

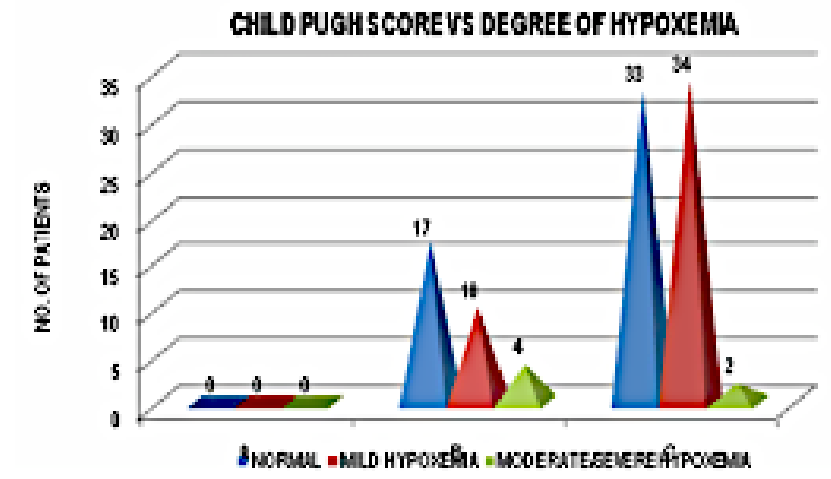
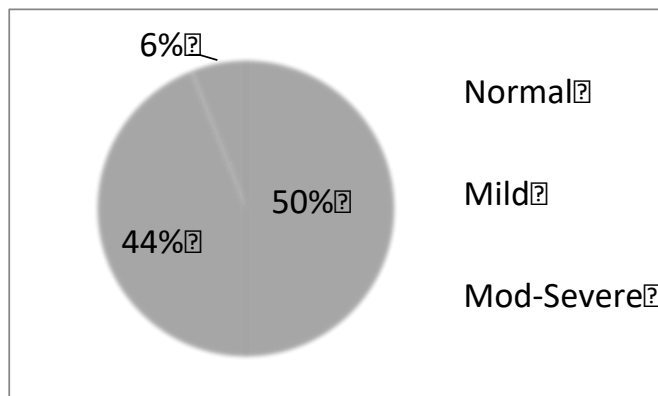
The Lungs in Liver Disease



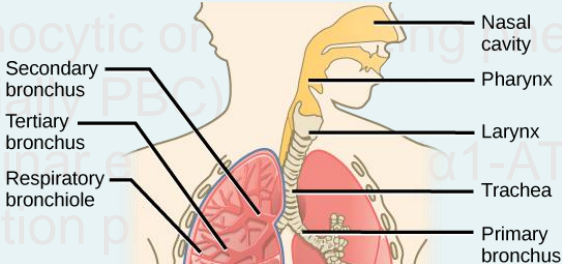

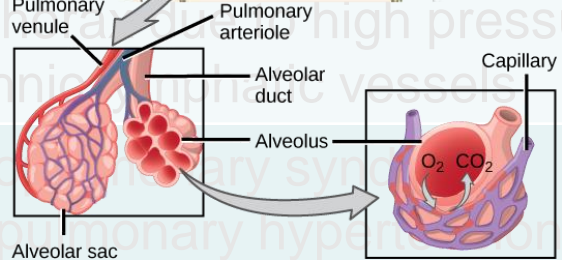
Andrew Berman, MD
Rutgers, New Jersey Medical School

Hypoxemia is common in advanced liver disease

- 11-69% of pts with chronic liver disease have some degree of hypoxemia
- Severe hypoxemia uncommon
- ~50% of Child-Pugh C pts with cirrhosis had hypoxemia
- Lack of correlation with pulmonary symptoms: asymptomatic hypoxemia



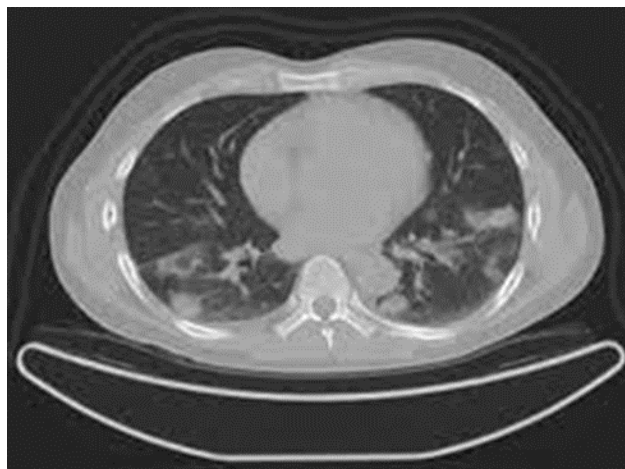
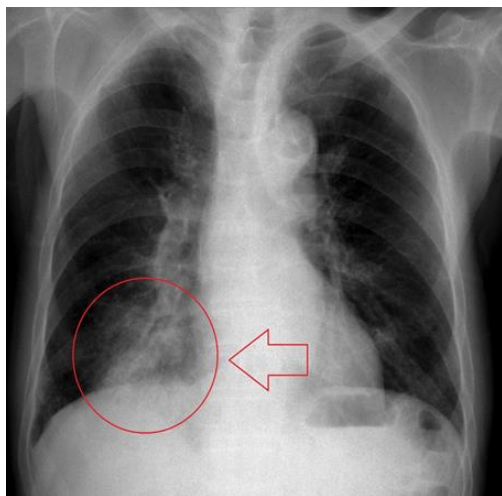
Advanced liver disease and pulmonary consequences

Location of Disorder	Consequences
Parenchyma	 <ul style="list-style-type: none"> -Lymphocytic or neutrophilic pneumonia (especially PBC) -Panacinar emphysema (α1-AT deficiency) -Aspiration pneumonia
Pleura or diaphragm	 <ul style="list-style-type: none"> -Hepatic hydrothorax -Massive ascites pushing up diaphragm -Chylous pleural effusion -High pressure in splanchnic vessels
Pulmonary vasculature	 <ul style="list-style-type: none"> -Hepatic hydrothorax -Porto-pulmonary hypertension

