Hepatopulmonary syndrome and Portopulmonary hypertension

Mohsen Hasanin

01/19/2017

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

Prevalence

Ranges from 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

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: -*
- Overproduction of the vasodilators from injured hepatobiliary system.
- Decrease in their clearance by the liver.
- Production of a vasoconstrictor inhibitor.
- 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.

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

Pathophysiology

II- Right to left shunting of the blood:

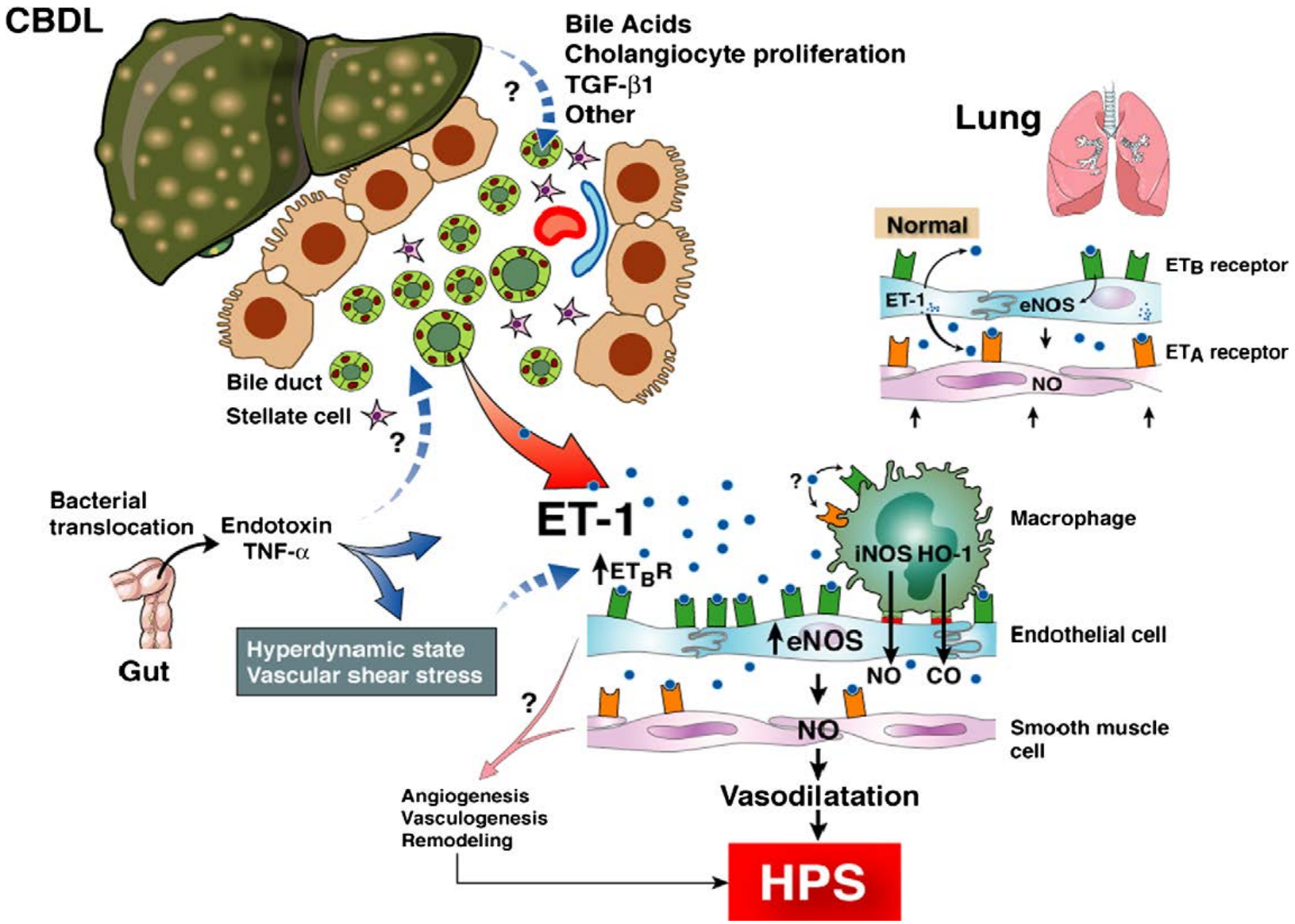
- AV communications that have no contact with breathed air. If numerous, they can give rise to severe hypoxemia unresponsive to 100% oxygen.

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.)*

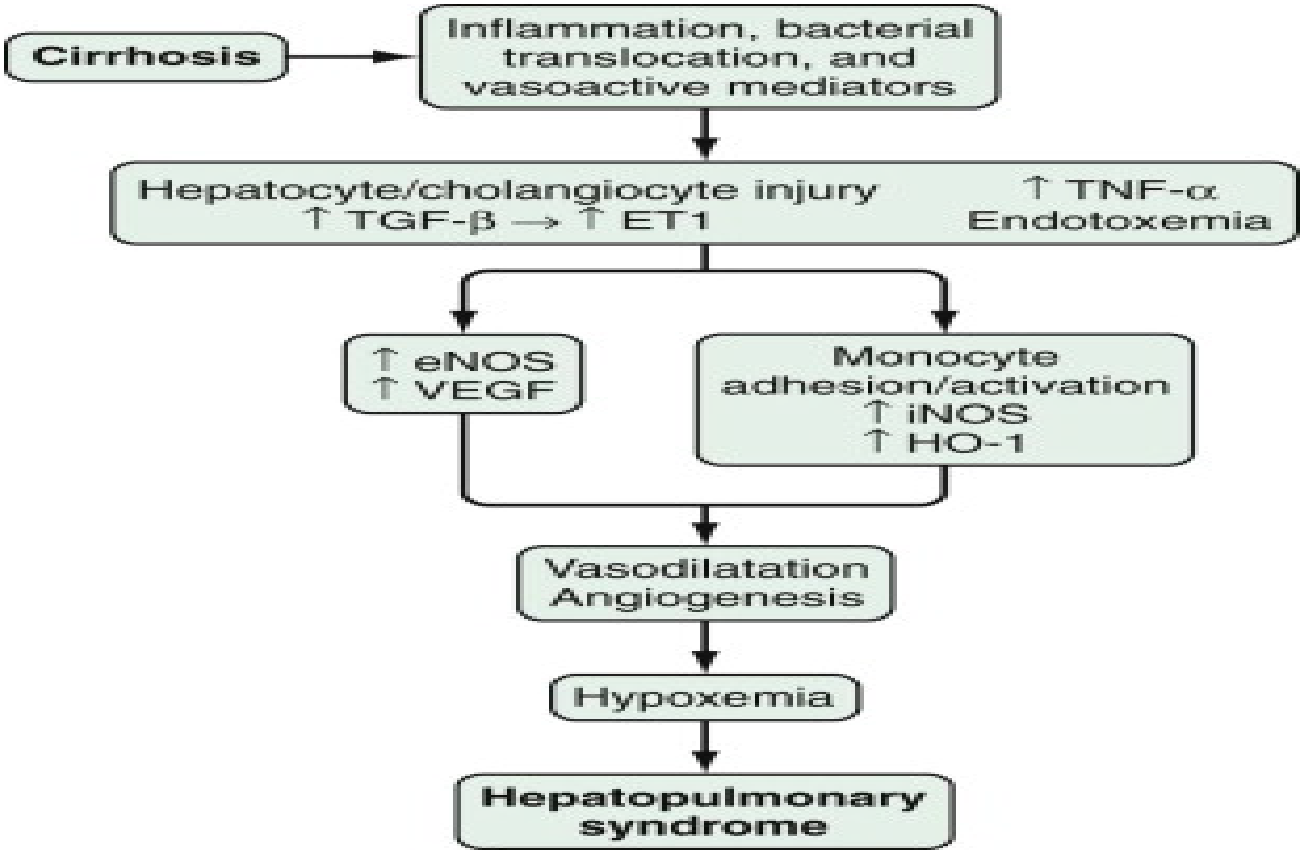
Genovesi MG, et al. Am Rev Respir Dis 1976

