Pulmonary complications of liver disease

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Dutch Liver Week 2019

No disclosures

Learning objectives

Recognition and diagnosis of pulmonary complications of liver disease

Implications on prognosis

Management options – place of liver transplantation

Case

40-year old woman with alcoholic cirrhosis, MELD 22

History:

- childhood asthma
- 1999: cholecystectomie
- 2001: reflux esophagitis
- 2004: cirrhosis, varices, mild ascites

Meds:

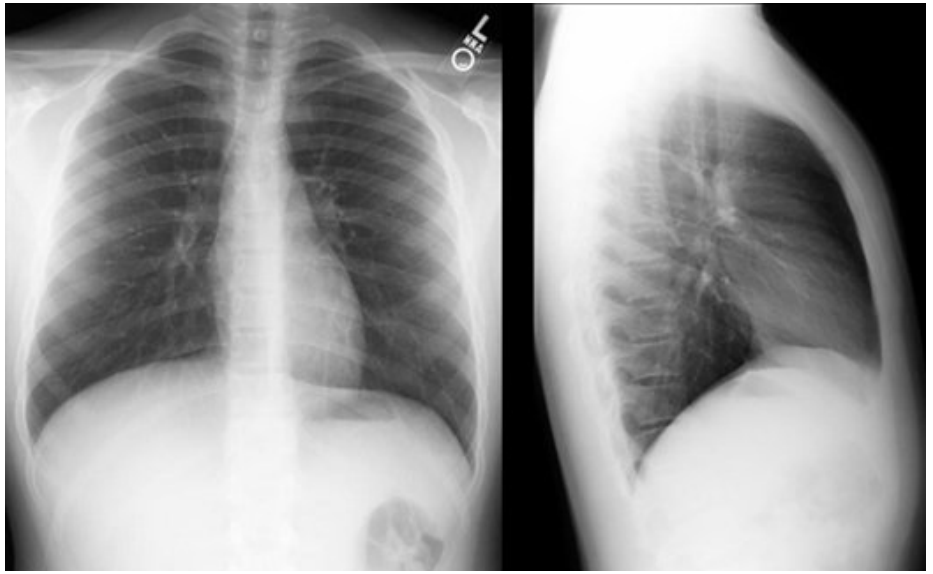
- Furosemide 40 mg
- Spironolactone 150 mg
- Propranolol 40 mg 2dd
- Pravastatin 40 mg

Progressive dyspnea 2 months…

Differential diagnosis – investigations?

Investigations

Labs: unchanged, normal leukocytes, normal CRP



SaO2: 93%

Pulmonary function test:

- DLCO 40% predicted
- No obstruction
- Mild restrictive changes

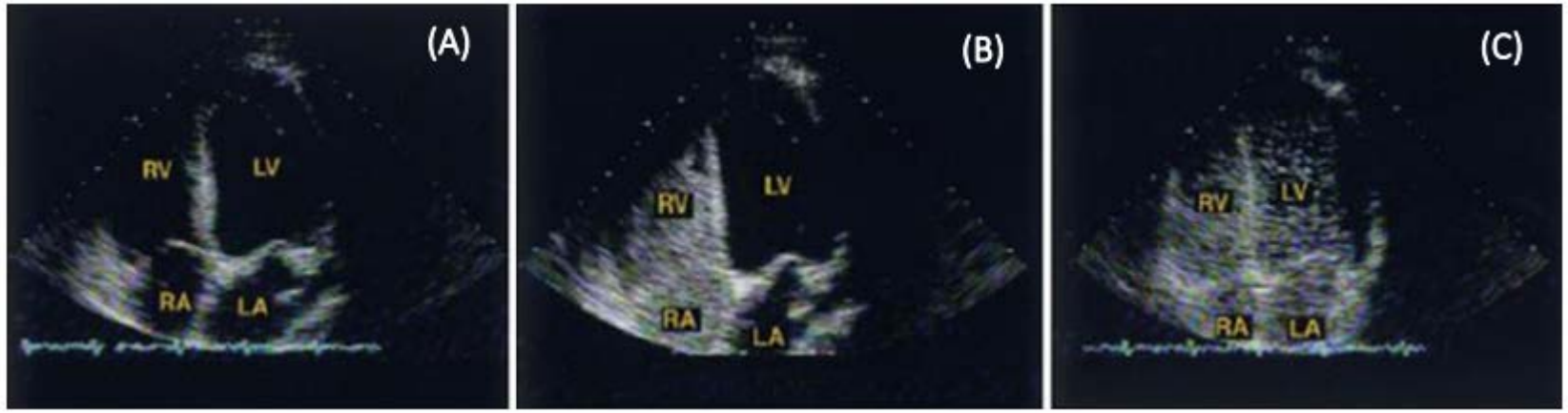
Differential diagnosis – exclusions – further examinations?

Investigations

ABG: pH 7,6, PaO2 69 mmHg, PaCO2 26 mmHg

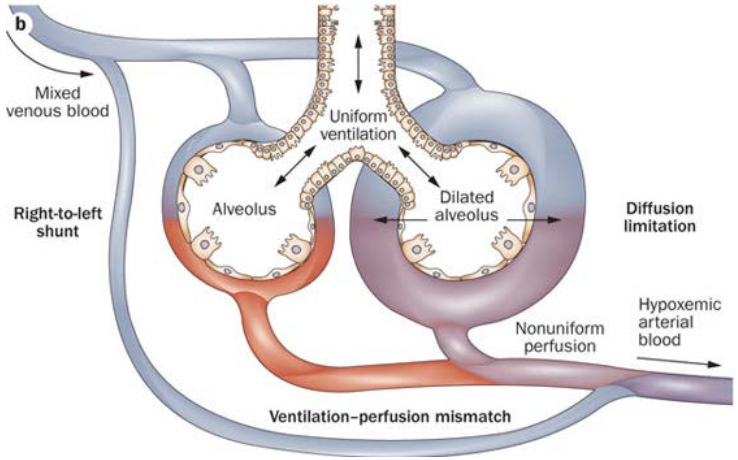
Echocardiography: EF 55% nl Ao valve, nl Mi valve, RVSP: 32 mmHg

Microbubble echocardiography: delayed opacification of the left system

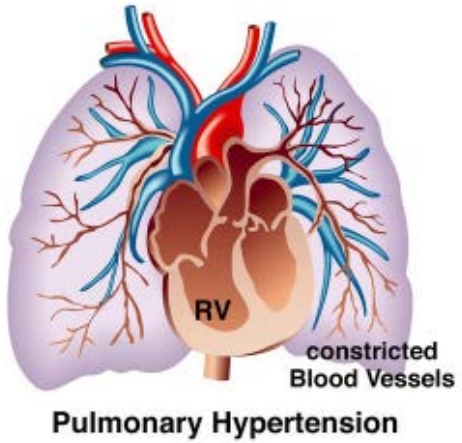


Differential diagnosis?

Pulmonary complications of liver disease



HEPATOPULMONARY SYNDROME



PORTOPULMONARY HYPERTENSION

state of the art and what's new

Hepatopulmonary syndrome (HPS)

Diagnostic criteria – triad

1. liver disease, most commonly cirrhosis
2. intrapulmonary vascular dilations (IPVDs) – shunts
3. abnormal gas exchange: P(A-a) O2 gradient ≥ 15 mmHg

$$\text{A–a Gradient} = \begin{cases} \left(150\ \text{mmHg} - \frac{5}{4}(P_aCO_2)\right) - P_aO_2 & \text{or} \\ \left(20\ \text{kPa} - \frac{5}{4}(P_aCO_2)\right) - P_aO_2 \end{cases}$$

Stage	*PaO_2*
Mild	≥ 80 mmHg
Moderate	60-79 mmHg
Severe	50-59 mmHg
Very severe	< 50 mmHg

Prevalence: +- 30%, underrecognized

No association with severity of liver disease

Clinical features

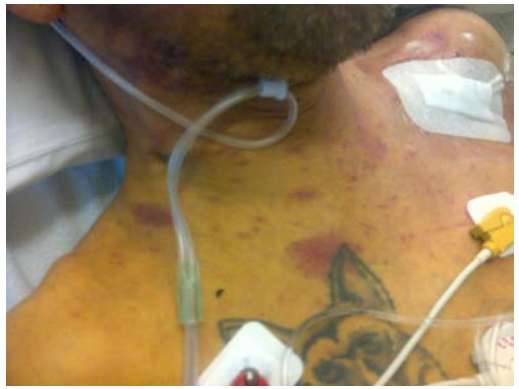
ASYMPTOMATIC!

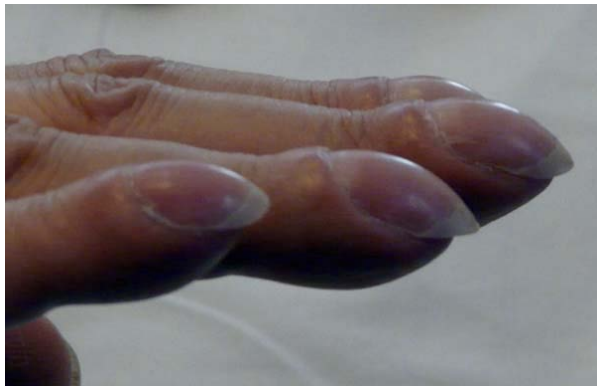
Cyanosis

Clubbing

Spider angiomata

Platypnea - orthodeoxia





Screening and diagnosis

1. liver disease

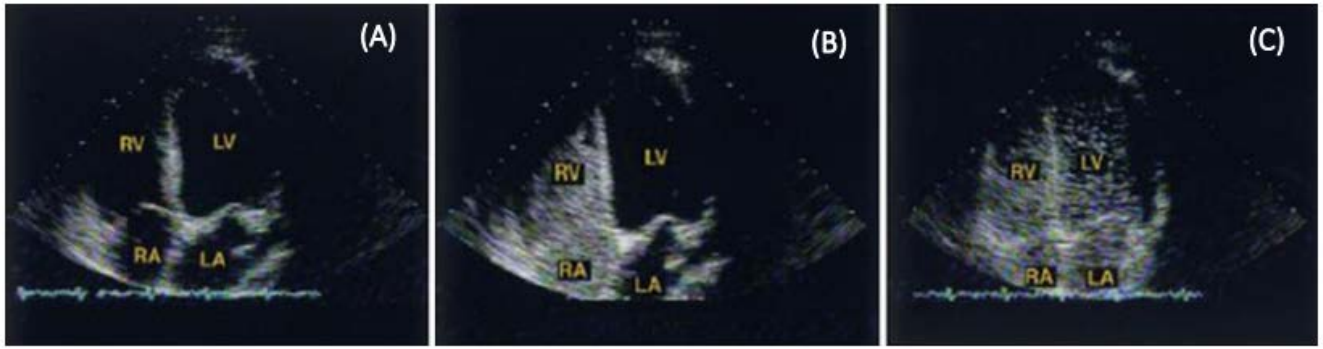
2. IPVDs

contrast-enhanced echocardiography

gold standard

hand-shaken saline → microbubbles >10 micron

+: DD intracardiac shunts (<3 heart cycles)



