10. Pulmonale Hypertonie-Biennale 23.05.2024: *«Es lebe die Interdisziplinarität»*

Porto-pulmonale Hypertonie

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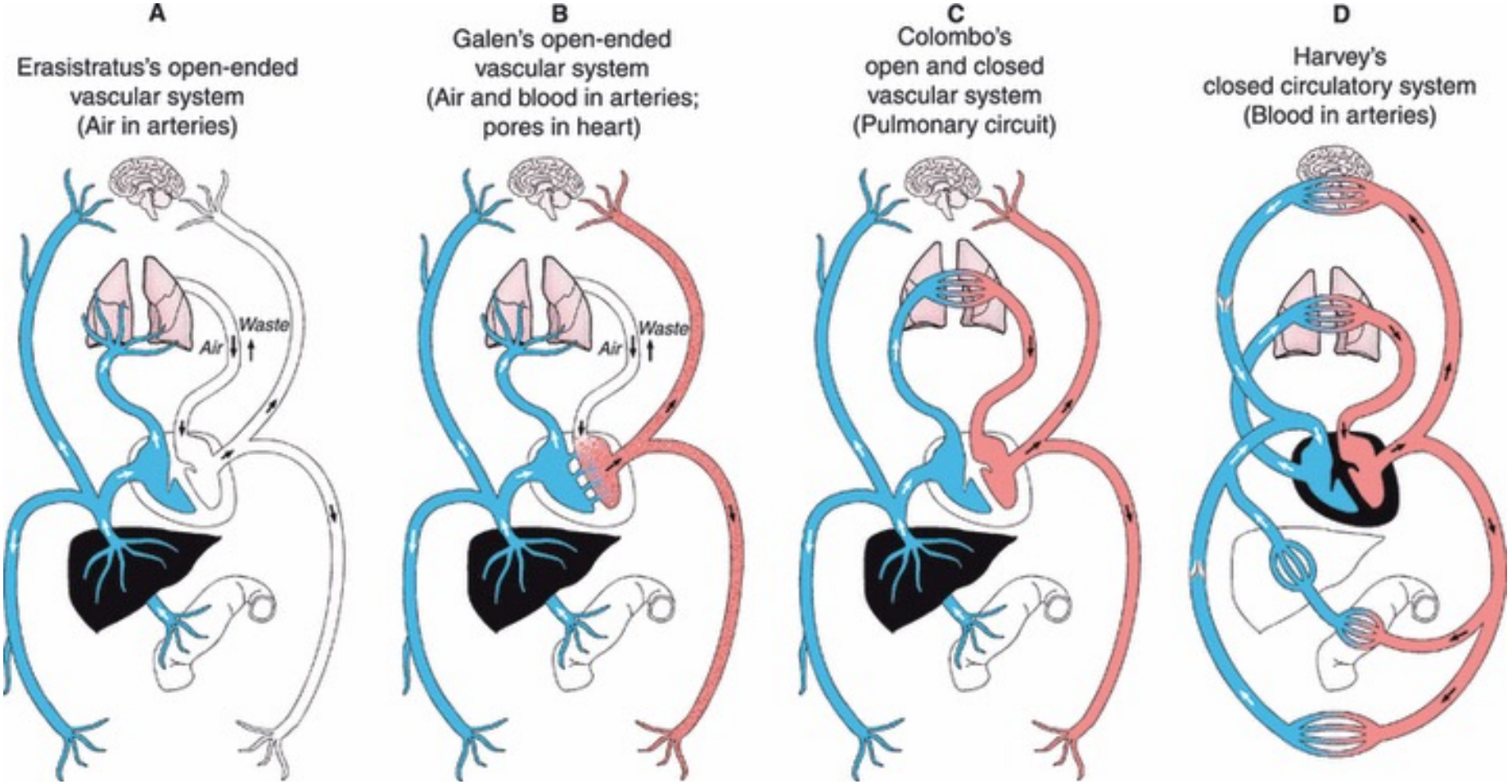
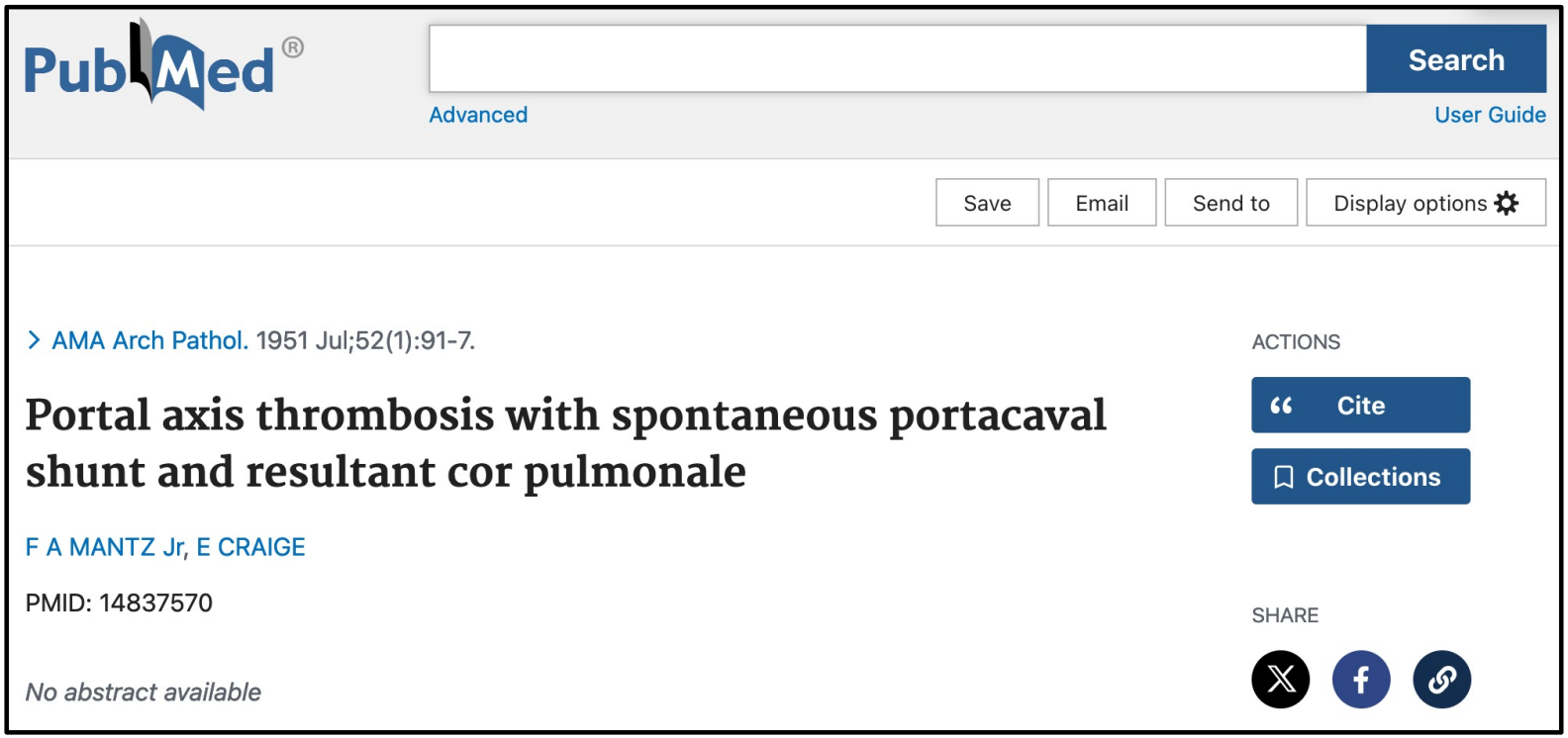
Discovery of the cardiovascular system: From Galen to William Harvey



400 BC *200 AD* *1559* *1628*

Aird WC, J Thromb Haemost 2011

First clinical and pathologic report of PoPH published by Mantz & Craige in 1951



*Since the **1980s,** enhanced recognition and renewed importance of **PoPH has evolved with the evolution of liver transplantation** and potential outcomes associated with PoPH.*

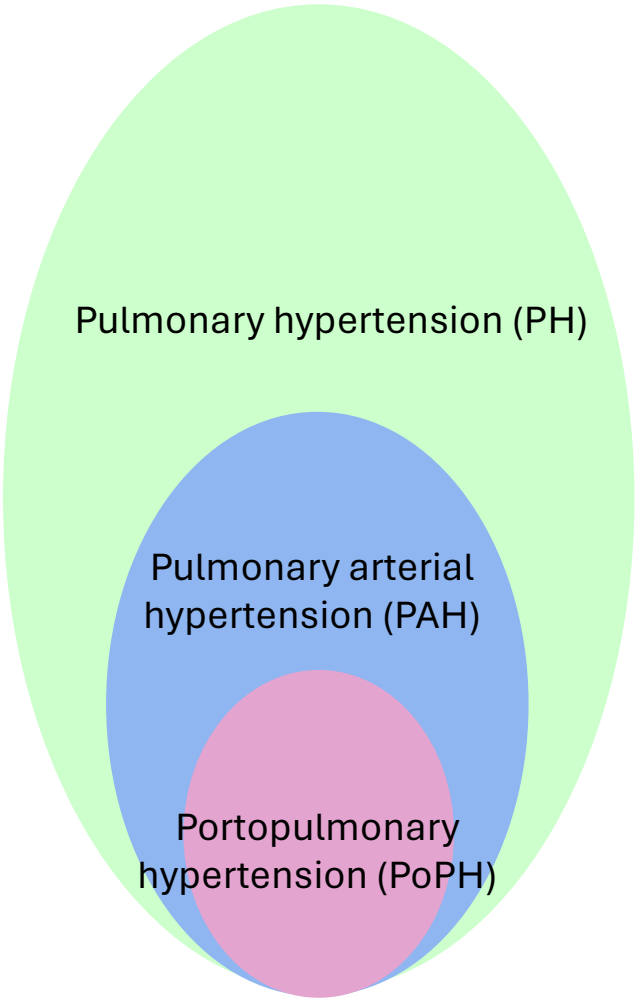
Overview Portopulmonary Hypertension (PoPH)

- Definitions
- Portal Hypertension 1x1
- Pathophysiology PoPH
- Epidemiology, Natural History & Prognosis
- Screening & Diagnosis of PoPH
- Management & Medical Treatment of PoPH
- Liver Transplantation with/for PoPH

1

Definitions

WHO classification of pulmonary hypertension (PH)



Group 1: Pulmonary **arterial** hypertension (PAH)

- Idiopathic PAH, heritable, drug/toxin-mediated
- Associated i.e. with HIV, portal hypertension

Group 2: Pulmonary **venous** hypertension

- i.e. left-heart disease, valvular disease

Group 3: PH due to **lung disease** and/or hypoxemia

Group 4: Chronic **thrombembolic** PH

Group 5: PH of **unclear mechanisms**

- i.e. hematologic and systemic disorders

Definition portopulmonary Hypertension (PoPH)

Development of pulmonary arterial hypertension (PAH) due to **increased resistance with:**

- Mean pulmonary arterial hypertension **(mPAP) > 25 mmHg**
- Pulmonary vascular resistance **(PVR) > 240 dynes/sec/cm^5**
- Pulmonary artery wedge pressure **(PAWP) < 15 mmHg**
- Transpulmonary gradient **(TPG) > 12 mmHg ***
- Presence of **portal hypertension** (with or without cirrhosis)

* In case when PAWP is > 15 mmHg (abnormal)

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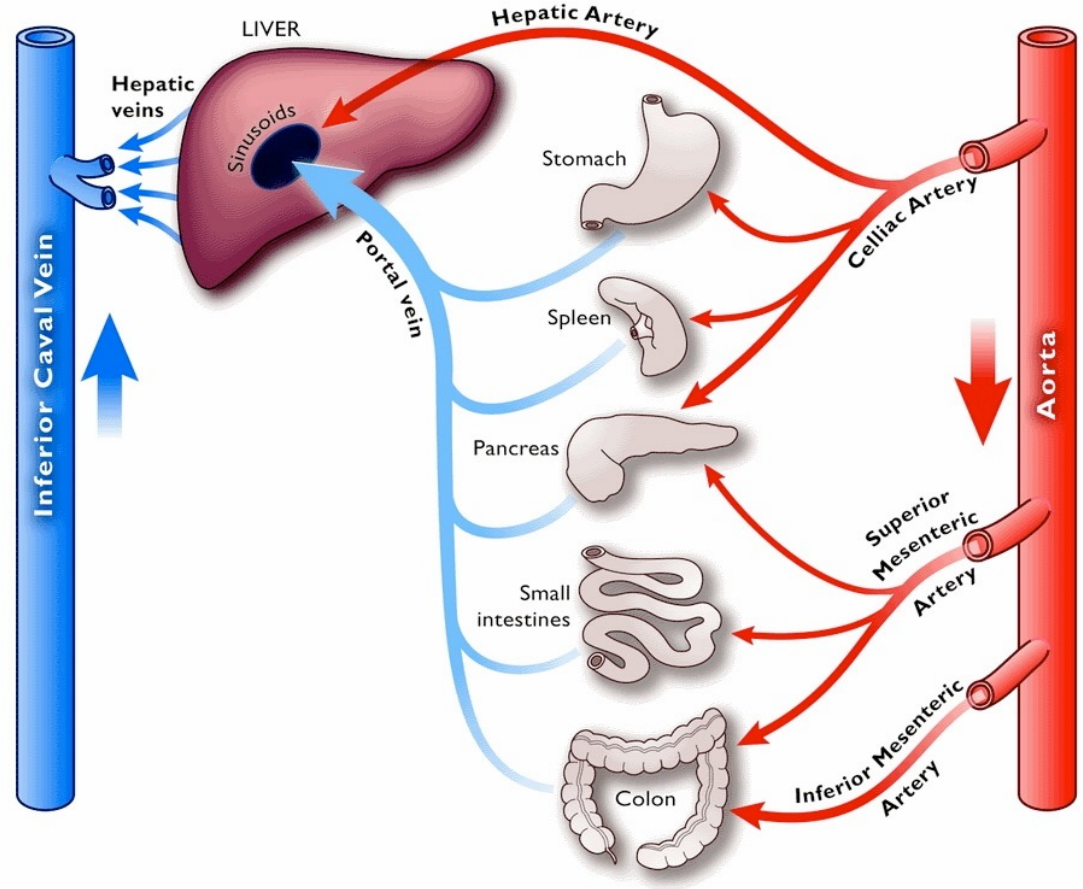
Portal Hypertension:

