

Hepatopulmonary Syndrome and Portopulmonary Hypertension

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Pulmonary dysfunction in cirrhosis/liver disease

- Diseases that can affect liver and lung:
 - A1AT deficiency
 - Cystic fibrosis
 - Drug toxicity
 - PBC
 - Sarcoidosis
- Related to portal HTN
 - Ascites
 - Hepatic hydrothorax
- Co-morbidities
 - COPD
- Pulmonary vascular changes
 - **Hepatopulmonary syndrome**
 - **Portopulmonary hypertension**

Outline

- Definition
- Prevalence
- Pathophysiology
- Clinical manifestations
- Diagnosis
- Treatment
- Prognosis

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HEPATOPULMONARY SYNDROME

Definition

- HPS is a disease process with a triad of:
 - 1- Liver disease
 - 2- Pulmonary vascular dilatation
 - 3- Gas exchange abnormality presenting with increased A-a gradient on room air(sitting, at rest), that results ultimately in hypoxemia.

Historical background

- 1884 Fluckiger described a 37 WF with cirrhosis, cyanosis, & digital clubbing
- 1956 Hoffbauer & Rydell demonstrated AVM's in lungs of a pt. with cirrhosis
- 1966 Berthelot et al first suggested that marked pulmonary vascular dilatation may play a role in this condition (autopsy study)
- 1977 Kennedy and Knudson introduced the term hepatopulmonary syndrome to describe a patient with exercise induced hypoxemia and alcoholic cirrhosis

Prevalence

- Ranges from 5 to 32%.
- The most common liver disease responsible for HPS is liver cirrhosis.
- Other liver diseases may contribute:
 - Non cirrhotic portal hypertension.
 - Extrahepatic portal vein obstruction.
 - Chronic active hepatitis.
 - Fulminant hepatic failure

Schenk P et al. Gut 2002;51:853-9.

Pathophysiology

- I. **Vasodilatation:** gross dilatation of the pulmonary pre-capillary and capillary vessels
 - imbalance of vasodilator and vasoconstrictor agents favoring vasodilators. This could be due to:
 - a- Overproduction of the vasodilators from injured hepatobiliary system.
 - b- Decrease in their clearance by the liver.
 - c- Production of a vasoconstrictor inhibitor.
 - d- Normal sensitivity of the pulmonary vessels to vasoconstrictors in response to hypoxemia is blunted in HPS.
 - Numerous vasodilators are suspected but nitric oxide (NO) is the most appreciated one. Other mediators include VIP, calcitonin related peptide, glucagon, substance P and platelet activating factor.

Rodriguez-Roisin R, et al Am Rev Respir Dis 1987;135:1085-92.

Pathophysiology

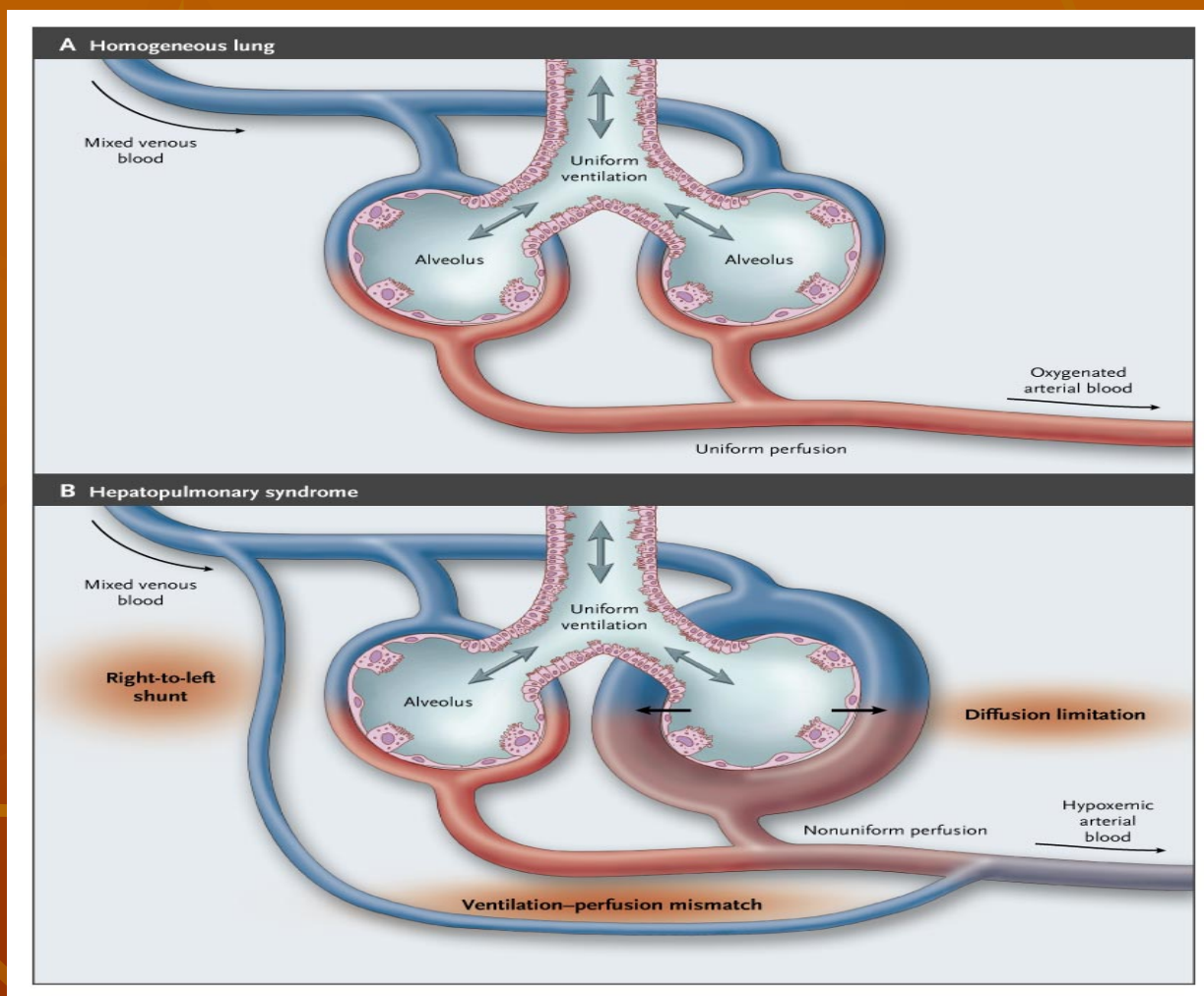
II- Right to left shunting of the blood:

- AV communications that have no contact with breathed air. If numerous, they can give rise to severe hypoxemia unresponsive to 100% oxygen.