Screening and diagnosis

1. liver disease

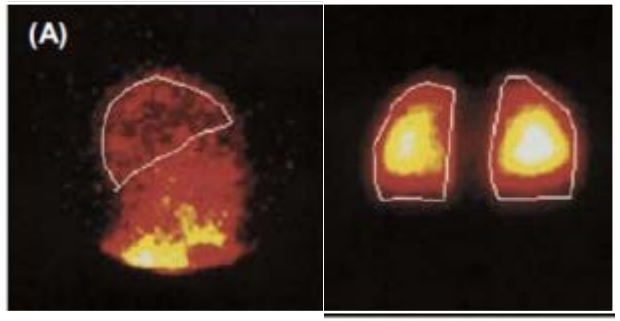
2. IPVDs

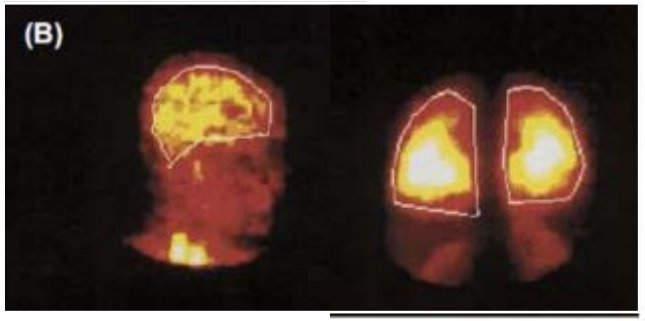
contrast-enhanced echocardiography

99m-Technetium-labeled macroaggregated albumin (MAA) scan

MAA >20 micron → uptake in brain and kidneys

+: quantification of shunting, -: no DD intracardiac shunts





Screening and diagnosis

3. impaired gas exchange

- diagnosis: always with ABG: P(A-a) O2 gradient ≥ 15 mmHg
- screening: pulse oximetry: SaO2 <94% detects all HPS pts with PaO2 <60 mmHg (spec 88%)

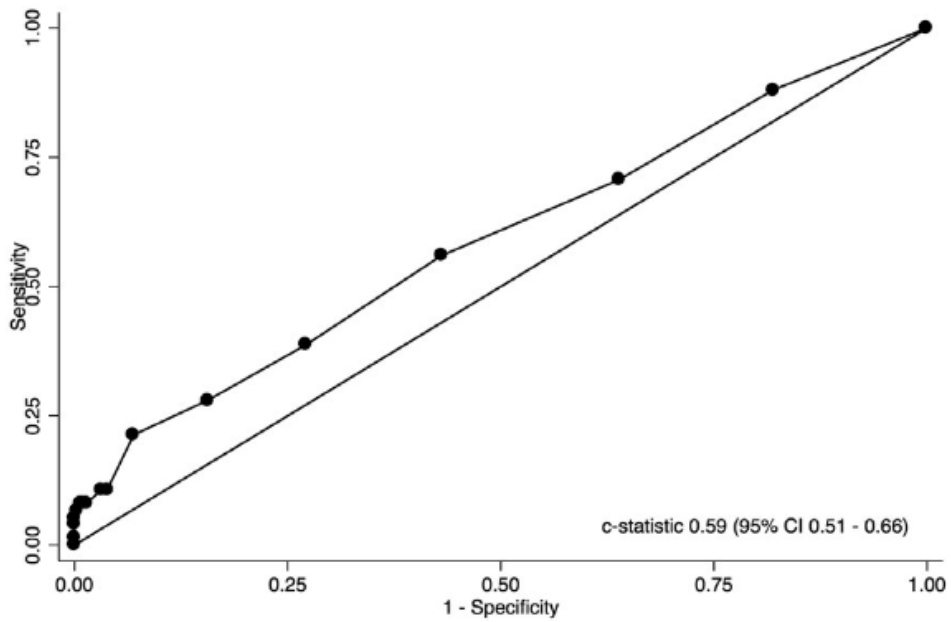
Abrams et al, Liver Transp 2002

Pulse oximetry is not sufficiently sensitive to screen for HPS in LT candidates

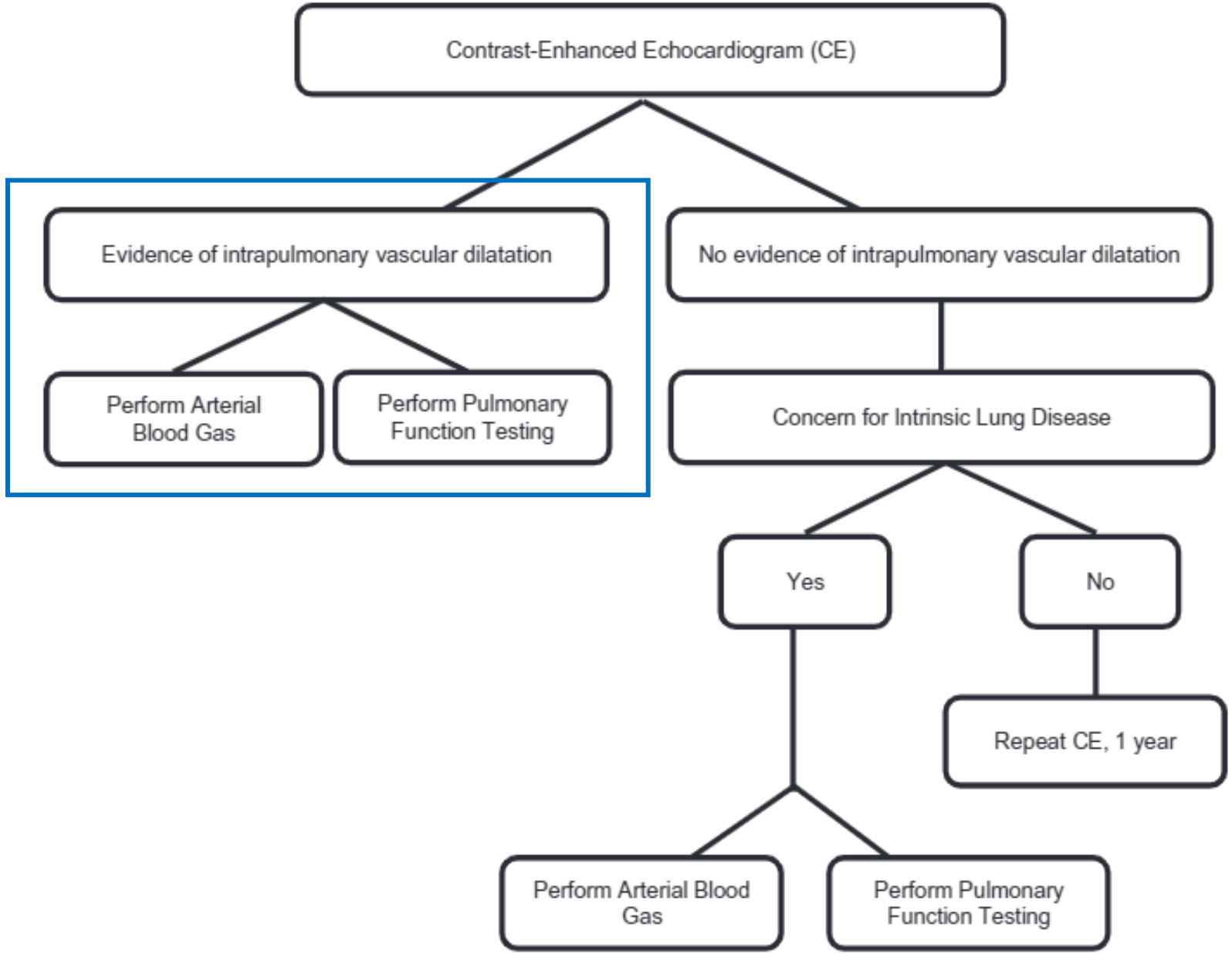
PVCLD2 study: multicenter, prospective cohort study USA

363 pts evaluated for LT, 75/363 HPS

SpO_2 cutoff	Sensitivity (95% CI)	Specificity (95% CI)
All-comers		
<96%	0.28 (0.18-0.38)	0.84 (0.80-0.89)
≤94%	0.21 (0.12-0.31)	0.93 (0.90-0.96)
≤97% (optimal)	0.56 (0.45-0.67)	0.57 (0.51-0.63)
Patients without lung disease		
<96%	0.28 (0.18-0.38)	0.91 (0.86-0.96)
≤94%	0.21 (0.12-0.31)	0.96 (0.93-0.99)
≤97% (optimal)	0.56 (0.45-0.67)	0.68 (0.60-0.76)
HPS with PaO_2 <60 mm Hg and all-comers		
<96%	0.71 (0.38-1.00)	0.83 (0.79-0.87)
≤94%	0.71 (0.38-1.00)	0.91 (0.88-0.94)
≤88% (optimal)	0.71 (0.38-1.00)	0.99 (0.98-1.00)

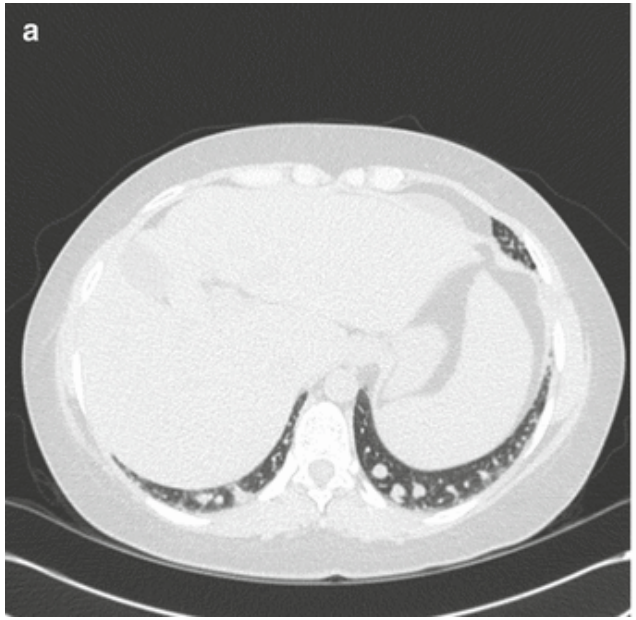


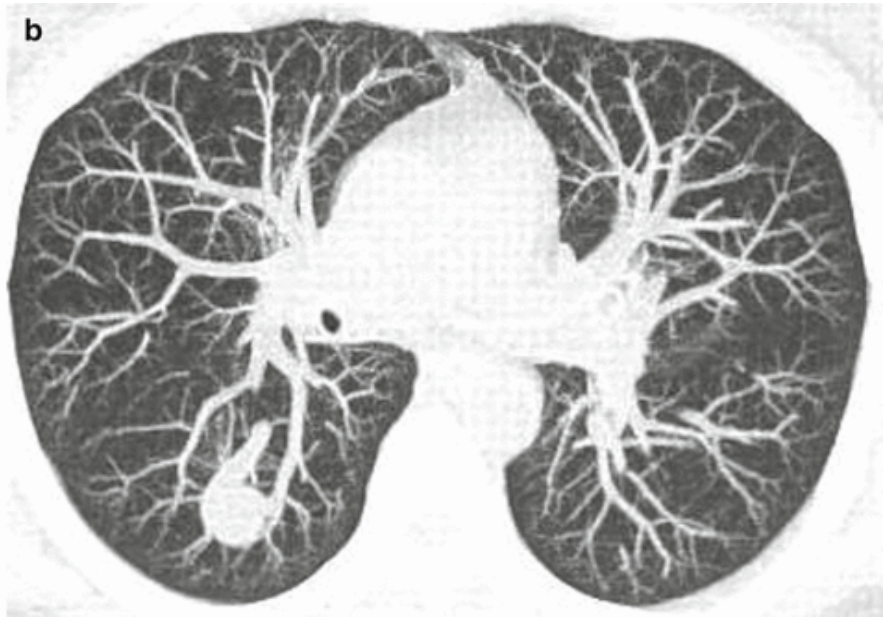
Forde et al, Hepatology 2019

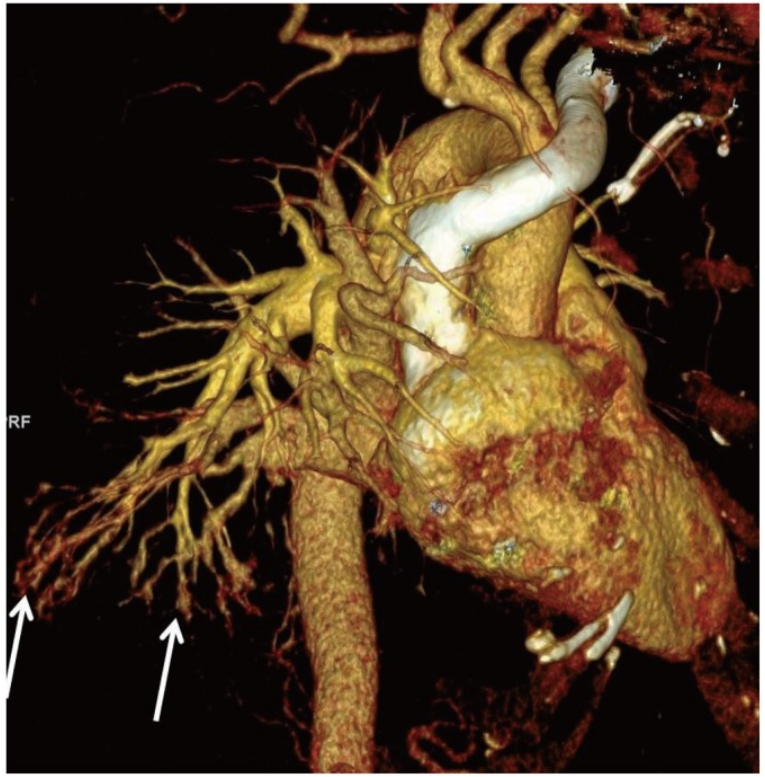

Contrast-Enhanced Echocardiogram (CE)
Evidence of intrapulmonary vascular dilatation
No evidence of intrapulmonary vascular dilatation
Perform Arterial Blood Gas
Perform Pulmonary Function Testing
Concern for Intrinsic Lung Disease
Yes
No
Repeat CE, 1 year
Perform Arterial Blood Gas
Perform Pulmonary Function Testing

