], precordial electrocardiogram voltage (sum of R wave in $V1$ and maximum S wave amplitude in $V5$ or $V6$)[18], QRS duration[19], and QTc duration[20] have been shown to have prognostic impact in patients with IPAH, ES, or CTEPH.

ECG in acute Cor pulmonale

a. Sinus tachycardia
b. Right axis deviation, Undetermined axis
c. T inversion in V1-V3
d. S in I and/or aVL
e. S1Q3T3 – McGinn-White syndrome
f. Transition zone may shift to left
g. Complete or incomplete RBBB. (Amount of RV conduction delay correlates with extent of obstruction in pulmonary circulation)
h. RBBB+ Anterior divisional block can occur in acute massive PE
i. Slurred upstroke of S in V1
j. Negative T in inferior leads
k. ST elevation in aVR and V1
l. Generalised low QRS voltage in extremity leads < 5mm.
m. Slow R progression and persistent S upto V6.

Electrocardiogram in chronic Cor pulmonale

Padmavati et al published data of 544 patients with proven chronic cor pulmonale in British Heart Journal in 1972. She suggested that for the diagnosis of right ventricular hypertrophy in cor pulmonale, when criteria of classical right ventricular hypertrophy and incomplete

right bundle-branch block are absent, associated ECG abnormalities are to be taken. These are a combination of rS in V5-V6, right axis deviation, qR in aVR, and P pulmonale, the last being the least important.

Other than the Sokolow and Leon criteria associated findings like right axis deviation, QS, QR, and qR patterns in VI-V3, and r/S ratio in V5 <1 can be used to diagnose RVH. Less diagnostic but suggestive are giant P pulmonale, cRBBB, well-developed or embryonic 'r' in right chest leads, and R/S above 1 in aVR ,clockwise rotation, qR in aVR in a case of chronic cor pulmonale in which the classical pattern is absent.

RVH in COPD can be diagnosed by (1) S1Q3 pattern (2) RAD > 110 degree (3) S1S2S3 pattern (4) R/S ratio in V6 < 1.0

Predicting RV pressure from ECG in PAH

The ECG pattern with the highest positive predictive value for severe pulmonary hypertension (PASP≥60 mm Hg) is right axis deviation with the QRS axis≥110° [24].

Predicting RV systolic dysfunction in PH from ECG.

Toshiyuki Nagai et al showed that the combination of ECG-RVH findings, especially in lead V1, predicts the presence of RVSD defined by CMR. The presence of the qR pattern in lead V1 remained as an independent determinant of RV systolic dysfunction.

Electrocardiographic and Hemodynamic Correlations in Primary Pulmonary Hypertension

Nariaki Kanemoto studied ECG hemodynamic correlation of PH and published the data in Angiology, The Journal of Vascular diseases.

a. Right atrial pressure

Patients with an S in V_s < 0.2 mV had a mean right atrial pressure of 8.7 ± 5 versus 5.8 ± 3 mmHg in patients with an S in V_s > 0.2 mV (p < 0.001). Inverted T waves in leads 2, 3, and aV, were associated with a mean right atrial pressure of 8.2 ± 4 versus 5.4 ± 3 mmHg or those without inverted T waves (p < 0.001).

b. Pulmonary artery Pressure

Positive correlations were noted between the pulmonary artery systolic pressure and the R in V1 (p < 0.01), the R/SV1 (p < 0.01), the R/SV5 (p < 0.01), and the R/SV6 (p < 0.05). There were also positive correlations between PA mean pressures and these three ECG parameters. The sensitivity, specificity, and percent diagnosis of RVI > 1.2 mV and R/SVI >7 for the identification of PA systolic pressures is reasonable. ECGs with an R in V1 >0.7 mV showed significantly high PA mean pressures than those with an RV1 < 0.7 mV. No significant differences in PA pressures are found for the presence or absence of an SIQ3 pattern; inverted T waves in leads 2, 3, and aVF or the number of chest leads showing T wave inversion.

c. Cardiac Index (CI)

Statistically significant positive correlations were noted between the CI and the amplitude of the R in Vs and V6 (p < 0.01), R/SVS (p < 0.05), and R/SV6 (p < 0.01). A significantly decreased CI was found when the ECG showed any one of the following: AQRS > 100°, an RV6< 1 mV, an S in V6 > 0.7 mV, R/S in V6 < 1.

Importance of P pulmonale in PAH

 It is defined as P wave >0.25 mV in lead II. P amplitude in lead II increases as a result of progressive RV hypertrophy, associated diastolic dysfunction, and RV dilatation associated TR in PAH patients.[7]

QRS duration and adverse outcome in PAH

Studies have shown thatincreased QRS duration is associated with clinical severity in patients with IPAH and has an independent association with mortality and predict adverse outcome in patients with IPAH. QRS complex prolongation is reported in 16% of patients with IPAH including 9.9% with RBBB and 6.6% with nonspecific intraventricular conduction delay (IVCD). The incidence of prolonged QRS duration increases in proportion to the severity of the WHO functional class ranking. Although patients with QRS widening shows a tendency to have a lower CO and higher mRAP, the differences are not shown to be statistically significant when compared with those with normal QRS duration[10].

The Prognostic Role of the ECG in Pulmonary Hypertension

1. Predicting survival and deciding therapeutic options in primary pulmonary hypertension

Eduardo Bossone et al showed that ECG parameters reflective of physiologic and anatomic abnormalities in the RV are associated with decreased survival in patients with PPH, and may be even useful for deciding therapeutic choices including the timing for lung transplantation. The p wave amplitude in leads II and III and in aVF, p 0.25 MV in lead II, qR in V1, and

WHO RVH criteria were each significantly associated with increasingmortality.While ECG lacks sufficient sensitivity to serve as an effective screening tool for PAH, it can contribute important prognostic information.

2. Predicting timing of death during follow up of pulmonary hypertension

Adriano R et al showed that when compared with the ECG performed at the time of PAH diagnosis, the ECG close to patient's death revealed longer PR interval, QRS complex and QTc interval; more pronounced rotation of the frontal QRS axis to the right and higher *R/S ratio in V1 as well as higher prevalence of RBBB and negative T waves in inferior leads.*

3. Assessing response to treatment

Regression of RVH in new-borns as well as the ECG changes that are seen in people living at high altitudes is well known. In patients in whom PAH treatment is very effective as in those patients who respond to calcium channel blockers have shown dramatic ECG changes from a pattern of RVH to near-normal pattern[8].

ECG markers of hemodynamic improvement in patients with pulmonary hypertension

Electrocardiogram may be useful in predicting hemodynamic effects of PAH therapy in precapillary PAH. Decrease of $RV1$, max$RV1,2$ + maxSI, aVL-$SV1$, and PII corresponds with hemodynamic improvement after treatment. Of these changes a decrease of R wave amplitude in $V1$ is associated with better survival.

ECG markers of hemodynamic improvement following pulmonary endarterectomy

In one cohort of 99 patients with CTEPH who underwent pulmonary endarterectomy (PEA), the decrease of PII, $RV1$ and normalization of negative $TV1$–$T3$ were observed 1 month after PEA. Additional changes such as increase of $SV1$, increase of R: $SV6$, and decreased prevalence of $SIQIII$ pattern were observed at 1-year follow-up[30]. Of these changes only a decrease in PII correlated with lowering of mPAP and PVR[11].

Evolutionary ECG changes suggesting progression of RV pressure in PAH

Animal studies have shown that even mildly elevated RV pressure load is associated with substantial changes in myocardial electrical properties, detectable in surface ECG recording. In contrast to the wide inter-individual variability in electrocardiographic characteristics, the ECG is a reliable tool to detect intra-individual changes over the time course. Progressive axis deviation, increasing height of R in V1 and repolarisation abnormalities develop as RV pressure progresses[9].

Vectorcardiogram in PAH

It has been shown that vectorcardiogram (VCG), synthesized from the standard 12-lead ECG is useful for detection of elevated RV pressure.

RVE may take any or a combination of three forms:

1. Right axis deviation

2. Marked rightward and anterior direction of the initial QRS vector,resulting in an initial R in V1 that is taller or broader or both.

3. Marked rightward, anterior and inferior direction of terminal QRS resulting in R' of increased amplitude in V1.

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Echocardiography in Pulmonary Hypertension

V. Amuthan

Emeritus Professor of Cardiology,
The Tamil Nadu Dr. MGR Medical University

Formerly Professor & HOD, Department of Cardiology, Madurai Medial College
Director, 4D Echo Lab, Jeyalakshmi Heart Center, Madurai
Senior Interventional Cardiologist, Vadamalayan Hospital, Madurai.

RVA. Ananth

Jeyalakshmi Heart Centre, Madurai

INTRODUCTION

Echocardiography since its inception from the days of Elder, has revolutionalised the management of cardiac patients. From the days of single crystal probe to M Mode, 2D, Color flow mapping, the advancement has reached the stage of 3 Dimentional Echocardiogram with added fourth dimension of time (4D Echocardiography – The real-time 3D Echocardiography). Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of Pulmonary Hypertension.

AN ECHOCARDIOGRAPHIC APPROACH TO PULMONARY HYPERTENSION

Pulmonary hypertension is hemodynamically defined as a condition with mean pulmonary artery pressure (MPAP) > 25 mm of Hg at rest as assessed by right heart catheterization.[1] A virtual right heart catheterization can be carried out by modern transthoracic echocardiographic doppler techniques. Transthoracic Echocardiography provides direct and indirect evidence of pulmonary hypertensionand also aids in classification of pulmonary hypertension into precapillary and post capillary causes which is an easy algorithm for diagnosis and management of pulmonary hypertension.[2, 3, 4, 5, 6 & 7] (Fig1 and Table 1)

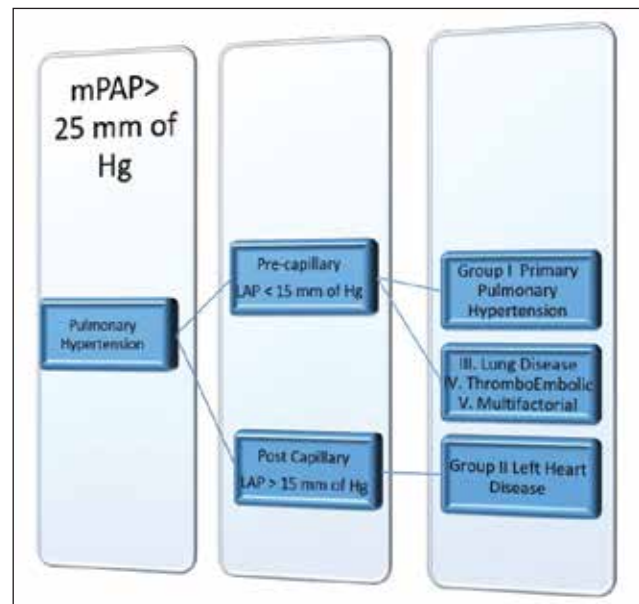Fig 1. Algorithm in the diagnosis of pulmonary hypertension

DIRECT EVIDENCE

(Doppler Echocardiography derived virtual right heart catheterization)

1. Pulmonary Artery Systolic Pressure: In the absence of pulmonary flow obstruction, Doppler

Address for correspondence: Dr. V. Amuthan, MD DM, HIG II/12, Karpaga Nagar, Avaniapuram, Madurai 625 012 India
Phone : +91 94433 53579, Email.: amuvee@yahoo.com

Table 1. WHO Classification of Pulmonary Hypertension

WHO Group	Etiology	PCWP	Example
1	Pulmonary Arterial Hypertension	Normal	Idiopathic, hereditary, drug or toxin induced, shuntsrelated to congenital heart disease, connective tissue disease, portal hypertension, chronic haemolyticanaemia
2	PH Secondary to left heart disease	Increased	Valvular heart disease, systolic dysfunction, diastolicdysfunction, pericardial disease, congenital/acquired left heart inflow/outflow tract obstruction, congenital cardiomyopathies
3	PH secondary to Lung disease	Normal	Chronic obstructive pulmonary disease, severe asthma,interstitial lung disease, sleep apnoea, long termexposure to high altitude, congenital lung abnormalities
4	Chronic Thrombo- Embolic pulmonary hypertension	Normal	Chronic pulmonary embolism
5	Pulmonary hypertension with unclear and/or multifactorial mechanisms	Normal	Systemic diseases, sarcoidosis, vasculitis, haematologicalmalignancies, chronic renal failure, metabolic disorders, lung tumours

Echocardiography derived tricuspid regurgitation and right ventricular outflow flow tract flow acceleration time have linear positive and negative correlation with systolic and mean pulmonary artery pressures respectively[8&9] (Fig 2). TR velocity (TRV) is used to calculate pulmonary artery systolic pressure (SPAP) in day to day practice by using the modified and simplified Bernoulli equation by Hatle. $SPAP = 4 \times TRV2 + RAP$. In 75% of patients, tricuspid regurgitation can be recorded. However, utmost care has to be taken in aligning the TR jet by moving the transducer medially and keeping the TR jet in the center of the 2 Dimensional color flow mapping as it is a Doppler derived entity, which is angle dependent.[10] Multiple off axis recordings have to be made.

2. Right Atrial Pressure(RAP) = Inferior Venae Cava (IVC) size and collapsibility are used to determine the elevated right atrial pressure. (>2.1 cm, collapse < 50%: RAP 15 mm of Hg)[11]. The maximal IVC diameter should be measured 1 or 2 cm proximal to IVC-RA junction during expiration and the IVC has to be cut by M Mode for long time to observe the respiratory collapse which is >50% with normal central venous pressure.

3. Mean Pulmonary Artery Pressure (MPAP): The pulmonary regurgitation derived peak early diastolic and end diastolic velocities correlate with mean pulmonary artery pressure (MPAP) and diastolic pulmonary pressures respectively[12,13,14]. $MPAP = 4 \times PRV2 + RAP$ (> 25 mm Hg) $MPAP = 0.61 \times SPAP + 2mmHg$ $MPAP = 90 - 0.62 \times$ Acceleration time RVOT (Fig 3).
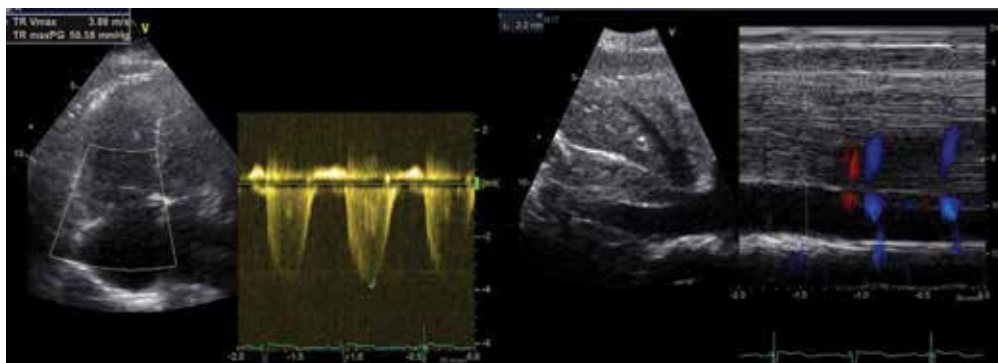

Fig 2. Calculation of Systolic Pulmonary Arterial Pressure (SPAP) = 4 x TRV2 + Right Atrial Pressure (RAP) = IVC size and collapsibility (>2.1 cm, collapse < 50% during sniffing or <20% during quiet breathing: RAP 15 mm Hg) 60+15 = 75 mm of Hg. Normal (TRV > 2.8–2.9 msec: SPAP36 mm Hg)
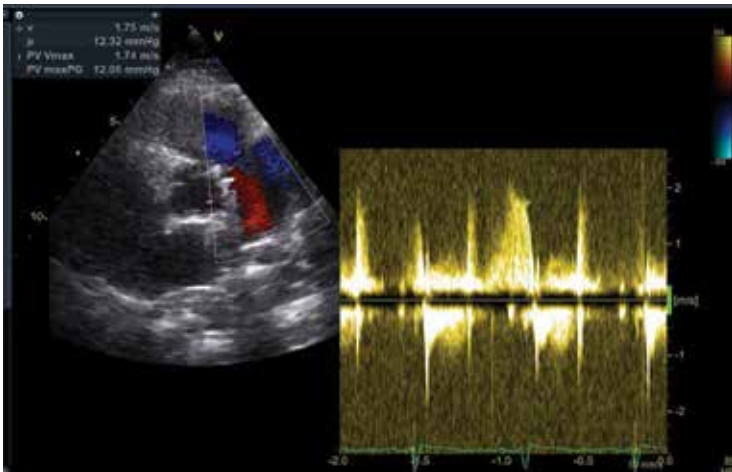
Fig 3 Calculation of Pulmonary Artery Diastolic Pressure (DPAP) and mean PA pressure (MPAP) DPAP = 4 PRVed2 (Pulmonary Regurgitation Velocity End Diastole) +RAP; MPAP = 4 x PRV2 (Peak Pulmonary Regurgitation Velocity) + RAP (> 25 mm Hg)

4. The pulmonary vascular resistance (PVR) may be derived by dividing the TR peak velocity in cm, by RVOT velocity time integral in cm as PVR is directly related to

pressure changes and indirectly to pulmonary flow.[14&15] (Fig 4) The RVOT flow can be recorded in parasternal short axis view by placing the pulsed wave Doppler cursor in the center of RVOT and envelope tracing may be made to calculated the velocity time integral. This helps to distinguish pulmonary hypertension due to increased pulmonary blood flow from that due to increased pulmonary vascular resistance. Calculation of PVR is also helpful in patients with unchanged MPAP with worsening of clinical symptoms and falling RV ejection fraction and RV stroke volume.

5. Pulmonary capillary wedge pressure and Pre vs Post Capillary Pulmonary Hypertension: The PCWP can be acquired by measuring the Mitral E velocity and Mitral annular tissue doppler echocardiography derived E' and using the simple formula PCWP = 1.9 + 1.24 x E/E' (E/E' >15: PCWP > 15 mm Hg) or by calculating the left atrial volume index. LAVi (>31 mL/m2)[16,17,18] (Fig 5 and 6). The LA volume is measured during the maximal LA volume (during left ventricular

Fig 4 The pulmonary vascular resistance (PVR) may be derived by dividing the TR peak velocity in m/sec, by RVOT velocity time integral in cm (In the example shown below 4.22(TR peak Velocity)/ 19.7 (RVOT VTI) = 0.21)
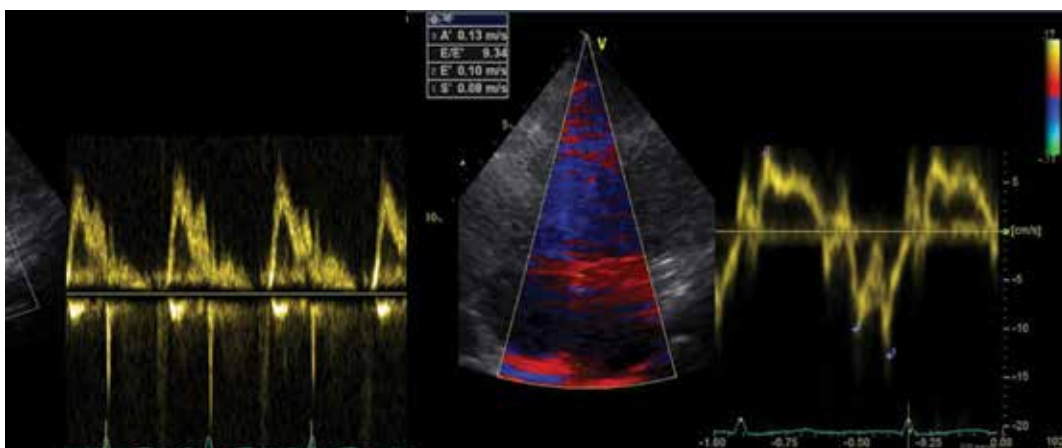

Fig 5 Estimation of Pulmonary Capillary Wedge Pressure from Mitral Doppler E velocity and Tissue Doppler techniques (PCWP = 1.9 + 1.24 x E/E') or (E/E' >15: PCWP > 15 mm Hg)

Fig 6 Calculation of maximal LA volume during left ventricular End systole

systole) in the apical four and two chamber planes for biplane measurements or apical four chamber plane for single chamber measurements. The tracings are made at the blood tissue barrier after carefully excluding left atrial appendage and pulmonary veins and connecting both medial and lateral mitral annulus points by a straight line. Pre-capillary Pulmonary Hypertension is characterized by MPAP ≥25 mm Hg, PAWP ≤15 mmHg and is due to Primary Pulmonary arterial hypertension (WHO group 1), PH due to lung diseases (WHO group 3), Chronic thromboembolic PH (WHO group 4) and PH with unclear and/or multifactorial mechanisms (WHO group 5). Post-capillary Pulmonary Hypertension is characterized by MPAP ≥25 mm Hg & PAWP >15 mm Hg and is commonly due to left heart diseases (WHO group 2)[2,7]

INDIRECT EVIDENCE: Echocardiographic evaluation of the right ventricle and right atrium

RV size: Normally, left ventricle to right ventricle ratio is > 1.3. In patients with pulmonary hypertension, the right ventricular pressure overload results in hypertrophy, dilatation and increased contraction.[19] This results in LV/RV size < 1.0., and a D shaped left ventricle or persistent flattening of the interventricular septum with left ventricular eccentricity index > 1.1 in systole and diastole. (Fig 7) The normal values for right ventricular chamber sizes have been extensively reviewed and published by the American Society of Echocardiography in their guidelines on chamber quantification[18,19]. (Table 2) A simple rule of thumb is measurement of RVOT Proximal and distal diameters, RV basal, Mid cavity
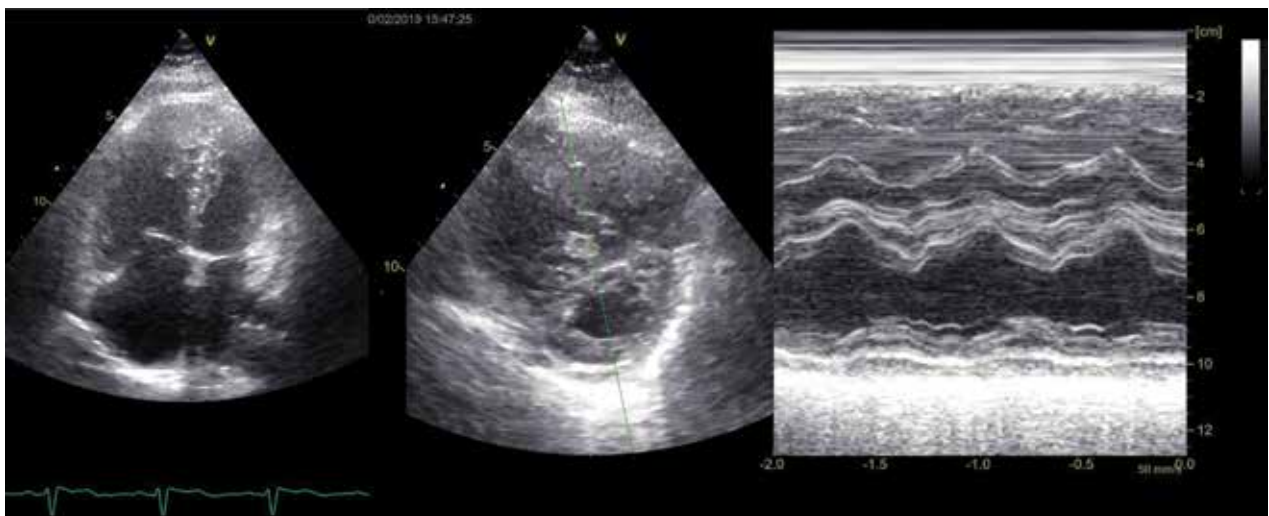

Fig 7 2D Echocardiographic RV size in apical 4 chamber plane showing LV/RV ratio <1 and short axis showing D shaped LV

Table 2. Normal and abnormal RV size and function (Modified from Lang et al[18])

Parameter	Normal range	Abnormal
RV basal diameter (mm)	25-41	>41
RV mid diameter (mm)	19-35	>35
RV longitudinal diameter (mm)	59-83	>83
RVOT PLAX diameter (mm)	20-30	>30
RVOT proximal diameter (mm)	21-35	>35
RVOT distal diameter (mm)	17-27	>27
RIMP or Tissue Doppler Myocardial Performance Index	0.38 + 0.08	>0.54
Tricuspid Lat. Annular S' by TDI (cm/sec)	14.1 + 2.3	<0.95
TAPSE (mm)	24 + 3.5	<17
FAC (Fractional area change)%	49 + 7	<35
RV Free Wall Strain	-29 + 4.5	>-20 (ie., <20 absolute value)
RVEF (3D)%	58 + 6.5	<45

and longitudinal diameters along with the RV free wall thickness in subcostal four chamber view exceeds 5 mm. The RV has triangular shape in two dimensional examinations and RVOT and infundibulum are better visualized by three dimensional echocardiography and special software.

RV function: RV function can be evaluated by multiple parameters including RIMP (RV myocardial performance index or Tei index), Tissue Doppler Imaging derived Tricuspid annular lateral s' Velocity, TAPSE (Tricuspid Annular Plane Systolic Excursion), 2D- FAC (Fractional Area Change), 3D RVEF, RV free wall strain and tissue doppler derived s' wave velocity[19].

RIMP or RV Tei index has to be measured from the Tissue Doppler Imaging of the Tricuspid annulus and can be calculated by the simple formula: RIMP = (IVRT + IVCT) /ET. In RV dysfunction RIMP by tissue Doppler imaging is > 0.54. (Fig 8)

TDI derived s' velocity is easy to measure from the lateral tricuspid annulus and indicates RV dysfunction, if < 9.5 cm/sec[20].
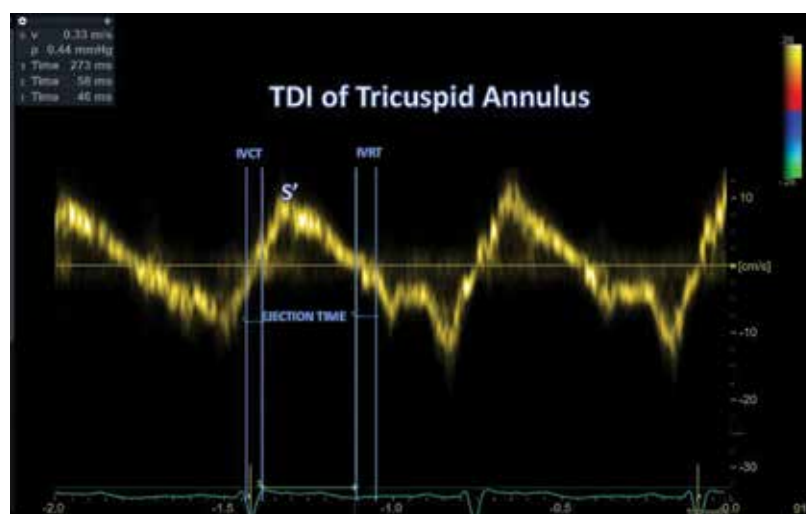
Fig 8 Showing the tissue doppler imaging based RIMP (Tei index) calculated by Isovolumic contraction time + Isovolumic relaxation time/ ejection time RIMP = (IVRT + IVCT)/ET
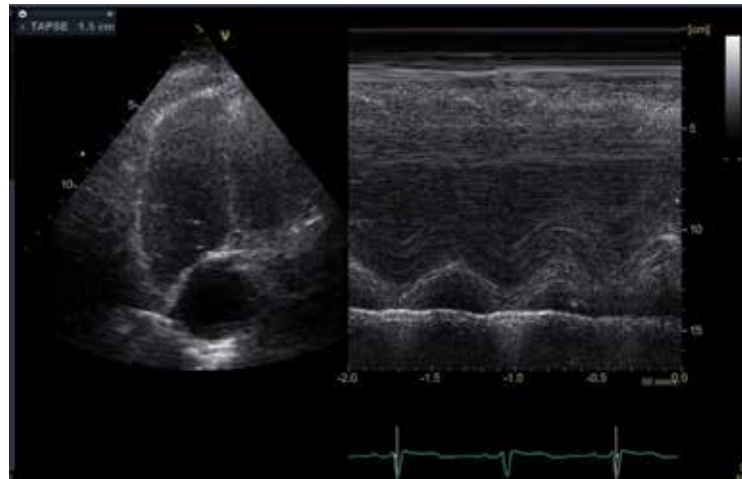
Fig 9 Showing aligning and M Mode cutting for TAPSE

Tricuspid Annular Plane Systolic Excursion (TAPSE): TAPSE is measured from apical 4 chamber plane by aligning the Tricuspid annulus in the center and by M Mode cutting. (Fig 9) Although single plane measurement, TAPSE correlates very well with RV systolic function.[21] TAPSE <17mm indicates RV dysfunction.

RV Fractional Area Change: In the apical four chamber plane, tracing of entire RV cavity including RV free wall and apex is done during Diastole and systole and RV FAC is calculated with the formula FAC = (RVAd − RVAs)/RVAd. RV FAC <35% indicates RV dysfunction.

Speckle Tracking Echo derived RV Free wall strain: has been well studied and reproducible. However, this strain is recorded from software for LV and adapted to RV. The strain value is recorded in three free wall segments from the RV focused Apical 4 chamber plane and is averaged. The RV free wall strain is abnormal when it is >-20% (<20% Absolute value)[22,23,24].

3D RV Ejection Fraction: The three dimensional RV ejection fraction is calculating by acquiring the RV focused apical four chamber view with a frame rate of >35/sec.

Step 1: The image is aligned for the line drawn from coaptation point of the Tricuspid valve to RV apex and drawing the line at basal RV level, Mid RV level and also in the coronal plane from inter ventricular septum to free wall.

Step 2: The RV land mark points are recorded (1. Free wall Tricuspid Annulus, 2. Septal Tricuspid Annulus, 3. RV apex. 4. Posterior RVFW/LV junction, 5. Anterior RVFW LV junction and 6. RV Free wall in coronal plane).