NEJM. 2008. 358:2378-87

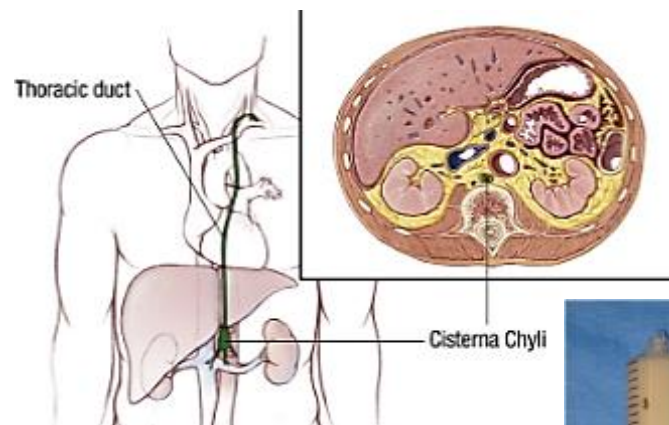
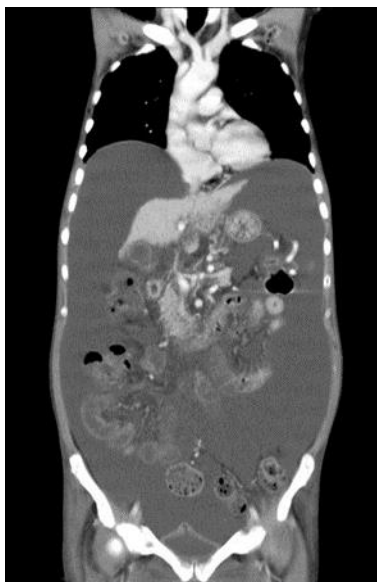
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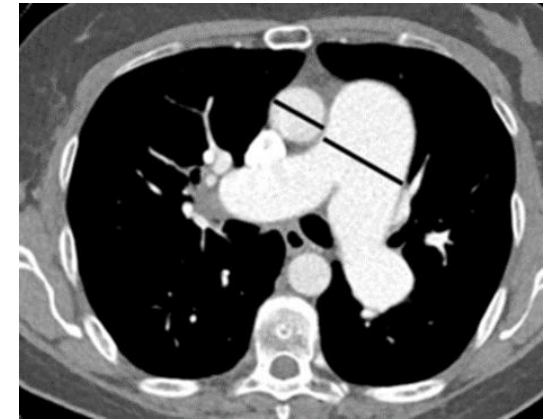
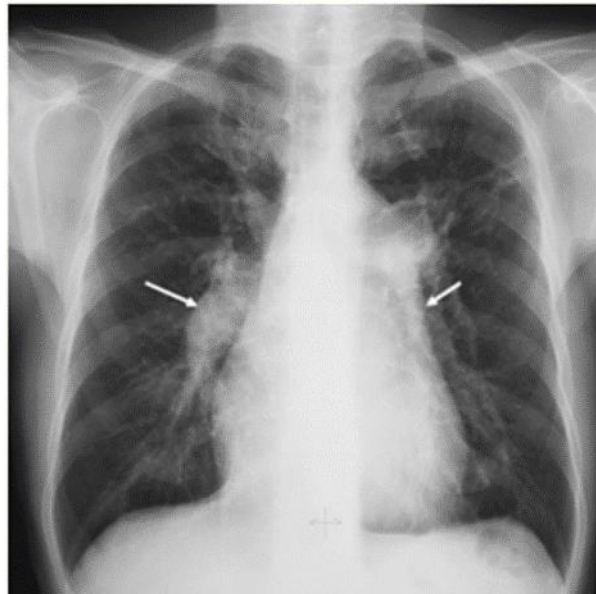
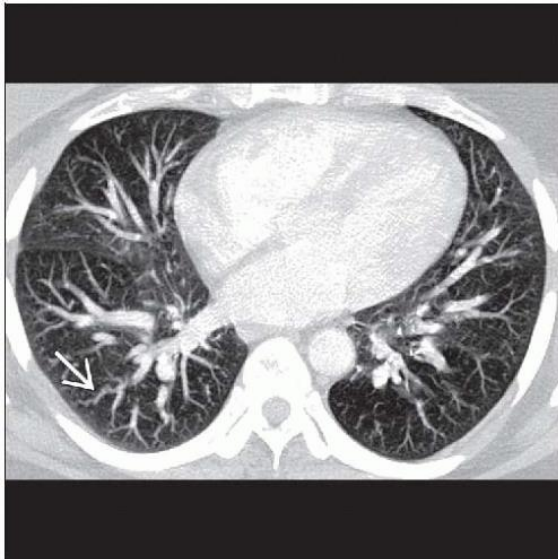
Advanced liver disease and pulmonary consequences

Location of Disorder	Consequences
Pleura or diaphragm	<ul style="list-style-type: none"> -Hepatic hydrothorax -Massive ascites pushing up diaphragm -Chylothorax due to high pressure in splanchnic lymphatic vessels



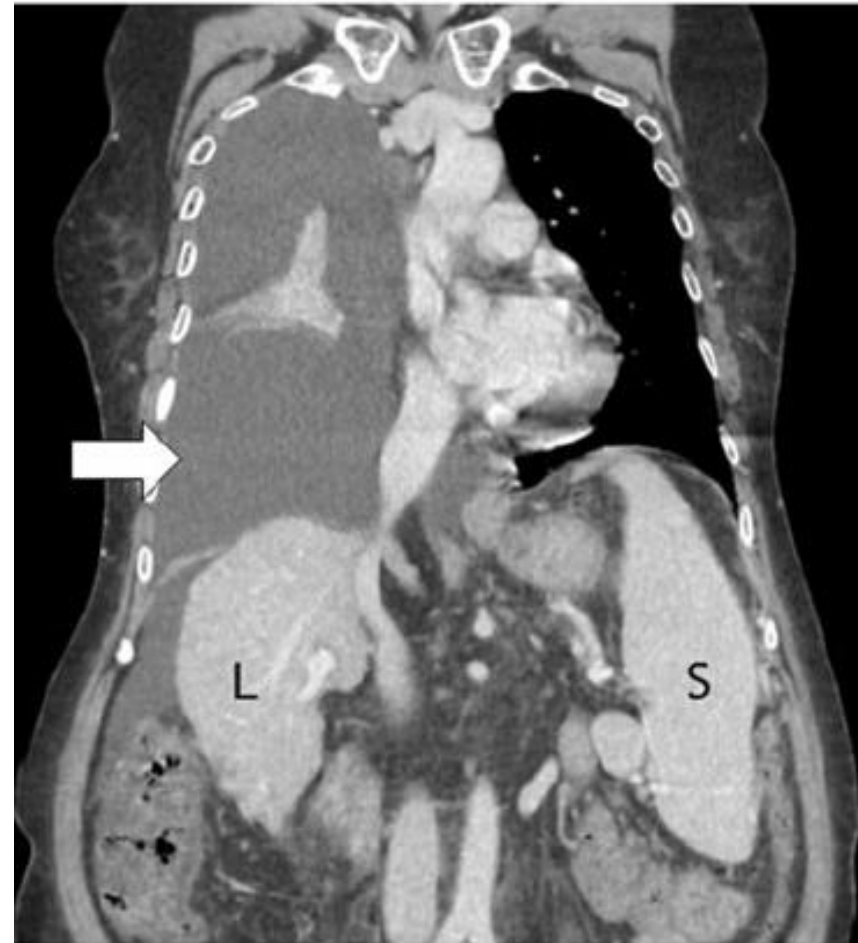
Advanced liver disease and pulmonary consequences

Location of Disorder	Consequences
Pulmonary vasculature	<ul style="list-style-type: none"> -Hepatopulmonary syndrome -Porto-pulmonary hypertension



