A puzzling case of pulmonary hypertension

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Case presentation - 1

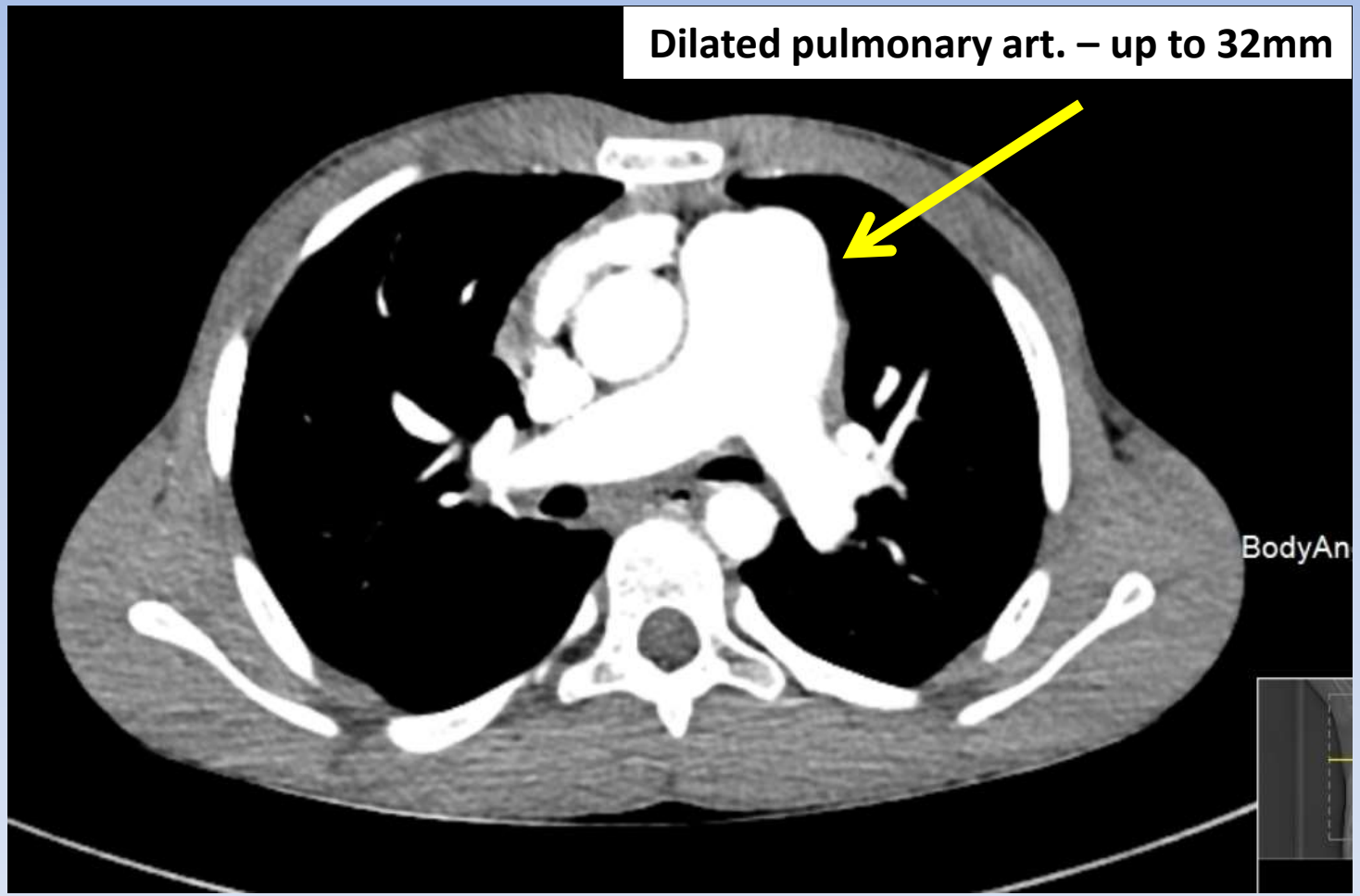
- 13 years old boy
- Premature birth, 28+5 week, c/s, one of twins
- PICU:
  - Respiratory – mechanical ventilation → support for 4 months; discharged without oxygen
  - 3 operations due to NEC
  - PDA closure – age 4 mts
  - Fulminant hepatic failure (due to TPN); candidate for liver transplantation → eventual recovery
- Treated with budicort until age 1 yr
- Normal cardiac echo March 2005 (age 7 mts)