Pathophysiology



D.T. Palma, M.B. Fallon / Journal of Hepatology 45 (2006) 617–625

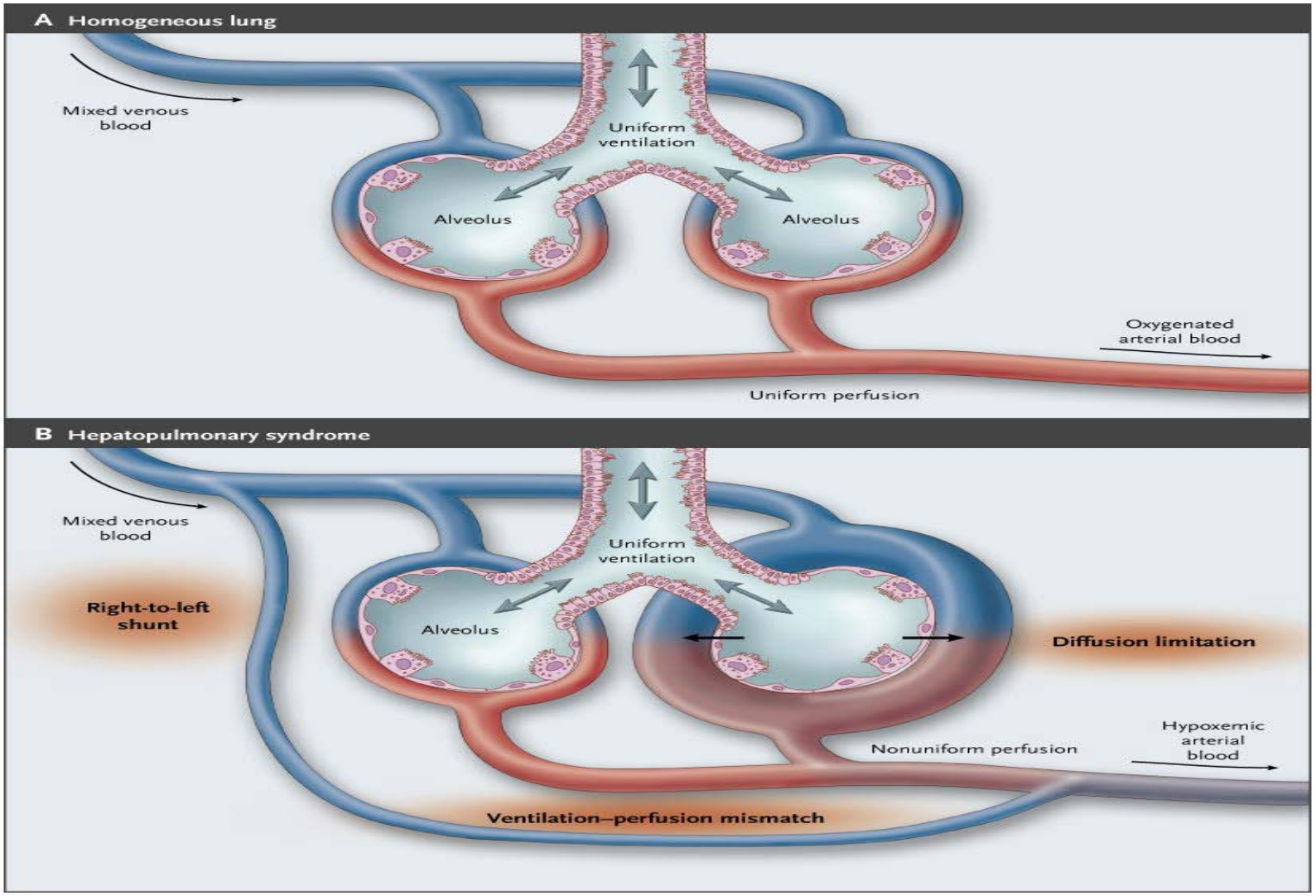
Pathophysiology



eNOS, endothelial nitric oxide synthase; ET1, endothelin 1; HO 1, heme oxygenase; iNOS, inducible nitric oxide synthase; TGF , transforming growth factor ; TNF , tumor necrosis factor ; VEGF, vascular endothelial growth factor. endothelin-HO-TGF-β, factor-β; TNF-α, factor-α
Sleisenger and Fordtran's Gastrointestinal and Liver Disease