Hepatic hydrothorax

- 5-15% patients with cirrhosis and portal hypertension
- Pressure gradient favors movement of ascitic fluid via diaphragmatic defects
- Right side=85%
- Relatively small amounts of fluid in the pleural space can lead to severe sx's and hypoxia (in contrast to ascites)
- Usually greater than 500cc



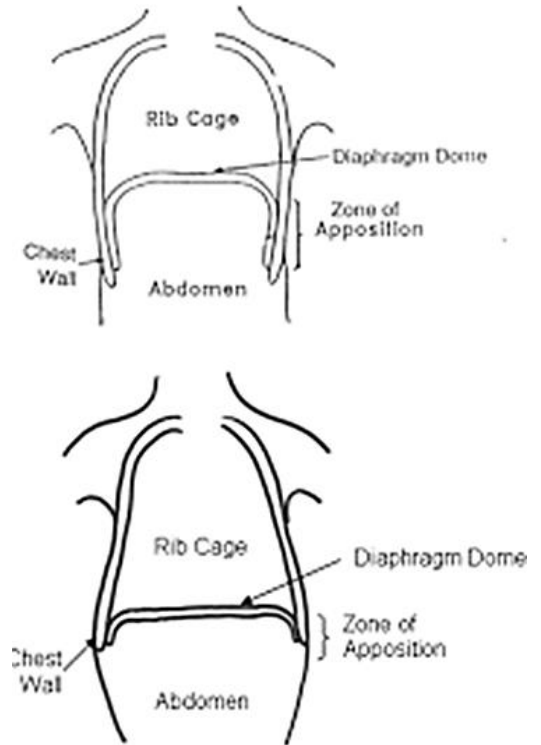
Hepatic hydrothorax: diagnostic thoracentesis

- Transudative
- Can have a diagnosis other than hepatic hydrothorax:
 - SBE: Spontaneous Bacterial Empyema (13-16%)
 - infection of the pleural space in patients with hepatic hydrothorax in the absence of pneumonia
 - 40% SBE occurs in the absence of peritonitis (it's not SBP)
 - rx: antibiotics usually without chest tube drainage
 - mortality rate ~ 20%
 - Tuberculosis
 - Malignancy



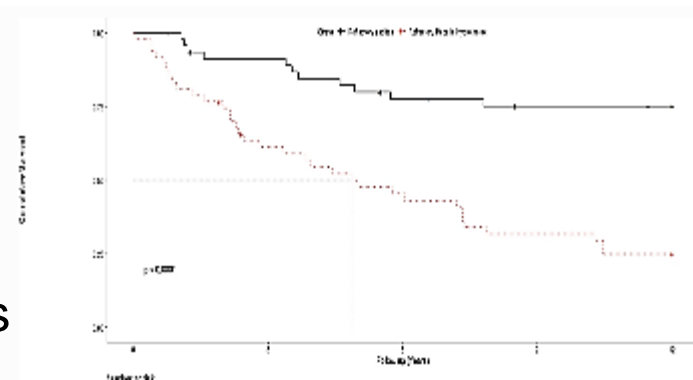
Hepatic hydrothorax: management

- Sodium restriction (<2gm/day)
- Diuretics
- Avoid beta-blockers
- Therapeutic thoracentesis
 - Paracentesis should be done prior to thoracentesis to improve respiratory mechanics and minimize the recurrence of hepatic hydrothorax immediately after thoracentesis
 - Albumin support is not usually necessary as the volume of fluid removed is relatively small



Hepatic hydrothorax: refractory

- ~20% of pts (though many nonadherent to rx)
- Serial thoracentesis
- TIPS if no contraindications
- Liver transplant is the definitive treatment
 - No MELD exception in the majority of cases
- Indwelling pleural catheters
 - Generally avoided due to complications and increased mortality
 - protein and electrolyte depletion
 - increase infection risk
 - renal insufficiency
 - Bridge to TIPS or transplant
 - Role in palliative management
 - Attempt pleurodesis

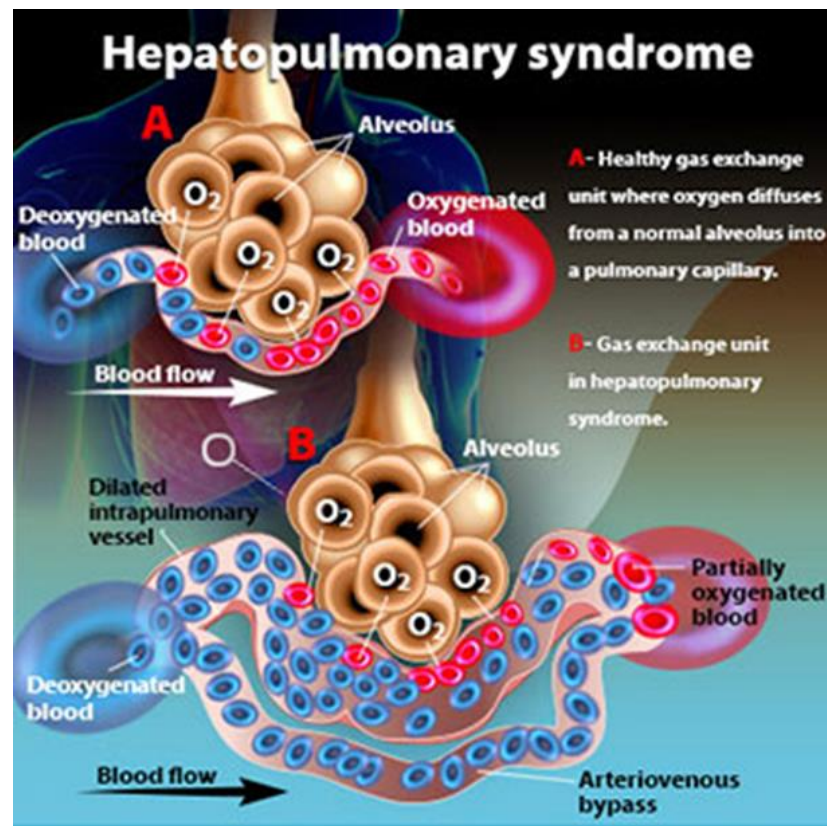


Digestive Diseases Sciences, 2022



Hepatopulmonary Syndrome

- Average prevalence is ~ 20%
- Diagnosis:
 - 1) Liver disease
 - Occurs in pts with portal hypertension with/without cirrhosis
 - Mostly chronic (not acute) liver disease
 - 2) Increased alveolar-arterial gradient while breathing room air
 - 3) Intrapulmonary vascular abnormalities: precapillary and capillary dilation and occasionally direct arteriovenous connections