III– Diffusion impairment:

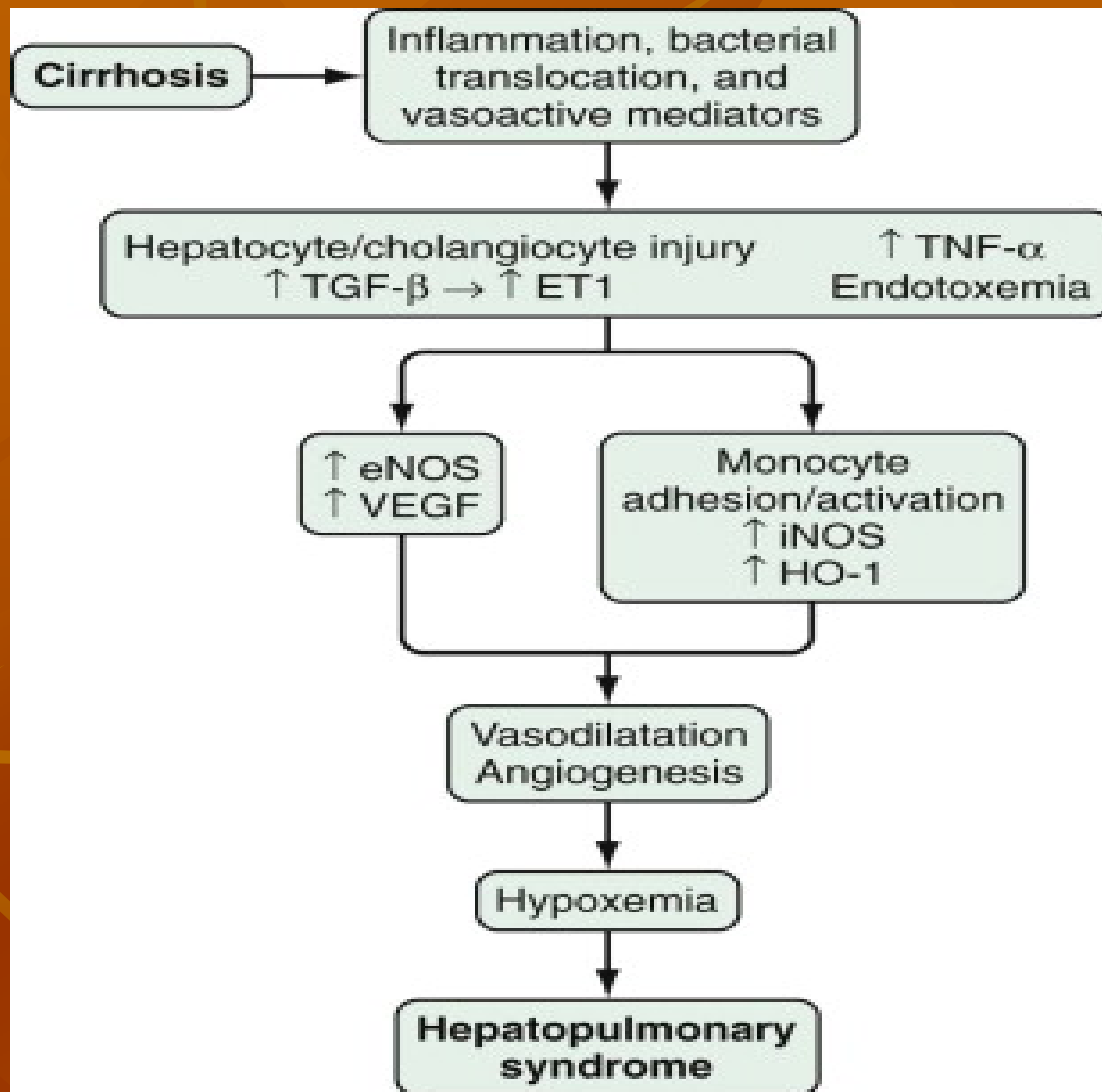
- Excessive vasodilatation causes O₂ molecules not to reach the center of dilated capillaries readily.
- Increased cardiac output and decreased transition time (*diffusion-perfusion defect or alveolar capillary oxygen disequilibrium.*)

Mechanisms of Arterial Hypoxemia in the Hepatopulmonary Syndrome



Imbalance of vasoactive substances (such as NO) caused by the diseased liver leads to pulm. vascular dilatations

Pathophysiology



eNOS, endothelial nitric oxide synthase; ET1, endothelin-1; HO-1, heme oxygenase; iNOS, inducible nitric oxide synthase; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α ; VEGF, vascular endothelial growth factor.

Clinical manifestations

- Asymptomatic
 - SOA
 - Platypnea (AVMs in bases)
-
- Telangiectasias
 - Clubbing, Cyanosis
 - Hypoxia, Orthodeoxia (Dec PaO₂ by 5% or 4 mm Hg)
 - severe hypoxemia (Po₂, <60 mm Hg) strongly suggests HPS
 - Heart and lung exam generally normal



Clinical manifestations

- Most cases of the hepatopulmonary syndrome are associated with clinical evidence of cirrhotic and noncirrhotic portal hypertension (e.g., gastroesophageal varices, splenomegaly, or ascites).
- **No relationship between the presence or severity of the HPS and the severity of liver disease**

Diagnosis

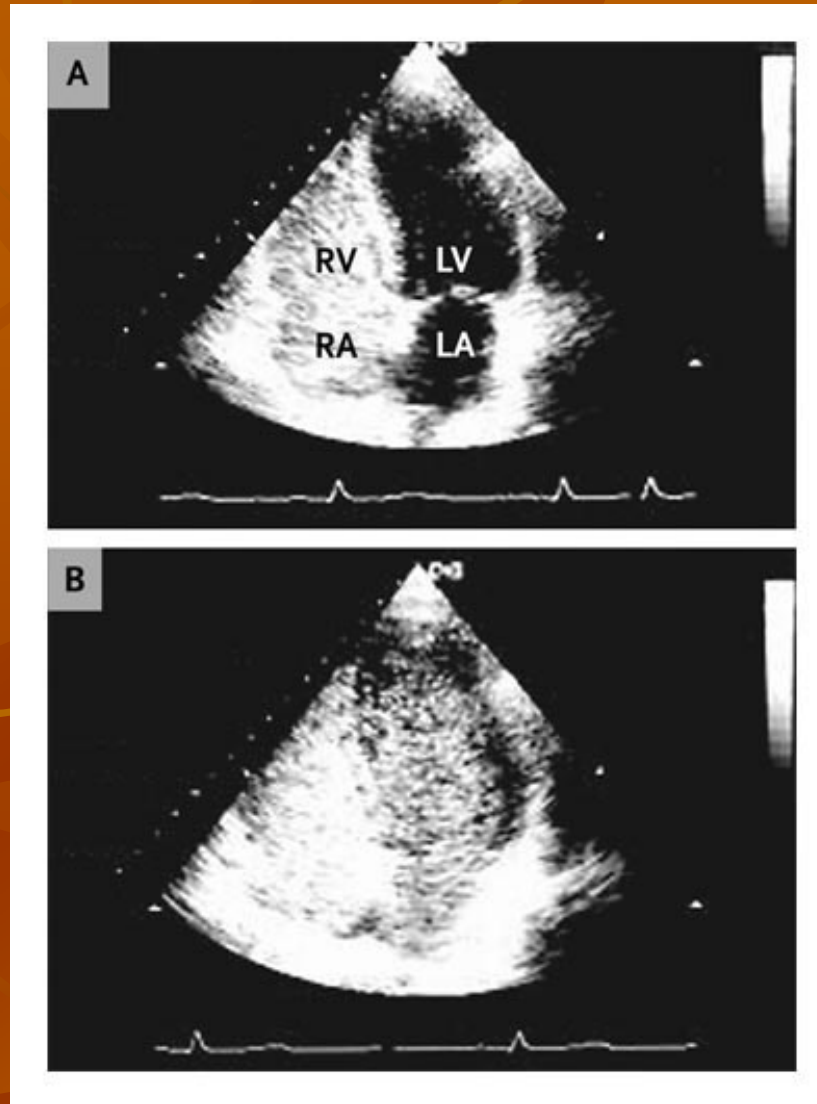
Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome.*