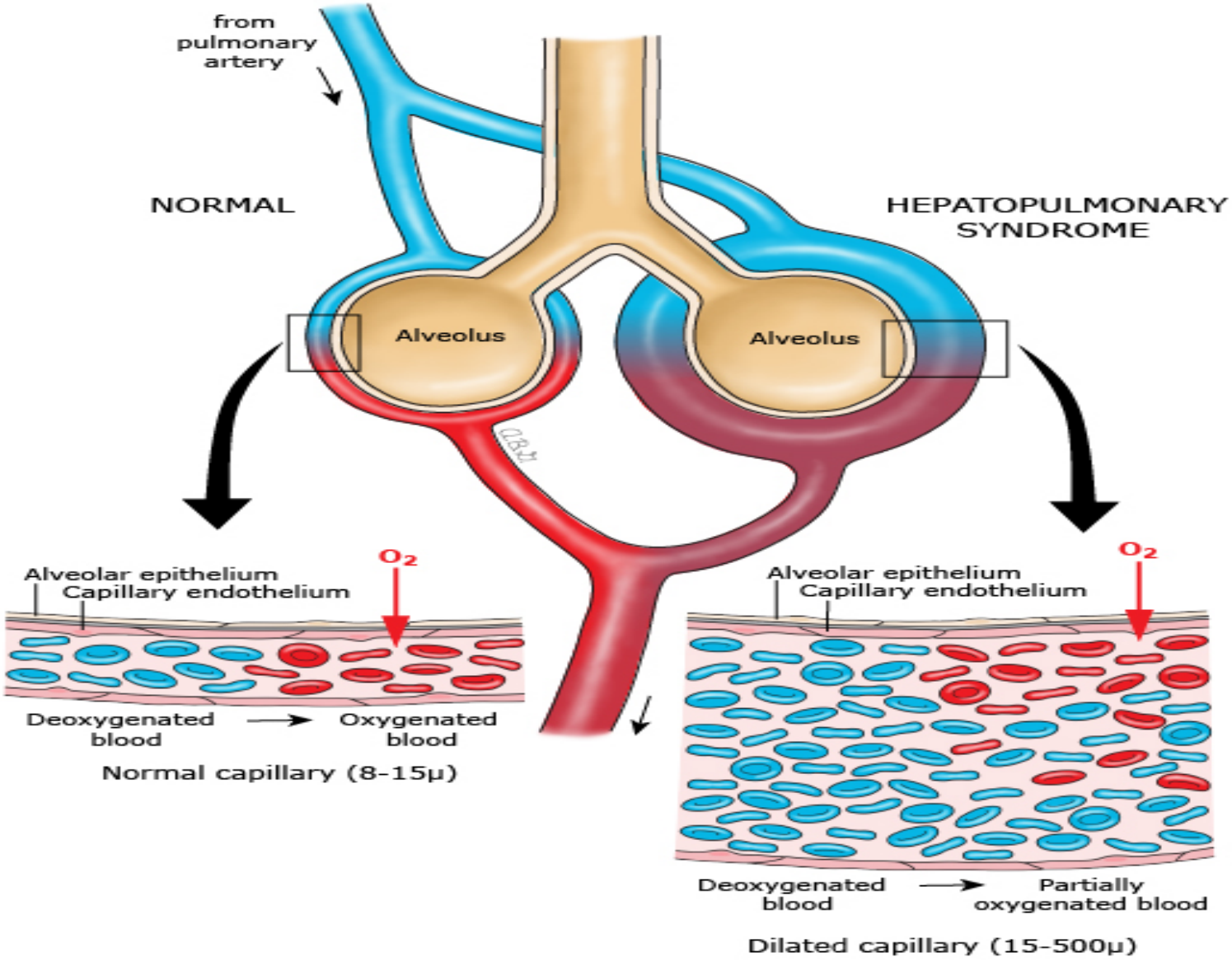
Rodríguez-Roisin R et al. N Engl J Med 2008

Mechanisms of Arterial Hypoxemia in the Hepatopulmonary Syndrome



2008 Imbalance of vasoactive substances (such as NO) caused by the diseased liver leads to pulm. vascular dilatations.

Rodríguez-Roisin R et al. N Engl J Med 2008


from pulmonary artery
NORMAL
HEPATOPULMONARY SYNDROME
Alveolus
Alveolus
Alveolar epithelium
Capillary endothelium
O2
Deoxygenated blood
Oxygenated blood
Normal capillary (8-15μ)
Alveolar epithelium
Capillary endothelium
O2
Deoxygenated blood
Partially oxygenated blood
Dilated capillary (15-500μ)

Clinical manifestations

- Asymptomatic
- SOA
- Platypnea (dyspnea worsened by an erect position and improved by a supine position). (AVMs in bases)
- Telangiectasias
- Clubbing, Cyanosis
- Hypoxia, Orthodeoxia (Dec PaO2 by 5% or 4 mmHg in an upright position)
- 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)