Hepatopulmonary syndrome: physical exam

Platypnea-orthodeoxia

Intrapulmonary shunt

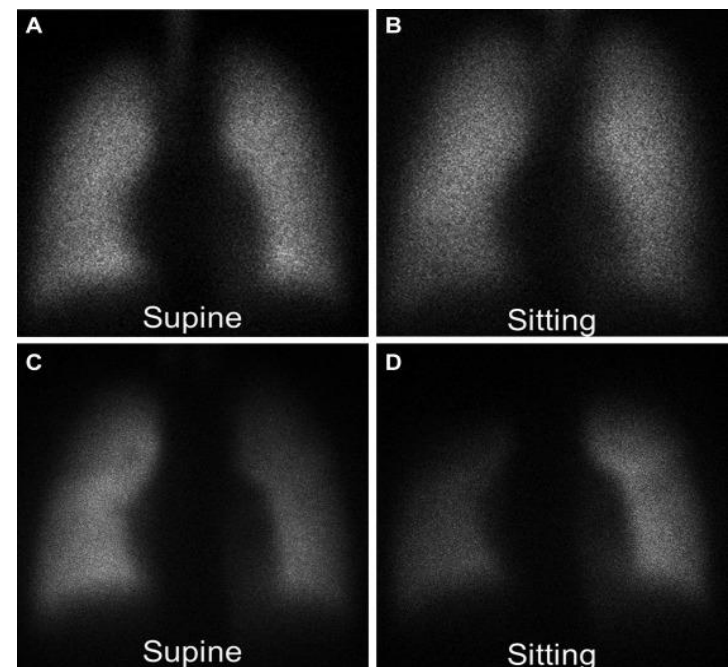
- Hepatopulmonary syndrome
- Pulmonary AVMs

