HEPATO-PULMONARY DISORDERS

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BACKGROUND

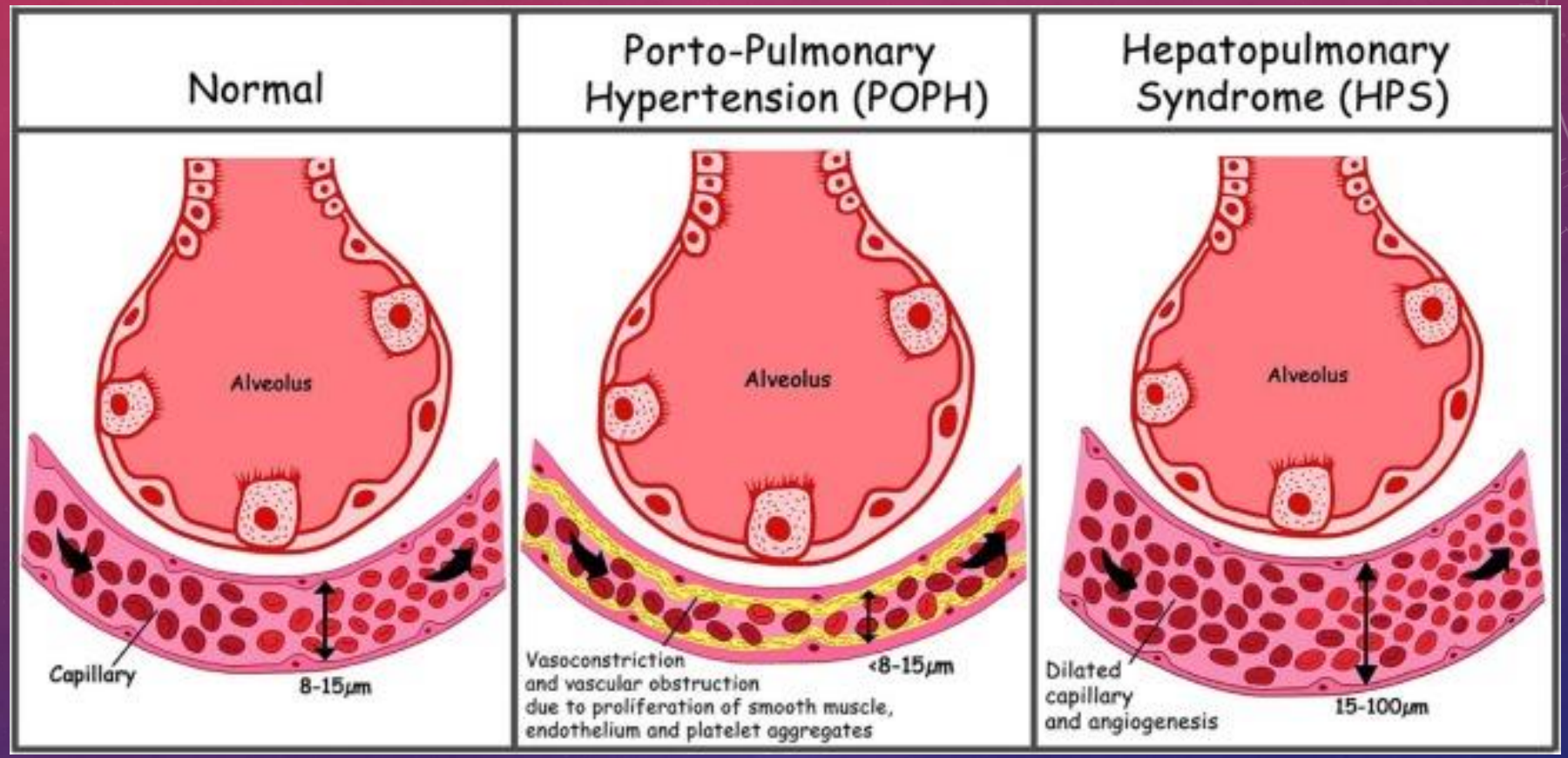
- In 1951, Mantz and Craige reported case -53 F year old expired for hematemesis
- Authors noted that the PA enlarged and exhibited forceful pulsations more characteristic of the aorta
- Subsequent autopsy revealed a stenotic portal vein, a portocaval shunt, and esophageal varices.
- Pulmonary arteries demonstrated intimal thickening, endothelial proliferation and thrombotic changes.
- In retrospect, this patient suffered - portopulmonary hypertension-a syndrome characterized by pulmonary hypertension in the setting of portal hypertension.

Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale

AMA Arch Pathol, 52 (1) (1951), pp. 91–97

HEPATO - PULMONARY

- (POPH) and hepatopulmonary syndrome (HPS) are two frequent complications of liver disease.
- Both conditions arise- lack of hepatic clearance of vasoactive substances
- These substances cause mainly pulmonary vascular remodeling and vasoconstriction in POPH
- In HPS the vasoactive mediators cause intrapulmonary shunts or IPVD (intrapulmonary vascular dilatation)


Normal
Porto-Pulmonary Hypertension (POPH)
Hepatopulmonary Syndrome (HPS)
Alveolus
Capillary
8-15μm
Alveolus
Vasoconstriction and vascular obstruction due to proliferation of smooth muscle, endothelium and platelet aggregates
<8-15μm
Alveolus
Dilated capillary and angiogenesis
15-100μm

POPH

- POPH is defined as pulmonary arterial hypertension associated with portal hypertension and no alternative cause of the PAH exists
- WHO classifies PoPH -Group 1 (pulmonary arterial hypertension): mPAP > 25 mmHg and pulmonary artery occlusive pressure (PaOP) < 15 mmHg at rest
- There are 5 groups of pulmonary hypertension

GROUPS FOR PULMONARY HYPERTENSION

Table 1: Classification Pulmonary Hypertension

Group 1	Pulmonary Arterial Hypertension
Group 2	PH from left-sided heart disease
Group 3	PH from chronic hypoxic lung disease
Group 4	PH from chronic blood clots
Group 5	Unclear multifactorial mechanisms (sarcoidosis, hematological disorders, etc)

EPIDEMIOLOGY

- PoPH accounts for 5%–10% of WHO Group 1 PH
- MC cause PoPH - liver cirrhosis, it can occur in patients with non-cirrhotic liver disease -10%
- Female sex and autoimmune liver disease - associated with a higher risk of PoPH

CLINICAL PRESENTATION

- Most patients with PPHTN have clinical evidence of both portal hypertension and PAH.
- Manifestations of portal hypertension typically precede those of PAH, from 2 to 15 years
- Stigmata of portal hypertension may be present including ascites, splenomegaly, esophageal varices, “caput medusae”. In addition, signs of c/c liver disease may be present.

