The Liver-Lung Connection in Portopulmonary Hypertension

Pulmonary Hypertension Grand Rounds
Stanford University
May 8, 2017

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Disclosures

- No conflicts of interest

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Objectives

- Compare and contrast the pathophysiology, management and prognosis of portopulmonary hypertension (POPH) and idiopathic pulmonary arterial hypertension
- Examine the role of liver transplantation in the management of POPH

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A Case…

- What does my liver have to do with my lungs?
- Why do I have “pulmonary hypertension” when I have “hypotension” in the rest of my body?
- Will my pulmonary hypertension get better with liver transplant?

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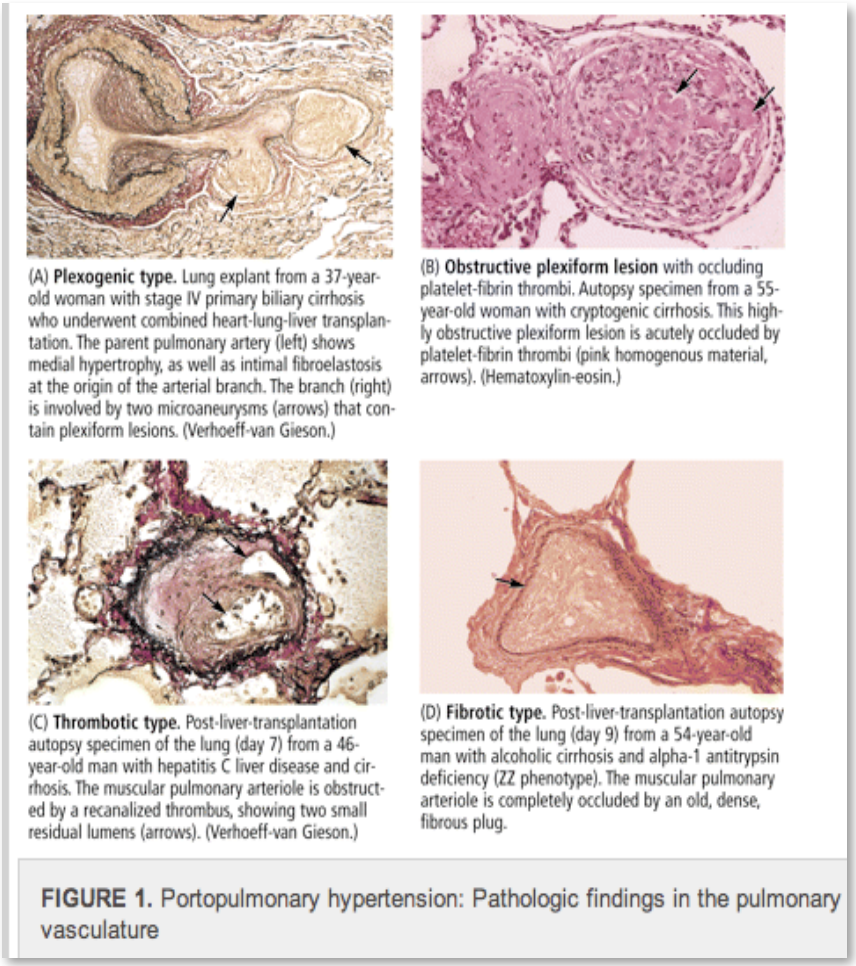
Portopulmonary Hypertension

- A subtype of WHO Group 1 pulmonary arterial hypertension (PAH) that develops as a complication of portal hypertension
- Affects 5-8% of patients evaluated for liver transplant
- 5% of PAH
- Pathologically indistinct from idiopathic PAH



(A) **Plexogenic type.** Lung explant from a 37-year-old woman with stage IV primary biliary cirrhosis who underwent combined heart-lung-liver transplantation. The parent pulmonary artery (left) shows medial hypertrophy, as well as intimal fibroelastosis at the origin of the arterial branch. The branch (right) is involved by two microaneurysms (arrows) that contain plexiform lesions. (Verhoeff-van Gieson.)

(B) **Obstructive plexiform lesion** with occluding platelet-fibrin thrombi. Autopsy specimen from a 55-year-old woman with cryptogenic cirrhosis. This highly obstructive plexiform lesion is acutely occluded by platelet-fibrin thrombi (pink homogenous material, arrows). (Hematoxylin-eosin.)

(C) **Thrombotic type.** Post-liver-transplantation autopsy specimen of the lung (day 7) from a 46-year-old man with hepatitis C liver disease and cirrhosis. The muscular pulmonary arteriole is obstructed by a recanalized thrombus, showing two small residual lumens (arrows). (Verhoeff-van Gieson.)

(D) **Fibrotic type.** Post-liver-transplantation autopsy specimen of the lung (day 9) from a 54-year-old man with alcoholic cirrhosis and alpha-1 antitrypsin deficiency (ZZ phenotype). The muscular pulmonary arteriole is completely occluded by an old, dense, fibrous plug.

FIGURE 1. Portopulmonary hypertension: Pathologic findings in the pulmonary vasculature

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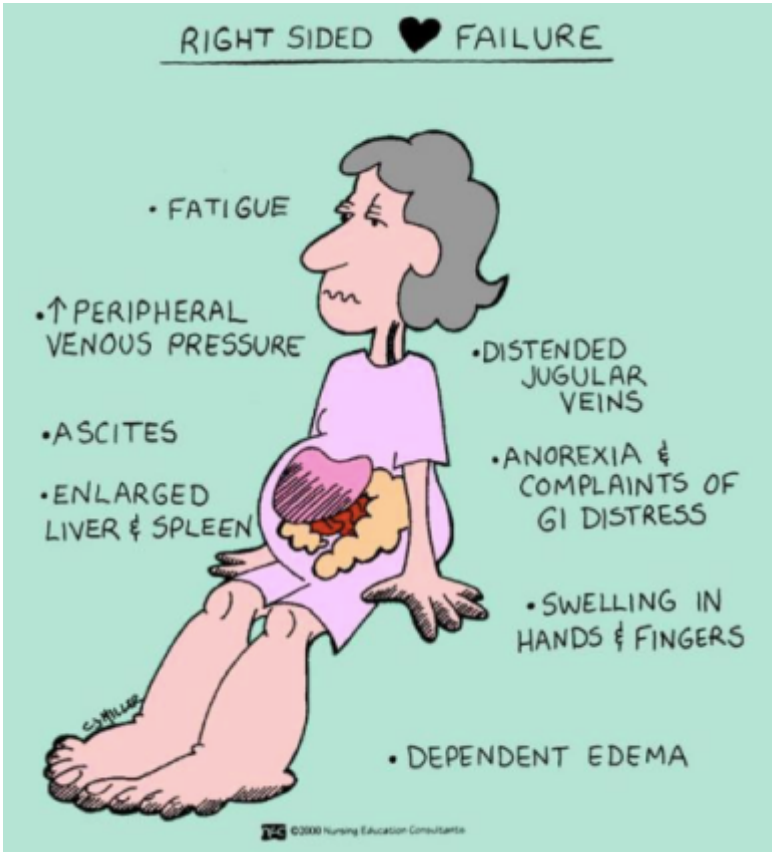
Krowka et al. Hepatology 2006
Rodriguez-Roisin et al. ERJ 2004
Krowka et al. Liver Trans[plant 2000
Krowka et al. CHEST 2012