Step 3: Corrections are made so that the RV trabeculae are included in RV cavity[25] 3D derived RV EF <45% is indicative of RV dysfunction.
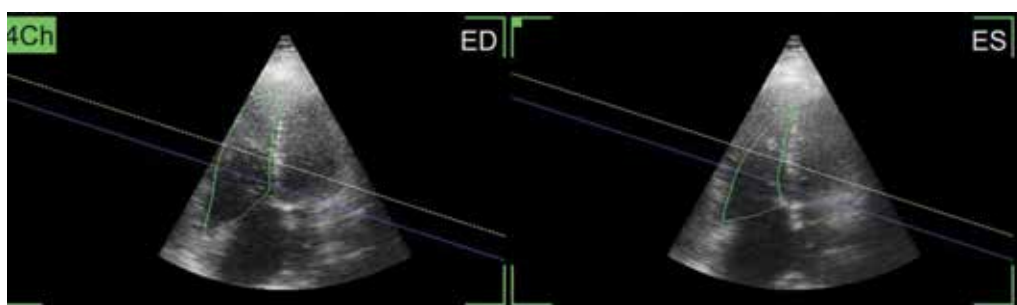
Fig 10 Showing RV Fractional Area Change. RV FAC (%) = 100 x (EDA - ESA) / EDA (EDA: End diastolic area and ESA: End systolic area)
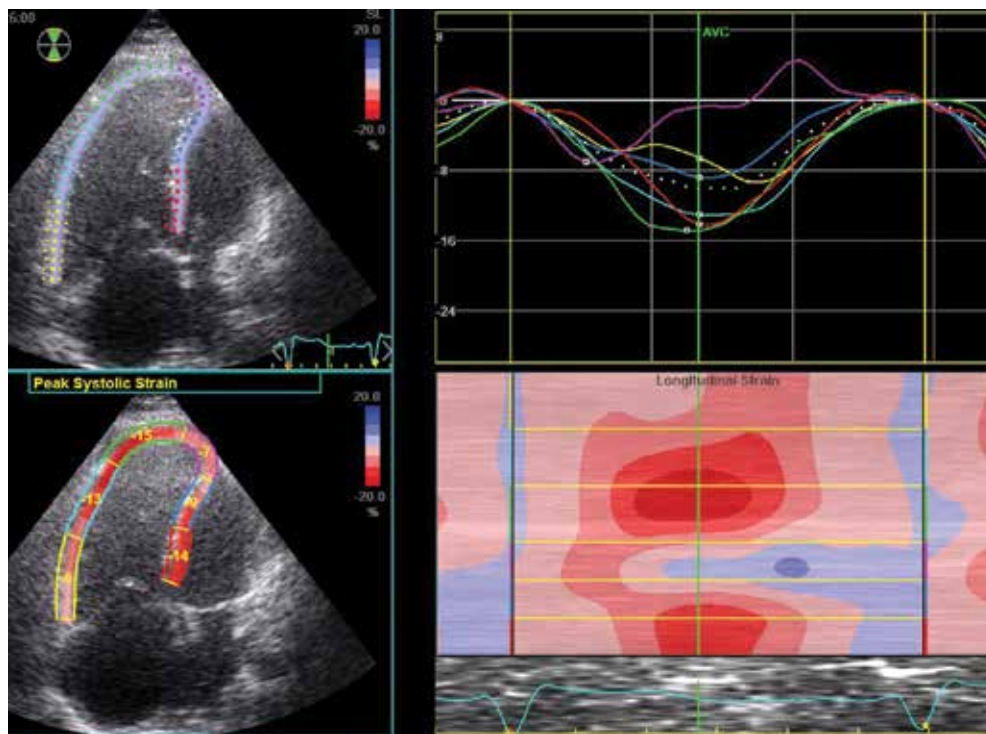
Fig 11 Showing RV free wall strain averaged over the three segments of the RV free wall in RV-focused apical four-chamber view (%)
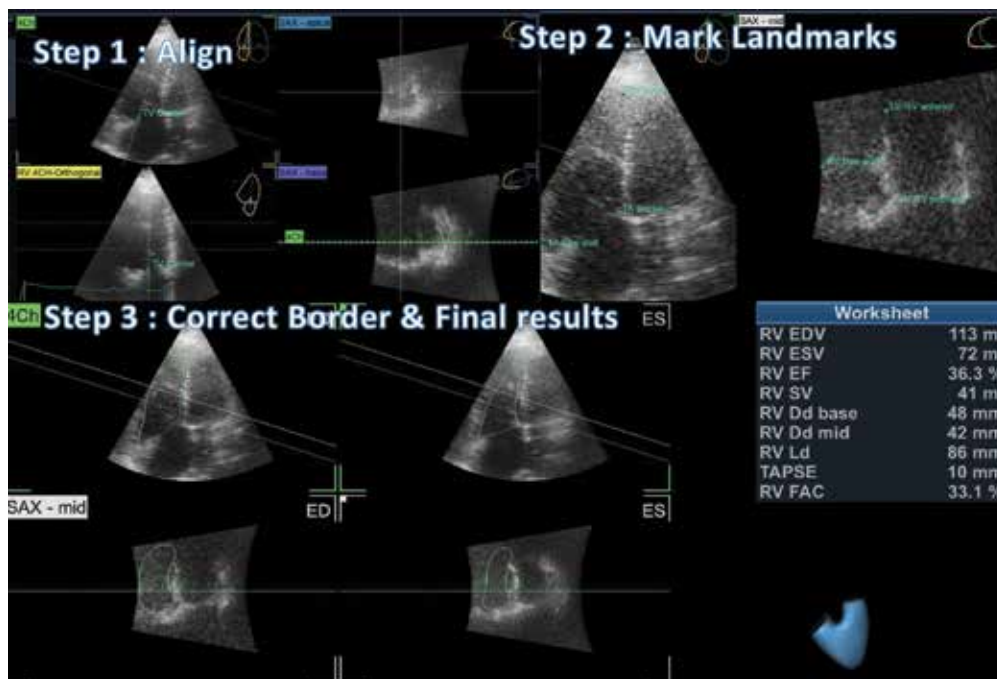
Fig 12 3D Evaluation of RV function. RV EF (%) = 100 x (EDV - ESV)/EDV

TRANS ESOPHAGEAL ECHOCARDIOGRAPHY:

Trans Esophageal Echocardiography should be considered in the following conditions:

1. To identify thrombus in RPA and MPA (Fig 13)

2. To assess the severity of mitral valve disease
3. To characterize Right sided intra cardia mass and
4. To guide interventional procedures such as device closure of ASD
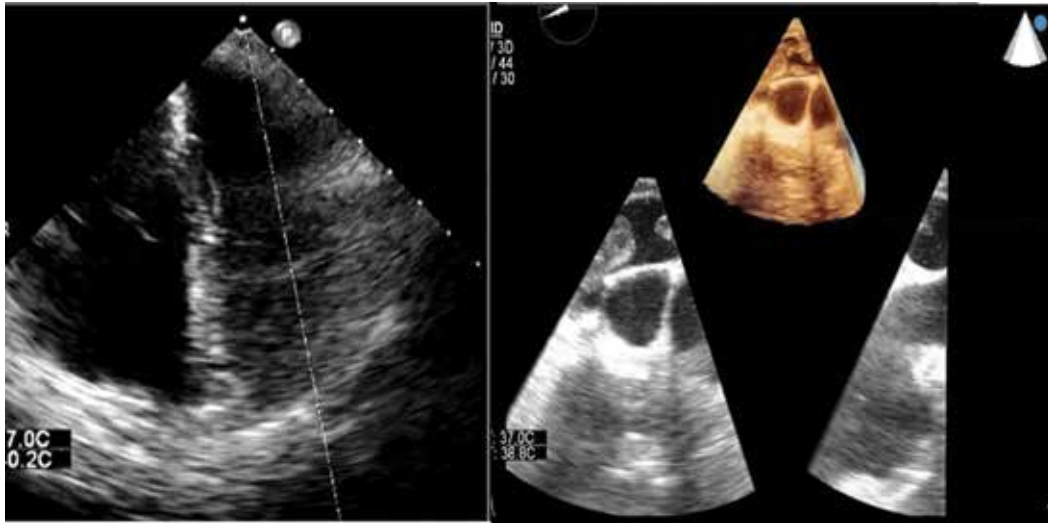
Fig 13 TEE in a patient with Acute Pulmonary Embolism. The left panel shows the Mcconnell sign (Regional wall motion abnormality that spares the RV apex) and the right panel shows the Right Pulmonary Artery with multiple emboli

CONCLUSION AND KEY MESSAGES

In conclusion, it must be remembered that right heart catheterization is the gold standard for assessment of pulmonary hypertension and cardiac magnetic resonance is the gold standard for assessment of RV size and function. However, as the bed side non-invasive tool and the initial and economically the best modality, echocardiography excels others. The following parameters have to be recorded by echocardiography:

1. Peak TR velocity.
2. The Ventricle: Eccentricity Index, basal LV/RV diameter ratio, RV function
3. Pulmonary Artery: RVOT acceleration time, Pulmonary artery diameter and early diastolic PR velocity
4. IVC size and respiratory variability

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Cardiac Catheterisation in Pulmonary Hypertension

Harikrishnan S

Professor of Cardiology, Sree Chitra Tirunal Institute for
Medical Sciences and Technology, Thiruvananthapuram, Kerala

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ≥25 mm Hg at rest, measured during right heart catheterization1. Exercise induced PH is not generally included in the current defintion[1].

We have to make distinction between PH and PAH. PH is elevation in pulmonary artery pressure due to any reason.

The term **pulmonary arterial hypertension (PAH)** describes a subgroup of PH characterized by the presence of pre-capillary PH - pulmonary artery wedge pressure (PAWP) ≤15 mm Hg (measured at end expiration) and a pulmonary vascular resistance >3 Wood units[1].

Even though the definition of PH is > 25 mmHg, the patients with mPAP 21-24 was found to have a worse outcome than those with mPAP<20 mmHg. So this group is recommended to be followed up closely. But these patients with 21-24 are still not categorised as "borderline PH".

Fig 1 Pulmonary artery pressure tracing

Address for correspondence: Dr. Harikrishnan S., MD, DM, Professor of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala. Email: drharikrishnan@outlook.com

Pulmonary vascular resistance (PVR)

PVR is calculated by the following formula:

$$\frac{\text{Mean PAP} - \text{LA (or PAW) Pressure}}{Qp} = \dots \text{ mmHg/L/min (Wood Units)}$$

(PAP – pulmonary artery pressure, LA – left atrial, PAW -pulmonary arterial wedge).

PVR or pulmonary vascular resistance is not part of general definition of pulmonary hypertension. But it is required in the definition of pulmonary arterial hypertension (PAH).

The new guidelines recommend that PVR should be reported in Wood Units. PVR is expressed most frequently as dyn·s·cm-5 and Wood units (mm Hg/L·min). To convert Wood units to dynes.s.cm[-5], multiply Wood units by 80.

Normal PVR at rest is age dependent, but PVR >2 WU is considered elevated in all age categories[2].PVR >3 WU is used as part of the hemodynamic definition of PAH and not PH[3]. PVR >6 is considered as a contraindication for cardiac transplantation.

We also need to know few other definitions.

TPG – Transpulmonary gradient = PA (mean) - PA Wedge (mean) - A value of >12 is considered significant and indicative of out-of-proportion PAH in cases of left heart disease. Recently this parameter is found to have problems in assessing patients with left heart disease and the new parameter DPG is found to be more accurate[4].

DPG – Diastolic pulmonary gradient = Diastolic PA Pressure - PA Wedge (mean). A value of $\geq$ 7 is found to be indicative of an additional pre-capillary component in post-capillary PH[5].

Why DPG is superior to TPG ?[4]

The transpulmonary gradient is sensitive to changes in cardiac output and both recruitment and distension of the pulmonary vasculature, which reduce the upstream transmission of the left atrial pressure. In addition we know that pulmonary blood flow is pulsatile, with systolic PA pressure and mean PA pressure is determined by stroke volume and arterial compliance. So it is argued that it is preferable to rely on a gradient between diastolic pulmomary artery pressure and the PCWP or the LA pressure.

Pulmonary Hypertension – mechanisms

Pulmonary hypertension can be due to many hemodynamic alterations. Each component either alone or together can contribute to PH. To describe the hemodynamic alterations in PH, we can take the example to mitral stenosis, where all the three components contribute to PH.

1. Passive transmission of left atrial pressure – Proportional to the LA pressure, if we do a balloon mitral valvotomy and reduce the LA pressure, the PA pressure will decrease correspondingly.

2. Vaso-reactive component – This is the response of the pulmonary vasculature in response to the high LApressue or PAWP. The pulmonary arterioles and arteries increase their tone in response to the high LA pressure. This leads to PH. This is reversible, but it may take varying amount of time from minutes to few months.

3. Pulmonary vascular disease – This is the structural alterations which occur in the pulmonary arteries on long standing Pulmonary hypertension. This is also the pathology in idiopathic PAH.

Each of the components described above contribute to PH in various degrees. For example, in COPD, factors 2 and 3 contribute to PH.
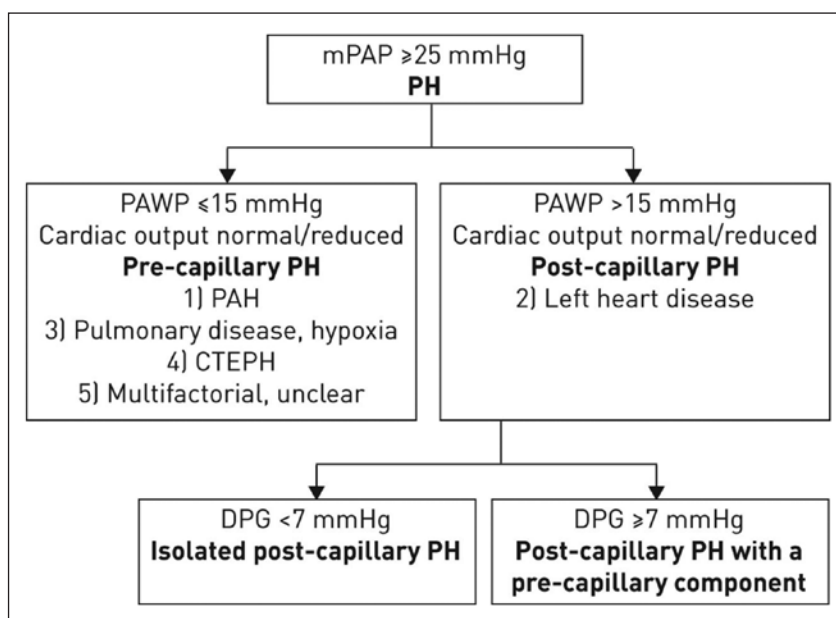
Fig 2 Hemodynamic Categories of Pulmonary hypertension[5]
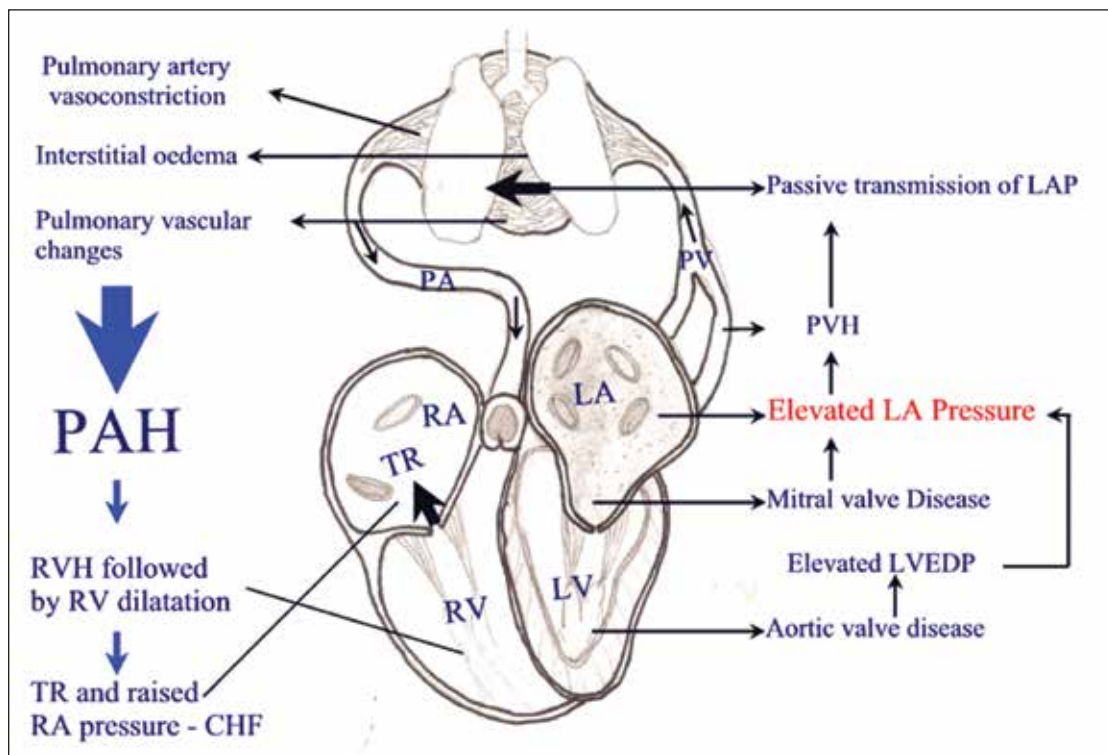
Fig 3 Pathophysiology of PH in valvular heart disease.
(**LV** - left Ventricle, **LVEDP** – left ventricular end-diastolic pressure, **LA** - left atrial, **PVH** – pulmonary venous hypertension, **LAP** - left atrial pressure, **PV** - pulmonary veins, **PA** - pulmonary artery, **PAH** - pulmonary arterialhypertension, **RVH** – right ventricular hypertrophy, **RV** – right ventricular, **TR** - tricuspid regurgitation, **RA** - rightatrium, **CHF** - congestive heart failure.)
(Published with permission from Medknow publications, Bombay, India from the article, S Harikrishnan, Chandrasekharan C Kartha, Pulmonary hypertension in rheumatic heart disease, PVRI Review 2011:1:1:13-17.)

Cardiac catheterisation in pulmonary hypertension

Even though there are many non-invasive methods to assess, pulmonary hypertension, the right heart catheterization is considered the gold standard diagnostic tool.

What we should aim for?

Right heart catheterisation (RHC) should be a comprehensive haemodynamic assessment and the person doing it should plan it meticulously so that no information is missed out. It is better to have a check list in the cathlab so that no major information is missed out.

What are the risks involved?

Catheterisation to assess PH is usually safe, but many patients with severe pulmonary hypertension are sick and minor hemodynamic deterioration can make them worse all on a sudden and they can even have mortality.

Arrhythmias

Tachyarrhythmias: Atrial and ventricular ectopy is very common during catheter manipulation. Usually, atrial premature beats and ventricular ectopic beats are transient and self-limited. Atrial tachycardia and NSVT are common and self limited on repositioning or removal of the catheter. Atrial flutter or fibrillation or sustained VT can occur, which can make the patient unstable. Electrical cardioversion or pharmacologic antiarrhythmic therapy should always be available should the arrhythmia persist.

Bradyarrhythmias. One of the dreadful complications of cardiac catheterization in PH is the development of vasovagal episodes leading to bradycardia and hypotension. Once these vagal episodes ensue, profound bradycardia and hypotension often develop within one or two minutes. In patients with severe PH, occasionally, it may become extremely difficult to resuscitate such a patient.Therefore, staff and physicians in the cathlab should be adequately sensitised that a vaso-vagal episode is anticipated and recognized at the earliest and treated with atropine early in its course. Temporary

pacemaker should be available on standby in the cathlab to treat resistant cases.

LBBB: Patients who already have baseline LBBB can develop complete heart block on manipulation of catheters in the right heart. We have to be watchful and TPI support should be available as back-up.

Reliability of measurements in the cath lab:

We should realise that we are doing an invasive measurement which involves a significant amount of risk, radiation exposure and cath-lab time. So we should be extremely careful to make sure that the measurement obtained are reliable and accurate. The following points should be kept in mind.

A. EQUIPMENT

1. Zeroing the transducer- The phlebostatic axis - at the level of the stopcock (where the 3-way opens to the atmosphere), mid-chest, 4th LICS irrespective of the position of the body.
2. Optimal length of tubing – 4 feet
3. Optimal damping, remove air bubbles
4. If there are two transducers, both should be zeroed at same level.
5. Transducers should be calibrated periodically against standard mercury manometer reference at 25, 50 and 100 mmHg.

Patient preparation and monitoring: We need a patient in steady hemodynamic state to obtain an accurate hemodynamic data. It is generally recommended that adult patients be kept awake during catheterization. Some patients may be very anxious, leading to tachycardia and increased systemic pressure, such patients may need mild sedation. Small doses of benzodiazepines are useful for controlling anxiety. Continuous monitoring with pulse oximetry is required, reduction in SPO2 may be an indication of a hemodynamic deterioration.

Adequate hydration: Patient must be adequately hydrated to obtain accurate hemodynamic measurements. If patient is not adequately hydrated it will lead to spuriously low PCWP or filling pressures which will defeat the said purpose of the study. So, when you start the study first measure the right atrial pressure. If it is very low, say below 2 mm Hg, it is better to give fluids (300 ml or more) intravenously to ensure that RA mean is at least 3 mm Hg.

Access: Femoral venous access is the most commonly used but right internal jugular vein or the subclavian vein access can also be used. The IJV approach may be easier in some patients because it allows the catheter to form a natural curve on the floor of the dilated right ventricle and point upward into the main pulmonary artery, making it easier to advance the catheter into the pulmonary artery. Femoral approach is easier and when combined with femoral arterial access (in patients where we need to exclude left heart pathology when direct measurement of left ventricular end diastolic pressure or a coronary angiogram is necessary), may be much more convenient to the patient.

With the shift of left heart procedures through radial route, the shift from femoral to cubital or jugular for right heart catheterisation has become a viable and convenient alternative for the patient and clinician. IJV access can also get complicated by pneumothorax or hemothorax, which is not a problem with femoral venous access.

Left-heart catheterization may be considered during catherization for PH in the following situations:

a. Validation of abnormal PCWP /evaluation of LV diastolic dysfunction
b. Suspected left-sided valvular lesion (mitral, aortic), Intra-cavitary obstruction – supramitral ring.
c. Suspected coronary artery disease

B. TECHNIQUE

Cardiac catheterization measurements should be made preferably when the patient is supine, when the patient is at rest and at hemodynamically steady state. Spontaneous variation in hemodynamics occurs over time which is a known shortcoming of cardiac catheterization. To minimise this problem, ensure that all measurements are taken in close proximity of each other. For example in some patients entering the pulmonary artery can be difficult and time consuming, so pullback from PA to RV and RV and great veins may be a better strategy, so that we can obtain the samples pretty close.

C. HARDWARE

The catheters used are usually balloon tipped end hole catheters, the most common one is the Swan-Ganz catheter. The catheter has a lumen (port) that opens at the tip of the catheter distal to the balloon. This port is connected to a pressure transducer. Other end hole catheters like multipurpose or even GL – Goodale Lubin catheter with an end-hole and very close side-holes can also be used for right heart catheterisation and obtaining PCWP.

Usually the Swan-Ganz catheter come with a thermistor at the tip to measure thermodilution cardiac output.

What all information should be collected ?

Saturations: Pulmonary artery (Mixed Venous saturation), {Mixed venous satsderived from SVC and IVC in selected cases to calculate shunts)} , and Aorta. (If pulmonary veins (PV) can be entered always obtain PV also).

Pressure data: Right atrial pressure (RAP), right ventricular pressure including RVEDP, Pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP). Aortic pressure and   LV pressure including LVEDP.

PAWP – Pulmonary Arterial Wedge Pressure: PAWP is an important pressure as it indirectly reflects the LA pressure and in-turn the LV filling pressure - LVEDP. The term PCWP and Pulmonary Capillary Occlusion Pressure is also used interchangeably with pulmonary Arterial wedge pressure – PAWP is the term recommended by the recent definition1.

PAWP pressure measurements are made when the balloon of the catheter is inflated after the catheter has been properly advanced into the distal pulmonary artery branch. The inflated balloon prevents blood flow or the transmission of pressure from the proximal pulmonary arteries. The static column of blood transmits the left atrial pressure to the catheter tip, providing a reliable estimate of left atrial pressure and thus measurements recorded from the tip of the catheter reflect LA pressure / LVEDP. There is a delay of 55 – 100 msec for PCWP Vs directly measured LA pressure. This is the time for the waves to travel from LA to the wedge position.

Methods to confirm wedge position

a) PAWP mean is less than or equal to the diastolic PAP,
b) the tracing has the "atrial pressure waveform", two / three waves per cardiac cycle vs one wave per cardiac cycle in the pulmonary artery tracing.
c) Fluoroscopy shows a stationary catheter tip after inflation,
d) Free flow is present within the catheter (flush test),
e) Arterial blood (can be confirmed by oxygen saturation) obtained from the distal port in balloon occlusion position.

End-Expiratory measurement

PAWP may be significantly affected by respiratory variations, which affect intrathoracic pressure. These changes are marked in patients with COPD and those who are obese. PAWP should be recorded as the mean of three measurements at end expiration.

The recommendation for measuring PAWP at end-expiration arises from the observation that this period in the respiratory cycle is at functional residual volume, when the intra- and extra-thoracic pressures are equal and near to zero. When we ask the patient to hold breath to avoid respiratory variation, make sure that the patient is not performing a Valsalva manoeuvre, which can raise the intrathoracic pressure.

Cardiac output measurement

Measurement of CO is an important component of cardiac catheterisation especially in patients with PAH. Either the thermodilution method or the Fick method can be used. Since it is a big topic by itself, we are not discussing it in much detail in this article.
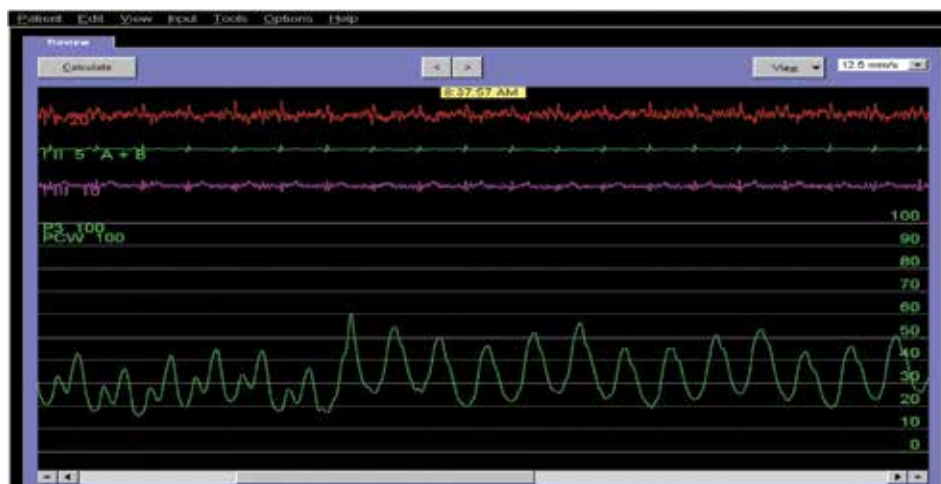

Fig 4 PCWP to PA pullback tracing

The Fick method is based on the principle that consumption oxygen must equal the product of blood flow to the organ multiplied by the A-V (arteriovenous) oxygen difference. By this method, cardiac output is calculated as follows:

CO = oxygen consumption per minute (VO2) / (arterial oxygen content – venous oxygen content). [oxygen content = 1.34 x [Hb] x oxygen saturation/100.]. The arterial sample is obtained from the aorta and the venous sample is from the pulmonary artery. Measurement of oxygen consumption is often difficult, ideally obtained using Douglas bag /polarographic method. Most often one refers nomogram charts based on Lafarge and Meittinen's formula[6]

Assessment of intracardiac shunts

As recommended by the consensus statement of PVRI, pulmonary hypertension "associated with unrepaired congenital heart disease, hemodynamic evaluation bycardiac catheterization plays a key role in the assessment of suitability for shunt closure, especially in patients who present late or without clinical signs of excessive pulmonary blood flow despite an anatomically large defect or signs of right-to-left shunting"[7].

In patients suspected to have intracardiac shunts (with a pulmonary artery oxygen saturation >75%, detected incidentally) or those patients being evaluated for operability for shunt lesions, we have to calculate the shunts by obtaining the mixed venous saturation (2SVC + 1 IVC / 3). In such patients both right and left cardiac catheterization is often performed to acquire systemic pressures and saturations. We also need to calculate the ratio between pulmonary and systemic artery resistances (PVR / SVR) which is an important measure of operability of a shunt lesion.

When we do oximetry to calculate shunts and assess operability, Oxygen content need to be calculated as dissolved oxygen can affect the calculations significantly. Oxygen content = total oxygen carrying capacity + dissolved oxygen. We calculate using the formula 1.36 x Hb g% x 10 x SO2% + 0.03 ml x pO2.

Vasoreactivity testing

Vasoreactivity testing is done in two groups of patients.

1. To know the response to pulmonary vasodilators – Now recommended for idiopathic PAH or drug / toxin induced PAH – So that we can identify patients who will respond to calcium channel blockers (CCB) leading to improved survival at low cost. But only 10% of the patients respond to CCB and some of them become non-responders on follow-up.

2. In patients with pre- and post-tricuspid systemic-to-pulmonary shunts, acute vasodilatory testing is used to assess operability.

   Positive vasodilatory response (PVD) is currently defined as a reduction in mean pulmonary arterial pressure (mPAP) by >10 mmHg leading to an mPAP of <40 mmHg and normal cardiac output (CO) upon acute pulmonary vasodilator challenge.

Agents available for PVD testing

1. 100% oxygen is used in most of the institutions in the developing world for pulmonary vasoreactivity testing. A tight mask with O2 flow at 10L/min is enough for adequate oxygenation for this purpose. There are certain disadvantages for oxygen, but most of the cathlabs still rely on oxygen,.

   a. VO2 calculations are erroneous when we use 100% oxygen as we use nomograms
   b. Hyperoxia may increase the SVR and the shunt.
   c. Oxygen may decrease the accuracy of flows calculated by the Fick method because the minor differences in A-V oxygen difference magnifies any saturation error, and calculated shunts will tend to be larger and resistances will be lower7.

2. Inhaled nitric oxide (iNO) at 10 to 40 ppm is the "gold standard" for pulmonary vasoreactivity testing. This requires a special equipment to deliver nitric oxide through a ventilator.

3. Intravenous adenosine = 50–250 μg/kg/min dose titration: 50 μg/kg/min every 2 min

4. Oral Sildenafil - Single dose of 25 mg of oral sildenafil. (Pulmonary hemodynamics to bemeasured every 15 minutes for 60 minutes after the administration of sildenafil)[8].

5. Intravenous Sildenafil - 10 mg intravenous sildenafil[9].

Response to acute vasodilatory response

The Sitbon criteria[10] for a positiveresponse (decrease in mean pulmonary arterial pressure of>10 mmHg reaching <40 mmHg, with no decrease in cardiac output) is the one which is followed for response in idiopathic PAH.

In patients with intracardiac shunts, there is a general consensus that a decrease in PVRI below 4 Wood units (WU)•m2 and/or in the ratio of pulmonary : systemic

vascular resistance (PVRI : SVRI [SVR index]) below 0.3 indicates that closure of the defect may be undertaken safely with a good long-term prognosis[11, 7]. If the PVRI is between 4 and 8 WU•m2, balloon occlusion of the shunt during catheterisation, and reassessment of the pressures and shunt can give more information[7]. In developing countries where patients with CHD present late in their life, we may have to follow a less stricter criteria to give the benefit of doubt to such patients. The Table provides a broad guideline on how patients are assessed for operability.

Table: Commonly used criteria for operability (This is only an indication, go by the overall clinical picture, ECG, and CXR)

	L-R shunt	PVR/SVR	PVR (Wood units)
ASD	>/= 2:1	<0.5	<6
VSD	>/= 1.5:1	<0.7	<9
PDA	>/= 1.3:1	<0.8	<9

Exercise and PAH

Previously PAPm with exercise >30mmHg was one of the criteria to define PH. But later it was found that the exercise protocolsare poorly defined and PA pressure varies in different age groups on exercise. So the definition of exercise induced PH was dropped[12]. In the cathlab we can either use bicycle ergometer or we can employ the technique of lifting weights with hands till fatigue, to test the response of pulmonary artery pressure to exercise. Both techniques have its own advantages and disadvantages. Overall, exercise response in assessment of PAH is not standardized and is not routinely done.

Angiographic evaluation during cardiac catheterisation for PH

Patients with pulmonary hypertension are usually sick, and as far as possible evaluation using contrast angiography should be avoided, as it carries a definite amount of risk.   In the era of echocardiography, CT and MR the need for routine angiography for diagnosis is very minimal. Angiography should be performed only to answer specific questions which cannot be answered by other imaging modalities. For example for CTEPH, CT pulmonary angiography has become the imaging of choice and contrast pulmonary angiography is hardly performed.

In CTEPH, the angiogram will show large central pulmonary arteries with significant peripheral tapering. Contrast pulmonary angiography has the highest spatial resolution for evaluating segmental and sub-segmental branches, which will give an idea whether the vascular abnormalities are amenable for surgery. Centrally located lesions benefit from pulmonary thrombo-endarterectomy (PEA), whereas peripherally located small vessel lesions without a central vascular abnormality do not benefit from surgery. Contrast Pulmonary angiography is indicated when the results of V/Q scanning cannot exclude CTEPH as an etiology for the elevated PA. Contrast pulmonary angiography is also used when interventional procedures for CTEPH are carried out like intra-arterial thrombolysis and balloon angioplasty, in patients who are not good candidates for PEA.[13]

One emerging indication of pulmonary angiopgraphy is the evolving catheter-based interventional treatment for CTEPH. - balloon pulmonary angioplasty (BPA) / percutaneous transluminal pulmonary angioplasty. For patients with CTEPH who have technically inoperable disease or those at high risk for surgical pulmonary thrombo-endarterectomy, BPA is an evolving as an alternative therapeutic strategy.

Segmental branches of the narrowed pulmonary arteries are to be targeted and are selected on the basis of pulmonary angiography. Case selection is based on lesion morphology to identify target vessels for BPA. Targets are identified using the Kawakami classification[14]. Lesions with morphologies like "chronic total occlusion" and "pouch defects" should be avoided because we don't have the clear anatomic information about the distal vessels. The lesions which are found to be suitable are "webs and bands" and "abrupt narrowing". In these type of lesions, the peripheral vessel and branches can be readily visualized[15].