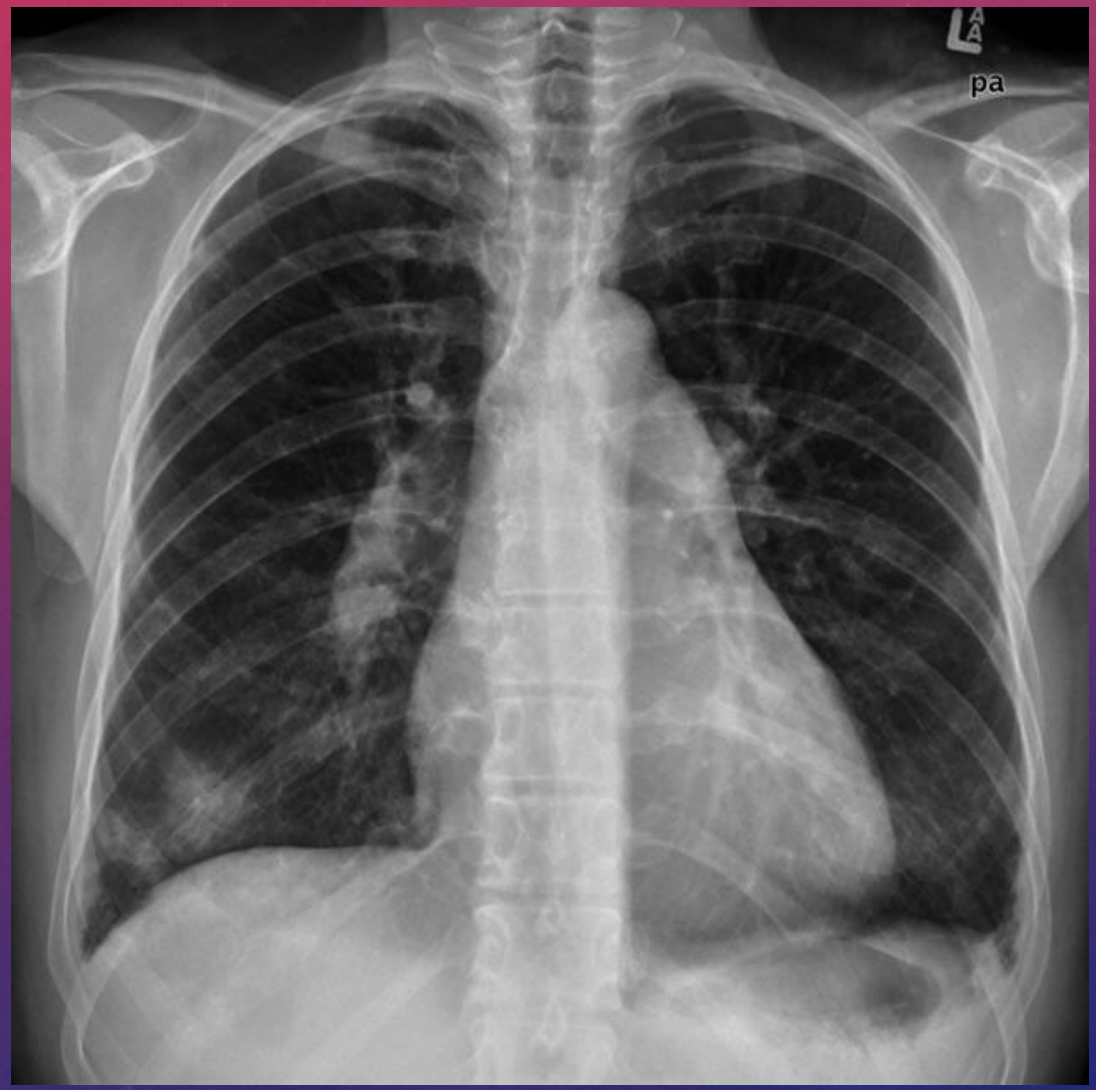
CF-PAH

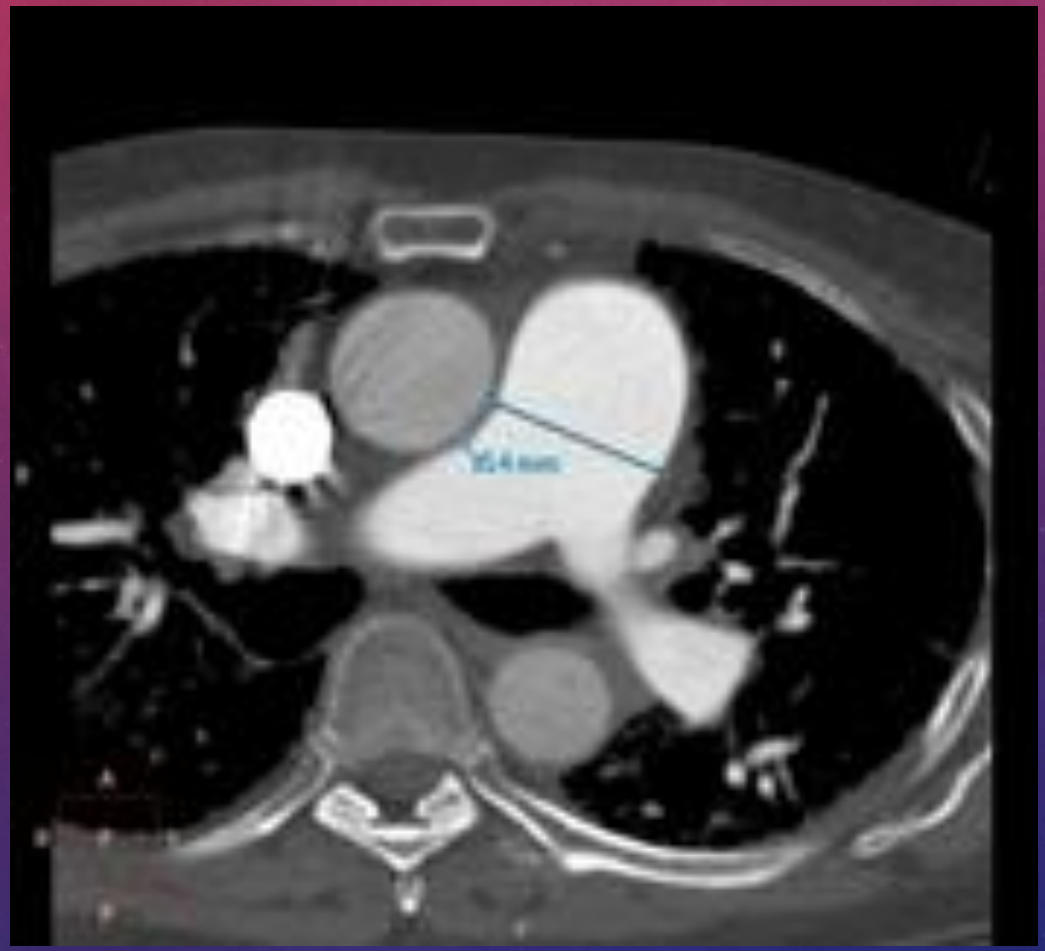
- Most common symptoms dyspnea on exertion.
- syncope, chest pain, fatigue, hemoptysis, and orthopnea .
- physical findings were an accentuated p2, a systolic murmur, and edema.