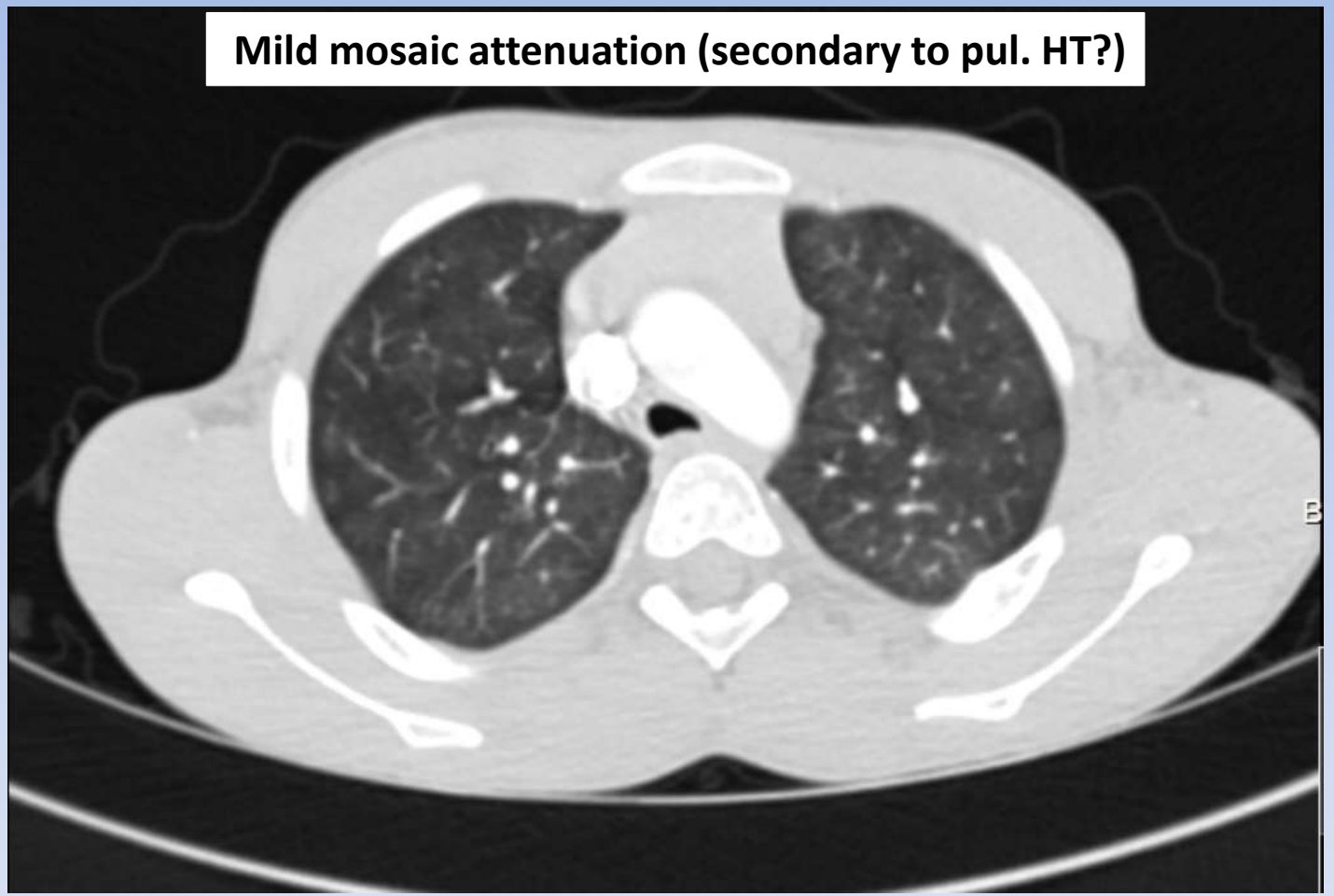
Case presentation - 2

- Currently –
- Mild CP – left diplegia
- Short stature – treated with growth hormone
- Mild leukopenia & thrompocytopenia
- **Respiratory** – effort dyspnea, no specific treatment; without respiratory exacerbations or pneumoniae
- May 2017 – routine cardiac echocardiogram (before swimming lessons) – good LV function; mild TR; **TRPG of 50mmHg**