Rodrguez Roisin R, et al . N Engl J Med 2008;358:2378 2387 Rodríguez-2378-

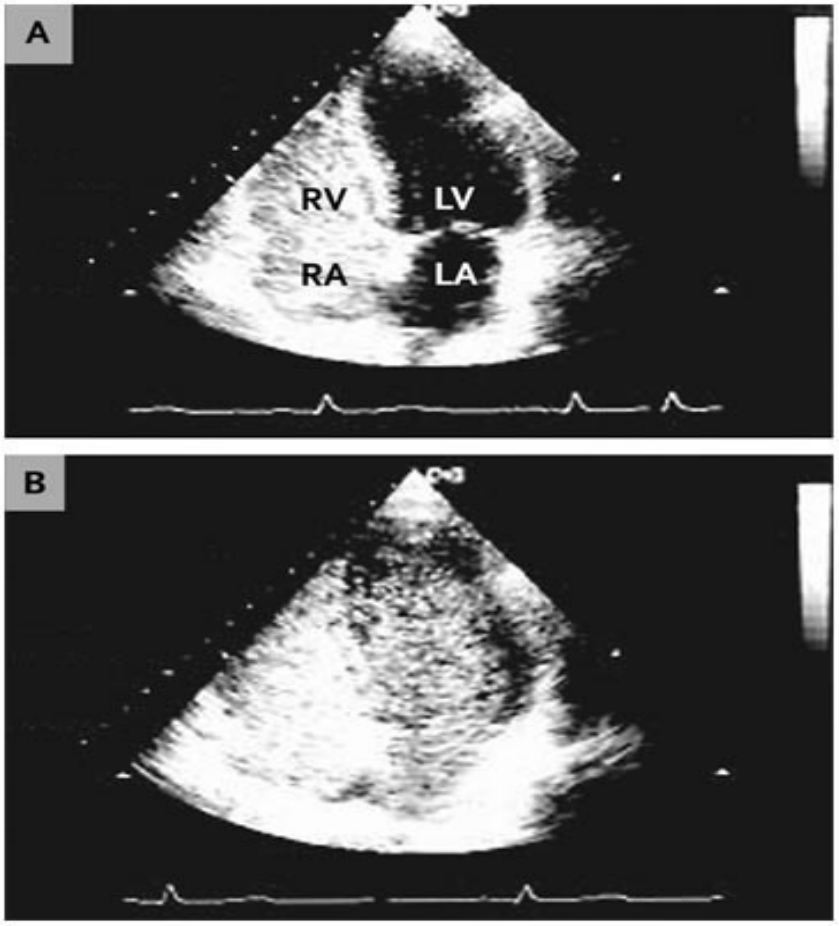
Contrast enhanced echocardiography

- For those with PaO2< 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



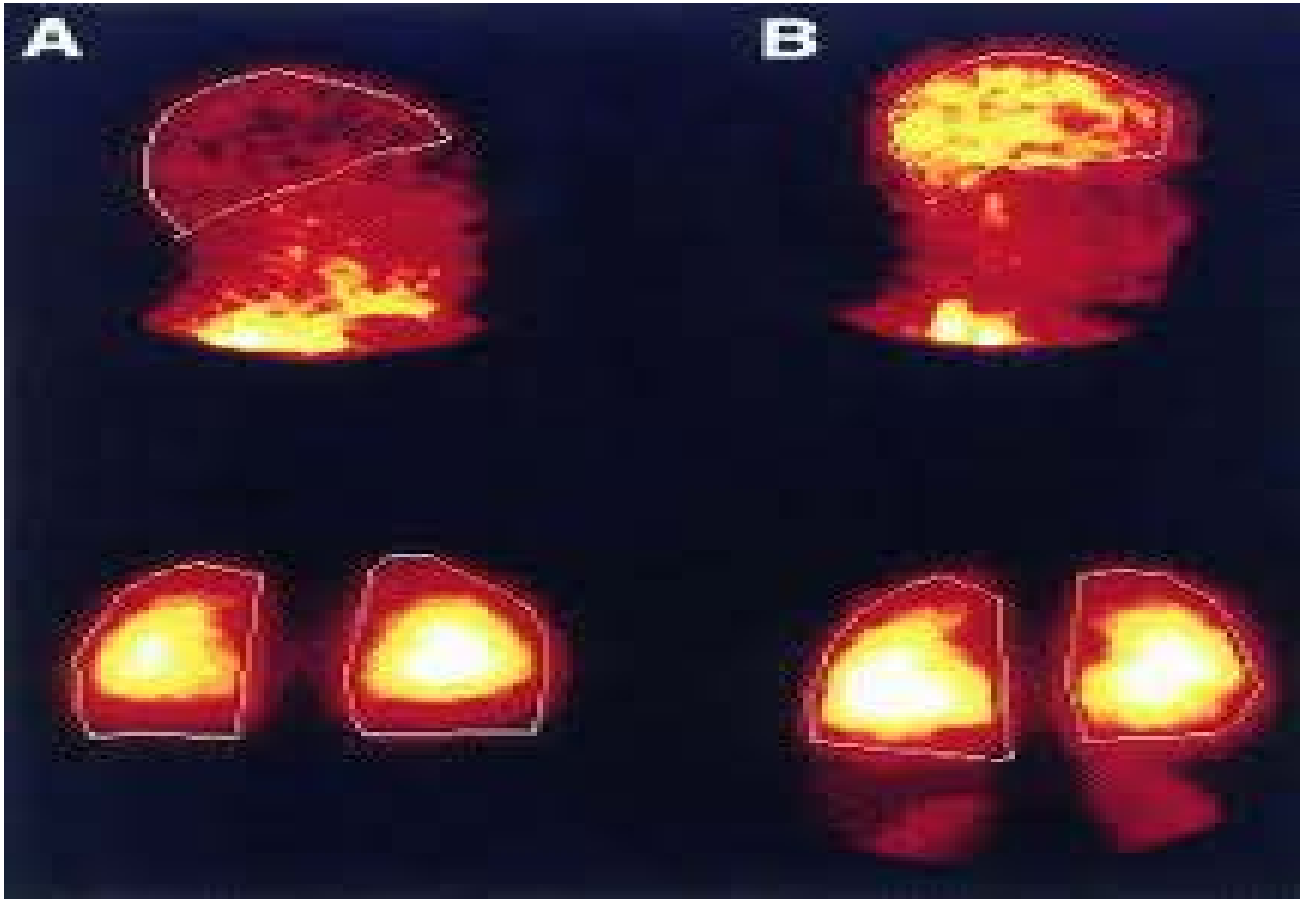
Technetium-labeled macroaggregated albumin scan (Tc-MAA)

- 99mTechnitium-labeled albumin (> 20 µm) is injected IV m) 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



Normal **Findings in HPS**

Abrams GA et al . Gastroenterology 1998; 114:305Abrams 305--10.10.