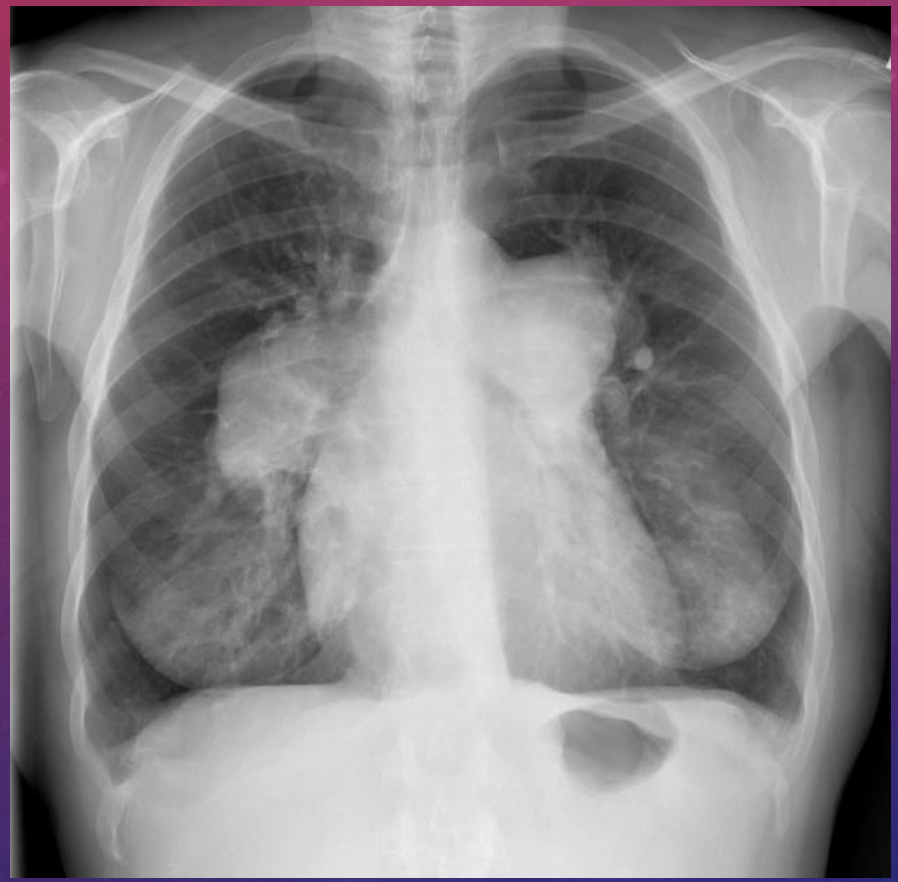
- Dependent pitting edema is a sign of right ventricular dysfunction.

- Chest radiographs demonstrate prominent pulmonary arteries and cardiomegaly in most patients.

- ECG often demonstrates right ventricular hypertrophy, right axis deviation, right bundle branch block.
- Pulmonary function tests demonstrating a reduced diffusing capacity


pa





DIAGNOSTIC EVALUATION

- It is imperative to diagnose PoPH early as progress to a life-threatening state and/or preclude LT
- All patients with portal hypertension + dyspnea should be screened for PoPH.

- A detailed diagnostic evaluation should be performed to exclude other potential causes of dyspnea