Table 1 Practical recommendations relating to parameters measured or derived from right heart catheterisation (Adapted and modified from Eur Respir Rev 2015; 24: 642–652 | DOI: 10.1183/16000617.0062-2015)

Haemodynamic variable	Method of measurement	Range in normal subjects	Range in PAH	Practical advice
PAWP mmHg (Pulmonary arterial wedge pressure)	Swan-Ganz / end-hole catheter	4–12 mmHg	≤15	PAWP is recorded as the mean of three end-expiratory measurements
mPAP mmHg (mean pulmonary artery pressure)	Calculated using: mPAP=diastolic PAP+ (systolic–diastolic PAP)/3	Systolic: 15–25 Diastolic: 4–12 mPAP: 14±3	mPAP: ≥25	The machine will usually give the electronically derived mean pressure
PVR(Pulmonary Vascular Resistance) Wood units and PVRI (PVR indexed) Wood units•m^{-2}	Calculated using: PVR=(mPAP–mean PAWP)/cardiac output PVRI=PVR/BSA	0.25-3 Wood Units (20-160 dynes.cm^{-5})	PVR: >3 PVRI: ≥6	PVR should be expressed in Wood units as per the recent consensus. It may also be expressed as dyn•s^{-1}•cm^{-5} (conversion: Wood units×80). If BSA is less than 1, we have to multiply to get indexed resistance
SVR (Systemic Vascular Resistance) Wood units	Calculated using: SVR=(mSAP–RAP)/cardiac output	8–20 (600-1400 dynes.cm^{-5})	PVR/SVR: <0.75	This ratio of PVR to SVR >0.75 indicates significant pulmonary vascular disease
RAP mmHg (right atrial pressure)	Ensure steady state before starting measurement	Mean 1–6 mmHg. a wave 4-6, v Wave 2-4 mmHg	Normal or elevated	Ensure adequate hydration, if too low, infuse normal saline to raise to normal range
RVP mmHg (right ventricular pressure)	Ensure steady state before starting measurement	Systolic: 15–25 End-diastolic 1–8	>30 elevated	Ensure that the catheter tip reaches the RV apex, as occasionally intra-cavitory gradients can be present, which will be missed on a routine pull-back from PA to RV-RA
TPG mmHg	Calculated using: TPG=mPAP–PAWP	≤12	>12	May be used to determine a pre-capillary component in post-capillary PH
DPG mmHg	Calculated using: DPG=diastolic PAP–PAWP	<6	>7	May be used to determine a pre-capillary component in post-capillary PH

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PRACTICE TEST 1
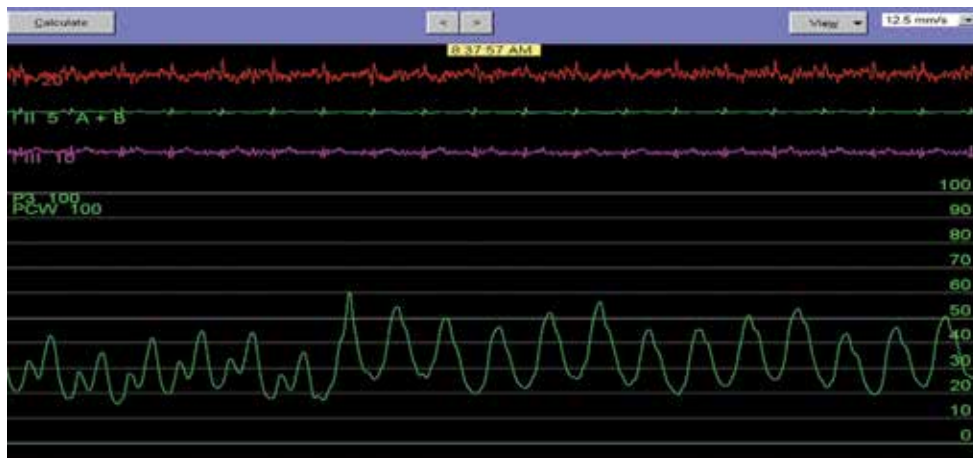
1. Interpret the tracings.

a. What is this tracing?

Pull back from PAW to PA. (PAWP - Two wave forms per cardiac cycle – atrial wave patterns in PAWedge as it indicates the left atrial pressure, PA -pulmonary artery – arterial wave form, single wave per cardiac cycle). The scale is 100.

b. What are the pressures?

PAW – PA pullback. PAWedge – a wave = 25-30 mm, V wave 35 mmHg, mean 25 mmHg\

PA 50/25 mean 32 mmHg
High PAWand mod PAH.

c. How do you interpret the tracing?

TPG = 7, DPG = 0
ie. TPG < 12 and DPG < 7 – Indicates Passive PAH.
Means if the reason for high PAWP corrected, eg: mitral stenosis, LV dysfunction, this pressure will come down.

PRACTICE TEST 2

1. Interpret the tracings.
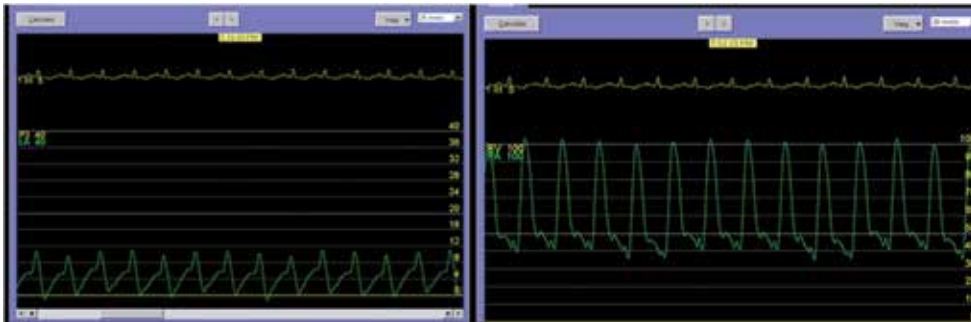
a. What are these tracings?

Left - The scale is 40, it is left atrial pressure.
Right – The scale is 100, it is PA pressure.

b. What are the pressures?

Left atrial mean = 5 mmHg
PA pressure – 100/ 38 mmHg,
PA diastolic – 38 , DPG = 33,

DPG = PA Diastolic – PAW mean or LA mean)>7 indicates PVD

c. How do you interpret the tracing?

DPG > 7
DPG > 7 – Indicates pulmonary vascular disease
Eg: Idiopathic PAH

Treatment of Pulmonary Hypertension: The State-of-the-art

Rajesh Muralidharan

Consultant Cardiologist, Baby Memorial Hospital, Calicut, Kerala.

Early detection and treatment of pulmonary hypertension (PH) is highly recommended because advanced disease may be less responsive to treatment[1]. Treatment of PH is no longer about prescription of drugs but rather a comprehensive multimodality approach aimed at improving survival and quality of life, periodic re-assessment of the response to therapy, treatment of intercurrent illness, escalation to combination drug therapy in patients who are poor responders or to consider for lung transplantation. In this review, we will focus on treatment aspects of WHO Group I Pulmonary Hypertension - Pulmonary Arterial Hypertension (PAH)[2].

Treatment of PH can be divided into:

1. Baseline assessment of the disease severity

2. General measures and supportive care

3. Primary therapy - directed at the pathophysiology of disease

4. Advanced therapy - directed at PH "per se"

1. BASELINE ASSESSMENT OF DISEASE SEVERITY: WHEN TO TREAT PAH?

A comprehensive evaluation as indicated in the previous session is warranted in all patients diagnosed with PH. Figure 1 provides a rough guide to the assessment of severity of pulmonary hypertension[3]. No single parameter provides diagnostic and prognostic information about PH. Most of the cut-off vales are based on expert consensus and must be used with caution in an individual patient and in causes of PH other than Group 1. Patients should be can be classified as low risk, intermediate risk or high risk for clinical worsening or death.[3]

The overall treatment goal in patients with PAH is to achieve a low risk status (Fig 1), which is usually associated with good exercise capacity, good quality of life, good RV function and a low mortality risk. Specifically, this means bringing and/or keeping the patient in WHO-FC II whenever possible. In most patients, this will be accompanied by a near-normal or normal 6MWD. Presently, as suggested during the 5th World Symposium on Pulmonary Hypertension a 6 minute walk distance (6MWD) of >440 metres is widely regarded as the threshold for good exercise capacity on treatment[4]. However, treatment goals should be individualised based on age and functional status.

In general, patients with WHO FC I do not require therapy. However, they should be monitored closely for disease progression to a functional level that may warrant therapy. Any reversible factor must be evaluated and treated[1,3,4].

Address for correspondence: Dr. Rajesh Muralidharan, MD, DM, Consultant Cardiologist, Baby Memorial Hospital, Calicut, Kerala.
Email: muralidharan.rajesh@gmail.com

Fig 1: Risk assessment in pulmonary arterial hypertension[3]

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

2. GENERAL MEASURES AND SUPPORTIVE CARE

Physical activity and Exercise

Despite potential risks, most studies agree that exercise training (ET) improves exercise capacity, quality of life (QoL), muscle function and pulmonary circulation. The rehabilitation program received a 1A recommendation at the PH world symposium in Nice in 2013[2]. This decision was mainly based on randomized controlled trials that investigated a limited number of clinically stable patients, in World Health Organization (WHO) Functional Class (FC) II–III on optimal medical therapies, with no recent history of syncope on exertion[5,6,7].

Many patients are often diagnosed at an advanced stage (WHO FC III-IV) and have poor functional status. During exercise, in severe PAH the right ventricle is forced to increase its output against a high resistance circuit. In addition, adaptation changes to exercise like vasodilation and the recruitment of new capillaries are no longer possible. If stroke volume cannot rise, increasing HR remains the only chance to increase CO. At this point, the primary parameter determining the symptoms and prognosis of the patient is the cardiac reserve[5]. The pulmonary vascular resistance (PVR)

together with the right ventricle (RV) adaptation define this parameter[6]. Thus, it becomes important to be able to discriminate those patients who can benefit from a more intensive training, reserving a more conservative treatment (mobilization in the bed, psychological support, breathing exercises) to patients with exhausted RV reserve. We should try to assess the functional status of our patients in the most objective way, as by CPET[9] or exercise echocardiography. Baseline RV function, RV Tei Myocardial Index (RV contractile reserve), RV afterload response to exercise (P/Q relationship), increase in pulmonary artery pressure (PAP) with exercise (>30 mm Hg) have all been applied for calculation of RV reserve. Recommendations regarding exercise is limited by gaps in the knowledge about the optimal method of exercise rehabilitation, intensity and duration of the training.

Contraception and Pregnancy

Pregnancy is still associated with a substantial mortality rate in PAH although the outcomes in the recently published series are slightly better[9,10]. Barrier contraceptive methods are safe for the patient, but with an unpredictable effect. Progesterone-only preparations such as medroxyprogesterone acetate and etonogestrel are effective approaches to contraception. It is preferable to avoid oestrogens such as those associated with the

old-generation mini-pill[11]. The likelihood of vasovagal reaction at the time of insertion of intra-uterine devices should also be considered. Bosentan may reduce the efficacy of oral contraceptive agents. A combination of methods may also be used. Patients who make an informed decision to continue pregnancy despite being counselled against, should continue to be treated with disease targeted therapies and planned for elective delivery.

Elective surgery

Major surgery in patients with PAH continues to be a high-risk procedure, particularly when emergency interventions are needed. Perioperative risk is high for noncardiac surgery, and many clinicians avoid regional anesthesia because of the potential deleterious hemodynamic effects[13]. Although mechanism is unclear, epidural is probably better tolerated than general anaesthesia[5]. The risk factors associated with high risk for peri-operative complications include emergency surgery, elevated right atrial pressure (>7 mmHg),six-minute walking distance (≤399 meters) and perioperative use of vasopressors.[12] Oral preparations may have to be temporarily substituted with intravenous/subcutaneous or inhaled agents in the peri-procedure period.

Air Travel

Roubinian et al[14] suggested that patients with PH who have a history of oxygen use, including nocturnal use only, be evaluated for supplemental in-flight oxygen. Furthermore, in view of the variability in aircraft cabin pressures, the statistically significant association of oxygen desaturation on longer flights, the increased likelihood of ambulation on longer flights, and the efficacy of oxygen in preventing in-flight desaturation, it is prudent to suggest that all patients with PH who will be traveling on flights of greater than 2.5 hour in duration be evaluated for in-flight supplemental oxygen. The known physiological effects of hypoxia suggest that in-flight O2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O2 pressure consistently <8 kPa (60 mmHg)[15]. A flow rate of 2 l/min will raise inspired O2 pressure to values seen at sea level. Similarly, such patients should avoid going to altitudes >1500–2000 m without supplemental O2.

Vaccination

Although there are no society guidelines, PH patients are routinely immunized with all age-appropriate as well as influenza and pneumococcal pneumonia vaccines in most expert centres.

Diuretics

Diuretics are used to treat fluid retention due to PH and to reduce hepatic congestion and peripheral edema. Moreover, diuresis can prevent a distended right ventricle from impending left ventricular filling. Since patients with PH are pre-load dependent, over-diuresis may result in under-filling of the RV, and a decline in RV stroke volume, thereby reducing left ventricle (LV) stroke volume resulting in systemic hypotension and sometimes shock. In addition, diuretics can be associated with arrhythmias induced by hypokalemia, and metabolic alkalosis (which can depress ventilation). Hence diuretics should be used with caution especially in advanced disease[3,16]. Although there are no randomized controlled trials of diuretics in PAH, clinical experience shows symptomatic benefits in patients with group 1 PAH when a decompensated right heart failure occurs. Occassionally, when RV hypertension is severe, diuretics may be ineffective and ultrafiltration may be required[17].

Oxygen Therapy

Oxygen therapy improves survival of chronic obstructive pulmonary disease (COPD) patients with hypoxemia[18,19]. Other benefits of oxygen therapy include improvements in sleep, cognitive function, emotional status and slowing the progression of hypoxic pulmonary hypertension (WHO Group III PH)[20]. Use of oxygen therapy has been extrapolated to other groups of PH as well. Oxygen is generally indicated in all PH patients with hypoxaemia either at rest, or with exercise or during sleep. Oxygen is generally administered at 1 to 4 L/min via nasal prongs and adjusted to maintain the oxygen saturation above 90 percent at rest and, if possible, with exercise and sleep[21].

Anticoagulation

A recently published metanalysis by Khan et al[22] showed that use of anticoagulation may improve survival in idiopathic PAH patients, while increasing mortality when used in scleroderma-associated-PH (SSc-PH) patients. They recommended that until randomized data are available, anticoagulant use in PAH should be tailored to PAH subtype. In most of the studies on anticoagulation thus far, SSc-PH is associated with worse survival and increased risk of bleeding. Hence most experts advise against anticoagulation in this group of patients[23,24,25].

3. PRIMARY THERAPY FOR PH

There are no effective therapies directed at the pathophysiology of the disease available currently for group 1 PH (PAH). Hence most of these patients will require advanced therapy. Patient in WHO FC I generally

do not require advanced treatment. However, careful and periodic re-assessment must be done in all such patients to diagnose clinical deterioration at the earliest.

4. ADVANCED THERAPY

CALCIUM CHANNEL BLOCKERS

Prior to the initiation of advanced therapy, it is recommended that patients with group 1 PAH undergo a vasoreactivity test, particularly patients with idiopathic PAH, heritable PAH, and anorexigen-induced PAH who are the groups of patients most likely to respond. Patients in other groups are rarely vasoreactive and as such vasoreactivity testing is not absolutely necessary in that population.

Vasodialatory testing involves administration of epoprostenol, adenosine or inhaled nitric oxide and measurement of hemodynamic response by right heart heart catheterisation (RHC). The test is considered positive if mean pulmonary artery pressure decreases at least 10 mmHg and to a value less than 40 mmHg, with an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure[27,28]. Initial treatment with calcium channel blockers is indicated in all patients who have a positive response on vasodialatory testing.

The choice of CCB is based on the patient's heart rate at baseline, with a relative bradycardia favouring nifedipine and amlodipine and a relative tachycardia favouring diltiazem. The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem and up to 20 mg for amlodipine. A complete re-assessment often involving RHC is warranted at 3-4 months after initiation of therapy. In patients with inadequate response (defined as WHO FCI-II and near normalisation of hemodynamics) advanced PAH therapys should be instituted[30].

Sitborn et al[31] reporting on long-term response to calcium channel blockers (CCB) in idiopathic pulmonary arterial hypertension concluded that long-term CCB responders represent <10% of IPAH patients evaluated. During acute vasodilator testing, these patients showed significantly lower levels of both mean PAP and PVR, which reached near-normal values. Whether vasoreactivity is an indicator of good prognosis is still unclear.

PATHWAYS TO PAH

There are three well known pathways that contribute to the pathogenesis of PAH: the endothelin, nitric oxide (NO) and prostacyclin pathways. Treatments targeting these pathways are well established in clinical practice, such as Endothelin Receptor Anatgonists (ERAs), Phosphodiesterase-5 inhibitors (PDE-5is) and Prostanoids (Table 1). Additional therapeutic strategies being explored with unsatisfactory results thus far include inhaled vasoactive intestinal peptide, tyrosine kinase inhibitors (platelet-derived growth factor inhibitors) and serotonin antagonists. Rho kinase inhibitors, vascular endothelial growth factor receptor inhibitors, angiopoietin-1 inhibitors and elastase inhibitors are in the early stages of development[32]. Gene therapy, stem cell therapy and pulmonary artery denervation using radio frequency ablation etc. are in experimental stages[33].

ENDOTHELIN RECEPTOR ANTAGONISTS

The endothelin (ET) system, especially ET-1 and the ET(A) and ET(B) receptors, has been implicated in the pathogenesis of pulmonary arterial hypertension (PAH). The ETA receptor is responsible for vasoconstriction, while the ETB receptor produces vasodilation through the release of NO and prostacyclin[34]. Overexpression of ET-1 and prolonged interaction with the ETA receptor leads to an increased state of vasoconstriction, and has chronic hypertrophic and antiapoptotic effects. ET-1 concentrations are elevated in patients with PAH and serve as an important therapeutic target for ERAs.

Bosentan blocks both ET(A) and ET(B) receptors, whereas the two other compounds, sitaxsentan and ambrisentan are more selective blockers of the ET(A) receptor. There is ongoing debate as to whether selective or nonselective ET receptor blockade is advantageous in the setting of PAH, although there is no clear evidence that receptor selectivity is relevant with regard to the clinical effects of these drugs[34].

Among these agents, only *bosentan* and *macitentan* (nonselective) and *ambrisentan* (selective) are available. Sitaxsentan was withdrawn from the European Union, Canada, and Australia in 2010 following several fatal cases of hepatoxicity and was never approved in United states[35].

Ambrisentan

Ambrisentan is a selective endothelin receptor antagonist approved for the treatment of idiopathic, heritable and connective tissue disease-associated PAH. Ambrisentan has been shown to improve exercise capacity and hemodynamics with an acceptable side-effect profile. It has also proven to be safely used in combination with other PAH-specific medications, especially with phosphodiesterase-5 inhibitors. In the recent randomized trial, AMBITION[36,37], it was shown that upfront combination therapy of ambrisentan and tadalafil significantly decreased the risk of clinical failure compared

with monotherapy. Oedema (17%), Hepatotoxicity (<2% at 2 years), anaemia (6%) are the most common side effects. In a sandwich-cultured human hepatocytes study of ERAs (ambrisentan, darusentan, bosentan and sitaxsentan), it was demonstrated that ambrisentan had little or no human hepatic transporter inhibition, compared with the other ERAs analysed[38]. This finding likely accounts for significantly less hepatic injury. The US FDA removed the blackbox warning regarding hepatotoxicity in 2011 and routine liver function testing is no longer indicated. In the AMBITION trial, peripheral edema was the most common adverse event. It was observed at a higher rate in the ambrisentan plus tadalafil combination group (45%) compared with ambrisentan (33%) and tadalafil (28%) monotherapy[36].

Bosentan

Bosentan was the first endothelin receptor antagonist (ERA) approved for use in PAH. Clinical studies (Study-351, BREATHE-1, BREATHE-2, BREATHE-5, EARLY and COMPASS 2), have shown that the use of bosentan is associated with improved exercise capacity, WHO functional class, cardiopulmonary hemodynamics, quality of life and delayed time to clinical worsening when compared to placebo. Further, long term studies have demonstrated improved survival with the use of bosentan when compared to historical controls although there is no placebo controlled data confirming a survival benefit. Increases in hepatic amino transferases occurred in approximately 10% of the patients andwere found to be dose dependent and reversible after dose reductionor discontinuation. For these reasons, liver function testing should be performed monthly in patients receiving bosentan[39].

Macitentan

In the SERAPHIN trial[40], 250 patients with symptomatic pulmonary arterial hypertension to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg for an average of 100 weeks. The primary endpoint was the time to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with i.v. or subcutaneous prostanoids or worsening of PAH. Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension in this event-driven study. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anemia. While no events of hepatotoxicity was reported, reduction in haemoglobin ≤8 g/dl was observed in 4.3% of patients receiving 10 mg of macitentan. Oedema may be less of an issue with Macitentan[40].

PHOSPHODIESTERASE 5-INHIBITORS (PDE5-Is)

PDE5 is an enzyme abundantly expressed in the lungs that hydrolyzes cGMP, a second messenger of the NO pathway within the lungs. PDE 5 inhibitors prevent the hydrolysis of cGMP, which has vasodilatory and anti proliferative effects on the pulmonary vasculature. In addition, PDE-5 inhibitors exert anti proliferative effects[41]. Currently, Sildenafil and Tadalafil are FDA approved for the treatment of pulmonary hypertension.

Sildenafil

In a systematic analysis[42] of nineteen patients with group 1 PAH participants treated with PDE5 inhibitors were more likely to improve their WHO functional class,to walk 48 metres further in 6MWD and were 22% less likely to die over a mean duration of 14 weeks compared to placebo.The number needed to treat to prevent one additional death was 32 participants. There was an increased risk of adverse events with PDE 5 inhibitors, especially headache, gastrointestinal upset, flushing and muscle aches and joint pains.

While there is robust evidence for benefit in the Group I PAH, data indicating definitive benefit in other groups of PH is lacking. The quality of evidence is low and there is marked heterogeneity amongst trials. Five trials compared PDE5 inhibitors to placebo in PH secondary to left-heart disease (PH-LHD). Those using PDE5 inhibitors walked 34 metres further compared to placebo. There was no evidence of a difference in mortality. Five trials compared PDE5 inhibitors to placebo in PH secondary to lung disease/hypoxia, mostly in COPD. There was a small improvement of 27 metres in 6MWD using PDE5 inhibitors compared to placebo in those with PH due to lung disease. There was no evidence of worsening hypoxia using PDE5 inhibitors, although data were limited. Three studies compared PDE5 inhibitors to placebo or other PAH-specific therapy in chronic thromboembolic disease. There was no significant difference in any outcomes.

Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type 5 (PDE5i). The approved oral dose of Sildenafil is 5- 20 mg thrice daily. In the clinical trials, no greater efficacy was achieved with the use of higher doses. Sildenafil injection is for the continued treatment of patients with PAH who are currently prescribed oral Sildenafil and who are temporarily unable to take oral medication. The recommended dose is 2.5 mg or 10 mg administered as an intravenous bolus injection three times a day. The dose of injection does not need to be adjusted for

body weight. A 10 mg dose of Sildenafil injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose. Most common adverse reactions (>3%) include headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea and dizziness. Concomittant use of nitrates in any form is contraindicated. Caution must be used when Sildenafil is used along with CYP3A inhibitors especially Ritonavir, alpha blockers, amlodipine and other drugs that have effect on blood pressure. Peak effect on pulmonary vasodilatation is achieved in approximately 60 min after intake[43].

There are no adequate and well-controlled studies of sildenafil in pregnant women (Category B).There was no evidence of teratogenicity, embryotoxicity, or fetotoxicity pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis. The safety and efficacy of Sildenafil during labor and delivery has not been studied. It is not known if sildenafil or its metabolites are excreted in human breast milk and caution is advised[43].

Other than inhaled Nitric Oxide (iNO) licensed for the treatment of newborns with PPHN and severe respiratory failure, there are no PAH therapies specifically approved for children. Sildenafil has been used extensively in an off-label manner for the treatment of neonates, infants, and children with PAH associated with diverse heart and lung diseases[44].

In August 2012, the USFDA released a strong warning against the use of sildenafil for pediatric patients (ages 1-17 years) with PAH. It stated that children taking a high dose of Sildenafil had a higher risk of death than children taking a low dose and that the low doses of Sildenafil is not effective in improving exercise ability[45]. The recommendation was based on 3-year follow-up data in children of START-1 study, showing dose-dependent increases in mortality (mortality ratio 3.5; P = 0.015) when using high doses (80 mg three times daily in children with body weight >45 kg) relative to low doses (10 mg three times daily in body weight >45 kg)[46].

Ironically, based on the same data, the EMEA recommended the use of sildenafil in children aged 1-17 years with a maximum daily dosage of 10 mg three times daily in children weighing less than 20 kg or 20 mg three times daily in those weighing over 20 kg.They cautioned against using higher doses[47].

The STARTS-2 results showed that factors associated with mortality were heridetary (HPAH) etiology, high PVRI, and high right atrial pressure and adjustment, for these three factors reduced the hazard ratios for mortality for the high versus the low dose[48].

In 2014, USFDA clarified the warning issued in 2012, stating that its warning was mainly against using high doses and chronic use of the drug, and that sildenafil may be considered in situations where the benefits of treatment with the drug are likely to outweigh its potential risks for each patient[49].

Tadalafil

Tadalafil has been shown to improve exercise tolerance in patients with PAH in studies that predominately included patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%)[50]. In PHIRST trial[51], Tadalafil (40 mg) significantly increased the six-minute walk distance and the time to clinical worsening and improved health related quality of life. This improvement of the six-minute walk distance was sustained for an additional 52 weeks in the PHIRST -2 trial[52], an uncontrolled extension trial. In patients with mild or moderate renal and hepatic impairment, the recommended starting dose is 20 mg once daily. The dose may be increased to 40 mg once daily based upon individual tolerability. It is preferably avoided in patients with severe renal and hepatic impairment[50,53].

Riociguat

Riociguat is a stimulator of soluble guanylate cyclase (sGC). Riociguat stimulates the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation.

In the PATENT-1 trial[53], 443 patients with symptomatic pulmonary arterial hypertension were randomized to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg-maximum group). By week 12, the 6-minute walk distance had increased by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (P<0.001). Prespecified subgroup analyses showed that riociguat improved the 6-minute walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, and Borg dyspnea score. The most common serious adverse event was syncope.In CHEST-1[54] multicenter, randomized,

double-blind, placebo-controlled study, 261 patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were randomised to receive placebo or riociguat. Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension. It can also be administered to patients as a bridge to surgery.

PROSTACYCLIN ANALOGUES AND PROSTACYCLIN RECEPTOR AGONISTS

The biological functions of prostacyclin in the pulmonary circulation are mediated by a specific cell-surface receptor. The binding of prostacyclin to the receptor triggers the activation of the G-protein and increases intracellular cAMP, which activates protein kinase A. This causes inhibition of platelet aggregation, relaxation of smooth muscle, and vasodilation of the pulmonary arteries. In this manner, prostacyclin and its analogues can counter the vasoconstrictive mediators, such as endothelin, which are active in PAH, enabling relaxation of the pulmonary arterial vasculature. However, because prostacyclin has a short half-life (only minutes) and primarily works locally, the clinical use of prostacyclin is challenging.

Epoprostenol

The efficacy of continuous i.v. administration of epoprostenol has been tested in three unblinded RCTsin patients with WHO-FC III and IV IPAH[57,58] and in those with PAH associated with the scleroderma spectrum of diseases[59]. Epoprostenol improves symptoms, exercise capacity and haemodynamics in both clinical conditions and is the only treatment shown to reduce mortality in IPAH in a single RCT study[58]. The meta-analysis for total mortality of the three epoprostenol RCTs[57,58,59] has shown a risk reduction for mortality of about 70%. Long-term persistence of efficacy has also been shown in IPAH as well as in non-operable CTEPH[60,61].

Infusion of Epoprostenol should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. If symptoms of pulmonary hypertension persist or recur after improving, the infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. Administration is by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorders. Most treatment-limiting adverse events were not serious[62].

Beraprost

Beraprost sodium, a chemically stable and orally active prostacyclin analogue, has similar pharmacologic properties to epoprostenol, its half-life is significantly longer. Patients treated with beraprost exhibited less evidence of disease progression at six months (p = 0.002), but this effect was not evident at either shorter or longer follow-up intervals[56]. Similarly, beraprost-treated patients had improved 6-min walk distance at 3 months by 22 m from baseline and at 6 months by 31 m (p = 0.010 and 0.016, respectively) compared with placebo, but not at either 9 or 12 months. Headache was the most common drug-related adverse events.

Ilioprost

Iloprost is a synthetic analogue of prostacyclin-PGI. Inhaled iloprost has theoretical advantages in targeting the lung vasculature and does not require intravenous administration. Inhalations of 2.5 or 5.0 microgram of iloprost (six or nine times per day; median inhaled dose, 30 microgram per day) was compared with inhalation of placebo in a study of 203 patients with severe PAH or CTEPH (NYHA FC III or IV). Inhaled Iloprost improved the combined primary end point of 6 MWD and functional class by 16.8 percent as compared with 4.9 percent of the patients receiving placebo (P=0.007). Overall, inhaled iloprost was well tolerated, with flushing and jaw pain being the most frequent side effects[63].

Treprostinil

Treprostinil is a stable, long-acting prostacyclin analogue which can be administered as a continuous subcutaneous infusion using a portable miniature delivery system. Subcutaneous treprostinil has been shown in a large multicenter randomized controlled trial to improve exercise capacity, clinical state, functional class, pulmonary hemodynamics, and quality of life in patients[64]. Side effects include facial flush, headache, jaw pain, abdominal cramping, and diarrhea, all typical of prostacyclin, and manageable by symptom-directed dose adjustments. Infusion site pain which may make further treatment impossible in 7%–10% of the patients. Long-term survival in pulmonary arterial hypertension patients treated with subcutaneous treprostinil is similar to that reported with intravenous epoprostenol[65]. There are uncontrolled data suggesting efficacy of subcutaneous treprostinil in chronic thromboembolic

Table 1

	DOSE	ADVERSE EFFECT
PHOSPHODIESTERASE 5 INHIBITORS (PDE 5i)		
SILDENAFIL	IV: 2.5mg or 10mg 3 times daily Oral : 20mg 3 times daily (The FDA approved dose).	Flushing, diarrhea, myalgia, priapism, visual disturbance, dyspepsia and epistaxis
TADALAFIL	Oral : 40mg once daily	Flushing, headache, nausea, myalgia, respiratory tract infection, nasopharyngitis
ENDOTHELIN RECEPTOR ANTAGONISTS		
AMBRISENTAN	Oral : Initial : 5mg once daily and is titrated upto 10 mg / day	Peripheral oedema, liver toxicity, anemia, teratogenecity, reduced hormonal contraceptive efficacy, reduced sperm count
MACITENTAN	10mg once daily , maximum 10mg daily	Headache, anemia, nasopharyngitis, bronchitis
PROSTANOIDS		
EPOPROSTENOL	IV: Initial : 2ng /kg / minute, Titrate 1 to 2 ng/kg / min at intervals of > 15 min until dose limiting side effects or clinical response.	Cardiovascular: Flushing, hypotension, diaphoresis, bradycardia, tachycardia, chest pain, dyspnoea CNS: Headache, dizziness, anxiety, agitation GIT: Abdominal pain, dyspepsia, nausea, vomiting Others: Injection site pain and reaction, Flu like syndrome
ILOPROST	Inhalation: Initial: 2.5 mcg/dose; if tolerated, increase to 5 mcg/dose. Administer 6 to 9 times daily (dosing at intervals ≥2 hours while awake according to individual need and tolerability). Maintenance dose: 2.5 to 5 mcg/dose; maximum daily dose: 45 mcg (ie, 5 mcg/dose 9 times daily)	Cardiovascular: Flushing, hypotension. Central nervous system: Headache, trismus. Gastrointestinal: Nausea. Neuromuscular & skeletal: Jaw pain. Respiratory: Cough, flu-like symptoms
TREPROSTINIL	Initial:18 mcg (or 3 inhalations) every 4 hours 4 times/day. If tolerated, increase dose by an additional 3 inhalations at approximately 1- to 2-week intervals; target dose and maximum dose: 54 mcg (or 9 inhalations) 4 times/day. Oral: Initial: 0.25 mg every 12 hours or 0.125 mg every 8 hours; may increase dose in increments of 0.25 mg or 0.5 mg every 12 hours or 0.125 mg every 8 hours every 3 to 4 days as tolerated to achieve optimal clinical response. **Conversion from injection to oral dosing:** Decrease the dose of parenteral treprostinil up to 30 ng/kg/minute per day while simultaneously increasing the dose of oral treprostinil up to 2 mg 3 times daily as tolerated. The following equation may be used: Treprostinil oral total daily dose (mg) = Parenteral treprostinil dose (ng/kg/minute) x weight (kg) x 0.0072.	Cardiovascular: Flushing (oral, oral inhalation:), vasodilatation (s/c) Central nervous system: Infusion-site pain, headache. Dermatologic: Skin rash. Gastrointestinal: Diarrhea,nausea. Local: Infusion site reaction, including erythema, induration, skin rash. Neuromuscular & skeletal: Limb pain. Oral: jaw pain. Respiratory: Cough (inhalation), pharyngolaryngeal pain (inhalation), throat irritation (inhalation)

pulmonary hypertension[66]. Treprostinil can also be administered intravenously, although increased doses, up to 2–3 times those given subcutaneously, appear to be needed to obtain the same efficacy. Oral treprostinil was approved by the U.S. Food and Drug Administration in December 2013 as the first oral prostacyclin analogue for the treatment of pulmonary arterial hypertension (PAH). The recommended starting dose is 0.25 mg twice daily (BID) or 0.125 mg three times daily (TID), with dose titrations of 0.25–0.5 mg BID or 0.125 mg TID every 3–4 days to the highest tolerated dose[67].