Other investigations

Pulmonary CT

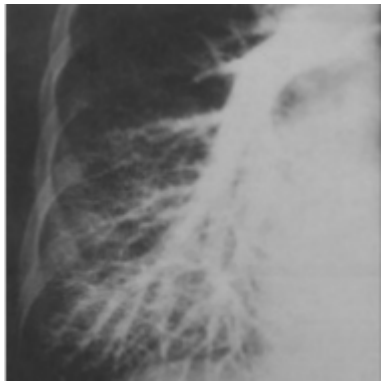






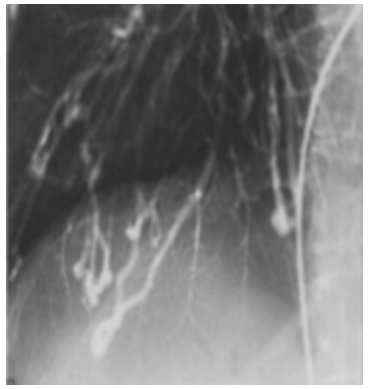
Other investigations

Pulmonary angiography



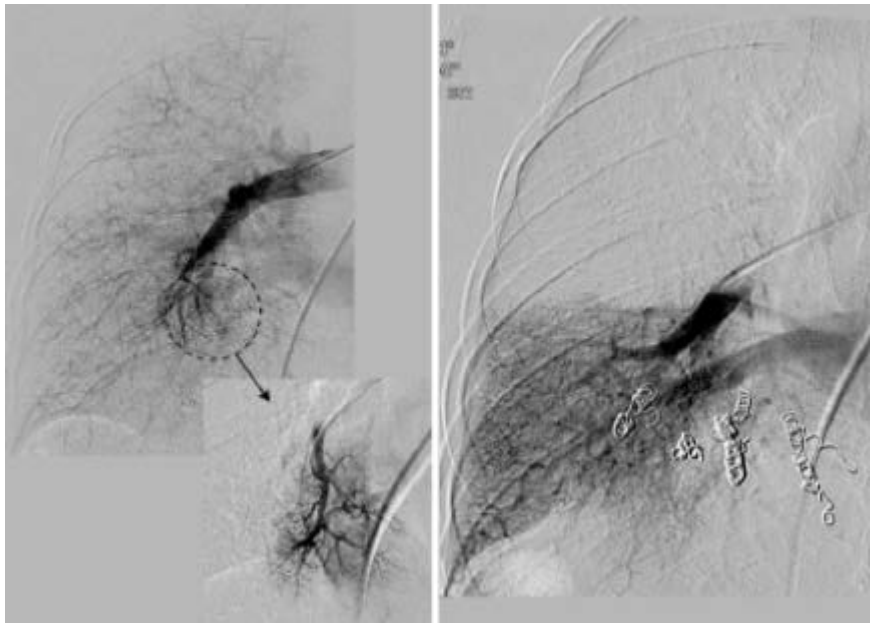
Type I

diffuse, small



Type II

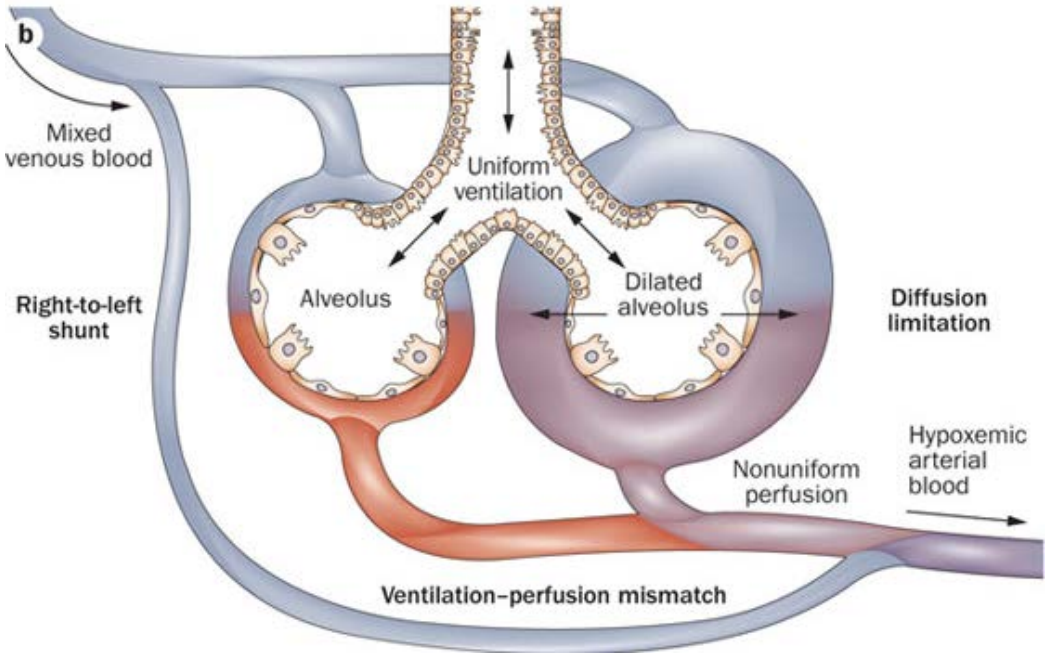
focal, big

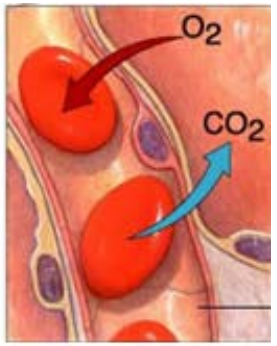


coiling

Pathophysiology

1. V/Q mismatch
2. Diffusion restriction
3. AV communications

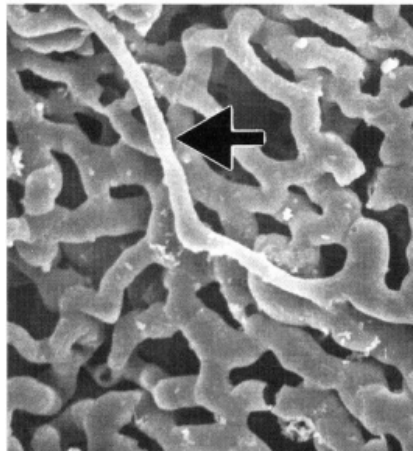




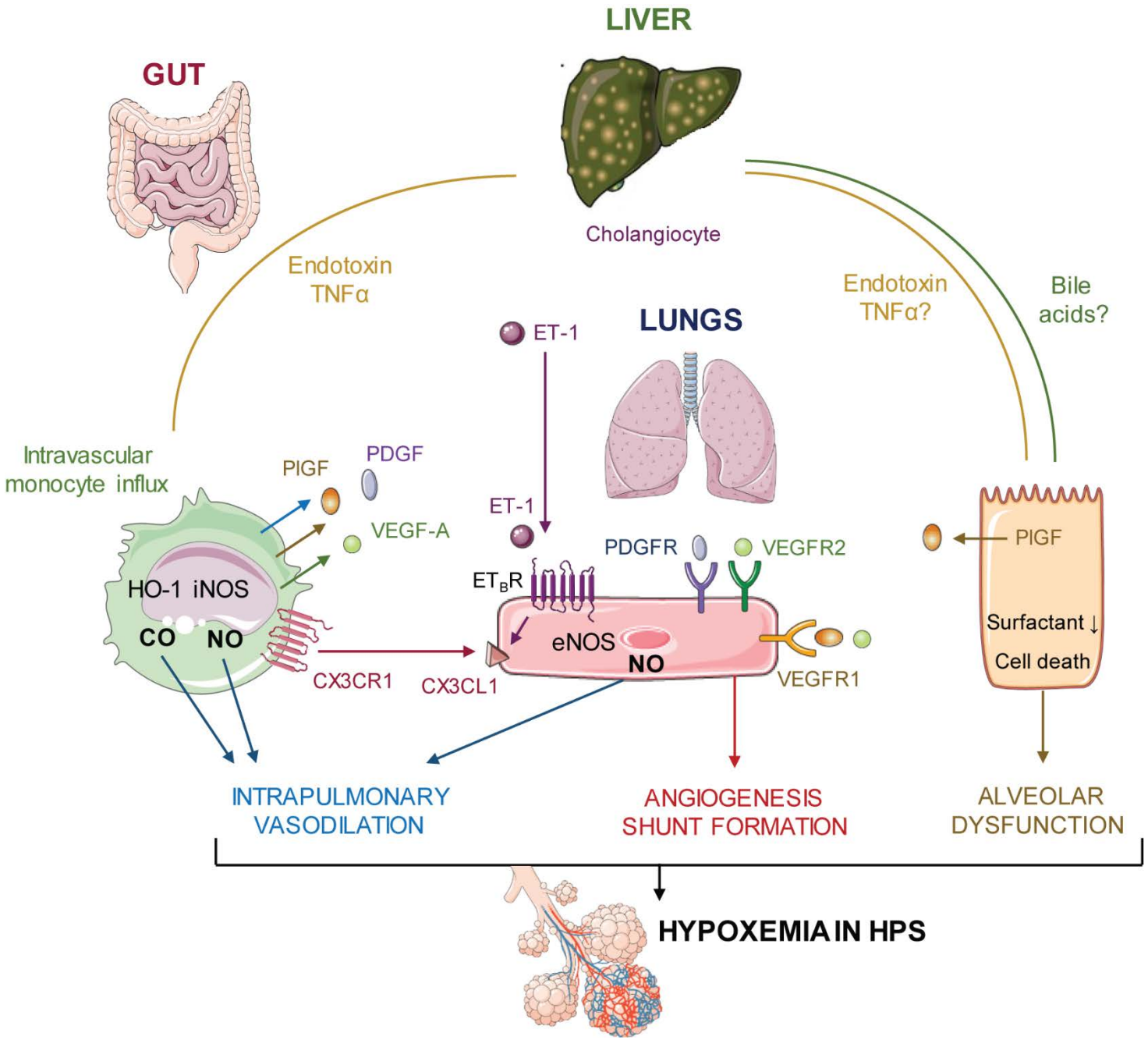
Pathogenesis

Rodent studies

Common bile duct ligation



shunt



Raevens et al, Hepatology 2019

Natural history and prognosis

PaO2 decreases in 85% of patients over time, average -5 mmHg per year

Untreated:

median survival 24 months, 5-year survival rate 23%

(non-HPS 87 months, 63%)