Case presentation - 3

- Hospitalized for evaluation of PH
- PE – Sat. 100%; heart & lungs – normal; no clubbing; spleen 2 cm under rib margin
- PFT – poor technique; FVC 65%, FEV1 71%; normal lung volumes – TLC 94%; normal diffusion
- Abdominal US & doppler – enlarged IVC; slight enlargement of spleen; mild peri-portal fibrosis without liver cirrhosis; no signs of portal hypertension
- CT angio – no signs of pulmonary emboli


Dilated pulmonary art. – up to 32mm
BodyAn


Mild mosaic attenuation (secondary to pul. HT?)

Case presentation - 4

- Cardiac catheterization-
  - Systolic PAP 48mmHg
  - Mean PAP 34mmHg
  - Wedge pressure 8mmHg
  - PVR 11.3 wood units →→ 7.9 with oxygen

Consistent with pulmonary arterial hypertension

- Further evaluation –
  - 6 minute walk test – 425m
  - 24 BP holter – normal
  - Nocturnal saturation - normal

Pulmonary hypertension (PH)

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

2015 ESC/ERS Guidelines

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
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1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
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  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
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  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
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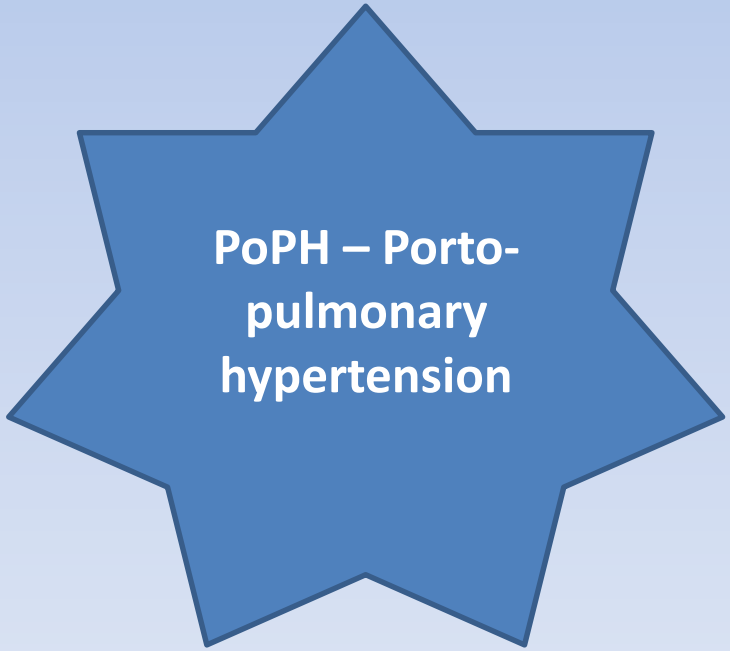
BPD