Variable	Criterion
Oxygenation defect	Partial pressure of oxygen <80 mm Hg or alveolar–arterial oxygen gradient ≥ 15 mm Hg while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis
Degree of severity†	
Mild	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 80 mm Hg
Moderate	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 60 to <80 mm Hg
Severe	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 50 to <60 mm Hg
Very severe	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen <50 mm Hg (<300 mm Hg while the patient is breathing 100% oxygen)

Contrast-enhanced echocardiography

- For those with $\text{PaO}_2 < 80$ or A-a gradient > 15 .
- Can also evaluate cardiac function and pulmonary artery pressures (r/o POPH).
- Contrast is enhanced by IV injection of either indocyanine green dye or agitated saline and then TTE is performed
- Interpretation (no quantitative information):
 - Normal: contrast seen in the right heart and then disappears (when filtered by pulmonary capillaries)
 - Intracardiac shunt: contrast seen almost immediately in left heart
 - Hepatopulmonary syndrome: contrast seen in the left heart within 3-6 cardiac cycles

Transthoracic Echocardiographic Features of the Hepatopulmonary Syndrome

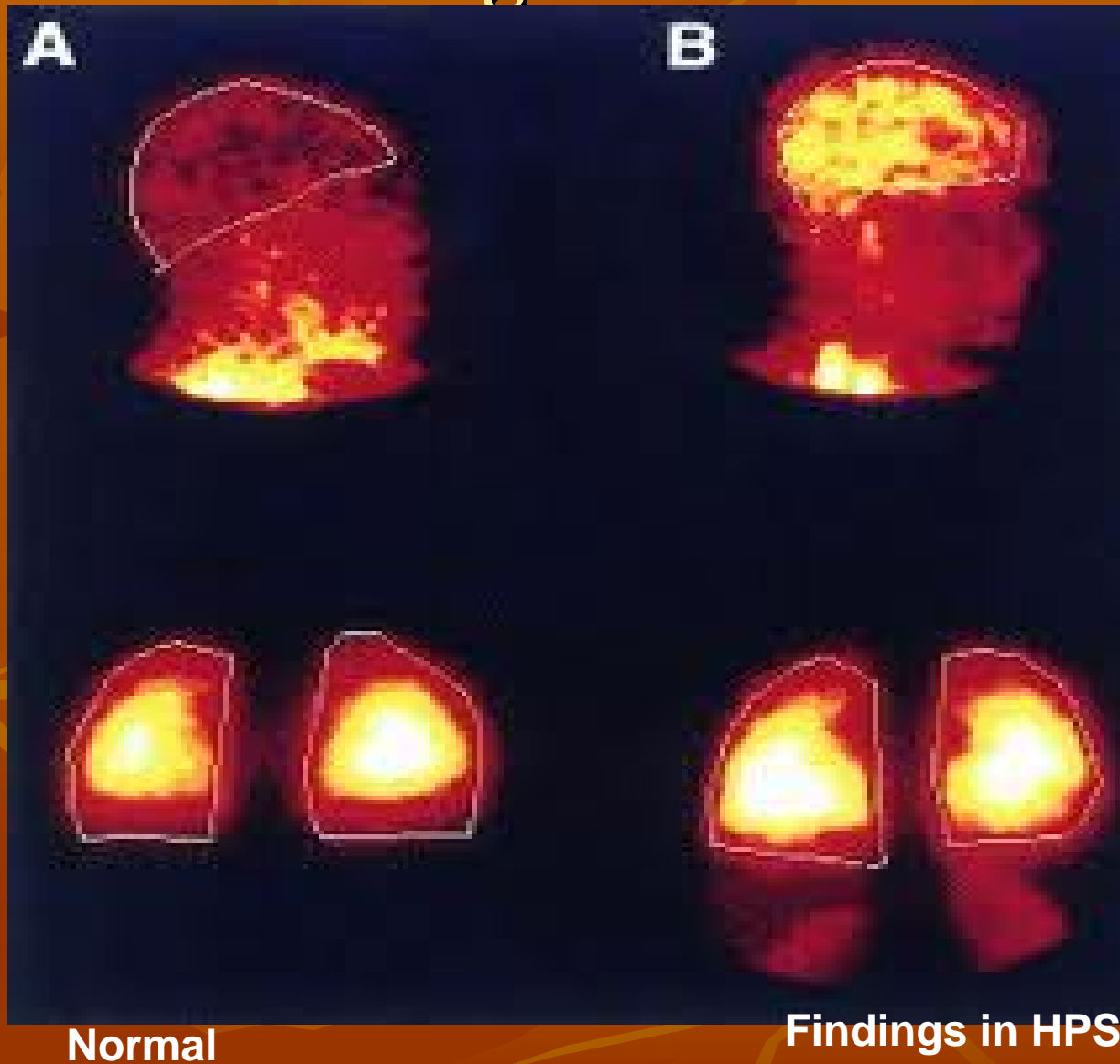


Rodríguez-Roisin R, Krowka M. N Engl J Med 2008

Technetium-labeled macroaggregated albumin scan (Tc-MAA)

- ^{99m}Tc Technitium-labeled albumin ($> 20\ \mu\text{m}$) is injected IV and then a body perfusion scan is performed
- Interpretation:
 - Normal: Tc detected almost exclusively in lungs
 - Intracardiac or intrapulmonary shunt: Tc is detected in other organs (brain, kidneys) as well as the lungs
- Calculate the shunt index (Quantitative):
 - Percentage of uptake in brain compared to that in lungs
 - $> 6\%$ is abnormal

Tc-MAA Lung and Brain Scans



Abrams GA et al . Gastroenterology 1998; 114:305-10.