PVCLD study

HR 2.41, 95%CI 1.31-4.41

after adjustment for age, sex, race, LT, MELD

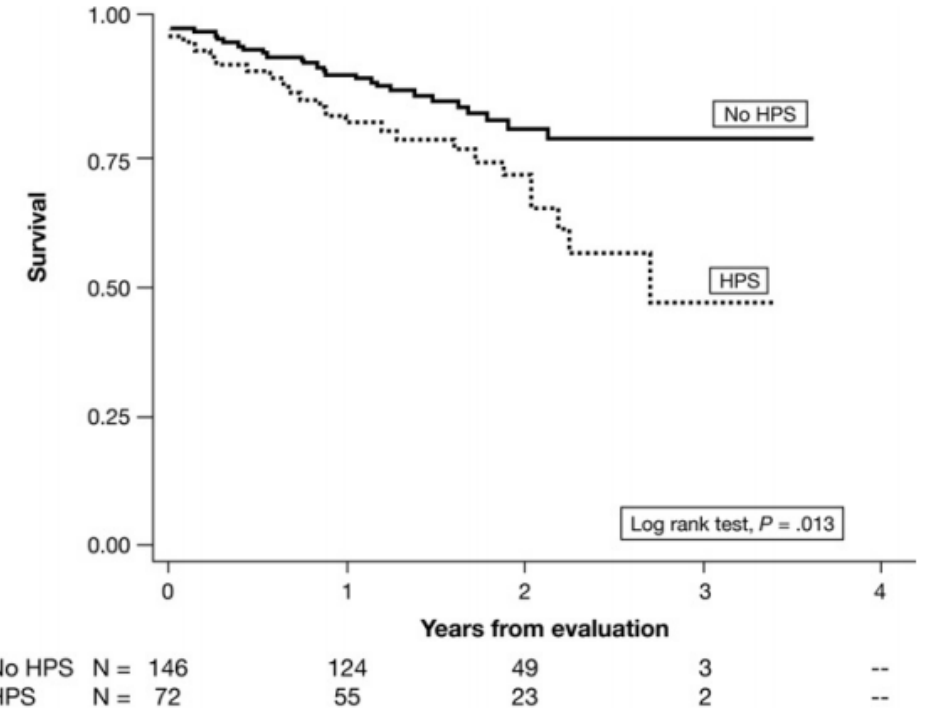


Figure 2. Kaplan–Meier survival estimates of patients with HPS and patients without HPS (No HPS) (n = 218).

Fallon et al, Gastroenterology 2008

Treatment options

Medical

methylene blue (guanylate cyclase inhibitor)

L-NAME (NO inhibitor)

pentoxifylline

norfloxacin

MMF

…

→ ALL FAILED

→ no effective medical therapy

Supportive - palliative

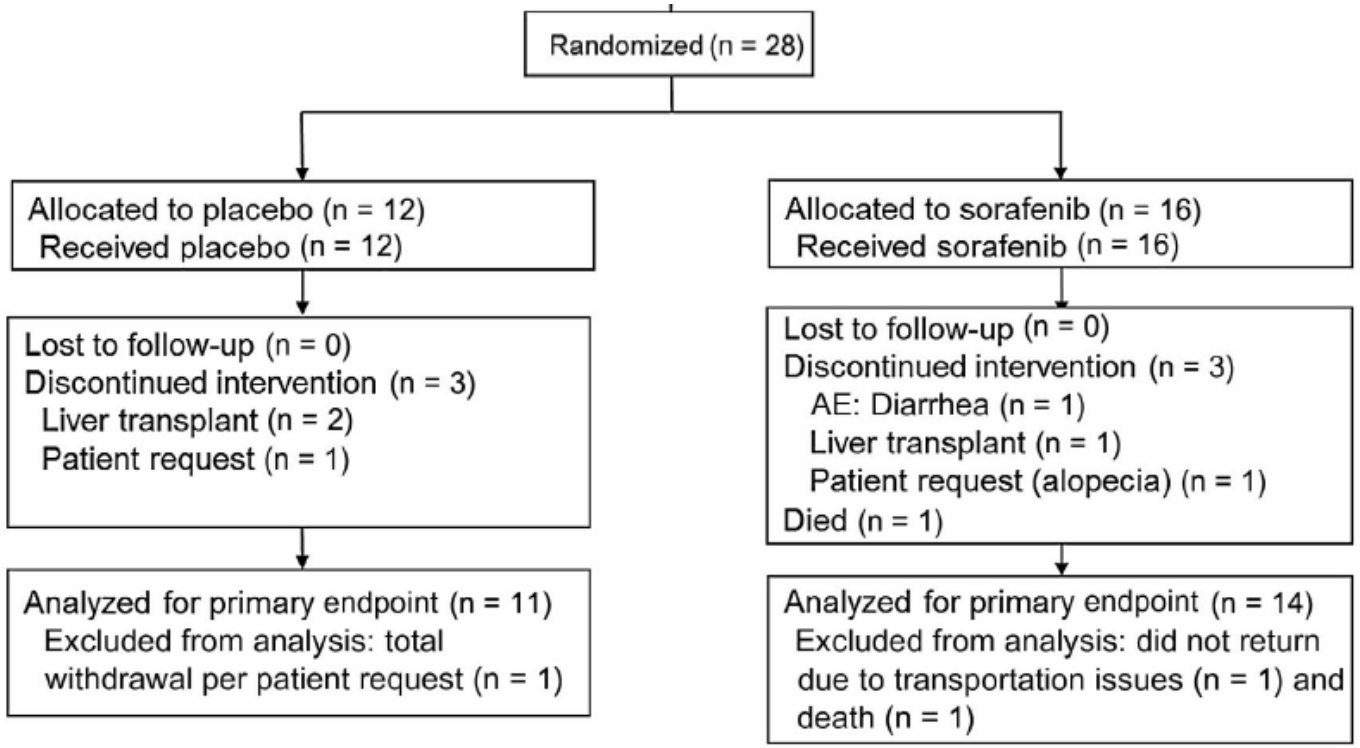
O2

coiling of large AV communications

Treatment options

Sorafenib - first RCT in HPS

28 HPS patients, CP-A-B, sorafenib 400 mg vs placebo



Kawut et al, Liver Transpl 2019

Treatment options

Sorafenib - first RCT in HPS

intrapulmonary shunting =

PaO2 =

6-MWD =

circulating angiogenic factors =

worse mental component score in sorafenib

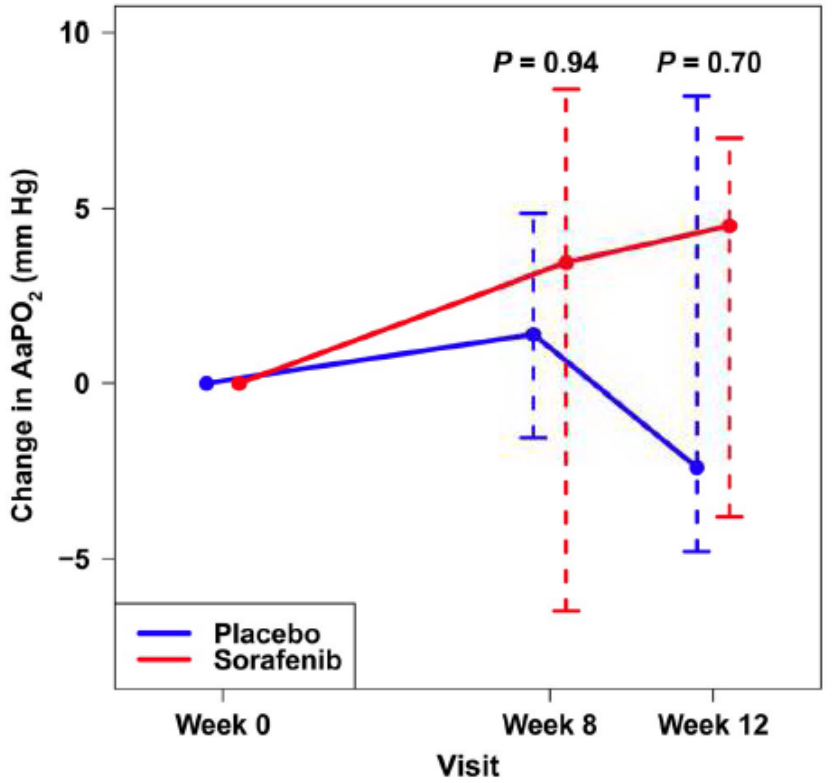


FIG. 2. Median (whiskers, IQR) absolute change in $AaPO_2$ (mm Hg) from baseline to 8 and 12 weeks in patients receiving sorafenib (red) or placebo (blue). *P* values are for comparison with baseline.

Kawut et al, Liver Transpl 2019

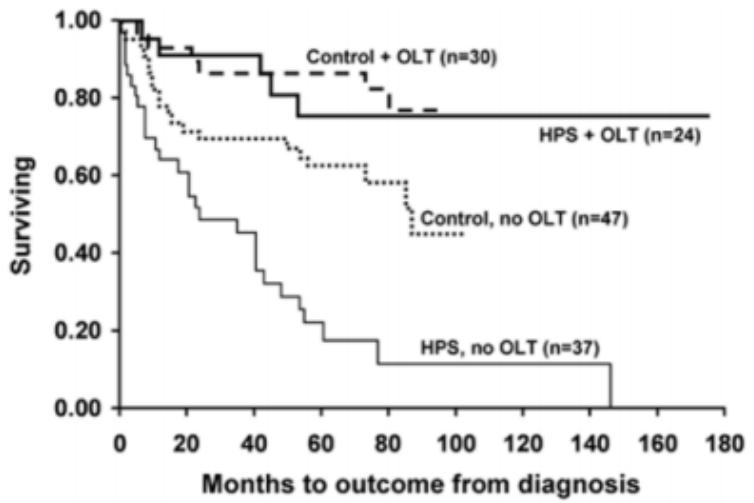
Treatment options

Liver transplantation

The only treatment proven to be effective

HPS with LT: 5-year survival 76%
HPS without LT: 5-year survival 23%

complete resolution in >80% of cases



Swanson et al, Hepatology 2005

Treatment options

Liver transplantation

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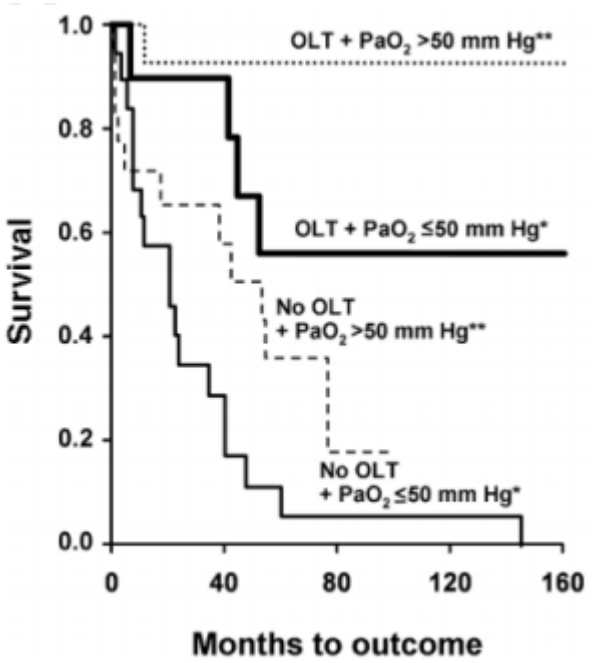
HPS with LT: 5-year survival 76%
HPS without LT: 5-year survival 23%

complete resolution in >80% of cases

Predictors of worse outcome

PaO2 <50 mmHg
shunt fraction >20%



Swanson et al, Hepatology 2005

Treatment options

Liver transplantation

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HPS with LT: 5-year survival 76%
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complete resolution in >80% of cases