Clinical features

- Fatigue
- Exertional dyspnea
- Exertional syncope
- New or increased ascites
- Lower extremity edema



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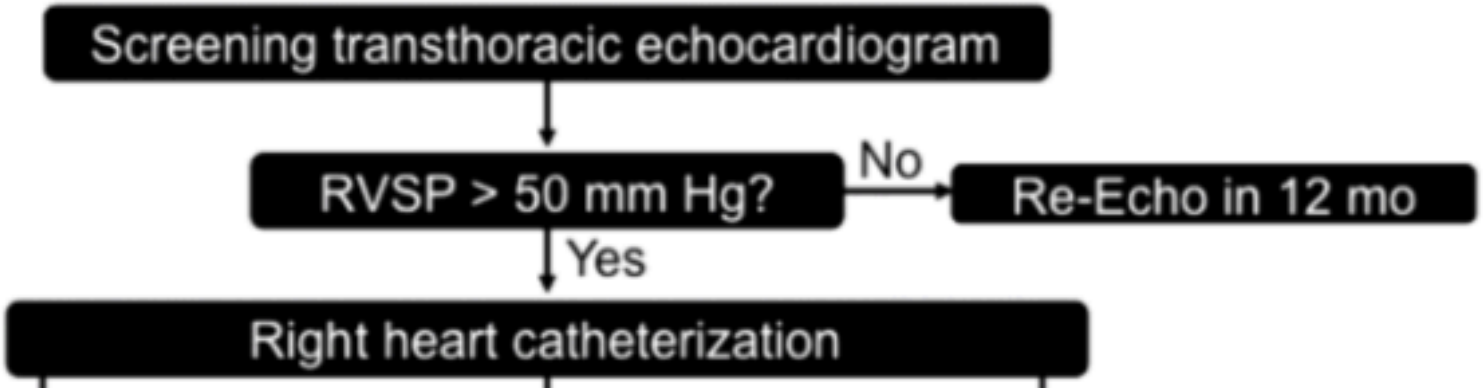
Nursing Education Consultants 2000

Screening

- Screening echocardiogram recommended in all LT candidates
- Mayo Clinic practice is to repeat echocardiogram annually and to refer all patients with RVSP>50mmHg for right heart catheterization
- RVSP>38mmHg: Sensitivity 100%, specificity 82%, NPV 100%, PPV 22%



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Raevens et al. Liver Transplantation 2013
Cartin-Ceba et al. Advances in PH. 2013

Diagnosis

International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension

Michael J. Krowka, MD,[1] Michael B. Fallon, MD,[2] Steven M. Kawut, MD, MS,[3] Valentin Fuhrmann, MD,[4] Julie K. Heimbach, MD,[5] Michael A. E. Ramsay, MD,[6] Olivier Sitbon, MD,[7] and Ronald J. Sokol, MD[8]

- mPAP >25mmHg
- PVR>3 Wood units
- PAWP<15mmHg
- Portal hypertension
- Absence of alternative etiologies of PAH

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Krowka et al. Transplantation 2016

Hemodynamic profiles of pulmonary hypertension in liver disease

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

DuBrock et al. Exp Rev. 2015

Pathophysiology

- Not associated with:
  - Severity of liver disease
- Associated with:
  - Autoimmune liver disease
  - Female sex, genetic variations in aromatase and higher serum estradiol levels
  - Decreased prostacyclin synthase expression
  - Higher serum endothelin-1 levels
  - Higher prevalence of large spontaneous portosystemic shunts

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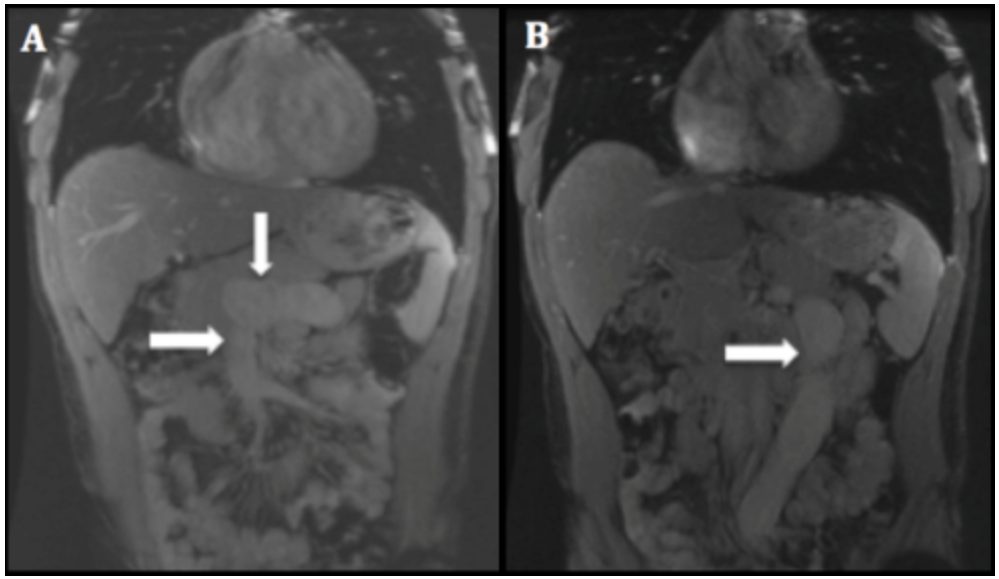
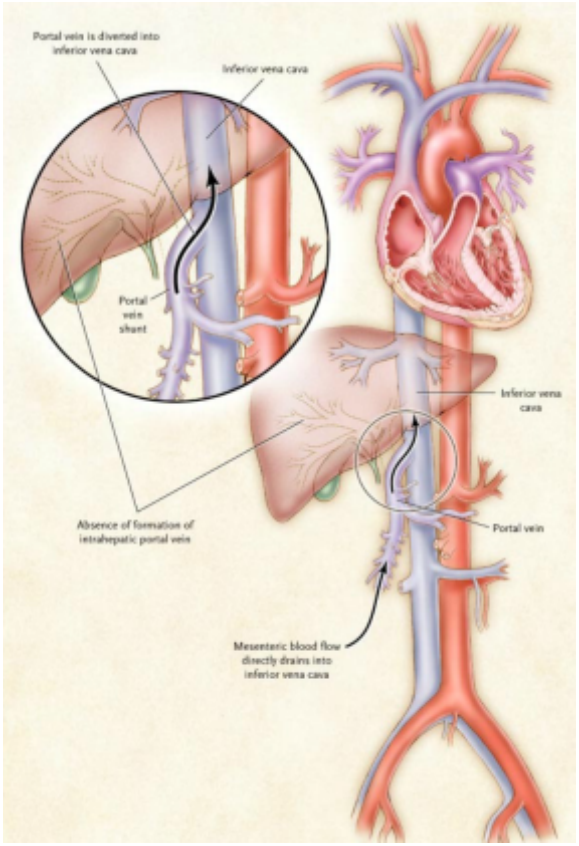
Roberts et al AJRCCM 2009
Kawut et al Hepatology 2008
Benjaminov et al Gut 2003
Tuder et al AJRCCM 1999
Talwalkar et al Gastro 2011