2015 ESC/ERS Guidelines

Pulmonary & liver disease



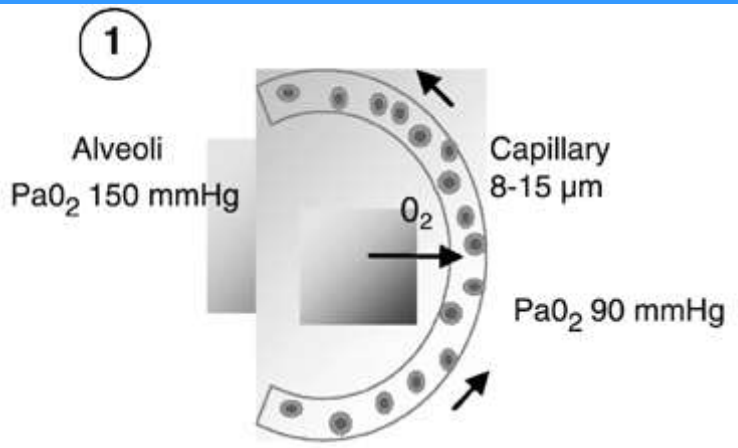
HepatoPulmonary Syndrome - HPS

- **Definition:**

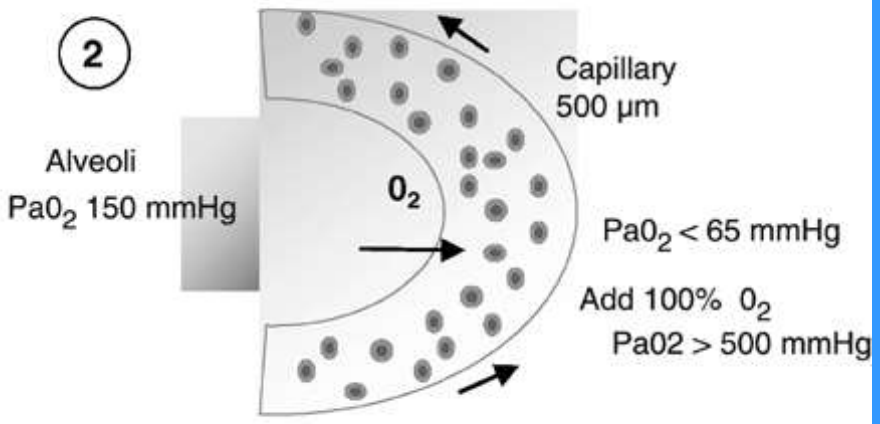
✓ Liver disease or portal HT

✓ ↑A-aPO_2 on room air

✓ Evidence of intrapulmonary vasodilatation

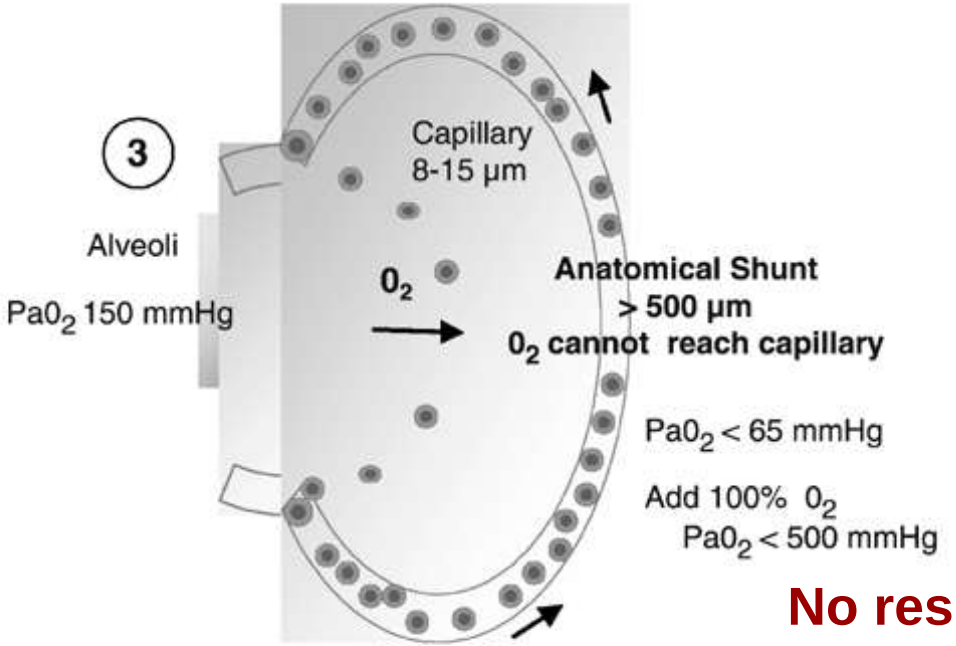


Normal Pulmonary Circulation



Hepatopulmonary Syndrome Type I

Response to O_2



Hepatopulmonary Syndrome Type II

No response to O_2

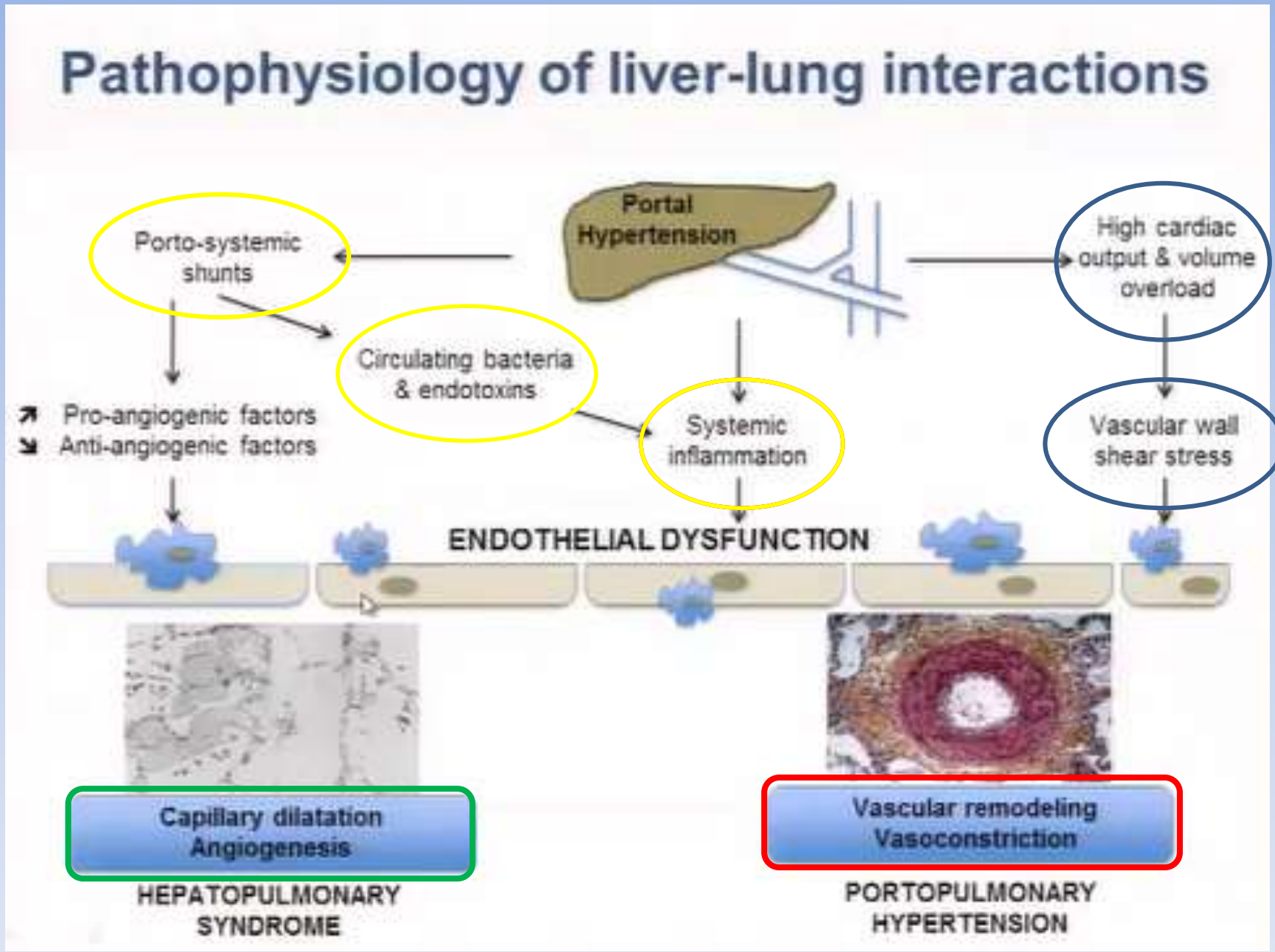
Ramsay, Int. Anesthesiol. Clin. 2006

PoPH and HPS

	POPH	HPS
Pathophysiology	Pulmonary arterial hypertension (PAH)	Intrapulmonary shunting
Pathology	PAH due to plexiform lesions, thrombosis, obliterative pulmonary arteriopathy	Intrapulmonary vascular dilatations (IPVDs) causing intrapulmonary shunting and hypoxemia