DLCO

- A decrease in the single-breath diffusing capacity for carbon monoxide is the only routine PFT that is consistently abnormal in patients with HPS.
- However, low diffusing capacity is not specific and may not normalize (as do other gas exchange indexes) after liver transplantation suggesting structural remodeling of the pulmonary vasculature

Pulmonary angiography

- Most invasive and **NOT** a standard diagnostic tool in HPS
- can be used to discern discrete arteriovenous communications from diffuse precapillary and capillary dilatations
- Indicated in
 - Severe hypoxemia (i.e., $PO_2 < 60$ mm Hg,
 - Poor response to 100% oxygen, and
 - when there is a strong suspicion (on CT) of direct AV communications that would be amenable to embolization.
- Two types of angiographic patterns in HPS:
 - Type 1- diffuse pattern- spongy or blotchy- diffuse areas of dilatations mostly in bases
 - Type 2- discrete lesions- less common- worse response to supplemental O₂
 - These focal arteriovenous malformations may be amenable to embolization

Treatment

- **Supportive care with oxygen**
- **Liver transplantation**
 - Significant improvement in gas exchange in 85%
 - Time to normalization varies and can be delayed up to 1 year
 - 5-year survival rate of 76% after OLT, a rate not significantly different from patients without the HPS who underwent OLT.
 - Postoperative mortality is higher in pts with severe HPS (Pre- XPT $\text{PaO}_2 \leq 50 \text{ mmHg}$ \pm Tc-MAA shunt fraction $\geq 20\%$ are strong predictors of mortality
 - $\text{PaO}_2 < 60 \text{ mm Hg}$ is an indication for OLT
 - MELD exception

Swanson KL et al. Hepatology 2005;41:1122-9
Arguedas MR et al. Hepatology 2003;37:192-7

Medical therapy

Potential targets for the Rx of HPS



Blocking NO synthesis by inhibition of NOS

- PTX
- MB
- Quercetin
- MMF



Inactivation of ET-1

- PTX
- Quercetin
- NAC



Inhibition of pulmonary angiogenesis

- PTX
- MB
- MMF
- Sorafenib



Inhibition of bacterial translocation and subsequent decrease in NO

- Norfloxacin

- PTX: pentoxifylline, MB: methylene blue, MMF: mycophenolate mofetil, NAC N- acetylcysteine

Treatment

- Beta-blockers, nitrates, octreotide, PGF2a have no benefit
- Methylene blue blocks guanylate cyclase (dec cGMP)
 - Proven in short term only
- Pentoxifylline has proven encouraging in animal models
- Garlic useful in some studies

Other Options

- IR
 - TIPs is controversial and not generally recommended
 - Vascular embolization (large focal AV malformations)
- Cavoplasty when it is associated with the Budd–Chiari syndrome

Garlic (*Allium Sativum*)

- Allicin (allyl 2-propenethiosulfinate) active ingredient-mechanism unknown (? Decreased V/Q mismatch by smooth muscle relaxation uniformly)
- Powdered garlic-bid x 6 months (2 gm- 3 gm/ day) in 15 patients (uncontrolled trial)
 - 6/ 15 (40%) had at least 10 mm Hg improvement in PaO₂ in 8 wks + improvement in hypoxemia and DLCO.
 - Garlic found to be more useful in younger patients and those with lower shunt fraction (21 versus 44%).

More on Garlic

- RCT (Garlic=21 Placebo=20; evaluated monthly over a period of 9 to 18 months.

Garlic

- 24.7% increase in PaO₂ (83 Vs 67 mmHg; P<0.001),
- 28 % decrease in A-a gradient (21 Vs 30 mmHg; P<0.001).
- Reversal of HPS was observed in 14 of 21 patients (66.7%)

Conclusion:

- Garlic – helps in reversal of intrapulmonary shunts as well as reducing hypoxemia and mortality.

Placebo

- Only 7.37% increase (68.75 Vs 64.05 mmHg; P=0.02)
- A-a Gradient 10.73% decrease (29.11 mmHg versus 32.61 mmHg; P=0.12)
- Reversal of HPS was in 1 of 20 patients (5%)