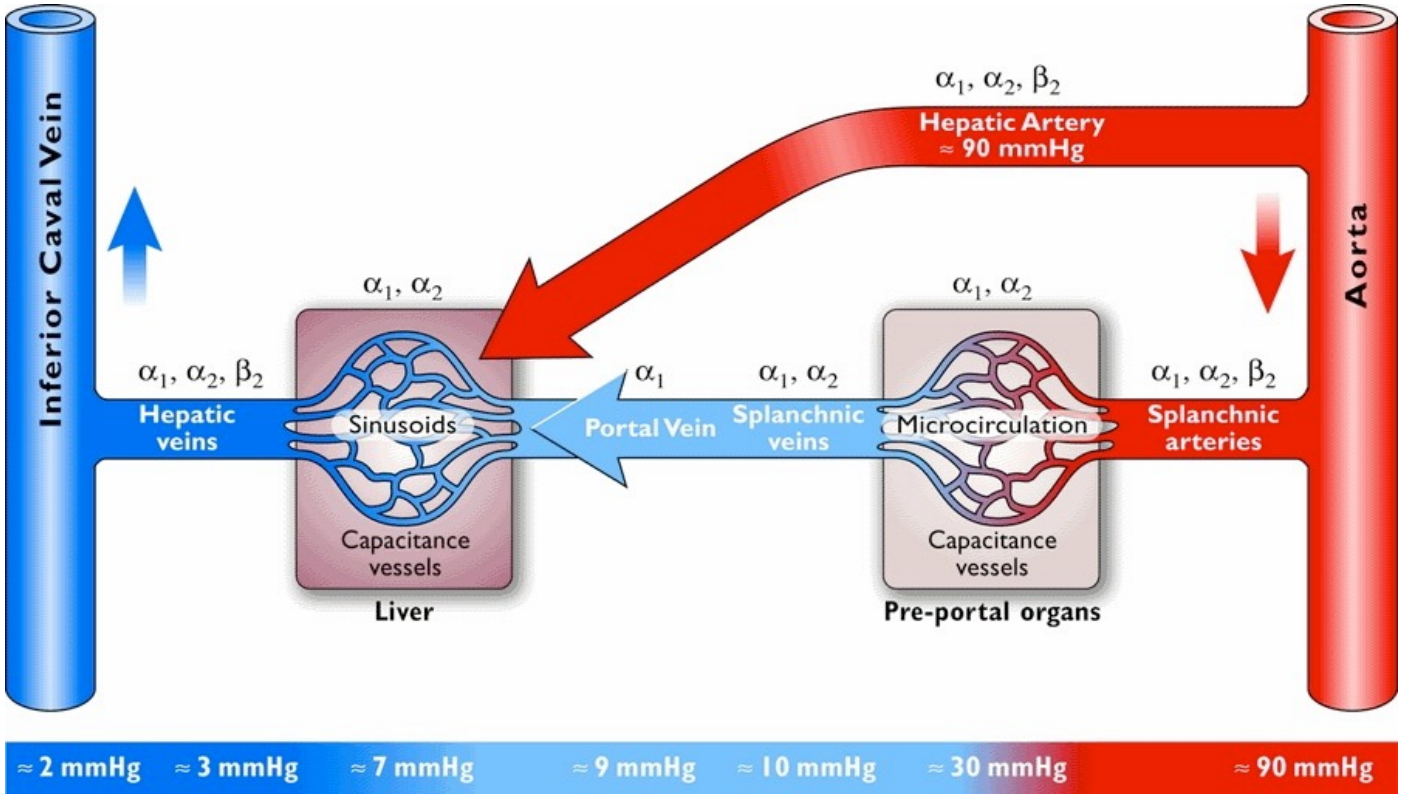
Everything you need to know in 5 minutes

Liver perfusion: 25% of cardiac outputs via 3 arteries & portal vein



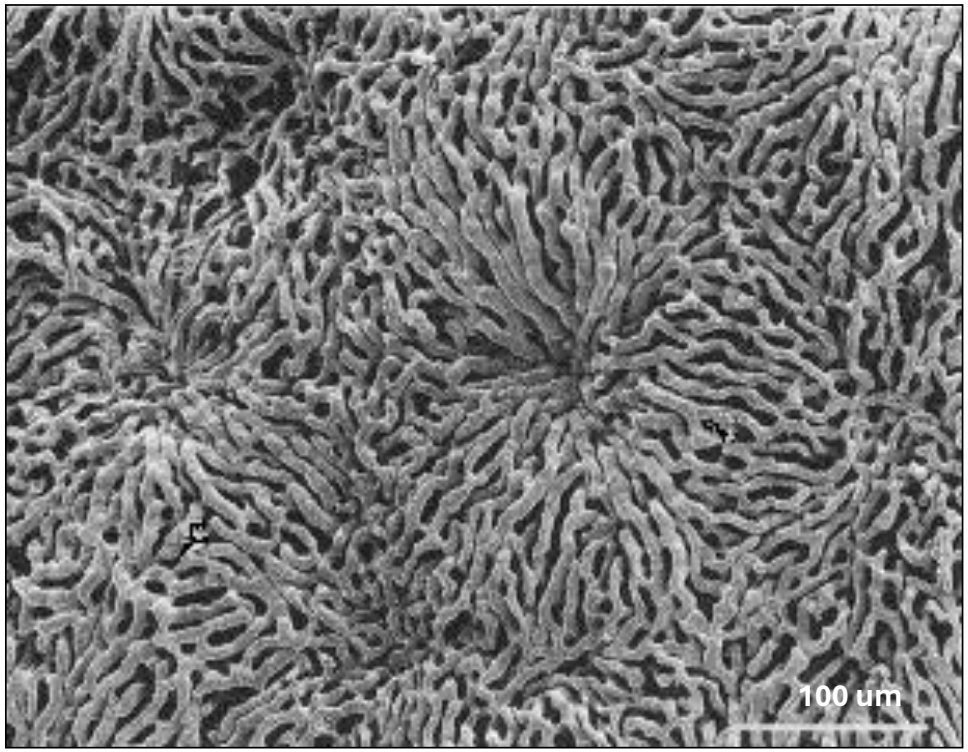
Gelman S et al, Anesthesiology 2004

The portal venous pressure is 7–10 mmHg, which is slightly higher than the pressure in the sinusoids

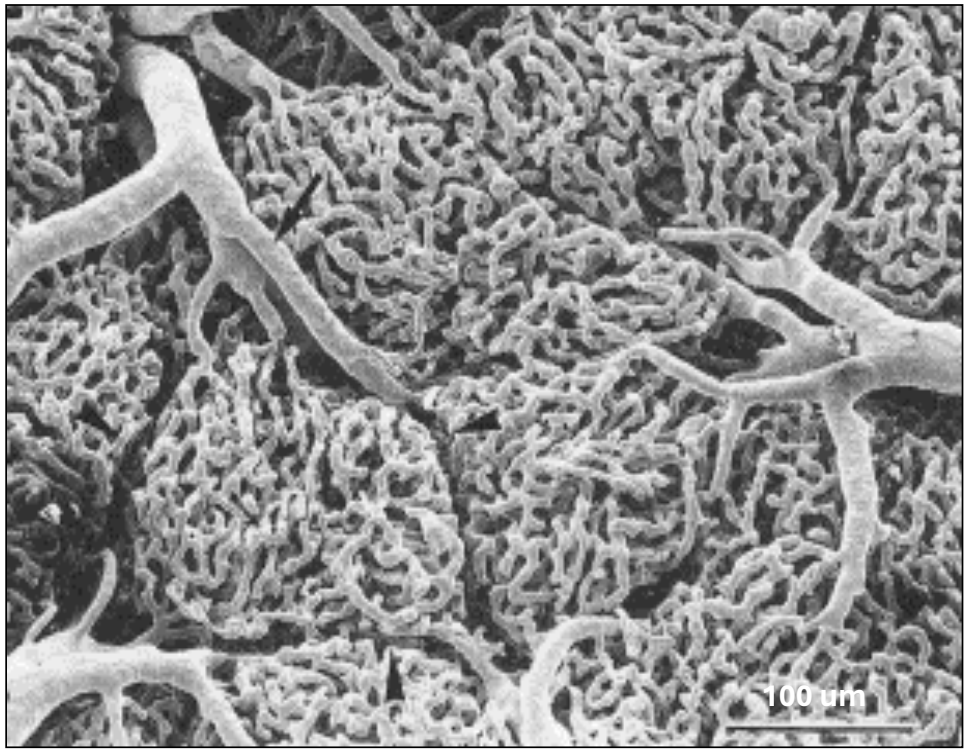


Gelman S et al, Anesthesiology 2004

Vascular remodeling in chronic liver disease



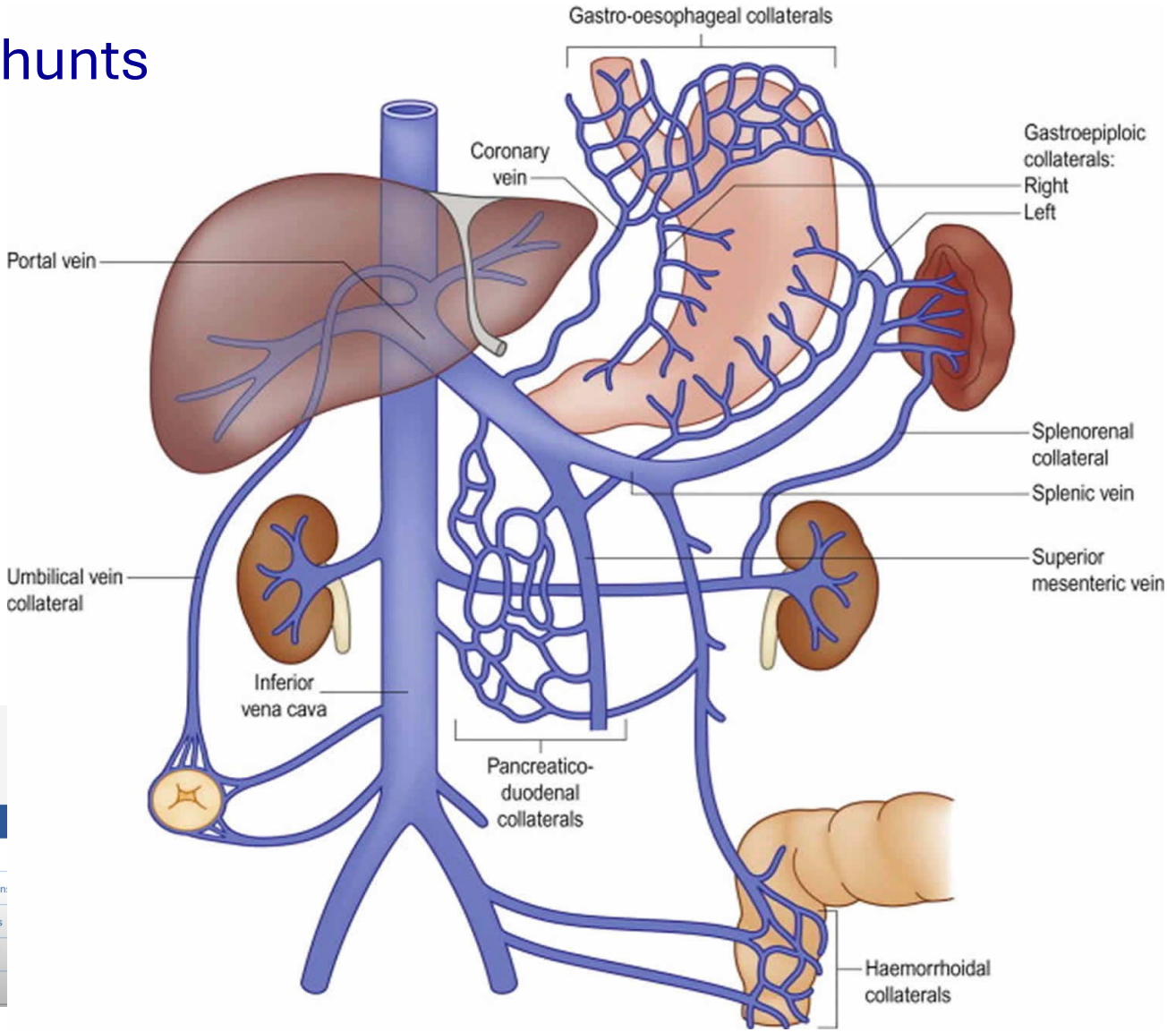
Normal hepatic microcirculation (sinusoids)