Severity of hypoxemia	Typically mild	Mild to very severe, depending on degree of shunting
Right ventricle (RV)	Significantly elevated right ventricular systolic pressure (RSVP) with RV dilatation, impaired systolic function and low cardiac output	Normal or mildly elevated RVSP (due to high-flow state) with normal RV size and function
Clinical findings	Loud second heart sound, systolic murmur, RV heave, lower extremity edema	Clubbing, cyanosis, systolic flow murmur, platypnea, orthodeoxia
Treatment	Pulmonary hypertension (PH) therapy (for example, ambrisentan, sildenafil, epoprostenol, others)	Supportive care until liver transplantation, which is curative for HPS
Is liver transplantation recommended/feasible?	Only in patients where PH is adequately controlled prior to transplantation	Recommended/feasible in all patients — even in severe hypoxemia
MELD exception points available?	Yes	Yes

Mayo Clinic clinical updates

Pathophysiology of liver-lung interactions



Adapted from Sitbon, Israeli PH conference 2015

Portopulmonary hypertension (PoPH)

Portal hypertension (with or without liver disease)

+

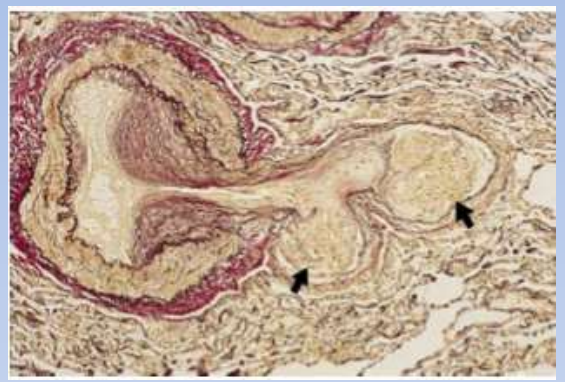
Evidence of PAH

- Incidence and prevalence not well defined
- 6.3% awaiting liver Tx (Kawut et al., Hepatology 2008); 5.1% in 3000 PAH patients (Benza et al., Circulation 2010)
- Average 4-7 yrs after diagnosis of portal HT
- Severity does not correlate with severity of liver disease (Porres-Aguilar et al., Eur Resp Rev 2012)

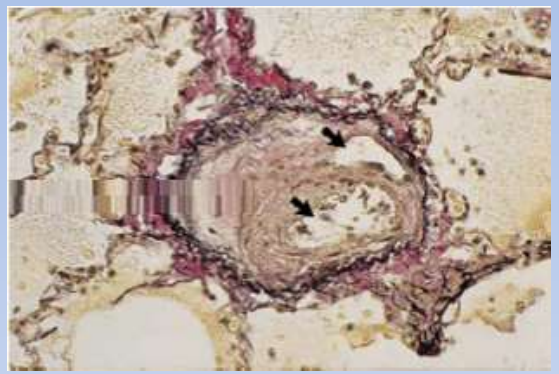
Pulmonary hemodynamics in portal hypertension

	PAP	PAWP	CO	PVR
Hyperdynamic	↗	N or ↗	↗↗	↘
Volume overload	↗	N or ↗	N or ↗	↘
PoPH	↗↗	N	N, ↘ or ↗	↗