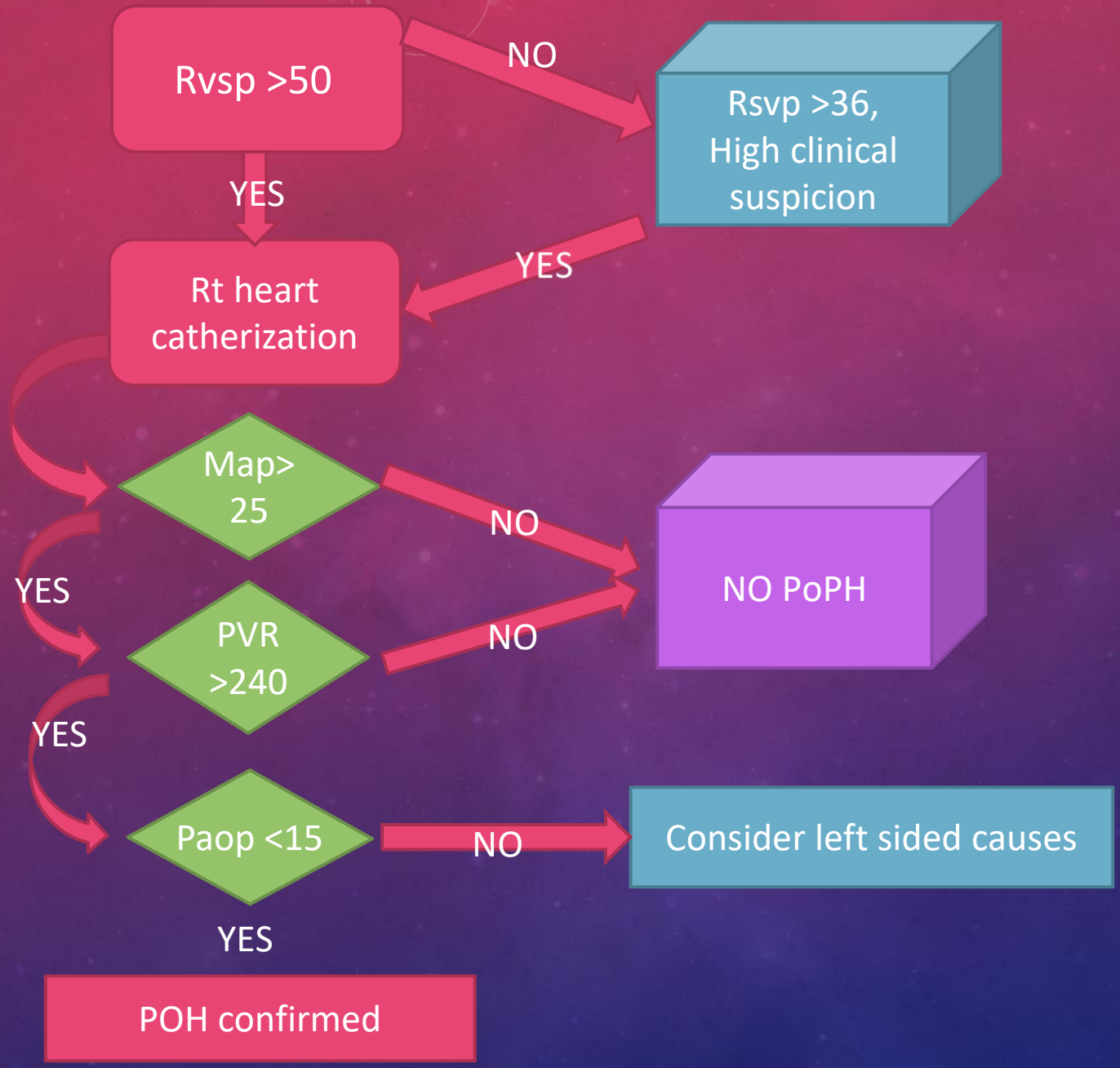
SCREENING

- 2D Echo provides an estimate of RVSP, but also evaluation of right-sided cardiac chamber

- In a prospective study of patients undergoing liver transplant evaluation,
- RVSP estimate of ≤30 mmHg on 2D Echo had a 100% sensitivity and negative predictive value for right-heart catheterization confirmed PH.
- RVSP > 50 mmHg has sensitivity and specificity of 97 and 77%, respectively

- Based on the available data, the ERS recommends that PAH should be considered unlikely if the 2D Echo estimate of RVSP is ≤ 36 mmHg and likely if the estimated RSVP is > 50 mmHg

I.O. Colle, R. Moreau, E. Godinho, et al.
Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study.Hepatology, 37 (2) (2003), pp. 401–409


Rvsp >50
NO
Rsvp >36, High clinical suspicion
YES
YES
Rt heart catherization
Map> 25
NO
NO PoPH
YES
PVR >240
NO
YES
Paop <15
NO
Consider left sided causes
YES
POH confirmed

DIAGNOSIS

The diagnosis of PoPH is established by right heart catheterization.

The following criteria are required:

- mean pulmonary arterial pressure >25 mmHg;
- PaOP <15 mmHg;
- PVR >240 dyn s cm^{-5}
- evidence of portal hypertension

CONVENTIONAL PAH THERAPIES

Long-term oxygen therapy

- Mild hypoxemia is common in PoPH.
- Hypoxemia can worsen pulmonary hypertension; therefore, supplemental oxygen therapy is recommended when the partial oxygen pressure (PaO_2) is < 60 mmHg at rest .

Diuretics

- Diuretics are often used for the treatment volume overload or ascites.
- RV is preload-dependent and excessive diuresis may decrease preload causing hypotension and systemic hypoperfusion.
- Therefore, diuretics should be cautiously used in PoPH.

DRUG OPTIONS

Treatment of PoPH is still not standardized

Reason- PoPH patients are typically excluded from PH trials;

Therefore, clinical data are meager concerning this condition

Summary of clinical trials on PoPH therapy.