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

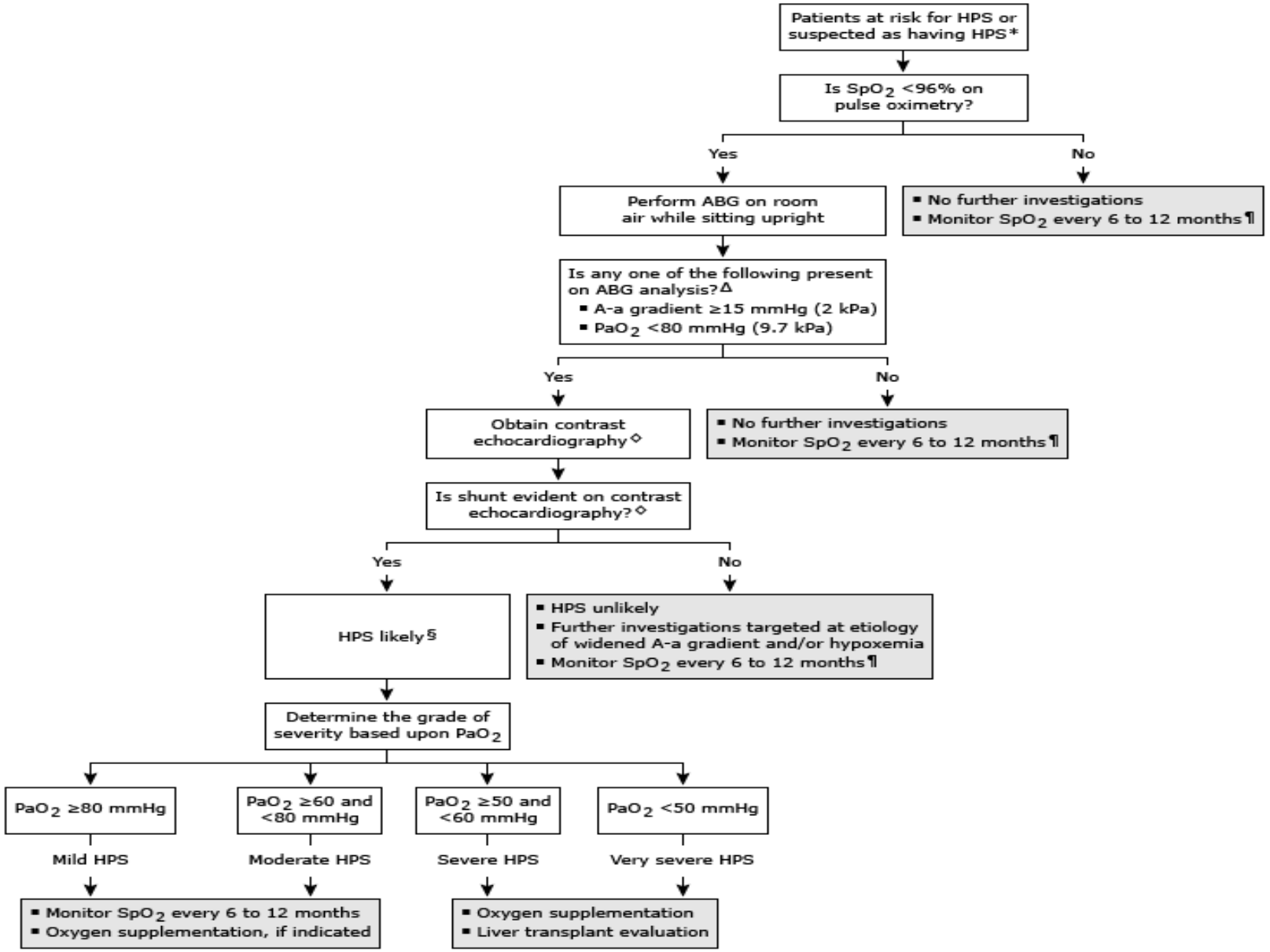
Severe hypoxemia (i.e., Po2 <60 mm Hg,

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


Patients at risk for HPS or suspected as having HPS*
Is SpO_2 <96% on pulse oximetry?
Yes
No
Perform ABG on room air while sitting upright
No further investigations
Monitor SpO_2 every 6 to 12 months¶
Is any one of the following present on ABG analysis?Δ
A-a gradient ≥15 mmHg (2 kPa)
PaO_2 <80 mmHg (9.7 kPa)
Yes
No
Obtain contrast echocardiography◇
No further investigations
Monitor SpO_2 every 6 to 12 months¶
Is shunt evident on contrast echocardiography?◇
Yes
No
HPS likely§
HPS unlikely
Further investigations targeted at etiology of widened A-a gradient and/or hypoxemia
Monitor SpO_2 every 6 to 12 months¶
Determine the grade of severity based upon PaO_2
PaO_2 ≥80 mmHg
PaO_2 ≥60 and <80 mmHg
PaO_2 ≥50 and <60 mmHg
PaO_2 <50 mmHg
Mild HPS
Moderate HPS
Severe HPS
Very severe HPS
Monitor SpO_2 every 6 to 12 months
Oxygen supplementation, if indicated
Oxygen supplementation
Liver transplant evaluation

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 $PaO_2 < 50$ mmHg + Tc-MAA shunt fraction > 20% are strong predictors of mortality
- $PaO_2 < 60$ 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


YOU MAY NOT NEED A LIVER TRANSPLANT AFTER ALL.
I'LL DRINK TO THAT!
©2008 HTTP://BALOOCARTOONS.WORDPRESS.COM

Medical therapy

Potential targets for the Rx of HPS

Blocking NO synthesis by inhibition of NOS
PTX-
MB-
Quercetin

Inactivation of ET-1
-PTX
-Quercetin
-NAC

Inhibition of pulmonary angiogenesis
-PTX
-MB
-Sorafenib

Inhibition of bacterial translocation and subsequent decrease in NO-
Norfloxacin

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

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

Hoeper MM et al. Lancet 2004;363:1461-8
Sztrymf B et al. Eur Respir J 2004;23:752-8

Garlic (Allium Sativum)

- Allicin active ingredient mechanism unknown (Decreased V/Q mismatch by smooth muscle relaxation uniformly)
- Powdered garlic-bid x 6 months (2-3 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%).

Abrams and Fallon, JCG, 1998

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%)