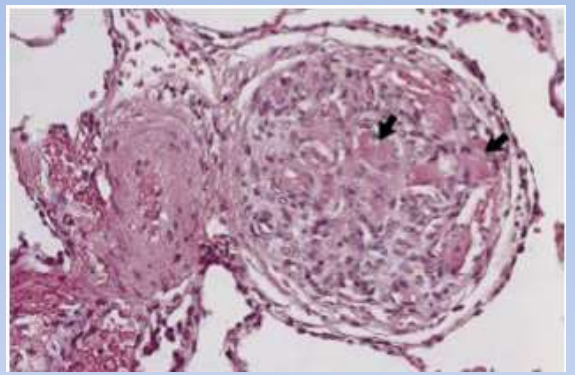
PoPH - pathology



Medial hypertrophy



Thrombotic lesion

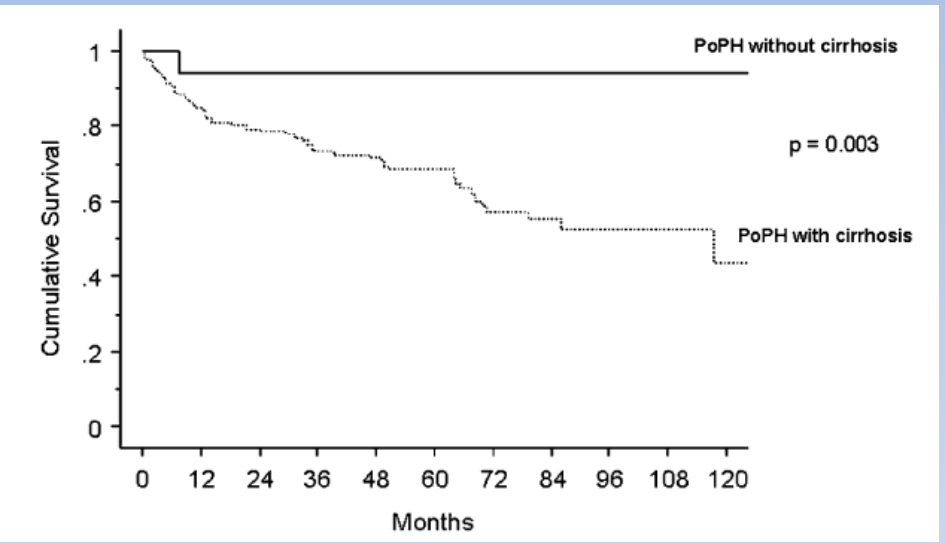


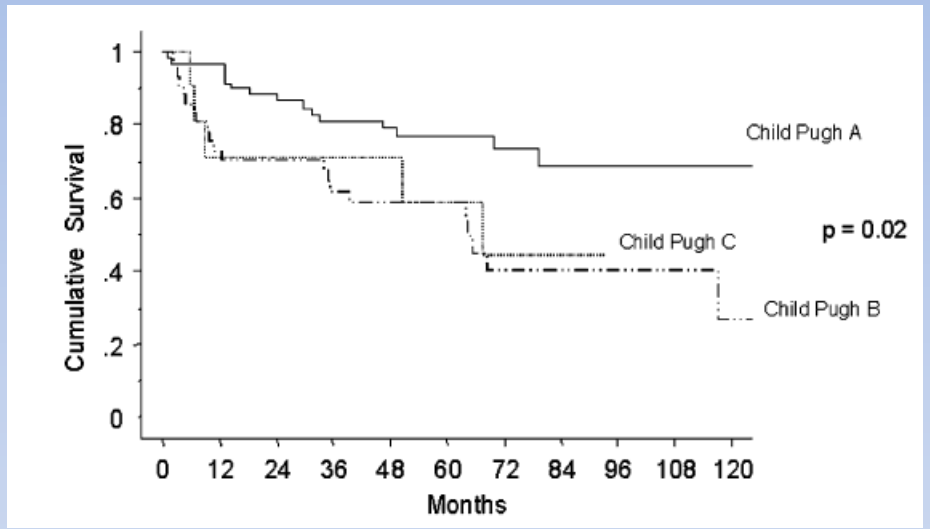
Plexiform lesion

- Lesions similar to iPAH; spectrum ranging from classic plexiform arteriopathy to microthrombotic forms

Golbin et al., Clin Chest Med 2007

PoPH - prognosis





Variables	Hazard Ratio*	95% Confidence Interval	*P* Value
Absence of cirrhosis	0.20	0.07–0.59	0.003
Child Pugh B cirrhosis	2.05	1.22–3.43	0.007
Child Pugh C cirrhosis	2.42	1.26–4.65	0.008
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	0.56	0.38–0.83	0.004

* Value > 1 indicates an increased risk of death.