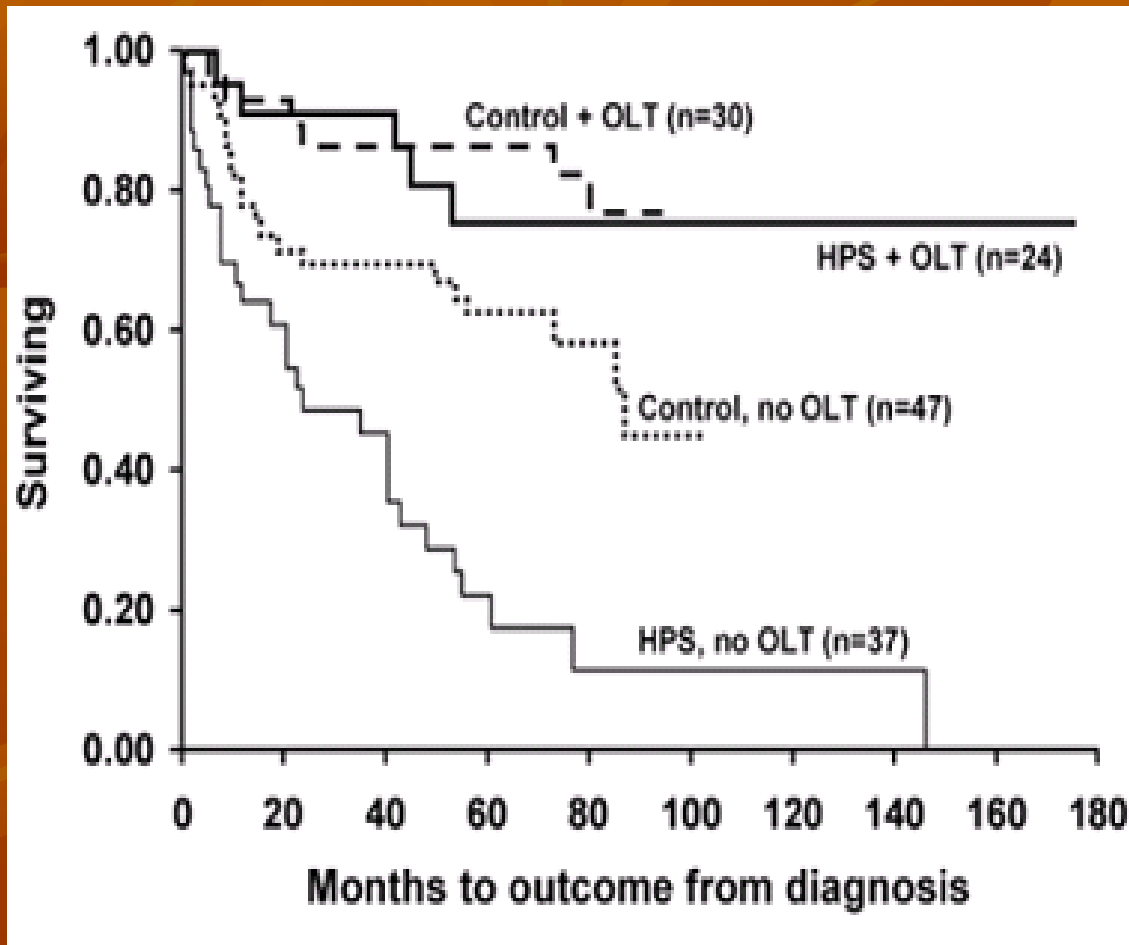
Prognosis

Median survival

5 yr survival

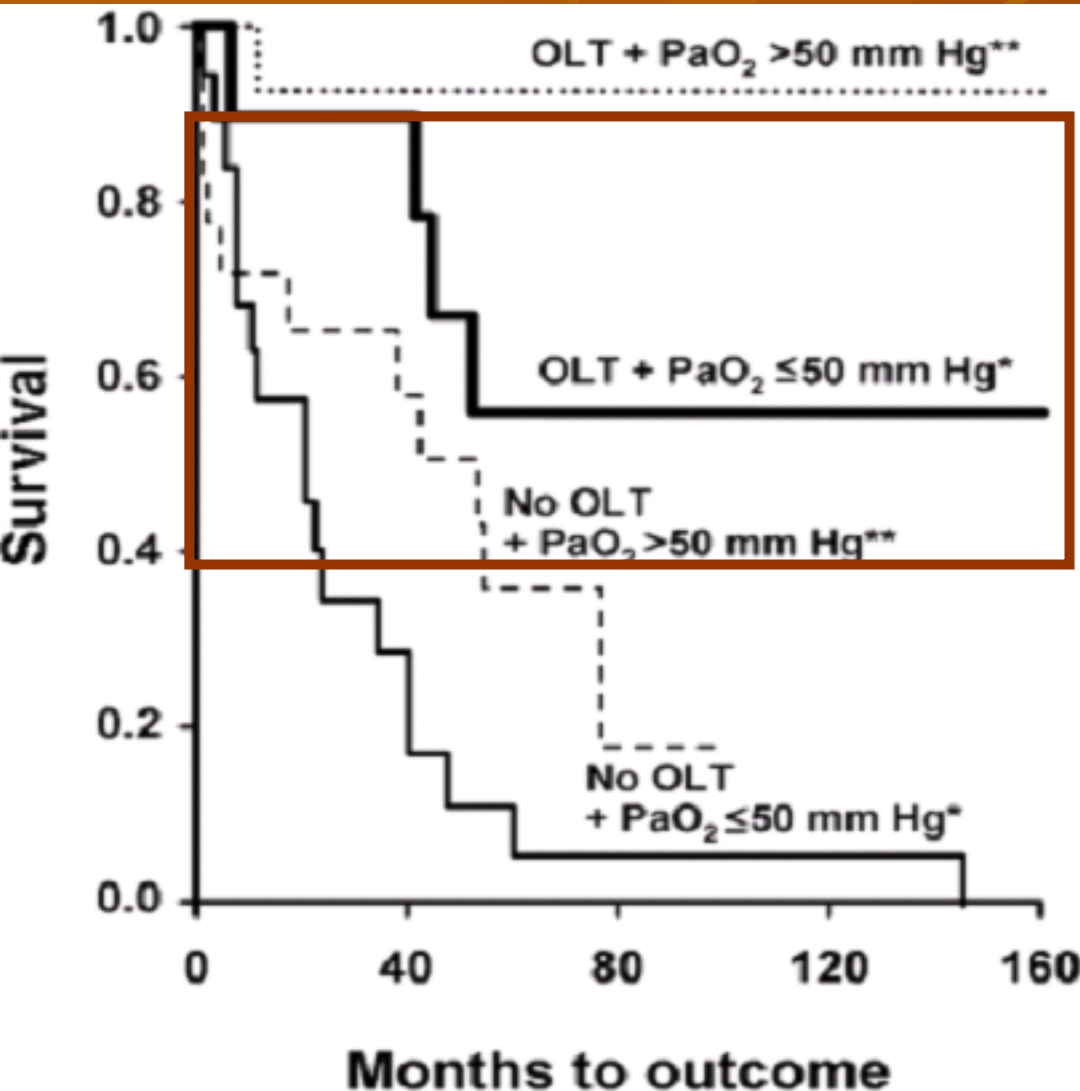
- HPS 24 mths 23%
- Matched w/o HPS 87 mths 63%
- Survival was significantly worse among patients with a $\text{PaO}_2 < 50 \text{ mm Hg}$

Prognosis in HPS



- HPS pts, 5-year survival:
 - 76% with OLT
 - 23% with no OLT
 - $P < .0001$
- Pts with no OLT:
 - HPS pts had worse 5-year survival than matched controls
 - $P = .0003$

Prognosis in HPS



Survival of the OLT group with PaO₂ > 50 mm Hg was better than the OLT group with PaO₂ ≤ 50 mm Hg ($P = .02$)

Hence, early detection of HPS can help in expediting Liver Transplant especially for those with PaO₂ between 50 and 60

The background of the slide features a pattern of stylized, overlapping leaves in various shades of orange and brown, creating a textured, autumnal effect.

Portopulmonary Hypertension (POPH)

Definition

- POPH is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension.
- Serious complication of cirrhosis that is associated with mortality beyond that predicted by the MELD score
- POPH is defined as an MPAP ≥ 25 mm Hg at the time of right heart catheterization that is associated with a PVR ≥ 240 dyn.s.cm⁻⁵ and PCWP ≤ 15 mm Hg
- Because patients may present with both fluid overload and POPH, the addition of the transpulmonary gradient (TPG; ie, MPAP - wedge pressure) has also been suggested.