Selexipag

Selexipag is an oral prostacyclin IP receptor agonist approved for use as monotherapy or in combination with other therapies to slow PAH progression and reduce the risk of hospitalization in patients with FC II or III symptoms. Its stability and relatively long half-life offer conveniences over conventional prostanoid therapies[68]. In the GRIPHON trial, the primary composite end point of death or a complication related to pulmonary arterial hypertension was significantly lower with selexipag than with placebo. There was no significant difference in mortality between the two study groups[69].

MONOTHERAPY, SEQUENTIAL THERAPY OR COMBINATION THERAPY?

It has been proposed that combining pharmacologic agents with different mechanisms of action may produce an additive effect or may induce the same effect at lower doses of each agent (Table 2). Combination therapy may be administered as two agents initiated together or as "add-ons" (ie, sequential therapy). The combination associated with the best efficacy is *tadalafil* and *ambrisentan* for patients with functional class II or III PAH[70].

In the AMBITION trial[71], patients with PAH WHO FC II-III who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy. The reduction in clinical failure rate was primarily driven by decreased hospitalizations for progressive PAH (which portends a poor prognosis), rather than by improved survival or WHO functional class. Adverse events including edema, headache, nasal congestion, anemia, and syncope were reported more frequently in those receiving combination therapy (45 versus 30 percent), but rates of hypotension were similar. The dosing based on AMBITION trial is to initiate Ambrisentan 5 mg once daily, with or without Tadalafil 20 mg once daily. Uptitration of the doses at 4 week intervals should be attempted based on clinical

tolerance (Max Ambrisentan 10 mg and Tadalafil 40 mg). However such responses should not be considered as a class effect and substituting with other drugs within the same family may not be associated with the same or improved outcomes. Bosentan significantly decreases the plasma concentration of sildenafil when co-administered to patients with pulmonary hypertension and is not of proven benefit[72]. The lack of interaction between Ambrisentan and Tadalafil probably explains the benefits reported.

Sequential combination therapy is the most widely utilised strategy, both in RCTs and in clinical practice. From monotherapy, there is an addition of a second and then a third drug in cases of inadequate clinical results or in cases of deterioration[3]. A structured prospective programme to evaluate the adequacy of clinical results is the so-called goal-oriented therapy[73], a treatment strategy that uses known prognostic indicators as treatment targets. The therapy is considered adequate only if the targets are met. The key difference between goal-oriented therapy and non-structured approaches is that patients who are stabilised, or even those who improve slightly, can still receive additional therapy if treatment goals are not met. The goal-oriented treatment strategy utilises different targets, including WHO-FC I or II, and the near-normalization of resting CI and/or of NT-proBNP plasma levels. A recent study[74] has confirmed a better prognosis in patients achieving these goals as compared with patients who did not.

Whether an initial pre-emptive upfront combination therapy (eg: Ambrisentan+Tadalafil) or a step wise sequential combination therapy based on clinical response and treatment response provides improved outcomes is unclear.

Table 2 Recommendations for Sequential drug therapy in PAH

1. Macitentan added to Sildenafil*
2. Riociguat added to Bosentan*
3. Selexipag added to ERA and/or PDE5i*
4. Sildenafil added to Epoprostenol ^
*Class I LOE B: WHO FC II-III Class II LOE C: WHO FC IV ^ Class I LOE B: WHO FC II Class II LOE B: WHO FC 1V

BALLOON ATRIAL SEPTOSTOMY (BAS)

Patients with idiopathic PAH (IPAH) and a patent foramen ovale (PFO) appear to live longer than those

without a PFO.[75] Individuals with Eisenmenger syndrome (anatomic right-to-left shunt) have a better prognosis than those with PAH without a shunt, based on a slowly progressive increase in pressure and gradual evolution of right ventricular hypertrophy that enables the ventricle to cope with very high pressures.[76] Creation of an interatrial communication has been shown to preserve systemic output by decompressing the dysfunctional right ventricle, offering temporary clinical benefit to very ill patients with IPAH in whom therapy is failing.

BAS is usually indicated in WHO-FC IV PH with right heart failure refractory to medical therapy, patients with severe syncopal symptoms, patients awaiting lung transplantation with unsatisfactory clinical response on maximal medical therapy or when medical therapy is not available. Unfortunately, BAS is contraindicated in those patients who are in the most dire need of intervention; those with markedly elevated pulmonary vascular resistance, arterial oxygen saturation < 80% at rest, and severe right-heart failure (low cardiac index and high right atrial pressure). In such patients, massive right-to-left shunting after BAS may result in inadequate pulmonary blood flow and severe hypoxemia. There appears to be a window of opportunity for this procedure, and the preferred approach for BAS is elective rather than "rescue".[77]

REFRACTORY RIGHT HEART FAILURE AND LUNG TRANSPLANTATION

Intensive care of patients with pulmonary hypertension (PH) and right-sided heart failure includes treatment of factors causing or contributing to heart failure, careful fluid management, and strategies to reduce ventricular afterload and to improve cardiac function. Extracorporeal membrane oxygenation (ECMO)[78] should be considered in distinct situations, especially in candidates for lung transplantation (bridge to transplant) or, occasionally, in patients with a reversible cause of right-sided heart failure (bridge to recovery)[79]. ECMO should not be used in patients with end-stage disease without a realistic chance for recovery or for transplantation.

For patients with refractory disease, lung transplantation remains an important treatment option. Patients should be referred to a transplant centre when they remain in an intermediate- or high-risk category despite receiving optimised pulmonary arterial hypertension therapy.

Meticulous peri-operative management including the intra-operative and post-operative use of ECMO effectively prevents graft failure.

Patients with ESC/ERS intermediate or high risk or REVEAL[80] risk score >7 on appropriate PAH medication, progressive disease or recent hospitalisation for worsening of PAH, need for i/v or s/c prostacyclin therapy, known or suspected high risk variants such as pulmonary veno-occlusive disease, scleroderma, large and progressive pulmonary artery aneurysms should be reffered early for listing for lung transplantation[80,81].

Currently, the vast majority of patients worldwide receive bilateral lungs, as indicated by the International Society for Heart and Lung Transplantation Registry figures although heart-lung, isolated lung and bilateral lung transplantation with repair of intra-cardiac defect if any are also possible options[82].

According to the 2018 registry report, the median survival of all adult recipients is 6.5 years, but bilateral lung recipients have a better median survival than single lung recipients (7.6 versus 4.7 years)[83].

CONCLUSION

PAH is a condition with unique diagnostic and therapeutic challenges. Although there are gaps in knowledge, the availability of three different classes of drugs has greatly expanded our therapeutic options. All PAH patients should be enrolled in a comprehensive PAH care programme at an expert centre. Patients with Idiopathic PAH (IPAH), Drug induced PAH (DPAH), Hereditary PAH (HPAH) should undergo vasoreactive testing[3,84,85]. If vasoreactive, these patients should receive calcium channel blocker therapy. Patients who are not vasoreactive, as well as other groups of PAH should undergo comprehensive evaluation and risk assessment. They may be classified as low/intermediate risk (WHO FC II-III) or high risk (WHO FC IV). For patients in the low/intermediate risk groups therapy with one of the approved oral agents (ERA, PDE5i, sGC or IP agonist) may be started. Whether an upfront combination therapy with two agents is superior to sequential therapy is still being debated. Patients who have a poor response to drug therapy should be listed early for balloon atrial septostomy or transplantation (Fig 2).

Fig 2 Proposed treatment algorithm for Pulmonary Artery Hypertension
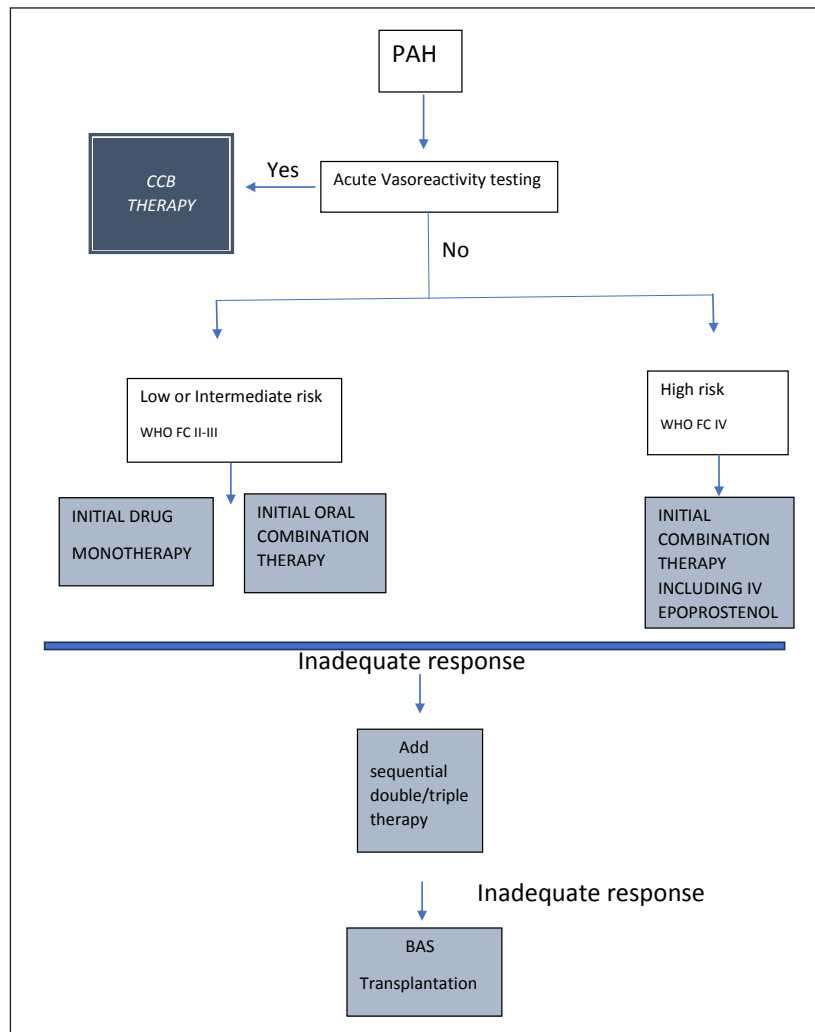
Adapted from Galie N et al. EHJ 2016 (Reference 3)
*Vasoreactivity testing only in idiopathic PAH, drug induced PAH, and hereditary PAH.
*Ambrisentan, Bosentan, Sildenafil – IA
*Macitentan, Tadalafil, Riociguat, Selexipag – IB
*Ambrisentan + Tadalafil was superior to either drug alone in delaying clinical failure

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Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction (PH-HFpEF), The Enigma

K Venugopal

Professor & Head, Department of Cardiology,
Pushpagiri Medical College, Thiruvalla, Kerala

INTRODUCTION

Left heart diseases (LHD) cause pulmonary hypertension (PH) and have been included as Group 2 PH in the classification of Pulmonary Pypertension[1]. It is defined as a elevated Mean PA pressure >25 mmHg at rest secondary to an increased PCWP(pulmonary capillary wedge pressure) >15 mm Hg. This elevation in PCWP is **unique** to Group 2 PH. Another distinguishing feature may be associated mitral regurgitation. PH-HFpEF may develop in the acute phase or in chronic phase . While both HFrEF and HFpEFcan cause PH, it is estimated that the prevalence of HFpEF is high and outnumbers the HFrEF group . This may be due to the high prevalence of Hypertension (HTN), Diabetes Mellitus (DM) and Obesity in the HF pEF group[2]. The term PH- HFpEF is now confined to chronic heart failure. It has been observed that some patients develop Out of proportion PAH due to a combined pre and post capillary hypertension mechanisms (CpcPH-HFpEF)with very poor prognosis. Therapeutic options in this group of patients are currently limited.

EPIDEMIOLOGY

Approximately 2.5 million patients are diagnosed to have HFpEF in the USA. PH in HFpEF is far more prevalent than considered and is the commonest form of pulmonary hypertension. PH is more common than in HFrEF. The New York heart Failure Registry[3] showed a prevalence of 44% and in the Olmsted county data base PH was seen in 80% patients when the main cause of HF was hypertension[4]. The TOPCAT trial showed that Doppler derived PH was seen in 36%[5]. Overall expected PH in HFpEF phenotypes may be as high as 50%. Thus around 1.25 million patients with HFpEF have PH in USA. Hemodynamic assessment by cath studies have shown that severe out of proportion PH develops in 7.5%. With the population of elderly patients increasing with high prevalence of DM, HTN and coronary artery disease (CAD), it is natural to assume that in India also, the PH-HFpEF is going to be a major problem in future.

PHENOTYPES

The 4th WHO symposium suggested that there are 3 different groups of patients with PH HFpEF. The vast majority of patients are elderly with LVH, left atrial enlargement in echo with radiological evidence of HF and increased BNP levels. The other 2 groups are one with young age and features of IPAH and the other group again small at any age with no comorbidities and echo showing little or no LVH. The two latter groups ideally require Right heart catheterisation to establish the diagnosis of PH HFpEF as they may be mistaken for IPAH/PH-HFpEF.

PATHOPHYSIOLOGY AND HEMODYNAMICS

The initial effect of a raised left atrial pressure can be a barotrauma to the lung microvessels resulting in stress failure of capillaries and alveolar membrane. This leads to endothelial dysfunction and loss of permeability. The clinical presentation would be acute pulmonary edema. There is also activation of the metalloproteinases which damage the alveolar unit. Sustained pressure injury alters the intima and media with deposition of collagen

Address for correspondence: Dr. K Venugopal, MD, DM, Professor & Head Department of Cardiology, Pushpagiri Medical College, Thiruvalla, Kerala.
E-mail: venugopalknair@gmail.com

and change in the character and function of the alveolar capillary membrane. These changes, unlike the initial stress failure of capillaries which can be reversed, tend to be progressive and later irreversible. Hemodynamically these may be compared to the classical passive and reactive pulmonary hypertension sub types.The passive type is characterized by a mean PAP of >25 Hg without any increase in trans pulmonary gradient . In the reactive group, there is increase in trans pulmonary gradient (Mean PAP-PCWP) more than 12 mmHg. There have been attempts to use DPG (Diastolic PAP –PCWP) as a better correlate of established pulmonary vascular disease[6]. The progressive vascular precapillary changes lead to an increase in RV afterload, hypertrophy and dilataion, Tricuspid regurgitation and impaired RV function and CHF. While the sequence of events may be the same in both HFrEF and HFpEF, the associated changes and progression of right sided heart failure and systemic derangement, especially renal dysfunction seems more rapid in HFpEF. Numerous studies have examined right ventricular function indices in HFpEF. The parameters studied include TAPSE, right Atrial Volume index, Mean systolic Ejection Rate, RV Global Longitudinal Strain, RV thickness, and RV fractional area. TAPSE/PASP ratio <0.31 was identified as as an ideal value to identify CpcPH-HFpEF[7] (Combined Post and Pre Capillary PH). One study in 548 patients with HFpEF documented a worse prognosis for those with PASP above the median of 47 mmHg and RV dysfunction with an increased risk of 2-3 fold[8]. Development of atrial fibrillation is also associated with a worse prognosis in PH -HFpEF.

The clinical phenotypes in PH-HFpEF can be of 3 types: 1) Type A with diastolic dysfunction and   exercise induced rise in LV filling pressures, 2) Type B with evident signs and symptoms of HF and detection of initial PAH, and 3) Type C with PH and overt right Heart Failure. This recognition may be important in choosing the right therapeutic options. A normal echocardiographic assessment of LV function without exercise may miss many cases of patients belonging to Group A who would be primarily coming with a complaint of dyspnea. Type B and C are more easily identifiable.

THERAPEUTIC OPTIONS

Currently, there are no specific treatment options for improving the mortality in HFpEF, unlike HFrEF. The mainstay of treatment includes optimization of treatment of concomitant comorbidities like hypertension, diabetes, CAD and obesity. Coexisting mitral regurgitation may be another confounding factor and will need careful assessment regarding surgical intervention or newer techniques of non surgical management like the Mitra clip. It is not clear whether targeting the pulmonary

vascular disease (precapillary) due to left ventricular pathology is going to affect the disease progression and prognosis as there are few studies examining this factor unlike patients with IPAH (Group 1). The drugs that have been postulated to be effective in this subset include prostacyclins,Endothelial receptor antagonists, PDE5 inhibitors, Ranolazine, and sGC agonists.

STUDIES WITH ENDOTHELIN RECEPTOR ANTAGONISTS

There are 2 trials with Ambrisentan and Bosentan. The trial with Ambrisentan was terminated due to poor enrolment. The BADDHY trial with Bosentan[9] did not show any benefit and even suggested that there could be some detrimental effect. Trials with Macitentan are ongoing. Current opinion does not favor the use of this group of drugs in PH-HFpEF.

PDE 5 INHIBIITORS

There have been 3 trials with Sildenafil in this group of patients. One trial where sildenafil was given for one year showed favorable hemodynamic response in PASP, mPAP, PVR, PCWP, decreased RAP, RVEDP, increased TAPSE and MRSE (mean rate of systolic ejection)[10]. Two trials where Sildenafil was given for short duration of 24 weeks and 12 weeks did not show any difference in the endpoints. In patients with severe PH with CpcPH (out of proportion PH), Sildenafil may be tried to see clinical response and improvement in quality of life.

SGC AGONISTS

In one trial with Riociguat[11], there was no significant reduction in PCWP or PVR, but the drug was well tolerated with favorable hemodynamic effects necessitating more studies with larger population.

RANOLAZINE

Ranolazine[12] has been evaluated in experimental studies in isolated RV myocardium from patients undergoing cardiac transplantation and it is thought that ranolazine may have a role in improving this subset of patients.

PROGNOSIS

Patients with HFpEF with severe PH have a poor prognosis compared to those without PH. PASP is an independent predictor of cardiovascular and all cause

mortality. Factors which are associated with poor prognosis include DBP <54 mmHg, PA saturation <55%, ILD, hypotension, RVH on echo, and creatinine >1.4 mg%. Identification of CpcPH-HFpEF group of patients and using drugs like Sildenafil may improve quality of life.

FUTURE DIRECTIONS

Currently, the diagnosis of severe CpcPH-HFpEF depends on right heart catheterisation as the gold standard. Newer risk scores and better imaging techniques could be developed to identify people at increased risk for developing CpcPH-HFpEF. Why only some patients develop combined pre and post capillary PAH in the setting of HFpEF remains unclear and enigmatic. As our understanding of the potential mechanisms become better, more useful therapeutic strategies may evolve .

KEY MESSAGES

1) Among patients with HFpEF, PH is common (post capillary)

2) A significant number of patients develop out of proportion PH due to a combination of pre and post capillary hypertension (CpcPH-HFpEF)

3) The prognosis in this group of patients is very poor

4) The response to conventional treatment used in IPAH (PDE5 inhibitors, ERA, sCG agonists) is not found to be effective. Sildenafil appears to be more promising to improve quality of life in this group of patients

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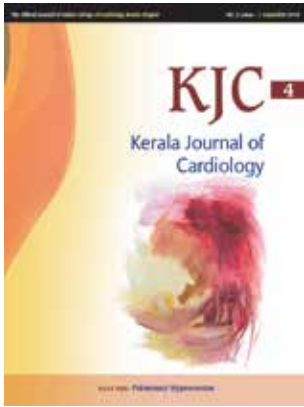
An Intelligent Resident's Guide to Clinical Spectrum of Eisenmenger Syndrome

Zulfikar Ahamed M

Professor of Paediatric Cardiology, Pushpagiri Medical College, Thiruvalla, Kerala
Consultant Paediatric Cardiologist, KIMS, Thiruvananthapuram, Kerala
Former Professor and Head, Department of Pediatric Cardiology, SAT Hospital, Government Medical College, Thiruvananthapuram

"The Horror, the Horror!"

The Heart of Darkness

Eisenmenger syndrome (ES) is a rare but serious condition with definite and inevitable premature morbidity and mortality, even in the current era. This was described in the 19th century, understood in the 20th century and ameliorated to some extent in the 21st century by medication and possibly could be 'eradicated'. However the relative helplessness in encountering and treating ES, which is essentially a preventable malady, generates a sense of guilt, a passive acceptance and to some, horror. Fortunately, over the years, its incidence has come down – In 1950s, 10% VSD developed ES; now only 1% do so.

PREAMBLE

Pulmonary Arterial hypertension refers to a PA mean pressure of more than 25 mm Hg with pulmonary artery wedge pressure of <15 mmHg. **PVR** is measured by the formula:

$$\frac{\text{Mean PA Pressure} - \text{LA Mean pressure}}{\text{QP}}$$

It is expressed in Wood units. Immediately after birth, PVR is more or less equal to SVR. Then PVR falls to near adult values by 7-10 days in a normal new born and reaches adult value by 4-6 weeks.

Operability of a shunt lesion depends on QP/QS, PVR and PVR/SVR ratio. Operability is feasible when:

- QP / QS > 1.5:1
- PVR < 6 wood units
- PVR / SVR ratio < 0.3

Correctability based on PVRI

< 4 Wood	Correctable
> 8 Wood	Not Correctable
4-8 Wood	Individualize

Address for correspondence: Dr. Zulfikar Ahamed, MD, DM, 'Sajan', T.C. 1072/4, Pazhaya Road, Medical College P.O., Thiruvananthapuram - 695011
E-mail: zulfikarahamed@gmail.com

'THE QUARTET'

PAH with Congenital Heart Disease (CHD) has four subsets.

1. Eisenmenger syndrome

2. Left to right shunt with PAH

3. PAH with coincidental CHD

4. Postoperative PAH

'HISTORY IS PROLOGUE'

William Shakespeare

An article titled 'Die angeborenen Defecte der Kammerscheidewand des Herzens' (The congenital ventricular defects of the heart) was published in 1987 by a personal physician to Archduke Ferdinand of Austria, Dr. Victor Eisenmenger. That article described the anatomy, physiology and diagnostic features of an important entity in practice of cardiology. This particular disorder described was later called, quite justifiably Eisenmenger complex and later the term Eisenmenger syndrome became an eponym to this particular physiology.

Eisenmenger was born in Vienna, Austria on 29th January 1864. He published the historical paper when he was 33 years old. He died on 11th December 1932. He had wanted to pursue a career of arts and natural science, but took to study medicine as he felt that 'his talent was not sufficiently pronounced and he had to make a living'!

Paul Wood, recognized as the gale force of British Cardiology was the leader of European cardiology during mid twentieth century. His epoch making article in BMJ, in 1958 titled *The Eisenmenger Syndrome or Pulmonary Hypertension with reversed central shunt* remains the basis of which we study this 'physiology' even after six decades. In 1951 he referred to the term Eisenmenger complex and in 1958, he coined, defined and refined the term of Eisenmenger Syndrome.

WHAT IS EISENMENGER PHYSIOLOGY?

Paul Wood's original definition of Eisenmenger Syndrome (ES) as **'Pulmonary hypertension due to a high pulmonary vascular resistance'** (PVR) with reversal or bidirectional shunt at aorto-pulmonary, ventricular or atrial level' is still the definition of choice.

Hemodynamically ES is defined as an elevation of the PVR to 12 wood units or to a pulmonary to systemic vascular resistance ratio equal to or greater than 1.0. The term was first coined in Wood's Croonian lecture.

The current Nice guidelines have placed ES as one of the four integral types of PAH-CHD, along with PAH with prevalent Left to Right Shunt, PAH with coincidental CHD and PAH after defect closure.

PAH associated with CHD (CHD-APAH) is present is 2/million of the population with Eisenmenger accounting for 5-10% of all CHD-PAH. Eisenmenger syndrome is now becoming rarer in both market economies and economies in transition like India. In the 1950s 8 -10 % of CHD had Eisenmenger but in the current era, it has dropped to < 1% of CHD. Still they do form an important subset of Adult CHD (ACHD).

Currently, ES is a heterogeneous disease with many underlying types of CHD with varying saturations, cyanosis and symptoms and signs. ES can occur in simple lesions like ASD or VSD or could have complex CHD like Truncus and Single Ventricle.

EISENMENGER SYNDROME

Classification

1. **Simple**
   i. Pre tricuspid   ASD
   ii. Post tricuspid   VSD. PDA. AP Window
                             AVSD

2. **Complex**
   i. Ventricular   Single Ventricle
   ii. Great vessel   Truncus Arteriosus
   iii. Others   d-TGA

3. **Surgical Palliation**
   i. Waterston Cooley shunt
   ii. Potts shunt
   iii. Central shunt

According to CONCOR data from Netherlands, of 5970 adult CHDs, 4.2% had PAH and 1% had Eisenmenger syndrome. Among 1824 septal defects, 6% had PAH and 60% of those had ES. Of the previously closed defects, 3% had severe PAH.

ES can establish itself as early as 2 or 3 years of life. It usually presents by the second or third decade of Life. Post tricuspid shunt can develop ES as early as 2 years. Atrio Ventricular Septal Defect (AVSD), Truncus Arteriosus, Single Ventricle, d-TGA. VSD can develop ES much earlier.

In ASD, PVR rises by third or fourth decade and due to Right Ventricle (RV) facing both volume and pressure, can develop right heart failure. Large VSD leads to RV facing volume and then systemic pressure in systole. In PDA and AP Window, PA is continuously subjected to volume and pressure both in systole and diastole. This leads to early PVOD.

Factors Leading to Eisenmenger Syndrome

The propensity of defects to develop ES is dependent on many factors.

1. Size of the defect

Small or moderate VSDs develop ES only in 3%, whereas large VSD and PDA can develop ES in 50-100% if untreated. The ASDs which develop ES are invariably large.

2. Location of the defect

Pre tricuspid shunt is less likely to develop ES and if so, latent period is long. Post tricuspid shunts are more likely to develop ES. They may establish PVOD even as early as two years.

3. Complexity of CHD

Complex lesions such as AVSD, Truncus and d-TGA.VSD are more likely to develop PVOD early.

4. Compliance of RV

In an ASD, RV tolerates volume easily. A non-compliant RV in an ASD can lead to PVOD.

5. Additional Lesions

Additional defects like Coarctation, mitral valve disease and aortic stenosis enhance the development of ES.

6. Genetic Factors

There is a growing belief that some of shunts, especially ASD which develop ES may have a genetic predisposition to lead to PVOD and ES, somewhat similar to IPAH.

Why does ES 'behave' better than IPAH?

1. In ES, the sub pulmonary ventricle has been exposed to high pressures since birth and is better adapted because of long standing volume and pressure overload.

2. Regression of adaptive RVH does not occur.

3. The right to left shunt serves as an excess flow valve

EISENMENGER SYNDROME

Table 1 Various Series of Eisenmenger Syndrome

	Wood: 127	Somerville: 132	Daliento: 188
ASD	19	6	21
VSD	21	45	71
PDA	29	12	36
AVSD	9	16	23
SV	6	13	9
Truncus	4	15	11
d-TGA	7	5	8
Others	32	20	9

EISENMENGER SYNDROME

How do they present?

ES can present usually in young adult after having a history of HF and respiratory problems in infancy. There could be an apparent improvement of symptoms. Later they develop symptoms. Some left to right shunts will continue to have high PVR and directly present in the young as PVOD.

Most of them will be symptomatic. Dyspnea on exertion is the predominant symptom, followed by fatigue, syncope and chest pain. They can present with hemoptysis, stroke and SCD. There will be cyanosis, which is variable and clubbing of varying grades. Pre syncope or syncope suggest serious disease.

Physical examination may reveal cyanosis, which can be variable – subtle to gross. Clubbing can accompany cyanosis. In a stable ES, Blood pressure and pulses are normal. JVP will be prominent with prominent A wave. Presence of significant TR would make one to look for a prominent V wave.

There is minimal or no cardiomegaly. The apex is right ventricular. LPH and palpable P_2 are usual. Thrill is unusual.

S_1 is normal. S_2 may be single / split with a loud P_2. RVS_4 is possible and loud. RVS_4 indicates severe RVH. S_3 is found late in the natural history of ES. An ejection click is found over pulmonary area. Murmurs are not

prominent, especially in early ES. The murmur could be that of Tricuspid Regurgitation (TR) or Pulmonary Regurgitation (PR). An ejection click is heard over pulmonary area accompanied by a mid-systolic murmur.

Table 2 Differing Characteristics of ES and IPAH

		ES	**IPAH**
1	Age of onset	Childhood. Adolescent	Any Age
2	Stimulus	Large defect	None
3	Development of high PVR	Predictable	Not predictable
4	Preventability	Preventable	Not Preventable
5	Progression	Steady	Rapid
6	Gender	Slight Female	Strong Female
7	Resting cyanosis	+	Rare
8	Cardiomegaly	No*	No**
9	S_2	Single/Split	Single usually
10	RVH with strain	Less common	Common
11	qR in VI	Only in ASD	Common
12	SCD	Common	More Common

*   Except in ASD. ES
**   In advanced RV failure

A significant amount of our information regarding the clinical, radiological and electrocardiographic differences in simple ES - ASD, VSD and PDA is derived from Paul Wood's two part treatise in BMJ in 1958. Many of these differences are soft or subtle. In fact when we search other literature, we realize that the specific differences are quite few. The following part of our discussion on the three types of usual ES (simple) is heavily based on Wood's data. He had studied 127 consecutive patients with ES over a period of 11 years. 18 of them died.

COMPARATIVE ANALYSIS OF CLINICAL, ELECTROCARDIOGRAPHIC AND RADIOLOGICAL FINDINGS IN EISENMENGER SYNDROME

1. Transition into PVOD
Around 10% of large ASDs develop ES. At least half of both moderate or large VSD and PDA develop ES.

2. The Numbers
In Wood's series of 127 patients, Eisenmengerisation of ASD, VSD and PDA occurred in 19, 21 and 29 numbers respectively.

3. Age of presentation
PDA presented at the earliest (mean age: 19 years), followed by VSD (22 years) and ASD (35 years).

4. Gender Ratio
A very strong female preponderance was seen in ASD (3:1). PDA had a sex ratio of 2:1. VSD was distributed more or less equally among the sexes.

5. Syndromic patient
As anticipated, AVSD.ES was more in Down syndrome. PDA.ES was seen in Rubella Syndrome.

6. Onset of PVOD
Onset of PVOD by as early as one year was found in 80% in both VSD and PDA. The establishment of PVOD in ASD was only 8%.

7. Dyspnea and functional status
ASD ES and VSD ES were the more symptomatic ones, among three CHDs. PDA ES had a better exercise tolerance.

8. Angina
Angina was more or less equally distributed among the three – 15% each in ASD and VSD and 20% in PDA.

9. Syncope
Syncope is a dangerous symptom in ES. It was present in 19%, 15% and 15 respectively in ASD, VSD and PDA.

10. Hemoptysis
Hemoptysis was more common in VSD.ES (35%). In ASD.ES it was found in 15%.

11. Heart failure
Features of heart failure were distributed equally among all the three lesions (10%).

12. Cyanosis and Clubbing
Differential cyanosis was the hallmark of PDA.ES. The usual values were, upper limb: 90-95% and lower limb: 80-85%. Half of PDA.ES had mild cyanosis of left upper limb.

13. Squatting
Squatting was more common in VSD.ES (15%). Both ASD & PDA had low incidence of squatting (< 5%).

14. Pulse
A low volume pulse was more seen in ASD.ES (80%). Both VSD and PDA had a small pulse in 50%.

15. Blood Pressure
There was no difference between the three in B.P. There was no widening of pulse pressure in PDA. ES.

16. JVP

JVP was variable. It was either normal or elevated with a prominent A wave. Prominent A was more conspicuous in ASD. ES. V wave was prominent in the presence of RHF and also in AVSD – due to left AV valve regurgitation.

17. Cardiac Size

Clinical Cardiomegaly was absent in both VSD and PDA. Majority of ASD.ES had cardiac enlargement,

18. Precordium

Precordium was hyperkinetic in ASD.ES. It was relatively quiet in VSD and PDA.

19. RVS$_4$

RVS$_4$ was more common in ASD.ES.

20. S$_2$

S$_2$ showed characteristic differences. In ASD.ES, 85% had wide split and 15% had close split S2 with a loud P2. None had single S$_2$. Single S$_2$ was heard in 60% in VSD. Half (45-50%) of PDA had close split. 10% had single S$_2$.

21. Mid systolic Murmur (MSM)

A short MSM was present in 80% of all ES.

22. Early Diastolic Murmur (EDM)

EDM over pulmonary area was present in 50% in all ES.

23. Pan Systolic Murmur (PSM)

PSM over Tricuspid area was present more in ASD.ES.

24. Electrocardiography

Right atrial enlargement in ECG was found in half in all ES. In a PDA.ES, Left atrial enlargement was occasionally seen. RVH was universal. qR in V$_1$ or V$_3$ was found in 25% of ASD.ES. qR in V$_5$, V$_6$ was found more in PDA. ES, in spite of RVH (50%). AVSD.ES. Showed LAD. Supraventricular arrhythmias were more common in ASD.ES.