Vascular remodeling in liver cirrhosis

Onori et al., J Hepatol 2000

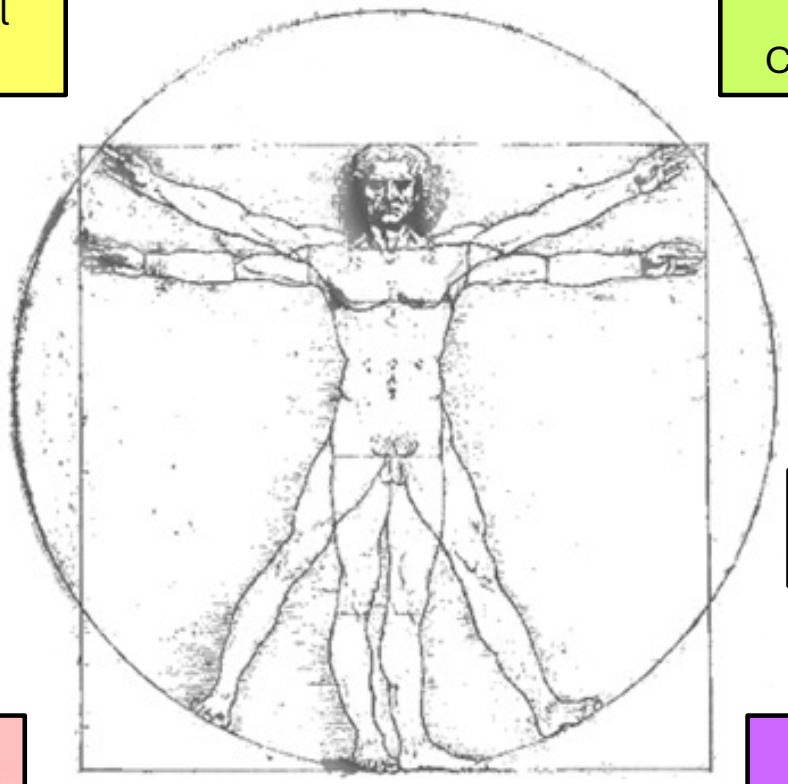
Portosystemic Shunts



PORTOSYSTEMIC SHUNTS (*I POUR*)

Site	Portal vein	Systemic vein
Oesophageal (*varices*)	**Left gastric** vein (oesophageal branches)	**Azygous** vein
Upper anal canal (*haemorrhoids*)	**Superior rectal** vein	**Inferior & middle rectal** vein
Paraumbilical (*Caput Medusae*)	**Paraumbilical** veins	**Superficial epigastric** veins
Retroperitoneal	**Colonic** veins	**Retroperitoneal** veins (e.g. posterior body wall)
Intrahepatic	**Left portal** vein	**Inferior** vena cava

Complications of clinically significant portal hypertension



Hepatic Encephalopathy

Gastrointestinal Varices

Cirrhotic Cardiomyopathy

Porto-pulmonary Hypertension

Hyperdynamic Circulation

Hepato-pulmonary Syndrome

Hepato-renal Syndrome

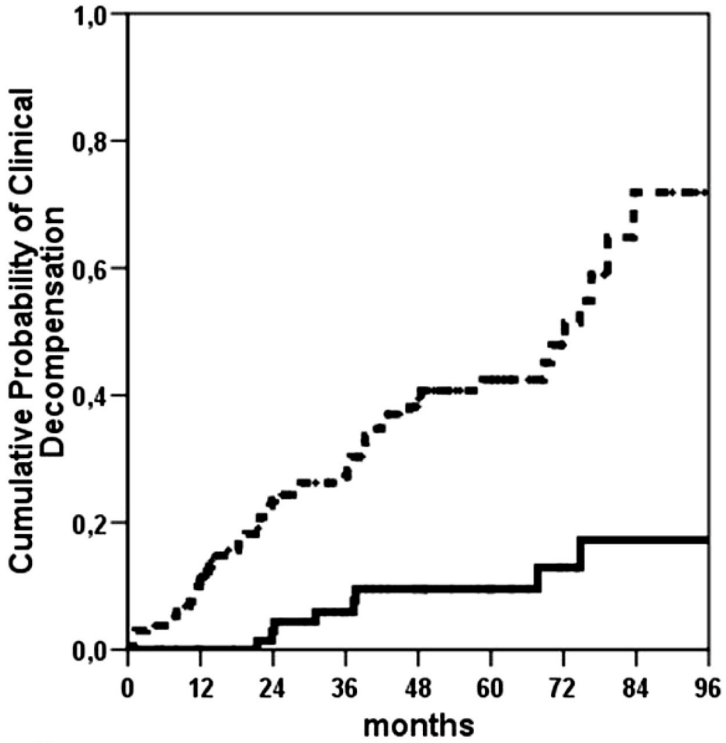
Spider naevi, Palmar Erythema

Splenomegaly, Hypersplenism

Ascites, Spontaneous Bacterial Peritonitis

Portal pressure predicts clinical decompensation in pts with compensated cirrhosis

213 patients with compensated cirrhosis and portal hypertension but without varices included in a prospective trial evaluating the use of beta-blockers in preventing varices



HVPG <10 mmHg							
At risk	79	72	66	55	44	32	14
Events	0	0	2	4	6	6	8
HVPG ≥ 10 mmHg							
At risk	134	112	86	73	49	34	3
Events	0	15	29	33	44	47	54

HVPG ≥ 10 mmHg

HVPG < 10 mmHg

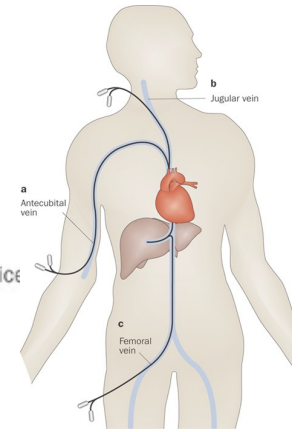
Patients with an **HVPG <10 mmHg** have a **90%** probability of **not developing clinical decompensation** in a median follow-up of **4 years**.

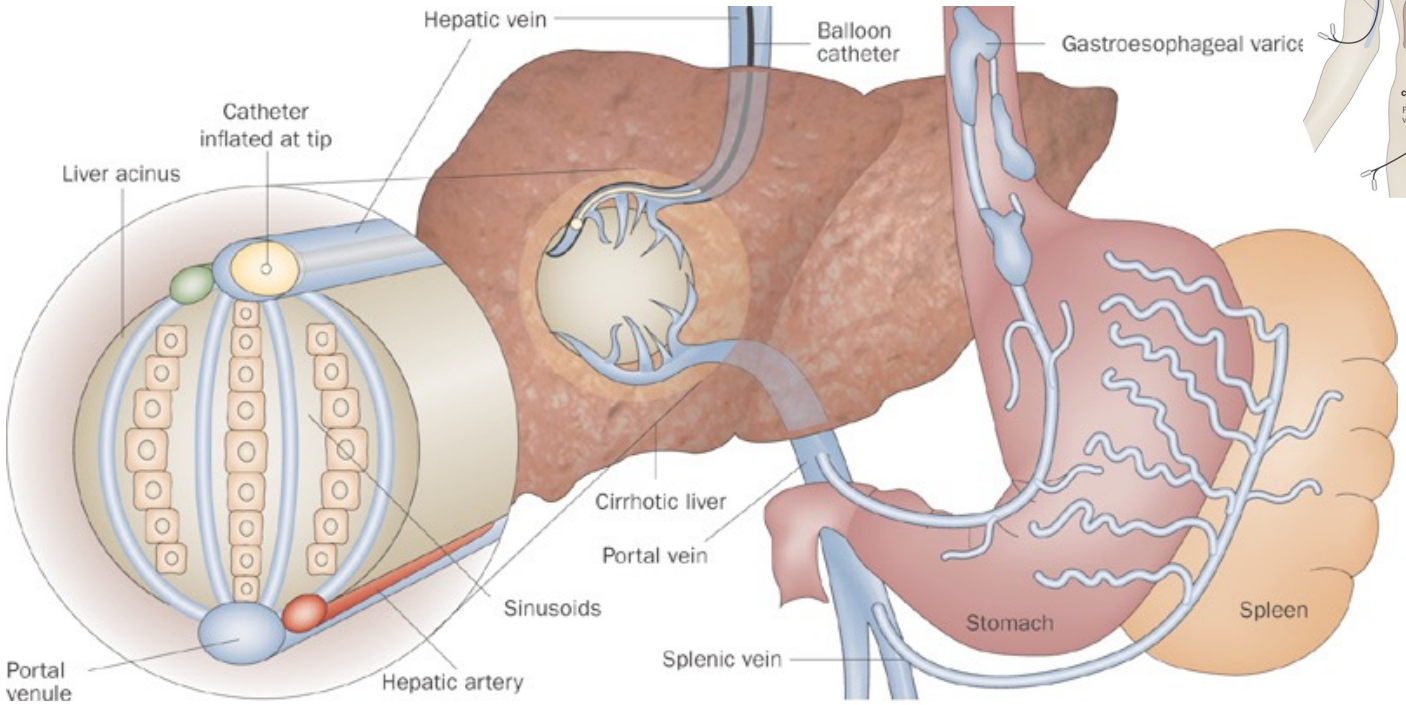
Ripoll C et al., Gastroenterology 2007

Gold standard for portal pressure measurement: **Hepatic venous pressure gradient (HVPG)**