Insights into Pathophysiology: Abernethy Malformation

- Rare congenital disease characterized by the absence of an intrahepatic portal vein
- Patients develop POPH (and/or hepatopulmonary syndrome) despite lack of intrinsic liver disease and POPH improves with liver transplant





Kinane et al NEJM 2004

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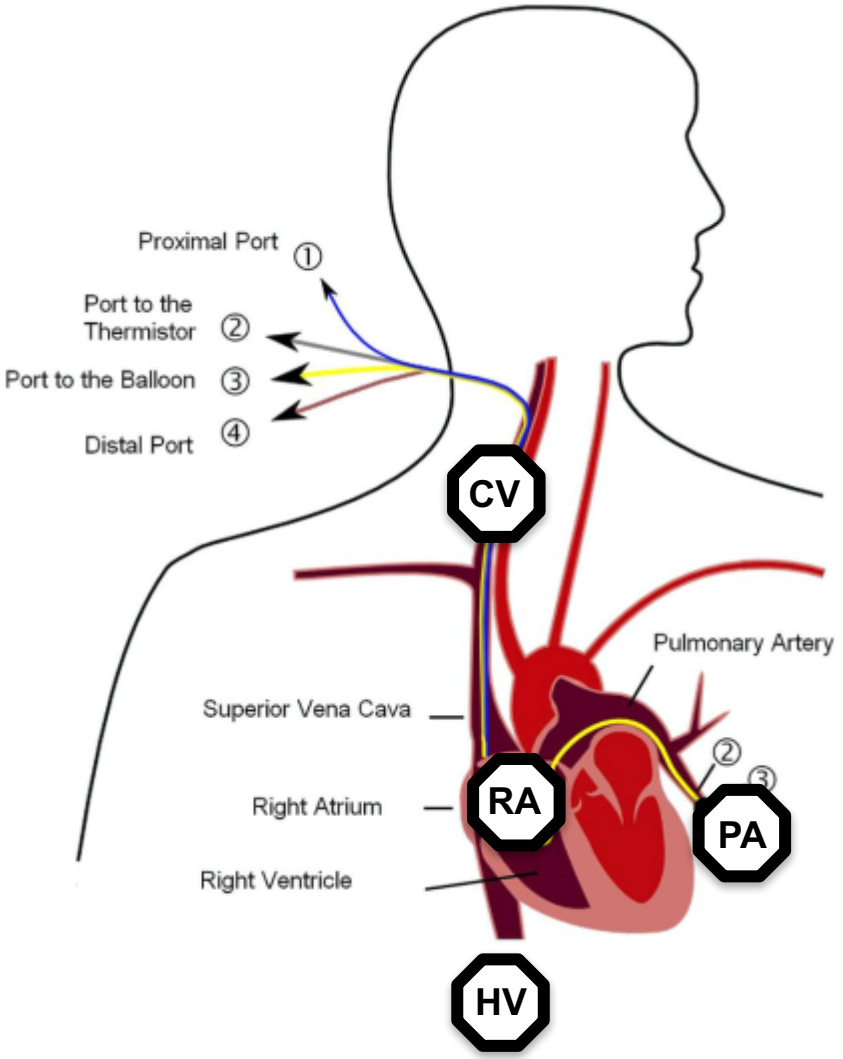
The liver-lung connection and novel biomarkers of POPH

- Prospective case-control study
- Plasma sample collection from across pulmonary and systemic circulation in prevalent and incident cases of POPH and liver disease controls
- 31 controls and 21 cases with POPH



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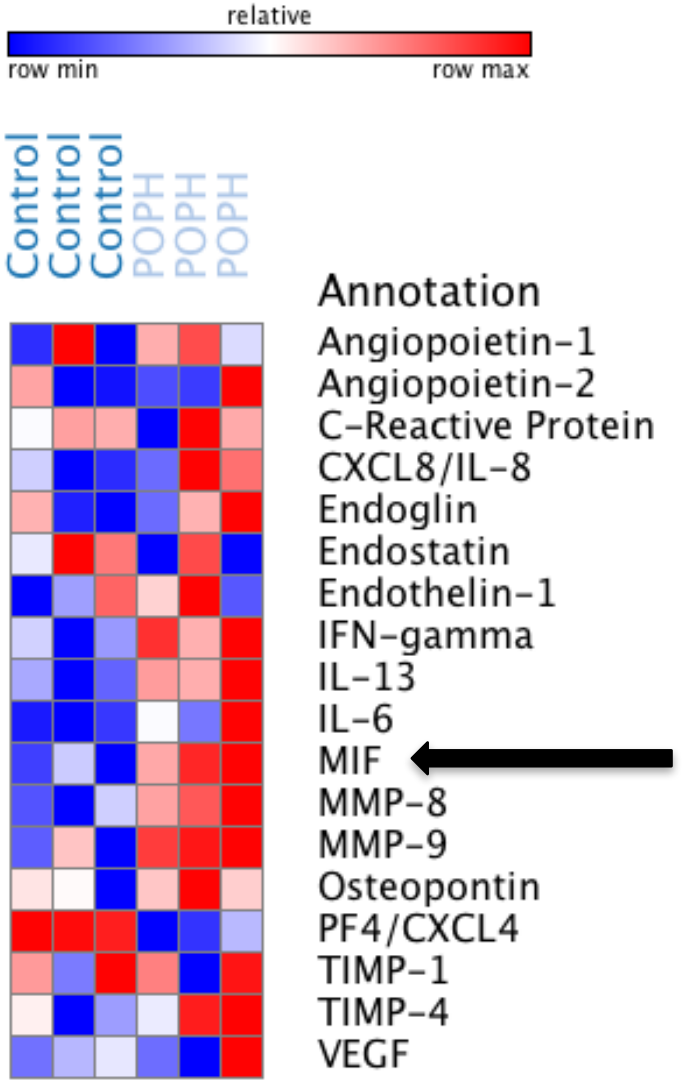
Antibody Microarray