Definition of POPH

Liver disease (clinical portal hypertension)

MPAP ≥ 25 mm Hg

PVR $> 240 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5*}$

PCWP < 15 mm Hg

- These diagnostic criteria were proposed by the European Respiratory Society/European Society for the Study of the Liver Task Force on Hepatic and Pulmonary Vascular Disorders of POPH

1 mm Hg min/l (Wood Unit) = $80 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$

Rodriguez-Roisin R et al. Eur Respir J 2004;24:861–880

Prevalence and severity

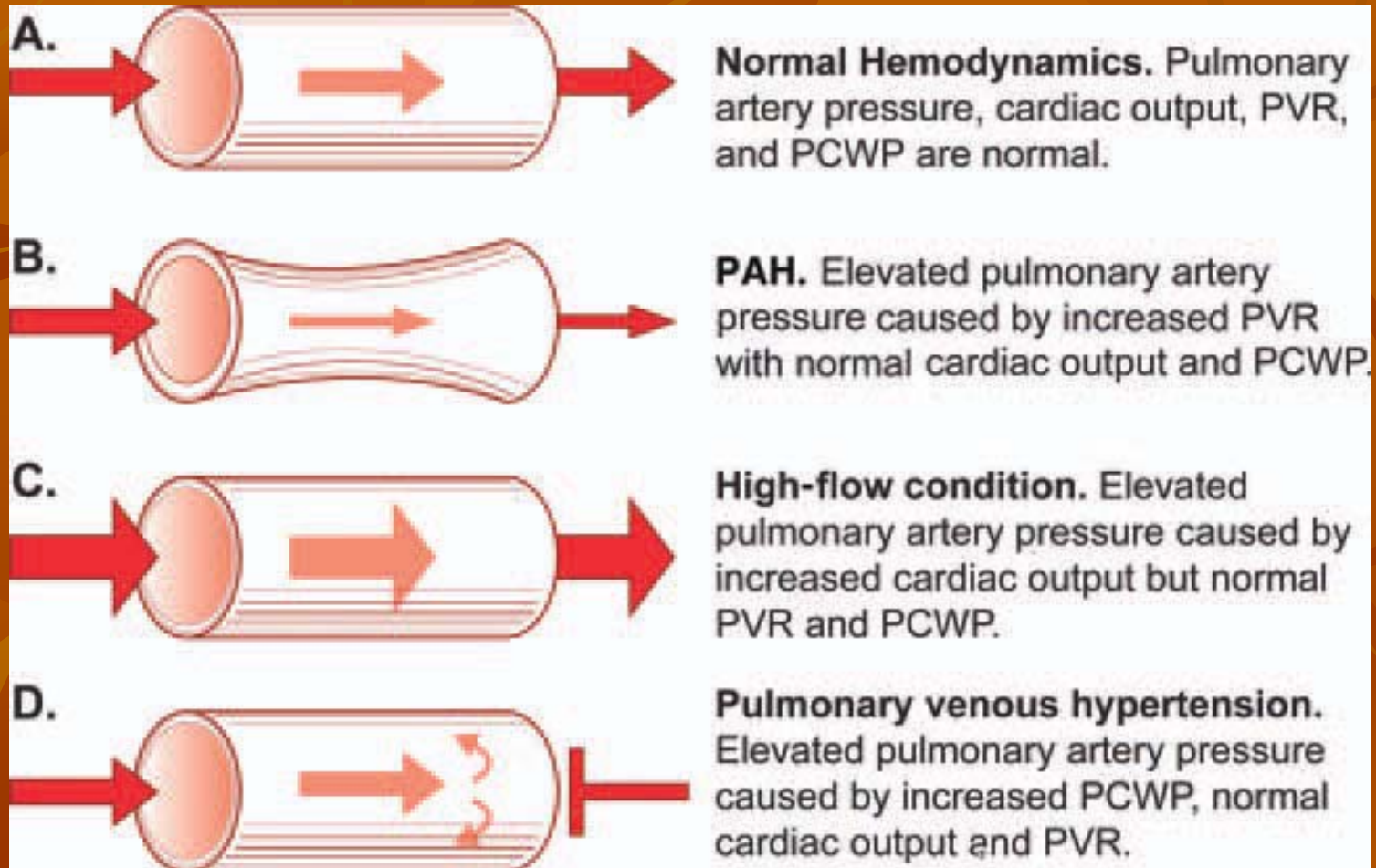
- 6% to 8% of patients with cirrhosis develop POPH.

Severity	MPAP (mm Hg)
■ Mild	25 to <35
■ Moderate	35 to <45
■ Severe	> 45

Kawut SM et al. Hepatology 2008;48:196-203.

- Moderate POPH (MPAP = 35 to <45 mm Hg) and severe POPH (MPAP \geq 45 mm Hg) are less common and are associated with a higher mortality rate.
- Historical data show that the mortality rate after OLT is 50% if MPAP is >35 mm Hg and 100% if MPAP is >50 mm Hg
- Routine screening for POPH during the evaluation for LT is included in the practice guidelines from the AASLD.
- LT centers typically screen transplant candidates for both POPH and HPS with contrast enhanced echocardiography

Potential causes of MPAP elevations in patients with POPH



Pathophysiology

- Common single-nucleotide polymorphisms showed associations with estrogen receptor 1, aromatase, phosphodiesterase 5 (PDE5), angiotensin 1, and calcium binding protein A4.
- Patients with POPH had significantly higher levels of endothelin 1 and IL-6, and this suggests that the targeting of these mediators may have a role in the treatment of POPH.

Pellicelli AM et al. Angiology

2010;61:802-806.

Clinical manifestations

- Exertional dyspnea may be a presenting feature, but the absence of symptoms should not prevent screening in appropriate populations.
- Physical findings - absent or subtle and nonspecific
- A loud P2 in 82% of patients and a systolic murmur in 61% of patients.

Natural history

- A retrospective analysis by Kawut et al. compared 13 patients with POPH to 34 patients with idiopathic PAH.
- Patients with POPH had a higher cardiac index and a lower PVR, but the RAP and pulmonary artery pressure values were similar.
 - Despite these favorable hemodynamics, patients with POPH were almost **3 times more** likely to die than patients with other types of PAH.

Kawut SM, et al. Liver Transpl 2005;11:1107-1111.