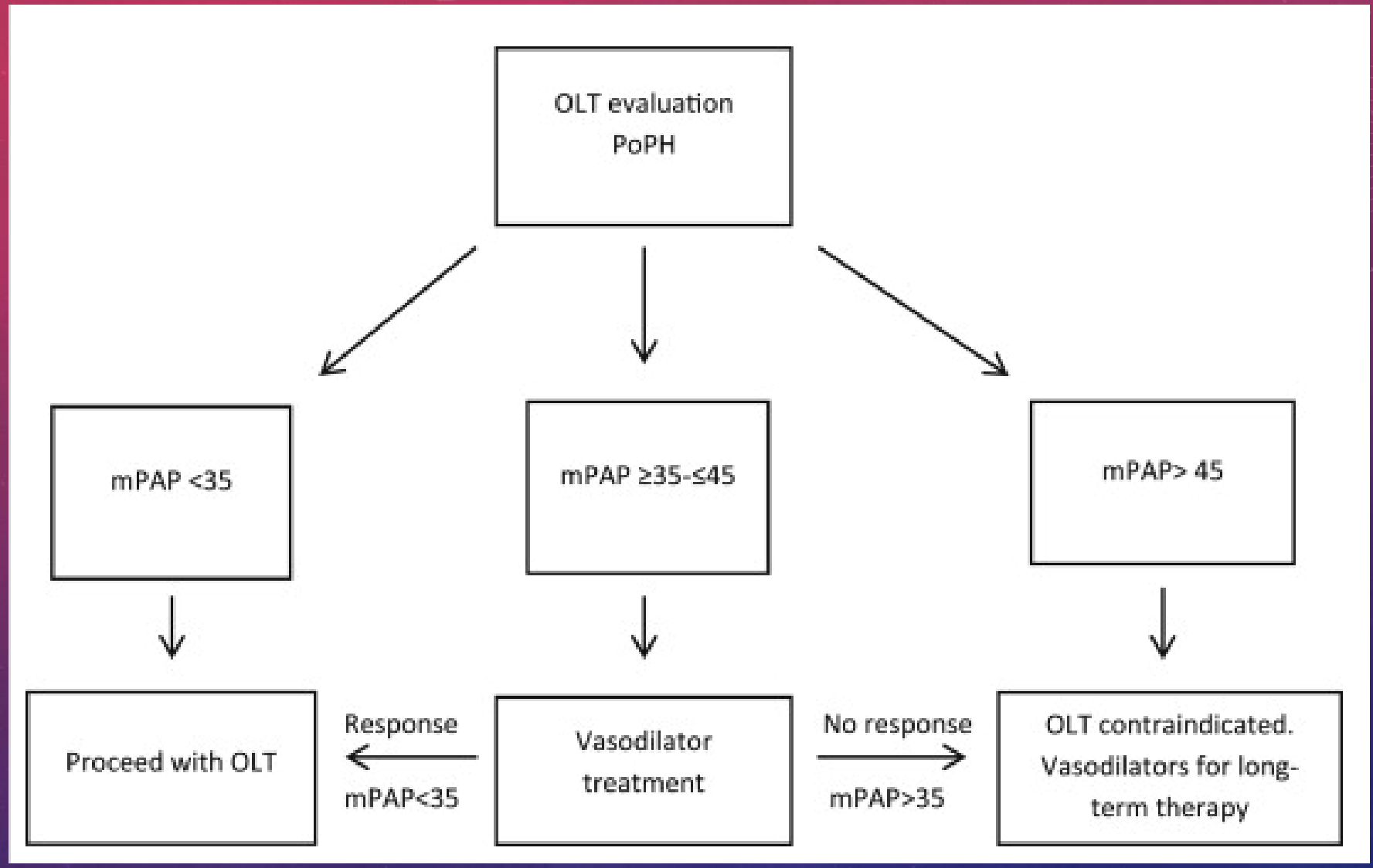
Vasodilators		N	Study design	Outcome	Reference
Prostanoids	Epoprostenol	15	Retrospective	Long-term improvement in hemodynamics	Krowka et el. [48]
		19	Retrospective	Improvement in hemodynamics, no difference in survival	Fix et al. [49]
		20	Prospective	Improved eligibility for successful OLT	Ashfaq et al. [50]
	Treprostinil	3	Case series	Improved hemodynamics	Sakai et al. [55]
	Ilioprost	21	Retrospective	Rapid reduction in PAP and PVR	Melgossa et al. [56]
		12	Retrospective	Long-term Improvement in NYHA class and exercise capacity	
ERA's	Bosentan	11	Prospective case series	Improve exercise capacity and hemodynamics	Hoeper et al. [60]
	Ambrisentan	13	Prospective case series	Improvement in hemodynamics PAP, PVR. No adverse effects on the liver	Cartin-Ceba et al. [63]
PDE-5 inhibitors	Sildenafil	14	Retrospective	Improved hemodynamics and exercise capacity	Reichenberger et al. [64]
	Tadalafil	1	Case report	Improvement in PA pressures.	Bremer et al. [67]

GUIDELINES

- The ERS Task Force Pulmonary-Hepatic Vascular Disorders Scientific Committee Guidelines state that OLT may be considered in mild pulmonary hypertension (mPAP < 35 mmHg) with good cardiac function

- In OLT candidates with moderate PH (mPAP 35–45 mmHg), vasodilator therapy should be initiated and OLT could be considered if the mPAP can be successfully lowered to or below 35 mmHg.

- OLT is contraindicated in PoPH patients with a mPAP ≥45 mmHg


OLT evaluation
PoPH
mPAP <35
mPAP ≥35-≤45
mPAP> 45
Proceed with OLT
Response
mPAP<35
Vasodilator treatment
No response
mPAP>35
OLT contraindicated. Vasodilators for long-term therapy

PROGNOSIS

- Individuals
- A dismal m

H even when matched for hemodynar

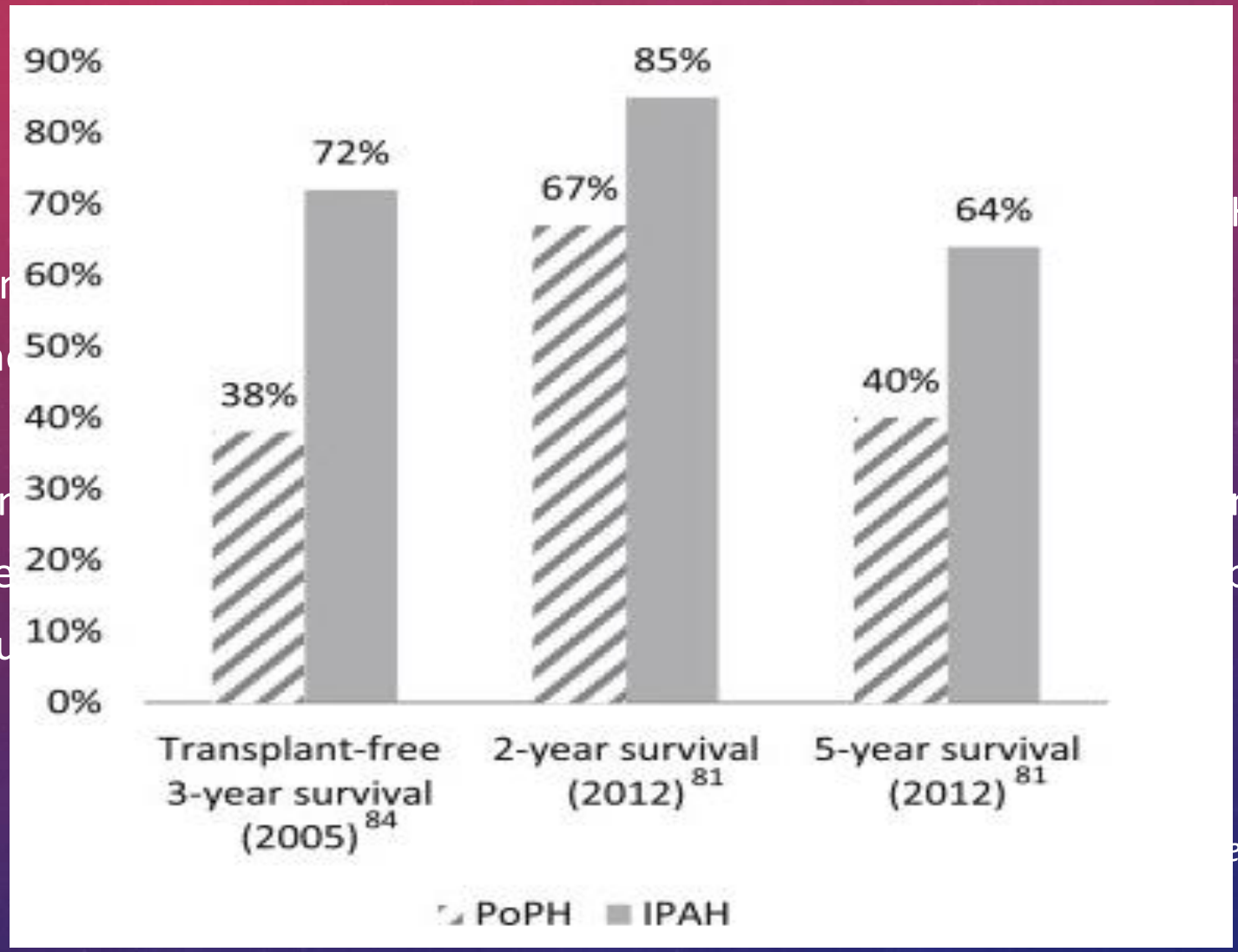
of specific vasodilator therapy .