25. X-ray Chest

Cardiac enlargement was characteristically found in ASD.ES. No cardiomegaly was found in 15% of ASD.ES. Nearly 2/3rd of VSD and PDA had no cardiomegaly. MPA, LPA and RDPA were dilated nearly in all (90%). RDPA was more prominent in AS.ES. Calcification of Ductus was found in some PDA. ES. Right arch was found in some VSD (10-15%. Oligemia of peripheral lung fields with rat tailing was common to all ES.

Significant cardiomegaly was found in 50% of ASD. ES, 15% each in VSD and PDA. Aortic Knuckle was prominent in PDA. ES and least prominent in ASD. ES.

A SPECIAL SUBSET OF ES

Four CHDs – VSD, Truncus, Single ventricle and DORV pump to PA at systemic pressure from the beginning. They will have some peculiar behavior in natural history.

Large VSD.ES will have more or less equal gender ratio and mean age of presentation between 2nd and 4th decade. Childhood cyanosis can be noted in 15% and will have saturation of 75-85%. Mean age of death is 45 years.

Truncus Arteriosus.ES can have neonatal cyanosis (35%), will have childhood cyanosis and higher propensity to

Table 3 Comparative Clinical Analysis of Eisenmenger Syndrome

No.		ASD	VSD	PDA
1	Gender ratio	3:1	1:1	2:1
2	Presentation	3rd decade	2nd decade	2nd decade
3	Squatting	Rare	Present	Rare
4	Cyanosis	Uniform	Uniform	Differential
5	JVP	Very prominent	Prominent	Prominent
6	Cardiomegaly	Present	No/Less	No/Less
7	LPH	Prominent	Present	Present
8	S$_2$	Wide; Fixed	Single	Split / Single
9	TR murmur	Prominent	Less	Less
10	qR in V1	Present	Absent	Absent
11	Asc. Aorta	Small	Normal	Large
12	Ductal Calcium	No	No	Present
13	Right Arch	No	Possible	No

arrhythmias. Saturation will be between 75-85%. Mean age of death is 42 years.

Single ventricle will have neonatal cyanosis in 30% and is often blue in childhood. Arrhythmias are common and saturation ranges between 73 and 85%. Mean age of death is 32 years.

SURVIVAL IN EISENMENGER SYNDROME

What Do Studies Say?

i. India

A major retrospective study on prognosis of Eisenmenger syndrome came from SCTIMST, Trivandrum, and Kerala in 1994. 201 patients were studied, from 1976 to 1992. The mean age of presentation was 19 $\pm$ 12 years. Twelve different anatomical lesions contributed to the study population. The three common lesions were VSD (33.3%), ASD (29.8%) and PDA (14.2%). The major causes of death were SCD (30%), Heart Failure (25%) and hemoptysis (15%). Poor prognosis was correlated to syncope, elevated RA mean pressure and arterial saturation below 85% .Survival was 87% at five years, 80% at ten years and 77% at fifteen years.

ii. Japan / Korea

A total of 198 patients with ES were analyzed from 1998 to 2009. The median age was 35 years with a female predominance (64%). The eight year survival was 85%. SCD accounted for 15% of deaths.

iii. Belgium

In the Belgium registry on ACHD, 266 VSDs were studied, out of which, 15 had Eisenmenger syndrome. There was a female predominance (73%) with a mean age of 44$\pm$14 years at latest follow up, Majority were in NYHA II. 3 patients died.

iv. Europe / USA / China

A 13 countries study was published in EHJ 2017. A total of 1564 Eisenmenger syndrome was studied. This was a 38 year cumulative experience. Mean age was 39 $\pm$ 15 years, with 64% females. The median follow up was for 6 years. 558 patients died. The leading causes of death were heart failure (35%), Infection (25%), SCD (10%), Thromboembolism (8%), Hemoptysis (7%) and peri procedural (7%). This recent study stresses on the current causes of death and emphasizes the change in pattern of cause of death. Hemoptysis, bleeding and thromboembolism are coming down. Median survival

improved over the previous era – 52 years as against 35 years.

v. USA

Seventy three patients with Eisenmenger syndrome (VSD, Truncus and Single Ventricle) were studied. Mean age of study population was 35 +/- years. 35% of the ES died and two third of deaths were sudden. Longevity was least in Single ventricle group.

NATURAL HISTORY

ES establishes by early childhood, presents in the second or third decades and die between 30 to 50 years.

Survival of ES

1 Year	-	97%
5 Years	-	87%
10 Years	-	80%
15 Years	-	77%
25 Years	-	42%

Causes of death are heart failure, Hemoptysis, Thromboembolism, Sudden cardiac death, pregnancy and surgery. Currently less death occurs due to hemoptysis, bleed, and thromboembolism.

DISCLAIMER

Even though the clinical, electrocardiographic and radiological distinctions between three common Eisenmenger Syndrome (ASD, VSD, and PDA) have been historically and continuously highlighted, in clinical practice, there are only a few clues that point to a particular lesion responsible for Eisenmenger state, emphasizing the limitations of clinical cardiology.

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Persistent Pulmonary Hypertension of Newborn

Shine Kumar K.H.

Clinical Associate Professor &
In charge, Pulmonary Hypertension Clinic
Amrita Institute of Medical Sciences,
Amrita Vishwa Vidyapeetham, Kochi, Kerala

INTRODUCTION

Persistent pulmonary hypertension of newborn (PPHN) denotes failure of normal resolution of high pulmonary vascular resistance (PVR) in the immediate newborn period resulting in persistently elevated pulmonary artery (PA) pressures. The estimated incidence of PPHN varies between 0.6 to 6.8 per 1000 live births[1,2]. Though typically occurs in near term and term infants, 2% of preterm infants may develop PPHN especially with prolonged rupture of membranes and oligohydramnios[3,4]. The disease still has serious mortality rate in recent era ranging from 7% to 20% inclusive of one year follow up[5,6]. The immediate post discharge morbidity is concerning[7] and has significant neurodevelopmental issues on long term follow up[8,9,10].

PATHOPHYSIOLOGY

In utero, fetal lung is a solid organ with no ventilation and receives only approximately one fifth of combined cardiac output. This peculiar state results in high PVR in unborn fetus. After birth there is precipitous drop in PVR resulting from lung expansion by breathing and increased oxygen tension from multifold increase in pulmonary blood flow[11]. There after, a sustained reduction in PVR from remodelling of thickened pulmonary vasculature[12] results in near normal PVR levels by 4 to 6 months of life. There is complex interplay of vasoactive substances facilitating these changes and involves endothelium derived nitric oxide, arachidonic acids, prostacyclins and various natriuretic peptides[13].

The pathophysiology of PPHN is multifactorial. Neonatal risk factors described are male gender, delivery by caesarean section, delivery before 37 and after 41 weeks of gestation and small or large for gestational age[14]. Idiopathic PPHN results from elevated PVR due to remodelled pulmonary vasculature with normal lung parenchyma where increased vascular smooth muscle proliferation extend into intra acinar arteries. Maladaptation of structurally normal pulmonary vasculature occurs in lung parenchymal disorders like meconium aspiration syndrome, respiratory distress syndrome (RDS) with surfactant deficiency, pneumonia and sepsis.

Congenital diaphragmatic hernia (CDH) results in lung hypoplasia from normal developmental arrest impairing normal alveolarization and pulmonary vascular bed development and is often associated with PPHN. High PVR in CDH is due to vasoconstriction, pulmonary vascular remodelling, reduced vascular density and left ventricular dysfunction[15,16]. CDH associated with PPHN has poor outcome during postoperative period and on long term follow up[15].

Trisomy 21 is prone to PPHN independent of associated congenital heart disease (CHD) from abnormalities of lung vasculature. Surfactant protein B deficiency and mutations in ATP-binding cassette transporter 3 gene are associated with refractory PPHN. Another well described cause of refractory and often fatal PPHN is alveolar capillary dysplasia (ACD). ACD is a rare interstitial lung disease presenting with refractory hypoxemia and familial cases have been linked with deletions in FOXF1 transcription factor gene[17].

Address for correspondence: Dr. Shine Kumar K.H., Clinical Associate Professor & In charge, Pulmonary Hypertension Clinic, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India. E-mail: shinesreehari@gmail.com

Common CHDs mimicking PPHN are obstructed total anomalous pulmonary venous connection (TAPVC) and Vein of Galen malformation. The association between PPHN and antenatal use of non steroidal anti-inflammatory drugs (NSAID) and late trimester use of selective serotonin reuptake inhibitors (SSRI) remains inconclusive.

Single nucleotide polymorphisms (SNP) in the corticotropin-releasing hormone receptor 1 and corticotropin releasing hormone-binding protein genes are significantly associated with PPHN[18]. SNP in Endothelin 1 was found to increase the risk of PPHN in newborns with respiratory distress[19]. Recently SNP in CPS1, NOTCH3 and SMAD9 were identified as risk genes for late preterm and term PPHN in a single center Chinese cohort[20].

Hemodynamically, elevated PA pressures results in right to left shunt across the patent ductus arteriosus (PDA) or patent foramen ovale. The former shunt results in desaturation in lower half of body resulting in differential cyanosis while latter causes systemic desaturation. Right ventricular (RV) dysfunction is well known and recently involvement of left ventricle (LV) is being recognised possibly secondary to complex RV-LV interactions[21].

CLINICAL FEATURES

The hallmark of PPHN is varying degree of hypoxemia with labile hemodynamics requiring mechanical ventilation. Being a nonspecific symptom, it is essential to rule out secondary causes and mimickers before making a diagnosis of PPHN. Differential cyanosis indicate significant right to left shunt across PDA. Grossly shifted apex beat with reduced air entry suggests CDH. Clinically the second heart sound is loud and systolic murmur of tricuspid regurgitation may be present. Poor peripheral perfusion with prolonged capillary refill time and hypotension point towards low cardiac output from myocardial dysfunction. Hepatomegaly occurs with ventricular dysfunction.

MANAGEMENT

Investigations

1. Complete blood count, c reactive protein, blood culture - septicaemia, pneumonia

2. Renal, liver function tests and electrolytes - assessment of end organ damage

3. Chest X ray - lung parenchymal abnormalities, surfactant deficiency, CDH, TAPVC

4. Arterial blood gas - acidosis, pO2, pCO2 and lactates

5. Nterminal pro Brain natriuretic peptide - marker for ventricular strain and dysfunction

6. Echocardiography - ruling out structural heart disease, assessment of pulmonary pressures and ventricular function

General measures

Nursing the baby in a thermoneutral environment with minimal handling is the key. Appropriate sedation, maintaining euglycemia, acid base and electrolyte balance are essential.

Mechanical ventilation

The aim of mechanical ventilation is to achieve normoxemia. A target saturation of >90% (PaO2 between 50-80 mm Hg) is appropriate and hyperoxia should be avoided. The severity of hypoxemia is usually estimated by oxygenation index. Appropriate ventilation strategies including high frequency oscillatory ventilation (HFO) should be considered to improve lung recruitment and maximise oxygenation.

Pulmonary vasodilator therapy

Inhaled nitric oxide (iNO)

iNO is the recommended first line pulmonary vasodilator therapy when available. iNO reduces oxygen requirement and need for extra corporeal membrane oxygenation (ECMO) in late preterm and term infants with PPHN but doesn't reduce mortality or duration of hospitalisation[22-25]. The standard starting dosage is 20 parts per million (ppm), higher dose doesn't have added benefit. iNO is usually initiated when oxygenation index is 25 with evidence of right to left shunting in echocardiography[26]. Clinical response is defined as improvement in PaO2 by at least 20 mmHg and once optimal effect is attained weaning is done in decrements of 5 ppm 4th hourly till 5 ppm and then 1 ppm[27]. Gradual weaning of iNO is recommended to prevent rebound elevation of PA pressures. Monitoring for iNO toxicity is done by measuring serum methaemoglobin levels. LV dysfunction and other causes of pulmonary venous hypertension should be excluded before initiation of iNO since effect could be detrimental. Among the

responders, majority (73%) respond within 30 minutes of initiation of iNO while 6% responded as late as 24 hours and among who finally required ECMO, 83% had initial response[28]. Patients non responsive to iNO may have serious underlying pulmonary vascular pathology like ACD. In subsets with CDH, iNO is indicated when PA pressure is suprasystemic without LV dysfunction and adequate lung recruitment[29].

Sildenafil

Sildenafil, the phospho diesterase 5 inhibitor has potential to reduce mortality and improve oxygenation in newborn with PPHN especially in resource limited setting with non availability of iNO[30]. It is also helpful while weaning off iNO to prevent rebound PAH. Intra venous (iv) dosage is loading dosage of 0.4 mg/kg iv over 3 hours followed by 0.07 mg/kg/hour[31]. The oral dosage ranges from 1 mg/kg/dose to 3 mg/kg/dose 8th to 6th hrly[30]. In patients with CDH sildenafil might be useful when refractory to or while weaning off from iNO[29]. Hypotension from peripheral vasodilatation is a potential complication.

Bosentan

Currently there is insufficient data to recommend routine use of endothelin receptor antagonist bosentan for treatment of PPHN[32], except meriting on an individual case basis.

Prostacyclins

Very limited data exists regarding use of prostacyclins in PPHN. Inhaled epoprostenol and iloprost have shown beneficial effects on selected patients in PPHN refractory to iNO and in comparison to sildenafil respectively.

Inotropes

Inotropes are indicated with echocardiographic evidence of RV or LV dysfunction or with systemic hypotension. Milrinone is the most studied inotropic agent in PPHN. The drug has safe pharmacological characteristics in newborns with PPHN[33]. In addition to inotropic and systemic vasodilatory effects milrinone improves pulmonary vasodilatation and reduces oxygen demand[34,35,36]. The usual dosage is a loading dose of 50 microgram/kg as bolus and 0.3 - 0.7 microgram/kg/minute infusion. With unstable hemodynamics and significant hypotension other pressors like dopamine, adrenaline, vasopressin is required. At times

prostaglandin E1 infusion can be considered to open a constricting PDA to decompress failing RV at the cost of lower body desaturation.

Surfactant therapy

Surfactant therapy helps in improving outcomes in conditions with deficiency or inactivation like RDS, MAS and pneumonia.

Extra Corporeal Membrane Oxygenation

ECMO is indicated when maximal conventional therapy fails to achieve cardiopulmonary stability (oxygenation index ≥ 40). It is known to improve survival in refractory PPHN with acceptable long term disability. The beneficial effects of ECMO in CDH still remains uncertain[37].

CONCLUSION

PPHN remains a serious illness in the newborn. Even with advancement in neonatal care, mortality remains concerning. The morbidity and long term outcomes in survivors are substantial and mandates follow up.

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KJC Pearls

Surgical Management of Pulmonary Hypertension

Julius Punnen
Senior Consultant, Department of Cardiac Surgery, Surgical Lead – Heart and Lung transplant and MCS, Narayana Health, Bangalore.

Deviprasad Shetty
Senior Consultant Cardiac Surgeon, Surgical Lead of CTEPH program and Group Chairman, Narayana Health, Bangalore.

Varun Shetty
Consultant, Department of Cardiac Surgery, Narayana Health, Bangalore.

Abhijit Joshi
Department of Cardiac Surgery, Narayana Health, Bangalore

ABSTRACT

There are only few subgroups of Pulmonary Hypertension (PH) that can be addressed surgically. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is one of them and is completely curable with surgery in experienced centres. CTEPH is included in Group IV Pulmonary hypertension. In the recent World Symposium on Pulmonary Hypertension (WSPH), a few other diseases have been added to the group, like neoplasms and parasitosis which are not commonly seen in clinical practice but surgery may have a role in the treatment of some these as well. The importance of looking for and diagnosing CTEPH correctly in all PH patients lie in the fact that this is probably the only subtype of PH that has a curative treatment option. Unfortunately, the diagnosis is not always made and when made, it is done late. The awareness of the disease and the availability of all treatment modalities in our country have not gained widespread understanding, resulting in late referrals.

Not all patients with CTEPH are operable, because of distal disease or due to comorbidities. Before labelling a CTEPH patient inoperable, it is recommended that they be sent to an expert centre for evaluation for surgery.[3,14] Other options of treatment include balloon pulmonary angioplasty (BPA) and medical treatment with the drugs approved for treatment of this disease. Medical treatment is recommended only for those who cannot be offered surgery and those who have recurrent or persistent PH following surgery after adequate clearance of the fibrotic tissue from pulmonary arteries.

INTRODUCTION

Pulmonary hypertension (PH) is generally not thought of as a surgically treatable disease and therefore has not been of much interest to the surgical community. However, there are surgical options in several forms of pulmonary hypertension, the classical indication would be congenital heart disease with left to right shunt

Address for correspondence: Dr. Julius Punnen, M S, M Ch, F I A C S, Narayana Institute of Cardiac Sciences, 258/A Hosur Road, Bommasandra Industrial Area, Anekal Taluk, Bengaluru 560099, Karnataka, India. Ph: 9980072785, Email: jpunnen@hotmail.com

causing pulmonary hypertension where closure of the shunt is done either surgically or by catheter-based techniques. The other group that lends itself to surgery from time to time is pulmonary hypertension due to left heart disease where the treatment is essentially aimed at correcting the left heart disease, some of which involves surgical correction of valvar heart disease, congenital or acquired forms of post capillary pulmonary hypertension and advanced therapy for heart failure due to reduced or preserved ejection fraction including heart transplantation and left ventricular assist device implantation. Apart from these, there are other conditions where surgery is aimed for cure of the pulmonary hypertension and is the primary form of treatment, like Pulmonary thrombo endarterectomy (PTE) in Chronic thromboembolic pulmonary hypertension (CTEPH). Palliative surgery in the form of Potts shunt is performed in few centres to prevent sudden death from right ventricular failure when transplant cannot be offered. Bilateral sequential single lung transplantation or heart lung transplantation are other forms of surgical treatment that may benefit a selected group of patients with pulmonary hypertension including those with Eisenmenger physiology.

Since the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, PH has been arbitrarily defined as mean pulmonary arterial pressure (mPAP) $\geqslant 25$ mmHg at rest, measured by right heart catheterisation. Recent data from normal subjects has shown that normal mPAP was 14.0 ± 3.3 mmHg. Two standard deviations above this mean value would suggest mPAP >20 mmHg as above the upper limit of normal (above the 97.5thpercentile). This definition is no longer arbitrary, but based on a scientific approach. However, this abnormal elevation of mPAP is not sufficient to define pulmonary vascular disease as it can be due to an increase in cardiac output or elevated Pulmonary Arterial Wedge Pressure (PAWP). The 6th WSPH Task Force proposed to include pulmonary vascular resistance $\geqslant 3$Wood Units in the definition of all forms of pre-capillary PH associated with mPAP >20 mmHg. Prospective trials are required to determine whether this PH population might benefit from specific management.[1]

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

CTEPH is a form of pre-capillary pulmonary hypertension, resulting from incomplete resolution of pulmonary emboli, progressively organized into fibrotic material obstructing large pulmonary arteries. CTEPH is classified under group 4 Pulmonary hypertension along with other pulmonary artery obstructions which include benign and malignant tumours and other conditions listed in table 1. The accepted diagnostic criteria for CTEPH are

the following: Mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, Pulmonary artery wedge pressure (PAWP) $\leq$ 15 mm Hg, Abnormal Ventilation-Perfusion scintigraphy (V/Q scan) showing at least one mismatched segmental perfusion defect and abnormal computed tomography (CT) scan and / or pulmonary angiography showing typical findings of CTEPH after at least 3 months of anticoagulation[2]. Currently, a new threshold for PH (mean PAP (mPAP) >20 mmHg) and pre-capillary PH (combination of mPAP >20 mmHg, pulmonary arterial wedge pressure $\leqslant 15$ mmHg and pulmonary vascular resistance (PVR) $\geqslant 3$Wood Units) has been proposed by the 6th WSPH Task Force on PH diagnosis and classification.[1] While there is good evidence to suggest these new thresholds, the consequences for CTEPH and Chronic thromboembolic disease (CTED), respectively, are not yet established. In the future, however, these new thresholds might also be applied to group 4 PH[3].

Table 1[1]

4.1	Chronic thromboembolic PH
4.2	Other pulmonary artery obstructions
4.2.1	Sarcoma (high or intermediate grade) or angiosarcoma
4.2.2	Other malignant tumours
	Renal carcinoma
	Uterine carcinoma
	Germ cell tumours of the testis
	Other tumours
4.2.3	Non-malignant tumours
	Uterine leiomyoma
4.2.4	Arteritis without connective tissue disease
4.2.5	Congenital pulmonary artery stenoses
4.2.6	Parasites
	Hydatidosis

CHRONIC THROMBOEMBOLIC DISEASE (CTED)

Chronic thromboembolic disease (CTED) is characterised by similar symptoms and perfusion defects, but without PH at rest. Exercise limitation in CTED has been attributed either to exercise-induced PH, with an increased slope of the pulmonary arterial pressure–flow relationship, or to dead-space ventilation, with increased ventilatory equivalents for carbon dioxide[4,5] CTEPH treatment recommendations should not yet be applied to CTED, since additional prospective studies are needed.[13] There is insufficient data to show that CTED progresses to CTEPH. Though there are groups who offer surgery to select patients with CTED, the indications for this is not clearly established. For implementation of the European Guidelines on Diagnosis and Treatment of Pulmonary Hypertension in Germany, the Cologne Consensus Conference 2016 was held and last updated

in spring of 2018. One of the working groups was dedicated to CTEPH, practical and controversial issues were commented and updated.[14] This consensus group recommended that, with similar symptoms and reduction in quality of life, CTED patients are offered the same surgical or interventional treatment as patients with CTEPH.[15]

PATHOGENESIS

The precise pathogenesis of CTEPH remains unclear, but appears to be incited by acute pulmonary embolism[6] An international CTEPH registry (Europe and Canada) indicated that 75% of patients with CTEPH had a documented antecedent history of acute pulmonary embolism[7], while in Japan, the rates of acute pulmonary embolism preceding CTEPH range from only 15% to 33%[8,9] The incidence of acute pulmonary embolism that led to CTEPH has also varied widely in literature. In a study conducted in Narayana Hrudayalaya, Bangalore, India, 20% of patients with acute pulmonary embolism progressed to CTEPH[10]. In published prospective studies with the diagnosis confirmed by right heart catheterisation, the incidence of CTEPH after symptomatic acute pulmonary, embolism is reported to range from 0.4% to 6.2%, giving a pooled incidence of 3.4%.[7] The proportion of patients who develop CTEPH after acute PE still remains controversial and may vary between 0.1% to 9.1%[11] Studies that used echo for diagnosis of pulmonary hypertension may report a higher incidence than those that have used right heart catheterisation for diagnosis. Determining the precise CTEPH incidence is complex. CTEPH is likely both underdiagnosed and the incidence of CTEPH after acute pulmonary embolism prone to overestimation, making the actual incidence difficult to quantify. To date, there is no proof that aggressive treatment of acute pulmonary embolism can prevent CTEPH. Complete resolution of thrombi is usually not achieved after acute PE, as 30–50% of patients still have persistent defects 1 year after diagnosis.[20]

Sometimes the first presentation of CTEPH is as acute pulmonary embolism. In a study on the prevalence of CTEPH after acute pulmonary embolism, the authors observed that at the time of pulmonary embolism diagnosis, patients later diagnosed with CTEPH (4.8%) had a higher systolic PAP (43–102 mm Hg) and at least two signs of CTEPH on the initial computed tomographic scan.[21] They suggested that a majority of patients with CTEPH had previously unknown pulmonary hypertension and that the first clinical presentation of CTEPH may mimic acute PE. Other studies had previously shown that high PAP at pulmonary embolism diagnosis was predictive for the development of CTEPH (22) or for further increases in PAP during long-term follow up.[23]

Although CTEPH is a thrombo embolic disease, patients generally do not have a defined disturbance in coagulation and/or fibrinolysis. However, elevated levels of Factor VIII[16] and phospholipid antibodies/lupus anticoagulant are significantly more common in CTEPH than in PAH.[16,17] CTEPH patients have higher percentages of blood types A, B and AB compared with the general population, which is linked to elevated plasma Factor VIII levels.[17]

DIAGNOSIS

All patients who are diagnosed to have PH should be evaluated for CTEPH since this is a subgroup that can potentially be cured with appropriate surgical treatment. A normal V/Q scan effectively excludes CTEPH with a sensitivity of 90 – 100 percent and specificity of 94 – 100%. A more recent study has shown that both V/Q scan and Computerised Tomographic Pulmonary Angiogram (CTPA) are accurate methods for the detection of CTEPH with excellent diagnostic efficacy (100% sensitivity, 93.7% specificity and 96.5% accuracy for V/Q scan; 96.1% sensitivity, 95.2% specificity and 95.6% accuracy for CTPA). However encouraging, V/Q scan remains the preferred initial imaging test for CTEPH screening.

The median age of patients at diagnosis is 63 years with both sexes being affected equally.[18] Data from Narayana Health in India however shows that the disease affects a much younger population in India with mean age 39.48 ± 11.68 and there is a predominance of males over females 2.5:1. The predominant symptom of CTEPH is exercise-induced dyspnoea; other symptoms are non-specific or absent in early CTEPH. Signs of chronic right-sided heart failure only become evident in advanced disease. Early diagnosis remains a challenge and should be pursued for reasons of prognosis.[19] There is a median latency period of 14 months between the onset of symptoms and diagnosis at expert centres in the west and it is likely to be longer in India and presentation with advanced right heart dysfunction or massive haemoptysis is not uncommon. Though screening of asymptomatic survivors of acute pulmonary embolism was not recommended by the consensus conference in Cologne,[14] the European guidelines on pulmonary embolism,[24] or on pulmonary hypertension[25] it may be prudent to do so in the Indian population considering the higher incidence of acute pulmonary embolism survivors developing CTEPH. Other authors also recommend close follow up of patients having persisting signs, symptoms or risk factors.[26] Most CTEPH will be identified within 2 years of the diagnosis of acute pulmonary embolism.[27]

IMAGING

In the assessment of patients presenting with breathlessness echocardiography is usually the first

investigation to show PH. For further investigation to determine the cause of PH, all patients should undergo a V/Q scan and if the V/Q scan shows perfusion defects, a CTPA is performed as the next step. Cardiac catheterisation and pulmonary angiography, coronary angiography and angiographic evaluation for aorto pulmonary collaterals by additional injection to the internal mammary arteries and bronchial arteries when possible or aortogram to demonstrate collaterals is performed. CTPA may also demonstrate presence of aorto pulmonary collaterals. Presence of large quantity of aortopulmonary collaterals indicate that there is a low-pressure area beyond the obstruction and may indicate a more favourable outcome. It may also indicate that there is a higher possibility of reperfusion edema and airway bleeding. It may be useful to do more than one mode of imaging and establish concordance between imaging modalities. When concordant across all imaging modalities, factors that would indicate lower risk are having a clear history of deep vein thrombosis (DVT) or Pulmonary Embolism (PE), absence of right heart failure or comorbidities, lower (I and II) functional class, disease limited to bilateral lower lobes and Pulmonary Vascular Resistance (PVR) <1000 dyn.sec.cm-5.[3]

CASE SELECTION

Case selection is done in most established PTE centres by an interdisciplinary team meeting which includes experts in PH and CTEPH from Cardiology, Pulmonology, Cardiac Surgery and Radiology and others as needed. Given the fact that the learning curve for diagnosis and management of CTEPH is quite steep, the experience of the surgeon and of the managing team appears to be the most important predictor of outcome for the individual patient with CTEPH.[28] The important questions to be answered at the multi-disciplinary team meetings for case selection would be: Is there pulmonary hypertension and is CTEPH the cause for pulmonary hypertension? At our institution, we do not see many CTED patients and as of now we do not have a uniform policy of offering them surgical treatment or not and each patient is considered individually. It can be quite difficult to exclude small vessel disease and in-situ thrombosis with certainty in some cases where the pulmonary hypertension is not caused by CTEPH. Next would be to assess the potential benefit from the operation. For this, the important question to answer would be whether there is significant lung disease which would affect ventilation of the affected area, and which will not improve even after normalising perfusion. This would be followed by assessing the risk of the operation itself in terms of co morbidities and considering alternate therapies like Balloon Pulmonary Angioplasty (BPA) and medical treatment if risk of operation is deemed to be formidable. Severe RV dysfunction should not

be considered a contraindication to surgery since the RV tends to recover once the afterload is normalised. However, some time is spent on preparing patients with severe RV dysfunction preoperatively with diuretics or hemofiltration which will help in better post-operative recovery. In patients with active haemoptysis, catheter embolization a day or two prior to surgery may help in preparing for surgery. Carefully analysing the data from cardiac catheterization and various imaging modalities form the key to the initial evaluation in order to answer the first two important questions

SURGICAL CLASSIFICATION

According to a new surgical classification proposed by the group at the University of California, San Diego (UCSD), there are different levels of pulmonary occlusive disease related to organized thrombus. *Level 0* denotes no surgical evidence for chronic thromboembolic disease. *Level I* disease indicates the obstructive material and the plane of dissection involve one of the main pulmonary arteries (figure 1). In case of complete obstruction of one of the major arteries, and complete nonperfusion of the entire lung, the letter "C" (i.e., Level IC) (figure 1) is

Figure 1: UCSD Level I disease

Figure 2: UCSD Level III disease

added; this distinction is important, given the technical differences in endarterectomy required in this setting. In *Level II* disease, the fibrous tissue starts at the level of lobar branches or past the take-off of the upper lobe artery. *Level III* disease presents a more challenging surgical situation, where the disease is distal and starts at the segmental branches where occlusive disease may not be evident initially. The endarterectomy plane must be carefully and painstakingly raised in each segmental branch (Figure 2). *Level IV* disease symbolizes chronic thromboembolic disease starting at the sub segmental level only. This represents the most challenging of patients, in whom endarterectomy can be quite difficult, and extensive surgical experience is required to achieve optimal results.[28]

SURGICAL TREATMENT

Pulmonary endarterectomy (PEA), also referred to as pulmonary thrombo endarterectomy (PTE), remains the preferred and potentially curative option for patients with CTEPH. The advancements in the surgical techniques of this operation are built on the fundamental principles of the procedure. The procedure follows four basic principles: (1) the endarterectomy must be bilateral, therefore the approach through a median sternotomy; (2) perfect visualization is essential by use of cardiopulmonary bypass and use of periods of circulatory arrest that are usually limited to 20 minutes

at a time and supported by cooling to about 20^0C;(3) identification of the correct dissection plane is crucial; and (4) a complete endarterectomy is essential. Once the endarterectomy is completed on both sides, circulation is restarted, and the patient is rewarmed. Although tricuspid valve regurgitation is variable in these patients and is often moderate to severe, tricuspid valve repair is not necessary unless there is an anatomic abnormality with the valve leaflets, chords, or overall structure. Tricuspid regurgitation secondary to annular dilation is left alone, as right ventricular remodelling occurs within a few days, with the return of tricuspid competence.[28]

There are some groups in Europe who do this operation without Deep Hypothermic Circulatory Arrest (DHCA). However, at Narayana Health, we have followed the practice of using intermittent DHCA in all cases. The Pulmonary EndArtercetomy COGnitive (PEACOG) trial demonstrated that the established technique of cooling to 20^0C with periods of complete circulatory arrest for 20 minutes at a time was both necessary for complete clearance and well tolerated, without cognitive deficit.[29] The Updated Recommendations from the Cologne Consensus Conference 2018 has recommended Surgical PEA in deep hypothermia and circulatory arrest for CTEPH patients at an experienced PEA centre (30–50 operations per year), giving the level of recommendation as 1 and level of evidence as C.[14]
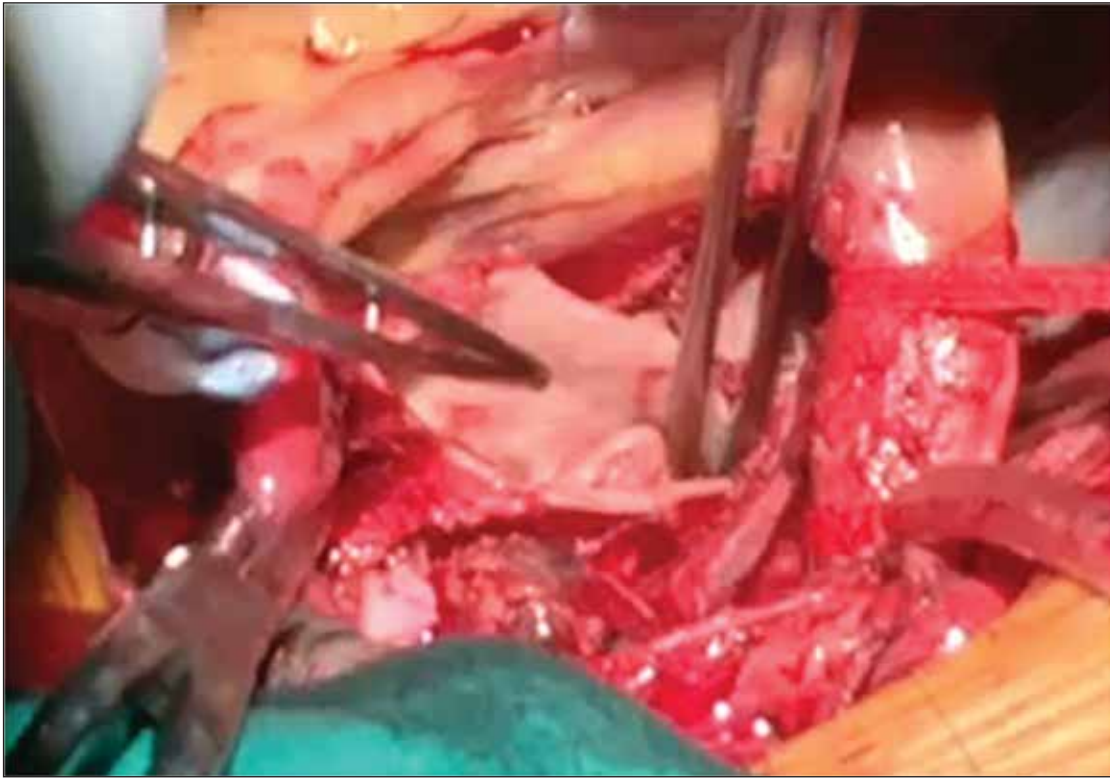
Figure 3. Showing open Right Pulmonary artery and dissection of the fibrotic material from with the artery on DHCA

COMPLICATIONS

Intraoperative airway bleeding can be the result of rupture of a pulmonary artery branch from injury, with bleeding into the parenchyma/airway or from aorto – pulmonary collaterals. A technique described at Narayana Health by Shetty et al has resulted in effective control of this potentially fatal complication by identifying and packing the bleeding subsegmental vessel intraoperatively.[30] Reperfusion injury leading to pulmonary edema intra or post operatively, can occur up to 72 hours or occasionally later than that. This is prevented by severe fluid restriction and fluid removal during and after the operation with ultrafiltration and diuresis. Depending on the severity, if oxygenation is affected, early use of veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is considered. Right ventricular failure following surgery can be recognised haemodynamically by a high central venous pressure (CVP) with low pulmonary artery pressure (PAP). This
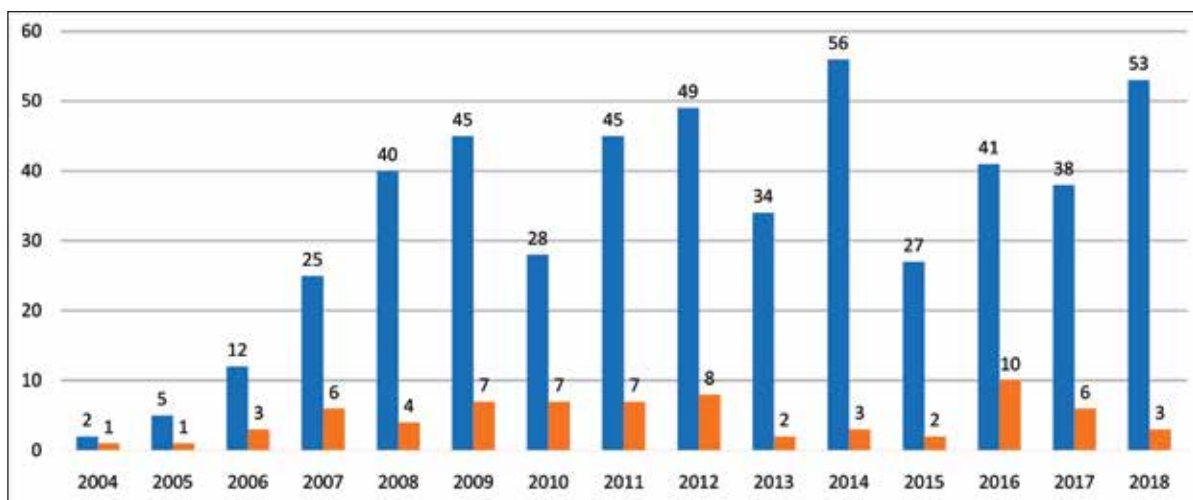

Figure 4 Narayana Hrudayalaya Experience: Annual numbers in blue and hospital mortality in orange.

is treated with inotropes or with veno arterial (VA) ECMO when severe. The 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension states that postoperative ECMO is recommended as a standard of care in PEA centres for severe cases. Early postoperative reperfusion oedema may require veno-arterial ECMO, and severe persistent PH may be bridged to emergency lung transplantation with veno-venous ECMO.[31] However most practising ECMO specialists and CTEPH specialists including our centre would use VA ECMO in severe persistent PH and VV ECMO to treat reperfusion edema. Persistent PH is not clearly defined haemodynamically. PVR>500 dynes.sec. cm-5 immediately after CPB or mPAP >25 mmHg and PVR>300 dynes.sec.cm-5 six months after PEA can be considered as persistent PH. They may need to be managed medically with one of the medications approved for use in this situation or with lung transplantation.