Predictors of worse outcome

PaO2 <50 mmHg
shunt fraction >20%

Recurrence of HPS post-LT *is* possible…
Transition to POPH *is* possible…

Swanson et al, Hepatology 2005

Treatment options

Liver transplantation

hypoxemia in HPS is progressive and post-LT mortality is highest in patients with very severe HPS

no correlation between HPS severity and the severity of the underlying liver disease

only effective treatment option

→ *HPS indication for LT*

→ *Creation of standard exception for severe HPS*

Treatment options

Liver transplantation

Eurotransplant criteria

N°	exceptional MELD criteria	A	B/L	G	NL	SLO	CRO
1	Proof of liver disease	✓	✓	✓	✓	✓	✓
2	PaO2 <60 mmHg at rest (sitting/ supine ambient air)	✓	✓	✓	✓	✓	✓
3	Proof of intrapulmonary shunt and exclusion of intracardiac shunts by contrast-enhanced echocardiography	✓	✓	✓	✓	✓	✓
4	No alternative pulmonary disease to explain hypoxemia	✓	✓	✓	✓	✓	✓

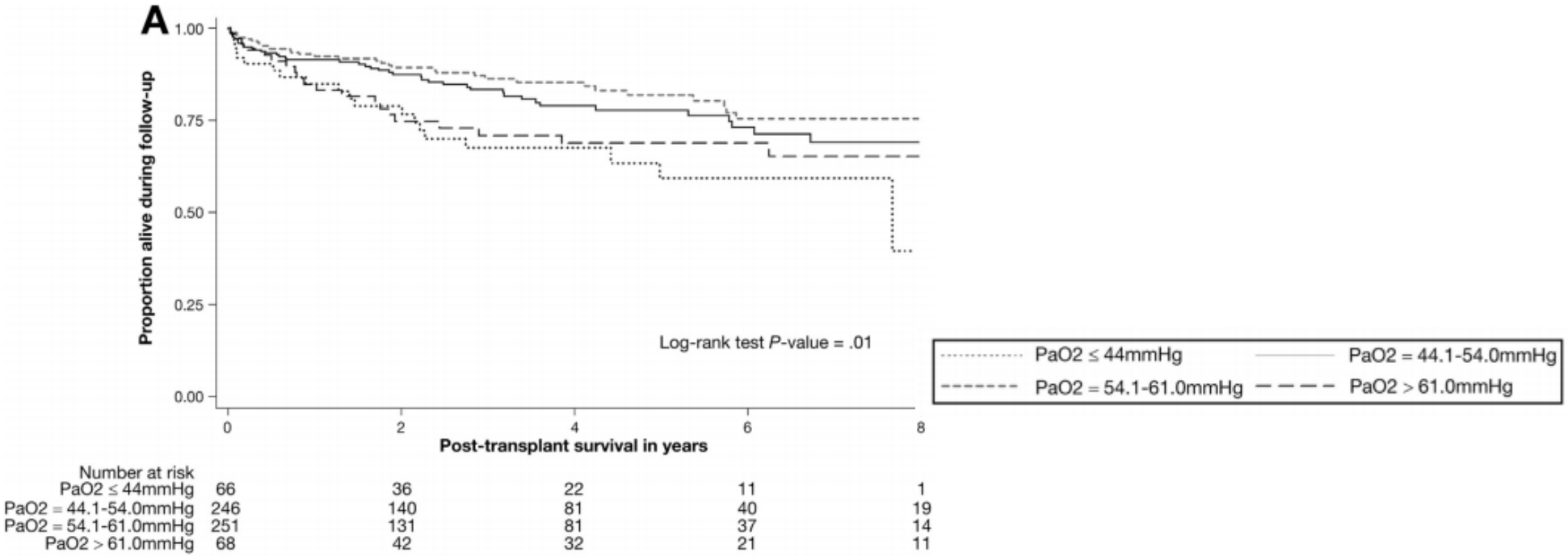
Initial SE MELD compatible with a 3-month probability of death of
15% (a score of 22) in Austria, Belgium, Luxemburg, Germany, Slovenia and Croatia
10% (a score of 20) in the Netherlands

Exceptional MELD is reconfirmed every 90 days, update of +10% MELD equivalent

Treatment options

Liver transplantation PVCLD study USA, 2000-2012, 973 HPS SE

- Overall survival is better in HPS compared to non-HPS
- Pre-transplant mortality lower in HPS compared to non-HPS
- Post-LT mortality non-HPS = HPS
- PaO2 ≤44 mmHg: significantly increased post-LT mortality, 5-y survival 59%

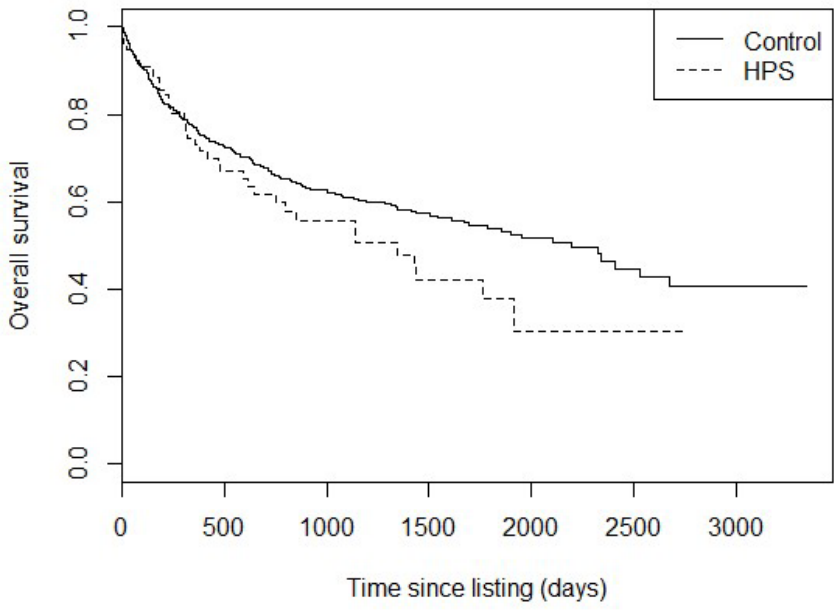


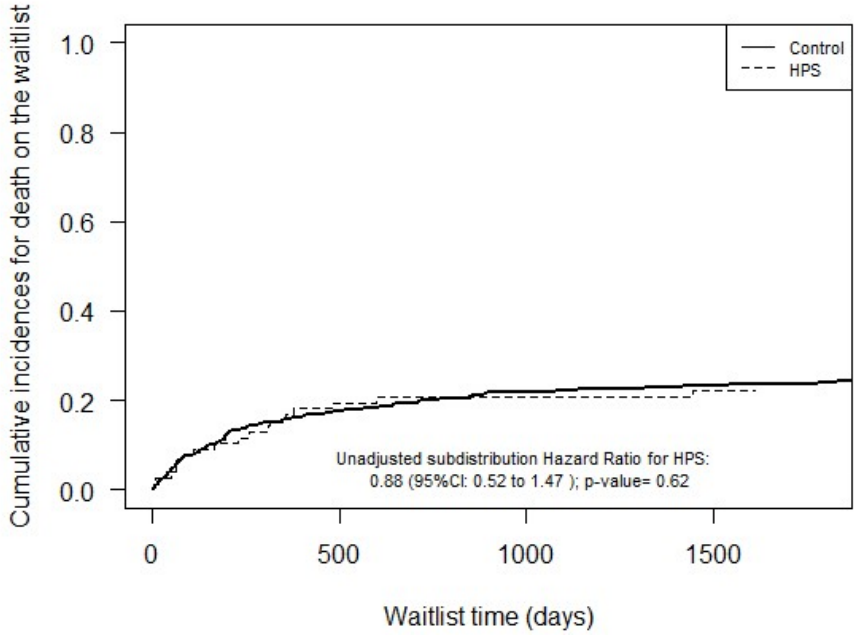
Goldberg et al, Gastroenterology 2014

Treatment options

Liver transplantation Eurotransplant study, 2006-2016, 88 HPS SE matched to 442 non-HPS

- Overall mortality HPS = non-HPS
- Pre-transplant mortality HPS = non-HPS
- Post-LT survival rates 77% in HPS and 85% in non-HPS at 6m, 70% in HPS and 81% in non-HPS at 1y





Raevens et al, Eur Resp J 2019

Case

40-year old woman with alcoholic cirrhosis, MELD 22

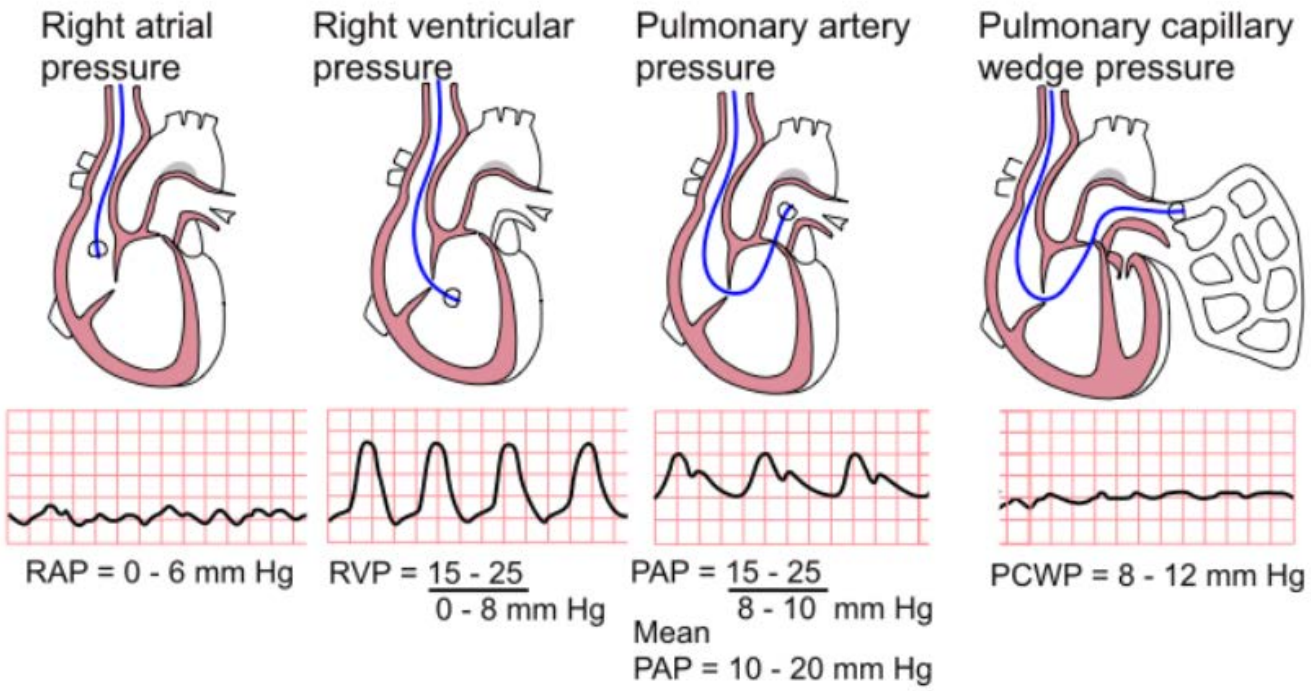
Progressive dyspnea 2 months…

Echocardiography: EF 55% nl Ao valve, nl Mi valve, RVSP: 32 mmHg

Quid?
normal?
further investigation?

Case

Right heart catherization: mPAP 27 mmHg, PVR 290 dyne.s.cm-5, PCWP 12 mmHg



PVR = (80x(mPAP–PCWP))/CO

What's next?

Portopulmonary hypertension (POPH)

Diagnostic criteria – triad

1. Portal hypertension (with or without cirrhosis)
2. mPAP >25 mmHg
3. PCWP <15 mmHg
4. PVR >240 dyne.s.cm-5

Stage	*mPAP*
Mild	> 25 - < 35 mmHg
Moderate	≥ 35 - < 45 mmHg
Severe	≥ 45 mmHg

Prevalence: 5%

No association with severity of liver disease

Screening and diagnosis

1. portal hypertension

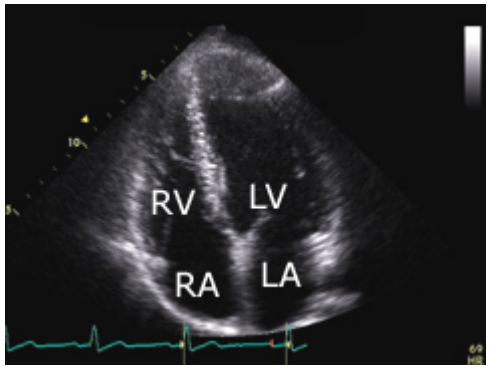
2. pulmonary hypertension

   screening: echocardiography

   RVSP as an estimation of the sPAP

   Bernouilli equation: $sPAP = 4 \times (TR)^2 + mRAP$

   repeat every 3 months



diagnosis: ALWAYS right heart catheterization!

when?