- Swanson ar
- Overall, the

medical therapy and/or OLT .

by or OLT as compared to those who were u

either used alone.



ed with portopulmonary hypertension.

SUMMARY

- PoPH is an important complication of advanced liver disease.
- The etiology of PoPH remains unclear
- It has a major impact on suitability for liver transplantation.
- Timely diagnosis is essential to improve survival, and assess the perioperative risk of orthotopic liver transplantation.
- Treatment of PoPH is similar to the treatment of other types of PAH.
- Medical therapy and OLT improve survival in PoPH.

HEPATO PULMONARY SYNDROME

- triad of **liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation and evidence of intrapulmonary vascular dilatations**.

CF

- Most patients with HPS have symptoms and signs of chronic liver disease, none of which are sensitive or specific for HPS.
- These may include weakness, fatigue, anorexia, ascites, a large or small liver, splenomegaly, spider angiomata, palmar erythema, jaundice, asterixis, anasarca, nail changes, digital clubbing, hypertrophic osteoarthropathy, caput medusae, gynecomastia, and testicular atrophy

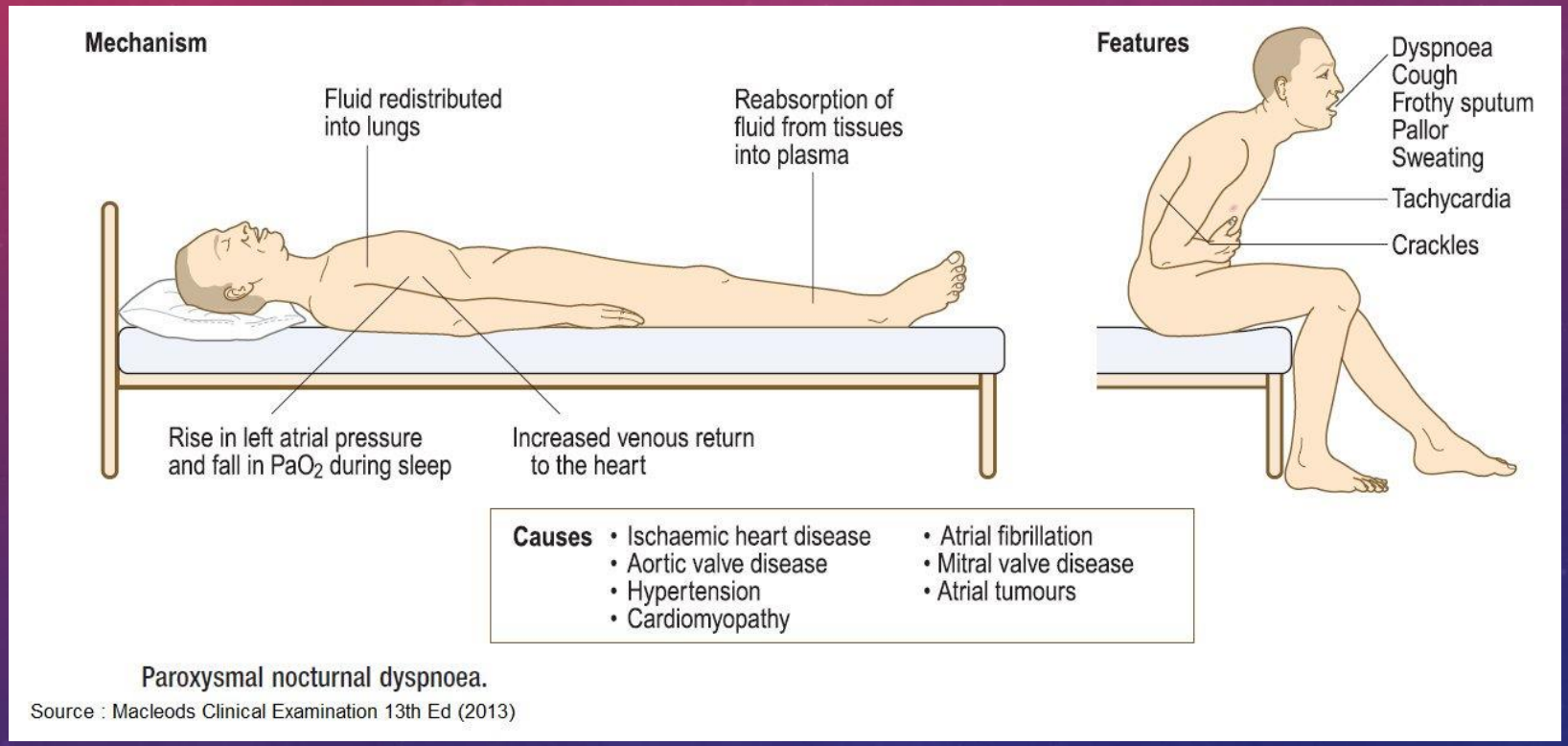
FEATURES OF INTRAPULMONARY VASCULAR DILATATIONS

- **Dyspnea** — Most patients with HPS eventually develop dyspnea on exertion, at rest, or both
- **Platypnea and orthodeoxia** — Platypnea and orthodeoxia are classic manifestations that are more specific for HPS, but not pathognomonic
- Platypnea
- Orthodeoxia – Orthodeoxia refers to a decrease in the arterial oxygen tension (by more than 4 mmHg [0.5 kPa]) or arterial oxyhemoglobin desaturation (by more than 5 percent) when the patient moves from a supine to an upright position, which is improved by returning to the recumbent position.