HVPG = Wedged HVP - Free HVP = WHVP - FHVP

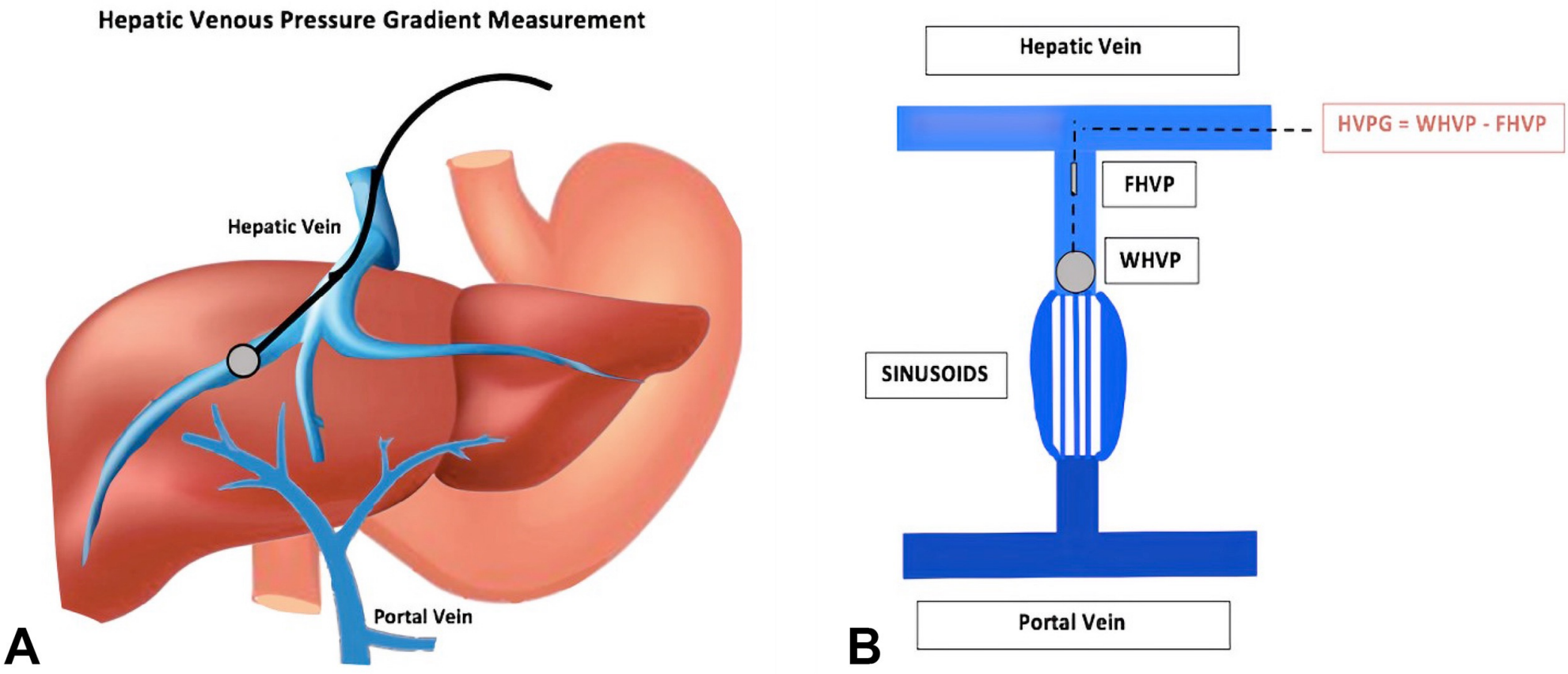
Normal HVPG = **3 - 5 mmHg**





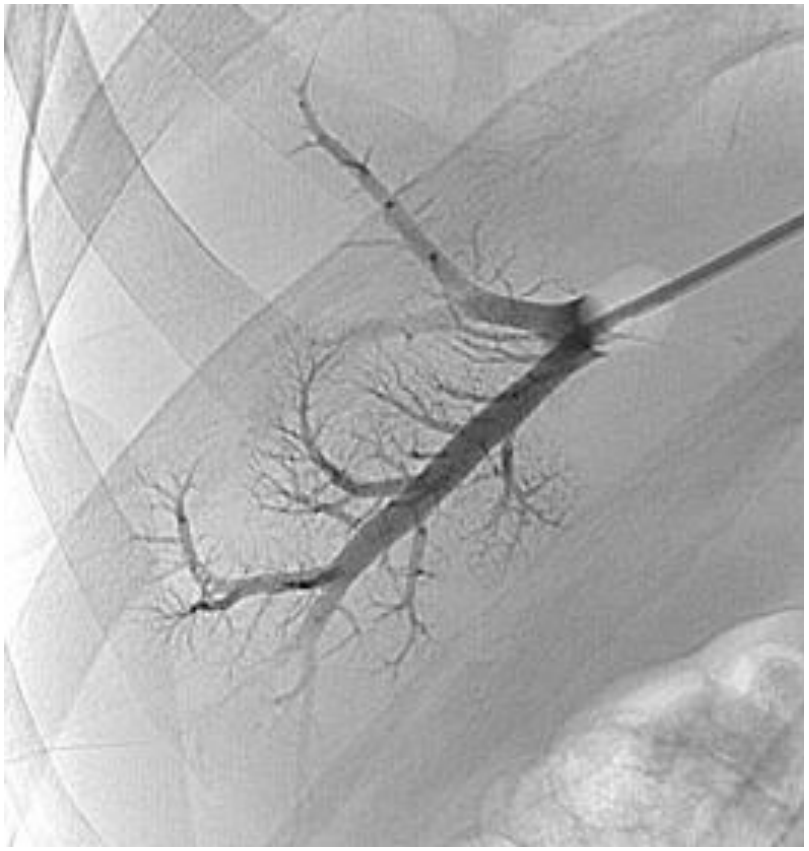
Bosch J et al. Nature Reviews 2009

HVPG: Retrograde (indirect) measurement of portal pressure

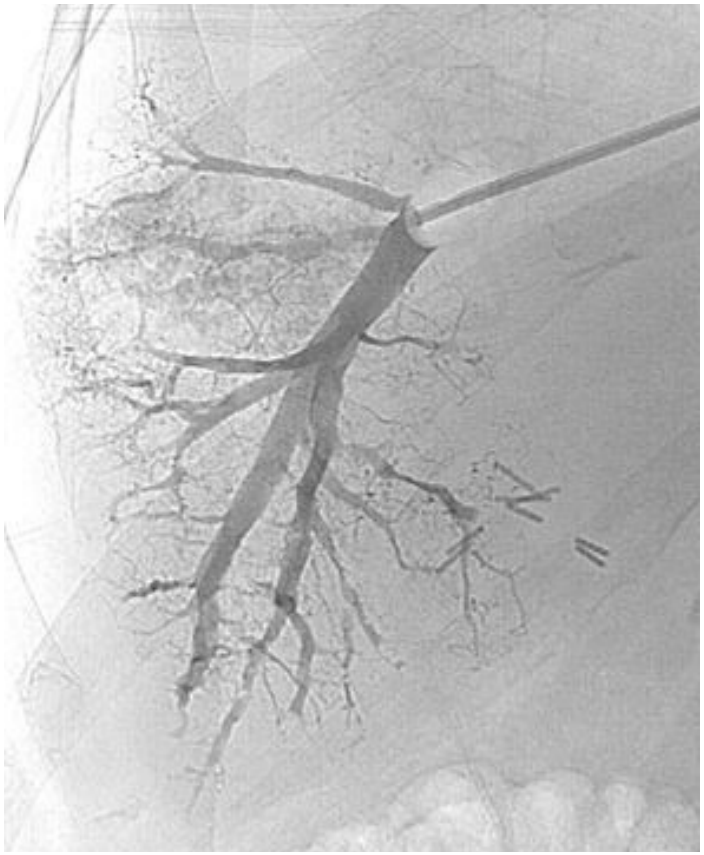


Bazarbashi AN et al., Gastrointerstinal Endoscopy 2021

HVPG: Retrograde (indirect) measurement of portal pressure

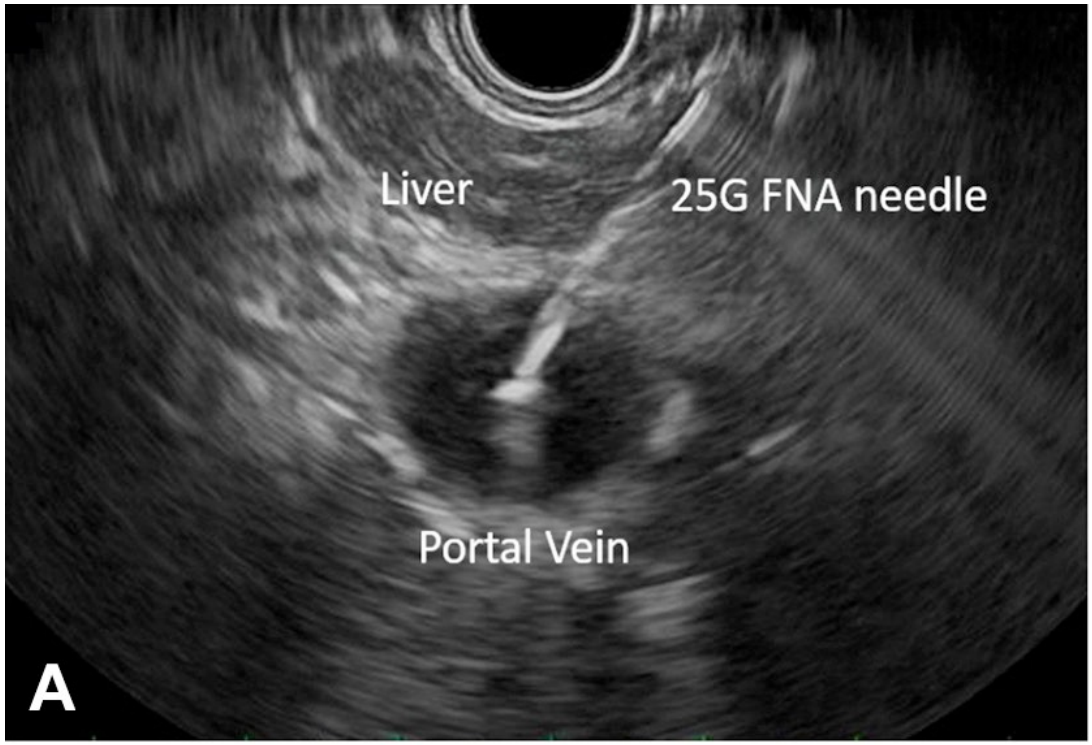


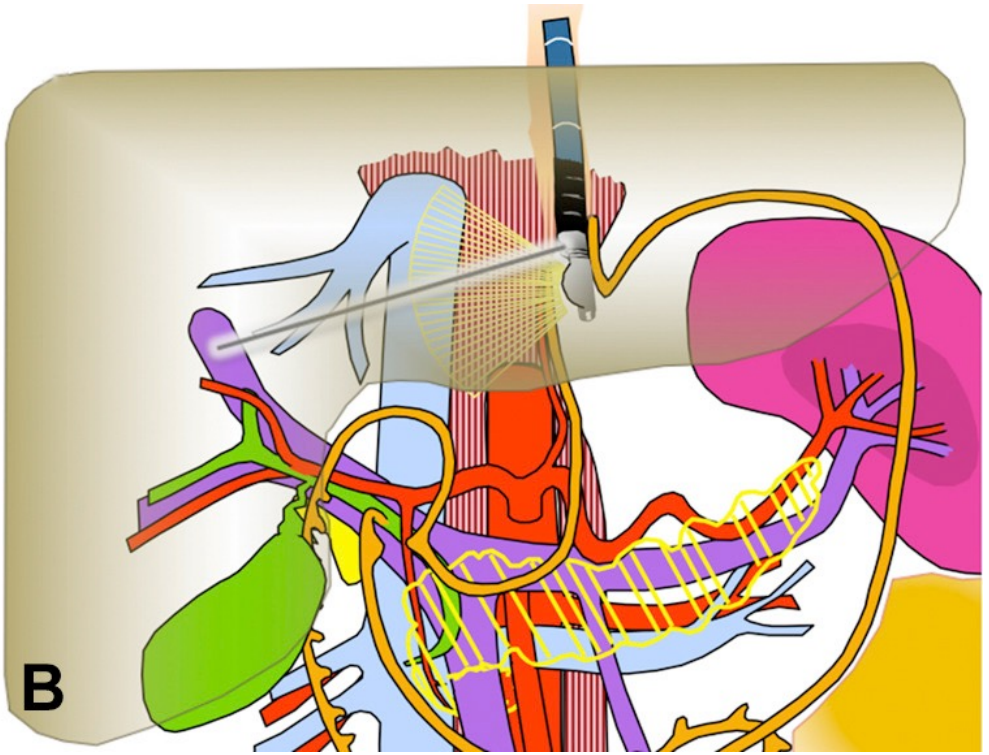
Normal



Liver cirrhosis

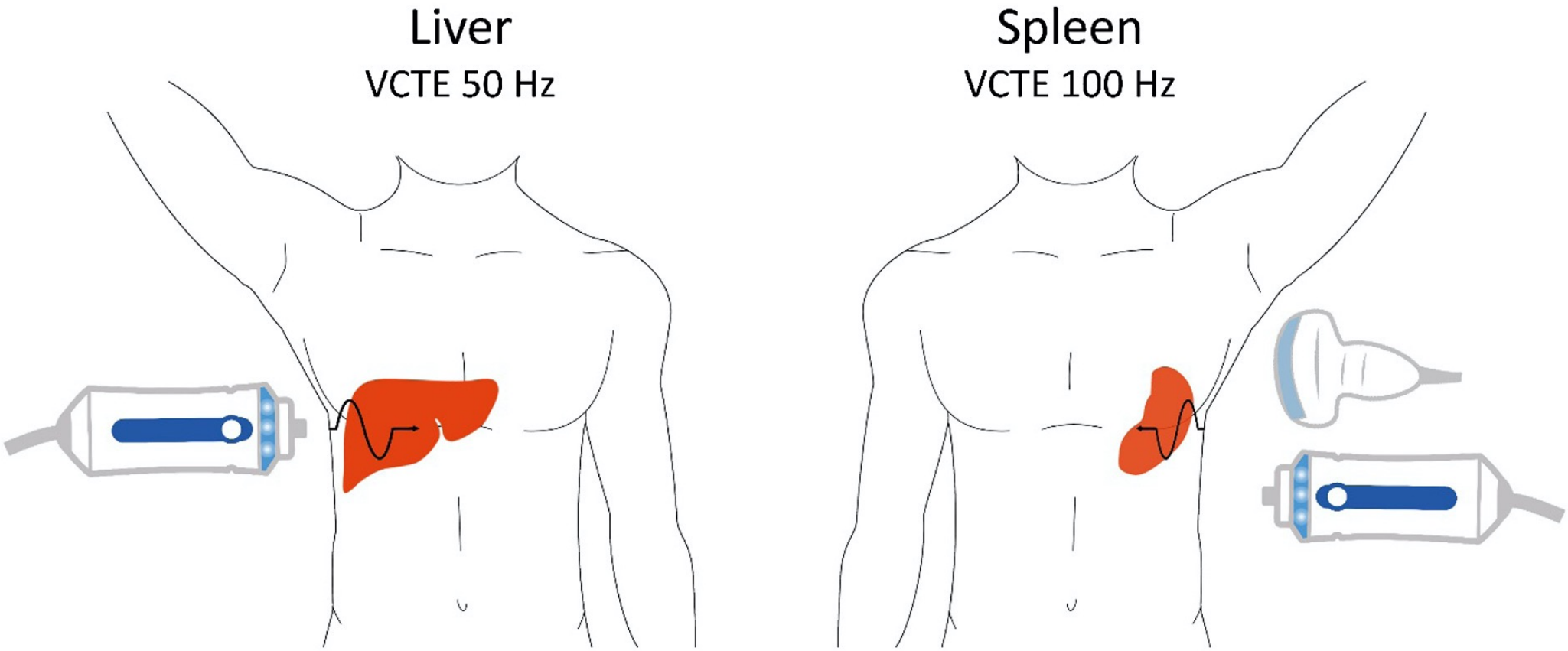
EUS-guided direct portal pressure gradient measurement
with a simple novel device: A human pilot study





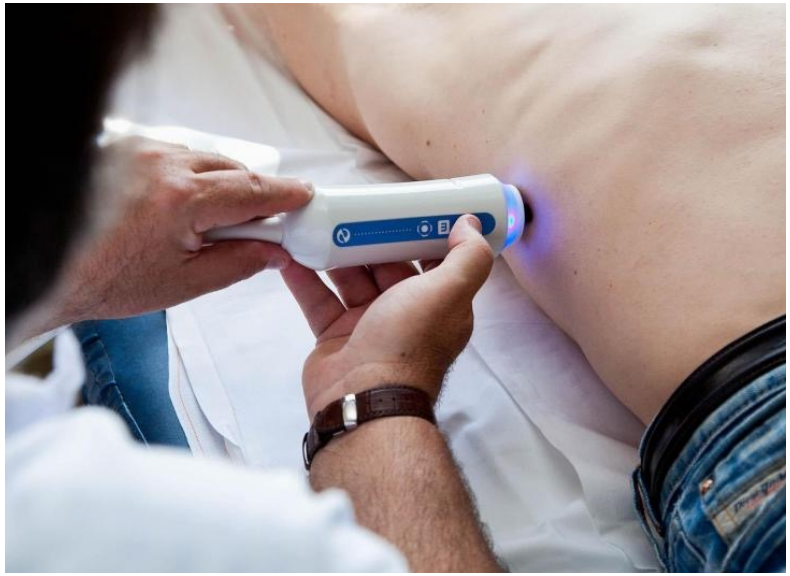
Samarasena JB et al., VideoGIE 2018

FibroScan can **estimate portal pressure non-invasively** by measuring **liver and spleen stiffness**