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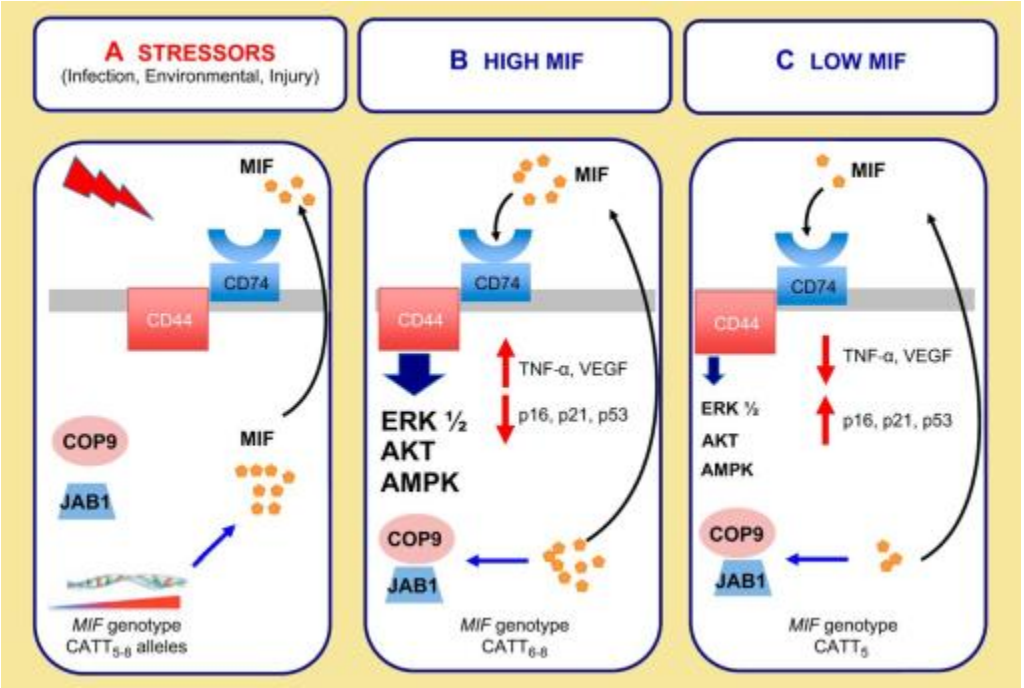
Macrophage migration inhibitory factor (MIF)

- A pro-inflammatory and proliferative cytokine involved in the regulation of innate immunity
- MIF promoter polymorphisms and elevated MIF levels linked to susceptibility and severity of several autoimmune diseases, including autoimmune liver disease
- Elevated in idiopathic PAH and PH associated with ILD and scleroderma



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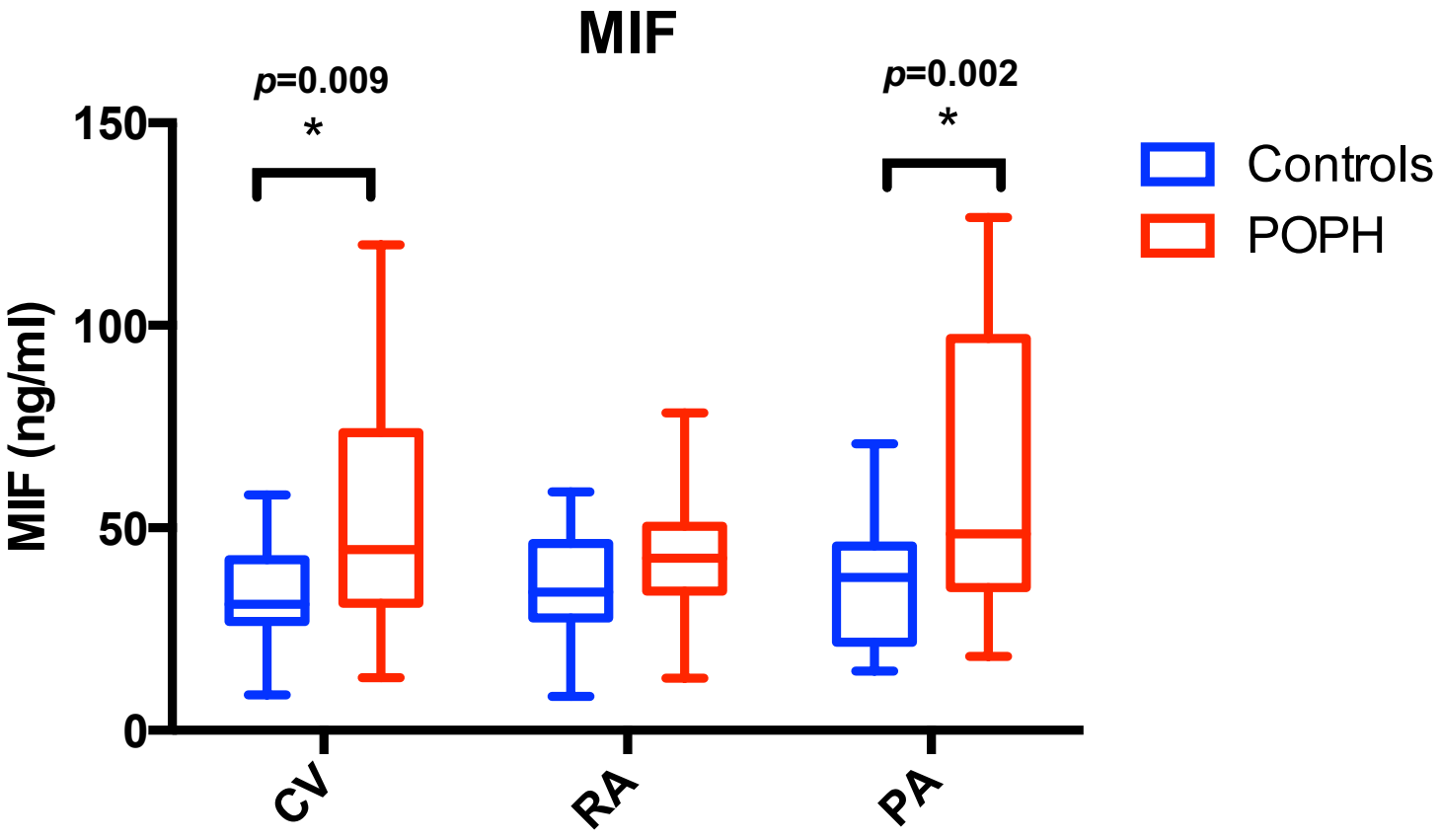
Zhang et al. Mol Med 2012
Assis et al. Hepatology 2014
Le Hiress et al AJRCCM 2015
Maor Sauler et al AJP 2015