CONCLUSION

In conclusion, CTEPH is the only subset of PH where a definite surgical cure is possible. For CTEPH patients deemed operable, quality of life and life expectancy following PTE is better when compared to medical therapy. Patients with CTEPH labelled inoperable should be referred to "expert" centres for a second opinion. A three-step stratified definition of expert surgical centre has been proposed at the 6th WSPH which factors the following important goals: surgical mortality (<5%), surgical volume (more than 50 PEAs per year) and ability to perform segmental endarterectomy.[32] In our experience , CTEPAH is often seen in young patients, and correct diagnosis and prompt surgery can provide symptomatic benefits, improve quality of life and prevent mortality in many cases.

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Pulmonary Vascular Abnormalities in Chronic Liver Disease - A Primer

Rizwan Ahamed Z

Consultant Gastroenterologist, Ernakulam Medical Centre, Kochi, Kerala.

ABSTRACT

Pulmonary involvement is common in patients with chronic liver disease. This is usually attributable to four different complications: hepatic hydrothorax, pneumonia, hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). While the former two are commonly encountered in clinical evaluation, HPS and POPH as distinct entities are notoriously under recognized and contribute to considerable morbidity and mortality in patients with chronic liver disease. Even though both these disorders originate from aberrant pulmonary microvascular remodeling, they have distinct pathophysiological mechanisms leading to either intrapulmonary vascular dilatations and shunting in the case of HPS leading to gas exchange disturbances and increased pulmonary vascularity in POPH resulting in hemodynamic failure. Their clinical presentations are markedly varied and as most of the patients are asymptomatic it is important to identify and distinguish these syndromes adequately. HPS is diagnosed by arterial blood gas analysis and contrast echocardiography while POPH requires transthoracic echocardiography and additional right heart catheterization for confirmation. At present, no medical management is recommended for either syndromes even though HPS is an indication for Liver transplantation (LT).

INTRODUCTION

The liver is uniquely situated in series between the portal system and the lung. The pulmonary vascular endothelium is exposed to the venous blood constituents arising from the liver and portal circulation and may undergo microvascular changes leading to respiratory complications. These complications include the hepatopulmonary syndrome and portopulmonary hypertension. Though they co-exist infrequently, these are usually distinct clinicopathological entities with different manifestations. HPS arises as a result of intrapulmonary vascular dilatation and right to left shunting leading to an increased alveolar arterial oxygen gradient resulting ultimately in deoxygenation of blood. POPH results from increased pulmonary artery pressure in the setting of high pulmonary vascular resistance due to an altered pulmonary microvascular response. Even though these entities result from mutually exclusive pathophysiological phenomena, they are both driven by an abnormal response of pulmonary vasculature to the *porto-hepato-pulmonary* axis. During the last two decades sufficient interest has been generated by these syndromes owing to its clinical implications especially in the background of increasing rates of liver transplantation. They are both associated with increased morbidity and mortality in the cirrhotic patient.

Address for correspondence: Dr. Rizwan Ahamed Z, MD, DM, Consultant Gastroenterologist, Ernakulam Medical Centre, Kochi, Kerala.
Email: rizwiz87@gmail.com

Therefore, it is absolutely vital to detect these disorders at an early stage for the purposes of prognostication and therapy. This review will try to shed light on the recent advances in our understanding of the pathophysiology of HPS and POPH and also discuss the epidemiology, screening modalities and therapeutic options for these not infrequently common complications of liver disease

HEPATOPULMONARY SYNDROME

HPS is defined by the European Respiratory (ERS) Task Force as "*an arterial oxygen defect induced by intrapulmonary vascular dilatations associated with hepatic disease*".[1] It is essentially a gas exchange abnormality leading to arterial deoxygenation occurring in patients with various forms of chronic liver disease.

DIAGNOSTIC TRIAD OF HPS

1. Liver disease (chronic liver disease and/or portal hypertension);
2. Intrapulmonary vascular dilatation and/or shunting and
3. Increase alveolar arterial oxygen gradient (PA-aO2)>15 mm Hg or > 20 mm Hg in patients >65 years of age.

The prevalence of HPS is known to range from 4-47% in patients of chronic liver diseaseand is the most common cause of respiratory insufficiency in cirrhotic patients.[2] The wide range is explained by the heterogeneity of diagnostic criteria employed by different researchers. It is seen in the same frequency in males and females and is most commonly diagnosed in the sixth decade of life. It has no specific relation to the etiology of liver disease, neither have studies discovered any overwhelming evidence of association between HPS and severity of liver disease vis-à-vis Child Pugh or MELD scores.[3] Although commonly seen in the setting of cirrhosis with portal hypertension it has been well documented even in situations of acute/chronic hepatitis without portal hypertension as well as in the presence of portosystemic shunts in the absence of cirrhosis.

SEVERITY CLASSIFICATION OF HPS

The *ERS Task Force* has proposed the following severity staging based on PaO2 determination:

- Mild: PaO2 >80 mm Hg
- Moderate: PaO2 <80 to >60 mm Hg
- Severe: PaO2 <60 to >50 mm Hg
- Very severe: PaO2 <50 mm Hg

However, *a mere fall in PaO2 in a patient of cirrhosis is not sufficient grounds for diagnosis even in the setting of an increased PA-aO2 unless there is evidence of intrapulmonary vascular dilatation* as will be discussed further.

PATHOGENESIS

The central abnormality in the pathophysiology of HPS is intrapulmonary arteriovenous shunting and capillary dilatation.[4] The diameter of pulmonary capillaries in normal individuals is approximately 8-15 μm. In affected patients the average diameter increases to approximately 65 μm and sometimes even up to 500μm. More significant dilatation is usually noted in the lung bases probably due to increased blood flow as a result of gravity. This brings about a ventilation perfusion defect leading ultimately to arterial deoxygenation. This simply means that for the same amount of alveolar ventilation there is an overperfusion of the capillary bed leading to incomplete oxygenation of the incoming blood column. There are three main mechanisms by which oxygenation is impaired

1. Ventilation perfusion mismatch due to increased blood supply for the same amount of ventilation per alveolar unit as explained above

2. Intrapulmonary shunting leading to right to left shunting at the pre capillary and capillary level

3. Limitation to oxygen diffusion or "perfusion diffusion mismatch" refers to the increased alveolar capillary diameter as a result of vasodilation. This means that oxygen has to travel a longer distance to interact with the stream of RBCs which usually move through the center of the vascular column. Also, the shorter transit time of blood column due to increased cardiac output normally seen in cirrhotic patients worsens gas equilibration.

Recent research has shown that the abnormal vasodilatation and shunting is due to release of various vasoactive mediators like nitric oxide(NO) and carbon monoxide(CO).[5] NO is released through inducible (iNOS) and endothelial (eNOS) Nitric Oxide Synthase enzymes. In the setting of portal hypertension, there is disproportionate intrahepatic secretion of Endothelin-1(ET-1) which leads to a preferential induction of Endothelin-B receptors in the pulmonary vasculature. Activation of ET-B receptors leads to activation of iNOS resulting in synthesis of NO. There is also renewed interest in the role of systemic endotoxemia resulting from bacterial translocation of the gut which may lead to aggregation of pulmonary macrophages. These macrophage/monocyte complexes release NO through activation of eNOS. The other culprit mediator CO
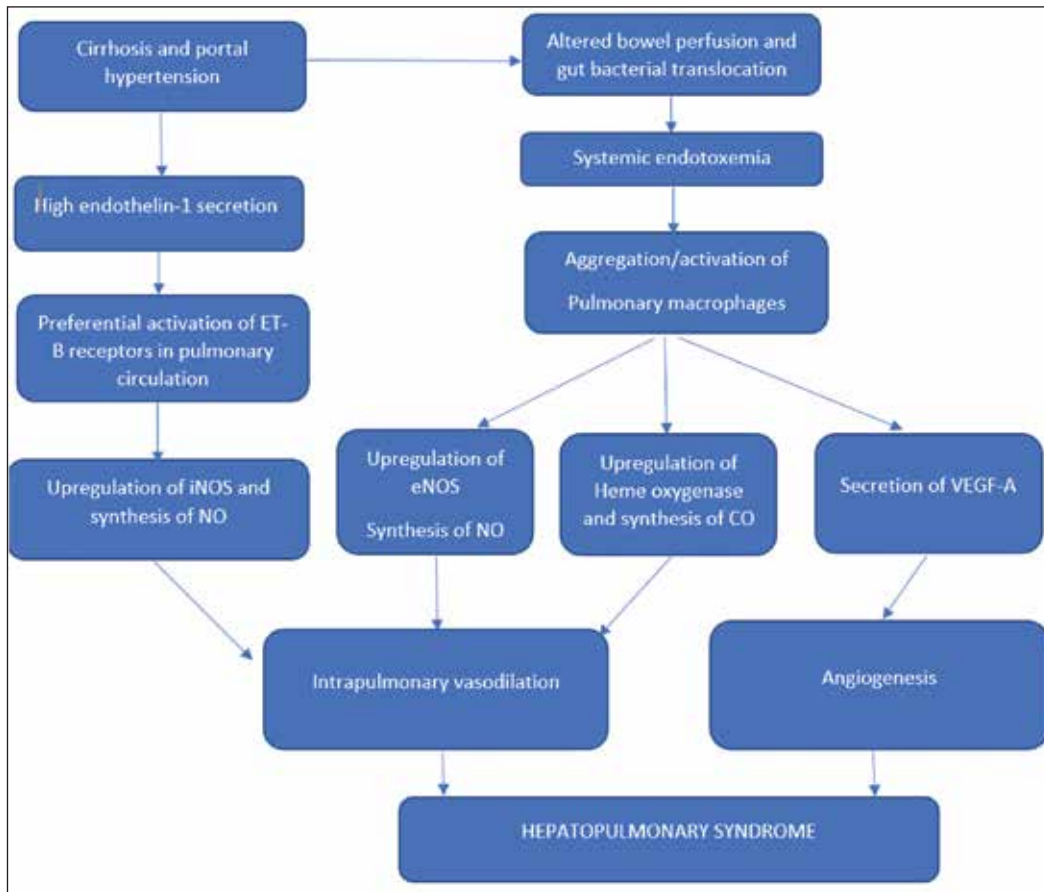
Fig 1: Flowchart explaining the role of different mediators in the pathogenesis of HPS.

is released in a similar fashion by the activation of intravascular macrophages and stimulation of Heme Oxygenase-1.[6]

Apart from vasoactive mediator induced relaxation of pulmonary vascular tone, permanent anatomic shunting at the capillary level has also been noted though not universally (the so-called Type 2 HPS pattern on pulmonary angiography). This could also explain why some patients of HPS take up to more than a year after liver transplantation for complete symptomatic relief. These changes are brought about by extensive angiogenesis in response to vascular growth factor stimulation. Experimental HPS studies in mice (bile duct ligation) have revealed the role of Vascular endothelial growth factor A(VEGFA) released by resident monocytes in the vasculature behind this phenomenon.[7]

PRESENTATION AND NATURAL HISTORY

The most common symptom in patients with HPS is exertional dyspnea even though majority are asymptomatic prompting an active case seeking approach in all cirrhotic patients listed for LT. The classical features of platypnea and orthodeoxia

(worsening oxygen saturation in the upright position) is seen in around 25% of these patients.[8] This probably arises from gravitational pooling of blood in the lung bases which has the highest concentration of IPVD (Intra Pulmonary Vascular Dilatation) and shunts as discussed earlier leading to improper gas exchange. The cut off value for orthodeoxia is a decrease in PaO2 of 5% or 4mm from supine position. HPS patients are also more likely to be cyanotic in late stages or present with clubbing and extensive spider naevi or skin telangiectasias. Indeed, the latter may be an external clue for underlying pulmonary vascular abnormalities as both these manifestations result from the same mechanism of aberrant angiogenetic signaling.

Though its natural history is not characterized completely, patients with HPS have a two-fold higher risk of mortality than patients of cirrhosis without it. Most patients progressively develop worsening IPVD and shunting leading to further gas exchange abnormalities. Patients who were on a transplant waiting list showed a decrease in Pa02 of 5.2 mm per year. A recent prospective study has shown a median survival duration of 10.6 months for HPS patients as compared to 40.8 months for cirrhotics without HPS.

DIAGNOSIS AND SCREENING

Diagnosis of HPS requires the following in a patient with portal hypertension/cirrhosis:
1. Arterial blood gas analysis showing a PaO2 < 80 mm Hg or PA-aO2 (pul alveolar arterial gradient) > 15 mm Hg and
2. Demonstration of intrapulmonary vascular dilatation (IPVD) and shunting through contrast echocardiography (CE)

All cirrhotic patients waitlisted for LT or any cirrhotic patient with unexplained dyspnea should be screened for HPS. Though an ABG is ideal for diagnosis, pulse oximetry is a good screening method as an SpO2<96% has been found to be highly sensitive in detecting HPS in patients with PaO2 < 70mmHg. ABG analysis may therefore be reserved for the above group.

CONTRAST ECHOCARDIOGRAPHY (CE)

This is the standard investigation for the diagnosis of HPS. CE employs the method of generating microbubbles >15 μm by agitating normal saline and injecting it into a peripheral vein. As mentioned above the normal diameter of pulmonary capillaries is less than 15 μm and these microbubbles will not be visualized in the left atrium on echocardiography as they will be absorbed in the vascular bed. However, in patients of HPS, due to the abnormally dilated capillaries these microbubbles escape the pulmonary circulation and enter the left atrium after three to six cardiac cycles. The timing of visualization is important as in intracardiac shunts the microbubbles make an appearance within three cardiac cycles. It has also been shown that due to the maximum concentration of IPVD in the lung bases, CE should preferably be performed in a sitting/standing position rather than supine position to increase sensitivity.[9]

However, CE suffers from a disadvantage that it cannot adequately quantify the severity of HPS. Technetium labelled Macroaggregated Albumin perfusion scintigraphy scan (MAA scan) overcomes this pitfall. The basic principle of this test is similar to CE. Radiolabelled albumin molecules of approximately 20 μm in diameter are injected into the venous system and further observed on perfusion scan. In normal individuals, as these aggregates are trapped in the pulmonary vascular bed, scintigraphy shows almost all the uptake in the lungs. However, in the setting of HPS or intracardiac shunting significant uptake is noted in systemic circulation which can be quantified. *By convention, a shunting fraction of >6% noted in the brain denotes a diagnosis of HPS.* However, MAA scan is a poor modality for screening as it is unable to differentiate HPS from intracardiac

shunting and neither can it rule out other associated cardiopulmonary pathologies like portopulmonary hypertension or cirrhotic cardiomyopathy.[10] Its main use comes in clinical settings where the patient has concomitant chronic respiratory disorders and it is unclear how much the contribution to hypoxemia is by pulmonary shunting. In such cases, a MAA fraction more than 6% noted in the brain proves that arterial deoxygenation is due to HPS and not the intrinsic lung disease.

Pulmonary angiography is not routinely performed unless there is a strong suspicion of an underlying major pulmonary arteriovenous shunt which may be amenable to embolization or coiling. On angiography, Type 1 HPS refers to a spidery capillary appearance denoting only dilatation as compared to Type 2 with definite anatomical arteriovenous shunting. The Type 2 HPS has clinical implications in therapy (embolization) and prognosis (persistent hypoxemia even after LT).[11]

MANAGEMENT

There is presently no specific medical therapy prescribed for HPS. Liver transplantation seems to be the only effective management strategy in these patients and most recipients show good response post LT. For patients who are hypoxic (PaO2 <60 mm Hg) continuous oxygen supplementation is recommended.

Based on its pathophysiological mechanisms, many drugs have been tried for its management but to no significant success. Pentoxyphylline with its antagonism against TNF and NO has shown conflicting response in limited studies. Interestingly, garlic capsules showed some improvement in hypoxemia in a small randomized study, even though the mechanism by which it works is unclear.[12] Injection methylene blue by its action against NO has been shown to reduce hypoxemia in critically ill pre-LT patients and has been used as a bridge to LT.[13]

The standard of care for HPS with severe hypoxemia remains Liver transplantation. LT results in significant or complete improvement in gas exchange in 85% of patients within 6 months to one year.[14] However not all patients of HPS are ideal candidates for LT as shown by many prospective studies. A PaO2 < 60 mmHg or severe HPS and a MAA fraction >20% has been known to be indicators of poor response to LT or indeed worsening in some cases.[15] This has prompted the trend of providing MELD exception points of 22 to patients of cirrhosis with HPS and a PaO2 <60 mmHg (severe HPS) to avoid unnecessary delay towards Liver transplantation. Transjugular intrahepatic portosystemic shunts in the management of HPS has shown conflicting results and is not a therapeutic option currently. Supplemental
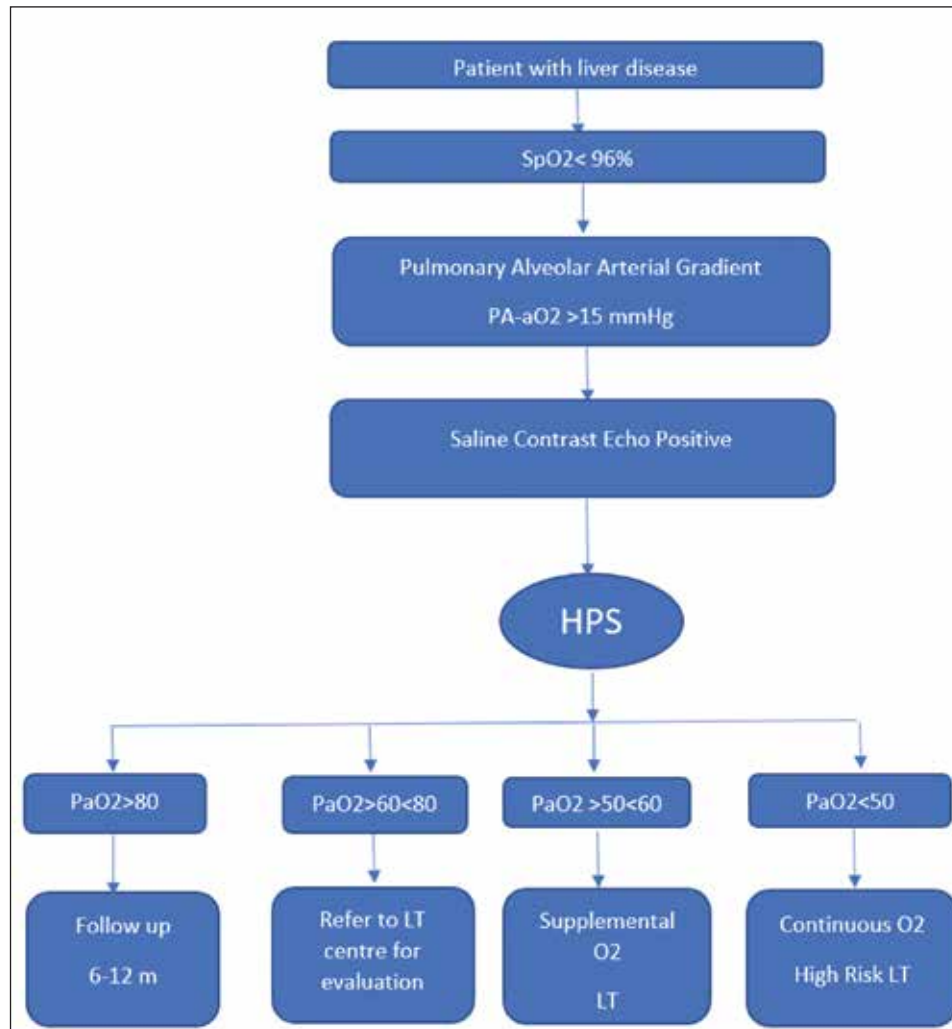
Fig 2: Flowchart showing approach to diagnosis and management of HPS
HPS-hepatopulmonary syndrome; PaO2- partial pressure of oxygen in mm of Hg; LT- liver transplantation

oxygen remains the only effective management at present for patients of HPS till they are considered for liver transplantation. Cirrhotic patients without HPS on transplant waiting lists should be actively screened (CE) on a yearly basis and if detected positive, should undergo three monthly testing to monitor for worsening of hypoxemia.

PORTOPULMONARY HYPERTENSION

POPH is defined as a pulmonary vasculopathy seen in the setting of portal hypertension characterized by pulmonary arterial hypertension(PAH) in the absence of other causes of PAH. It is classified under Group 1 Type of Pulmonary arterial hypertension associated with portal hypertension according to the revised WHO classification.[16] The other causes that should be ruled out include chronic thromboembolism, left heart failure and long standing lung disorders.

DIAGNOSTIC CRITERIA OF POPH:

1) The presence of portal hypertension but not necessarily the presence of cirrhosis; and

2) Haemodynamic measurements from right heart catheterisation (RHC) including mean pulmonary artery pressure (mean PAP) >25 mm Hg at rest, mean pulmonary capillary wedge pressure (mean PCWP) <15 mm Hg, and pulmonary vascular resistance (PVR) >240 dyn.s.cm-5.[17]

It is worth noting that up to 20% of cirrhotic patients have a mild increase in PAP (25-35 mmHg) due to the increased cardiac output seen in these group of patients however the PVR remains within normal limits and therefore this does not fall under the POPH group.

EPIDEMIOLOGY AND RISK FACTORS

POPH is a very rare complication of cirrhosis/portal hypertension in comparison to HPS and occurs in approximately 0.5-5% of all cases.[18] 10% of these cases are due to non-cirrhotic liver disease including extrahepatic portal hypertension. It is the third most common cause of pulmonary hypertension and accounts for 10% of all cases.

Even though it is almost always seen only in the setting of portal hypertension, the incidence or severity of POPH is not associated with the stage of cirrhosis (MELD, Child class) or the severity of portal hypertension. POPH is usually detected around 4-7 years after the diagnosis of portal hypertension and it presents during the fifth decade of life. This is an important differentiating factor from idiopathic pulmonary hypertension as the latter is diagnosed at a much younger age.[19] The chances of developing POPH is known to increase with the duration of portal hypertension. Also, a multicentre study has shown that female sex and autoimmune hepatitis as etiology of cirrhosis are risk factors for POPH as opposed to HPS which has no relation to etiology.[20] Presence of large portosystemic shunts is also a risk factor for development of POPH. Interestingly enough, the first ever case of POPH was reported in 1951 as an autopsy finding in a patient of portal vein thrombosis with a large portocaval shunt.

PATHOGENESIS

The characteristic hemodynamic phenomenon noted in cirrhosis is an unrestricted sphlanchnic vasodilatation and increased portal venous blood flow which in turn result in a hyperdynamic circulation. The classic theory behind the onset of POPH is the continuous shear stress on the pulmonary vascular endothelium and the consequent vascular remodelling leading to changes similar to that seen in idiopathic pulmonary artery hypertension. These include endothelial cell proliferation, intimal fibrosis, plexogenic arteriopathy and insitu thrombosis.[21] Additionally, similar to HPS, the role of neurovascular mediators cannot be overlooked. One of the most prominent mediators secreted in cirrhosis state is endothelin-1 (ET-1) whose levels have been measured to be disproportionately high in patients with POPH. Conversely there is relative deficiency of vasodilatory mediators like prostacyclins in the pulmonary vasculature.

CLINICAL COURSE AND NATURAL HISTORY

Most patients at presentation are asymptomatic or suffer from dyspnea on exertion which may mimic any cardiopulmonary disorder. In advanced stages they may present with fatigue, syncopal attacks or even hemoptysis which is important to be differentiated from the much more common complication of hematemesis seen in these group of patients. Lower limb swelling or oedema that is disproportionate to the level of ascites may be a subtle clue for further probing. The most frequent clinical signs are a pronounced pulmonic component of the second heart sound and the systolic murmur of tricuspid regurgitation, although in later stages frank signs of right heart failure ensue like elevated jugular venous pulse and a pulsatile liver. One study has shown that the presence of systemic hypertension, a loud P2 and a parasternal heave have a high sensitivity for POPH in cirrhotics.[22]

The natural course of the disease is dismal with worsening right heart failure, limitation of activity and increased mortality. In the Mayo clinic experience, a 5-year survival of only 14% has been recorded in patients not on any therapy whereas it increased to 45% and 67% respectively in patients who received PAH specific therapy and Liver transplantation.[23] The two factors associated with increased chance of death are a low cardiac index and a higher severity of cirrhosis according to Child Pugh scoring. An interesting comparison between POPH and idiopathic PAH is that the cardiac indices are much more favourable in the former with a higher cardiac output and a lower PVR. Despite this positive hemodynamic profile, mortality is three times higher in POPH.[24] Ultimately patients die either from worsening liver function and its complications or due to right heart failure.

DIAGNOSIS AND SCREENING

As the majority of patients can be asymptomatic it is important to actively search for the disease in all patients listed for LT or any patient of liver disease presenting with exertional dyspnea. A detailed evaluation to exclude other commoner causes of exertional breathless is mandatory before reaching a diagnosis of POPH. Indeed, just the existence of pulmonary arterial hypertension in the setting of portal hypertension is not sufficient as mentioned earlier.

The most valuable test in the screening of the disease is a two-dimensional transthoracic echocardiography (TTE) even though the diagnostic investigation of choice is right heart catheterization (RHC). Multiple studies have attempted to find an appropriate cut off value for right ventricular systolic pressure (RVSP) on TTE. Most of these studies have shown that an RVSP < 30 mmHg can be safely used to exclude POPH and a RSVP >50mmHG to include POPH. Therefore, the latter group may be advised for a cardiac catheterization study.[25] All

patients with even a borderline rise in pulmonary artery pressure if accompanied by a strong clinical suspicion should be advised for a right heart catheterization. Only RHC can differentiate between true POPH and the relative PAH seen due to the hyperdynamic circulation of cirrhosis. It does this by measuring the pulmonary vascular resistance which is increased in POPH. Another parameter of significance is the transpulmonary gradient which refers to the difference between the mean pulmonary artery pressure(MPAP) and the pulmonary artery occlusion pressure (PAOP) which is usually employed to differentiate this from hyperdynamic circulation. A TPG >12 is highly indicative of POPH.[4] RHC also helps to stratify the severity of the disease according to pulmonary hypertension.

SEVERITY CLASSIFICATION OF POPH

- Mild (early): mean PAP 25-35 mmHg
- Moderate: mean PAP 35-45 mmHg
- Severe: PAP >45 mmHg

MANAGEMENT

The general principles in the management of POPH include providing symptomatic relief, improving quality of life and adequately selecting patients for transplantation. Despite its hemodynamic and histopathological similarity to Idiopathic pulmonary hypertension, there are a few cardinal differences in the approach to management. One, owing to the procoagulant nature of underlying cirrhosis and increased risk of gastrointestinal haemorrhage, anticoagulation is never an optimal option of treatment for these patients. Similarly, calcium channel blockers though used selectively in PPH, are avoided in patients of POPH as they are known to negatively affect the hemodynamic profile by causing mesenteric vasodilatation and worsening of portal hypertension.[26]

A large subset of cirrhotic patients is usually on beta blockers for prophylaxis of variceal bleed. However, betablocker use in patients of POPH has been associated with worsening of exercise tolerance due to a negative inotropic and chronotropic effect. Therefore, patients with POPH should be advised to stop betablockers and instead opt for endoscopic ligation of varices.

In patients with frank symptoms of fluid overload, diuretics like spironolactone and furosemide may be used in moderation and in the setting of hypoxemia (PaO2< 60 mmHg) supplemental oxygen has to be started.

SPECIFIC MEDICAL THERAPY

Most of the evidence of PAH specific therapy arise from extrapolation of data from studies performed on idiopathic pulmonary arterial hypertension as POPH patients were initially excluded from randomized controlled trials. There are predominantly three groups of agents that have been used to bring down pulmonary artery pressures

1. **Endothelin receptor antagonists (ERA)** have demonstrated significant improvement in hemodynamic parameters and reduction in morbidity by countering the increased vascular tone at the microcirculation level. The non-selective ETA Bostentan as well as the ET-1 selective antagonist Ambrisentan have shown good results in selected studies.[27]

2. **Prostacyclin analogues,** especially the intravenous Epoprostenol is one of the best studied drugs in this condition. It has been shown to bring about improvement in pulmonary hemodynamics and increase cardiac output in a large study however it suffers from the drawback of requiring continuous intravenous drug delivery system in the form of central venous access and constant monitoring.