ORTHOPNEA

- Orthopnea is due to increased distribution of blood to the pulmonary circulation when a person lies flat or closer to a horizontal position.
- Increase in the right sided venous return. In a normal person, this redistribution of blood has little effect on respiratory function as the left ventricle has the adequate capacity to suddenly increase its stroke volume (as a result of Frank-Starling mechanism).
- In a person with heart failure, the left ventricle has an inadequate capacity to respond to increased arrival of blood from the pulmonary circulation. This leads to the pooling up of blood in the pulmonary circulation.
- The increased intra-parenchymal pulmonary intravascular pressure can also result in hydrostatic pressure related fluid transudation into the alveoli, thus causing pulmonary edema and further worsening shortness of breath.
- Thus, shortness of breath is commonly experienced after a reasonably short time lying near to flat for a person with left ventricular failure

PND



Paroxysmal nocturnal dyspnoea.

Source : Macleods Clinical Examination 13th Ed (2013)

- Platypnea is an increase in dyspnea that is induced by moving into an upright position and relieved by recumbency.

- It is hypothesized that platypnea and orthodeoxia in HPS are caused by preferential perfusion of intrapulmonary vascular dilatations (IPVDs; which disproportionately occur in the lung bases) when the patient is upright [56]. Although these manifestations are suggestive of HPS, other conditions can present with similar symptoms.

CLINICAL STATES ASSOCIATED WITH THE PLATYPNEA-ORTHODEOXIA SYNDROME

- :
- **Intracardiac right-to-left shunts** (patent foramen ovale or atrial septal defect)
  - After pulmonary resection (eg, pneumonectomy, lobectomy)
  - Associated cardiac abnormality (eg, aortic aneurysm, pericardial effusion)
  - Associated skeletal deformity (kyphoscoliosis)
- **Intrapulmonary right-to-left shunts**
  - **congenita**l: *Osler-Weber-Rendu* syndrome(characterized by pulmonary AV malformations-Pulmonary AVMs may cause enough right-to-left shunting)
  - **acquired**: vascular dilations in Hepatopulmonary syndrome
- **Hepatopulmonary syndrome**
- **Pulmonary diseases**
  - Chronic obstructive pulmonary disease
  - Pulmonary embolism

- It is hypothesized that platypnea and orthodeoxia in HPS are caused by preferential perfusion of intrapulmonary vascular dilatations (IPVDs; which disproportionately occur in the lung bases) when the patient is upright . Although these manifestations are suggestive of HPS, other conditions can present with similar symptoms.

DIAGNOSTIC EVALUATION

- HPS should be suspected in patients with chronic liver disease who have dyspnea, platypnea/orthodeoxia, spider nevi, and/or evidence of impaired oxygenation, such as a peripheral arterial oxygen saturation <96 percent

TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY (TTCE)

- Under normal resting circumstances, the contrast opacifies only the right heart chambers because it is filtered by the pulmonary capillary bed . However, the contrast may opacify the left heart chambers if a right-to-left intracardiac or intrapulmonary shunt is present.
- Intracardiac shunt – contrast (microbubbles) generally appears in the left atrium within one cardiac cycle after its appearance in the right atrium.
- ●Intrapulmonary shunt – contrast generally appears in the left heart three to eight heart beats after its appearance in the right atrium, though even later appearance has been described [69].
- ●Indeterminate location – contrast appears in the left atrium within one to three cardiac cycles.