MIF is elevated in POPH



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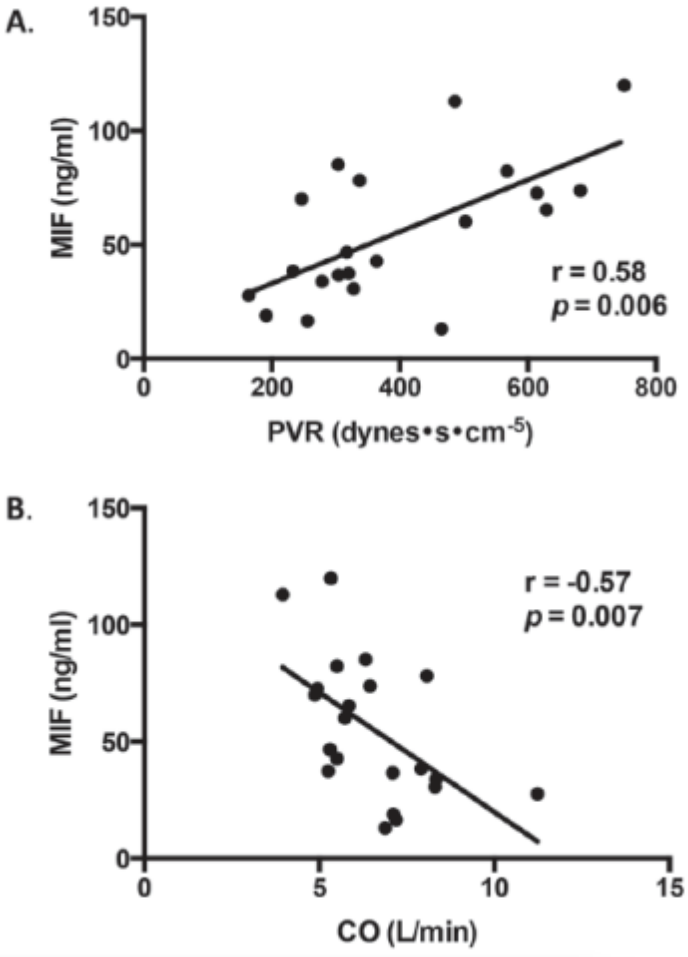
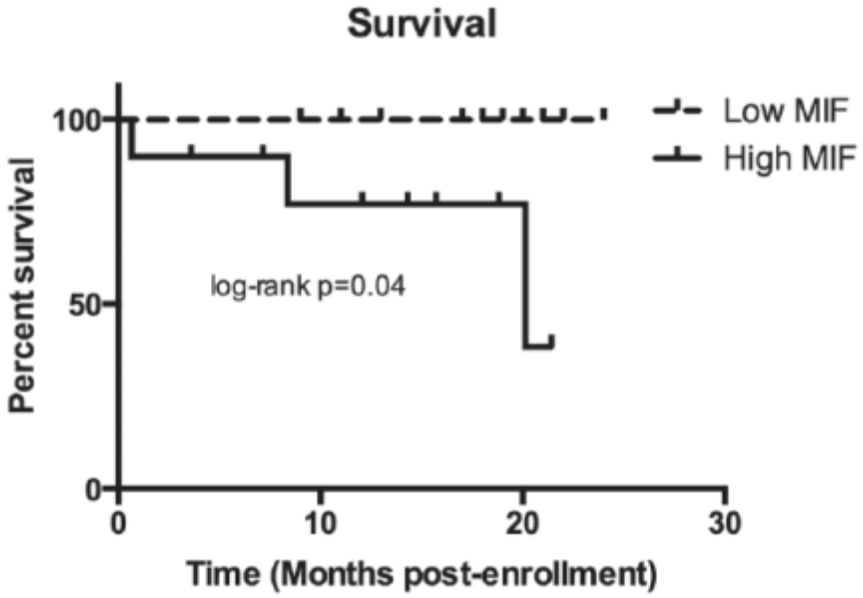
DuBrock et al. Pulmonary Circulation 2016

MIF is correlated with pulmonary hemodynamics and survival





DuBrock et al. Pulmonary Circulation 2016

Interim Summary

- The pathogenesis of POPH is poorly understood, but vasoactive factors from the gut that bypass the liver may play a role in disease development
- MIF, a proinflammatory and proliferative cytokine, is associated with the presence and severity of POPH

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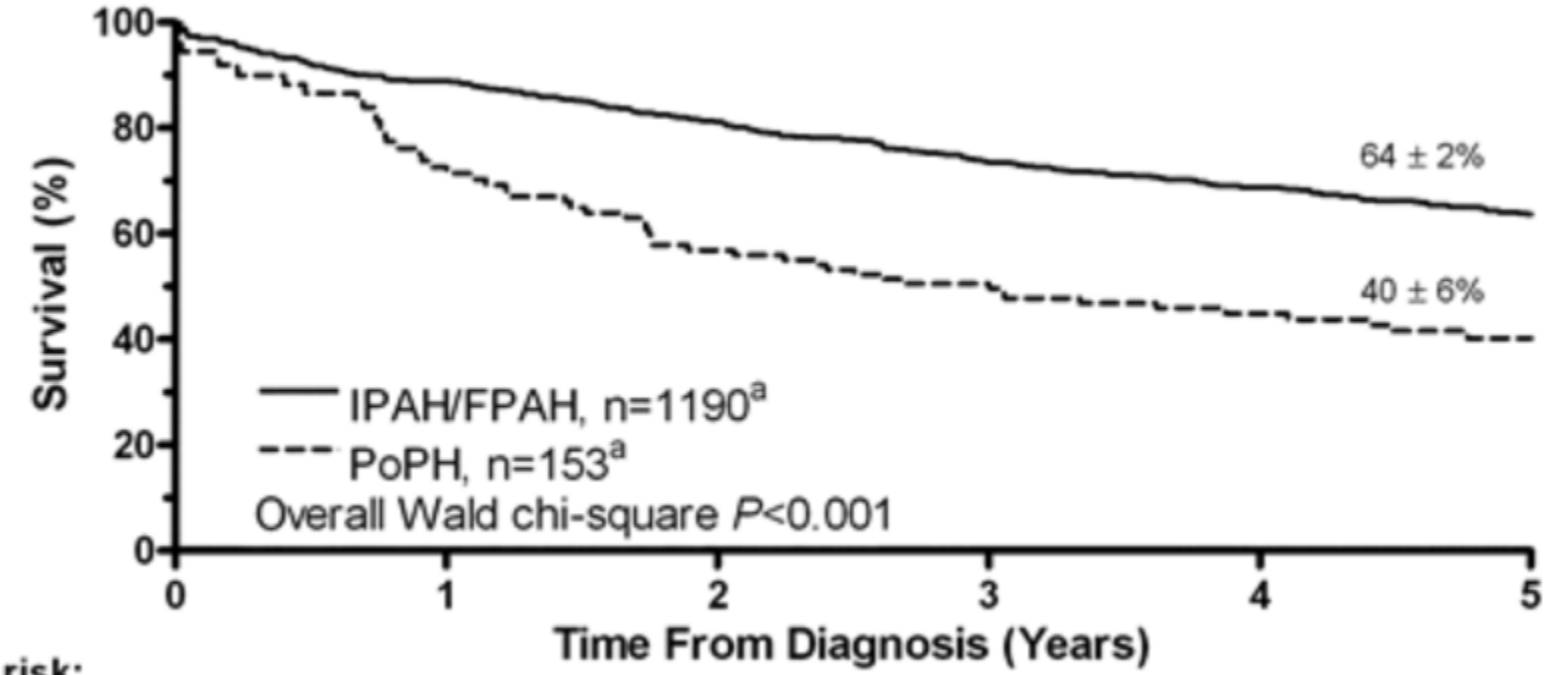
POPH is associated with significant morbidity and mortality