Intracardiac Rt -> Lt shunts

- PFO
- ASD
- Rt atrial compression
- Constrictive pericarditis
- PE

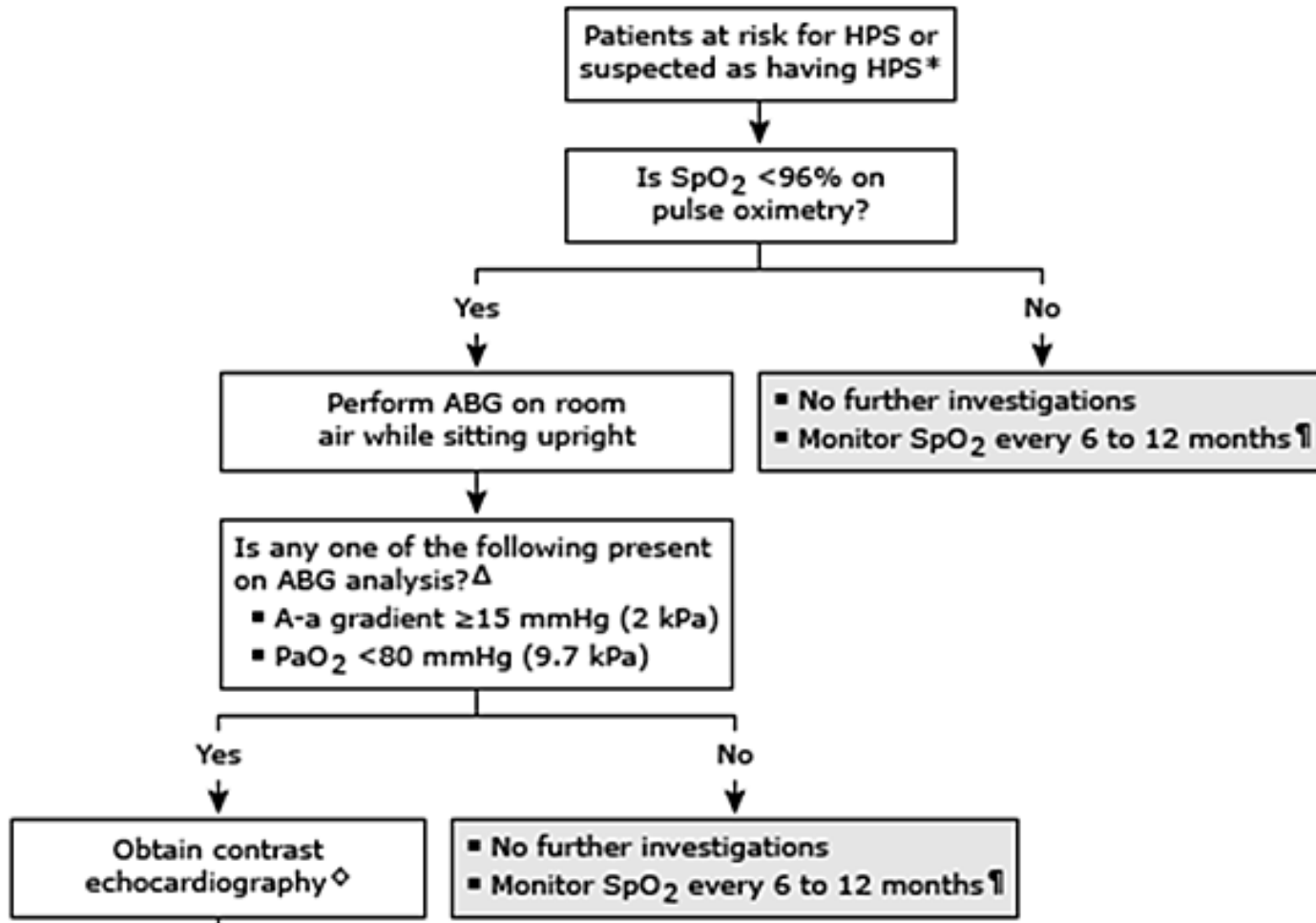
Severe V/Q mismatch

- COPD
- ILD

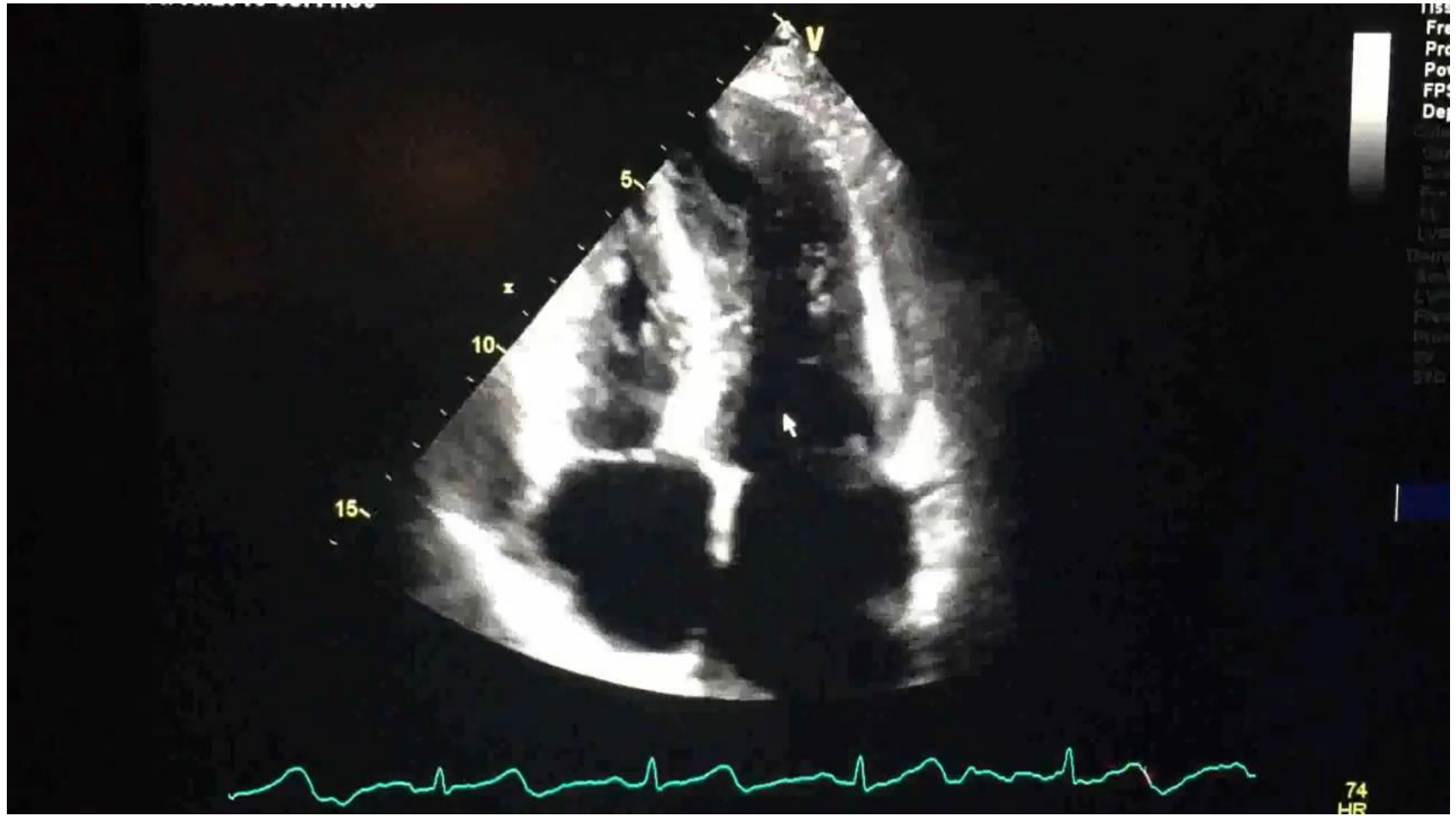


Can J Card. 2020. 36(4):590

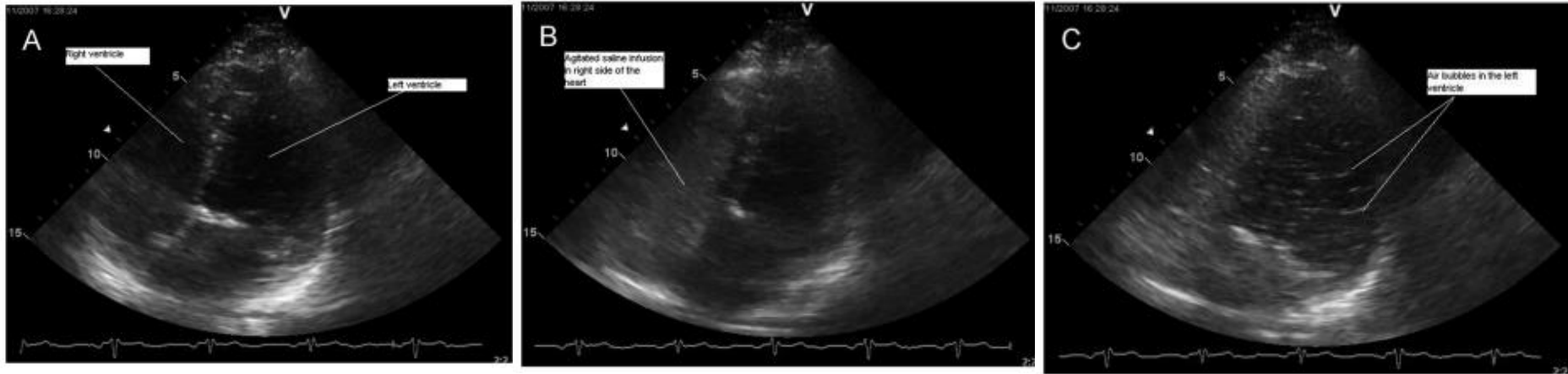
Diagnostic algorithm for hepatopulmonary syndrome