Mladenovic A et al., CLD, 2022

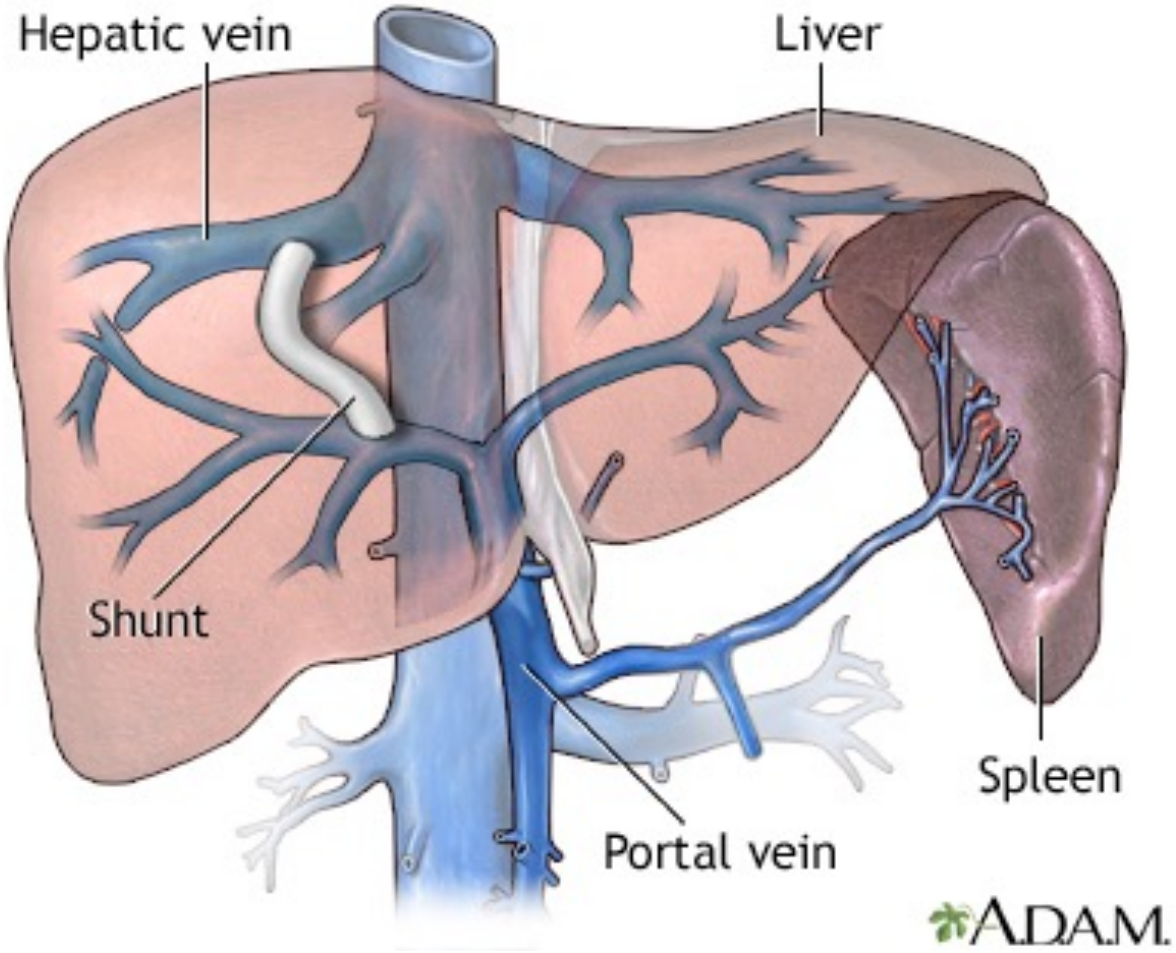
FibroScan can **estimate portal pressure non-invasively** by measuring **liver and spleen stiffness**



Treating portal hypertension in 2024

- Treatment of **underlying liver disease**
- Non-selective betablockers (NSBB): **propranolol, carvedilol**
- Transjugular intrahepatic portosystemic shunt **(TIPS)**

Transjugular intrahepatic portosystemic shunt **(TIPS)**



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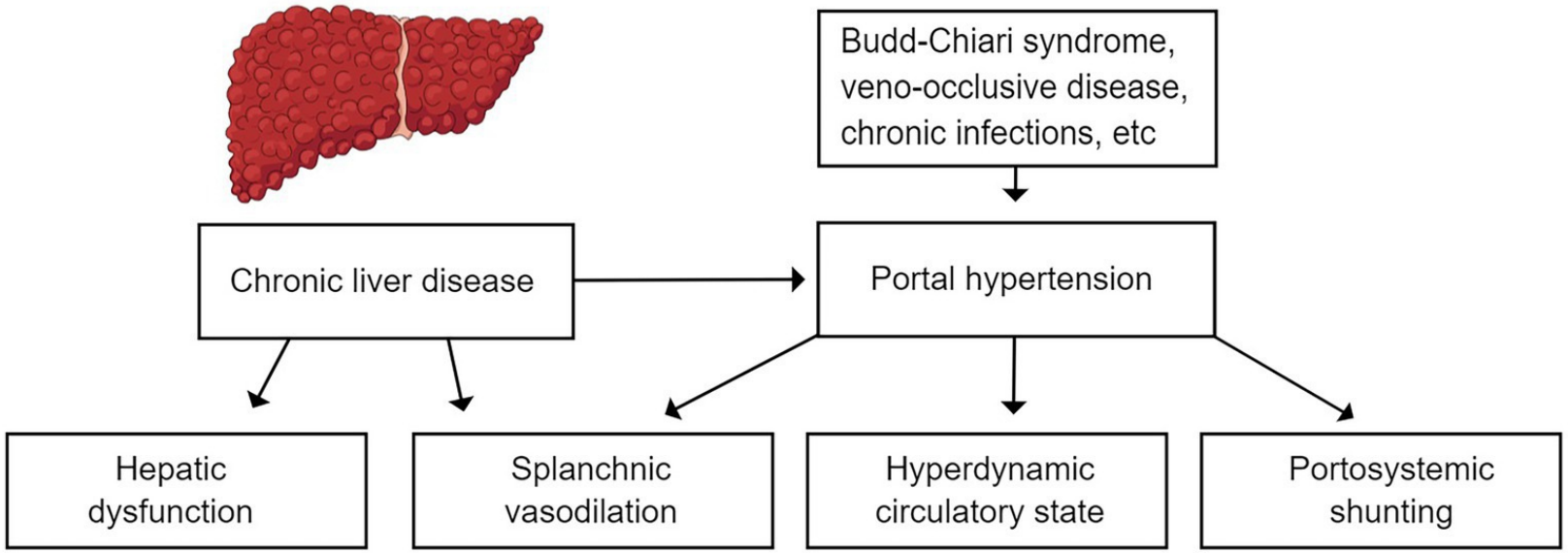
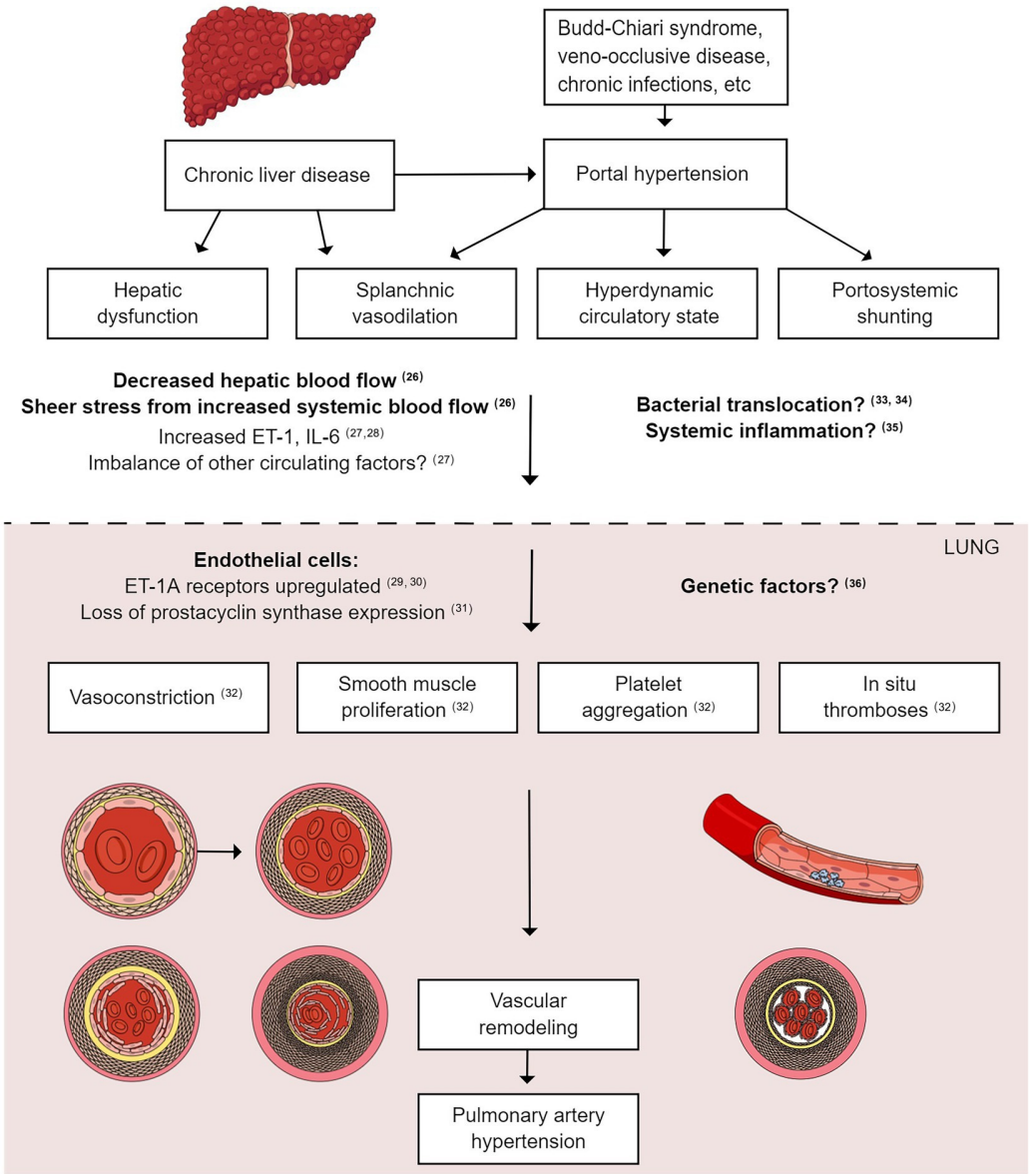
PoPH Pathophysiology



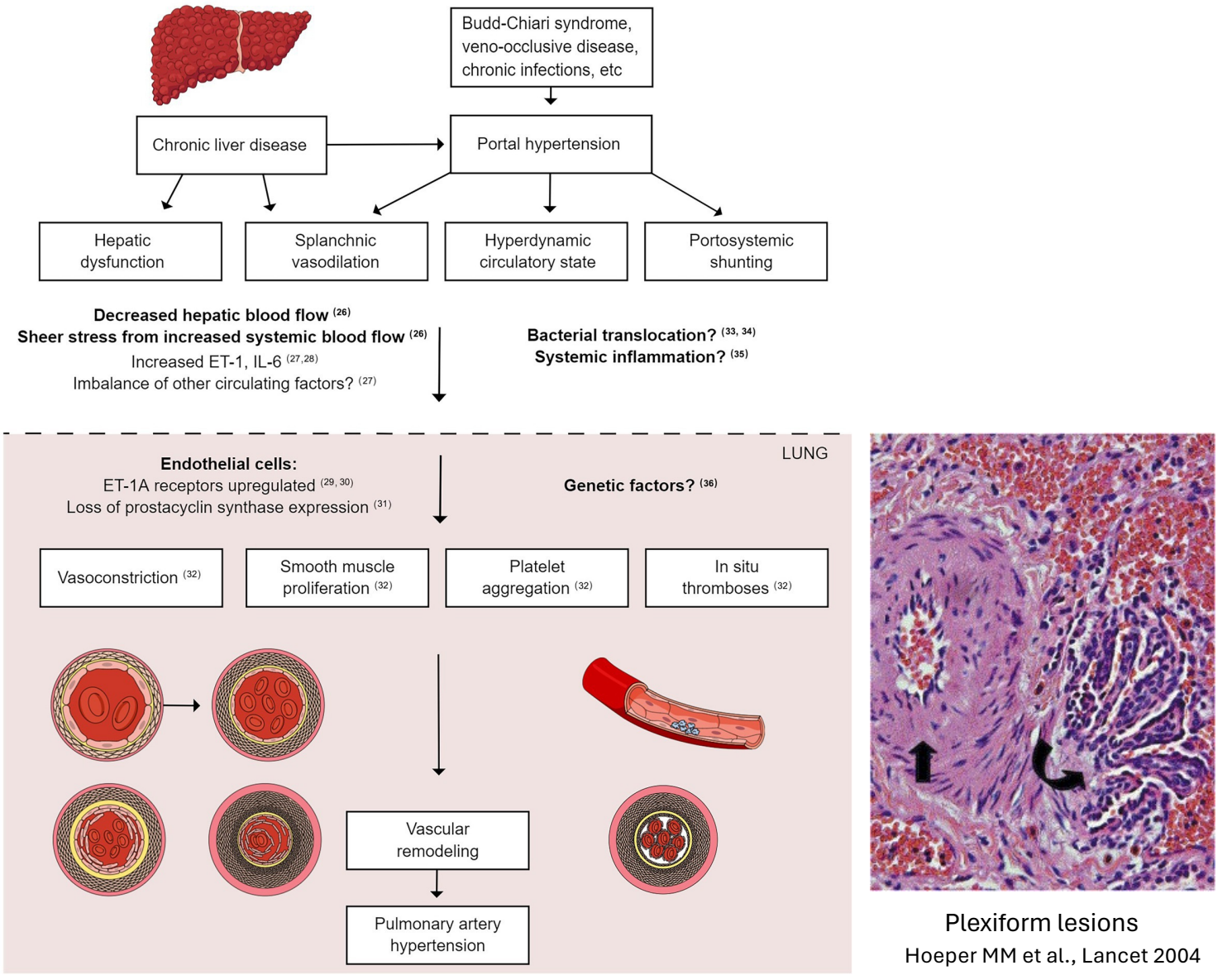
Decreased hepatic blood flow [26]
Sheer stress from increased systemic blood flow [26]
Increased ET-1, IL-6 [27,28]
Imbalance of other circulating factors? [27]