Binay KD et al ,Can J Gastroenterol. 2010; 24(3): 1832010; 183—188

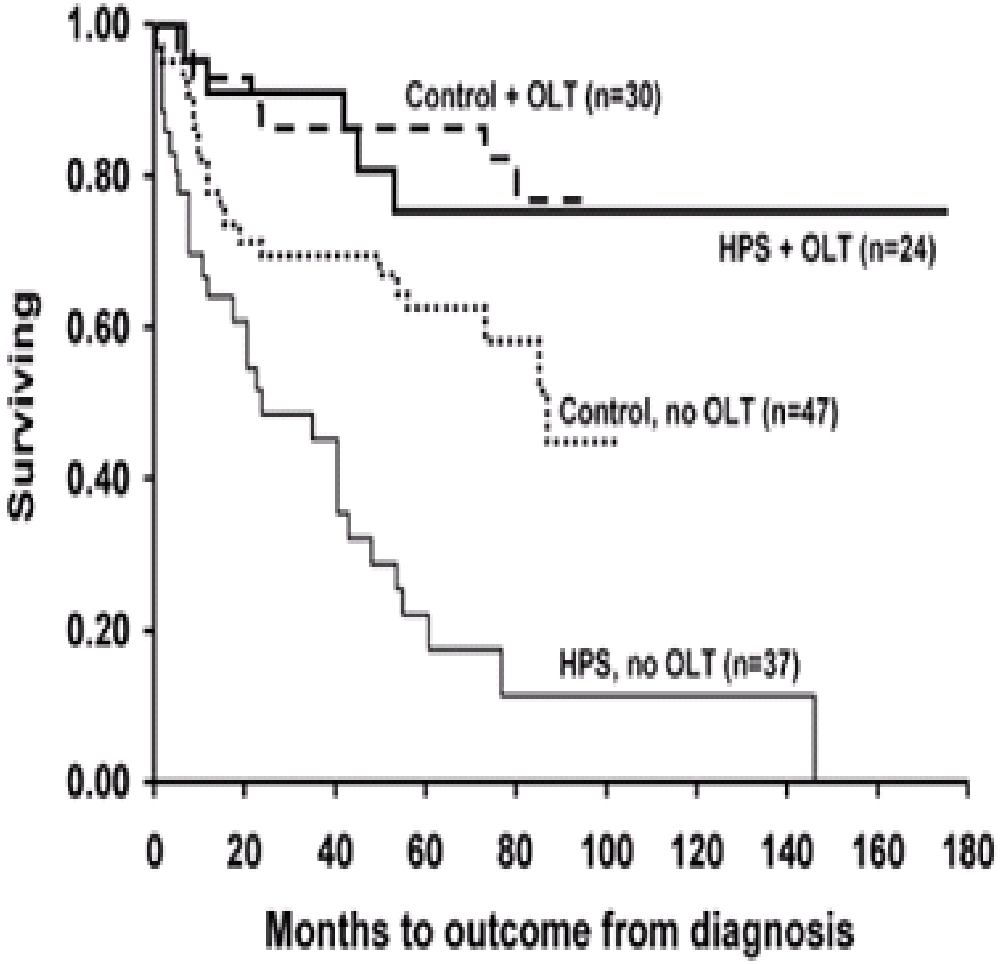
Prognosis

	Median survival	5 yr survival
• HPS	24 mths	23%
• Matched w/o HPS	87 mths	63%

- Survival was significantly worse among patients with a PaO2 < 50 mm Hg

Swanson KL et al. Hepatology 2005;41:1122-9

Prognosis in HPS

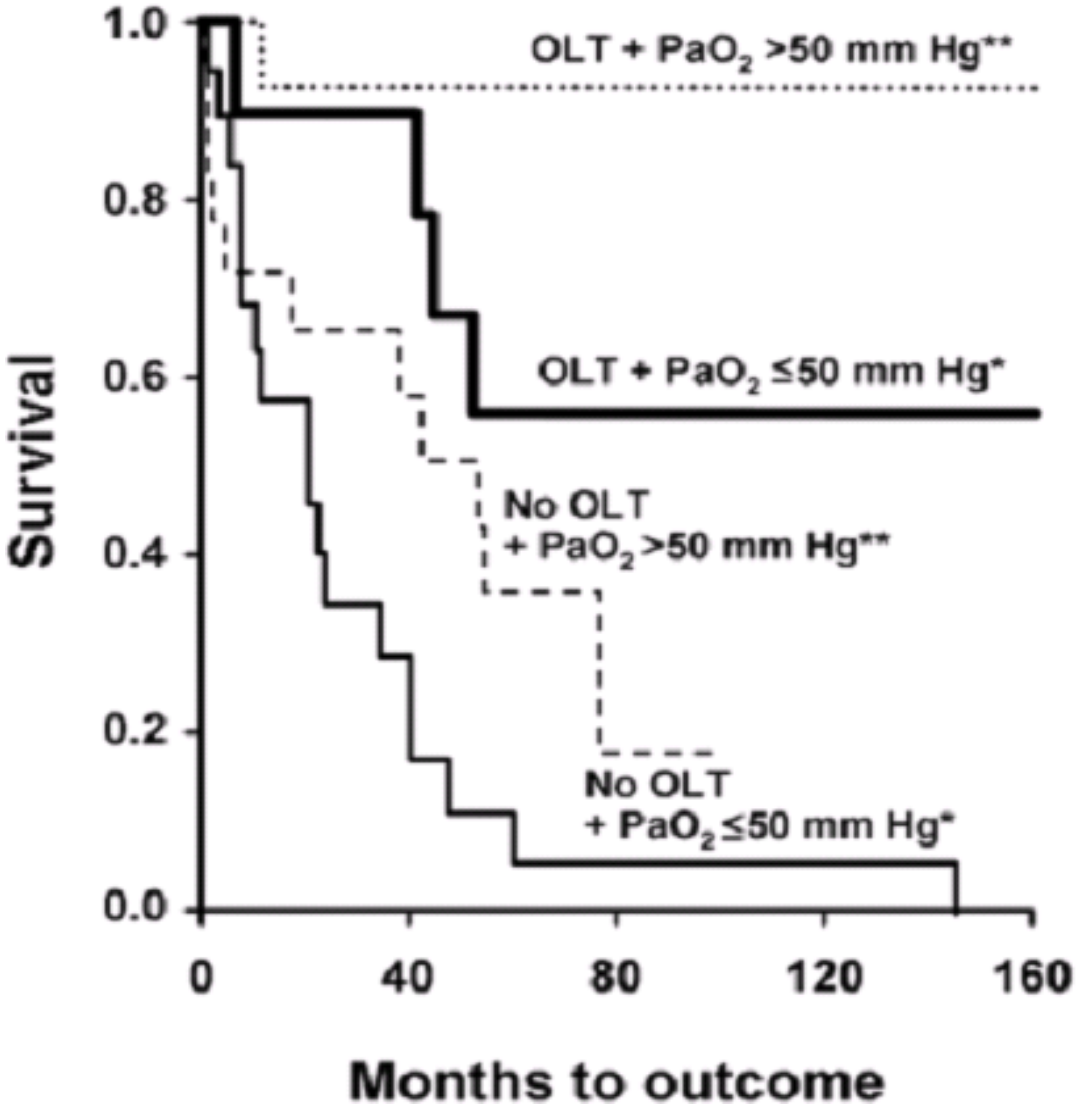


HPS pts, 5 year survival:
76% with OLT
23% with no OLT
P < .0001

Pts with no OLT:
HPS pts had worse 5-year survival than matched controls P = .0003

Swanson KL et al. Hepatology 2005;41:1122-9

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

Swanson KL et al. Hepatology 2005;41:1122-9

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 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 $\geq$ 25 mm Hg
PVR $>$ 240 dyn·sec·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

Rodriguez-Roisin R et al. Eur Respir J 2004;24:861–8801

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. 196-

- Moderate POPH (MPAP = 35 to <45 mm Hg) and severe POPH (MPAP >45 mm Hg) are less common and are associated with a higher mortality rate.
- 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.

Krowka MJ et al L iver Transpl 2000;6:443 --450. Liver 443
Swanson KL et al. Am J Transplant 2008;8:2445 --2453 2445