Le Pavec et al., AJRCCM 2008

PoPH and liver transplantation

PoPH and liver transplantation (OLT)

Operative risk / haemodynamic criteria

mPAP	Guidelines	Cardiovascular Mortality
< 35 mmHg	Perform OLT	0%
35 – 50 mmHg	RVP < 250 dynes Perform OLT	0%
	RVP > 250 dynes Cancel OLT	50%
> 50 mmHg	Cancel OLT	100%

Krowka M, *et al. Liver Transplantation* 2000.

PoPH – treatment - 1

- Goals of therapy – symptomatic relief, improve quality of life, exercise capacity; facilitate liver Tx
- General approach similar to iPAH
- Specific considerations:
  - **Ca channel blockers –** contraindicated (mesenteric vasodilatation → worsen portal HT)
  - **β blockers –** prophylaxis in GI varices; deterioration in exercise capacity & pul. hemodynamics in PoPH
  - **Oral anticoagulants –** not recommended
  - **Diuretics –** use with caution
  - **Oxygen** if PaO_2 < 60mmHg

PoPH - treatment – 2

- Specific PAH treatment:
  - **ERA –** Bosentan superior to iloprost; monitor liver function tests; Ambrisentan – selective ET_A inhibitor – benefit in 13 patients
  - **Prostacyclin analogues –** Epoprostenol IV (Flolan) – has proven survival benefit in PAH, most studied in PoPH; complications related to IV route
  - **PDE-5 inhibitors –** Sildenafil – short term benefit, not sufficient as a monotherapy
  - Combination therapy

Troy et al., Ther Adv Gastroenterol 2009
Porres-Aguilar et al., Eur Respir Rev 2012

BPD and pulmonary HT - 1

- Pediatric Pulmonary Hypertension Network (PPHNet) recommendations 2017 (Krishan et al.)

- Screening for PH in premature infants:
  - Severe hypoxemic respiratory failure shortly after birth
  - Continued ventilatory support at postnatal day 7
  - At the time of formal BPD diagnosis
  - Repeat echo if an infant develops increasing oxygen/ respiratory support requirements (during the initial or subsequent hospitalizations), as PH may develop despite having a normal echocardiogram at discharge

BPD and pulmonary HT - 2

- Treat underlying disease!
- Home pulse oximetry during sleep/ a formal PSG
- Consider specific therapy if sustained PH after optimal treatment of underlying respiratory and cardiac disease

BPD and pulmonary HT - 3

- Few studies on long term follow up
- **No evidence of new-onset PH in former BPD**

- ≤32 weeks of gestation (28 CLD, 32 preterm controls), and 30 term-born controls
- Age 8-12 yrs – **Normal PAP even after hypoxic exposure[1]**

- 34 VLBW children with BPD; age 7-8 yrs – normal echo; BPD –FEV1↓; ↑RV/TLC
- **The increased pulmonary vascular resistance associated with BPD appears to resolve with time more rapidly than abnormalities in respiratory function[2]**

[1]Joshi S et al. Arch Dis Child Fetal Neonatal 2014

[2]Korhonen et al., Early Human Develop 2005

…Back to our patient

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BPD

Our patient

- Treated with Viagra 15mg/kg/day
- Repeated echo – no change
- Repeated abdominal US – similar findings, no signs of cirrhosis or portal hypertension
- Planned for genetic counseling
- Twin brother planned for echo
- ETA will be added – Bosentan/ Macicentan (in clinical trial)

In summary

- ✓ No evidence of BPD
- ✓ No evidence of portal hypertension
- ✓ No signs of underlying systemic diseases
- ✓ No OSA

So, can we call it idiopathic PAH?

THANK YOU!