Contrast echocardiography

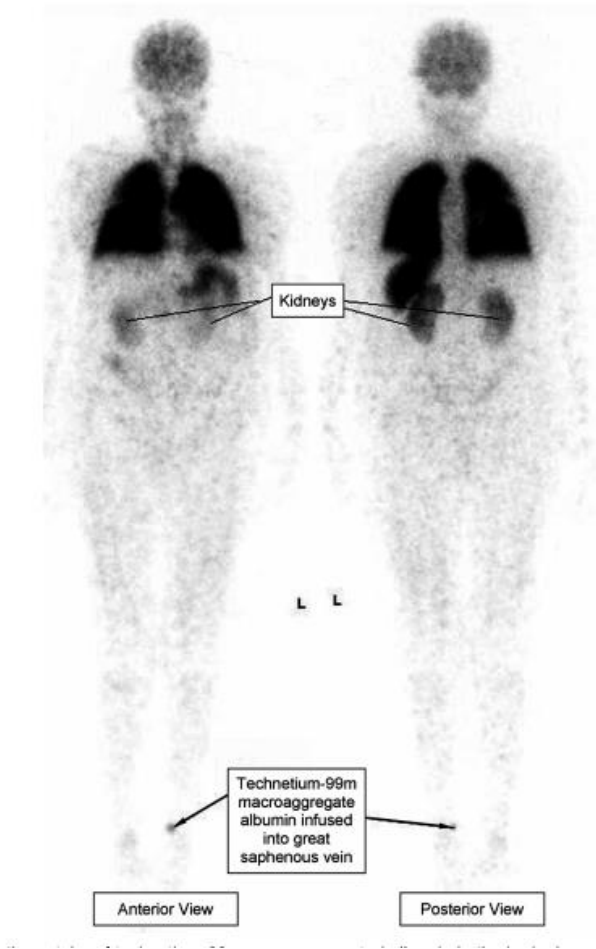


Contrast echocardiography



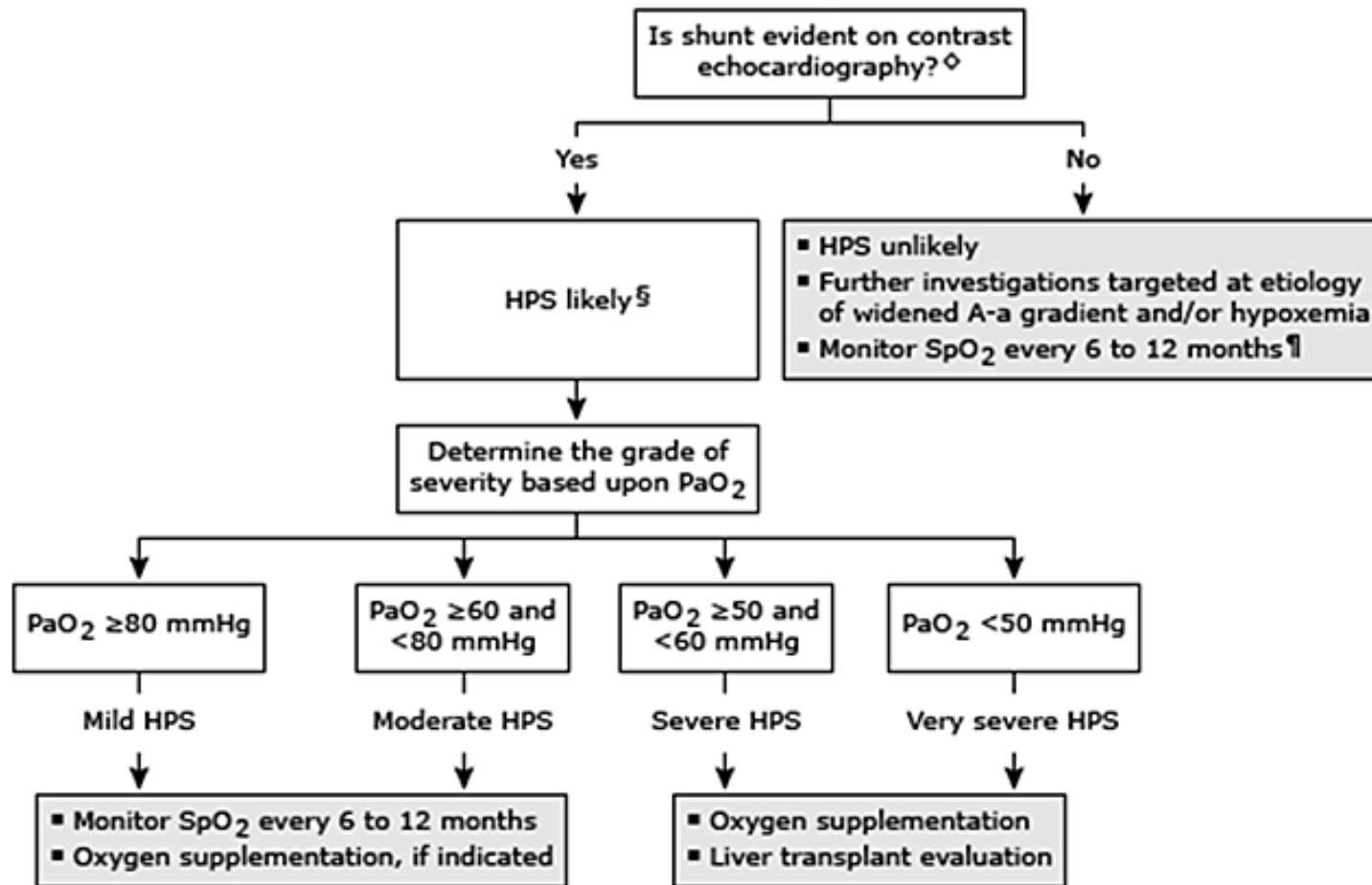
- A: Normal 4 chamber view
- B: Right side shows bubbles in agitated saline
- C: Bubbles in agitated saline in left heart after 6 beats

Lung-perfusion scan: Tc-99m-labeled macroaggregated albumen



- Less sensitive than contrast echo
- Cannot differentiate location of shunt
- Uptake of Tc-99m by the kidneys and/or brain suggest that the macroaggregates passed through either an intrapulmonary or intracardiac shunt
- Can quantify shunt: proportion of Tc-99m taken up by the kidneys and brain (normal brain uptake is $< 6\%$)

Diagnostic algorithm for hepatopulmonary syndrome

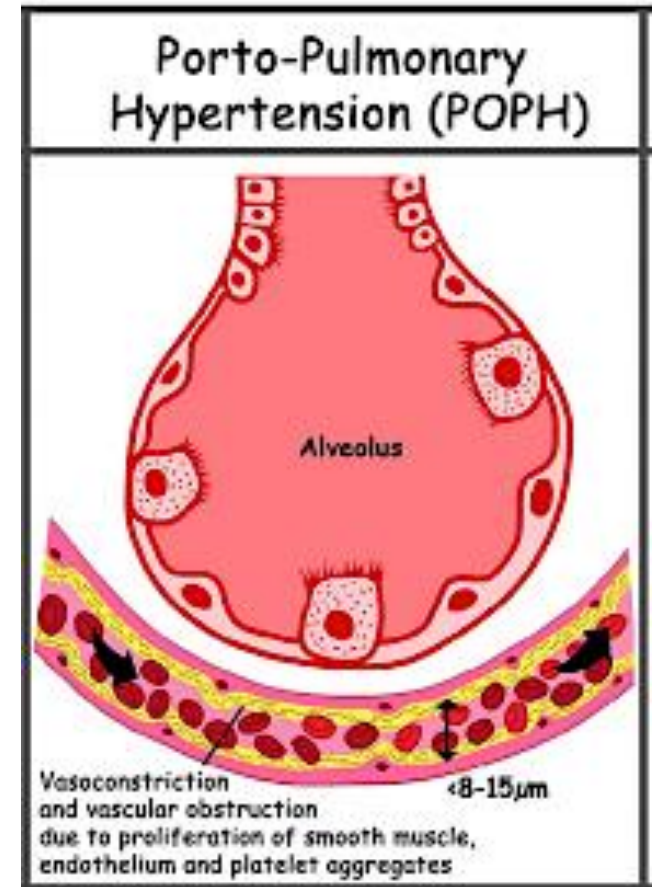


Hepatopulmonary Syndrome: transplant

- Liver transplant is the only known effective rx
- Most pts have complete resolution of HPS within a year
- MELD exception points for HPS: PaO₂ of ≤60 mmHg
- HPS pts have high transplant rate in 1st 12 months of listing
- Pre-transplant: severely decreased DLCO on pulmonary function testing portends a poor prognosis
- Pre-transplant initial PaO₂ ≤ 44 associated with worse post-transplant survival [though median survival ~11.5 years, with group separation occurring at 2.6 years, JHep Rep, 2021]
- Patients with a PaO₂ <45 vs those with a PaO₂ 45–50 more often died from cardiovascular causes rather than respiratory