TABLE 3. Diagnostic Accuracy of Doppler Echocardiography Using Different Cutoff Values

AUROC 0,974

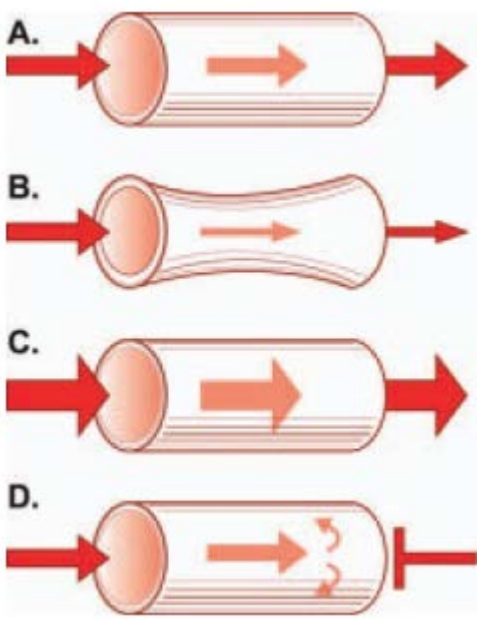
	sPAP					
	30 mm Hg	35 mm Hg	38 mm Hg	40 mm Hg	45 mm Hg	50 mm Hg
Sensitivity (%)*	100	100	100	86	86	86
Specificity (%)†	54	70	82	84	92	95
Positive predictive value (%)‡	10	14	22	21	33	46
Negative predictive value (%)§	100	100	100	99	99	99
Positive likelihood ratio††	2.2	3.3	5.6	5.4	10.8	17.2
Accuracy (%)‡	56	71	84	84	91	95
Prevalence (%)	4.6	4.6	4.6	4.6	4.6	4.6

-: false +

-: false -

Raevens et al, Liver Transpl 2014

Interpretation of right heart catheterization measurements

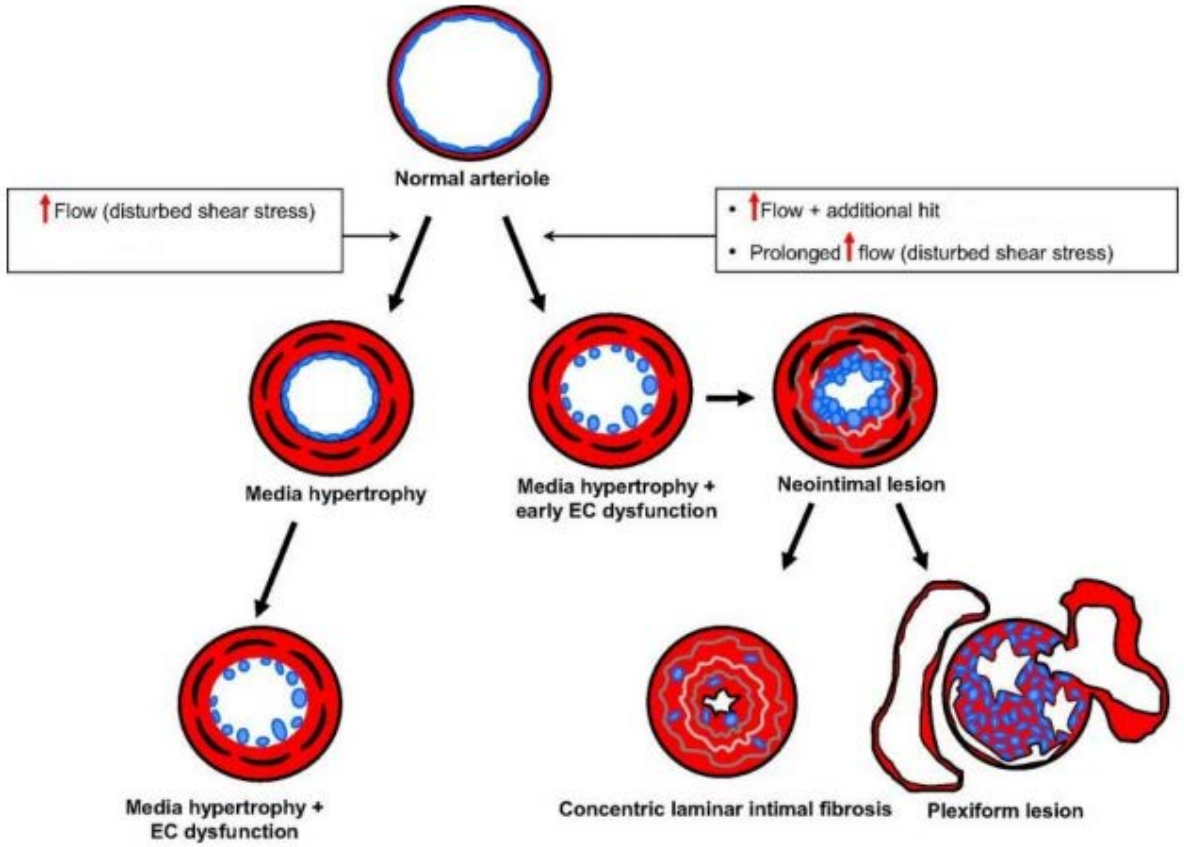


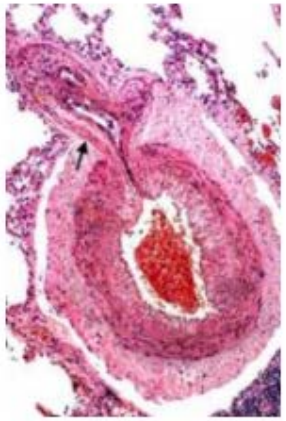
mPAP	PVR	PCWP	CO	
nl	nl	nl	nl	normal
↑	↑	nl	nl	pulmonary arterial hypertension
↑	nl	nl	↑	hyperdynamic circulation
↑	nl	↑	nl	fluid overload

Pathogenesis

Hyperdynamic circulation → shear stress → endothelial injury → VC and vascular remodeling

Vaso-active substances (ET-1, IL etc) and portosystemic shunts

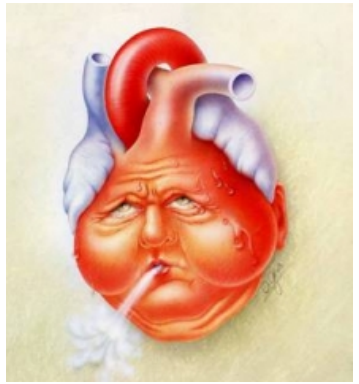




obstruction of flow

increased PVR

right heart failure



Natural history and prognosis

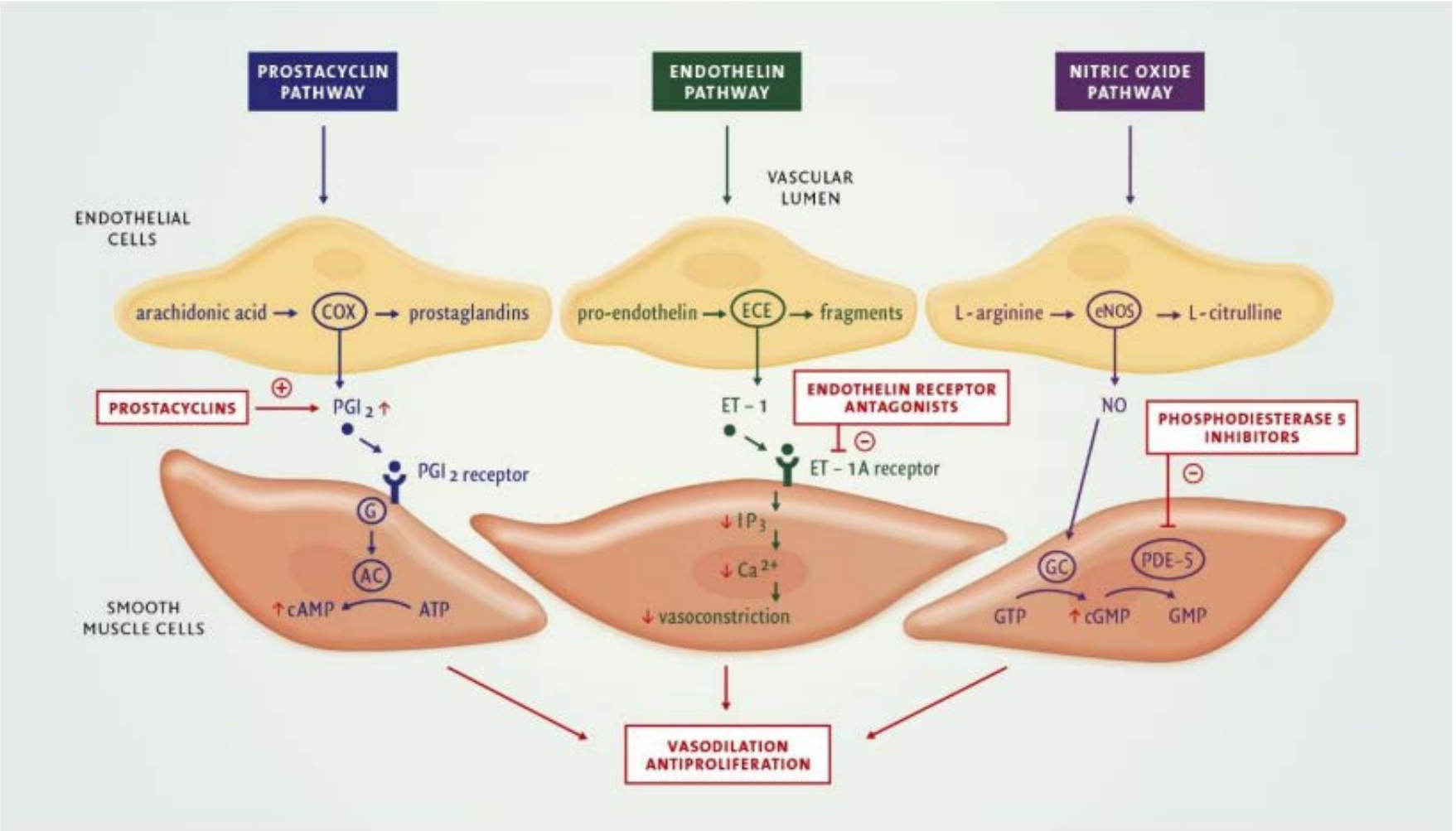
POOR PROGNOSIS IF LEFT UNTREATED!

Mean survival 15 months, 5-year survival 14%

Swanson et al, Am J Transpl 2008

Treatment options

Medical: vasodilators

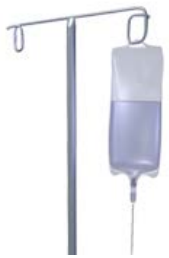


Treatment options

Medical: vasodilators, based on experience in PAH!

Class	*Drug*	*Route*
Prostacyclin analogs	Epoprostenol	IV
	Treprostinil	IV and SC, INH, PO
	Iloprost	INH
Endothelin receptor antagonists	Bosentan	PO
	Ambrisentan	PO
	Macitentan	PO
Phosphodiesterase 5 inhibitors	Sildenafil	PO
	Vardenafil	PO
	Tadalafil	PO
Soluble guanylate cyclase stimulators	Riociguat	PO
Prostacyclin receptor agonists	Selexipag	PO

IV, intravenous; SC, subcutaneous; INH, inhalation; PO, oral



Treatment options

Medical: vasodilators, based on experience in PAH!