Bacterial translocation? [33, 34]
Systemic inflammation? [35]

Tamura Y. et al., Front Med 2023



Tamura Y. et al., Front Med 2023



Plexiform lesions

Hoeper MM et al., Lancet 2004

Tamura Y. et al., Front Med 2023

4

Epidemiology of PoPH

Epidemiology of PoPH

- **Incidence** of all types of **PAH is <10 per million** population, and **PoPH 3rd** most common form (**10-15%**)[1]

PoPH prevalence depends on the population studied, i.e.:

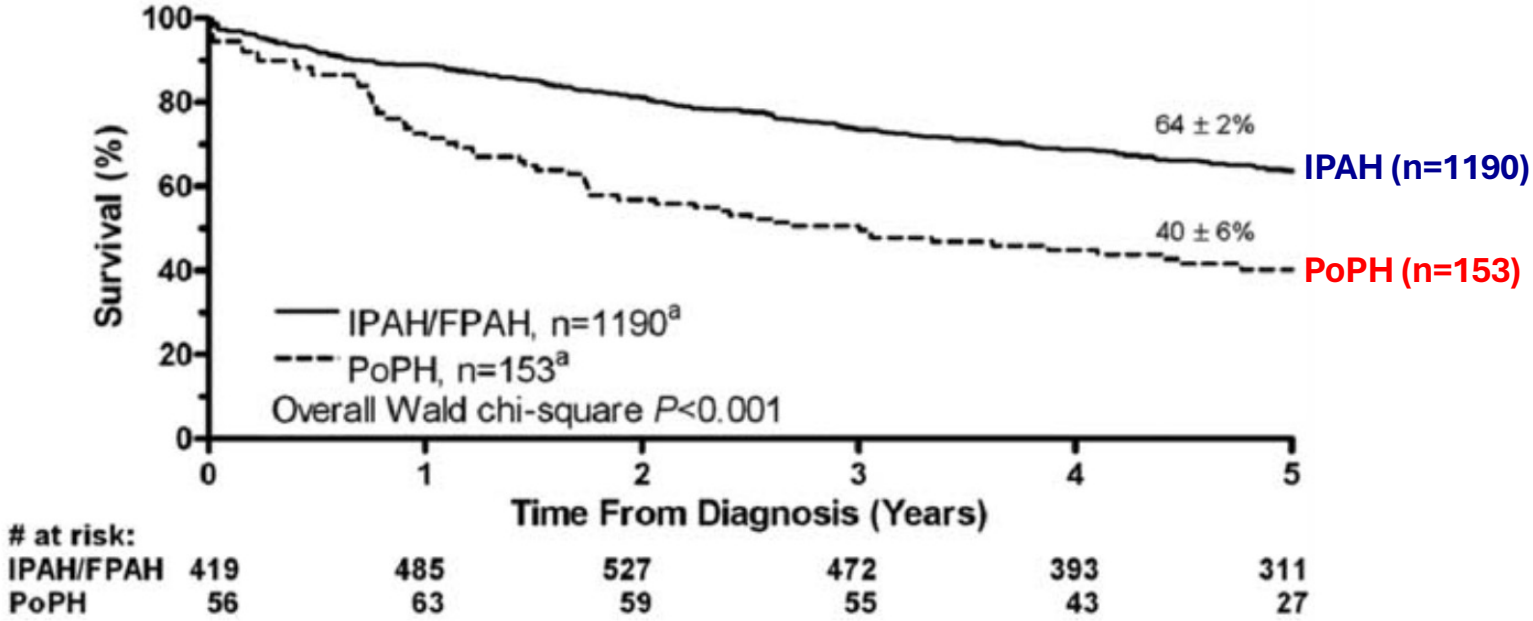
- **2% prevalence** in an early series of **507 consecutive pts with portal hypertension**[2]
- **4.9% prevalence** in the **REVEAL registry** of **3'900 pts with PAH** had associated portal hypertension[3]
- **5-6% (15%) prevalence** in cohorts of pts undergoing **liver transplantation evaluation**[1]
- More common in **females** than males, **more** commonly seen in **autoimmune hepatitis**
- **Not directly** correlated with severity of **liver disease** (MELD) or severity of **portal pressure**

[1]Thomas C et al., Front Med 2020
[2]Hadengue A et al., Gastroenterology 1991
[3]Krowka MJ et al., Chest 2012

5

Natural History & Prognosis

PoPH is associated with poor survival



- PoPH 2-year survival rate **67%**, 5-year survival rate **40%**
- PoPH pts less likely to receive **PAH therapy** compared to other types of PAH
- **RV failure, sudden death, hepatic decompensation**
- Prognosis related to presence of cirrhosis

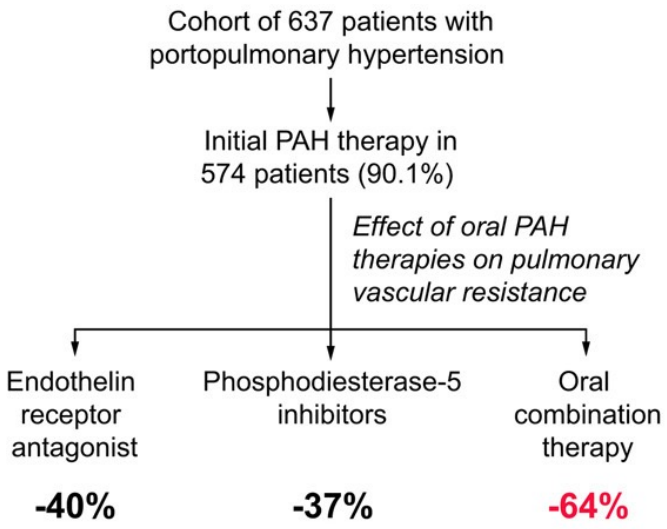
Krowka MJ et al, Chest 2012

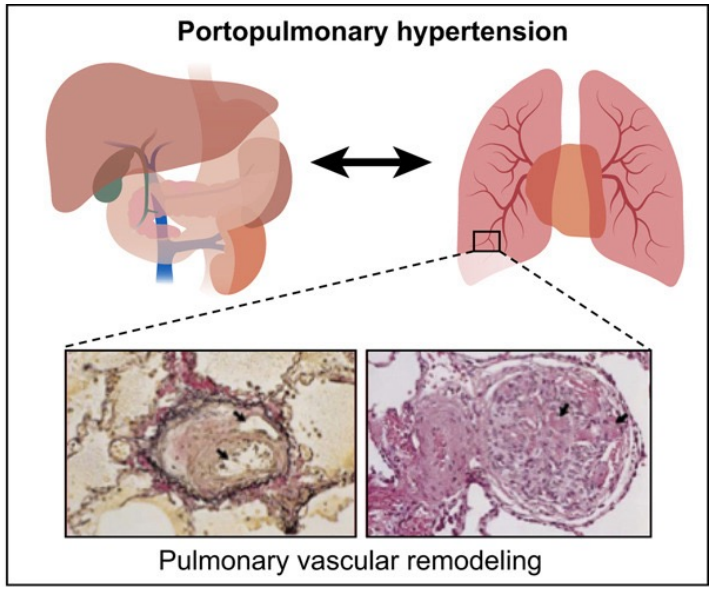
Management of PoPH

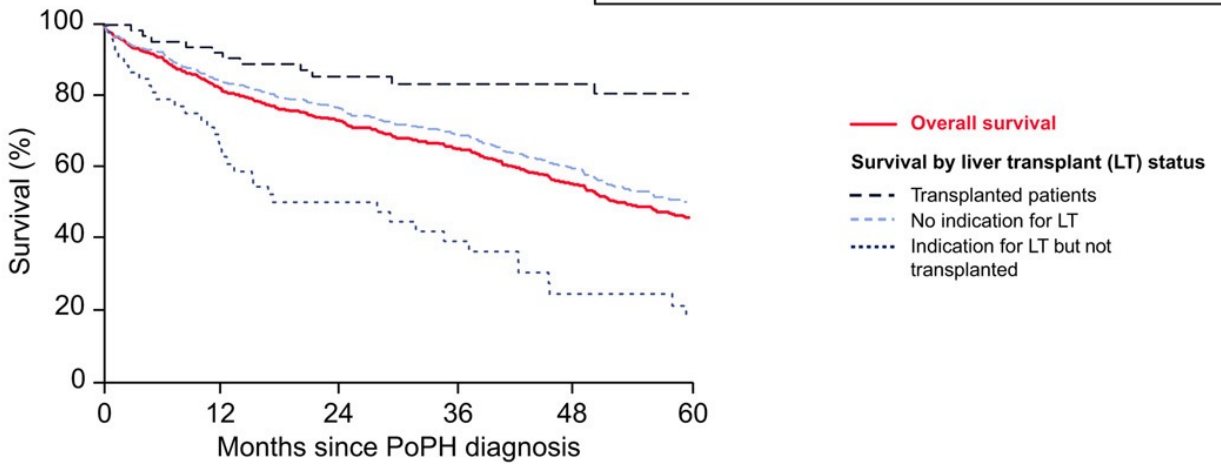
Strategy	5-year survival rate
No therapy	14%
Liver transplantation alone	25%
Medical therapy alone	45%
Liver transplant with pretreatment of PAH	67%

Swanson KL et al, Am J Transplant 2008

PoPH in the current era of pulmonary hypertension management







Savale L et al., J Hepatol 2020

6

Screening & Diagnosis of PoPH

Screening for PoPH: How & whom?

- Transthoracic **echocardiography (TTE) best screening tool** for PH in chronic liver disease
- Screening of all **liver transplantation candidates** recommended
- Repeat **annual screening** echocardiography if waiting on liver transplantation list
- Patients **evaluated for TIPS** and **cirrhotics with pulmonary symptoms** should also be screened for PoPH by echocardiography
- TTE to assess **right ventricular systolic pressure (RVSP)** and/or **tricuspid regurgitation velocity (TRV)**

Krowka MJ et al Hepatology 2006

EASL Clinical Practice Guidelines & AASLD Practice Guidelines on Liver Transplantation, 2015 & 2013

Screening & Diagnosis of PoPH

TTE to assess **right ventricular systolic pressure (RVSP)** and/or **tricuspid regurgitation velocity (TRV):**

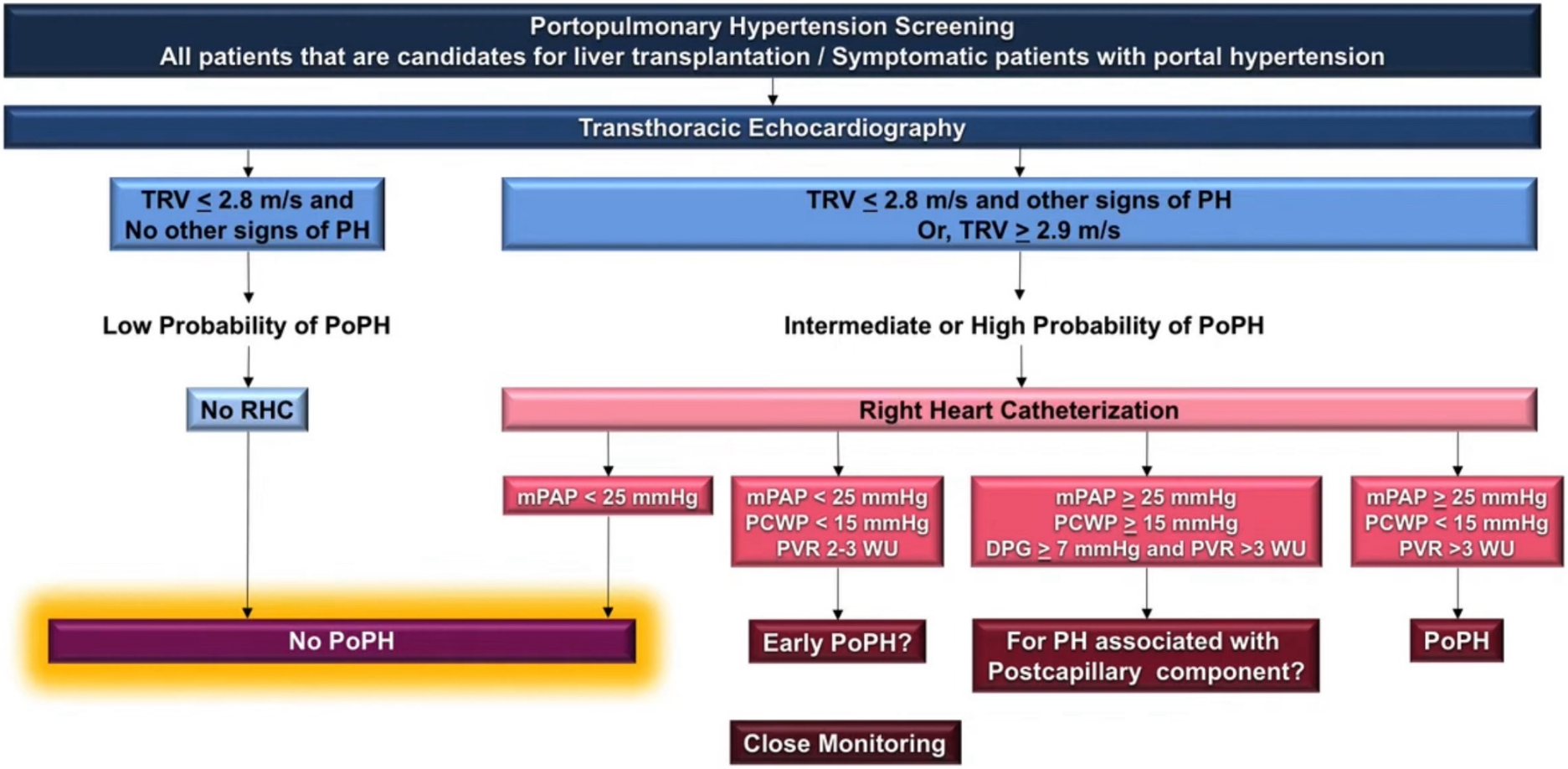
- If **RVSP > 40-50 mmHg** proceed with **right heart catheterization** (sensitivity 80%, specificity 96% to detect moderate to severe PoPH)
- If **RVSP 30-39 mmHg** and **RV enlargement** or other **evidence of PoPH** present, also proceed with RH catheter
- **Tricuspid regurgitation velocity (TRV)** may indicate presence of PH:
  - Peak **TRV < 2.8 m/s** = low to intermediate probability of PH
  - Peak **TRV 2.9 to 3.4 m/s** = intermediate to high probability of PH
  - Peak **TRV > 3.4 m/s** = high probability of PH