Pathophysiology

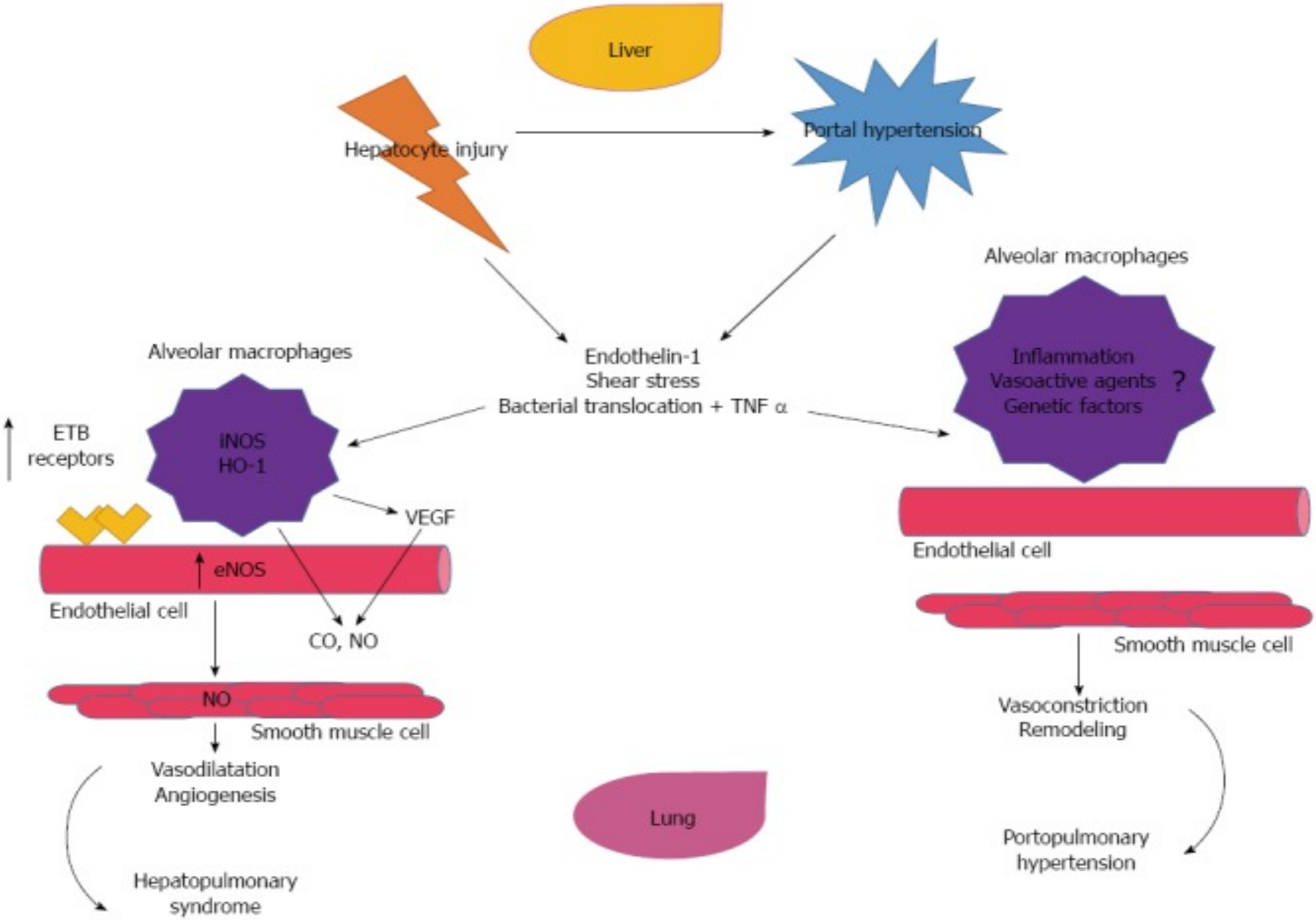
- a humoral substance (which would normally be metabolized by the liver) is able to reach the pulmonary circulation through portosystemic collaterals. mediators include VIP, calcitonin related peptide, glucagon and platelet activating factor.

- a genetic predisposition may exist with a common single nucleotide polymorphisms showed associations with estrogen receptor 1, aromatase, phosphodiesterase 5 (PDE5), angiopoietin 1, and calcium binding protein A4.

- inflammatory processes which advances to concentric intimal fibrosis, and smooth muscle hyperplasia and hypertrophy

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.


Liver
Hepatocyte injury
Portal hypertension
Endothelin-1
Shear stress
Bacterial translocation + TNF α
Alveolar macrophages
ETB
receptors
iNOS
HO-1
VEGF
eNOS
Endothelial cell
CO, NO
NO
Smooth muscle cell
Vasodilatation
Angiogenesis
Hepatopulmonary
syndrome
Lung
Alveolar macrophages
Inflammation
Vasoactive agents ?
Genetic factors
Endothelial cell
Smooth muscle cell
Vasoconstriction
Remodeling
Portopulmonary
hypertension

Clinical manifestations

- Progressive dyspnea on exertion
- Fatigue
- Palpitations
- Syncope
- Chest Pain
- Jugular Venous Distention
- Loud P2 in 82% of patients and a systolic murmur in 61% of patients
- Lower Extremity Edema

Robalino BD,et al. J Am Coll Cardiol 1991;17:492 498.

Diagnosis

- Transthoracic Echocardiogram
- V/Q Scan
- A Right Heart Catheterization is the Gold Standard.

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. 1107-

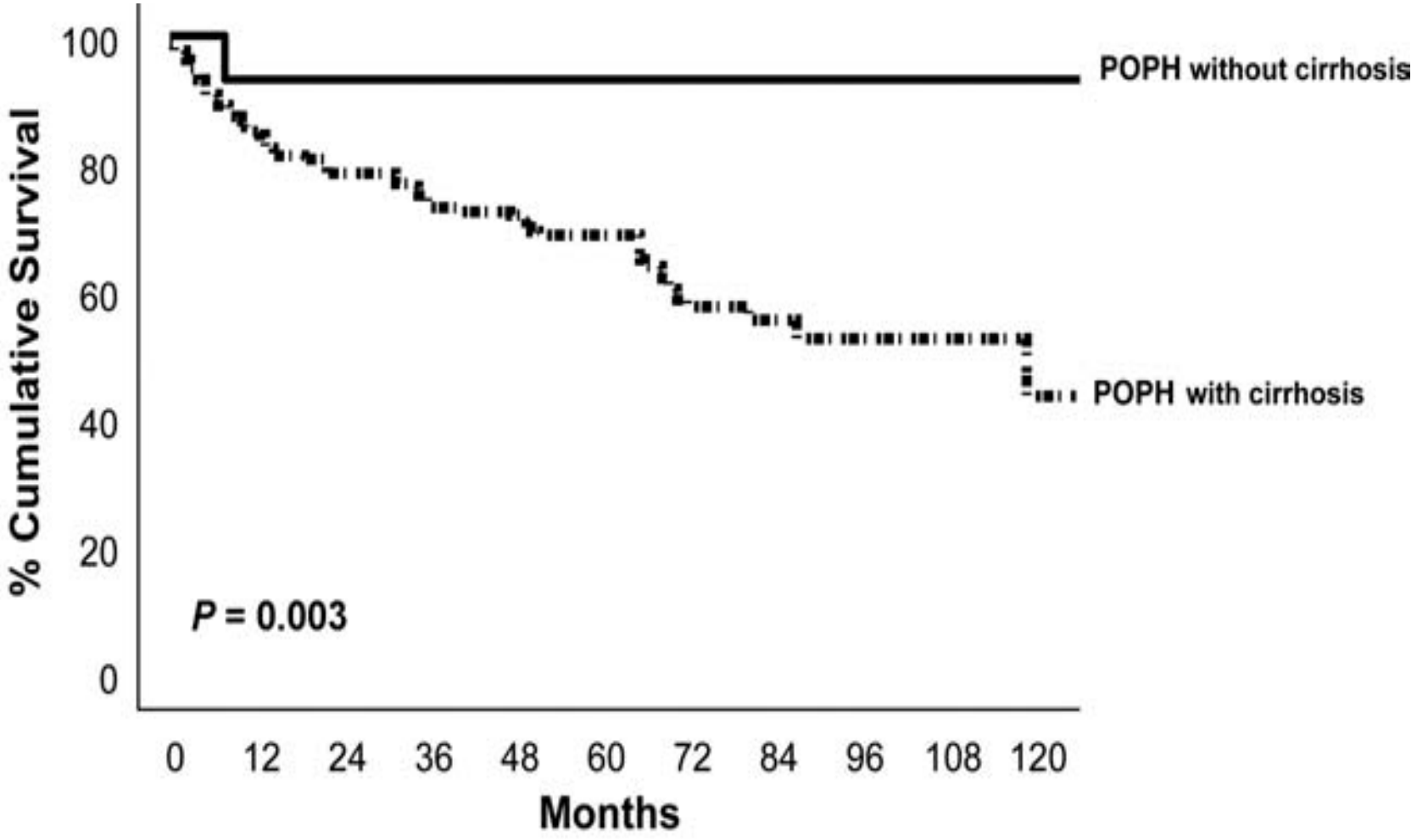
- A French retrospective analysis 154 patients with POPH from 1984 to 2004 : 60% belonged to NYHA class III or IV, and this was associated with a low cardiac index
- The survival rates at 1, 3, and 5 years were 88%, 75%, and 68%, respectively, and they were significantly better than the rates reported 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).