Class	*Drug*	*Route*	
Prostacyclin analogs	Epoprostenol	IV	potent, safety issues, rebound effects
	Treprostinil	IV and SC, INH, PO	
	Iloprost	INH	
Endothelin receptor antagonists	Bosentan	PO	non-specific ETA and ETB receptor antagonist, 20:1 ETA/ETB receptor selectivity
	Ambrisentan	PO	selective ETA receptor antagonist, 100:1 ETA/ETB selectivity
	Macitentan	PO	50:1 ETA/ETB selectivity, RCT in POPH NCT02382016
Phosphodiesterase 5 inhibitors	Sildenafil	PO	
	Vardenafil	PO	caution: hypotension, worsening portal hypertension!
	Tadalafil	PO	
Soluble guanylate cyclase stimulators	Riociguat	PO	currently in trial for POPH
Prostacyclin receptor agonists	Selexipag	PO	not tested yet

IV, intravenous; SC, subcutaneous; INH, inhalation; PO, oral

Treatment options

Liver transplantation

may be curative

mortality increases with worsening pulmonary hypertension

→ *Creation of standard exception for POPH*

→ *To prevent the progression of pulmonary hemodynamics that would preclude successful LT*

Treatment options

Liver transplantation

Eurotransplant criteria

N°	exceptional MELD criteria	A	B/L	G	NL	SLO	CRO
1	Proof of underlying liver disease	✓	✓	✓	✓	✓	✓
2	PAP: 25 < PAPm < 35 mmHg (with or without therapy)	✓	✓	✓	✓	✓	✓
3	Pulmonary vascular resistance (PVR) ≥240 dyn.s.cm^{-5}	✓	✓	✓	✓	✓	✓
4	Pulmonary capillary wedge pressure (PCWP) ≤15 mmHg	✓	✓	✓	✓	✓	✓
5	All mentioned values have to be documented by right heart catheterization	✓	✓	✓	✓	✓	✓

Initial SE MELD compatible with a 3-month probability of death of 25% (a score of 25) in Austria, Belgium, The Netherlands, Luxemburg, Germany, Slovenia and Croatia

Exceptional MELD is reconfirmed every 90 days, update of +10% MELD equivalent

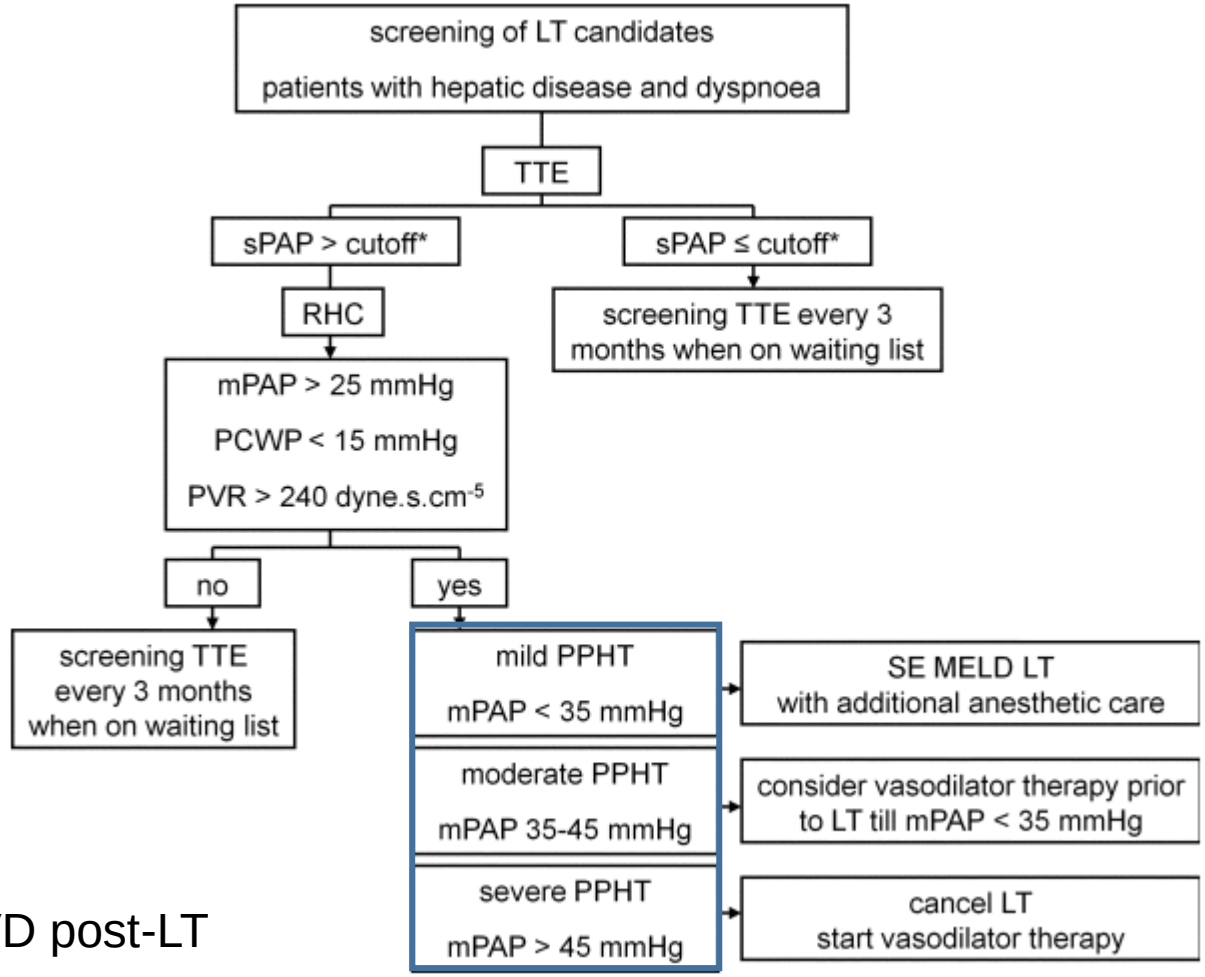
Treatment options

Liver transplantation

May be unpredictable…

mPAP 35-50 mmHg: 50% mortality

mPAP >50 mmHg: 100% mortality



29-64% of moderate/severe POPH can stop VD post-LT

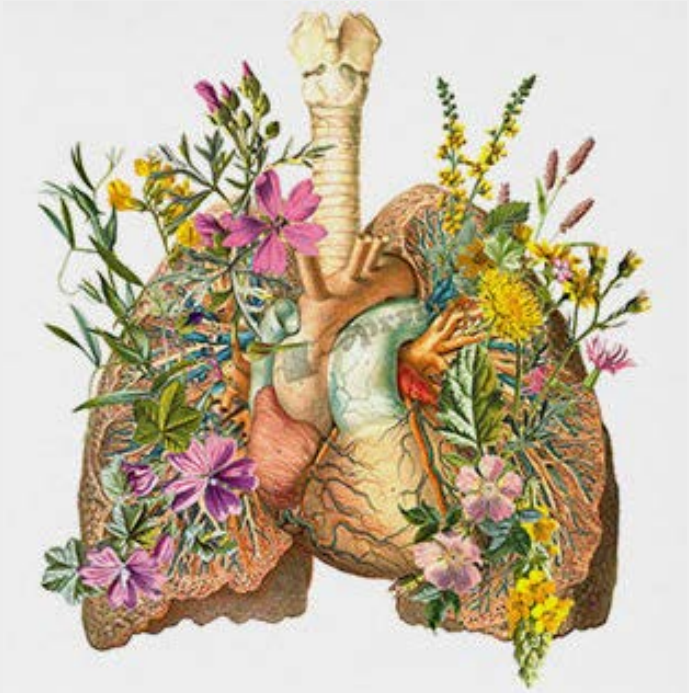
TAKE HOME MESSAGES

- Pulmonary complications of liver disease are frequently asymptomatic and significantly affect prognosis.
  Therefore active screening during the pre-LT evaluation is required.

- No medical therapies are available for HPS. LT is the only curative treatment option with excellent post-LT outcomes.

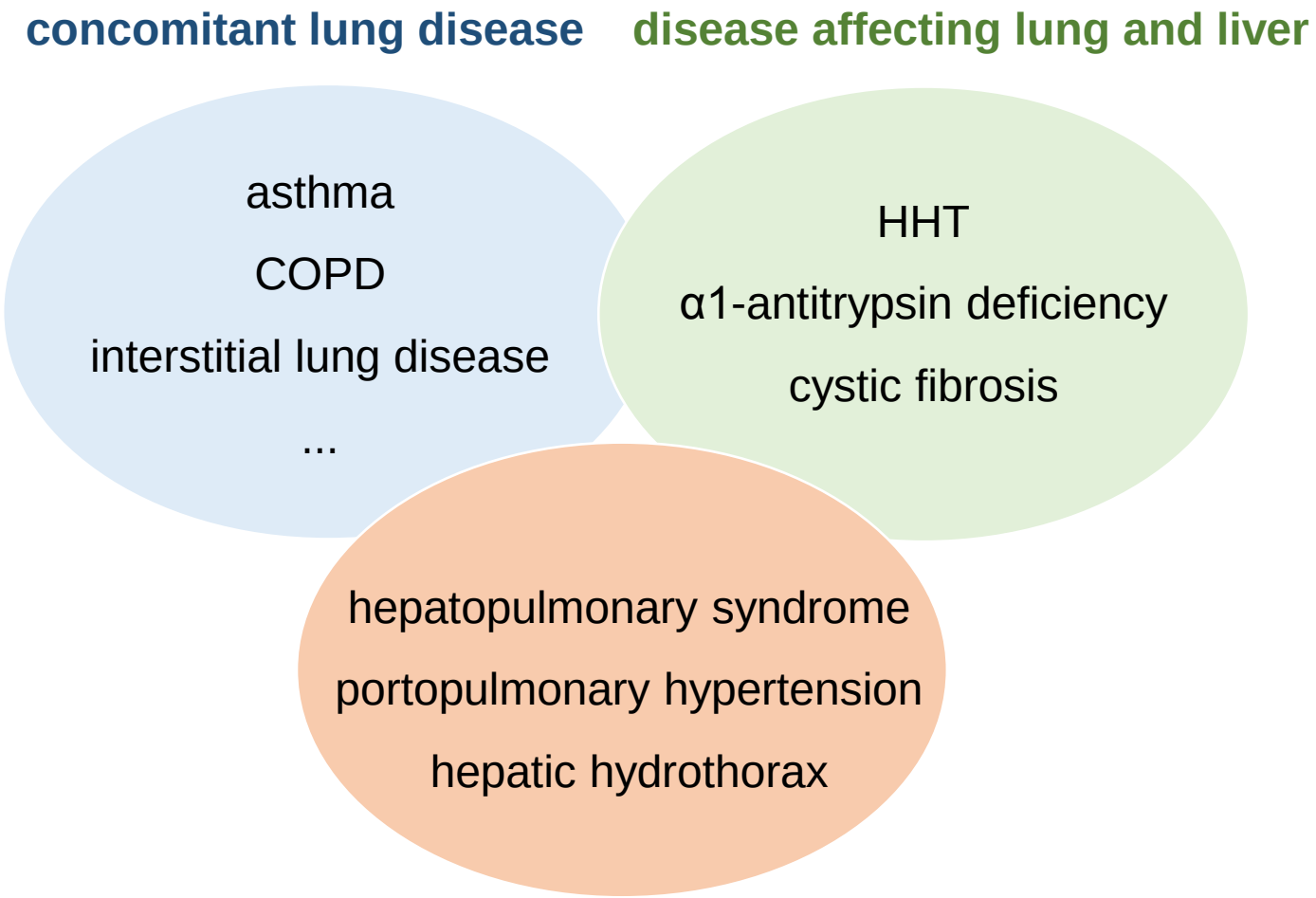
- The mainstay of POPH is vasodilator treatment, which might represent a bridge to LT.

- Both severe HPS and POPH with controlled pulmonary pressure can be granted a standard exception.