3. **The oral phosphodiesterase inhibitors,** sildenafil and tadalafil have recently been shown to be attractive add on drugs in the case of severe portopulmonary hypertension in addition to the above modalities.

LIVER TRANSPLANTATION

The presence of any level of pulmonary hypertension increases the perioperative mortality and chances of long-term complications in the setting of liver transplantation. Therefore, POPH is not an indication for LT unlike HPS. However, without LT, the 5-year survival of POPH patients is dismal (<30%) and recently studies have shown that appropriate use of vasodilator drugs significantly reduces the perioperative risk of LT.

Mortality after LT was 100% for patients withPOPH with mPAP greater than 50 mm Hg, 50%for those with mPAP 35 to 50 mm Hg, and 0% for those lower than 35mmHg. Therefore, patients with PAP<35 mmHg (mild POPH) can undergo LT safely, those with PAP >35<45 mmHg have to be treated with vasodilator agents to bring their pressures below 35mm Hg and only drug therapy should be offered to those with PAP> 45 mmHg. Similar to HPS patients, to improve access to LT and to reduce waitlist mortality, MELD exception of 22 points have been given to patients of POPH with PAP >35 mmHg. All patients should be periodically monitored for worsening of pulmonary hemodynamic indices.
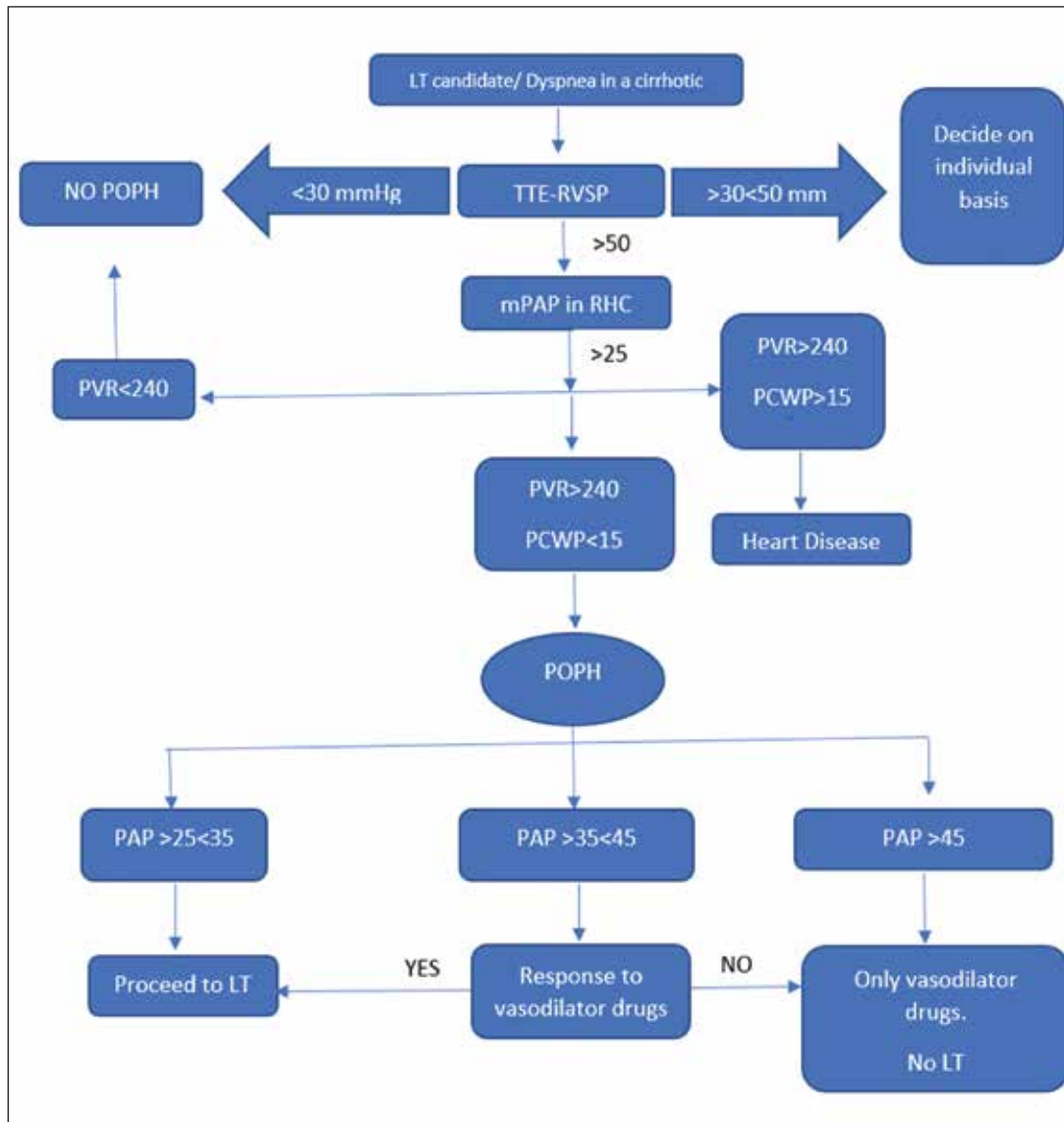
Fig 3: Flowchart showing approach to diagnosis and management of POPH
POPH- portopulmonary hypertension; TTE-transthoracic echocardiography; RVSP- right ventricular systolic pressure; PVR- pulmonary vascular resistance; PCWP-pulmonary capillary wedge pressure; PAP- pulmonary artery pressure; LT- liver transplantation.

CONCLUSION

Liver disease is complicated by dyspnea and hypoxemia due to diverse mechanisms and pulmonary vascular manifestations are by far the most important due to the dismal prognosis associated with it and as it has far reaching implications for liver transplantation. POPH and HPS is commonly seen in patients waiting for LT and should be actively screened for by echocardiography and detected at an early stage. Although both diseases may benefit post LT, only HPS is presently considered a specific indication. Except for the most severe forms of HPS, these patients should be routinely offered an option for transplantation. Careful selection of patients of POPH for LT is absolutely vital with the growing awareness of high periprocedural complications in patients with severe forms of the disease. Novel therapeutic modalities are constantly being sought for these unique complications of liver disease.

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PTCA in anomalous LCx from right sinus

Jinesh Thomas M

Consultant Interventional Cardiologist and Electrophysiologist, Lourdes Hospital, Kochi, Kerala

THE CASE

A 52 year old gentleman presented with a 'peculiar' feeling in the chest of 4 days duration which worsened with exertion. He was diabetic and hypertensive for 5 years (on Ayurvedic medication). On examination, pulse rate was 75 per minute, blood pressure was 140/80 with normal heart sounds. ECG showed sinus rhythm [Figure 1.] and Echo showed no wall motion abnormality with normal LV function [EF 68%].

He was taken up for coronary angiogram which showed long left main with LAD and Ramus arising from the left main with absent circumflex artery [Figure 2]. Mid LAD had minor disease. Right sinus injection showed separate origin of right coronary artery (RCA) and left circumflex (LCx) [Figure 3]. Selective cannulation of anomalous LCx was done with 5F Amplatz Right [AR1] diagnostic catheter - angiography showed 95% stenosis of OM (obtuse maginal) [Figure 4].

LCx was cannulated with 6F Amplatz Right AR 2 Guide Catheter. The lesion was crossed with 0.014" Fielder FC wire and parked distally. Predilatation was done with 2.0 x 15 mm balloon [Figure 5]. Initial attempt to track a 2.75 x 29 mm drug eluting stent (DES) failed even after realigning the guide catheter. The lesion was then successfully stented with 2.75 x 23 mm DES @ 14 atm x 12 secs [Figure 6] with good result [Figure 7].
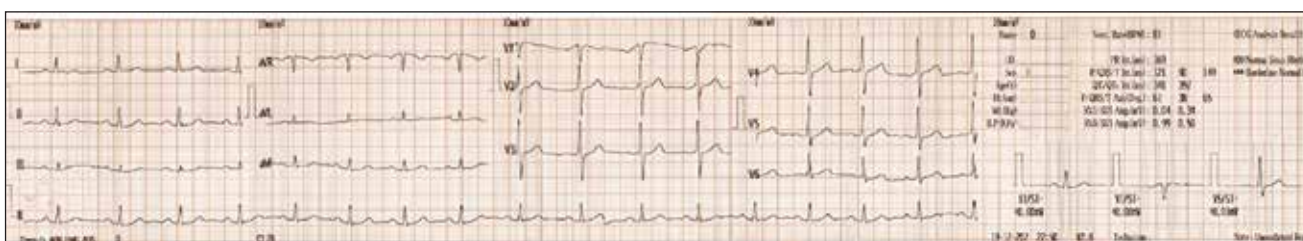

Figure 1. Presenting ECG

Address for correspondence: Dr. Jinesh Thomas M, MD, DM, DNB, PDF (EP), FNB (IC), PDF (PC), Consultant Adult and Paediatric Interventional Cardiologist and Electrophysiologist, Lourdes Hospital, Ernakulam. Email.: jineshthomasm@yahoo.com
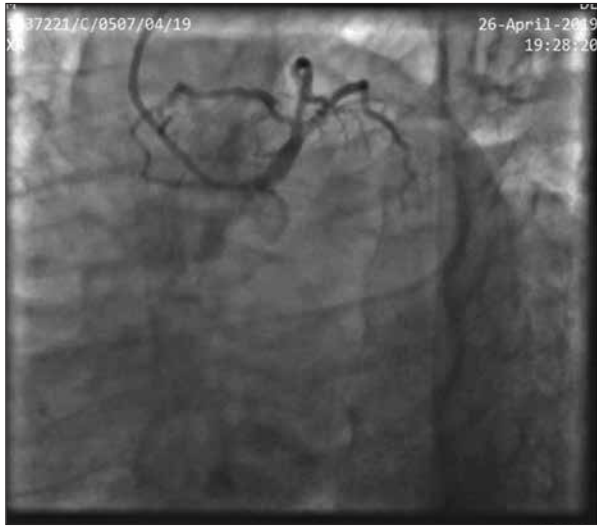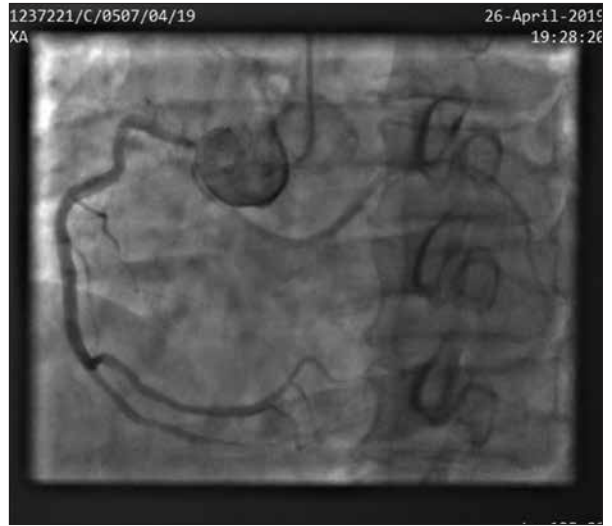
Figure 2. LAO caudal - Absent LCx

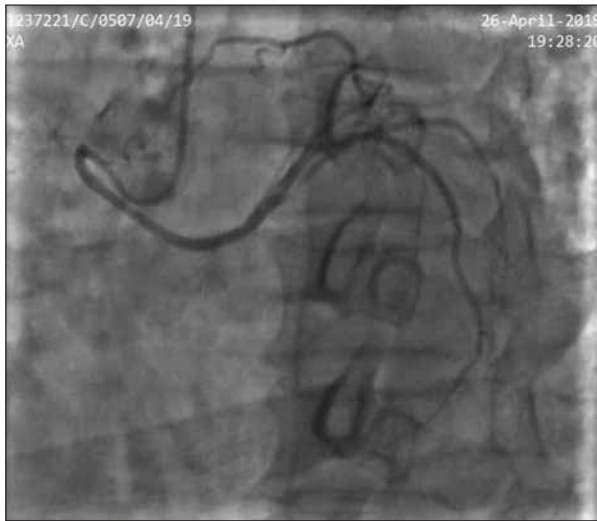Figure 3. RCA and LCx from the right sinus

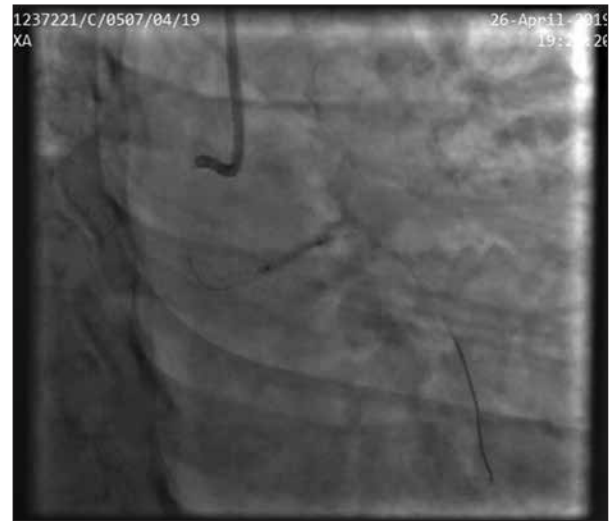

Figure 4. LCx lesion

Figure 5. LCx lesion predilated with 2.0 x 15 mm balloon

Figure 6. Stented with 2.75 x 23 mm DES

Figure 7. Final angiographic picture

LEARNING POINTS

Angiographic signs to suspect an anomalous LCx include the following:

- The Angiographic Dot Sign – Profile view of the artery behind the aortic root during left ventriculography in RAO view

- Sign of Non-perfused myocardium - absent arterial inflow to a significant area of the posterior lateral left ventricle during selective injections of the left main coronary artery

- Absence of visible vessel in the left AV groove on left coronary angiography

- Long left main coronary artery

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Do We Need the 'p' Value?

V Raman Kutty

Professor Emeritus,
Achutha Menon Centre for Health Science Studies,
Sree Chitra Tirunal Institute for Medical Sciences and
Technology, Thiruvananthapuram, Kerala

For any young assistant professor aspiring to build a career in any branch of academic medicine, the 'p' value looms large in her nightmares. It stands between her research, which she has painstakingly done over so many hours, days, and months, and publication in peer reviewed indexed journals, which is the only yardstick that universities and assessment committees will acknowledge as the measure of quality. (Here, I don't mean publication in predatory and suspicious journals that extend you a sweet invitation to publish in their journal, though sometimes also asking for a fee. Young assistant professors will be well advised to keep out of such journals, since in these days where everyone is tracked on the internet, one such publication may mar your reputation for ever).

So what is the 'p' value? With very few notable exceptions, I find that the medical course we all go through, and the residency to follow, scarcely prepares the young doctor for assessment of evidence, let alone conduct of research. Hence till such time as it really hits you hard, the 'p' value is some vague thing, a short note you mugged up for getting through the Community Medicine exam or the entrance test, or something that statisticians seem to be obsessed about. It may not seem worth spending time about. Sadly, in these days of evidence based medicine, statistical evidence is becoming ever more important as the gold standard against which any claim to efficacy will be judged. And statistical evidence squarely rests on the 'p' value.

The 'p' value, is the measure of a particular probability. Probability can be loosely translated as chance. **So the 'p' value reflects the chance or probability of observing the data in your study (or more extreme patterns of data), if the 'null' hypothesis is true.** Because the 'p' value is a probability, it can only vary between '0' and '1'. A probability of zero indicates the dead certainty that the event will not happen (the data will not be distributed like this), and a probability of 1 reflects the equally sure position that it will happen (the data will be exactly like this). In normal situations, these two extreme certainties never happen. Hence the 'p' value is always between 0 and 1.

Address for correspondence: Dr. V Raman Kutty, MD, M Phil, MPH (Harvard), Professor Emeritus, Achutha Menon Centre for Health Science Studies,
Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram 695011, Kerala, India. Phone: 91-471-2524240, E-mail: kuttyr@gmail.com

What is the 'null' hypothesis?

I have stated above that the 'p' value reflects the conditional probability that given the null hypothesis is true, what is the chance of observing our data. To understand this, we should know something about hypotheses, and how they are tested.

Most research is about exploring associations between characteristics of interest. For example, does smoking lead to cancer of the lung? Can drug 'X' cure disease 'Y'? Do males have more complications from disease 'Z' compared to females? These are the research questions from which the study starts. If you put the question in a statement format, it becomes a hypothesis. In our examples above, we have given rise to three such hypotheses:

Smoking leads to cancer of the lung

Drug 'X' cures disease 'Y'

Males have more complications compared to females with disease 'Z'

Hypotheses are the starting point of most types of research. We attempt to test our hypotheses in any research study, For this, we look at the data related to the hypotheses. These data may be already present from other studies, or we may do an observational study or an experiment to generate such data. If our data are compatible with the hypotheses, we say that our hypotheses is 'not rejected'; if we find our data are incompatible with what we have set up as a hypothesis, we say that the hypothesis is rejected, and we have to look for a new one.

Why do we not 'accept' hypotheses? This is because strictly speaking, no one really knows the absolute truth. So we will 'not reject' this hypothesis till such time as there is any cause to doubt it. This is the way science progresses in general. This is called the 'hypothetico-deductive' approach. (There are philosophical issues and some challenges to this method, but for our purposes, we need not be concerned with them. The hypothetico-deductive approach is broadly accepted as a method of science.

You will notice that so far I have talked only about the hypothesis; what about the 'null' hypothesis? The 'null' hypothesis is the exact reverse of your hypothesis. For our examples above, the 'null' hypotheses will be:

Smoking does NOT lead to cancer of the lung

Drug 'X' does NOT cure disease 'Y'

Males do NOT have more complications compared to females with disease 'Z'

The formal process of research then proceeds to try and reject the null hypothesis. Here is where the 'p' value comes in. The 'p' value, as stated above, is the probability of observing the data in your study, if the null hypothesis is true. So if this probability is low, we conclude that the null hypothesis is unlikely to be true; we proceed to reject it. We conclude that the alternate hypothesis, which is our original hypothesis, is more likely to be true compared to the null hypothesis.

What if the 'p' value is not low? It tells us that if the null hypothesis (which is exactly the opposite of our hypothesis) is true, we are very much likely to observe the data in our study if the 'null' hypothesis is true. Hence we cannot reject the null hypothesis; till we find different data, we should conclude that the null hypothesis represents the truth.

Why the 'null' hypothesis?

A natural question which follows is: why should we create a 'null' hypothesis and then try to reject it? Why can't we test the hypothesis as it is?

The straight answer to this is that technically, it is possible. We can devise statistical tests to assess whether given the hypothesis is true, the data will be like what we have observed. However, the formal process of research introduces the concept of the 'null' hypothesis for a special reason. This is to keep down the chances that new hypotheses, which are essentially challenges to the status-quo, will be believed to be true. In other words, the method of science is very conservative- it changes the status quo only when there is overwhelming evidence.

To understand this, we should think about the probability of error. When we reject a 'null' hypothesis, we can't be sure that our test, which is based on data from a single study, is completely error free. It could be that when we take the decision, we go wrong.

We are likely to commit two types of error here: (1) rejecting a 'null' hypothesis which is in fact, true; and (2) not rejecting a null hypothesis which is not true.

Let us look at the consequences of each error in decision making. If we reject a 'null' hypothesis which is in fact, true, we will be changing the status quo unnecessarily. If we take our second example, if the null hypothesis, 'drug X does not cure disease Y' is rejected, we tend to accept that drug X as an effective cure for disease

Y, when in fact it is not. If this drug replaces routine practice, we are not only denying patients with disease Y whatever medication they were getting before, we may also be exposing them to an ineffective agent X which will not cure the disease and may have complications. So this type of mistake should be strictly guarded against.

On the other hand, let us review the consequences of the other error: not rejecting a 'null' hypothesis which is not true. In our example, we will not reject the null hypothesis that drug X is not effective when in fact it is effective; the consequence will be that patients will continue to get the treatment which they had been receiving. This may not be a big deal if we imagine that sooner or later, in some other study, drug X will be found to be effective and it will replace routine therapy.

Thus in most situations, the consequences of rejecting a null hypothesis which is true, far outweighs the consequences of not rejecting a null hypothesis which is not true. The first type of error is called 'alpha' error or type I error; the second one, 'beta' error or type II error. We start our testing with the premise that the alpha error should be really low, below a certain level. Conventionally this is taken as 0.05, or 1 in 20. The 'p' value in statistical tests reflect the actual alpha error rate in that particular analysis; we want this to remain low. So it is conventionally fixed as below 0.05. Getting a 'p' value below this tells you that the probability that you will observe the data in your study, provided the null hypothesis is true, is pretty low; consequently, you can reject the null hypothesis and proceed as if your alternative hypothesis, which is your original hypothesis, is true.

This is easy to understand in comparison with the judicial process. Our judicial system starts with the assumption that the accused is NOT guilty- the 'null' hypothesis. The evidence produced in court- the data- is the attempt to get the null hypothesis to be rejected by the judge. If the judge is not convinced, he says that the evidence is 'insufficient'- can't reject the null hypothesis. This is not an exoneration- the judge does not ever pronounce anyone 'innocent' (though the media seems to believe otherwise)- he only says that there is not enough evidence to find the accused guilty. The reason why we start with the presumption of innocence on the part of the accused is to protect against judicial indictment of the innocent- 'even if a thousand guilty persons are allowed to go free, not a single innocent person should be punished'. This is the alpha error that the judge can commit and we want to protect against that.

Beta error or type II error, is the error we make when we do not reject a null hypothesis that is not true. This in other words is the same as not detecting a true difference. As we have seen, this is a less serious error- and we generally allow up to 20% for this error. The converse of beta- or (1- beta) tells us the ability of the test to find a true difference- discriminatory power- and is naturally called the power of the statistical test.

What the 'p' value is not

Often the 'p' value is described as the probability that the null hypothesis is true. This is a wrong notion. There is no probability associated with the null hypothesis- it is either true, or not true: the only thing is, we don't know.

The future of the 'p' value

Recently the American Statistical Association came out with a statement which in essence said that there is too much emphasis on the 'p' value in scientific writing now-a-days. So they have strongly recommended moving away from the 'p' value in statistical testing. The cut-off point- 0.05- is an arbitrary value which is followed more because of convention than any scientific rationale. To judge the quality of a body of work merely based on such an arbitrary criterion doesn't seem to be a good rule. Statisticians- and journals nowadays- emphasize more on confidence intervals rather than 'p' values. But that is a story for another day!

A Letter from the Bundles of the Heart…!

Abhilash S P

Additional Professor, Cardiology
Sree Chitra Tirunal Institute for Medical Sciences and
Technology, Thiruvananthapuram, Kerala

Note: **This "class room" article is prepared like a letter to the author's imaginary cousin who has just finished MD Medicine and soon joining DM Cardiology course.**

My dear Swaraj,

Congratulations for getting selected to DM Cardiology course; I knew this from your childhood days that you wanted to become a doctor, a cardiologist to be precise. Now you are about live your dream…wow..! But I heard from aunt that you have some concerns about your choice nowadays. No dear Swaraj, don't hesitate. Cardiology is as fascinating as ever; both exciting as well as satisfying. After 11 years in cardiology, I can assure you that.

I can tell you an example; the story of a six year old girl - from the bundles of my heart….err…from the table of cardiac catheterisation laboratory! The girl had a small ASD and a small VSD. Both were kept for medical follow up. During the course of follow up, she was found to have complete heart block. (See Figure 1). You can see that there is AV dissociation with more P waves than QRS & P rate is around 140 bpm and QRS rate is around 40 bpm. She had one episode of syncope and her echo showed mild LV dysfunction.
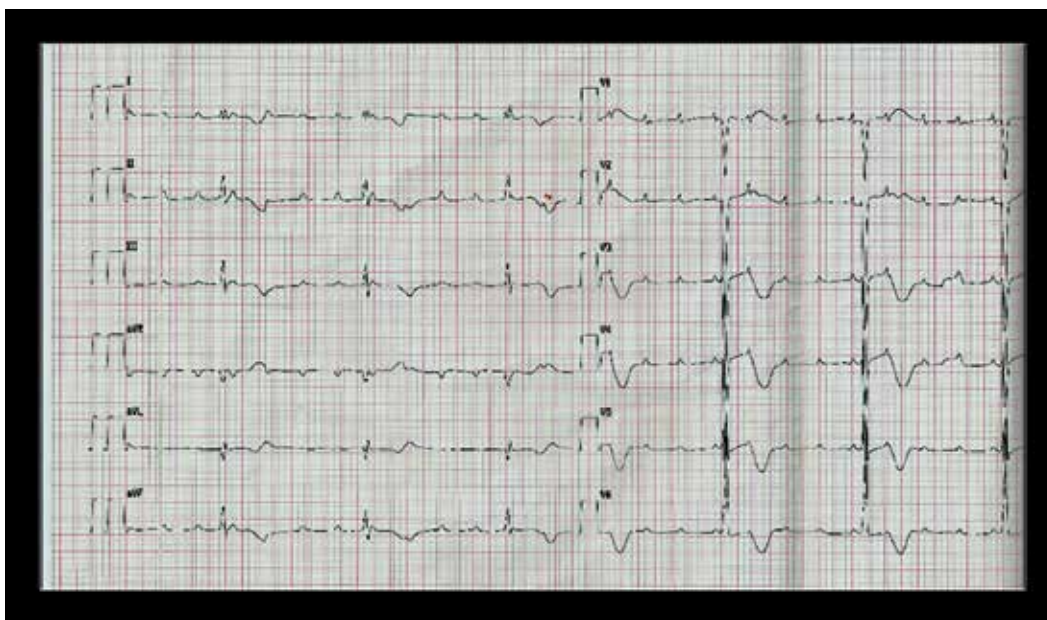

Figure 1. ECG showing complete heart block (CHB)

Address for correspondence: Dr. Abhilash S P, MD, DM, Bhavani, TC 7/491 (6), NLRA 333, Neerazhi Lane, Ulloor, Thiruvananthapuram - 695 011. E-mail: abhispin@gmail.com

You should be knowing that narrow QRS complete heart block in a kid who is asymptomatic with reasonable heart rate is not necessarily paced. The indications for permanent pacing are development of symptoms, very low heart rate for age, bradycardia induced tachy-arrhythmias, QT prolongation, repolarisation abnormalities like T wave alternans and finally, occurrence of heart failure. Our girl had symptoms (syncope), low heart rate and LV dysfunction. She was planned for a permanent pacemaker implantation at our hospital. We opted for a rate responsive single chamber pacemaker (considering her age), ie; a VVI-R pacemaker.

Dear Swaraj, I wanted to be a smart guy and did a few tricks prior to procedure - all of them back fired in this case though! Patient being a kid, I programmed the pulse generator to 80 bpm in VVI-R mode prior to implantation of pace maker. That was done because the child requires a higher pacing rate than adults to do her routine activities. I was feeling elated that how meticulous I was! My pride did not last much though.

It is more difficult to implant a pace maker in a child because of limited space at delto-pectoral region and smaller veins. We need to give extra loop to leads considering the physical growth of child in coming years. Lead was screwed in at the RV apical septum and we started checking the threshold of the lead. This is done via pacing system in lab prior to connecting to pulse generator. We are supposed to check the R wave, impedance, threshold and current of injury in EGM (Electrogram) tracing (we use screw-in leads as a routine). The trouble started then.

The R wave and impedance were good and EGM showed more than 50% injury (showing that the lead was in a satisfactory position). But the lead was not capturing 1:1 at even high outputs. It showed 2:1 capture (See Figure 2). I was planning to change lead position to another location assuming that the threshold was not good at the implanted site. But luckily, we had smarter people in the cath lab - my seniors Ajit Kumar Sir and Narayanan Namboodiri Sir! They picked up one more abnormality in that CHB tracing. Please have one more look at Figure 1. They found out that, apart from CHB, there was significant QT prolongation. Now look at Figure 2 once more. You can see that alternate pacing beats are not captured because they fall on the refractory period of the myocardium due to prolonged QT interval.

I became wiser with suggestions of Ajit Sir and Namboodiri Sir. I had missed the prolonged QT and its implications in pacing capture. Now I started pacing at a slower 70 bpm rate. (See Figure 3). At 70 bpm, same lead position showed consistent 1:1 capture. I could see the pacing artifact falling after ventricular repolarisation and getting captured fully. Threshold at the same lead position was 0.8V and hence I did not have to change the lead position. Don't you remember, the saying "eyes can't see what the mind doesn't know!"

The issues did not settle there. I told you already that I had programmed the pacemaker pulse generator to 80 bpm in VVI-R mode. This pre-programmed pulse generator was connected and at 80 bpm per minute, capture was inconsistent. And as the child woke up from
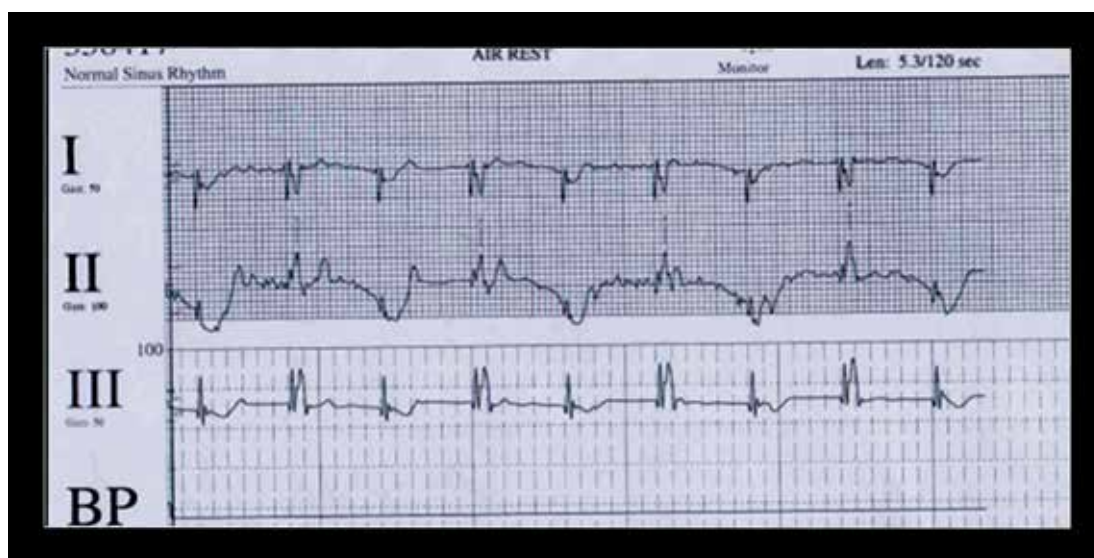

Figure 2. Alternate pacing beats were not capturing since they fell on the refractory period of myocardium when paced at 100 bpm. Please note the prolonged QT.
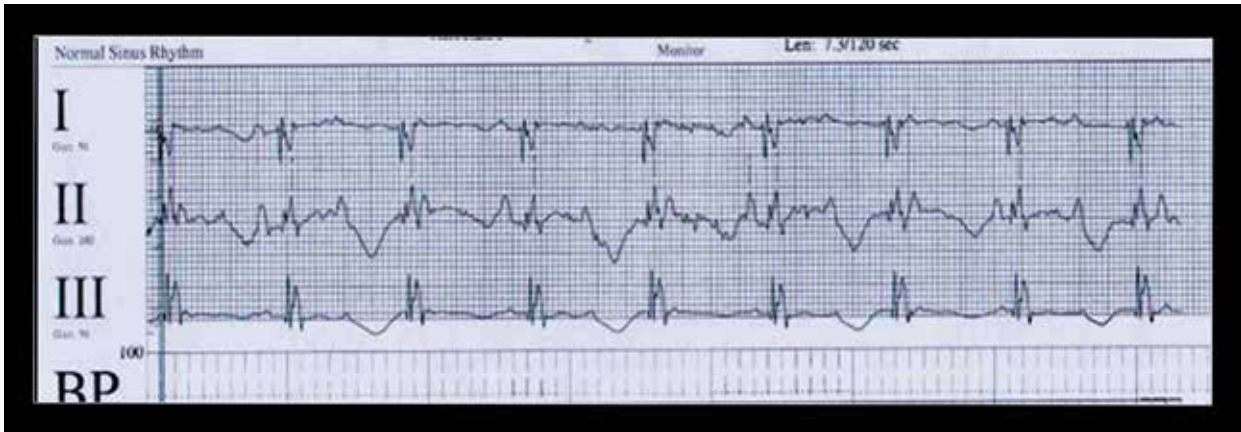
Figure 3. Showing 1:1 capture at 70 bpm. Note each pacing artifact falling beyond the prolonged QT segment.

general anaesthesia, rate responsive pacemaker was increasing the heart rate to 100 bpm, further affecting the capture. All my "initial tricks" flopped miserably. So I had to re-programme the pace maker to 70 bpm VVI mode. (rate responsiveness was switched off as well).