# at risk:						
IPAH/FPAH	419	485	527	472	393	311
PoPH	56	63	59	55	43	27

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Krowka et al. Chest 2012

Perioperative mortality risk can be stratified by mPAP

mPAP	Perioperative cardiopulmonary mortality in POPH
<35mmHg	0%
35-50mmHg	50%
>50mmHg	100%

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Krowka Liver Transplantation 2000

LT may be beneficial in POPH

POPH Management	5-year survival
No PAH therapy or LT	14%
PAH therapy alone	45%
PAH therapy + LT	67%

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Swanson et al. AJT 2008

MELD Exception for Liver Transplant in POPH

	Criteria for MELD Exception
Initial	1. Diagnosis of POPH AND 2. Adequate hemodynamic response to PAH therapy (mPAP<35mmHg AND PVR<400 dynes•s•cm^{-5})
Extension	Sustained hemodynamic response to PAH therapy on follow-up right heart catheterization every 3 months

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Limitations of the MELD Exception for POPH

- The system does not allocate points based on disease severity or waitlist mortality risk
- It is not known whether POPH in the absence of decompensated liver disease should be an indication for liver transplant
- Misclassification of patients is common- 47% of patients who received POPH MELD exception did not meet criteria

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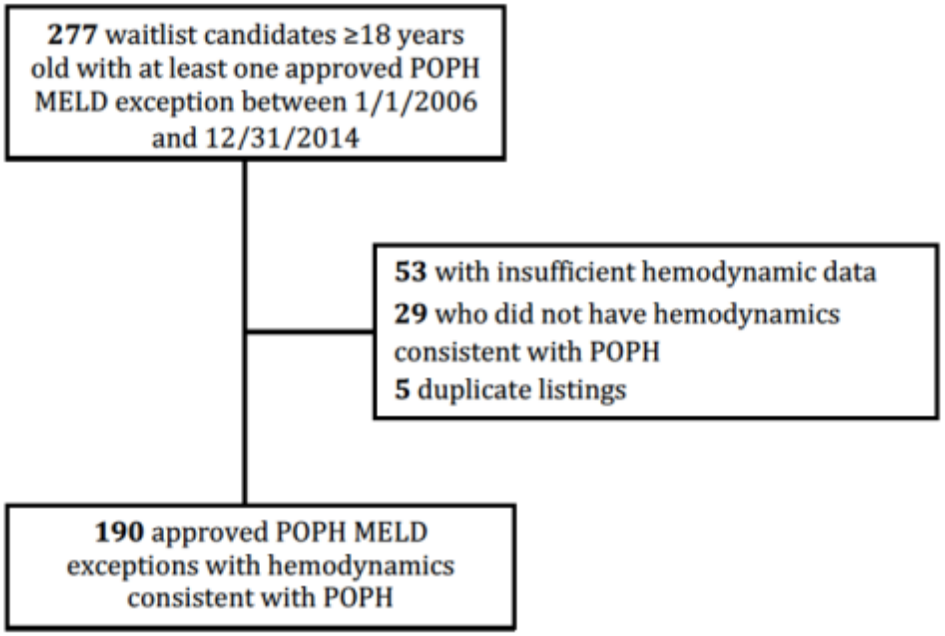
Goldberg et al. AJT 2015

POPH MELD Exceptions 2006-2014

- Retrospective analysis of UNOS database
- Patients with mPAP>25 and PVR>3 WU
- Aim: Identify predictors of waitlist mortality



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DuBrock et al. Transplantation 2017

Patient Characteristics (n=190)	
Age at listing, years	54 (48-58)
Male	103 (54.2)
Race	
White	146 (76.8)
Black	7 (3.7)
Hispanic	23 (12.1)
Other	14 (7.4)
Diagnosis	
Hepatitis C	73 (38.4)
Alcohol	34 (17.9)
Hepatitis C and Alcohol	17 (9.0)
Autoimmune	15 (7.9)
Primary biliary cirrhosis	10 (5.3)
Non-alcoholic fatty liver disease	7 (3.7)
Other	34 (17.9)
Initial Native MELD Score	12 (9-15)
Initial Pulmonary Hemodynamics	
mPAP, mmHg (n=190)	46 (40-54)
PVR, dynes (n=190)	450 (360-608)
CO, L/min (n=55)	6.1 (5.2-7.4)

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DuBrock et al. Transplantation 2017

Predictors of Waitlist Mortality

Variable	Univariate Model		Multivariate Model	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age at listing	1.04 (1.00-1.08)	**0.0499**	1.05 (1.00-1.09)	**0.03**
Female gender	1.37 (0.76-2.48)	0.30		
Initial Native MELD	1.11 (1.05-1.17)	**<0.001**	1.13 (1.08-1.20)	**<0.001**
Initial Hemodynamics				
mPAP, mmHg	1.02 (0.98-1.05)	0.40		
PVR, per 100 dynes	1.12 (1.02-1.23)	**0.02**	1.21 (1.09-1.33)	**<0.001**
CO, L/min (n=55)	0.67 (0.42-1.08)	0.10		

- MELD and PVR were not predictive of post-transplant mortality, but may have been under-powered

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DuBrock et al. Transplantation 2017

Back to our case...

- 56 year old man with cirrhosis and POPH treated with sildenafil and IV treprostinil on the liver transplant list
- MELD exception score 28
- Right heart catheterization demonstrates mPAP 38mmHg, PVR 2.1 WU, PAWP 15mmHg, CO 11L/min
- What next?

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Management of an elevated mPAP and normal PVR in treated POPH

- Inactivate from transplant list?
- Appeal to regional review board?
- Diurese?
- Wean Treprostinil?
- Midodrine?
- Change the system?

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mPAP>35mmHg at time of LT

- Single-center retrospective study
- 2010-2013
- mPAP≥35 in 31/300 (10.3%) patients
- Transplant hospital mortality 0%
- 1-year mortality similar to those <35mmHg
- If normal PVR and RV function, it may be safe to proceed with LT in setting of mPAP 35-50mmHg