Le Pavec J et al . Am J Respir Crit Care Med 2008

- A report from the Registry to Evaluate Early And Long 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. al. 906-

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

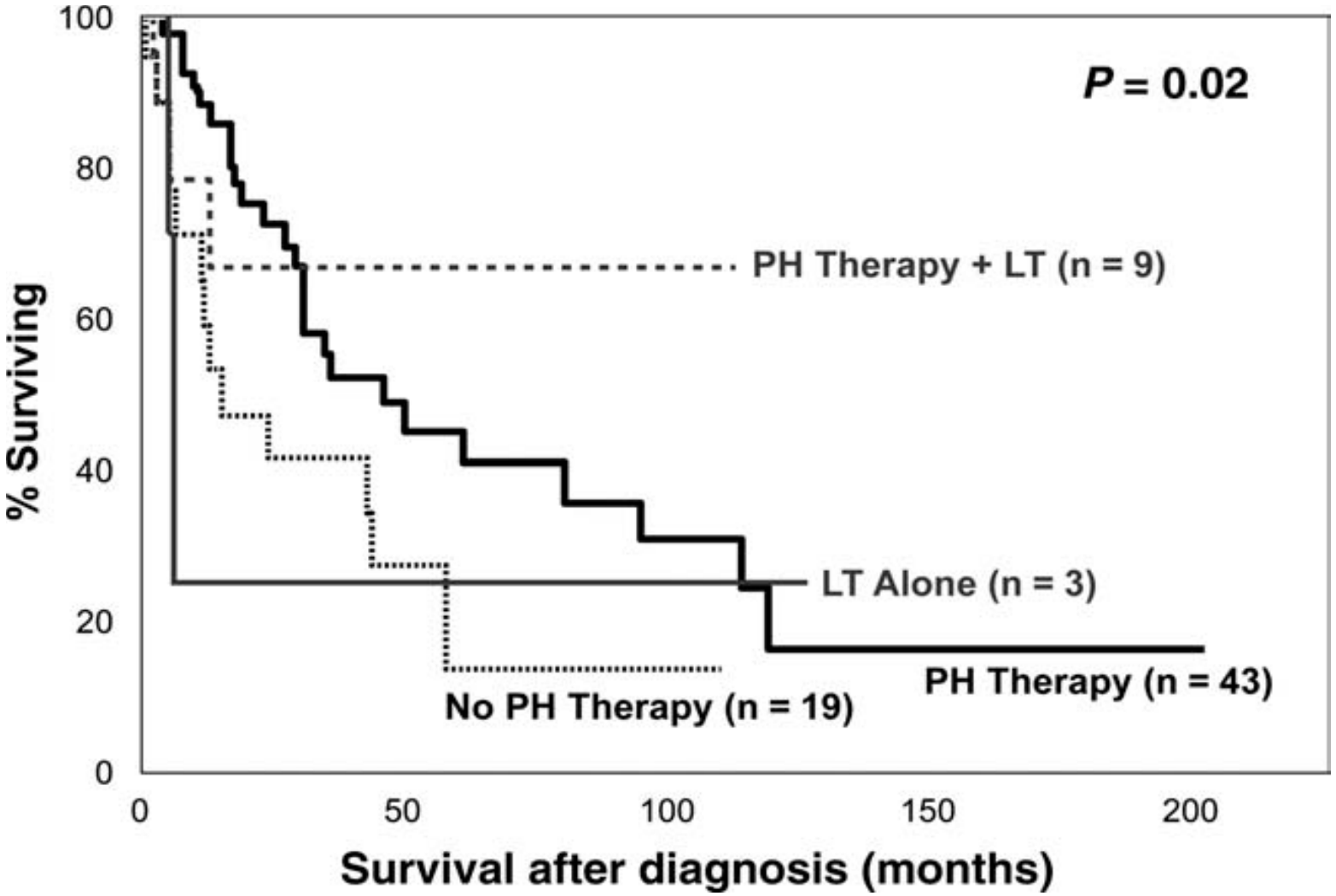
Natural History of POPH

	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.

Swanson KL et al . Am J Transplant 2008;8:2445Swanson 2445--24532453

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

Management outline

- Diuretics for Volume Overload
- O2 Supplementation for Hypoxemia
- Prostacyclin Analogs ----Epoprostenol
- Oral Endothelin Receptor Antagonists----Bosentan
- Phosphodiesterase-5 Inhibitors----Sildenafil

Treatment

- 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 PTx generally
- 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.

Ricci GL et al. Liver Transpl 2007;13:1506Ricci 1506--1514

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.

Provencher S,et al . Gastroenterology 2006;130:120-126

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.
- the mortality rate after OLT is 50% if MPAP is >35 mm Hg and 100% if MPAP is >50 mm Hg
- LT can be performed safely if the hemodynamics are suitably controlled.

Krowka MJ. Semin Liver Dis 2006;26: 265Krowka 265-272.
Ramsay M. Curr Opin Anaesthesiol 2010;23:145.150.

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/UN OS November 16/ 17, 2009. Orlando, Florida. Summary

HPS Summary-

- HPS - unique complication of chronic liver disease that portends poor prognosis
- Early detection (hypoxia at rest, PaO2 <80) can help expediting OLT – mainstay of treatment
- Dx: bubble echo, technetium macroaggregated albumin scan, or pulmonary angiography
- Those with PaO2 b/w 50 and 60 prioritized for OLT (22 -24 MELD points), PaO2< 50 or shunt fraction >20% might preclude OLT (center dependent)

POPH Summary-

- 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.