The QT prolongation in this kid is due to long duration of bradycardia and this is potentially reversible with correction of heart rate. We observed the child for 3 more days in ICU. Beta blockers were started to reduce the QT dispersion. See the surface ECG on the next day of implantation (Figure 4) and pre discharge interrogation of pace maker (Figure 5). I hope you can make out that the myocardium was not capturing 1:1 at 100 bpm 3 days back. But once the QT got corrected, it was capturing at 120 bpm now. We programmed the pacemaker now to VVI-R at 80 bpm. Our plan with beta blocker was to continue it for one more month.
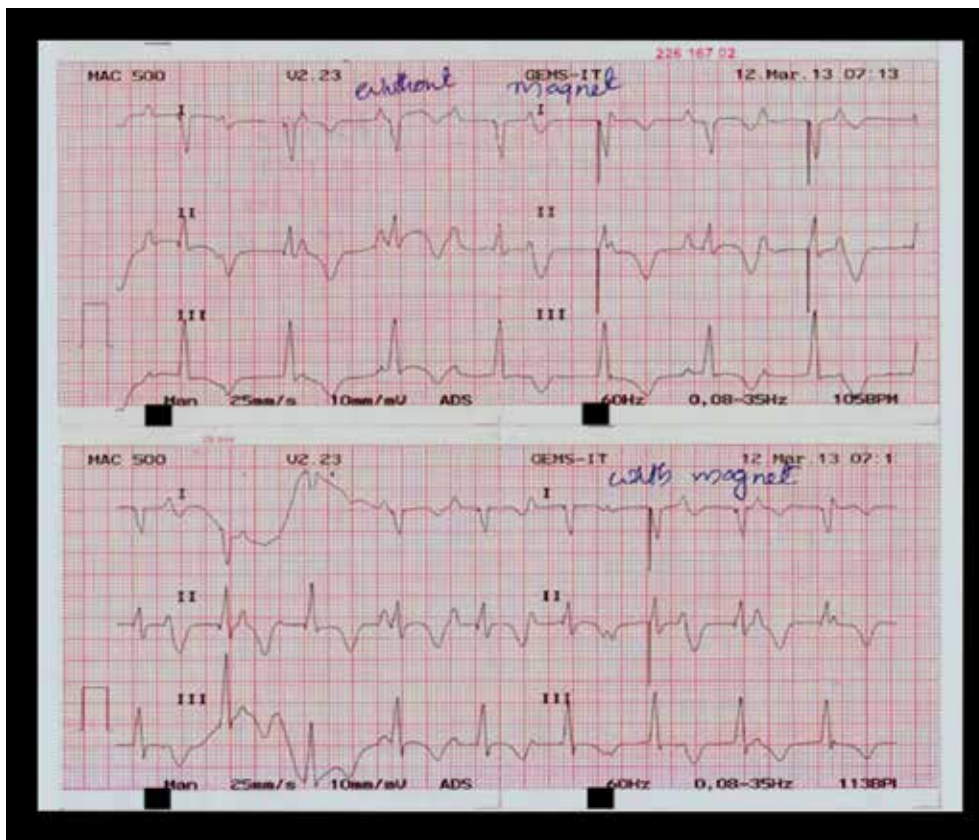

Figure 4. Surface ECG on the next day of pace maker implantation. Upper panel shows consistent capture at 70 bpm with reduction in QT interval. Lower panel shows 1:1 capture at 85 bpm(at magnet rate).
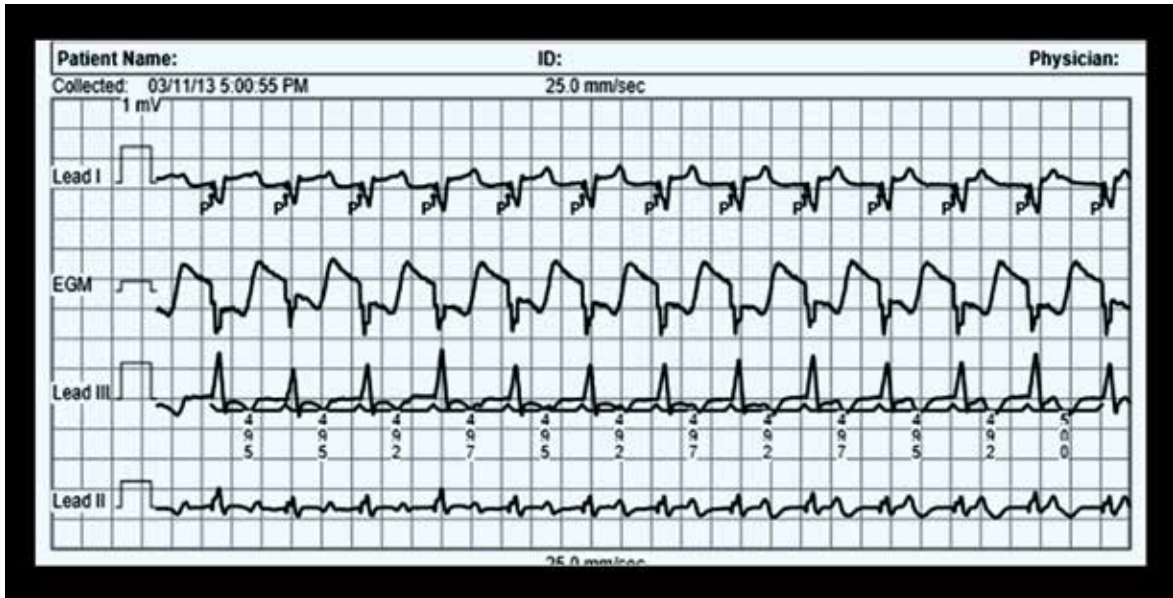
Figure 5. Pre discharge pace maker interrogation showing 1:1 ventricular capture at 120 bpm.

Dear Swaraj, don't you think the story I just enumerated was exciting? I am sure you do. I agree, I made a few mistakes, but I could correct myself and learn a lot with this particular patient. You can see the power of knowledge, how it simplifies a difficult situation and how it solves the miseries of a small girl. When we start to see each cardiology case as a puzzle, problem solving becomes a game and a lot entertaining too. Try to look for an explanation for everything. I know, I don't have to say this to you, medical profession still has the charm and it is a very gratifying profession. And, Cardiology is second to none. Come, this Wonderland is waiting for you.

Just Like Alice – "Imagination is the best weapon in the war against reality..!! Enjoy Cardiology with vision and of course, imagination!

With love and regards.

Abhilash

The Papers of Paul Wood - Remembering the Legend

Tiny Nair

Head, Department of Cardiology, PRS Hospital, Thiruvananthapuram, Kerala

INTRODUCTION

Imagine for a moment that you are working in a remote hospital, with lots of patients; but no echocardiogram, no cath-lab or MRI, you have no access to a computer or internet, and you are asked to produce a contemporary academic paper; a work that would be revered and respected by the future generations of doctors even 50 years later; most of us would take it as a big joke.

Except Paul Wood.

The story of Paul Wood papers is not just legendary, they are intellectually stimulating, philosophically motivating and clinically relevant even today.

For the 'smart-phone' wielding, time constrained 'app-happy' cardiologists of today, who have very little time and interest to think and see beyond the C arm, for whom only oblique view straighten out things, the Paul Wood papers are a rejuvenation.

A narrative remembrance of his life and papers.

EARLY LIFE

India boasts of being the birthplace of 'zero', Ayurveda and plastic surgery, but most people are unaware that the legendary Dr. Paul Hamilton Wood (aka Paul Wood) was also born in India, his father was working as a commissioner of income tax. Subsequently, the commissioner changed his mind and took up apple farming in faraway Tasmania, taking with him young Paul, who was schooled there. Paul Wood graduated in Medicine from the Melbourne University Medical School, Australia. His residency at Christchurch was punctuated by adventures like falling in love with Betty (the daughter of the surgery professor) with whom he eloped and subsequently married. They went to London to start a new life. After a short stint at National Heart hospital, he joined the Hammersmith Hospital where he became the consultant in 1937.

PAUL WOOD PAPERS

Most of Paul Wood papers start from the point of view of clinical medicine, either a sign, a symptom or an established pathology. But then they dive into great depths, dissecting and delving deep into pathophysiology, etiology and hemodynamics.

His first paper came out in 1936 on ESR in heart disease, and venous pressure in heart failure. He tried to derive maximal information at the bedside by observing the patient, documenting them and trying to explain these findings in the light of known medical knowledge base. The end result was, not just brilliant diagnosis, but an excellent discourse of hemodynamic derivation and prediction of prognosis. His presentations and classes attracted scores of students from all over the globe, to train under his tutelage to gain knowledge, and master the art of clinical diagnosis. He taught them simple signs of distinguishing between the flick of an 'a' wave versus the surge of a 'v' wave in the jugular venous pressure.

Address for correspondence: Dr. Tiny Nair, MD, DM, Head, Department of Cardiology, PRS Hospital, Trivandrum, Kerala.
Email: tinynair@gmail.com

In 1937, he described ECG changes in pericarditis and in stab wounds to the heart, perhaps because daggers and knives were more prevalent to steering wheels and airbags as a cause for cardiac trauma. These descriptions later paved the way for understanding the evolution of ST-T changes of pericarditis timeline, they also made way to subsequent understanding of post myocardial infarction Dressler's syndrome.

In 1939, he authored 3 more papers, one on chest leads in ECG, second, on signs of LVF and third on effect of vitamin B deficiency in cardiovascular system.

Declaration of war made this patriotic doctor offer his services to the military, where again his clinical acumen made him diagnose out-of-the-box cases. He described in details cardiac anxiety disease, 'the soldier's heart'. With an accurate description of 200 cases he clearly noted the clinical features of the condition. He went ahead one more step and showed that the spectrum afflicted not just soldiers on the battlefront, but young ladies at home as well – naming them as 'cardiac neurosis'. 'Both are same disease, one comes clad in battle dress, while the other in nylon' he commented in his usual humorous way.

His 1940 paper talks about the action of digitalis on heart in details.

By 1945, as Cournand introduced cardiac cath, Paul Wood knew that now a technology has come that would have the answer to many of his unanswered questions in cardiology. Not just that, by measuring cardiac pressures and hemodynamic, now he could prove and confirm his clinical impression that he generates at the bedside. Notably, he never saw technology as a fast-lane short cut to correct diagnosis, but a confirmation of a clinical diagnosis that he would so painstakingly make. He wanted his students to follow the same philosophy to the core.

He joined the Brompton hospital and established the cath-lab, the first cardiac catheterization being done on 15 April 1945.

In 1950, Paul Wood was ready to publish the collection of his compiled work titled 'Disease of the Heart and Circulation'. Just before going to print, the draft, stored carefully in a briefcase, was stolen during his journey across Italy. While for most, it would have been an end of the world, the genius Dr. Wood had stored a copy safe

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by PAUL WOOD

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in the God-given hard disk with infinite capacity. He wrote to a collogue 'it was ok because it was all in my head'.

The book became a success instantly needing newer editions to be printed and published.

His papers and lectures mainly focused on congenital heart disease, rheumatic heart disease and pulmonary hypertension and pulmonary vascular disease. His understanding of pulmonary vascular pathology and progression of pulmonary vascular changes was incomparable. His concept of progression of a 'pink' VSD to a 'blue' Eisenmenger syndrome is contemporary even today.

PERSONALITY

Patients, students, residents, visitors – all wanted to have a glimpse of the legend at work making a clinical diagnosis; making bedside rounds lengthy. Demand on papers, lectures, classes increased.

Despite being a charismatic legend, Paul Wood was never described always as mild, soft, docile or even, pleasing. His sarcastic and scathing comments hurt and offended many; but this often erupted out of his inability to accept intellectual dishonesty, shoddy notes, and slow thinking.

Bedside mannerism was an area of no compromise for the brilliant academician. A comment like 'enlarged heart' or cancer by the resident in front of the patient was strongly reprimanded.

Paul Wood had the habit of grading everything, from murmurs to effort intolerance, from disease severity to hemodynamics. One of his colleagues commented that he should grade baldness, awarding him 4/4.

Paul wood was a strong believer in use of anti-coagulants in ischemic heart disease and he was at loggerheads with contemporary cardiologists like William Evans who were antagonistic to the use of 'rat poison' for their patients. Despite the academic flick and surge, Evans insisted that his students learnt to differentiate the flick and surge of the JVP waves so ardently taught by Dr. Wood.

DEMISE

On July 13, 1962, Paul Wood died of cardiac arrest presumably a VT; he was suffering from angina. He had clearly consented against resuscitation. Autopsy showed a single vessel coronary disease afflicting the LAD.

Two months later, External defibrillation was invented.

Paul Wood left everlasting mark on the sands of time, even the deluge of technological tsunami could not efface.

Paul Wood Papers are written in indelible ink on a future proof media.

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Scoring Systems in Cardiology - Part 1

Sulthan Raslin Salih
Senior Resident, Department of Cardiology,
Pushpagiri Medical College, Thiruvalla, Kerala.

Nilay K Patel
Senior Resident, Department of Cardiology,
Amrita Institute of Medical Sciences, Kochi, Kerala.

INTRODUCTION

Scoring systems and classification play a fundamental role in decision making in current cardiology practice. A comprehensive list of the important and useful scores, their calculation and application is discussed below. This will help the clinicians for a rapid access and also be a "one place for scores" for the cardiology fellows facing their exams.

The scores can be categorised into four groups, as given in the table below: 1) Clinical scores, 2) Echocardiographic and investigation related scores, 3) Intervention related scores and 4) Surgery related scores. This article will discuss the clinical scores. The rest of the scores will be covered in subsequent issues.

Category	Clinical scores	Echocardiography and other investigation related scores	Intervention related scores	Surgery related scores
Scores	TIMI risk score for STEMI TIMI risk score for NSTEMI HEART score GRACE risk score ASCVD risk score CHA_2DS_2VASc score ATRIA stroke risk score HAS-BLED score $HEMORR_2HAGES$ score PRECISE-DAPT score HCM SCD Risk score Wells score PESI score RCRI for pre-operative cardiac risk in Non- cardiac Surgical Procedures Schwartz score Shanghai score Short QT syndrome	Wilkins score Cormier score Padial score Reynolds risk score Duke treadmill score Agatston score CT-RECTOR score	SYNTAX and SYNTAX II score J-CTO score Progress CTO score ORA score Mehran score for CIN	EURO score, EUROscore II STS score

Address for correspondence: Dr. Sulthan Raslin Salih, DM Senior Resident, Department of Cardiology, Pushpagiri Medical College, Thiruvalla, Kerala
Email: dr.sulthanraslin@gmail.com

CLINICAL SCORES

1. TIMI RISK SCORE FOR STEMI

Developed from the inTIME trial in 15000 STEMI patients by Morrow DA et al[1]. Predicts 30 day mortality in STEMI patients eligible for fibrinolysis. Patients with cardiogenic shock, patients with severe hypertension (> 180/100 mmHg) and those taken up for PCI were excluded from the study. The scoring is as follows:

	TIMI risk score for STEMI		
History	Age	< 65 years	0
		65-74 years	2
		≥ 75 years	3
	Diabetes Mellitus or Hypertension or Angina		1
Examination	Systolic BP < 100 mmHg		3
	Heart Rate > 100		2
	Killip Class II-IV		2
	Weight < 67kg		1
Presentation	Anterior ST Elevation or Left Bundle Branch Block		1
	Time to Treatment > 4 hours		1

Risk score	Odds of death at 30 days	Mortality at 30 days
0	0.1	0.8
1	0.3	1.6
2	0.4	2.2
3	0.7	4.4
4	1.2	7.3
5	2.2	12.4
6	3.0	16.1
7	4.8	23.4
8	5.8	26.8
>8	8.8	35.9

2. TIMI RISK SCORE FOR NSTEMI

Developed from TIMI11B and ESSENCE trials from a merged database of about 7000 patients by Antman et al.[2] is easily calculated at patient presentation, does not require a computer, and identifies patients with different responses to treatments for UA/NSTEMI. DESIGN, SETTING, AND PATIENTS Two phase 3, international, randomized, double-blind trials (the Thrombolysis in Myocardial Infarction [TIMI] 11B trial [August 1996-March 1998] and the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI trial [ESSENCE; October 1994-May 1996] Predicts 14 day mortality in Unstable angina/NSTEMI patients. Higher TIMI Score resulted in increase in all-cause mortality, MI, or urgent revascularization.

TIMI risk score for UA/NSTEMI	
Age ≥65 years	1
≥3 CAD risk factors(DM,HTN,DLP, F/h/o CAD, smoking)	1
Known CAD (stenosis ≥50% on angiogram)	1
Aspirin use in past 7 days	1
Severe angina (≥2 episodes in 24 hrs)	1
ECG ST changes ≥0.5mm	1
Positive cardiac marker	1

Risk score	End point at 14 days(%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

The endpoint was a composite of all-cause mortality, myocardial infarction, or urgent revascularization at 14 days

3. HEART SCORE

Developed in the emergency department setting to risk stratify undifferentiated chest pain patients into low moderate or high risk groups[3]. Developed in a cohort of 122 patients. They excluded patient with definite ST elevations. HEART stands for history, ECG, Age, risk factors and Troponin. It has been externally validated in multiple cohorts and was found to be better than TIMI and GRACE scores. The end point was MACE (MI,PCI, CABG or death) at 6 weeks.

HEART Score			
	0 points	1 point	2 points
History	Slightly suspicious	Moderately suspicious	Highly suspicious
EKG	Normal	Non-specific repolarization changes	Significant ST deviation
Age	<45years	45–64 years	≥65 years
Risk factors	No known risk factors	1–2 risk factors	≥3 risk factors or history of atherosclerotic disease
Initial troponin	Within normal limits	1–3× upper reference of normal limit	>3× upper reference of normal limit

Risk factors – DM, HTN, DLP, obesity (BMI >30Kg/m2), smoking or family history of CAD

HEART score	MACE
0-3	2.5%
4-6	20.3%
7-10	72.7%

It is intended for use in the emergency department for risk stratifying undiagnosed chest pain patients.

4. GRACE RISK SCORE

It was developed in diagnosed ACS patients to quantify in-hospital and 6 month all-cause mortality and was developed from data of about 11000 patients[4]. It uses 8 variables and each variable is given a point. Points and variables differ for in-hospital and 6 month mortality. Points are added to get the GRACE risk score. Use needs online calculator.

GRACE risk score		
Variable	Points for in hospital mortality	Points for 6 month mortality
Age	0-100	0-100
Heart rate	0-46	0-43
Systolic BP (lower-higher)	58-0	24-0
S. Creatinine	1-28	1-20
Killip Class (I; II; III; IV)	0; 20; 39; 59	
Cardiac arrest at admission	39	
ST segment deviation on ECG	28	11
Elevated cardiac markers	14	15
History of CCF		24
History of MI		12
No in-hospital PCI		14

GRACE Score	Probability of in-hospital mortality
≤60	≤0.2%
70	0.3%
80	0.4%
90	0.6%
100	0.8%
110	1.1%
120	1.6%
130	2.1%
140	2.9%
150	3.9%
160	5.4%
170	7.3%
180	9.8%
190	13%
200	18%
210	23%
220	29%
230	36%
240	44%
≥250	≥52%

Grace Score	6 month Mortality Risk
≤87	0-2%
88-128	3-10%
129-149	10-20%
150-173	20-30%
174-182	40%
183-190	50%
191-199	60%
200-207	70%
208-218	80%
219-284	90%
≥ 285	99%

Newer GRACE 2.0 risk score for 1 year mortality have also been developed. Both calculators can be accessed online from www.outcomes.org/grace

5. ASCVD RISK SCORE

Estimates 10 year mortality risk from heart disease or stroke. From the ACC/AHA 2013 guidelines. Mainly to decide on statin use (indicated if ≥7.5% 10 year mortality risk)[5]. Used for age 40-79 years without ASCVD and LDL<190 mg/dl and not on LDL lowering therapy. Has been validated in various studies but shows some over estimation and underestimation certain races. Derivation is a complex equation and hence not discussed.

Variables
Age (40-79)
Diabetes
Sex
Race (White/African American/Other)
Systolic BP
Diastolic BP
Treatment for hypertension
Total cholesterol
HDL cholesterol
Smoker (Current/Former/Never)

6. CHA$_2$DS$_2$VASc SCORE

Most widely used AF stroke risk prediction tool. Update from the old CHADS2 score due to a large proportion of patients in the intermediate group. Developed in about 1000 patients in Birmingham in 2009 by Lip et al[6].

CHA$_2$DS$_2$VASC score	
CCF history	1
Hypertension	1
Age ≥65 years	1
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease	1
Age ≥75years	2
Sex (Female)	1

CHA$_2$DS$_2$VASc Score	Stroke Risk %
0	0
1	1.3
2	2.2
3	3.2

4	4.0
5	6.7
6	9.8
7	9.6
8	12.5
9	15.2

Intervention based on CHA$_2$DS$_2$VASc score	
0	No anticoagulation
1	Consider anticoagulation
≥2	Anticoagulation indicated

7. ATRIA (Anticoagulation and Risk factors in Atrial Fibrillation) STROKE RISK SCORE FOR AF

Another stroke risk predictor for AF patients. Developed from 10000 patients with 32000 patient-years of follow up off anticoagulation in 2013[7].

Risk factor		Points	
		Without stroke	With stroke
Age	≥85	6	9
	75–84	5	7
	65–74	3	7
	<65	0	8
Female		1	1
Diabetes mellitus		1	1
Chronic heart failure		1	1
Hypertension		1	1
Proteinuria		1	1
eGFR < 45 or ESRD		1	1

Risk group	ATRIA score	Stroke risk
Low risk	0-5	<1%
Intermediate risk	6	1-2%
High risk	>6	>2%

8. HAS-BLED SCORE

Risk factors that increase stroke risk in patients with atrial fibrillation mostly are risk factors for bleeding as well. HAS-BLED score was developed to predict 1 year risk of bleeding in patients with AF. Developed from about 4000 patients in Euro Heart Survey[8].

Risk Factor	Points
Hypertension (>160mmHg)	1
Abnormal Kidney/Liver function	1 each
Stroke history	1
Prior major bleeding or predisposition to bleeding	1
Labile INR	1
Elderly (age >65)	1
Drug increasing bleeding (aspirin, clopido-grel, NSAIDs) or alcohol use	1 each

HAS-BLED Score	Major bleeding risk
0	1.10%
1	3.40%
2	4.10%
3	5.80%
4	8.90%
5	9.10%
≥6	>9.10 %

HAS-BLED score was found to perform better than ATRIA and HEMORR$_2$HAGES score for predicting bleeding.

9. HEMORR$_2$HAGES

Developed from the national registry of AF with the data on 3700 patients of AF on warfarin using medicare data[9]. Has been validated in multiple studies. Quantifies bleeding risk over 100 patient years in percentage. Used ICD-9 codes for event identification. Wrong ICD-9 coding and out of hospital events not tracked. Main disadvantage is complexity of calculation. HEMORR$_2$HAGES score had the highest specificity compared to HASBLED and ATRIA bleeding scores.

Criteria	Points
Hepatic or renal disease	+1
Ethanol abuse	+1
Malignancy	+1
Older (age > 75)	+1
Reduced platelet count or function	+1
Rebleeding (Prior Bleed)	+2

Hypertension (uncontrolled)	+1
Anemia	+1
Genetic factors (CYP 2C9 single-nucleotide polymorphisms)	+1
Excessive fall risk	+1
Stroke	+1

HEMORR$_2$HAGES score	Bleeding risk (per 100 patient years)
0	1.9%
1	2.5%
2	5.3%
3	8.4%
4	10.4%
5-12	12.3%

HEMORR$_2$HAGES score	Risk category
1	Low risk
2-3	Intermediate risk
≥4	High risk

10. PRECISE DAPT SCORE

To predict out of hospital bleeding with dual antiplatelet therapy. Developed from about 15000 patient on DAPT[10] but increases bleeding. Guidelines support weighting bleeding risk before the selection of treatment duration, but no standardised tool exists for this purpose. A total of 14 963 patients treated with DAPT after coronary stenting-largely consisting of aspirin and clopidogrel and without indication to oral anticoagulation-were pooled at a single-patient level from eight multicentre randomised clinical trials with independent adjudication of events. Using Cox proportional hazards regression, they identified predictors of out-of-hospital Thrombosis in Myocardial Infarction (TIMI Uses age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding. Validated in the PLATO and BernPCI cohorts. Online calculators are available for easy calculation.

11. HCM SCD RISK CALCULATOR

Estimates 5 year SCD risk. Recommended in the 2014 ESC guidelines on HCM. A risk more than 4% at five years identified >70% of those HCM patients with SCD endpoint[11].

Predictor variable	Definition	Value
Age	Age at evaluation	In years
Family history of SCD	History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post- or ante-mortem diagnosis	yes = 1 no = 0
Maximal wall thickness	The greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles, and apex using parasternal short-axis plane using 2-D echocardiography at time of evaluation	mm
Fractional shortening	(LV end-diastolic dimension-LV end-systolic dimension)/ LV end-diastolic dimension measured by M-Mode or 2D echocardiography at time of evaluation	%
Left atrial diameter	Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation	mm
Maximal left ventricular outflow tract gradients	The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three- and five-chamber views. Peak outflow tract gradients were determined using the modified Bernouilli equation: Gradient $= 4V^2$, where V is the peak aortic outflow velocity	mmHg
Non-sustained ventricular tachycardia	≥3 consecutive ventricular beats at a rate of ≥120 bpm and <30 s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation	yes = 1 no = 0
Unexplained syncope	History of unexplained syncope at or prior to evaluation	yes = 1 no = 0

Uses a complex formula to predict SCD, for which online calculators are available. Should not be used in paediatric patients (<16 years), elite athletes, individuals with metabolic diseases (e.g. Anderson-Fabry disease) and syndromes (e.g. Noonan syndrome) or those with secondary indication for ICD.

Risk	ESC Recommendation for ICD
<4% (low risk)	Not indicated
≥4-<6% (intermediate risk)	May be considered
≥6% (high risk)	Should be considered

12. WELLS INDEX FOR PULMONARY EMBOLISM (PE)

Developed in 2001 based on studies on 900 patients with suspected pulmonary embolism[12]. Risk stratifies patients into a pretest low intermediate and high risk group (3 tier) or unlikely and likely (two tier), with each group having different plan for evaluation and confirming diagnosis. Although the initial study group had a high PE prevalence, Wells score has been validated in other groups with lower PE prevalence. Prevalence of PE in the high risk group was 37.5% in the original study and hence even in the high risk group about 2/3rd don't have PE.

Criteria	Points
Signs or Symptoms of DVT	3
No alternative first diagnosis	3
HR> 100 bpm	1.5
Immobilization (≥ days) or surgery in the last 4 weeks	1.5
Prior history of DVT or PE	1.5
Hemoptysis	1
Malignancy	1

Score	Risk / Probability
Three tier	
0 or 1	Low risk
2 to ≤6	Moderate risk
>6	High risk
Two tier	
≤4	Unlikely
≥5	Likely

Two tier model is currently preferred. In unlikely cases d-dimer is done to rule out PE. In d-dimer negative cases PE was found in 0.5%. CTPA is done for likely cases. 20% of likely cases had evidence of PE on CTPA.

13. PESI

PE severity index uses 11 clinical criteria to risk stratify diagnosed pulmonary embolism patients. Derived from a retrospective data of 10000 patients of PE based on 30 day mortality[15]. No laboratory criteria used. As it was derived from a cohort excluding terminal illness or renal failure, PESI should not be used in these group of patients.

	Criteria	Points
Demographics	Age (in years)	1 per year (1-100)
	Male sex	10
Comorbidities	Malignancy history	30
	Heart failure history	10
	Chronic lung disease history	10
Examination findings	HR >100 bpm	20
	SBP< 100 mmHg	30
	Respiratory rate ≥30/min	20
	Temperature <36 °C	20
	Altered mental status	60
	O2 saturation	20

PESI Class	Score	Mortality risk	Treatment plan
I (very low risk)	≤65	1.1%	Outpatient management can be considered
II (low risk)	66-85	3.1%	
III (intermediate risk)	86-106	6.5%	Hospitalization needed
IV (high risk)	106-125	10.4%	
V (very high risk)	>125	24.5%	Consider ICU care

14. REVISED CARDIAC RISK INDEX

To be used in patients (>18years) planned to undergo elective non-cardiac surgery. Not to be used for emergency surgeries. Developed from 1000 patient undergoing elective non-cardiac surgeries by Goldman et al in 1977 and the revised score was developed in 1999[14, 15].

Criteria	Points
High-risk surgery(Intraperitoneal; intrathoracic; Vascular)	+1
History of ischemic heart disease	+1
History of congestive heart failure	+1
History of cerebrovascular disease (TIA or stroke)	+1
Diabetes mellitus requiring insulin therapy	+1
Creatinine >2 mg/dL	+1

RCRI Score	MACE risk
0	3.9%
1	6.0%
2	10.1%
≥3	15%

Various validations studies and systematic review were done and found that the event rates were higher than that in the original study by upto 10 times. Pooled data from 5 studies and the corresponding risk is given in the table above. This was because of the development of high sensitivity troponin and BNP/NTBNP assays.

15. SCHWARTZ SCORE FOR LQTS

Uses criteria in 3 headings namely ECFG, history and family history to diagnose LQTS[16] This is an improvement on the previous 1985 criteria. Genetic studies showing low penetrance and normal or only slightly prolonged QTc in LQTS patients support the newer Schwartz criteria.

Heading	Criteria	Points
ECG Findings	A. QTc	
	≥480 ms	3
	460–479 ms	2
	450–459 ms (in males)	1
	B. QTc 4th minute of recovery from exercise stress test ≥480 ms	1
	C. Torsade de pointes	2
	D. T wave alternans	1
	E. Notched T wave in 3 leads	1
	F. Low heart rate for age	0.5
Clinical history	A. Syncope	
	With stress	2
	Without stress	1
	B. Congenital deafness	0.5
Family history	A. Family members with definite LQTS	1
	B. Unexplained sudden cardiac death below age 30 among immediate family members	0.5

Schwatrz score	Probability of LQTS
≤1	Low probability
1.5-3	Intermediate probability
≥3.5	High probability

These should be applied when patient is not on any medications known to prolong QTc. QTC must be calculated with the Bazett's formula for use in the ECG criteria.

16. SHANGHAI SCORE FOR BRUGADA SYNDROME

Uses criterias in 4 headings namely ECG, clinical history, family history and Genetic testing to diagnose Brugada syndrome (BrS). Was developed from the 2016 J-wave syndromes consensus report and further validated[17].

Headings	Criteria	Points
ECG findings	A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
	B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
	C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
Clinical history	A. Unexplained cardiac arrest or documented VF/ polymorphic VT	3
	B. Nocturnal agonal respirations	2
	C. Suspected arrhythmic syncope	2
	D. Syncope of unclear mechanism/unclear etiology	1
	E. Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
Family history	A. First- or second-degree relative with definite BrS	2
	B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
	C. Unexplained SCD <45 years in first- or second- degree relative with negative autopsy	0.5
Genetic	A. Probable pathogenic mutation in BrS susceptibility gene	0.5

Only the highest score in each heading should be used for scoring. At least one ECG finding must be present for diagnosis.

Shanghai Score	Probability of Brugada syndrome
≥3.5 points	Probable/definite BrS
2–3 points	Possible BrS
<2 points	Nondiagnostic

17. SHORT QT SYNDROME DIAGNOSTIC CRITERIA

Uses criteria in 4 headings namely ECG, clinical history, family history and genetics to diagnose SQTS. Being a rare disorder the criteria was developed from a cohort of 61 patients with SQTS by Gollob et al in 2011[18].

Headings	Criteria	Points
ECG findings	QTc <370ms	1
	QTc <350ms	2
	QTc <330ms	3
	Jpoint-Tpeak interval <120 milliseconds	1
Clinical history	History of sudden cardiac arrest	2
	Documented polymorphic VT or VF	2
	Unexplained syncope	1
	Atrial fibrillation	1
Family history	First- or second-degree relative with high probability of SQTS	2
	First- or second-degree relative with autopsy-negative sudden cardiac death	1
	Sudden infant death syndrome	1
Genetic	Genotype positive	2
	Mutation of undetermined significance in a culprit gene	1

Atleast one ECG criteria is needed to diagnose SQTS.

SQTS Score	Probability of SQTS
≥4 points	High probability
3 points	Intermediate probability
≤2 points	Low probability

The rest of the scores listed in the introduction will be discussed in the upcoming issue of KJC.

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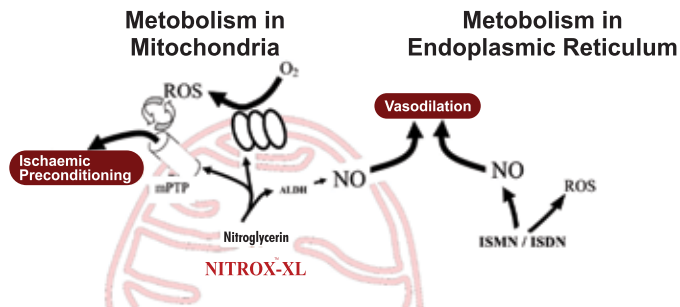
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