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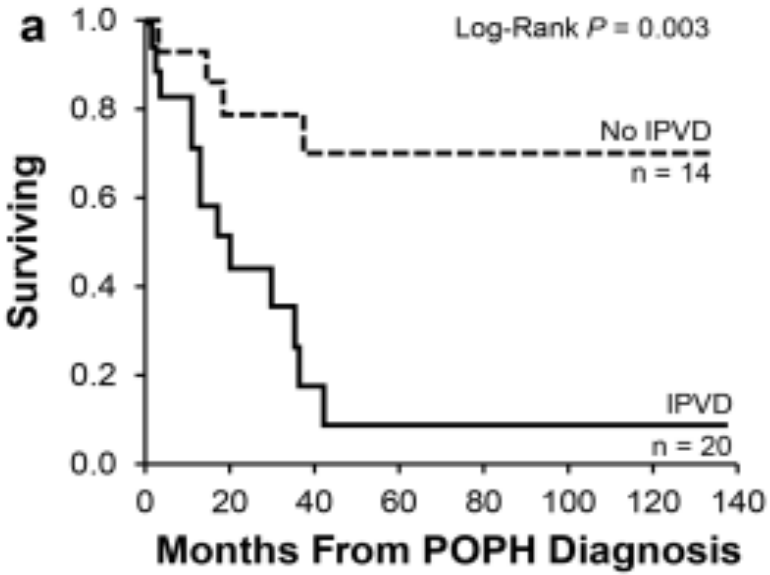
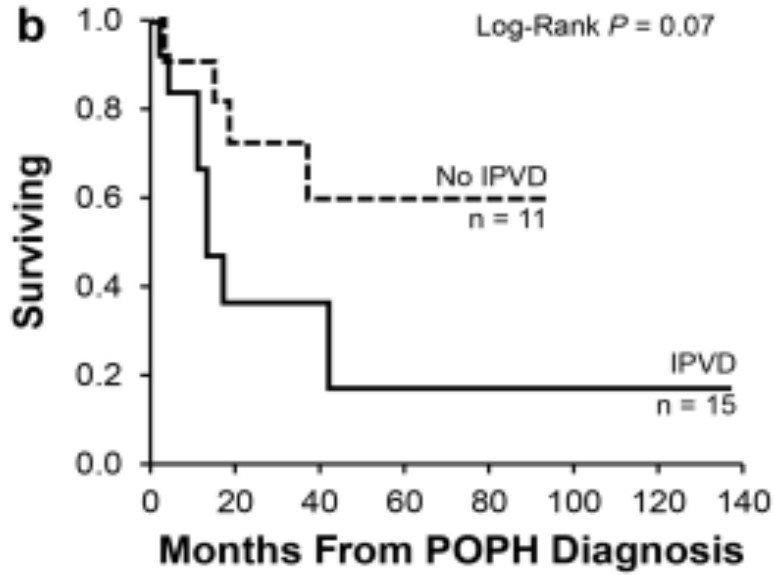
DeMartino et al. Transplantation 2017

Other Prognostic Factors: Intrapulmonary Vascular Dilatation



	Surviving (%)		
	1 Year	3 Years	5 Years
IPVD	71	18	9
No IPVD	93	79	70



	Surviving (%)		
	1 Year	3 Years	5 Years
IPVD	68	39	19
No IPVD	91	73	61

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Fussner et al. Liver Transplantation 2016

A tale of two transplants…

- Case 1: POPH associated with autoimmune hepatitis, underwent liver transplant
- Case 2: POPH associated with portal hypertension secondary to portal vein thrombosis, received single lung transplant

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Yoshida et al. Transplantation 1993

A tale of two transplants…

TABLE 1. Case 1: pulmonary artery pressure (mmHg)[a]

	Systolic	Diastolic	Mean
Pretransplant	75	26	45
Posttransplant			
6 Weeks	75	33	50
12 Months	42	21	30
22 Months	39	18	26

[a] Case 1 received a liver transplant. PAP regressed posttransplant and has been sustained for 22 months.

TABLE 3. Case 2:[a] pulmonary artery pressure and right ventricular pressure

	PAP			RVP
	Systolic	Diastolic	Mean	(systolic)
Pretransplant	95	44	64	—
Posttransplant				
3 Months	—	—	—	<30[b]
5 Months	64	25	40	60,[b] 55–60[c]
9 Months	67	47	56	—

[a] Case 2 received a single-lung transplant. Pulmonary hypertension regressed but recurred by 5 months posttransplant.

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Yoshida et al. Transplantation 1993

Post-transplant outcomes

United States UNOS 2002-2010

- 85% 1-year survival, 81% 3-year survival
- Patient and graft survival inferior to non-POPH exception patients

UK LT Registry 1992-2012

- 5 year post-transplant survival 53.8%
- 12 patients (42.9%) died within 5 years of LT with the majority of deaths (10/12) of deaths within 6 months post-transplant
- Only 8 (28.6%) of patients were on PH therapy
- 1992-2002: 60% early post-operative mortality vs. 27% early post-operative mortality 2002-2012

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Salgia et al Gig Dis Sci 2014
Verma Liver Transplantation 2016

Post-transplant outcomes

French PH Registry

- 35 patients who underwent LT
- 8 (23%) died after LT, including 5 due to POPH (Deaths at 1 and 7 days, 1 month, 2 and 6 months)
- Among survivors, all patients treated with epoprostenol were weaned off
- ERA or PDE5 were continued in 15/27 (55%)
- Post-LT survival 80%, 77%, 77% at 6 months, 1 year and 3 years, respectively
- “Stabilization or reversibility of POPH seems to be an attainable goal using the combination of PAH targeted therapy and LT”

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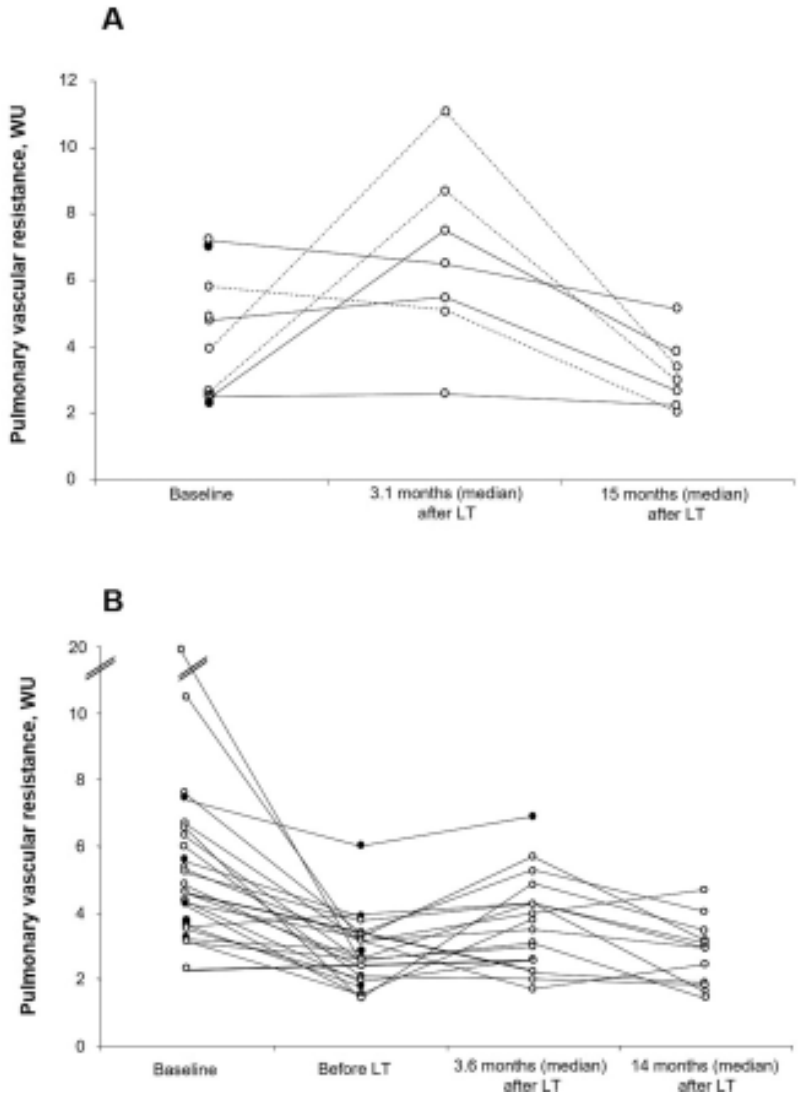
Savale et al Hepatology 2017