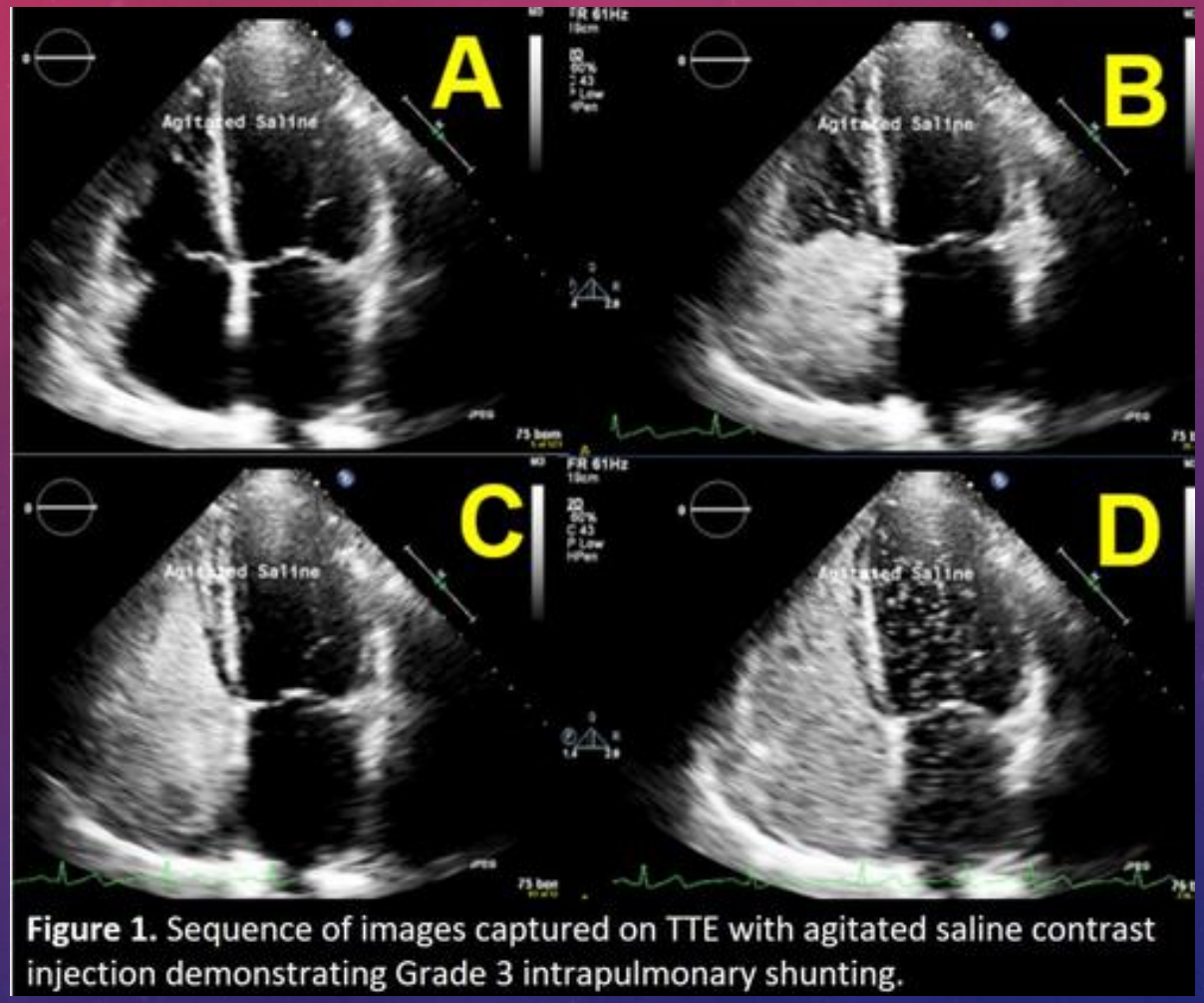


Figure 1. Sequence of images captured on TTE with agitated saline contrast injection demonstrating Grade 3 intrapulmonary shunting.

- **GRADING DISEASE SEVERITY**Most experts use the following grading system in those with an alveolar-arterial (A-a) oxygen gradient ≥15 mmHg (2 kPa) (table 3) [17,52]:
- ●Mild – Arterial oxygen tension (PaO_2) ≥80 mmHg (10.7 kPa) while breathing room air
- ●Moderate – A PaO_2 ≥60 mmHg and <80 mmHg (≥8 kPa and <10.7 kPa) while breathing room air
- ●Severe – A PaO_2 ≥50 mmHg and <60 mmHg while breathing room air
- ●Very severe – A PaO_2 <50 mmHg (6.7 kPa) while breathing room air or a PaO_2 <300 mmHg (40 kPa) while breathing 100 percent oxygen.

	HPS	PPHTN
Symptomatology	Progressive dyspnoea	Progressive dyspnoea
		Chest pain
		Syncope
Clinical examination	Cyanosis	No cyanosis
	Finger clubbing	RV heave
	Spider angiomas (?)	Pronounced P2 component
ECG findings	None	RBBB
		Rightward axis
		RV hypertrophy
Arterial blood gas levels	Moderate–to–severe hypoxaemia	No/mild hypoxaemia
Chest radiography	Normal	Cardiomegaly
		Hilar enlargement
CEE	Always positive; left atrial opacification for >3–6 cardiac cycles after right atrial opacification	Usually negative; however, positive for <3 cardiac cycles (if atrial septal defect or patent foramen ovale exists)
^{99m}TcMAA shunting index	≥6%	<6%
Pulmonary haemodynamics	Normal/low PVR	Elevated PVR
		Normal mPAOP
Pulmonary angiography	Normal/"spongy" appearance (type I)	Large main pulmonary arteries
	Discrete arteriovenous communications (type II)	Distal arterial pruning
OLT	Always indicated in severe stages	Only indicated in mild–to–moderate stages

HEPATIC HYDROTHORAX

- Hepatic hydrothorax refers to the presence of a pleural effusion (usually >500 mL) in a patient with cirrhosis who does not have other reasons to have a pleural effusion (eg, cardiac, pulmonary, or pleural disease)

- Hepatic hydrothorax occurs in approximately 5 to 15 percent of patients with cirrhosis.
- Patients who develop hepatic hydrothorax are more likely to have ascites, hepatic encephalopathy, acute kidney injury (AKI), and increased risk of mortality

PATHOGENESIS

- Although the exact mechanisms involved in the development of hepatic hydrothorax are incompletely understood, it probably results from the passage of ascites from the peritoneal cavity into the pleural cavity through small diaphragmatic defects.

- Hepatic hydrothorax becomes apparent when the absorptive capacity of the pleural space is exceeded.

WHICH SIDE?

- The diaphragmatic defects are more often found in the right hemidiaphragm, likely due in part to the fact that the left hemidiaphragm is thicker and more muscular.
- Hepatic hydrothorax develops on the right side in approximately 73 to 85 percent of patients, on the left side in approximately 13 to 17 percent, and bilaterally in approximately 8 to 24 percent

DIAGNOSIS

- The diagnosis of hepatic hydrothorax includes documentation of a pleural effusion and exclusion of alternative causes for the effusionDiagnostic tests that should be performed on the pleural fluid include
- ●Cell count and differential
- ●Gram stain
- ●Culture
- ●Protein, albumin, lactate dehydrogenase (LDH), and bilirubin concentrations
- ●Pleural fluid pH

- Pleural effusions deriving from portal hypertension are transudative in nature and therefore similar to the ascitic fluid, with a low protein concentration (<2.5 g/dL) [1] and with a serum-to-pleural fluid albumin gradient >1.1 g/dL

MANAGEMENT

- Treatment of hepatic hydrothorax is similar to the treatment of ascites .

- Management then includes dietary sodium restriction and diuretics.
- TIPS/ **Pleurodesis**
- In addition, patients with confirmed hepatic hydrothorax should be referred for liver transplantation if they are otherwise suitable candidates.

CHEST TUBES

- Chest tubes should not be placed for the treatment of hepatic hydrothorax (though they may be needed for patients with spontaneous bacterial empyema (SBEM) and frank pus, or in patients undergoing pleurodesis). Placement of chest tubes in patients with hepatic hydrothorax can result in massive protein and electrolyte depletion, infection, renal failure, and bleeding