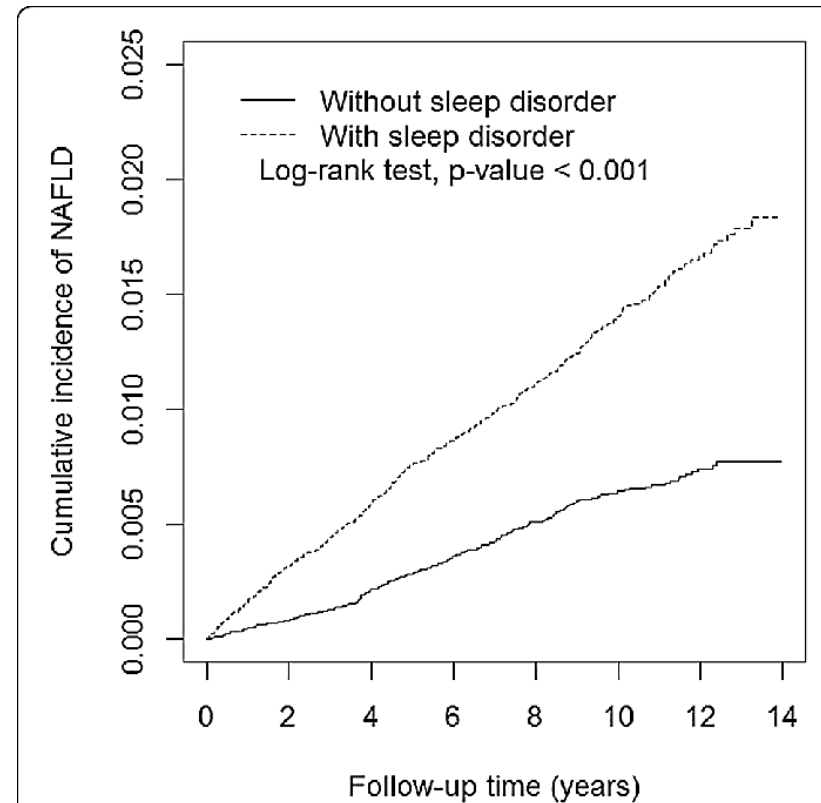
Portopulmonary hypertension (POPH)

- Pulmonary arterial hypertension in the absence of other causes of PAH
- Survival strongly associated with severity of liver disease
- TIPS can increase right ventricle preload and worsen heart failure and is consequently generally avoided
- Medical rx



Sleep disorders and liver disease

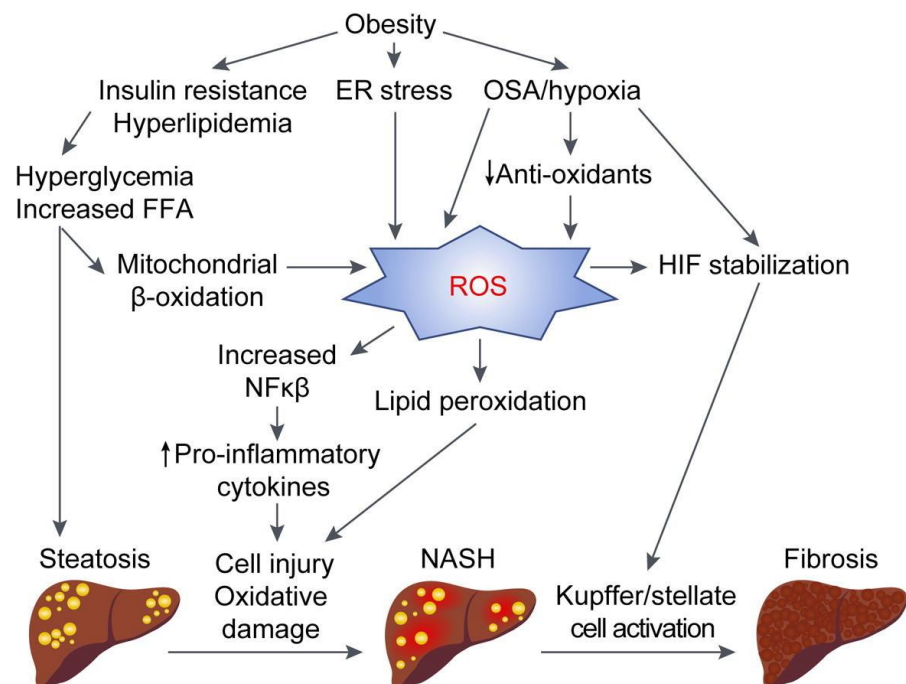
- Sleep disturbance is a common feature of chronic liver disease
- Patients with cirrhosis may have a slightly higher risk of OSAS
- Conflicting reports about the relationship of OSAS and the severity of liver disease
- OSAS is an independent risk factor for the development of NAFLD attributed to intermittent hypoxia



MC Gastroenterol. 2020

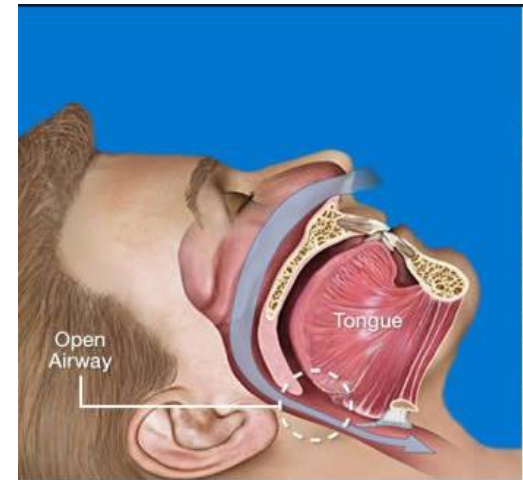
Obstructive sleep apnea and NAFLD

- Hypoxia is tightly associated with lipid homeostasis
- Obesity and OSAS synergistically accelerate tissue hypoxia leading to the development of hepatic steatosis
- Effect of CPAP with mixed results
- Effect of liver transplant not yet known
- Manipulation of Hypoxia Induced Factors (HIFs) activity may be a desirable therapeutic target for NAFLD
- ? Screen NAFLD pts for OSAS (and vv)