Hemodynamic outcomes



Savale et al Hepatology 2017

PAH Targeted Therapy

- Similar to other subtypes of Group 1 PAH

Pathway	Therapeutic Class	Drug
Nitric Oxide	Phosphodiesterase-5 inhibitors	Sildenafil Tadalafil
	Soluble guanylate cyclase stimulators	Riociguat
Endothelin	Endothelin receptor antagonists	Bosentan Ambrisentan Macitentan
Prostacyclin	Prostacyclin analogues	Epoprostenol Treprostinil Iloprost
	Prostacyclin IP receptor agonist	Selexipag

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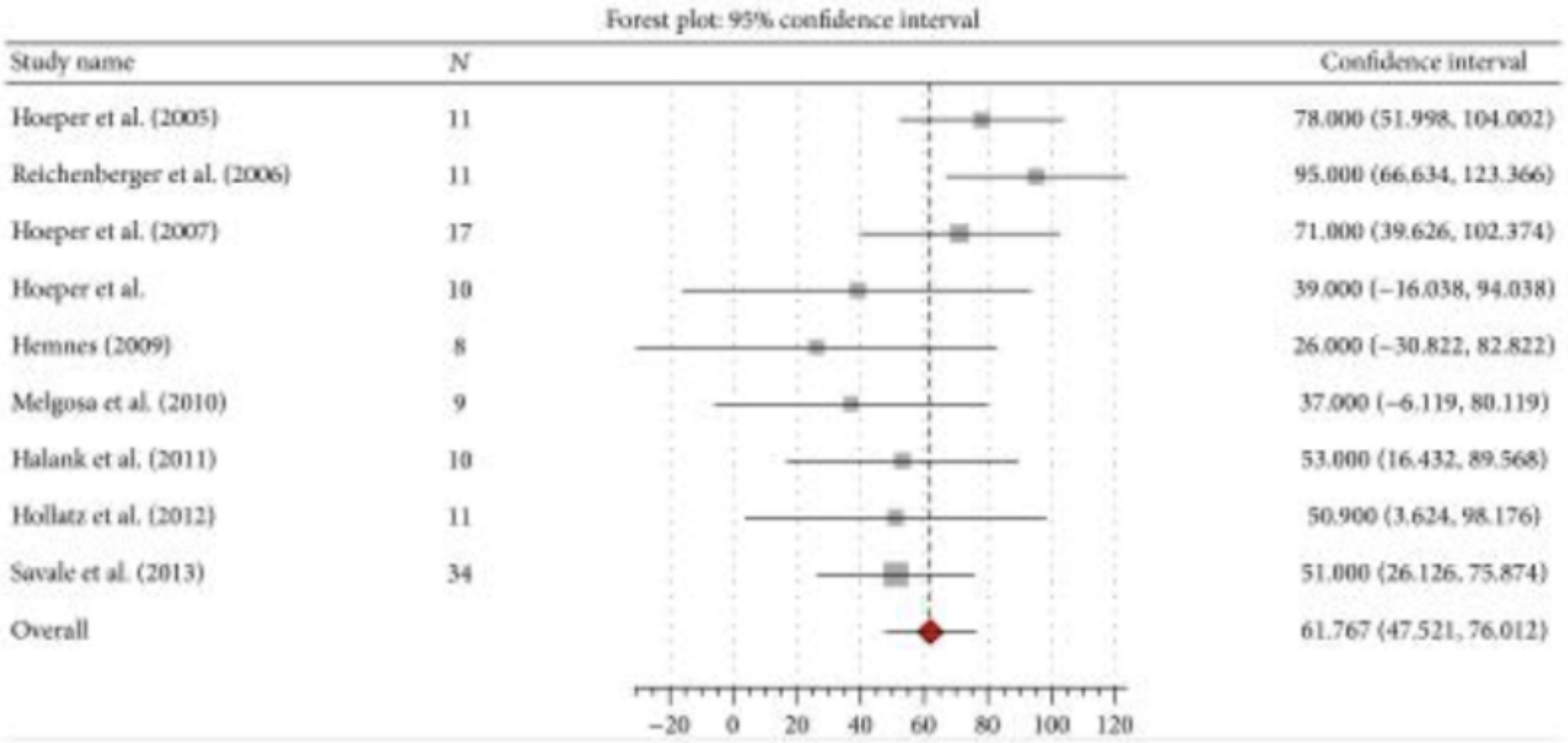
PAH Therapy in POPH

- Improved 6MWD and pulmonary hemodynamics



Faisal M et al Pulm Med 2014

Special Considerations Regarding PAH Therapy in Liver Disease

- Use of parenteral prostanoids has been associated with worsening thrombocytopenia, splenomegaly and ascites
- Typically use lower doses of parenteral prostanoids
- Calcium channel blockers not recommended
- Treatment goals often driven by liver transplantation candidacy
- If MELD score is high, important to treat PH aggressively to facilitate LT

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Perioperative Management

- Monitoring
  - Swan-Ganz catheter
  - Intra-operative transesophageal echocardiogram
- Treatment
  - Inhaled nitric oxide
  - Intravenous epoprostenol
  - Milrinone
  - ECMO

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Krowka et al. Transplantation 2016

Additional Management

- Diuretics
- Supplemental Oxygen
- Consider discontinuation of prophylactic beta blockers
- Avoid TIPS
- Liver Transplant

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Provencher et al. Gastro 2006
DuBrock et al Exp Rev 2015

Why don't we know more about POPH?

- Small sample sizes
- Most studies are retrospective and often include patients over a long period of time
- Misclassification of patients with pulmonary hypertension associated with a hyperdynamic state or postcapillary pulmonary hypertension
- Difficult to study outcomes in isolation of liver transplantation
- Is all POPH created equal?

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Future Directions

- Identify non-invasive biomarkers to improve screening for POPH and to monitor treatment response and disease progression
- Define the short-term and long-term effects of liver transplant on pulmonary hemodynamics and POPH outcomes
- Identify predictors of hemodynamic improvement with liver transplant… does immunosuppression play a role?

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Conclusions

- The pathogenesis of POPH is poorly understood, but vasoactive factors that bypass the liver may play a role in disease development
- Compared to idiopathic PAH, POPH is associated with worse survival
- LT is beneficial in a select group of patients with POPH, but pulmonary hemodynamics may worsen within the first 6 months

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Questions

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