Natural history

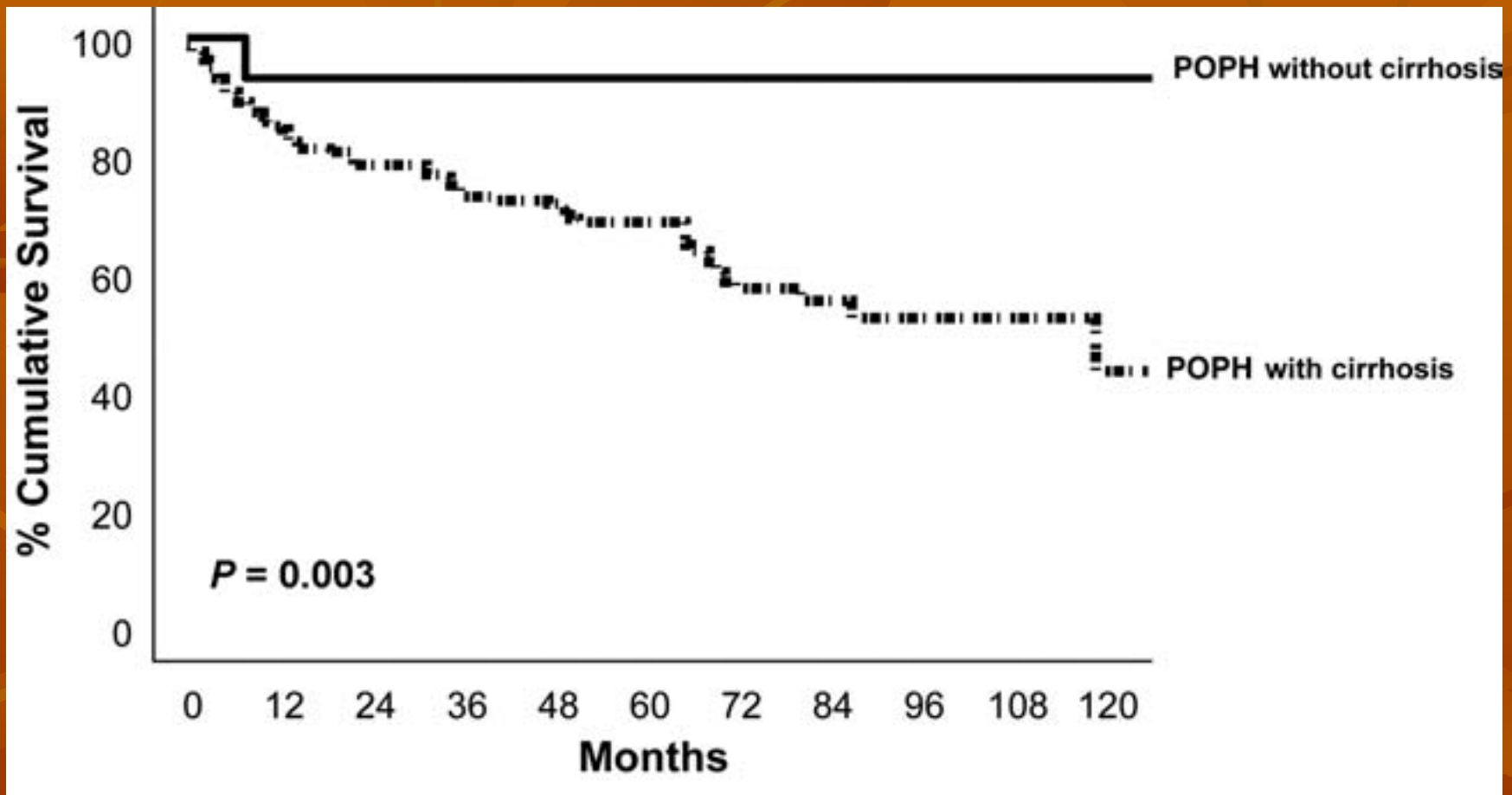
- A French retrospective analysis 154 patients with POPH from 1984 to 2004 : 60% belonged to NYHA class III or IV, and this was associated with a low cardiac index
- The survival rates at 1, 3, and 5 years were 88%, 75%, and 68%, respectively, and they were significantly better than the rates reported for other series.
- Mortality was related to the severity of cirrhosis (it was higher for Child-Pugh B/C patients) and to the cardiac index (it was worse for patients with a low cardiac index).

Natural history

- A recent report from the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) registry describes an observational study
- 174 patients with POPH were compared to 1392 patients with idiopathic PAH and 85 patients with familial PAH.
- Despite better hemodynamics, the 2- and 5-year survival rates were lower for the patients with POPH (**67% versus 85% at 2 years and 40% versus 64% at 5 years**).

Krowka MJ, et al. Chest 2012;141:906-915.

The relationship
between POPH in the presence or absence of cirrhosis
and mortality



Le Pavec J et al . Am J Respir Crit Care Med 2008;178:637-643

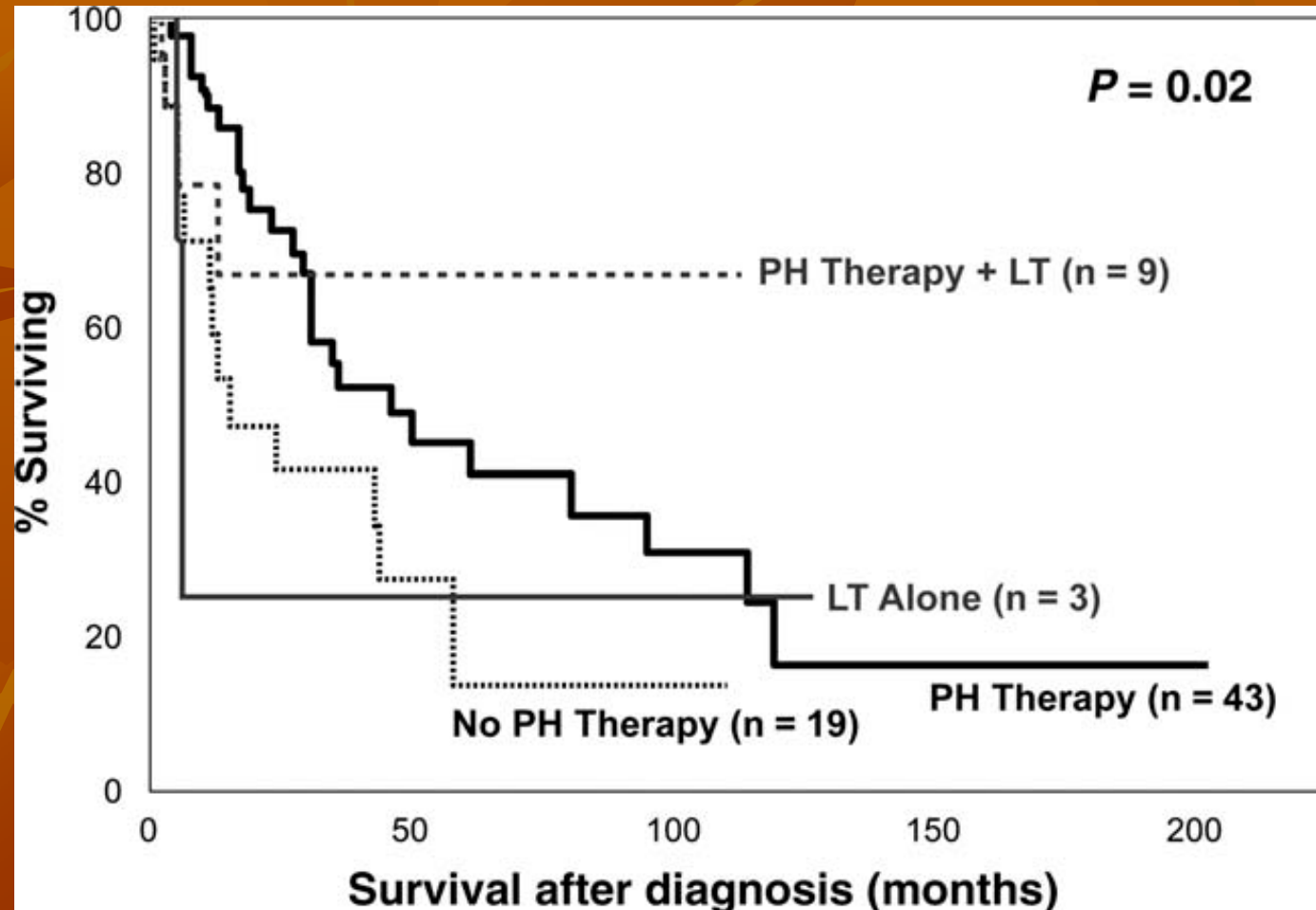
Survival in portopulmonary hypertension, Mayo experience

Natural History of POPH

	No Therapy (n = 19)	Vasodilators Without Subsequent OLT (n = 43)	Vasodilators Followed by OLT (n = 12)
5-year survival rate (%)	14	45	67*
Mortality rate one year after diagnosis (%)	54	12	Not available

*The survival rate was 25% (1/4) for patients who underwent transplantation without previous vasodilator therapy.