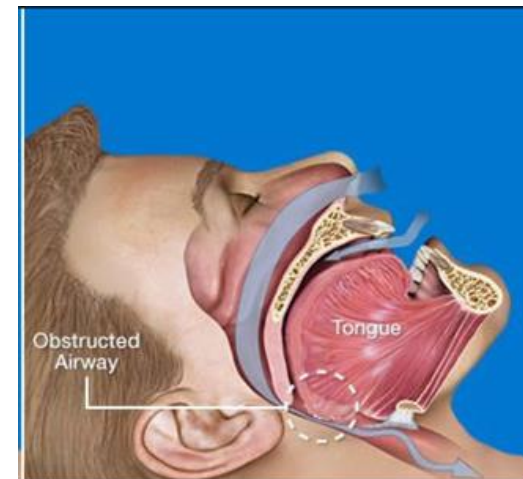


Obstructive Sleep Apnea

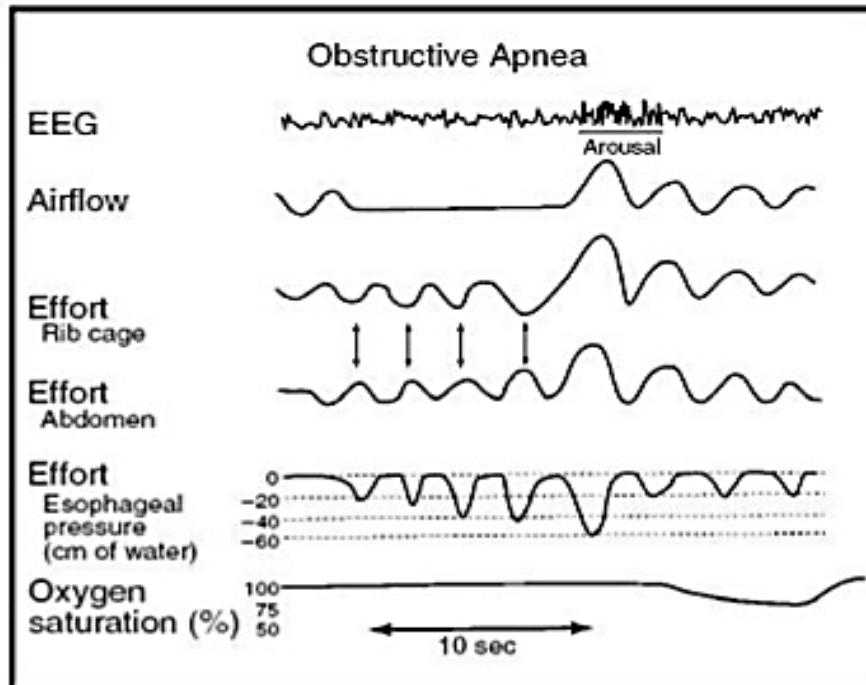
- Respiratory efforts persist but airflow is absent/reduced at the nose and mouth
- Severe OSAS: adjusted hazard ratio:
~2x risk for stroke or death



Non-Obstructed Airway



Obstructed Airway



SCREEN: STOP-BANG

OSA Risk related to # Yes responses:

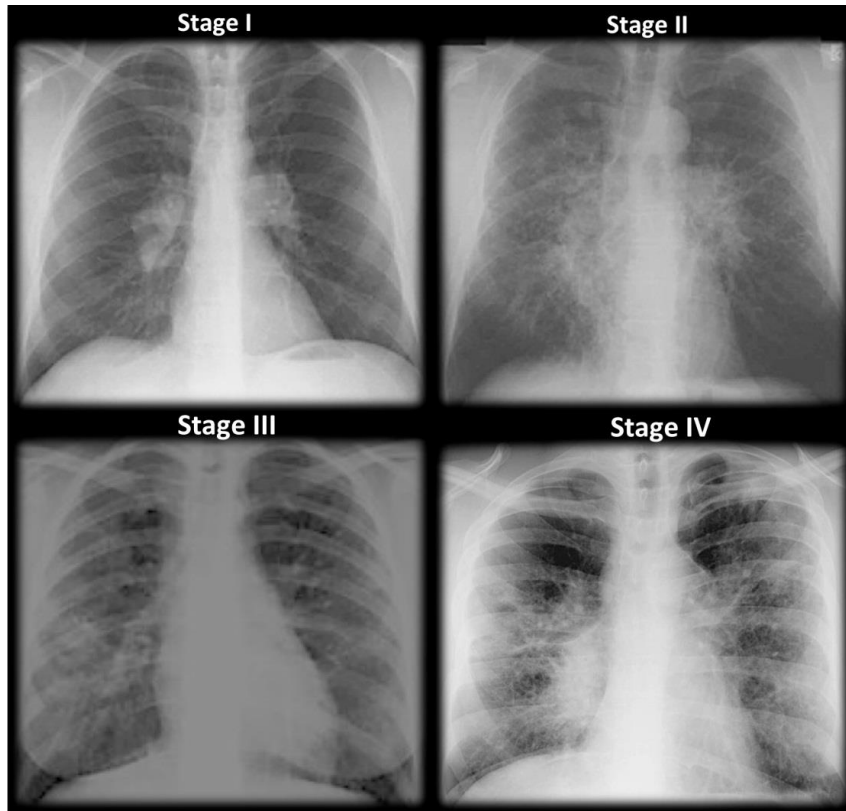
0 - 2 questions: Low risk

3 - 4 questions: Intermediate Risk

5 - 8 questions: High Risk

- **S**noring ?
 - Do you Snore loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
- **T**ired ?
 - Do you often feel Tired, fatigued, or sleepy during the daytime (take naps, fall asleep during driving or talking to someone)?
- **O**bserved ?
 - Anyone Observe you to stop breathing/choking/gasping during sleep?
- **P**ressure ? Do you have or are being treated for High Blood Pressure?
- **B**ody Mass Index more than 35 kg/m²?
- **A**ge older than 50?
- **N**eck size large ? Men \geq 17 inches (43 cm); Women \geq 15 inches (38 cm)
- **G**ender = Male ?

Sarcoidosis and the liver



- Sarcoid liver involvement is more common in patients with sarcoid changes in lung parenchyma rather than in those with only hilar adenopathy
- Hepatopulmonary syndrome should be considered in patients with hepatic sarcoidosis if gas exchange abnormalities are out of proportion to lung involvement

Clinical spectrum of hepatic sarcoidosis

Feature	Presentation (%)
Asymptomatic	50-80%
Abnormal liver enzymes	30%
Hepatomegaly or splenomegaly	50% by imaging; < 20% clinically
Symptoms	Abdominal pain 15% Pruritus and jaundice <5%
Cirrhosis	6-8%
Portal hypertension	3-18%
= Severe liver dysfunction	Rare
Advanced disease requiring transplantation	0.012% of all transplants in the United States

Main differential diagnosis of hepatic sarcoidosis

Condition	Histology	Associated Findings
Sarcoidosis	Well-differentiated noncaseating granuloma	Pulmonary adenopathy Pulmonary interstitial disease
Primary biliary cholangitis	Poorly differentiated noncaseating granuloma	Positive antimitochondrial antibody No pulmonary hilar adenopathy
Primary sclerosing cholangitis	“Onion-skin” periductal fibrosis	Association with inflammatory bowel disease Typical magnetic resonance cholangiography findings
Drug-induced hepatic granulomas	Variable, depending on drug; presence of eosinophils in granulomas suggests diagnosis	Medication history

Summary

- Cirrhosis can involve the lung parenchyma, the pleura, the diaphragm and/or the pulmonary vasculature and result in hypoxemia
- Pleural fluid obtained from pts with cirrhosis should be sent for complete studies
- All pts with cirrhosis whose O₂ sat < 96% should be evaluated for hepatopulmonary syndrome
- Obstructive sleep apnea is associated with NAFLD
- Treatment of pulmonary disease in the patient with advanced liver disease ranges from medical therapy to liver transplant