- **Right heart catheterization** recommended if **intermediate or high probability for PoPH**

Krowka MJ et al Hepatology 2006

EASL Clinical Practice Guidelines & AASLD Practice Guidelines on Liver Transplantation, 2015 & 2013

Diagnostic algorithm for PoPH



Adapted from Savale L et al., Semin Respir Crit Care Med 2017 & Elwing JM et al., Med Ed OTG 2020

Pulmonary hemodynamic profiles of different pathologic mechanisms of pulmonary hypertension in liver disease

	mPAP	PVR	CO	PAWP	TPG
Hyperdynamic state	↑	↓	↑	↓ ↔	↓
Pulmonary venous congestion	↑	↑↓	↑ ↔	↑	↓
POPH (Vasoconstriction and remodeling)	↑	↑	∩	↔	↑

DuBrock HM et al, Expert Rev Gastroenterol Hepatol 2015

Grading of PoPH severity

Normal mPAP:	mPAP < 25 mmHg
Mild PoPH:	mPAP < 35 mmHg
Moderate PoPH:	mPAP ≥ 35 mmHg
Severe PoPH:	mPAP ≥ 45 mmHg

EASL Clinical Practice Guidelines on decomensated liver cirrhosis, J Hepatol 2018

7

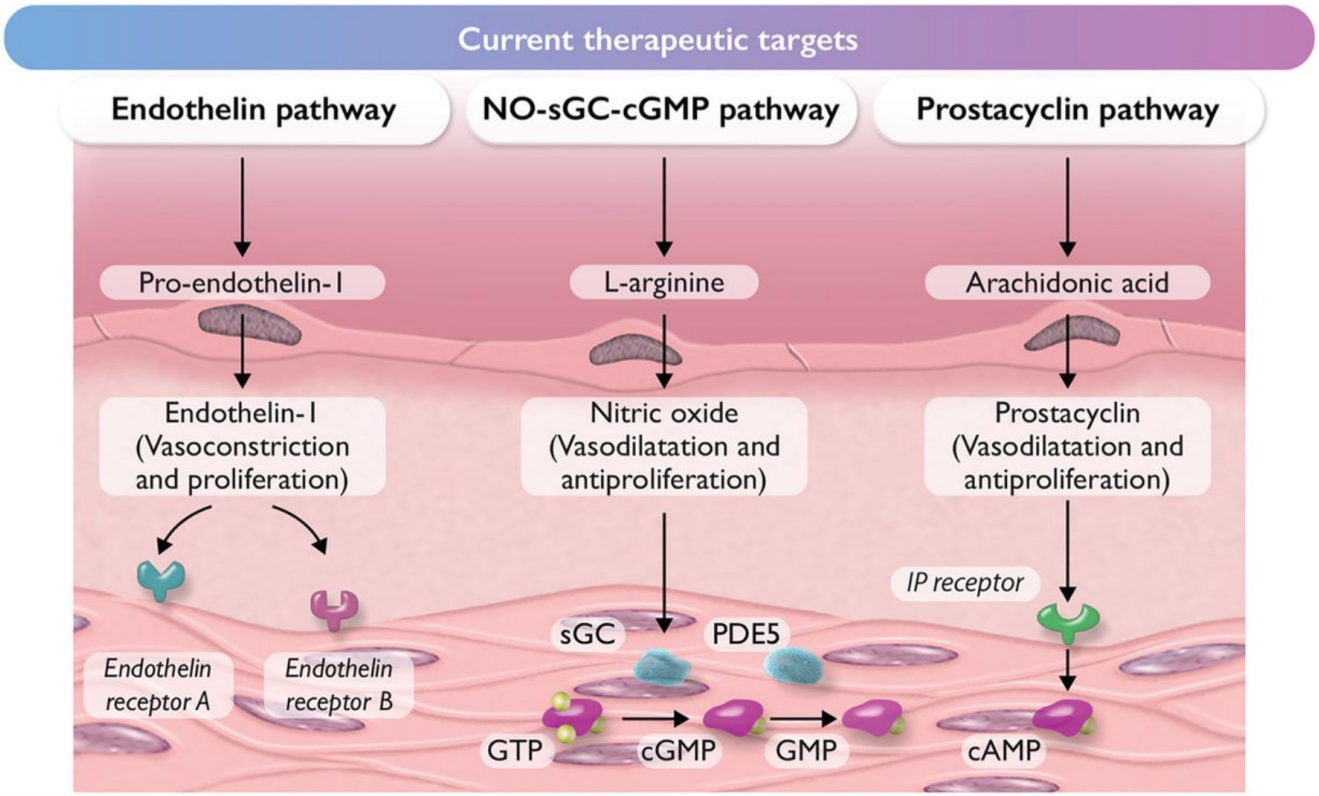
Management & Medical Treatment

General management of patients with PoPH

- **Diuretics** (maintain euvolemic state, avoid fluid overload)
- **Prophylactic betablockers** may be harmful and are contraindicated[1] (worsening of exercise capacity and pulmonary hemodynamics (CO↓, PVR↑))
- **Calcium channel blockers**: no indication in PoPH and might worsen portal hypertension
- **Anticoagulation** not recommended in PoPH[2] (thrombocytopenia, varices)
- Avoid **transjugular intrahepatic portosystemic shunt** (TIPS)

[1]Provencher S et al., Gastroenterology 2006
2Galie N et al., Eur Heart J 2016

Management of PoPH: PAH-specific therapies



Endothelin receptor antagonists

- Bosentan, Ambrisentan, **Macitentan**

Phosphodiesterase-5 inhibitors

- Sildenafil, Tadalafil, Vardenafil

Soluble guanylate cyclase stimulators

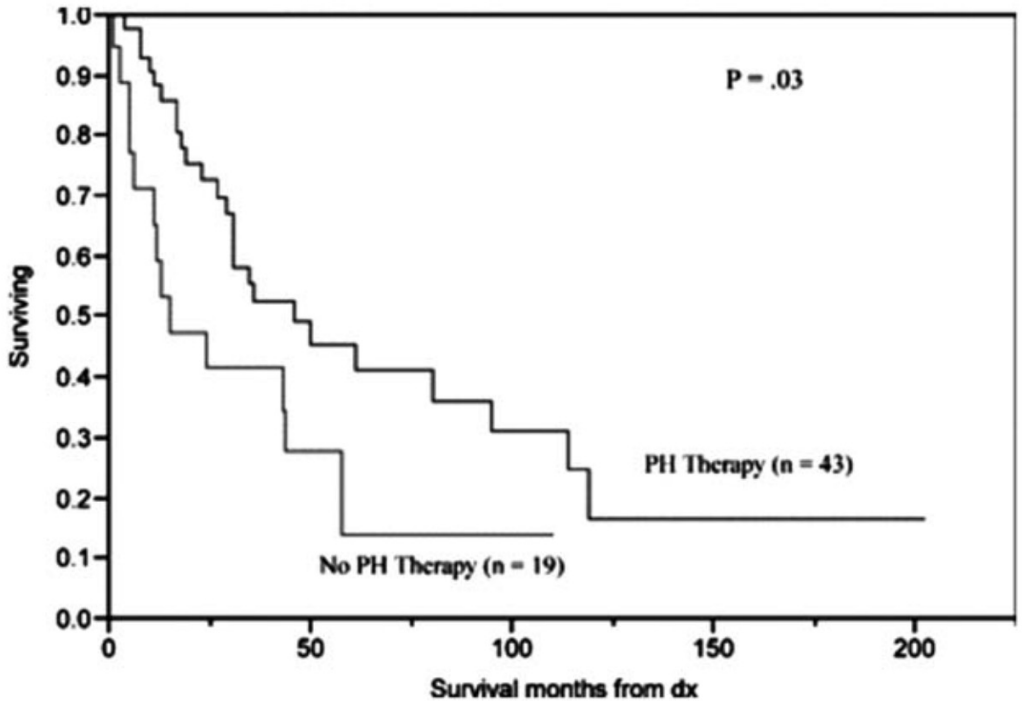
- Riociguat

Prostacyclin and analogues

- Epoprostenol, Iloprost, Treprostinil

Humbert M et al., Eur Respir J 2023

Pulmonary vasodilatator therapy improves survival in PoPH



PAH Therapy (n=43)

No PAH therapy (n=19)

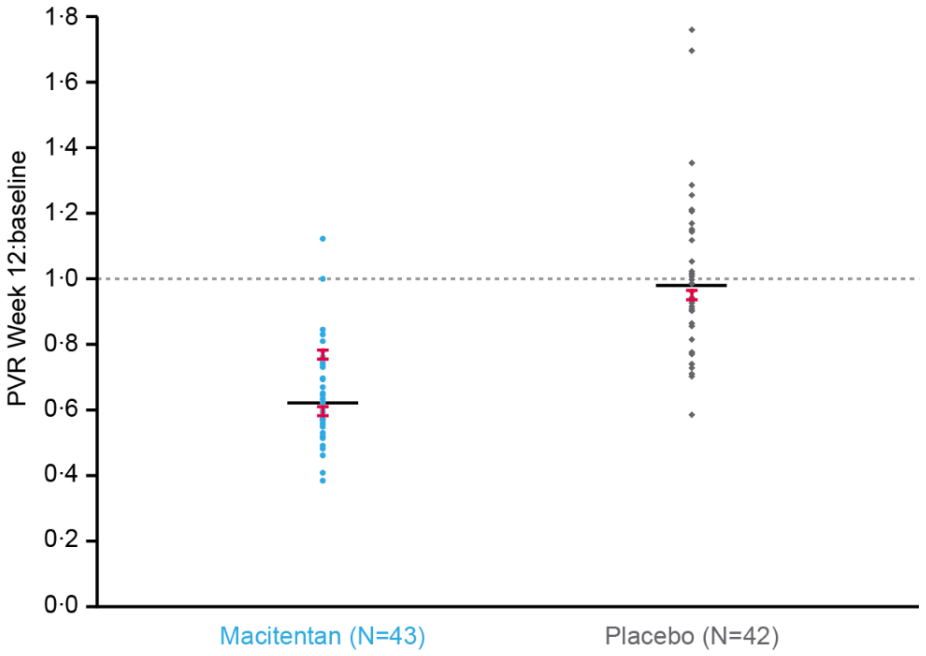
- PAH therapy with **pulmonary vasodilatators** improved **5-year survival** from **14%** **to** **45%**
- **MELD score** was **not prognostic**

Swanson KL et al, Am J Transplant 2008

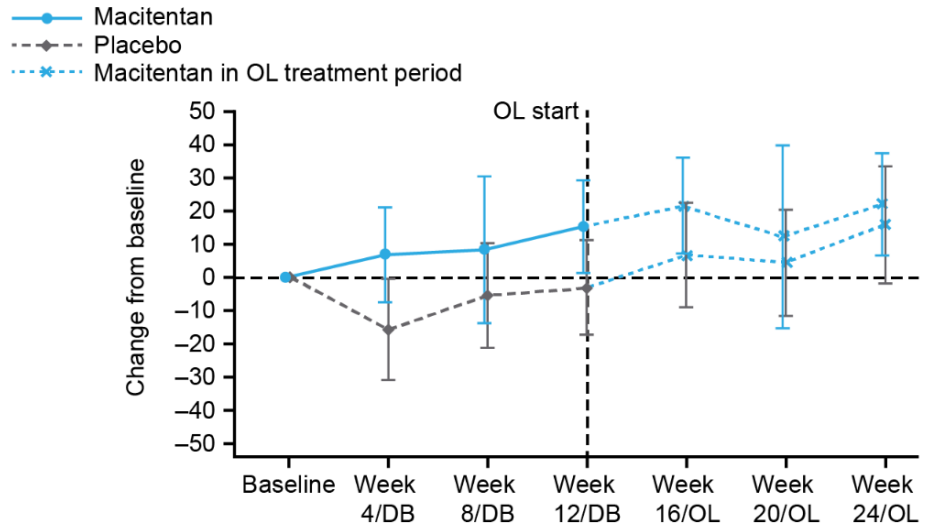
Macitentan for the treatment of portopulmonary hypertension (**PORTICO**): A multicentre, randomised, double-blind, placebo-controlled, phase 4 trial

Phase 4 study in 36 centres/7 countries, **12-week** double-blind period (**macitentan 10 mg qd vs. placebo**) followed by a 12-week open-label period. **85 adults** with PoPH, a 6-minute **walk distance of ≥ 50 m**, and with **PVR of ≥ 320 dyn·s·cm-5** without severe hepatic impairment (**Child A/B** or **MELD score <19**) were eligible. **Primary endpoint: PVR at week 12.**

PVR at Week 12 expressed as ratio of baseline



Change in 6MWD during the double-blind and open-label treatment periods



Number of patients							
Macitentan	43	41	39	38	37	36	32
Placebo/macitentan	42	41	40	40	37	37	34