Survival curves for 74 patients divided by the type of treatment for PH with or without LT..



Swanson KL et al .Am J Transplant
2008;8:2445-2453

Bottom line

- Multiple studies suggest that vasodilator therapy not only is helpful but also might make OLT possible if POPH is controlled.

Treatment

- Different classes of drugs, including prostanoid analogues, endothelin receptor antagonists, and PDE5 inhibitors, have been used to treat POPH.
- Pulmonary vasodilators are generally effective in the treatment of PH, but they should be used only after the diagnosis has been hemodynamically confirmed by right heart catheterization

Prostanoids

- Epoprostenol (EPO), also known as synthetic prostaglandin I₂ (PGI₂) or prostacyclin, was the first therapy approved by the FDA as a continuous intravenous infusion for the treatment of PAH in 1995.
- Potent pulmonary and systemic vasodilator and an inhibitor of platelet aggregation, and it may modulate pulmonary vascular remodeling.
- EPO might be used to predict the ultimate reversibility of POPH.
- EPO used to reduce MPAP before transplant and generally continued for 48 hrs after XPT
- Other prostanoids: treprostinil (SQ, IV or neb.) and iloprost (neb)
- An oral synthetic prostacyclin analogue, beraprost, is available in Japan and Europe but not in US.

Endothelin Receptor Antagonists

- Three receptors have been described: endothelin A, endothelin B1, and endothelin B2.
- Nonspecific antagonist bosentan and the endothelin A-specific agents ambrisentan and sitaxsentan (not FDA approved).
- Bosentan use in POPH patients has been limited, in part because of fears about its idiosyncratic hepatotoxicity but a number of studies have shown the tolerability of bosentan in this population without evidence of liver injury in a small number of POPH patients.
- Ambrisentan monotherapy was non hepatotoxic

Hoeper MM, et al. Eur Respir J 2007;30:1096-1102.

Hoeper MM et al Eur Respir J 2005;25:502-508.

PDE5 Inhibitors

- PDE5 inhibitors prevent the breakdown of cGMP, which is the mediator of nitric oxide–induced vasodilation, and thus reduce the pulmonary artery pressure.
- Sildenafil, which has been proven to be effective and safe in several small POPH series.
- Other drugs in this class include vardenafil and tadalafil.
- The patients treated showed improved walk distances and reductions in BNP levels.

Milrinone

- Milrinone is a potentially useful agent because of its combination of inotropic and vasodilator properties

Beta-Blockers

- They have deleterious effects
- In a study by Provencher et al. 10 patients with moderate to severe POPH (MPAP = 52 mm Hg) were examined with a 6-minute walk test and right heart catheterization at the baseline and 2 months after **beta-blocker withdrawal**.
- After beta-blocker withdrawal, 9 of the 10 patients increased their 6-minute walk distance, 28% Increased CO (with no change In MPAP), 19% dec in PVR
- They concluded that patients with moderate to severe POPH should not use beta-blockers.

Therapeutic Options

- Because of the relative paucity of data specific to the POPH population, most PH centers use a treatment strategy comparable to that used for other types of PAH.
- Specifically, a risk assessment is performed to account for the patient's functional capacity, hemodynamics, right ventricular function, and liver status (the MELD score).
- Sicker patients (ie, those with a higher risk of decline over the next year) are often considered for more aggressive therapy with a prostaglandin infusion.
- Patients with more favorable hemodynamics and a more favorable functional status may first try an oral medication regimen, with more aggressive medications added if they have a suboptimal response to therapy.

Liver Transplantation

- The role of LT is still evolving.
- OLT in the setting of uncontrolled POPH has an unacceptably high mortality rate, and most transplant centers consider severe POPH an absolute contraindication to transplantation.
- LT can be performed safely if the hemodynamics are suitably controlled.

Krowka MJ. Semin Liver Dis 2006;26: 265-272.

Ramsay M. Curr Opin Anaesthesiol 2010;23:145-150.

Liver Transplantation

- The majority of patients with POPH in Western countries have cirrhosis.
- The mortality rate is high, so LT is an attractive therapy because it is potentially curative.
- When the danger of uncontrolled PH was recognized, many centers refused to perform transplantation for patients with POPH.
- With the availability of potent vasodilators and their use in patients with idiopathic PH, several centers reported successful OLT after medical control of POPH was achieved.

Krowka MJ. Semin Liver Dis 2006;26: 265-272.

Ramsay M. Curr Opin Anaesthesiol 2010;23:145-150

Sussman N, et al.. Am J Transplant 2006;6:2177-2182.

Liver Transplantation

- MELD upgrade points for POPH have been suggested to account for the increased mortality of these patients versus patients with similar MELD scores on the LT wait list.
- However, the utilization of MELD upgrades and the particulars of the upgrade process have been under responsibility of individual regional review boards.
- UNOS policy suggests an upgrade to a MELD score of 22 with an increase every 3 months as long as MPAP remains <35 mm Hg and PVR remains <400 dynscm⁵.

Swanson KL et al. Hepatology 2005;41:1122-1129.
OPTN/UNOS November 16-17, 2009. Orlando, Florida. Summary.

Summary- HPS

- HPS - unique complication of chronic liver disease- that portends poor prognosis
- Early detection (hypoxia at rest, $\text{PaO}_2 < 80$) can help expediting OLT – mainstay of treatment
- Dx: bubble echo, technetium macroaggregated albumin scan, or pulmonary angiography
- Those with PaO_2 b/w 50 and 60- prioritized for OLT (22-24 MELD points), $\text{PaO}_2 < 50$ or shunt fraction $> 20\%$ might preclude OLT (center dependent)

Summary- POPH

- POPH is a rare complication of cirrhosis that is caused by a combination of pulmonary arteriolar vasoconstriction and intimal and smooth muscle thickening.
- POPH is becoming easier to treat with the availability of multiple vasodilator but LT has superior outcome.
- MPAP must be controlled before LT, but the decision to perform transplantation must include the entire hemodynamic profile and not focus on MPAP alone.
- Beta-blockers may have an adverse effect and should be avoided.
- POPH usually improves after LT, although ongoing oral medication may be required.



Thanks