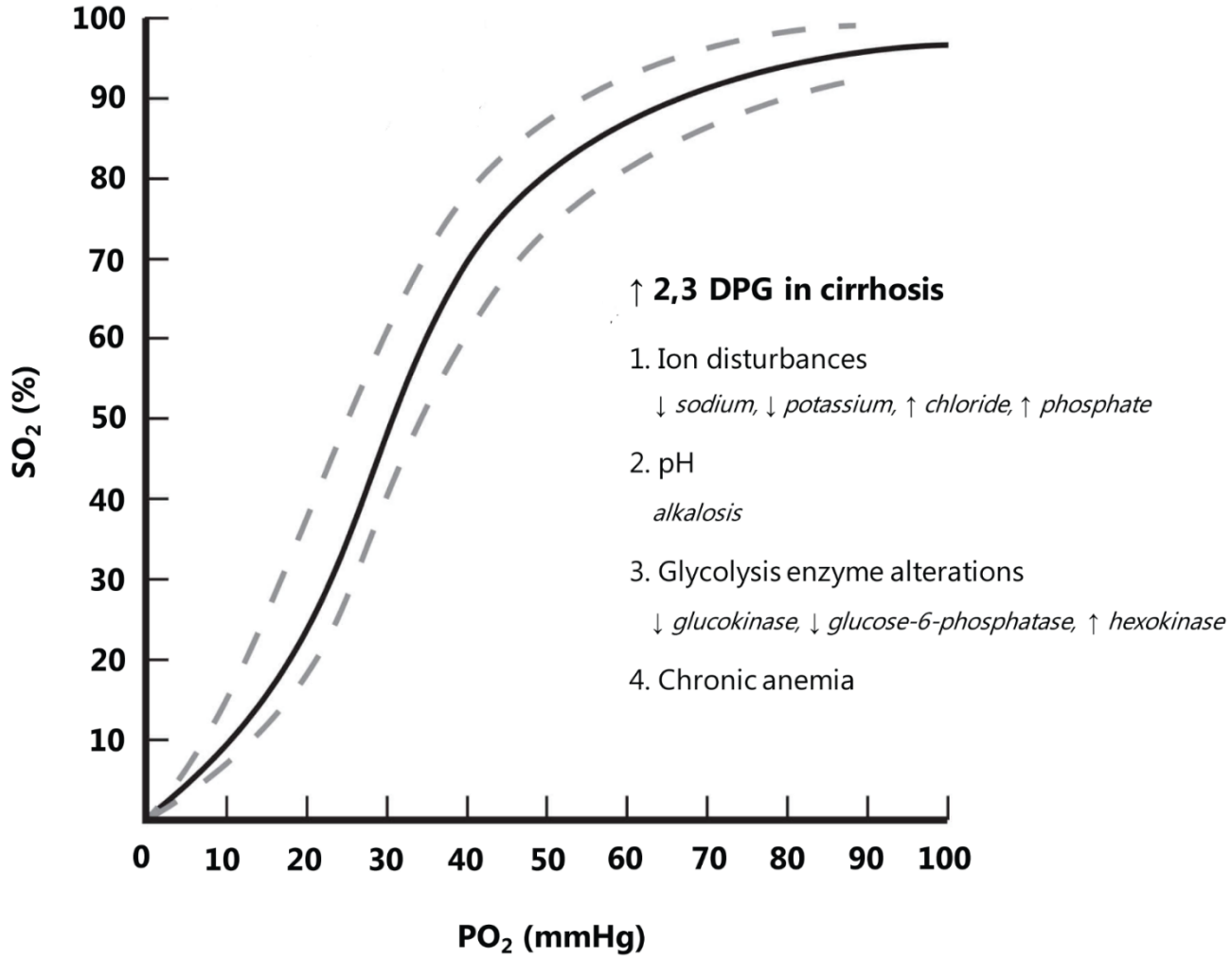


THANK YOU FOR YOUR ATTENTION!

Dyspnea in patients with liver disease – differential diagnosis



Oxygen dissociation curve in cirrhosis



Raevens et al, Hepatology 2019

Sorafenib study

We excluded patients with recent chronic heavy alcohol consumption, active hepatic encephalopathy, portopulmonary hypertension, congenital long-QT syndrome, previous liver or other solid organ transplantation or expectation of liver transplant within 4 months of randomization, hepatocellular carcinoma that did not meet certain criteria, uncontrolled hypertension, or World Health Organization class 4 functional status. Complete inclusion and exclusion criteria are provided in Supporting Table 1. Participants were recruited from liver disease and pulmonary clinics at the University of Pennsylvania, Columbia University, University of Texas at Houston, Mayo Clinic Rochester, Mayo Clinic Arizona, Northwestern University, and the Medical University of South Carolina. All participants provided written informed consent.

TABLE 3. Patients Experiencing AEs

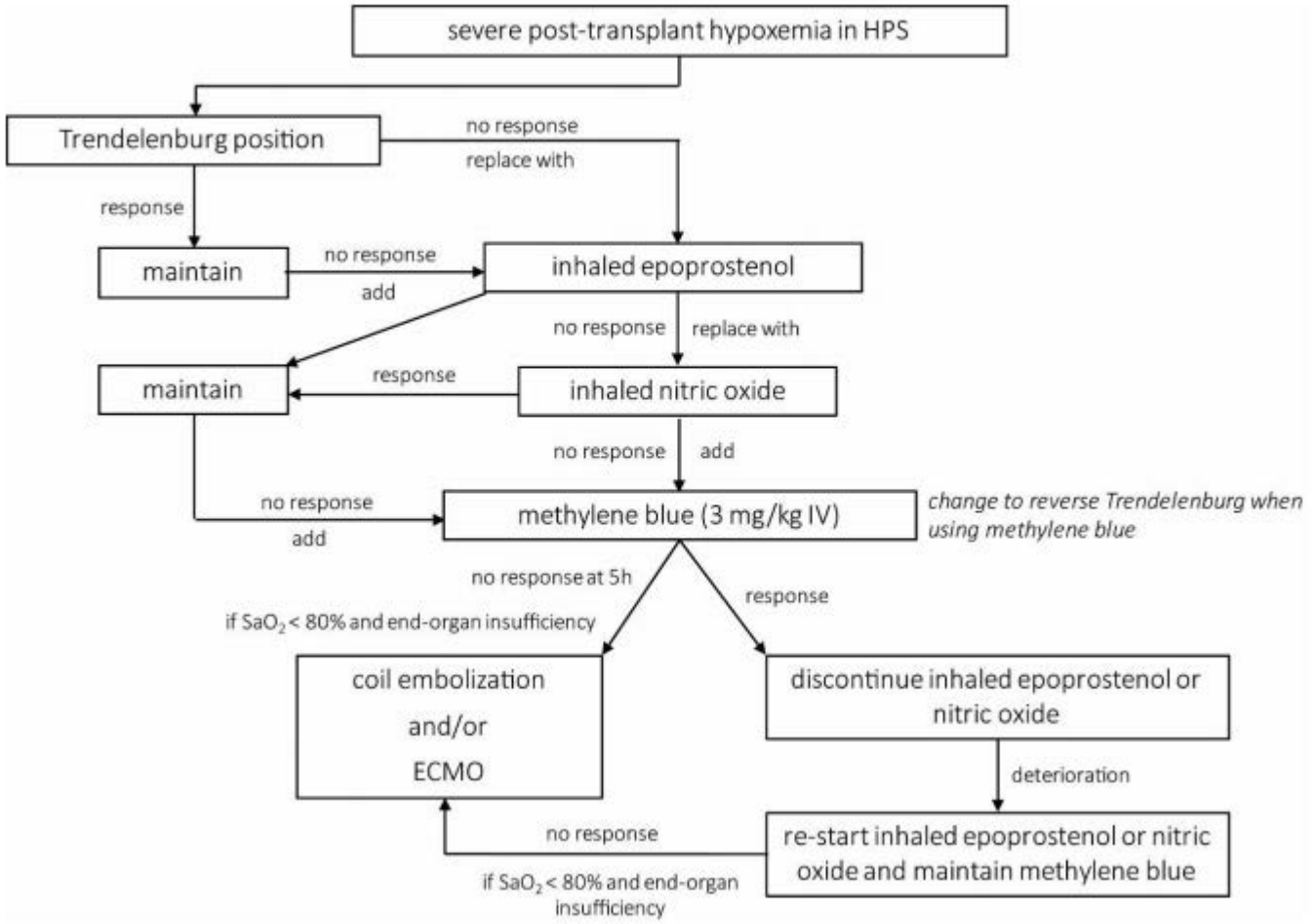
AE	Placebo Group (n = 12)	Sorafenib Group (n = 16)
Diarrhea/loose stools	4 (33)	5 (31)
Abdominal pain	5 (42)	2 (13)
Weight loss	2 (17)	5 (31)
Fatigue	3 (25)	3 (19)
Nausea	3 (25)	3 (19)
Pruritus	3 (25)	3 (19)
Cough	3 (25)	2 (13)
Hypertension	2 (17)	3 (19)
Rash (maculopapular)	1 (8)	4 (25)
Headache	0 (0)	4 (25)
Myalgia	2 (17)	2 (13)
Alopecia/abnormal hair growth	1 (8)	2 (13)
Dry skin	0 (0)	3 (19)
Edema/edema in the limbs	1 (8)	2 (13)
Mucositis (oral)	0 (0)	3 (19)
Nasal congestion	2 (17)	1 (6)
Pain in extremity	1 (8)	2 (13)
Upper respiratory infection	2 (17)	1 (6)

NOTE: Data are given as n (%). AEs that occurred in 3 or more individuals are shown, and all AEs were CTCAE grade 1 or 2.

Severe post-transplant hypoxemia = need for 100% FiO2 to maintain a saturation of ≥ 85%

6-21% of HPS patients

Mortality of 45%



Nayyar et al, Liver Transpl 2014

Treatment options

Liver transplantation

Considerations:

- monitoring hemodynamics
- have TEE available
- cancel if mPAP >50 mmHg or therapy fails to lower mPAP below 40 mmHg
- reperfusion phase = critical, have inhaled NO, IV prostacyclins and milrinone ready
- ECMO for rescue

Other

TIPS: contra-indicated!

beta-blockers: to be avoided, EBL preferred

PORTICO was a phase 4 study done in 36 centres in seven countries, consisting of a 12-week double-blind period (randomly assigned 1:1 to macitentan 10 mg or placebo once daily) followed by a 12-week open-label period. Adults (≥18 years) with portopulmonary hypertension, a 6-minute walk distance of 50 m or more, and with pulmonary vascular resistance of 320 dyn·s·cm^{-5} or more without severe hepatic impairment (Child-Pugh class C or model for end-stage liver disease score ≥19) were eligible. The primary endpoint was pulmonary vascular resistance at week 12, expressed as ratio of baseline in the full analysis set. Safety was assessed throughout. This trial is registered at ClinicalTrials.gov, number NCT02382016.

Findings

Between June 23, 2015, and July 28, 2017, 85 patients were randomly assigned to macitentan (n=43) or placebo (n=42). At baseline, 54 (64%) were receiving background therapy for pulmonary arterial hypertension. Most patients were WHO functional class II (50, 59%) or III (33, 39%) with a mean 6-minute walk distance of 384·5 m (SD 103·9). At week 12, the geometric mean ratio of baseline pulmonary vascular resistance was 0·63 (95% CI 0·58–0·67) in the macitentan group and 0·98 (95% CI 0·91–1·05) in the placebo group, corresponding to a ratio of geometric mean for pulmonary vascular resistance of 0·65 (95% CI 0·59–0·72, p<0·0001), which in turn represented a 35% (95% CI 28–41) reduction in pulmonary vascular resistance with macitentan versus placebo. During the double-blind period, 36 (84%) macitentan-treated and 33 (79%) placebo-treated patients had adverse events, and nine (21%) and six (14%), had serious adverse events. Four (9%) macitentan-treated patients had an adverse event leading to discontinuation versus none in the placebo group. The most frequent adverse event during the double-blind period was peripheral oedema (11 [26%] in the macitentan group and five [12%] in the placebo group).