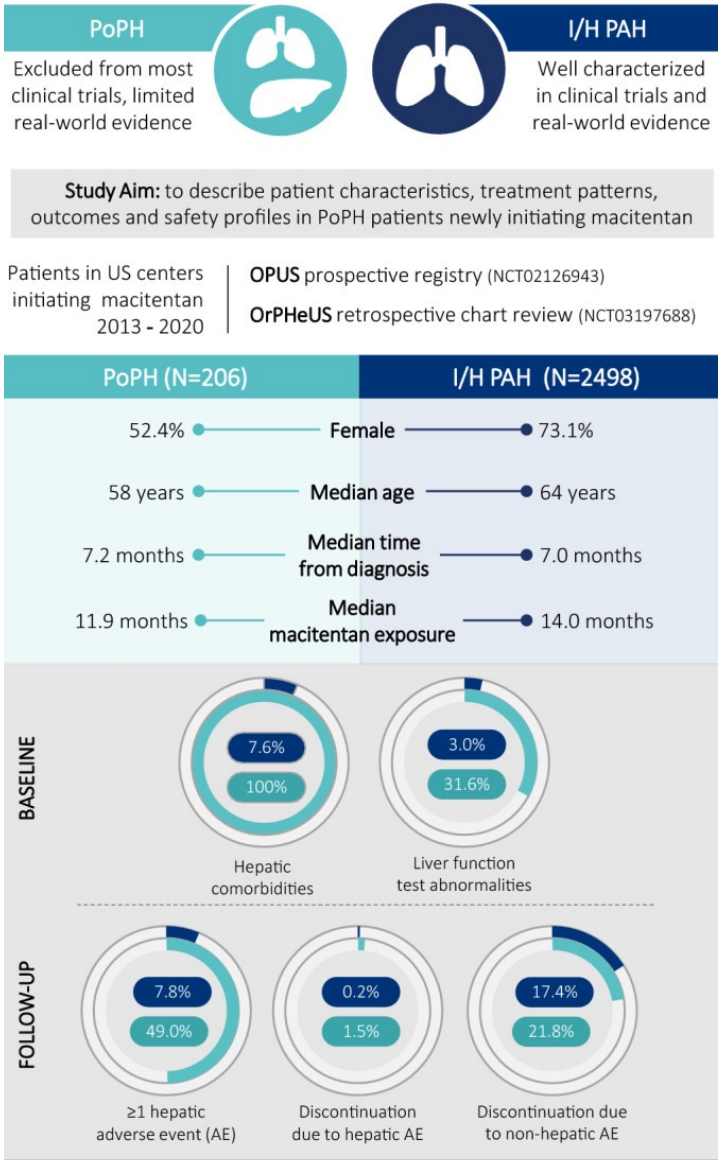
Macitentan significantly **improved pulmonary vascular resistance by 35%** versus placebo, with **no observed worsening of hepatic function or portal hypertension**, or unexpected hepatic safety concerns. In PoPH, improvement in hemodynamics may not only be essential to **delay disease progression** but also to **increase eligibility for a liver transplant**, which offers the best chance of survival.

Sitbon O et al., Lancet Respir Med, 2019

Safety of Macitentan for the Treatment of Portopulmonary Hypertension:

Real-World Evidence from the Combined OPUS/OrPHeUS Studies

Conclusion:
No unexpected safety findings in pts with PoPH treated with macitentan.



Kim NH et al., Pulm Ther, 2024

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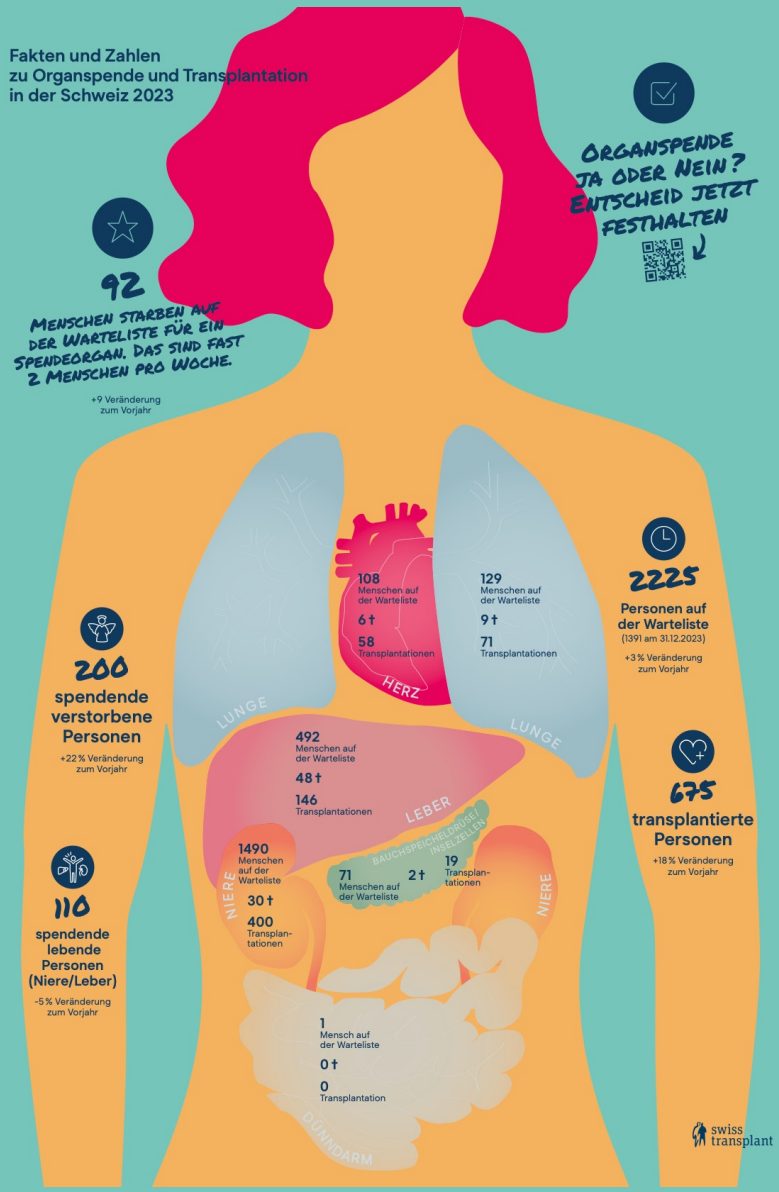
Liver Transplantation


Fakten und Zahlen
zu Organspende und Transplantation
in der Schweiz 2023
92
Menschen starben auf der Warteliste für ein Spendeorgan. Das sind fast 2 Menschen pro Woche.
+9 Veränderung zum Vorjahr
Organspende ja oder nein? Entscheid jetzt festhalten
200
spendende verstorbene Personen
+22 % Veränderung zum Vorjahr
110
spendende lebende Personen (Niere/Leber)
-5 % Veränderung zum Vorjahr
2225
Personen auf der Warteliste
(1391 am 31.12.2023)
+3 % Veränderung zum Vorjahr
675
transplantierte Personen
+18 % Veränderung zum Vorjahr
108 Menschen auf der Warteliste
6 †
58 Transplantationen
HERZ
129 Menschen auf der Warteliste
9 †
71 Transplantationen
LUNGE
LUNGE
492 Menschen auf der Warteliste
48 †
146 Transplantationen
LEBER
BAUCHSPEICHELDRÜSE
INSELZELLEN
1490 Menschen auf der Warteliste
30 †
400 Transplan-tationen
NIERE
71 Menschen auf der Warteliste
2 †
19 Transplan-tationen
NIERE
1 Mensch auf der Warteliste
0 †
0 Transplantation
DÜNNDARM
swiss transplant

PoPH and liver transplantation

- **PoPH is not *per se* an indication for liver transplantation**
- PoPH poses a **major threat** to patients who undergo liver transplantation when indicated for the severity of liver disease
- In liver transplantation candidates with PAH, **targeted medical therapy** successfully improves haemodynamics and establishes **eligibility for transplantation**
- The Int. Liver Transplant Society proposed **haemodynamic targets** of **mPAP <35 mmHg and PVR <5 WU** (400), or **mPAP ≥35 mmHg and PVR <3 WU** (240) in patients receiving PAH therapy
- An **mPAP ≥45 mmHg** is regarded as an **absolute contraindication** to liver transplantation
- In PoPH pts who successfully **underwent liver transplantation, de-escalation or discontinuation** of PAH medication is often feasible, but this has to be performed on an individual basis

Humbert M et al., Eur Respir J 2023

Mayo Clinic intraoperative guidelines concerning hemodynamics in pts with PoPH

Mean Pulmonary Artery Pressure	Intraoperative Guideline	Reported Mortality
< 35 mmHg	Proceed with OLT	0/14 (0)
35-50 mmHg	If PVR < 250* proceed with OLT If PVR ≥ 250* cancel OLT	0/6 (0) 7/14 (50)
≥ 50 mmHg	Cancel OLT °	6/6 (100)

* PVR in dynes / sec / cm^5

°If untreated, refer for additional pulmonary hypertension evaluation/therapeutic considerations and re-evaluate for OLT

Krowka MJ et al., Liver Transp 2000

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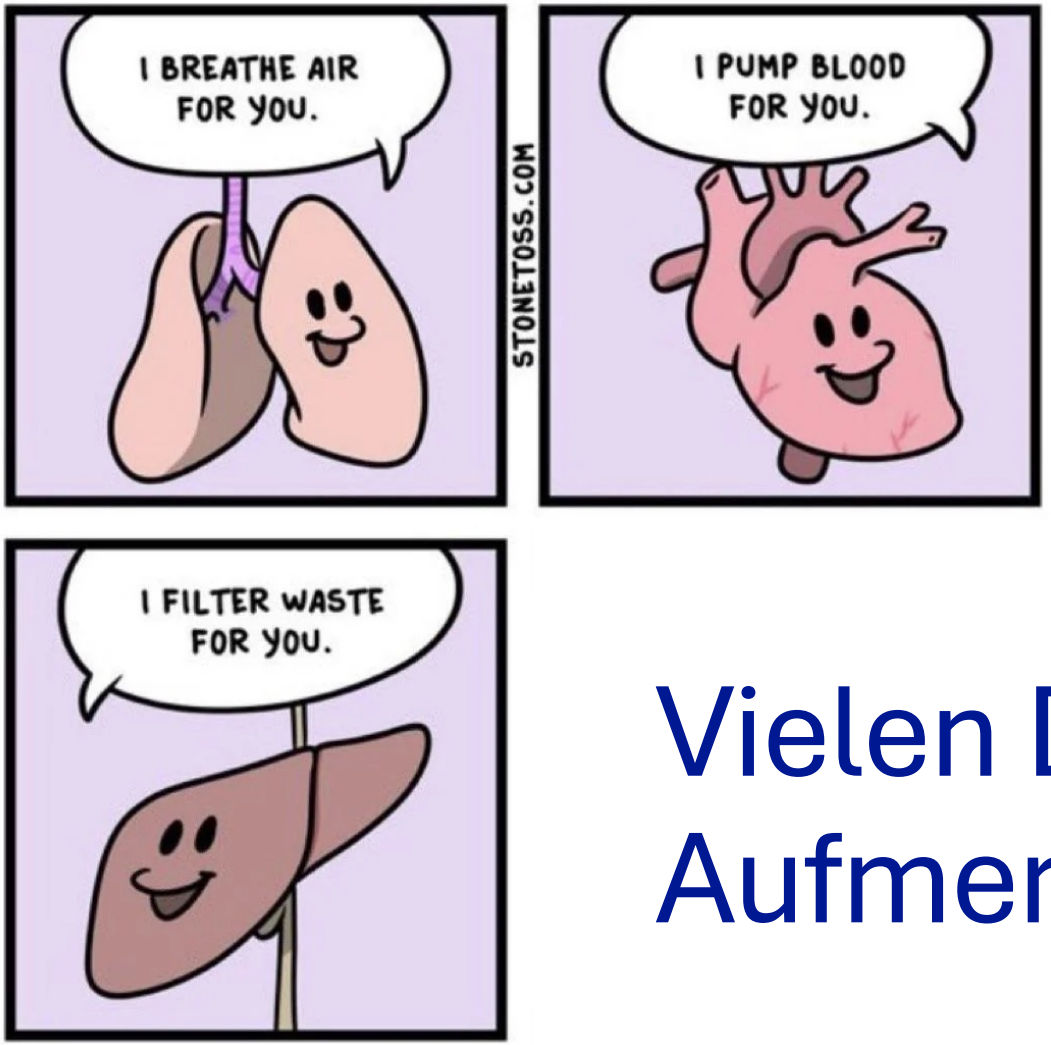
Summary

Summary: Portopulmonary hypertension

- PoPH = elevation of **mPAP ≥ 25 mmHg**, occurring in the **presence of portal hypertension**
- PoPH is detected in **2-15%** of patients with **liver cirrhosis** and carries a **dismal prognosis**
- **PoPH screening in liver disease** and **pulmonary symptoms,** before **TIPS placement** or **liver transplantation**
- **Echocardiography** is the initial **screening test** to estimate right ventricular systolic pressure (**RVSP**)
- **Right heart catheterization** as the **gold standard** confirmatory **definitive test**
- PoPH patients should be evaluated by a **pulmonary** & **cardiac specialist** for vasodilator therapy
- **Macitentan** has been shown to be **effective and safe** in PoPH patients in a first prospective study
- **Milder degrees of PoPH do not adversely affect outcome of liver transplantation**, but mortality rate climbs with more pronounced degrees
- However, if mPAP can be reduced by **vasodilator therapy to < 35 mmHg** and **PVR < 400 dynes/s/cm^5** OLT is possible, with acceptable short-term outcomes



Vielen Dank für Ihre Aufmerksamkeit!